



ASTAXANTHIN: THE RISING STAR FOR DEVELOPING NEW IMMUNE PRODUCTS

**Immune Health is an Insatiable Market Primed for
New Formulations in Supplements, Medical Foods,
Functional Foods, and Beverages**

*Immune health is the hottest segment
of the supplements market.*

*Demand for new formulations is driving
phenomenal growth.*

Top companies are going all out to satisfy it.

*The search for exciting new ingredients has hit the
bullseye with astaxanthin.*

*One company stands out for its branded,
science-backed research and marketing
support for their clients: AstaReal.*

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Executive Summary

Today an increasingly proactive consumer is seeking help with all aspects of healthy living. One segment of the market that's heating up the fastest is immune health. It's spawned in part by the COVID-19 pandemic.

Supplement companies have rushed in to fuel the rising demand for immune health products.

This is exactly where the best ingredients can shine.

Astaxanthin is clearly the rising star in a highly competitive marketplace.

Extensive scientific research shows exactly how powerful this nutrient can be for immune health. Research shows 5 ways in which astaxanthin supports immune function:

- 1. Anti-inflammatory properties that support immune fire management**
- 2. Antioxidant activity that help balance redox homeostasis**
- 3. Support for mitochondrial function that fuels immune cell activity**
- 4. Immunomodulatory action on both innate and adaptive immune cells**
- 5. Support for the Gut Mucosa and Microbiome**

That's where AstaReal, the world's leading producer and innovator of natural astaxanthin rises above the competition.

AstaReal continues to lead the way in clinical studies and patents based on its natural astaxanthin.

AstaReal does more than produce the finest natural astaxanthin in the world. It also fosters development of new formulations with its clients to ensure science-backed trust and credibility all the way to the end user.

Getting Ahead of the Post-Pandemic Curve: Immunity is the ‘New Normal’

And the trend is about more than supplements.

Obviously, immune health was the key headline of 2020.

*- Claire Morton-Reynolds
Nutrition Business Journal*

The health and nutrition industries are responding to a growing consumer demand for new food and beverage products that deliver immune support. To meet the global health challenges that are generating this demand, there is a need for functional ingredients that are credible, nature-inspired, science-driven, and effective at maintaining a healthy immune system.

*- Walt Pebley
VP of Technical Innovation
at Oregon Freeze Dry*

Why Develop Immune Health Products?

Immune health formulations alone skyrocketed about **70%** in 2020, with no end in sight.

The consumer focus on building immunity continues to accelerate.

At an estimated **\$6.3 billion**, the U.S. already accounts for **34%** of the global market.

Substantial demand also characterizes markets in China, Japan, Canada, western Europe, and South America.

People are taking extra care of their immune health, wanting to get back to the people and things they enjoy. This is driving innovation in immune formulation and ramping up the search for new stand-out ingredients.

*- Devin Kummer
Formulation Scientist
at Prinova Group*

The Landscape of Immune Ingredients is Expanding

Immune health supplements span a broad array of well-known vitamins, minerals, and herbs.

People rely on these foundational ingredients, but are looking for new products that deliver added benefits and optimize immune function.

In light of the COVID-19 pandemic, health-savvy consumers have developed a thirst for additional ingredients.

Consumers want to take charge and proactively manage their wellness.

More than ever, the immune health market is about moving forward, doing more, doing better, and being future-minded.

This is where one ingredient – **astaxanthin** – hits the bullseye.

The race is on for creating new and exciting astaxanthin-containing supplements, foods, and beverages.

For product formulators, the question becomes how to choose the best astaxanthin for meeting the accelerating needs of new product development.

Building customer trust begins with formulations containing only the highest quality ingredients.

And then making sure your customers know exactly why your ingredients are superior.

Addressing immune health with AstaReal® Astaxanthin is an excellent choice.

According to the Council for Responsible Nutrition (August 20, 2020), 9 out of 10 dietary supplement users reported increasing their supplement intake in 2020. Kendall Ridley, Senior Director of Communications at CRN, notes a broadening the scope for immune supplements outside the traditional confines. Immune health is about more than just taking vitamin C and zinc.

The quality of your customers' lives depends on the quality of your ingredients.

Your ingredient choices will not only affect their health, it will also impact your bottom line.

The Human Immune System 101

The immune system is a marvelous multitasker that shields us against disease and infection by coordinating a variety of immune cells and biochemical signals throughout the body.

Immune responses are classified into two types, the innate immune system and the adaptive immune system. Astaxanthin plays a role in supporting both.

The Innate Immune System

The first line of defense by innate immunity consists of physical barriers such as our skin, mucous, and other epithelial surfaces.

Once any of these physical barriers is breached, white blood cells of the innate immune system can detect and attack pathogens. Certain types of these cells – macrophages - hunt down, engulf, and destroy invasive microbes and other foreign substances.

Other cells, called natural killer (NK) cells, can also kill host cells that are virally infected.

Still other cell types secrete small proteins called cytokines. The primary roles of cytokines involve regulating inflammation. Their activities can be seen as the redness, soreness, and swelling associated with an injury or site of infection.

The Adaptive Immune System

When cells of the innate immune system are unable to handle microbial invasions swiftly and effectively enough, then the adaptive immune system gets activated to take a swing at neutralizing the threat.

Resistance to a specific pathogen is due to the ability of the adaptive immune system to “remember” the pathogen. This molecular memory is an antibody that responds to a specific foreign microbe or foreign substance known as an antigen.

Adaptive immune responses also entail reactions to antigens released by the activities of macrophages. Responses include antigen-antibody reactions and recruitment of still more white blood cells to the site of infection or injury.

Two types of white blood cells characterize adaptive immunity, B cells and T cells. They're so named based on where they mature – B cells in bone marrow and T cells in the thymus gland.

Both classes of adaptive immune cells release multiple kinds of cytokines. As with the cytokines of innate immunity, those of adaptive immunity also work to regulate inflammation. Mitochondria have a limited lifespan. That means each cell must constantly replace old, worn-out mitochondria with new ones

Energy Demands of Immunity

Maintenance and activation of immune cells require energy. Energy is required to turbocharge the immune response. Demands for energy increase as activated immune cells migrate, multiply, and produce cytokines.

Energy-intensive immune responses depend on the powerhouses of cells, mitochondria. Energy generated in mitochondria is like money for paying the energy bill of immune cells.

Mitochondria are the engines of immune cells that help keep us healthy throughout our lifetime.

In addition to their role in generating energy, mitochondria are also important for immune signaling. They can regulate the activation, differentiation, and survival of immune cells (Angajala et al. 2018).

Astaxanthin specializes in supporting mitochondrial function.

TOP 5 Ways Astaxanthin Supports Immune Health



Scientists focusing directly on immune health see five major categories of activity behind astaxanthin's immune benefits.

1. Immune Fire Management

Inflammation is essentially a metabolic fire. It occurs when chemicals from your white blood cells enter your blood or tissues to protect your body from invaders. This raises the blood flow to the area of injury or infection. It can cause redness, swelling, and warmth.

A healthy immune system lights up these internal fires when needed. Chemically this means producing inflammatory cytokines that trigger inflammation, and then dousing the inflammatory cytokine signaling once the danger has passed.

Astaxanthin's activity in putting out metabolic fires works by either quelling the production of inflammatory cytokines directly or by controlling a gene switch that enables their production.

That gene switch is a small protein, called NF- κ B.

The primary anti-inflammatory mechanisms entail either suppressing cytokine production directly or controlling the expression of NF-κB.

Astaxanthin exhibits many anti-inflammatory properties against a litany of additional cytokines, ROS, and other molecules running amok in our cells.

One more such molecule is worth mentioning here because it's been a huge target for drug development. It's an enzyme called "cyclooxygenase-2" (COX-2).

COX-2 catalyzes the formation of a hormone-like molecule, prostaglandin E2 (PGE2). Too much PGE2 can be highly inflammatory. Drugs to inhibit its production are designed to inhibit COX-2. The two most widely known COX-2 inhibitors are Celebrex and Vioxx. Unfortunately, their side effects are so troublesome that one, Vioxx, was removed from the U.S market in 2004.

"JAK/STAT" may sound like something out of a fairy tale involving beanstalks. Yet it's a crucial signaling system for controlling many aspects of immunity.

The hunt for natural COX-2 inhibitors with fewer side effects has been ongoing for many years. The darling of this ongoing search is emerging as astaxanthin, which can significantly decrease the expression of COX-2 without side effects (Chang and Xiong 2020).

Another aspect of inflammation gaining more attention regarding immunity involves the JAK/STAT pathway.

This pathway is comprised of a chain of molecular signaling interactions between proteins carrying molecular signals from outside a cell to the cell nucleus. As a result of this communication system, the JAK/STAT pathway has a far-reaching influence on inflammation associated with immunity (Mehta et al. 2020).

This view resurrects notice of an earlier study showing that astaxanthin modulates the JAK/STAT-3 pathway, which is in turn responsible for regulating gene expression in immune cells (Kowshik et al. 2014).

The overall effect of astaxanthin is to dampen inflammatory signaling by this pathway (Chang and Xiong 2020).

Research on astaxanthin clearly shows its multiple anti-inflammatory effects in support of a healthy immune response.

2. The Push and Pull Between Free Radicals and Antioxidants

The body is in a dynamic tug-of-war between oxidants and antioxidants. Oxidants are unstable molecules that cause damage, while antioxidants function to stabilize them. The goal is to strike a balance between these two forces, because even the destructive nature of oxidants, also known as free radicals, can have a purpose.

In addition to producing cytokines, immune activation also releases highly reactive free radicals that kill pathogens, but can also damage host tissues. The immune response can elevate free radicals to a degree that overwhelms the body's antioxidant capacity. Dietary antioxidants may serve as a supplement to the body's own antioxidant defense in times of need.

In order to strike a balance, immune cells are particularly rich in antioxidant vitamins that help to protect them against their own oxidant production. However, our body's antioxidant defenses drop under conditions of stress, and with advancing age. For example, T cells, B cells, and NK cells from elderly individuals appear to be more sensitive to the oxidant hydrogen peroxide than the same cells from young adults. When the tug-of-war shifts in favor of harmful oxidants, additional antioxidant support is necessary to boost and maintain a healthy immune system.

A study looking at neutrophils, which are white blood cells that are part of the innate immune system, examined oxidative damage in the presence of oxidative stress (Park et al. 2010a). Lipid peroxidation and the presence of carbonyl groups both indicate oxidative damage. This study showed that neutrophils experience less oxidative damage in the presence of astaxanthin compared with untreated neutrophils. Those same neutrophils did a better job engulfing and killing a yeast pathogen in the presence of astaxanthin than in the absence of astaxanthin. This study of human neutrophils in a dish showed that antioxidant protection can help boost the activity of immune cells.

In a double-blind placebo control clinical trial, 42 healthy individuals supplemented with 0, 2, or 8 mg/day of natural astaxanthin for 8 weeks. Concentration of the oxidative stress marker, 8-OHdG, was lower with both 2 mg/day and 8 mg/day natural astaxanthin at week 4 compared to placebo.

In the same clinical study, blood samples were collected on weeks 0 and 8 to assess B and T cell proliferation in response to various antigens. B and T cell proliferation increased by 26% or 28%, respectively, in the natural astaxanthin group at 8 mg/day after 8 weeks compared with the control group after 8 weeks. Natural astaxanthin supplementation also resulted in higher NK cytotoxic activity after 8 weeks compared with the placebo group. This study showed that astaxanthin helped support immune cells involved in both the adaptive and innate immune responses.

As Dr. Paris Kidd, PhD, author of the astaxanthin monograph published in Alternative Medicine Review explains: While most antioxidants lose their antioxidant status after snaring a free radical and becoming pro-oxidant, astaxanthin doesn't. It preserves its antioxidant status (Kidd 2011).

On top of all this, astaxanthin helps preserve your body's own antioxidant enzymes (Choi et al. 2011)

This further multiplies the antioxidant protection astaxanthin brings to your mitochondria.

Astaxanthin also provides additional protection by activating antioxidant enzymes via Nrf2 (Wu et al. 2014).

The antioxidant support provided by natural astaxanthin, and its preferred location in the mitochondria, may serve to protect immune cells against an overwhelming accumulation of free radicals.

3. Mitochondria – Tiny Machines Behind Immunity

Mitochondria are those submicroscopic parts of cells that every biology student has to know about. They're typically described as the energy powerhouses of the cells.

However, focusing on mitochondria only as energy producers is an oversimplification.

Healthy mitochondria are therefore the foundation of a healthy immune system

Research on how to nourish mitochondria has become more important than ever.

That's where astaxanthin steps up as an incredibly powerful mitochondrial nutrient.

MITOCHONDRIA = IMMUNE HEALTH

Indeed, they just may be the most important parts of cells running the whole immune show. Immunity and mitochondria are interlinked with each other. Their linkage is highlighted by the role of mitochondria in the activation, differentiation, and survival of immune cells (Angajala A et al. 2018).

Mitochondria can impact the immune system in many additional ways. A few of the better-known activities include:

- A. Mitochondrial ROS and their brethren, RNS (reactive nitrogen species), regulate gene expression in immune cells.
- B. A mitochondrial membrane protein, UCP2, helps control the production of ROS.
- C. Immune cell mitochondria send their DNA (mtDNA) into their cells, also helping to regulate immune cell genes.
- D. mtDNA can activate cytokine expression.
- E. Energy metabolism influences immune cells to be either pro-inflammatory or anti-inflammatory, depending on cell type.
- F. Release of amino acids from mitochondria fuels T-cell function.
- G. The mitochondrial antiviral signaling (MAVS) pathway in the mitochondrial membrane fosters its cell's inflammatory response to viral infections.

The term, "mitochondria" has already seeped out of the professional journals and into the mainstream media. Dr. Oz talks about mitochondria. Mitochondria have been discussed on Oprah. The Huffington Post as well as popular blogs – albeit for more of a sophisticated health crowd - MindBodyGreen.com, BeWell.com, DrMercola.com, MarksDailyApple.com and Bulletproof.com have all published featured articles on mitochondrial nutrition.

Popular home cooking guru, Leanne Ely, even has a Mitochondria Soup recipe listed on her Saving Dinner website.

And if you do a quick look on Amazon, you'll find nearly 450 supplements marketed specifically to help your mitochondria.

Astaxanthin – The Nutrient of Choice for Mitochondrial Health

Astaxanthin is perfectly designed to help mitochondria do their best in several ways.

A. It preferentially accumulates in the mitochondria.

In a study of the relative distribution and uptake percentages of natural astaxanthin in whole leukocytes and subcellular fractions of dogs, as much as 50% of the total membrane-bound astaxanthin was found in the mitochondria (Park et al. 2010b).

So, when we take natural astaxanthin, we know a significant amount goes right to the mitochondria.

B. It's perfectly designed to protect the mitochondria.

The mitochondrial membranes are where ATP production happens... and where most of the free radical damage occurs.

Astaxanthin is unique in its ability to safeguard mitochondrial membranes.

It has two hydrophilic ('water-loving') ends, meaning each molecule can anchor to both sides of the membrane's water-soluble exterior. Astaxanthin's lipophilic ('fat-loving') center can then span the membrane's lipid interior between its two hydrophilic sides.

Here's how Dr. Mark Miller, PhD, former AstaReal Global Ambassador and expert on astaxanthin explains what that means...

If Mother Nature were to design a new mitochondrial nutrient, she'd be hard put to surpass the properties of astaxanthin.

Imagine the membrane is like a river with two banks. The river is the inner part of the membrane made up of lipids, flowing through the center. And the banks are the outside of the membrane made up of hydrophilic protein-lipid molecules.

Like a net extending across a river, astaxanthin extends across each membrane and catches any of the destructive free radicals "swimming" up the lipid center of the membrane. Astaxanthin's two polar ends anchor it to each bank, the membrane's hydrophilic outside.

In contrast, other antioxidants like vitamin C, vitamin E and beta-carotene can't do the same job. They don't have the right shape, the right length or the right amphiphilic qualities that allow astaxanthin to both span the hydrophobic center of the membrane and anchor in the hydrophilic "banks."

In one experiment testing different carotenoids on a simulated membrane, all antioxidants except astaxanthin disrupted the phospholipid membrane structure and made its free radical damage worse.

Natural astaxanthin was the only antioxidant tested in the experiment that reduced the free radical damage (by 41%!) and helped maintain the integrity of the membrane (McNulty et al. 2007).

C. Natural astaxanthin turbocharges your mitochondrial engines by enhancing utilization of fat.

Fat is the most efficient fuel for your mitochondrial engine. One gram of fat can produce six times the amount of ATP as one gram of glucose. By shifting to fat for fuel, mitochondria increase their capacity for ATP production.

Research indicates astaxanthin increases fat burning while reducing carbohydrate use for fuel (Aoi et al. 2008). On the molecular level, astaxanthin significantly increases the coordination of the fat transfer molecules, carnitine palmitoyltransferase 1 (CPT 1) and fatty-acid translocase (FAT/CD36), which work together to carry out the rate-limiting step of fat oxidation in mitochondria. It also seems to protect CPT 1 from oxidation.

A recent study of recreationally trained cyclists confirmed its role in fat metabolism. Supplementation with 12 mg daily for 7 days enhanced whole-body fat oxidation rates as measured in the final stages of a 40-kilometer endurance event (Brown et al. 2021).

Savvy formulators have already put the two best mitochondrial biogenesis supplements together in an energy drink: astaxanthin and PQQ.

D. Natural astaxanthin promotes mitochondrial biogenesis.

Mitochondria have a limited lifespan. That means each cell must constantly replace old, worn-out mitochondria with new ones.

Two published studies on mice have shown astaxanthin consumption leads to higher levels of PGC-1 α in their skeletal muscles.

PGC-1 α triggers mitochondrial biogenesis (Kanazashi et al. 2014; Liu et al. 2014).

More recently, astaxanthin was found to stimulate mitochondrial biogenesis by activating the enzyme AMPK (adenosine 5' monophosphate-activated protein kinase) (Nishida et al. 2020). AMPK is known as the body's "master regulator of energy metabolism."

AMPK levels diminish as we age, leading to changes in appetite, body weight, and energy levels.

Building new mitochondria slows down all those changes.

The more healthy mitochondria you make, the more energy you can produce, regardless of your age.

The many positive influences of astaxanthin on mitochondria are more than a foundation for immune health. They're the basis for all health.

4. Direct Immunomodulatory Actions

In a nutshell, astaxanthin stimulates white blood cell proliferation, natural killer (NK) activity, and the total number of T- and B- immune cells (Park et al. 2010a).

It also stimulates the production of polyclonal antibodies (Okai and Higashi-Okai 1996), immunoglobulins (Jyonouchi et al. 1995), and a rapid increase in CD8+ T-cells (Diao et al., 2019).

Astaxanthin's role in boosting immunoglobulins is particularly astounding considering its effects on the most abundant immunoglobulin of all: immunoglobulin A (IgA).

IgA is produced by the mucosal immune system as part of the body's first line of defense against harmful microbes and food antigens. This system consists of mucous membranes secreting saliva in the mouth and mucous in the gut and lungs.

IgA accounts for most of the antibody production in the gut, where about 70% of our immune cells are produced. It's also the most abundant immunoglobulin in saliva.

Astaxanthin helps build immunity as soon as you open your mouth. It just gets better from there.

A person weighing 175 lbs. can produce a little over 5 grams of IgA every day, equivalent to roughly one teaspoon of sugar (Bakema and van Egmond 2011).

Immunoglobulin defense against invading pathogens begins with secretory IgA (sIgA) in saliva, where it binds directly to microbes to prevent them from passing through the epithelial cells lining the inside of your cheeks.

sIgA defense falters when its levels drop in response to stress and to aging.

Two studies show AstaReal® Astaxanthin's direct influence on sIgA levels in response to stress.

The first study revealed a significant increase in sIgA levels in exercise-stressed elite soccer players after 90 days of training and supplementation (Baralic et al. 2015).

Soccer players in general have been shown to benefit from astaxanthin in many ways. No matter the exercise-induced challenge, astaxanthin always reduces oxidative stress from exertion (Baralic et al. 2013; Djordjevic et al. 2012).

The second study reported results of astaxanthin's effects on older adults (avg. age, 48 years) after 8 weeks of regular stress induced by using a mental calculation task and by stationary bike exercise (Hongo et al. 2016). sIgA levels remained unchanged in the treatment group. In contrast, the equally stressed placebo group showed a significant decrease in sIgA levels.

These studies suggest that AstaReal® Astaxanthin may support mucosal immunity, which functions as a first line of defense against inhaled and ingested pathogens, under conditions of mental and physical stress.

5. Support for the Gut Mucosa and Microbiome

The amount of IgA produced in association with mucosal membranes is greater than all other types of antibodies combined (Fagarasan and Honjo 2003). However, boosting sIgA levels is just one aspect of how astaxanthin can aid mucosal immunity.

Astaxanthin also provides benefits to mucosal immunity by its influence on friendly gut bacteria protecting the mucosa.

Mucosal health is tied to a healthy microbiome. Gut bacteria are necessary for the complete development of mucosal innate and adaptive immunity (Neish 2014; Neish and Denning 2010).

A recent study in mice showed how astaxanthin supplementation led to beneficial changes in microbiome composition (Wu et al. 2020). These microbial changes directed a reduction in oxidative stress and gut inflammation.

This study confirms earlier work showing how astaxanthin benefits mucosal cells when they become inflamed by overgrowth of a common gut bacterium, *Helicobacter pylori*. A stomach bloom of this microbe can lead to chronic inflammation and stomach ulcers.

In this study astaxanthin reduced the harmful impact of *H. pylori*. It did so by dampening the rise in cytokines from Th1 cells associated with *H. pylori* overgrowth. In so doing, astaxanthin influenced a shift from pro-inflammatory Th1 cytokines to anti-inflammatory Th2 cytokines in the gut of a mouse model (Bennedsen et al. 1999; Talikdar et al. 2020).

This observation may in part explain why a clinical study of 132 individuals with functional dyspepsia resulted in significantly reduced reflux symptoms after 4 weeks of treatment with AstaReal® Astaxanthin (Kupcinskis et al. 2008).

Astaxanthin also helped promote friendly gut bacteria, as shown in pre-clinical studies described in US Patent #10894022. AstaReal® Astaxanthin increased *Akkermansia muciniphila* populations to a level 11.7 times greater than was found in the control group.

The AstaReal scientific team has garnered three patents germane to gut health centered around these studies.

They are:

Oral preparation for the prophylactic and therapeutic treatment of Helicobacter sp. infection.
US Patent #6,262,316.

Treatment of dyspepsia. US Patent #6,923,967.

A Method for Increasing Akkermansia in Intestinal Bacterial Flora by Ingesting Astaxanthin.
US Patent #10,894,022 B2.

The New Era of Immune Health: Science-Backed Opportunities for Astaxanthin

Formulations

According to PubMed, more than three dozen research articles on astaxanthin and immunity have been published just since 2020, equaling the number of studies released over the six years prior to that.

It's clearly a hot research topic, and it's getting hotter.

This research is timely for creating new products for immune health backed by science.

Market demand is certainly there.

The upward trend for immune health supplements continues to accelerate. According to a 2020 survey by the Council on Responsible Nutrition, more and more consumers report that immune health is a key consideration for using supplements

The COVID-19 crisis has made consumers around the world increasingly aware of the critical role a strong immune system can play in health maintenance and disease prevention - and they're taking action. Moreover, fears of possible additional outbreaks and new SARS-CoV-2 variants have created a new need for preparedness, which is likely to be the new normal - and a very big business opportunity going forward.

Dr. A. Elizabeth Sloan, President

*Dr. Catherine Adams Hutt, Chief Scientific and Regulatory Officer
Sloan Trends, Inc.*

Together, market demand and research combine to present business opportunities for creating immune health products with astaxanthin.

It's a bright future for a remarkable natural product.

AstaReal: The World's Leading Producer and Innovator of Natural Astaxanthin

What Makes AstaReal So Good?

Originality. AstaReal pioneered the development of natural astaxanthin as a nutritional ingredient.

High Potency. AstaReal® Astaxanthin has been shown to be the most potent product on the market

Safety. As other companies have more recently entered production, AstaReal has continued to lead the industry in research, safety, quality, technical innovation and reliability. AstaReal is backed by 40+ safety studies.

Research. AstaReal® Astaxanthin is the most studied form of the nutrient worldwide. Over 150 research studies (including 70+ clinical trials) have been completed on AstaReal® Astaxanthin.

Patents. With more than a dozen approved patents as of 2021, AstaReal is also the leading holder of patents related to the use of natural astaxanthin in humans.

Superior Production. AstaReal pioneered technology for cultivating of *H. pluvialis* using indoor photobioreactors. This is the only cultivation method for ensuring the highest quality and cleanest hygiene-controlled product, maximum astaxanthin stability, and consistently high yield in every batch. It's the only company to use indoor cultivation in the USA. And it's the only company to both cultivate and extract algae in the USA.

Chlorophyll Free. Cultivation control for growing *H. pluvialis* cells to full, chlorophyll-free maturity. Chlorophyll and chlorophyll breakdown products (pheophorbide) otherwise would detract from astaxanthin's stability.

Environmental Responsibility. Production at the facility in Moses Lake, Washington, relies on renewable hydroelectric energy from the Columbia River.

ASTAREAL LEADS THE ASTAXANTHIN INDUSTRY IN...

- Innovation
- Product quality, stability, and potency
- Safety
- Scientific research
- Patents
- Client support
- Production technology
- Environmental sustainability
- Significant certifications by federal agencies and third-party organizations

AstaReal generously provided a significant amount of high quality information and content to help support us in the building of an online platform and messaging for our 6 mg TrueAsta. We have great confidence in AstaReal's quality, science and people. Most important, many of our customers are happy with the benefits they experience and feel with AstaReal.

*- Carl Pradelli
CEO & President NatureCity*

Significant Certifications. AstaReal has obtained an impressive list of approvals from federal agencies and third-party organizations. They include:

1. USP (United States Pharmacopeia), Verified Dietary Ingredient, the gold standard for approving claims for identity, strength, purity, and quality of dietary ingredients
2. FDA Notified GRAS status
3. Health Canada, which recognized AstaReal as the only astaxanthin brand with a Natural Product Number (NPN)
4. The Paleo Foundation, the world leader in independent paleo certifications
5. National Animal Supplement Council, where AstaReal® Astaxanthin is the only preferred supplier of natural astaxanthin for pet supplements
6. Third-party tested as free of PAH carcinogens and skin irritants like pheophorbide (a chlorophyll breakdown product)
7. Kosher and Halal certifications

As the industry leaders in natural astaxanthin, we feel it is our responsibility to help educate everyone on the benefits of AstaReal® Astaxanthin through podcasts, webinars, social media, co-marketing campaigns, and our consumer education website. We work together with our B2B customers to help find the most impactful messaging tailored to your target consumer. So you can communicate the many reasons why AstaReal® Astaxanthin is a wellness powerhouse and get people excited about your product.

*- Arun Nair
President & CEO
AstaReal Inc*

The AstaReal team worked closely with us from concept through to product development and co-marketing post launch. They truly were key partners in the success of this innovative dog chew launch. Their expertise and level of service was exemplary, and we are excited about our future with AstaReal.

*- Kerri DaSilva
Director of Marketing
Ark Naturals Company*

Client Support

AstaReal provides valuable resources for helping clients with formulating, manufacturing, and marketing new products.

Formulating.

AstaReal offers broad experience for assisting in the design and implementation of new product formulations for piquing your customer's interest.

It includes access to on-call PhD-level technical support staff and a team with 30+ years of accumulated experience in natural astaxanthin product development.

No matter how imaginative your ideas might be.

Manufacturing.

The AstaReal team is a powerful resource for collaborative problem solving.

Production from indoor, climate-controlled bioreactors creates reliable throughput from a scalable supply chain.

AstaReal is the only astaxanthin producer whose entire manufacturing process, from algal cultivation to final product, occurs in the USA.

Streamlined manufacturing enables the shortest and most efficient path to new product creation.

Marketing.

Partnering with AstaReal will help you create a consistent and quality product that will promote compliance.

The company focuses on maintaining quality assurance and transparency for brand labels and keeping you informed on changing regulations.

You also benefit from impactful marketing support with messaging tailored to your target audience.

AstaReal recognizes that safety, efficacy and claim substantiation with quality human clinical studies are essential for building consumer trust and loyalty. This is why AstaReal has invested in a portfolio of 70+ human clinical studies, which our experts will help you navigate so you can find the best studies to support your desired claims with data and research.

Finding the big idea: Every great product starts with a big idea. AstaReal understands the power a big idea has for creating an effective marketing strategy that will result in a ton of repeat visitors and referral traffic over and over again.

The ease of working with AstaReal helps to reduce your workload and to avoid unnecessary risks when introducing a new immune health formulation.

It saves you time and money.

It also establishes trust and dependability you can count on.

The bonus is developing valuable personal relationships between AstaReal and your company.



"I have worked together with the AstaReal team to develop a delicious astaxanthin chocolate truffle. The team was clearly experienced in chocolate products and were able to advise on astaxanthin forms and formulations. I am very pleased with our work together and the final product. AstaReal material was of excellent quality and their expertise around the ingredient was a real value add and saved me time.

*- Bob Settineri
Biomedical Research Consultant
Sierra Productions*

Formulating with AstaReal® Astaxanthin

AstaReal® Astaxanthin is available in different forms for optimizing a wide range of formulations.

AstaReal® L10 is a high quality natural astaxanthin sCO₂ (solvent free) extract with excellent stability. L10 is suitable for use in food supplements, cosmetics and as a feed ingredient.

AstaReal® CWS25 is a spray dried, water dispersible powder containing 2.5% natural astaxanthin plant extract. This functional powder is specifically designed for use in powdered drinks and functional foods. Its excellent powder properties and extremely mild flavor and odor offer unsurpassed compatibility, and it fully dissolves in just 30 seconds!

AstaReal® P4AF is a high quality powdered natural astaxanthin extract exhibiting excellent potency. It is designed to fill multiple formulations. P2AF is directly compressible, cold water dispersible, very stable, flowable and free of the major allergens as identified by the FDA. This form is ideal for two-piece capsules, tablets, powdered drinks, nutritional bars and more.

AstaReal® EL25 is a high quality, water dispersible, astaxanthin extract beadlet, containing 2.5% natural astaxanthin. It's water dispersible, very stable, flowable and free of the major allergens as identified by the FDA. This form is ideal for two-piece capsules, powdered drinks, functional foods and more.

AstaReal® CLEAR100-C(S) is a high-quality water-dispersible natural astaxanthin with high heat stability, high clarity, a wide pH range and good taste compatibility. It's ideal for liquid supplements, ready to drink beverages, cosmetic and personal care formulations, gummy supplement formulations and many more product formats.

AstaReal® Softgels are a finished formulation containing high quality natural astaxanthin. It comes in 7.5 Oval capsules containing 2.0, 4.0, 6.0, or 12.0 mg natural astaxanthin per capsule.

AstaReal® Biomass is an astaxanthin-rich natural microalgal product consisting of crushed and dried whole algae with not less than 4.5% astaxanthin (determined as free form by HPLC). AstaReal® Biomass is suitable for use in pet and animal feed preparations as a customer-mix feed.

Working with AstaReal to develop a new dietary supplement gummy has been a fantastic experience. The technical expertise they demonstrate through their prototype development program made it easy to develop a great product. Their willingness to share research and development insight was immensely helpful to troubleshooting prototypes. Their team worked closely with me and gave me a deeper understanding of their product that was key to the success of my project. Both Astareal's products and service as a supplier are first class.

*- Tom Getz
Research and Development Scientist
Bettera Brands LLC*

Formulation Tips: Making AstaReal® Astaxanthin Work for You

Tip #1. Although close to 90% of current natural astaxanthin use is in supplements, adding astaxanthin to foods and beverages is also ideal. Astaxanthin's bioavailability is increased when taken right after a meal or as part of it. In Japan, astaxanthin has been used in everything from yogurt to coffee, energy drinks, and even alcoholic beverages. Other possibilities include baked goods, gummies, chocolate and other candies, sports nutrition beverages, trail-mix bars and powdered drink mixes.

Tip #2. Use the right form of astaxanthin. AstaReal® Astaxanthin is available in different concentrations as oil extracts, powder, cold water soluble powder, microencapsulated beadlets, and a water soluble emulsion.

Tip #3. Use the right dose. Low doses are effective without affecting quality or benefits. Clinical research indicates 6 mg per day. For additional benefits, a 12 mg dose has been used in several clinical trials.

Tip #4. Formulate with fats. Lipids help astaxanthin absorption. Astaxanthin can also help protect fats from rancidity. Mimicking its natural presence in krill oil, it makes a beautiful partnership with omega-3's.

Tip #5. Combine it with other key nutrients. Other antioxidants, like vitamins E and C as well as glutathione and ubiquinol (CoQ10), can help protect the antioxidant capacity and immune-boosting properties of astaxanthin. Pair it with zinc, elderberry, or other immune-enhancing ingredients for extra support.

Tip #6. Choose the right astaxanthin product, delivery system and packaging to protect against degradation from temperature and oxygen. Oil encapsulated forms and soft gel delivery systems offer the best bioavailability with protection for astaxanthin during manufacturing, transport and storage. In addition, some metals such as iron can also degrade astaxanthin. Beadlets can protect astaxanthin from contact with such other ingredients that might cause this issue. Packaging that protects against oxygen and light – like blister packs – also extends astaxanthin's shelf-life.

Tip #7. Natural Astaxanthin is easily recognizable thanks to its deep red color. You can tap into consumers' associations of vibrant color with antioxidants.

I love working with AstaReal because I know I will get the support I need to successfully develop astaxanthin products. They have invested in science and know it inside and out. AstaReal's cold water dispersible astaxanthin works like a charm and I have used it effectively in several formulations now on the market. I am an AstaReal fan!

*- Devin Kummer
Formulation Scientist
Prinova Group*

Putting AstaReal® Astaxanthin to Work for You

As the global demand for natural astaxanthin continues to grow, AstaReal will continue to be fully dedicated to ensuring the supply of premium, natural astaxanthin products.

The market is hot and getting hotter, so it's no time to dally.

Put our expertise to work for you in developing the best way to use natural astaxanthin in your product.

We're ready to help you.

Get started today.

Call us toll-free now at: 877-227-8287 (877-2-ASTA-USA)

Email us at contact@astarealusa.com

Visit us at astarealusa.com (corporate)

Or at astaxanthin.net (consumer education)

References

- Angajala A et al. 2018. Diverse roles of mitochondria in immune responses: Novel insights into immuno-metabolism. *Front Immunol.* 9: 1605. doi: 10.3389/fimmu.2018.01605
- Aoi W et al. 2008. Astaxanthin improves muscle lipid metabolism in exercise via inhibitory effect of oxidative CPT I modification. *Biochem Biophys Res Commun.* 366(4): 892-897. doi: 10.1016/j.bbrc.2007.12.019
- Bakema JE and van Egmond M. 2011. Immunoglobulin A: A next generation of therapeutic antibodies?. *MAbs.* 2011;3(4):352-361. doi: 10.4161/mabs.3.4.16092
- Baralic I et al. 2013. Effect of astaxanthin supplementation on paraoxonase 1 activities and oxidative stress status in young soccer players. *Phytother Res.* 10: 1536-1542. doi: 10.1002/ptr.4898
- Baralic I et al. 2015. Effect of astaxanthin supplementation on salivary IgA, oxidative stress, and inflammation in young soccer players. *Evid Based Complement Alternat Med.* 2015: 783761. doi: 10.1155/2015/783761
- Bennedsen M et al. 1999. Treatment of *H. pylori* infected mice with antioxidant astaxanthin reduces gastric inflammation, bacterial load and modulates cytokine release by splenocytes. *Immunol Lett.* 70(3): 185-189. doi: 10.1016/s0165-2478(99)00145-5
- Brown DR et al. 2021. The effect of astaxanthin supplementation on performance and fat oxidation during a 40 km cycling time trial. *J Sci Med Sport.* (1): 92-97. doi: 10.1016/j.jsams.2020.06.017
- Chang MX and Xiong F. 2020. Astaxanthin and its effects in inflammatory responses and inflammation-associated diseases: Recent Advances and Future Directions. *Molecules.* 25(22): 5342. doi: 10.3390/molecules25225342
- Choi HD et al. 2011. Effects of astaxanthin on oxidative stress in overweight and obese adults. *Phytother Res.* 25(12): 1813-1818. doi: 10.1002/ptr.3494
- Diao W et al. 2019. Astaxanthin protects against renal fibrosis through inhibiting myofibroblast activation and promoting CD8+ T cell recruitment. *Biochim Biophys Acta Gen Subj.* 1863(9): 1360-1370. doi: 10.1016/j.bbagen.2019.05.020
- Djordjevic B et al. 2012. Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players. *J Sports Med Phys Fitness.* 52(4): 382-92. <https://pubmed.ncbi.nlm.nih.gov/22828460/>
- Fagarasan S and Honjo T. 2003. Intestinal IgA synthesis: regulation of front-line body defences. *Nat Rev Immunol* 3: 63–72. doi: 10.1038/nri982 .1038/nri982

Hongo N et al. 2016. Randomized controlled trial of the anti-fatigue effects of astaxanthin on mental and physical loads simulating daily life. *Journal of Clinical Therapeutics & Medicines* 32(7): 277-291. [not available online]

Inoue M et al. 2012. Astaxanthin functions differently as a selective peroxisome proliferator-activated receptor γ modulator in adipocytes and macrophages. *Biochem Pharmacol.* 84(5): 692-700. doi: 10.1016/j.bcp.2012.05.021

Jyonouchi H et al. 1995. Astaxanthin, a carotenoid without vitamin A activity, augments antibody responses in cultures including T-helper cell clones and suboptimal doses of antigen. *J. Nutr.* 125(10): 2483-2492. doi: 10.1080/01635589509514373

Kanazashi M et al. 2014. Amelioration of capillary regression and atrophy of the soleus muscle in hindlimb-unloaded rats by astaxanthin supplementation and intermittent loading. *Exp Physiol.* 99(8): 1065-1077. doi: 10.1113/expphysiol.2014.079988

Kidd P. 2011. Astaxanthin, cell membrane nutrient with diverse clinical benefits and anti-aging potential. *Altern Med Rev.* 16(4): 355-364. <https://altmedrev.com/wp-content/uploads/2019/02/v16-4-355.pdf>

Kim SH et al. 2018. Astaxanthin inhibits mitochondrial dysfunction and interleukin-8 expression in *Helicobacter pylori*-infected gastric epithelial cells. *Nutrients.* 10(9): 1320. doi: 10.3390/nu10091320

Kowshik J et al. 2014. Astaxanthin inhibits JAK/STAT-3 signaling to abrogate cell proliferation, invasion and angiogenesis in a hamster model of oral cancer. *PLoS One.* 9(10): e109114. doi: 10.1371/journal.pone.0109114

Kupcinskas L et al. 2008. Efficacy of the natural antioxidant astaxanthin in the treatment of functional dyspepsia in patients with or without *Helicobacter pylori* infection: A prospective, randomized, double blind, and placebo-controlled study. *Phytomedicine.* 15(6-7): 391-399. doi: 10.1016/j.phymed.2008.04.004

Liu PH et al. 2014. The astaxanthin-induced improvement in lipid metabolism during exercise is mediated by a PGC-1 α increase in skeletal muscle. *J Clin Biochem Nutr.* 54(2): 86-89. doi: 10.3164/jcbtn.13-110

McNulty HP et al. 2007. Differential effects of carotenoids on lipid peroxidation due to membrane interactions: X-ray diffraction analysis. *Biochim Biophys Acta.* 1768(1): 167-174. doi: 10.1016/j.bbamem.2006.09.010

Mehta P et al. 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 395(10229): 1033-1034. doi: 10.1016/S0140-6736(20)30628-0

Neish AS. 2014. Mucosal immunity and the microbiome. *Ann Am Thorac Soc*. 11(Suppl 1): S28-32. doi: 10.1513/AnnalsATS.201306-161MG

Neish AS and Denning TL. 2010. Advances in understanding the interaction between the gut microbiota and adaptive mucosal immune responses. *F1000 Biol Rep*. 2: 27. DOI: 10.3410/B2-27

Nishida Y et al. 2020. Astaxanthin stimulates mitochondrial biogenesis in insulin resistant muscle via activation of AMPK pathway. *J Cachexia Sarcopenia Muscle*. 11(1): 241-258. doi: 10.1002/jcsm.12530

Park JS et al. 2010a. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. *Nutr Metab*. 7: 18. doi: 10.1186/1743-7075-7-18

Park JS et al. 2010b. Astaxanthin uptake in domestic dogs and cats. *Nutr Metab*. 7: 52. doi: 10.1186/1743-7075-7-52

Pizzorno J. 2014. Mitochondria-Fundamental to Life and Health. *Integr Med (Encinitas)*. 13(2): 8-15. PMID: PMC4684129

US Patent #6,262,316. Oral preparation for the prophylactic and therapeutic treatment of *Helicobacter* sp. infection. July 17, 2001. <https://patents.justia.com/patent/6262316>

US Patent #6,923,967. Treatment of dyspepsia. August 2, 2005. <https://patents.justia.com/patent/6923967>

US Patent #10,894,022 B2. A Method for Increasing Akkermansia in Intestinal Bacterial Flora by Ingesting Astaxanthin. January 19, 2021. <https://patents.google.com/patent/US10894022B2/en>

Vachharajani V and McCall CE. 2020. Sirtuins: potential therapeutic targets for regulating acute inflammatory response? *Expert Opin Ther Targets*. 24(5): 489-497. doi: 10.1080/14728222.2020.1743268

Wu et al. 2014. Astaxanthin activates nuclear factor erythroid-related factor 2 and the antioxidant responsive element (Nrf2-ARE) pathway in the brain after subarachnoid hemorrhage in rats and attenuates early brain injury. *Mar Drugs*. 12(12): 6125-6141. doi: 10.3390/md12126125

Wu L et al. 2020. Astaxanthin-Shifted Gut Microbiota Is Associated with Inflammation and Metabolic Homeostasis in Mice. *J. Nutr*. 150(10): 2687-2698. doi: 10.1093/jn/nxaa222