

A Safe & Natural Broad-Spectrum Anti-Inflammatory: Natural Astaxanthin

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Introduction

If you try to treat a health issue and another one crops up, what have you gained? Looking at this proposition from a slightly different, more troubling angle: If you try to treat a health condition that is not life-threatening and you end up with a health condition that is life-threatening, what have you lost?

People with chronic pain will do just about anything to get rid of it. Sufferers of nagging pain from arthritis or other conditions yearn to return to a pain-free state. There are many health issues associated with pain that are considered “chronic” because they last for a long time—months, even years. And sometimes, tragically, certain people will pass decades with the same painful condition without finding a cure. Those of us fortunate to not suffer from chronic pain probably can’t really fathom what it’s like to be in this state. Those of us who do experience chronic pain usually end up in the pharmacy or doctor’s office looking for solace. But what most pharmacists and doctors have to offer for chronic pain doesn’t amount to a cure but rather a band-aid to treat the symptoms, often with serious side effects.

We’re going to begin this paper by looking at the current options for people suffering from chronic pain, with important attention to the side effects associated with pain relieving drugs. Then we’ll get to the heart of our discussion—a review of Natural Astaxanthin as an anti-inflammatory and as a potential remedy for painful joint and tendon conditions:

- The first step in this process is to examine the mechanism of action for how Astaxanthin works as an anti-inflammatory.
- Next, we’ll look at how Astaxanthin combats the key marker for inflammation in our bodies: C-reactive protein (CRP).
- After this, one-by-one we’ll go through the human clinical trials on inflammatory conditions such as arthritis and tendonitis.
- We’ll also list a few of the supporting pre-clinical trials that corroborate the findings in humans to help us round out the body of medical research in this area.
- Lastly, we’ll discuss the vast differences between Natural Astaxanthin and Synthetic Astaxanthin to ensure our Readers make the right choice when deciding which form to use.

Common Treatments for Chronic Pain

Since time immemorial, doctors and healers have been called on to help patients combat pain. A great variety of folk remedies and traditional techniques were employed in past civilizations, and in fact, still are used extensively in many developing cultures.

In Western medicine, the normal treatments for pain come in pill form or in topical ointments or creams. Results for the topical treatments are limited, while internal pain pills generally have a better chance of success. The conventional internal treatments for chronic pain come in four categories:

- ✓ Over-the-counter anti-inflammatories and other OTC pain medications
- ✓ Prescription anti-inflammatories
- ✓ Steroids
- ✓ Opioids

And as most people are already aware, each of these classes of medication comes with corresponding side-effects that are as bad or worse than the condition they're treating. Let's look at each of these classes of drugs and their corresponding side effects:

- Over-the-counter pain medicines include a long list of familiar names that fill the pain section in your neighborhood pharmacy. Most of these fall into a class of drugs known as Non-Steroidal Anti-Inflammatory Drugs or NSAIDs. Among the best known NSAIDs are:
 - Aspirin (sold under many brand names including Bayer®, Anacin® and Bufferin®)
 - Ibuprofen (sold under brand names such as Advil® and Motrin®)
 - Naproxen (sold under the brand name Aleve®)

Even though many consumers are unaware, the list of over-the-counter NSAIDs is much longer than this, although many are seldom-used or have fallen out of favor as more effective products have taken over shelf space and gained in popularity. An example of one of these is magnesium salicylate which was marketed under many different names, the most recognized perhaps being Doan's Pills®.

One famous name missing from this list of NSAIDs is Tylenol® (chemical name acetaminophen). The reason it's not on the list is that Tylenol is not an NSAID. Tylenol and generic acetaminophen are from another class of drug called "analgesics" which work differently from NSAIDs. Tylenol at best has only a slight effect on inflammation. In fact, its exact mechanism of action for reducing pain is not known (Botting, 2016).

Side Effects: The list of side effects from NSAIDs and other over-the-counter pain remedies is long. The minor side effects such as vomiting, nausea, headaches and dizziness that are associated with OTC pain killers can result from a single dose.

However, in treating chronic pain over the long term, the side effects become much more serious. Aspirin is mostly associated with gastrointestinal issues such as bleeding of the stomach or intestines and ulcers. The other over-the-counter pain pills are associated with even more serious side effects than aspirin. Similar to aspirin, these anti-inflammatories can also induce ulcers and stomach bleeding. However, long-term use has also been associated with liver and kidney damage. They also can increase blood pressure in some cases.

- Prescription anti-inflammatories include Vioxx® which has been taken off the market due to its serious side effects and Celebrex® which is currently still on the market, albeit with a long list of precautionary warnings and disclaimers. These drugs are strong inhibitors of cyclooxygenase-2 (Cox-2) which is an enzyme in our bodies that is responsible for inflammation and pain. However, Cox-2 is only one of several different inflammatory markers in our bodies. So what happens when a patient uses a strong Cox-2 inhibitor like Vioxx or Celebrex is that the drug drastically reduces this enzyme in the body while not significantly affecting other inflammatory markers? This may mask the pain, but it throws our systems completely out-of-whack and causes oxidation to occur. What has happened is that the patient feels less pain, but the constant use of these drugs increases free radicals in the body which can cause much more serious problems.

Side Effects: Vioxx was taken off the market because it caused many users to have heart attacks. This is one possible result of increased oxidation due to pro-oxidants (substances that increase the prevalence of free radicals). The pharmaceutical company that marketed Vioxx (Merck) spent approximately \$5 billion on settling lawsuits from people who had suffered heart attacks or from family members of people who died from heart disease due to this drug. While Celebrex remains on the market because it didn't have as pronounced an effect as Vioxx, it carries extensive warnings. Basically they're telling the customer: "Take this drug and it can help with your pain, but it may ultimately kill you."

We're going to digress slightly here to explain an extremely interesting study that was done at the prestigious Harvard Medical School on the negative effects of Vioxx. This is the study that illuminated Vioxx's pro-oxidant effects. Specifically, the study pointed out that the dangerous cardiovascular effects of Vioxx emanate from its action of increasing the susceptibility of LDL and cellular membrane lipids to oxidation. This, in turn, contributes to plaque instability and thrombus formation (the formation of arterial blood clots). This is a direct result of pro-oxidation: An increased number of free radicals attack the cellular membranes and LDL and causes heart disease.

What the researchers in this study did was test to see what effect Astaxanthin would have on Vioxx. They most likely chose Astaxanthin as the substance to use because of the many studies showing how incredibly potent it is as an antioxidant as well as the fact that Astaxanthin never turns into a pro-oxidant (Beutner, et al, 2000; Martin, et al, 1999; Nishida, et al, 2007; Shimidzu, et al, 1996; Miki, et al, 1991; Capelli, et al, 2013a). The researchers concluded, "Remarkably, Astaxanthin was able to completely inhibit the adverse effects of Vioxx on lipid peroxidation...We have now demonstrated a

pharmacological approach to block the pro-oxidant effect of Vioxx using a high lipophilic chain-breaking antioxidant, Astaxanthin” (Mason, et al, 2006). So basically, if Merck had only known about Astaxanthin’s excellent antioxidant effects before beginning to sell Vioxx, they could have added Astaxanthin to Vioxx and prevented the death of many innocent people.

- Steroids are synthetically produced pain-reducing medications designed to resemble cortisol. (Cortisol is a hormone that is produced by the human body.) Steroids are injected or given orally, and can also be given trans-dermally as well. Steroids work by reducing inflammation. They also are known to limit immune activity.

Side Effects: The list of side effects from steroid use in treating pain is extensive. Generally, the higher the dose and the longer the treatment, the greater chance that some of these side effects will occur. They include less serious issues such as acne, bruising, insomnia, growth of body hair, nervousness, water retention and swelling. More troubling, they can adversely affect the eyes, increase blood pressure, induce weight gain, decrease resistance to infection, weaken muscles, and can lead to osteoporosis. Additionally, use of steroids in diabetics can lead to a worsening of their condition.

It’s interesting to note that a commonly prescribed steroid called prednisolone was tested directly against Astaxanthin in rats to see how they compared in reducing inflammatory markers in the rats’ bloodstream. Against all three markers tested, both prednisolone and Astaxanthin performed fairly equally. In fact, at higher doses Astaxanthin outperformed prednisolone in reducing key inflammatory markers Prostaglandin E-2 and Nitric Oxide (Ohgami, et al, 2003; Lee, et al, 2003).

- Most people would not include opioids in our discussion here since they are generally not used for chronic pain. The reason for this is that they are highly addictive. Doctors usually prescribe them for intense pain that is thought to be short-lived to prohibit patients from becoming addicted. Unfortunately, the overuse and misuse of opioids has led to epidemic levels of addiction over the last few decades. The other huge downside to opioid use is the potential for overdose. Patients who aren’t getting the reduction in pain they seek may increase their dose, or may take opioids in conjunction with conflicting drugs such as alcohol and wind up in a coma or dead from respiratory failure. While extremely effective in masking pain, we can’t in good faith consider this class of drugs as suitable treatment for chronic pain due to these two major issues—addiction and overdose.

Astaxanthin's Multiple Mechanisms of Action

How Astaxanthin Works as an Anti-Inflammatory: 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 several different inflammatory markers, but that it works in a gentle, broad-spectrum manner. As we mentioned above, this is in distinct contrast to anti-inflammatory drugs such as Celebrex® and Vioxx® 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 Alpha
- ✓ Nitric Oxide
- ✓ Nuclear Factor Kappa B
- ✓ Cox 1 & 2 enzymes (Lee, et al, 2003; Ohgami, et al, 2003; Choi, et al, 2008; Kishimoto, et al, 2010)

The big difference between Natural Astaxanthin and OTC and prescription drugs used to treat pain is that 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 numerous safety studies such as acute toxicity and chronic toxicity studies demonstrating that Natural Astaxanthin is completely safe (Capelli and Cysewski, 2014).

But because Natural Astaxanthin works gently on a variety of inflammatory markers, it takes significantly longer to work than the over-the-counter and prescription drugs. The prescription and OTC drugs can work the same day to combat pain, while Astaxanthin usually takes at least two weeks and up to six or even 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 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 that had purchased at least one bottle of Natural Astaxanthin one time 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 pain medications 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, Aleve 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 shown to have any side effects or contraindications—it's completely safe and natural—while OTC pain pills and prescription anti-inflammatories all have serious side effects, 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?

Research Review: The 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 Broad-Spectrum Mechanisms 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 Study on the Mechanisms of Action:** 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).

3. Comparative Study on Nitric Oxide Scavenging: In this study, researchers pitted Astaxanthin against another commonly used natural anti-inflammatory, curcumin, and also tested a few curcumin derivatives as well. This in-vitro study found that curcumin and its related compounds were all less effective than Astaxanthin in nitric oxide radical scavenging (Sumanont, et al, 2004).
4. Further Validation: Several years later, scientists from Korea University further validated the earlier results finding broad-spectrum anti-inflammatory activity (Choi, et al, 2008).
5. Inhibition of Mast Cells: Mast cells are the key initiators of inflammation. Research at Kyoto University showed an inhibitory effect by Astaxanthin in rats' mast cells (Sakai, et al, 2009).
6. "Remarkable" Results: Japanese researchers referred to Astaxanthin's anti-inflammatory activity as "remarkable" and found a statistically significant reduction in six different inflammatory markers tested (Kishimoto, et al, 2010).
7. Effective against UV-Induced Inflammation: 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).
8. Most Recent Findings: A study from last year done in-vitro found again that Astaxanthin can reduce inflammatory markers interleukin-6 and tumor necrosis factor alpha. This study also found an impact on nuclear factor kB/p65. The study concluded, "These results suggest that Astaxanthin could be useful for improving chronic inflammation such as that associated with oral lichen planus" (Miyachi, et al, 2015).

Reducing “Silent” Inflammation

“What if there was a condition that threatened to destroy the entire US healthcare system in a very short time? Every politician would be making speeches about it. There would be a mobilization of the entire medical establishment to combat it...Unfortunately, such a condition does exist and no one seems concerned about it. This condition is ‘silent inflammation’...Silent inflammation is different from classical inflammation in that it is below the threshold of perceived pain. As a result, no action is taken to stop it, and it lingers for years, if not decades, causing insults on the heart, the immune system and the brain.” This excerpt is from an article written by a famous health advocate, Dr. Barry Sears, President of the Inflammation Research Foundation. Dr. Sears points out that Americans have the highest level of silent inflammation in the world. In fact, over 75% of American adults are afflicted. And while no drug has been developed that can reverse silent inflammation, “there are anti-inflammatory diets and anti-inflammatory dietary supplements that can” (Sears, 2005).

The marker used by doctors to measure how much silent (also called “systemic”) inflammation is occurring in a person’s body is called C-reactive protein (CRP). Sporadic inflammation is normal in our bodies, and is, in fact, part of the healing process. But prolonged “silent” inflammation is not normal and is certainly not desirable. “A decade ago, researchers were blaming oxidative damage for everything from cancer to heart disease. Now, chronic, low-grade inflammation is seizing the spotlight. ‘Inflammation is the evil twin of oxidation,’ says neuroscientist James Joseph of Tufts University. ‘Where you find one, you find the other.’ That would include not only such obvious inflammatory conditions as asthma and rheumatoid arthritis, but also ailments never previously associated with inflammation—such as atherosclerosis, Alzheimer’s disease, colon cancer and diabetes” (Underwood, 2005). And this is only a partial list of diseases that have been linked to silent inflammation. The scariest part of this is that silent inflammation has no signs or symptoms—in order to find out if you have high levels of silent inflammation, you have to get a blood test for CRP.

A panel of experts convened by the American Heart Association and the Center for Disease Control and Prevention recommended CRP testing as a means of predicting heart disease risk. CRP tests are now becoming a routine part of adults’ annual physical exams in many countries, just like cholesterol and blood lipid testing became standard procedure back in the 1980’s. While the main target of this testing (as with cholesterol testing) is heart disease, in the case of CRP testing it can be a strong indicator for an extensive range of life-threatening illnesses, several of which we discussed above. It’s interesting to note that many scientists (including some from the world’s most prestigious institutions like Harvard University) now consider CRP levels a more reliable indicator of impending heart disease than cholesterol and blood lipid levels (Perry, 2006).

Fortunately, a few different clinical trials have shown that Natural Astaxanthin may help reduce levels of CRP in humans. One such study, a randomized, double-blind, placebo controlled clinical trial, was done to test Natural Astaxanthin’s effect on CRP levels in healthy volunteers. The subjects took either 12mg per day of Natural Astaxanthin or a placebo for eight weeks. CRP levels were measured before and after the eight week supplementation period. Results were very

good—in only eight weeks people taking Astaxanthin reduced their CRP levels by over 20%. Meanwhile, people taking placebo saw a slight increase in their CRP levels (Spiller, et al, 2006a).

A team of scientists 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 tested. In fact, at both dosage levels of 2mg per day and 8mg per day of Natural Astaxanthin, they found a statistically significant decrease in CRP levels after eight weeks of supplementation as well as a reduction of approximately 40% in DNA damage (Park, et al, 2010).

In addition to the studies on CRP above, a company experimenting with 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 for cardiovascular disease. 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; meanwhile, none of those taking placebo did (Mera, 2006).

Natural Astaxanthin and Pain

We've established the varied mechanisms of action for Astaxanthin as an anti-inflammatory. And we've seen from the human clinical trials above that Natural Astaxanthin appears to have a significant effect on the key marker for silent inflammation, CRP. Now let's look at clinical research specifically on how Natural Astaxanthin stands up against pain.

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 young men doing intense exercise. The variety of studies are strong support for Natural Astaxanthin's far-ranging anti-inflammatory effects—whether the pain is in the joints, the tendons or the muscles, Astaxanthin seems to be able to reduce it and make people feel better. But once again we must warn our Readers—don't expect it to work fast. You'll have to use Astaxanthin at least two weeks and more likely four to as much as eight weeks to get the desired results.

The other point we must warn our readers about is this: About 15 – 20% of the people who take Astaxanthin for pain don't obtain their desired results. This isn't very different from other anti-inflammatory products you find in a drug store; most of those don't work for 100% of the people 100% of the time either. The reason this happens with Astaxanthin is most likely due to different people's bodies having a different capacity to absorb carotenoids. Astaxanthin is a carotenoid, the family of molecules that includes other health-giving nutrients like lutein, lycopene, zeaxanthin and the most famous carotenoid, beta-carotene. When absorption of carotenoids is studied in humans, researchers find a huge disparity in people's ability to assimilate them. The range is massive—from about 5% absorption level up to over 90% absorption. So what is probably happening when someone takes Astaxanthin for a few months and doesn't feel a reduction in pain is that they are most likely in the very low absorption range. This person's body may only be absorbing 5% of the Astaxanthin in the capsule they're taking, so even if they're taking 12mg per day (which is generally the upper level recommended by most brands), their body isn't feeling the effects because so little is getting into their bloodstream. Meanwhile, a person whose body is absorbing at the upper end of the range is getting practically all the Astaxanthin they consume into their bloodstream where it can work its magic. This person could take as little as 2mg – 4mg per day and get an excellent result for painful conditions. Fortunately, with over 80% of people finding great results in the normal dosage range of 4mg – 12mg per day and considering that these benefits happen without any dangerous side effects, there is little reason for most people to try other pain remedies that may be unsafe.

As mentioned above, the research on humans has been done both on healthy people as well as people suffering from different painful conditions, and these studies have covered a variety of organs afflicted by pain including joints, tendons and muscles. Let's look at each of these studies to see how Astaxanthin's diverse anti-inflammatory activities work when treating people afflicted with pain:

Rheumatoid Arthritis. Astaxanthin reduced pain levels and increased satisfaction with the ability to perform daily activities in sufferers of rheumatoid arthritis. Rheumatoid arthritis is a chronic painful condition with no cure; it is very difficult to treat compared to osteoarthritis. In this double-blind, placebo-controlled study, people in the treatment group took 12mg per day of Natural Astaxanthin over the course of eight weeks. Results showed a steady trend toward improvement in both pain levels and satisfaction from the beginning of the study to a midway point after four weeks, and then increasing improvement during the last four weeks of the study. During the first month, subjects found slight improvements on average. But by the end of eight weeks, the pain scores had dropped by 35% and the satisfaction scores improved by 40% in the group taking Astaxanthin (Nir and Spiller, 2002a).

Carpal Tunnel Syndrome: Another disease with no cure, carpal tunnel syndrome (abbreviated as “CTS” and also known as “repetitive stress injury” in some countries) affects up to 2% of Americans at any given time. This is a debilitating tendon condition that causes pain in the wrists. Patients suffering from CTS were randomly separated into two groups. One group took 12mg per day of Natural Astaxanthin and the other group took a placebo. Similar to the study on rheumatoid arthritis, this study also lasted eight weeks with a mid-term assessment of pain levels after four weeks. Perfectly mimicking the results found by people with rheumatoid arthritis, the CTS group taking Astaxanthin had good results after four weeks, but much more significant results after the full eight-week course of treatment. Pain levels were measured as well as the duration of pain. After eight weeks, these dropped by 41% and 36% respectively. Some of the people taking Astaxanthin reported that they were able to make major changes in their lifestyle due to the positive effects they experienced (Nir and Spiller, 2002b).

Muscle Inflammation and Recuperation in Elite Soccer Players: Soccer is the world’s sport—the most closely followed competitive sport in most countries around the globe. This study looked at the effect of Astaxanthin supplementation on young elite soccer players in Europe. The study was randomized and placebo-controlled; it spanned 90 days of supplementation. Shane Starling, a leading nutraceutical industry journalist, summed up the results very well:

“They gave 4mg of Astaxanthin daily to 40 young, trained soccer players and found via plasma testing better results for the Astaxanthin group in inflammation, immune system function and muscle recuperation...the researchers said the study showed Astaxanthin ‘attenuates muscle damage, thus preventing inflammation induced by rigorous physical training’” (Starling, 2015).

Concluding the study, the researchers hypothesized that the mechanism of action may be that Astaxanthin “protects the cell membranes against free radicals generated during heavy exercise, thus preserving the functionality of muscle cells” (Baralic, et al, 2015). Once again we see the link between oxidation and inflammation—where you find one, you generally will find the other. Fortunately, Natural Astaxanthin is both an antioxidant and an anti-inflammatory, so the oxidation/inflammation in the muscles created by heavy training is combatted from both angles by this single supplement.

Increased Strength and Decreased Pain in Patients Suffering from Tendonitis: The next study we'll look at was done in a group of people that were not healthy; these people were suffering from tennis elbow, a form of tendonitis that affects the arms. The repetitive motion of hitting tennis balls with a racket can manifest as tennis elbow, which causes a loss of grip strength in the hands and pain while gripping objects in the hand. The clinical researcher responsible for studying Astaxanthin's effects on rheumatoid arthritis and carpal tunnel syndrome that we reviewed earlier did a different kind of study on people suffering from tennis elbow. His name is Gene Spiller, PhD. Dr. Spiller tested patients' grip strength and the pain in their hands from tennis elbow before and after Astaxanthin supplementation. He separated the sufferers into two different groups randomly. The first group took 12mg per day of Natural Astaxanthin for eight weeks, while the other group took an identical placebo. The results for people supplementing with Astaxanthin were outstanding: On average, their grip strength increased by almost double in only eight weeks. The average increase was 93% to be exact, and there was also a decrease in their self-assessment of pain in their hands. Dr. Spiller concluded that using Natural Astaxanthin may alleviate pain and increase mobility. "This improvement may greatly improve the standard of living for those who suffer from such joint disorders" (Spiller, et al, 2006b).

Prevention of Joint Soreness After Exercise: The first human clinical trial to test Astaxanthin's effectiveness against pain and inflammation was performed at the University of Memphis back in 2001 under the supervision of Andrew Fry, PhD. This study looked at Natural Astaxanthin's effect on healthy young men who were performing strenuous exercise. It's a very important study to consider since it was done on perfectly healthy subjects, unlike most of the other studies we're reviewing that were done on patients suffering from conditions that cause chronic pain.

Dr. Fry used a relatively low dose of Astaxanthin—only 4mg per day. Additionally, this study ran for a very short period of time—only three weeks. Dr. Fry wanted to see if Astaxanthin could help prevent the soreness that usually occurs after intense exercise. The young men who participated in this study were training regularly with weights. The subjects used a resistance-training apparatus for strenuous knee exercises during the three week treatment period and took either 4mg of Natural Astaxanthin or placebo every day.

The young men taking placebo had significant joint pain in their knees immediately after the exercise. This pain was tested 10 hours after the heavy exercise, and then again at 24 hours and 48 hours after the exercise. Whether immediately afterward or at the various test times up to and including 48 hours afterward, the pain persisted for those who took placebo. But the young men who were taking 4mg of Astaxanthin every day showed no change in knee soreness right after exercise. This pain-free state remained consistent at the three other test times of 10, 24 and 48 hours after exercise (Fry, A., 2001). This is a fantastic result in particular when you consider that the dosage was the lowest level commonly recommended and that the study only ran for three weeks. In research on chronic painful conditions that occurred after Dr. Fry's study, dosage was generally 12mg per day and the studies ran for eight weeks. After four weeks there was an improvement in pain levels, but it became much more pronounced after eight weeks as

the Astaxanthin concentrated throughout the body. However, in the University of Memphis study, the results were much quicker. The reason for this is not clear, but may have to do with the fact that these subjects did not start with painful conditions and were young and athletic. In any event, it is very important to understand that Natural Astaxanthin appears to reduce pain in people who suffer from chronic conditions, but also seems capable of preventing pain in healthy people who are exercising heavily. The implications for not only the millions suffering from arthritis and tendonitis but also for athletes and regular people doing heavy work on a daily basis are extremely promising.

Prevention of Muscle Soreness After Exercise: The trial that Dr. Fry did at University of Memphis was originally focused on another inflammation-related condition. In fact, the main goal Dr. Fry had with the study was to see if Natural Astaxanthin could help prevent the soreness in muscles that occurs after doing heavy exercise. This condition is called “Delayed Onset Muscle Soreness,” and it affects athletes, weight lifters, people doing hard physical work, and perhaps most notably, weekend warriors. Thankfully, the results he found about Astaxanthin preventing joint soreness are much more important than his original goal. There is no doubt that joint pain caused by strenuous exercise is a much more serious condition than muscle soreness that occurs after strenuous exercise. Pretty much everyone has had sore muscles after a tough day in the garden or a long game of volleyball at the beach, and most people are highly aware that it’s just a temporary condition that will go away in a couple days. But sore joints are a much more troubling issue that are a greater concern than normal muscle soreness.

In any event, Dr. Fry did not immediately find a statistically significant result showing that Astaxanthin could prevent muscle soreness. But years later, Dr. Fry reexamined the data and found that in a subset of the subjects in this trial, Astaxanthin did have an excellent result in preventing muscle soreness after heavy exercise. The people that were positively affected were those whose muscles had high fiber content (Fry, et al, 2013). So basically, it appears that Natural Astaxanthin can prevent joint soreness after heavy exercise in most people, but it can only prevent muscle soreness after heavy exercise in some people.

Reduced Muscle Soreness from Lactic Acid Buildup During Exercise: We saw in the study above that Natural Astaxanthin can help prevent muscle soreness in certain people doing heavy exercise. But how is this possible?

Lactic acid builds up during physical exertion and causes burning in the muscles and fatigue. A study in Japan had healthy adult men take 6mg of Astaxanthin daily for four weeks. They had both the placebo and the Astaxanthin group run 1200 meters and tested their lactic acid levels before and after running at the beginning of the study (before supplementation began). They repeated this at the end of the study and found a statistically significant reduction in lactic acid buildup due to exercise in the men taking Astaxanthin. The results were excellent—a 28.6% reduction in lactic acid on average from taking 6mg of Natural Astaxanthin per day for a month (Sawaki, et al, 2002). This is one more piece of evidence that Astaxanthin can prevent pain and soreness, in this case the burning pain due to heavy exercise. Plus, this study explains how this is possible—by Astaxanthin’s ability to reduce lactic acid levels.

Supporting Pre-Clinical Research

Along with the varied research in humans, there are dozens of pre-clinical trials in mammals and in-vitro experiments supporting Astaxanthin's anti-inflammatory activities. In particular, there has been a flurry of rodent studies over the last couple of years. Due to space constraints, we will not review all of these studies; however, a chronological listing of highlights from some of the most important pre-clinical studies includes:

- Astaxanthin provides neuroprotection by inhibiting inflammation in mice (Ying, et al, 2015).
- Astaxanthin reduces inflammation and oxidation in the kidneys of mice (Qiu, et al, 2015).
- Astaxanthin reduces pro-inflammatory cytokines and reactive oxygen species in mice (Li, et al, 2015a).
- Astaxanthin exerts anti-inflammatory and antioxidant effects in mice with kidney injury (Liu, et al, 2015).
- Astaxanthin reverses increases in several inflammatory and oxidative markers in rats with systemic inflammation (Zhou, et al, 2015).
- Astaxanthin protects against autoimmune hepatitis by reducing the release of inflammatory factors (Li, et al, 2015b).
- Astaxanthin protects against diabetes-induced hepatic inflammation and oxidative stress in rats (Park, et al, 2015).
- Astaxanthin inhibits the formation of pre-malignant colon lesions in mice by suppressing chronic inflammation and oxidative stress (Kochi, et al, 2014).
- Astaxanthin reduces inflammation and liver stress in mice fed a high fructose / high fat diet (Bhuvaneswari, et al, 2014).
- Astaxanthin protects cells from inflammation and oxidative stress caused by lipopolysaccharide reducing O₂-production (Franceschelli, et al, 2014).
- Astaxanthin may prevent inflammation-associated colon cancer in rodents (Tanaka, 2012).
- Astaxanthin exhibits anti-inflammatory and anti-coagulatory effects in diabetic rats (Chan, et al, 2012).
- Astaxanthin improves insulin sensitivity by reducing inflammation, oxidation and lipid accumulation in obese mice (Arunkumar, et al, 2012).
- Astaxanthin reduces inflammatory cytokines induced by UVB exposure (Terazawa, et al, 2012).
- In a dog study preceding a similar study he later did in humans, respected carotenoid researcher Boon Chew, PhD from Washington State University found that Astaxanthin heightens the dogs' immune response and reduces DNA damage and inflammation (as measured by CRP levels) (Chew, et al, 2011).

- Astaxanthin inhibits colitis and colon cancer formation in mice by modulation of inflammatory cytokines (Yasui, et al, 2011).
- Astaxanthin protects against inflammation, oxidative stress and apoptosis in epithelial cells exposed to high levels of glucose (Kim, et al, 2009).
- Astaxanthin's anti-inflammatory activity may result in prevention of age-related macular degeneration in mice (Izumi-Nagai, et al, 2008).
- Astaxanthin reduces inflammation in rats' eyes (Suzuki, et al, 2006).
- A mouse study backed up the human trial showing that Astaxanthin can reduce lactic acid levels to prevent sore, burning muscles after exercise. In this study they measured blood lactose levels in both the control and Astaxanthin groups. The mice fed Astaxanthin had lower lactic acid levels in their muscles, which is resulted in them being able to swim significantly longer before exhaustion (Ikeuchi, et al, 2006).
- An early study in this area had mice run on a treadmill until exhausted. The results they found were fantastic. Mice that were supplemented with Astaxanthin had decreased inflammation in their muscles by 50%. In addition, the Astaxanthin mice had:
 - Less DNA damage
 - Less oxidative damage in their heart muscles
 - Less oxidative damage in their calf muscles
 - Reduced oxidation in their plasma
 - Less peroxidation damage in their cell membranes

The study concluded: "Our data documented that Astaxanthin indeed is absorbed and transported into skeletal muscle and heart in mice, even though most carotenoids accumulate mainly in the liver and show relatively little distribution to other peripheral tissues, including skeletal muscle and heart. This unique pharmacokinetic characteristic of Astaxanthin makes it well suited to oxidative stress in gastrocnemius [calf] and heart...Thus, Astaxanthin attenuates exercise-induced damage by directly scavenging reactive oxygen species and also by down-regulating the inflammatory response" (Aoi, et al, 2003).

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, 2013a).

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, 2013a).

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

We've analyzed the body of evidence for Astaxanthin's effectiveness as an anti-inflammatory. Several studies have established its anti-inflammatory mechanism of action: A multi-pronged, broad-spectrum activity against a diverse list of inflammatory markers. And we've seen from multiple human clinical trials that Astaxanthin can reduce C-reactive protein, the key indicator of hazardous silent inflammation in humans.

When considering how to treat chronic pain, many physicians still guide their patients to prescription and OTC anti-inflammatories. However, this is probably not the best advice, as each of these comes with multiple side effects, some of which are life-threatening. We suggest that these prescription and OTC anti-inflammatories be considered more in the manner that doctors consider opioids in treating pain—for temporary pain that will most likely go away soon. The opioids have such serious and frequent side effects of addiction and overdose that they must be considered only for short-term use. But the prescription and OTC anti-inflammatories also have highly concerning side effects, even though they may not be as severe as opioids' side effects.

After seeing that Natural Astaxanthin has been analyzed in human clinical trials against a variety of painful conditions in both patients suffering from chronic pain as well as in healthy subjects doing heavy exercise, and considering that there have been absolutely zero side effects or contraindications associated with Natural Astaxanthin after over fifteen years of consumer use, myriad medical research studies and many safety studies, we see this remarkable supplement emerge as a clear candidate for both chronic pain as well as prolonged silent inflammation.

However, we remind our Readers once again that, since Natural Astaxanthin works as an anti-inflammatory in a gentle manner, consumers should not expect fast results. Generally, people tend to get similar results to the prescription and OTC pain killers, but it will most likely take two to as much as eight weeks to get the full benefit.

And a last word of caution—when choosing a brand of Astaxanthin to use, be sure that the source is Natural Astaxanthin from microalgae—it's the only source of Astaxanthin that's been shown to have extensive health benefits in humans and has been proven safe as well.

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