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KRILL OIL: THE MOST POWERFUL OMEGA 3 KNOWN ON EARTH

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ABSTRACT: A diet rich in marine fishes and general seafood has long been recommended by several medical authorities as a long-term nutritional intervention to preserve overall health and wellbeing. An association between consumption of fish and seafood and beneficial effects on a variety of health outcomes has been reported in epidemiologic studies and clinical trials. These effects are mainly attributed to the omega-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) abundant in fish and seafood, and in particular to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Reports on health benefits have led to increased demand for products containing marine n-3 PUFAs. Since fish is a restricted resource, there is growing interest in exploiting alternative sources of marine n-3 PUFAs. Antarctic krill (*Euphausia superba*) is a rich source of n-3 PUFAs. Most of the health benefits provided by frequent seafood consumption come from adequate uptake of omega-3 and omega-6 polyunsaturated fatty acids, n-3/n-6 PUFAs, and antioxidants. Optimal n-3/n-6 PUFAs ratios allow efficient inflammatory responses that prevent the initiation and progression of many inflammatory disorders. Moreover, interesting *in-vivo* and clinical studies with the marine antioxidant carotenoid astaxanthin (present in krill oil) have shown promising results against free radical activity in different diseases. This review presents the state-of-the-art applications of krill oil as a rich source of n-3/n-6 PUFAs and astaxanthin against diseases associated with exacerbated oxidative stress in human body.

INTRODUCTION: Krill are small crustaceans that can be found in all the world's oceans, but mostly in the Northern (Arctic) and Southern (Antarctic) polar seas. They belong to the same animal family as shrimp, lobsters and crabs. There are more than 80 different known krill species. Among these, the Antarctic krill, called *Euphausia superba*, is the kind of krill that can be fished, because it lives in large swarms and swims in open water.

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Krill swim in huge swarms that can be as long as six kilometers in length and have a density of up to one million individuals per cubic meter [1].

Krill oil is made from a species of krill [*Euphausia superba*]. It is composed of 40% PLs (phosphate-dylcholine), 30% EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid), astaxanthin, Vitamin A, Vitamin E and various other fatty acids and a novel flavanoid similar to 6, 8-di-C-glucosyl luteolin. The structure of the primary constituent in krill oil appears to contain choline, glycerophosphate and the fatty acids, EPA and DHA, eaterified to astaxanthin and the 6, 8-di-C-glucosyl luteolin like flavonoid respectively [2].

In common to fish oils, krill oil contains a high proportion of (n-3) fatty acids. However, krill oil

contains a major part of the (n-3) fatty acids in the form of phospholipids, which makes this oil different from fish oils which contain (n-3) fatty acids in the form of either triacylglycerol or fatty acid ethyl esters (such as Omacor / Lovaza) [2]. Phospholipids are the primary structures of human cell membranes and the "gatekeepers" of cells through the regulation of healthy cell membranes. The association between phospholipids and long-chain (n-3) fatty acids might facilitate the passage of fatty acid molecules through the intestinal wall, increasing their bioavailability and ultimately improving the (n-3):(n-6) ratio [3].

Reports of numerous health benefits have contributed to the popularity of n-3 PUFA enriched foods and/or supplements [4]. However, different sources of oils provide different types of n-3 PUFAs. Fish oils are rich in the n-3 LC-PUFAs (Long Chain Poly-Unsaturated Fatty Acids), EPA and DHA. Additionally, various fish oils have different EPA: DHA ratios [5]. Similar to fish oil, krill oil is rich in EPA and DHA. However, fatty acids from fish oils are mainly associated with triglycerides (TGs), whereas the n-3 PUFAs in krill oil are associated with phospholipids (PLs) and TGs [6]. PLs (phospholipids) and TGs are digested differently and in turn, this may affect n-3 PUFA bioavailability. In human studies, feeding infants DHA in PL form resulted in better absorption than feeding DHA in TG form [7]. Determining the digestibility of n-3 PUFAs provided as PL compared to TG is important because this influences n-3 PUFA incorporation into tissues. Increasing tissue n-3 PUFA exerts beneficial physiological effects by influencing cell membrane fluidity, membrane-bound receptors, signaling molecules, and gene expression [8].

Krill oil and Fish oil: Many people wonder why Krill oil is so much more powerful than fish oil. The answer lies in a little-known antioxidant powerhouse called “Astaxanthin”. Astaxanthin is the strongest antioxidant in the carotenoid family, creating the beautiful shades of pink found within shrimp, salmon and krill. Astaxanthin has been found to be up to 500x more effective than Vitamin E, 1x more effective than beta-carotene and 4x more effective than lutein in various measures of antioxidant effectiveness. It is one of the most astounding antioxidants known to scientists, yet rarely talked about in the mainstream media [9]. This antioxidant has a remarkable way of neutralizing free radicals trying to attack your cells. It’s one of the few antioxidants capable of crossing the blood-brain barrier and shuttle essential nutrients throughout your body [10].

There is no need to go through the hassle of seeking to add astaxanthin to your fish oil, as even though it will protect against further oxidation it does absolutely nothing to reverse oxidation in damaged fish oil fats. Once the fat is oxidized it is permanently ruined [11]. The beauty of astaxanthin in krill is that it is there in the krill right from the start, which protects the omega-3 fats along every stage of harvesting and processing. According to an article in Functional Nutrition, krill oil typically provides 14 percent EPA and DHA, along with 0.2 percent naturally occurring astaxanthin [12]. Fish oil typically provides 30 percent EPA and DHA. At first glance, it may appear as though fish oil is better simply because it contains a higher ratio of omega - 3 fats. However, krill oil is far more efficient, so you actually need far less.

What exactly is Astaxanthin? Astaxanthin is a carotenoid antioxidant produced only by the microalgae *Haematococcus pluvialis* when its water supply dries up, forcing it to protect itself from ultraviolet radiation. It's the algae's survival mechanism - astaxanthin serves as a "force field" to protect the algae from lack of nutrition and/or intense sunlight [13].

This pigment is the most commonly occurring red carotenoid in marine and aquatic animals and is what gives salmon their characteristic pink color. Astaxanthin is leaps and bounds more powerful than beta-carotene, alpha-tocopherol, lycopene and lutein, other members of its chemical family. It exhibits very strong free radical scavenging activity and helps protect your cells, organs and body tissues from oxidative damage and inflammation. This antioxidant has been found to impact your health in a number of beneficial ways, including:

Astaxanthin's unique "antioxidative artillery" provides for an impressive array of health benefits [14, 19].

The omega-3 fats found in fatty fish have been increasingly shown to have beneficial effects on

cardiovascular health, inflammation, mental health, and neurodegenerative diseases. But because fish are such a heavily polluted food source, this is one instance where you're typically better off getting the omega-3 fats from a purified, high quality, animal-based supplement. The most common of these is fish oil. Fish oil really started the omega-3 market and most of the research on the benefits of animal-based omega-3 fats (DHA and EPA), even to this day, is based on studies using fish oil [15].

TABLE 1: ANTIOXIDATIVE ARTILLERY

Acting as a natural sunscreen	Wrinkle prevention	Powerful anti-inflammatory
Improvements in vision, specifically depth perception	Reduction of lactic acid in muscle tissue	Boost endurance
Reduces your risk of cataracts, macular degeneration, blindness, dementia and Alzheimer's disease	Prevent free radical damage	Boost your Immune system

However, this, too, has a major downfall - oxidation. Omega-3 fats are extremely fragile and are highly susceptible to damage by oxygen, which can radially reduce their health benefits and even make them damaging to your body [16].

Fish oil is notorious for high mercury and PCB levels. Krill is not exposed to these toxins due to being harvested from the Antarctic Ocean, making these dangerous chemicals virtually non-existent. The Omega-3 fatty acids in Krill oil are structured in phospholipid form so they're more easily absorbed and broken down by your body. Most fish oils are structured in Triglyceride form, making them difficult for our bodies to break down and convert making them virtually useless [12].

The problem with most fish oils is that they are harvested from large, massive fish which contain as much as 5-10x as much mercury as Krill. They are also harvested in toxic waters. Krill oil is loved for its ability to give you much better results than fish oil, without any of the annoying "fish burps" you're probably used to. The health benefits of krill oil being clear, some have expressed concern that it is not a sustainable resource, but this could not be further from the truth. In fact, there are legitimate environmental concerns with harvesting fish, as 90 percent of the fish that swam in the oceans 60 years ago are now gone due to overfishing [17].

Krill, on the other hand, is the most abundant biomass on Earth, amounting to about 500 million tons. Despite its growing popularity as a food source, less than 2 percent is harvested. Krill harvesting is also one of the best regulated on the planet, using strict international precautionary catch limit regulations that are reviewed regularly to assure sustainability. For more on this, please read my article about this issue. Fortunately, you can enjoy the health benefits of krill oil (and its naturally occurring astaxanthin) with peace of mind, as it is the most eco-friendly source of animal-based omega-3 on the planet [18].

Biological activities of Krill oil:

Krill oil as cardioprotective: Consumption of long-chain omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been associated with reduced cardiovascular disease risk in both cohort studies and randomized clinical trials [20 - 23]. DHA and EPA are major constituents of krill oil. The metabolic and cardiovascular effects of EPA and DHA are well known and include lowering of triglyceride and very low-density lipoprotein cholesterol levels when provided in sufficient dosages [24, 25] and reduction of blood pressure [26, 27]. Additional effects that have been reported include improvement of vascular reactivity and anti-inflammatory, antithrombotic and antiarrythmic properties [28].

Krill oil attenuates left ventricular dilatation after myocardial infarction in rats [41]. This was the finding of Linn E Fosshaug *et al.,* [29]. In the western world, heart failure (HF) is one of the most important causes of cardiovascular mortality. Supplement with n-3 polyunsaturated fatty acids (PUFA) has been shown to improve cardiac function in HF and to decrease mortality after myocardial infarction (MI).This study investigated effects of krill oil on cardiac remodeling after experimental MI. Rats were randomized to pre-treatment with krill oil or control feed 14 days before induction of MI. It was shown that treatment with krill oil prior to induction of MI attenuates ventricular dilatation and hypertrophy.

These findings were further reflected by attenuated increase in lung weight, heart weight, and altered expression of various genes encoding peptides known as markers and mediators of myocardial remodeling.

Neuroprotective Properties of Krill Oil: The consumption of marine fishes and general seafood has long been recommended by several medical authorities as a long-term nutritional intervention to preserve mental health, hinder neurodegenerative processes, and sustain cognitive capacities in humans. Most of the neurological benefits provided by frequent seafood consumption come from adequate uptake of omega-3 and omega-6 polyunsaturated fatty acids, *n*-3/*n*-6 PUFAs, and antioxidants. Optimal *n*-3/*n*-6 PUFAs ratios allow efficient inflammatory responses that prevent the initiation and progression of many neurological disorders. Moreover, interesting *in vivo* and clinical studies with the marine antioxidant carotenoid astaxanthin (present in salmon, shrimp, and lobster) have shown promising results against free radical-promoted neurodegenerative processes and cognition loss. This review presents the state-of-the-art applications of *n*-3/*n*-6 PUFAs and astaxanthin as nutraceuticals against neuro-degenerative diseases associated with exacerbated oxidative stress in CNS [30].

Lena Burri *et al.,* [31] evaluated the effects of krill oil on cognition and depression-like behaviour in rats. Cognition was assessed using the Aversive Light Stimulus Avoidance Test (ALSAT). The Unavoidable Aversive Light Stimulus (UALST) and the Forced Swimming Test (FST) were used to evaluate the antidepressant-like effects of krill oil. Imipramine (IMIP) was used as the antidepressant reference substance. The data supported a robust antidepressant-like potential and beneficial cognitive effect of krill oil. Changes in expression of synaptic plasticity-related genes in the prefrontal cortex and hippocampus were also investigated. mRNA for brain-derived neurotrophic factor (Bdnf) was specifically upregulated in the hippocampus of female rats receiving 7 weeks of krill oil supplementation (p=0.04) and a similar trend was observed in males (p=0.08). Males also exhibited an increase in prefrontal cortex expression of Arc mRNA, a key protein in long-term synaptic plasticity (p=0.05). IMIP induced clear effects on several plasticity related genes including Bdnf and Arc. These results indicate that active components (eicosapentaenoic acid, docosahexaenoic acid and astaxanthin) in krill oil facilitate learning processes and provide anti-depressant-like effects. The findings also suggest that krill oil might work through different physiological mechanisms than IMIP.

Parris M. Kidd [32] stated that the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapen-taenoic acid (EPA) function exclusively via cell membranes, in which they are anchored by phospholipid molecules. DHA is proven essential to pre and postnatal brain development, whereas EPA seems more influential on behavior and mood. Both DHA and EPA generate neuroprotective metabolites. In double - blind, randomized, controlled trials, DHA and EPA combinations have been shown to benefit attention deficit/ hyperactivity disorder (AD/HD), autism, dyspraxia, dyslexia, and aggression. For the affective disorders, meta-analyses confirm benefits in major depressive disorder (MDD) and bipolar disorder, with promising results in schizophrenia and initial benefit for borderline personality disorder. Accelerated cognitive decline and mild cognitive impairment (MCI) correlate with lowered tissue levels of DHA/EPA, and supplementation has improved cognitive function.

Huntington disease has responded to EPA. Omega-3 phospholipid supplements that combine DHA/ EPA and phospholipids into the same molecule have shown marked promise in early clinical trials. Phosphatidylserine with DHA/EPA attached (Omega-3 PS) has been shown to alleviate AD/ HD symptoms. Krill omega-3 phospholipids, containing mostly phosphatidylcholine (PC) with DHA/EPA attached, markedly outperformed conventional fish oil DHA/EPA triglycerides in double-blind trials for premenstrual syndrome/ dysmenorrheal and for normalizing blood lipid profiles. Krill omega-3 phospholipids demonstrated anti-inflammatory activity, lowering C-reactive protein (CRP) levels in a double-blind trial. Utilizing DHA and EPA together with phospholipids and membrane antioxidants to achieve a “triple cell membrane synergy” may further diversify their currently wide range of clinical applications.

Krill oil Protects Against Rheumatoid Arthritis: K. Berge *et al.,* [33] stated that supplementation of diet with krill oil protects against experimental rheumatoid arthritis. Although the efficacy of standard fish oil has been the subject of research in arthritis, the effect of krill oil in this disease has yet to be investigated. The objective of the present study was to evaluate a standardized preparation of krill oil and fish oil in an animal model for arthritis. Consumption of krill oil and supplemented diet significantly reduced the arthritis scores and hind paw swelling when compared to a control diet not supplemented with EPA and DHA. However, the arthritis score during the late phase of the study was only significantly reduced after krill oil administration.

Furthermore, mice fed the krill oil diet demonstrated lower infiltration of inflammatory cells into the joint and synovial layer hyperplasia, when compared to control. Inclusion of fish oil and krill oil in the diets led to a significant reduction in hyperplasia and total histology score. Some other studies also suggested that that krill oil may be a useful intervention strategy against the clinical and histopathological signs of inflammatory arthritis [40].

Fat Lowering and Hypocholesteremic Activity of Krill Oil: Duo Li *et al.,* studied the effects of Krill oil on serum lipids of hyperlipidemic rats and human colon cancer cells (SW480 cells). Cardiovascular disease (CVD) and colon cancer incidence are known to be closely related to dietary Total cholesterol (TC), LDL-cholesterol (LDL-C) of all dose groups, Triglycerides (TG) of low and mid dose groups descended significantly, while there were no significant differences of HDL-cholesterol (HDL-C), compared with control group. Treatment of colon cancer cells with KO also resulted in time dependent inhibition of cell growth. Their findings indicated that the consumption of KO may provide benefits to control serum lipid levels in certain diseases and inhibit growth of colon cancer cells. Therefore, krill oil may be a good candidate for development as a functional food and nutraceutical [34, 39].

A Vincenzo Zara *et al.,* [35] found that Krill oil Supplemented Diet Suppresses Hepatic Steatosis in High Fat Fed Rats. Krill oil is a dietary source of n-3 polyunsaturated fatty acids, mainly represented by eicosapentaenoic acid and docosahexaenoic acid bound to phospholipids. The supplementation of a high fat diet with 2.5% Krill oil efficiently prevented triglyceride and cholesterol accumulation in liver of treated rats. This effect was accompanied by a parallel reduction of the plasma levels of triglycerides and glucose and by the prevention of a plasma insulin increase. The investigation of the molecular mechanisms of Krill oil action in high-fat fed animals revealed a strong decrease in the activities of the mitochondrial citrate carrier and of the cytosolic acetyl-CoA carboxylase and fatty acid synthetase, which are both involved in hepatic de novo lipogenesis.

In these animals a significant increase in the activity of carnitine palmitoyl-transferase I and in the levels of carnitine was also observed, suggesting a concomitant stimulation of hepatic fatty acid oxidation. The Krill oil supplemented animals also retained an efficient mitochondrial oxidative phosphorylation, most probably as a consequence of a Krill oil induced arrest of the uncoupling effects of a high-fat diet. Lastly, the Krill oil supplementation prevented an increase in body weight, as well as oxidative damage of lipids and proteins, which is often found in high fat fed animals.

Krill Oil in the Management of Premenstrual Syndrome and Dysmenorrhea: Fotini Sampalis *et al.,* Evaluated the Effects of Neptune Krill oil in the Management of Premenstrual Syndrome and Dysmenorrhea. The final results of the study suggested within a high level of confidence that Neptune Krill oil can significantly reduce the physical and emotional symptoms related to premenstrual syndrome, and is significantly more effective for the management of dysmenorrhea and emotional premenstrual symptoms than fish oil. Neptune Krill oil has a unique biomolecular profile of phospholipids, omega-3 fatty acids, and diverse antioxidants that surpasses the usual fish oil profile.

The association between phospholipids and long chain omega-3 fatty acids highly facilitates the passage of fatty acid molecules through the intestinal wall, increasing their bioavailability, and ultimately improving the omega-3:omega-6 ratio [36]. Furthermore, phospholipid molecules play a major role in membrane fluidity, which may in turn play

an active role in the management of emotional symptoms. Findings from this trial raise the possibility that Neptune Krill oil has a positive benefit to risk profile for PMS [37].

Krill Oil Regulates Blood Sugar and Boosts the Liver Function: Jeffery S Cohn *et al.*, investigated the effects of dietary Krill oil on cardio metabolic risk factors in male mice fed a high-fat diet. Dietary Krill oil supplementation caused a significant reduction in liver wt (*i.e*., hepatomegaly) and total liver fat (*i.e.*, hepatic steatosis), due to a dose-dependent reduction in hepatic triglyceride and cholesterol. Serum cholesterol levels were reduced by 20 ± 3, 29 ± 4, and 29 ± 5%, and blood glucose was reduced by 36 ± 5, 34 ± 6 and 42 ± 6% respectively. These results demonstrated that dietary krill oil is effective in improving metabolic parameters in mice fed a high-fat diet, suggesting that krill oil may be of therapeutic value in patients with the metabolic syndrome and/or nonalcoholic fatty liver disease [38].

CONCLUSION: Krill oil possesses various biological activities and has a considerable potential to be utilized in number of useful applications. However, many of the studies carried out to search bioactivities of krill oil do not provide detailed molecular mechanisms. In fact, it is hard to explain how exactly it exerts different activities. Therefore, future research should be directed towards understanding the molecular level details which may provide an insight into the unrevealed molecular level functions of the constituents of krill oil and help to accelerate the future applications of krill oil.

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