Abstract

Krill oil derived from miniature marine crustaceans has been discovered to be opulent with health promoting components. The oil is rich source of phospholipids, \( \omega-3 \) -fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DPA), also the antioxidant astaxanthin. Krill oil is now considered to be superior to the customary fish oil owing to its stability, less mercury and better bioavailability of the fatty acids. It is known to confer numerous health benefits such as cholesterol lowering, cardio protection, antiarthritic effect, suppression of hepatic steatosis, cancer remediation, menstrual disorder alleviation and cognitive enrichment. This review explores the validated and claimed health benefits of krill oil. Scouring the literature database revealed various stages of krill oil research providing fertile ground to further explore.

Key words: Krill oil, dietary supplement, omega-3 fatty acids, astaxanthin, cardioprotective.

Nutritional profile

A high performance liquid chromatography-electrospray tandem mass spectrometry was employed to elucidate the phospholipids in krill oil (9).
phosphatidylcholine concentration was estimated to be 34 g/100 g oil. These results confirm the complexity of the phospholipid composition of krill oil and the presence of long chained, heavily unsaturated fatty acids. Astaxanthins are marine carotenoid pigments with strong antioxidant, anti-inflammatory, anti-cancer, anti-obesity and insulin-sensitivity potential. The mechanisms underlying the insulin sensitizing effects of astaxanthin, derived from marine algae was investigated in high fat-high fructose diet fed insulin-resistant mice (10). Astaxanthin supplementation led to normalization of increased body weight, hyperglycemia, hyperinsulinemia, hyperlipidemia and increased plasma levels of tumor necrosis factor-α (TNF-α) and interleukin-6. It was demonstrated that long-term astaxanthin administration improves insulin sensitivity by activating the post-receptor insulin signaling and by reducing oxidative stress, lipid accumulation and proinflammatory cytokines in obese mice. Unlike algal astaxanthins, krill oil-derived astaxanthin has not been explored much. However, the above findings build prospect for similar outcome.

Health benefits of krill oil: Many health promoting aspects of krill has been validated so far. Fig 2 depicts the applications.

Anti-inflammation: The effect of Neptune krill oil on C-reactive protein (CRP) was evaluated in patients with chronic inflammation, especially on arthritic symptoms through a randomized, double blind, placebo controlled the study involving 90 patients (6). After 7 days of treatment, the oil reduced CRP by 19.3% as compared to an
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Increase by 15.7% with placebo. After 14 and 30 days of treatment, the oil further decreased CRP by 29.7% and 30.9% respectively. After 7 days of treatment, the krill oil reduced pain scores by 28.9%, reduced stiffness by 20.3% and reduced functional impairment by 22.8%. The results of study indicated that the krill oil at a daily dose of 300 mg significantly inhibits inflammation and reduces the arthritic symptoms within a short treatment period of 7 and 14 days (6). The effects of dietary ω-3 long chain polyunsaturated fatty acids (ω-3 LCPUFA) in the form of fish oil and krill oil were compared. In rats fed with the PUFA diet for 4 week, liver triglycerides and the peritoneal macrophage response to an inflammatory stimulus were significantly lower than those fed the control diet. Heart triglycerides were lower only in krill oil-fed rats. These effects were associated with a lower concentration of the endocannabinoids, anandamide and 2-arachidonoylglycerol, in the visceral adipose tissue and of anandamide in the liver and heart, which, in turn, was associated with lower levels of arachidonic acid in membrane phospholipids, but not with higher activity of endocannabinoid-degrading enzymes. The reduction of substrates for inflammatory molecules and endocannabinoids may account for the dampened inflammatory response and the physiological re-equilibration of body fat deposition in obese rats (11). A standardised preparation of krill oil and fish oil was evaluated in mice model for arthritis. The level of EPA + DHA was 0.44 g/100 g in the krill oil diet and 0.47 g/100 g in the fish oil diet. The consumption of krill oil and fish oil-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 as compared to the control (12). The effects of krill oil on inflammation and redox status were evaluated in dextran sulfate sodium (DSS)-induced colitis in rats (13). The colon length was significantly preserved after krill oil diet. Prostaglandin (PGE3) increased significantly in the krill oil group. Peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1α (Pparg1α) expression increased and the levels of protein oxidation markers decreased significantly in this group. Based on the elicited effects, it was inferred that krill oil exerts protection against DSS induced-colitis (13).

Cholesterol lowering and anti-obesity effect: Krill oil has shown efficacy for the management of hyperlipidemia. A 3-month randomized study was conducted to assess the effects of this oil on blood lipids, specifically total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) of 120 patients with hyperlipidemia (14). Krill oil taken at a dose of 1-3 g per day body mass index (BMI) was found to be effective for the reduction of glucose, total cholesterol, triglycerides, LDL and HDL, as compared to both fish oil and placebo (14). A randomized, double-blind study was conducted on 76 volunteers to determine the role of krill oil. When capsules containing 2 g/d of krill oil was administered for 4 weeks, plasma EPA and DHA concentrations increased significantly while blood urea nitrogen declined (15). The digestibility, tissue deposition, metabolism and tissue oxidative stability of the ω-3 PUFA were determined (8). Rats were fed ad libitum (as much as desired) isocaloric diets for 4 weeks with either 10% freeze-dried krill protein isolate or 10% casein, both added in corn oil. Fatty acid compositions of various tissues were analyzed by gas chromatography. Lipid peroxidation was determined by thiobarbituric acid reactive substances (TBARS). Total antioxidant capacity and urinary eicosanoid metabolites were determined by enzyme immunoassay. DHA concentration in the brain increased, while both DHA and EPA content in fat pads and liver increased. The ω-6 fatty acid, arachidonic acid decreased. Feeding the krill protein concentrate diet decreased pro-inflammatory 2-series prostaglandin and thromboxane metabolites (8). It was investigated whether an intake of 2 g/d of

Nutraceuticals from Marine Derived Krill Oil with Immense Heath Potential
Krill oil is able to modulate the level of plasma endocannabinoids in overweight and obese subjects. Increased levels of endocannabinoids were reported in overweight and obese subject with respect to normo-weight subjects. Krill oil was able to significantly decrease the endocannabinoid 2-arachidonoylglycerol (2-AG) selectively in obese subjects (16). The efficacy of two different sources of ω-3 PUFAs were evaluated on the liver of mice fed diets (17). The supplement derived from a phospholipid krill fraction downregulated the activity of pathways involved in hepatic glucose production as well as lipid and cholesterol synthesis. The data also suggested that the krill oil-supplementation increases the activity of the mitochondrial respiratory chain. Same dose of EPA and DHA derived from fish oil modulated fewer pathways than that of krill oil. Also, it did not modulate key metabolic pathways influenced by krill oil viz. glucose metabolism, lipid metabolism and the mitochondrial respiratory chain. Moreover, fish oil upregulated the cholesterol synthesis pathway, whereas krill oil showed the reverse effect (17). The influence of both oils on lipid homeostasis and inflammation was investigated in mice with persistent low-grade exposure to human TNF-α. Further, the roles of the structural forms of EPA and DHA were explored. A 6 week feeding with krill oil could modulate lipid metabolism by lowering plasma levels of triglycerides and cholesterol, and stimulating the mitochondrial and peroxisomal fatty acid β-oxidation, as well as improving the overall carnitine turnover. When quantitatively similar doses of ω-3 PUFAs are administered, krill oil seems to have a greater potential to promote lipid catabolism (18). A double-blind, crossover trial was performed on 12 persons to compare the uptake of EPA+DHA formulations derived from fish oil and krill oil (19). When capsules containing 1680 mg EPA+DHA were given, the highest incorporation into plasma phospholipid was by krill oil. Fatty acid analysis of the supplements showed that the krill oil contained 22% of the total EPA amount in free form, and 21% of the total DHA as free DHA, while the fish oil did not contain any free fatty acid (19). The effects of krill oil (whole as well as phospholipid-type krill oil) on plasma cholesterol and glucose levels were investigated in high-cholesterol diet-fed rats (20). The whole krill oil contained 37.63% triglycerides, 48.37% phospholipids, 13.54% free fatty acids and 0.66% cholesterol; whereas, for the phospholipid type, these parameters measured 0.59, 69.80, 28.53 and 1.09%, respectively. The phospholipid-type krill oil contained more PUFA (37.76%) than whole krill oil (28.36%). The intake of both forms of krill oil for 4 weeks caused a significant reduction in body weight gain, plasma levels of total cholesterol and LDL cholesterol in high carbohydrate diet-fed rats. Phospholipid-type krill oil was more effective in decreasing the above two parameters in plasma, which was credited to the higher ω-3 PUFA levels (20).

**Cardioprotection**: The effects of krill oil on serum lipids of hyperlipidemic rats were evaluated. Total cholesterol and LDL showed significant decrease, building promise that its consumption may be healthful (21). The dose-dependent effects of dietary ω-3 PUFA supplementation given as krill oil, was investigated on metabolic parameters in high fat diet-fed mice (22). Eight-week high fat diet increased endocannabinoid levels in most of the body tissues. Krill oil reduced anandamide and/or 2-arachidonoylglycerol levels in all tissues except the liver, in a dose-dependent manner. The levels of endocannabinoid precursors were down-regulated, indicating that krill oil affects levels of endocannabinoids in part by reducing the availability of their biosynthetic precursors (22). The effects of krill oil on cardiac remodeling after experimental myocardial infarction was investigated in rat models. The animals were pretreated with krill oil, 2 weeks prior to induction of the infarction. After 7 days of infarction, the rats were examined with echocardiography. The evaluation showed significant attenuation of left ventricular dilatation in the group pretreated with krill oil as compared to the control. Lowered heart weight, lung weight, and levels of mRNA encoding classical markers of left ventricular stress, matrix
remodeling and inflammation was observed. It became clear that supplementation with krill oil leads to a proportional increase of n-3 PUFA in myocardial tissue and its administration before infarction induction, attenuates left ventricular remodelling (23).

**Alleviation of hepatic steatosis**: The effects of dietary krill oil on cardiometabolic risk factors were investigated in mice fed with a high-fat diet for 8 weeks (24). The krill oil supplementation (1.25, 2.5 and 5 wt%) caused a significant reduction in liver weight (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 and blood glucose was reduced. Serum adiponectin was increased in krill oil-fed animals. It was confirmed that dietary krill oil is effective in improving metabolic parameters in mice fed a high-fat diet and beneficial for patients with the metabolic syndrome and/or nonalcoholic fatty liver disease (24). A time-dependent decrease in the activities of the mitochondrial tricarboxylate carrier and lipogenic enzymes was reported in rats fed with a diet enriched with 2.5% krill oil. It induced inhibition of hepatic lipogenesis. The decrease in the activity of the mitochondrial tricarboxylate carrier was traced to the reduced expression of the protein. Greater reduction in the levels of hepatic triglycerides and cholesterol was found in comparison to fish oil-fed rats (25). Also, it was reported that hepatic triglyceride and cholesterol accumulation is accompanied by the reduction in plasma levels of triglycerides and glucose; also by the prevention of a plasma insulin increase. A significant increase in the activity of carnitine palmitoyl-transferase I and the levels of carnitine was also observed, suggesting a concomitant stimulation of hepatic fatty acid oxidation (26).

**Antiglycemic effect**: The effect of krill oil on glucose tolerance in obese rabbits was studied (27). Results showed that the supplementation decreases fasting blood glucose and improves glucose tolerance in the test animals. Induction of insulin sensitivity and insulin secretion and modified gene expressions of some key enzymes involved in β-oxidation and lipogenesis in liver and skeletal muscle was assumed to the mechanism.

**Cancer management**: Krill oil is claimed to be efficient in inhibiting many types of cancer viz. colon, breast and skin. The effects of krill oil on human colon cancer cells SW480 was evaluated by (3-(4, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) MTT method (21). A time-dependent inhibition of cell growth was observed that suggested cancer prophylaxis potential of krill oil. The possible inhibitory effect of astaxanthin against inflammation-related mouse colon carcinogenesis and dextran sulfate sodium (DSS)-induced colitis was investigated in mice. Its intake led to significant inhibition in the occurrence of colonic mucosal ulcers, dysplastic crypts and colonic adenocarcinoma at week 20. Astaxanthin-feeding suppressed the expression of inflammatory cytokines, including nuclear factor (NF)-κB, (TNF-)α and interleukin (IL)-1β; also inhibited proliferation, and induced apoptosis in the colonic adenocarcinomas. When fed at 200 ppm dose, it significantly inhibited the development of induced colitis. It also lowered the protein expression of NF-κB, and the mRNA expression of inflammatory cytokines, including IL-1β, IL-6, and cyclooxygenase (COX)-2 (28). The results suggested that the dietary astaxanthin suppresses colitis and its-related colon carcinogenesis, partly through inhibition of the expression of inflammatory cytokine and proliferation. However, further research inputs are warranted for more concrete findings (28).

**Suppression of PMS symptoms**

The symptoms premenstrual syndrome (PMS) are cranky feeling, bloating and mood swings, which sometimes assume severe form. The effectiveness of Neptune krill oil (NKO) in the management of PMS and dysmenorrhea was evaluated and compared with that of fish oil (7). A double-blind, randomized clinical trial involving 70 PMS patients was conducted. After a treatment period of three months with both the oils, self-
Current Trends in Biotechnology and Pharmacy
Vol. 8 (4) 439-448 October 2014, ISSN 0973-8916 (Print), 2230-7303 (Online)

The assessment questionnaire was administered. The data analysis clearly indicated reduction in the number of analgesics used for dysmenorrhea in the krill oil group. It was inferred that NKO can significantly assuage dysmenorrhea and the emotional symptoms of PMS. Richness of krill oil in ω−3 fatty acid is regarded responsible for the beneficial effect. Better balance of hormonal and chemical changes is believed to suppress the unpleasant symptoms and provide relief (7).

Cognitive and antidepressant effect: Both DHA and EPA generate neuroprotective metabolites that benefit attention deficit/hyperactivity disorder, autism, dyspraxia, dyslexia and aggression (29). Promising results in schizophrenia and borderline personality disorder have been observed. The cognitive decline and mild cognitive impairment correlate with lowered tissue levels of DHA/EPA, which showed improvement on their supplementation. Huntington disease (muscle coordination and leads to cognitive deterioration and psychiatric problems) has responded to EPA. The effects of krill oil on cognition and depression-like behaviour were investigated in rats. After 7 week intake of the oil, the test animals showed better discrimination between the active and the inactive levers in the Aversive Light Stimulus Avoidance Test (ALSAT) from day 1 of training. Krill oil prevented resignation/depression on the third day in the Unavoidable Aversive Light Stimulus Test (UALST) (29). A shorter immobility time was observed for the krill oil and imipramine (standard antidepressant) groups compared to the control in the Forced Swimming Test. The mRNA for brain-derived neurotrophic factor (Bdnf) was specifically upregulated in the hippocampus of female rats receiving 7 weeks of krill oil supplementation. Males also exhibited an increase in prefrontal cortex expression of Arc mRNA, a key protein in long-term synaptic plasticity. It was confirmed that krill oil facilitates learning processes and provides antidepressant-like effects (29). For its cognitive-enhancement and cerebral stimulation of foetus brain, it is recommended for pregnant women.

Renoprotective effect: Nephrocalcinosis, a common renal abnormality has been implicated in subsequent renal failure in rats. The effect of 4 week consumption of krill protein concentrate was evaluated on renal health of rats and compared with that of casein (30). Tissue analyses showed that rats fed the protein concentrate had lower urinary n-acetyl glucosaminidase levels and minimal microtubular calcium deposition compared to rats fed casein. There was a tendency for higher glomerular filtration rates and lower proteinuria, and higher urinary output in rats fed krill protein concentrate compared to casein. Krill protein concentrate is expected to avert early renal injury and thus reduce nephrocalcinosis threat (30).

Extraction: The effect of pressure, temperature and extraction time on krill oil was assessed (31). The maximum oil yield was found at higher extraction temperature and pressure. The oil obtained by supercritical carbon dioxide (SC-CO2) extraction was more stable, contained a high percentage of EPA and DHA; whereas the acidity and peroxide value of krill oil obtained were lower than that of the oil obtained by hexane (31). The maximum yield of astaxanthin was found in krill oil extracted at 25 MPa and 45°C.

Novelty: Omega-3 fatty acids can be obtained from several sources apart from krill oil viz. algae, fish oil, plant, enriched dairy products, animal-derived food, seal oil (32). The advantage of phospholipid form of krill oil is that it gets better absorbed and transported as compared to the normal triglyceride form found in fish oil (33). Phospholipids spontaneously form micelles, which can be transported easily in the aqueous environment (25). Also, phospholipids can be absorbed intact or in their lysophosphatidylcholine form. A randomized study was conducted to find out the efficacy of krill oil and fish oil and the better between the two (34). Six capsules of krill oil or three capsules of fish oil were given daily for 7 weeks. EPA and DHA dose in the krill oil was 62.8% of that in the fish oil, yet it showed comparable increase in plasma EPA, DHA and DPA (34). Intake of krill oil does not produce fishy Seema Patel
burps or belching as this happens in case of fish oil. Krill occupies lower position in food chain, so it is free of heavy metals and other contaminants unlike the latter.

**Issues encountered** : The exoskeleton of krill contains fluorine, which is toxic in high concentrations, so it must be peeled before consumption. Krill oil is one of the most sensitive oils to rancidity. It requires immediate refrigeration after harvesting for keeping it unoxidized. The increase in demand for ω-3 fatty acid is likely to increase pressure on marine living resources. Overharvesting may result in sharp decline or extinction and may also disrupt the food chain. Further, the impact of emissions (global warming, ozone depletion, acidification and eutrophication), material and energy demands needs assessment. The cost of krill harvesting was assessed and the cost of fossil fuel burnt for operation of fishing vessel, transport and resupply vessel was found high. Concerns have been voiced in recent years regarding the environmental implications of the Antarctic krill fishery (35).

**Future directions** : Astaxanthin was able to prevent oxidative modification in lymphocytes from rat lymph nodes through the suppression of the oxidative stress condition imposed by fish oil. It was reported that the association of astaxanthin with fish oil could be a good strategy to potentiate immuno-modulatory effects of the latter (36). Many krill-based food products are expected in the near future. While some countries have been consuming it since long, in some other regions, its incorporation in food is at experimental stage. In Japan, it is ingredients in several seafoods. In Norway, krill paste used as dip. Russia is engaged in commercializing krill-based food products. Fermented krill (kapi) is a protein-rich, traditional food in Thai cuisine (Fig 3). Water-soluble fraction of this fermented product possessed radical-scavenging activity, as determined by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) methods (37). It also showed ferric reducing antioxidant power (FRAP) in a concentration-dependent manner. The fermented product demonstrated high stability to temperature (37). Currently, krill is being consumed as snacks, pizza toppings, omelettes, paste in soups and salads. Raw and boiled krill, krill meal and oil are being marketed for human as well as pet consumption. In recent times, many patents have been filed on novel krill meal cooking, powdering protocols and methods to use krill oil for treatment of metabolic syndromes.

**Conclusions**

The findings obtained so far are testimony to the krill oil’s effective nutritional attributes. More research input can reveal several other clinical applications. In this era of over-exploitation of bio-resources, krill is surprisingly under-utilized. These zooplanktons might tackle the global issue of looming starvation. Krill-based food developments are already picking up in many countries. While taking benefit of the generous marine supply, a balance must be struck not to deplete it for sustainable harvest and protection of ocean health. Krill oil is a relatively nascent field of nutraceutical research, given due emphasis, it could help tackle many health issues.

**References**


**Fig 3. Fermented krills (kapi)**


