Marine life, including fish, seaweed, and algae, represents a unique and growing global resource for the production of nutraceuticals and functional food ingredients.
Researchers may one day find in the ocean answers to questions that will help to realize dreams of lengthening life and memory, of retarding aging, and of cures for a variety of illnesses,” stated Jacques Cousteau, who is considered a pioneer of ocean exploration (Cousteau, 1975).

Much attention has been paid to exploration of potential nutraceuticals and pharmaceuticals derived from the ocean. While the majority of nutraceutical products in the marketplace are of botanical origin, marine-based nutraceuticals are gaining attention due to their unique features, which are not found in terrestrial-based resources. A growing body of research indicates the potential for the marine environment as a unique source of functional food ingredients. In recent years, a series of promising new marine nutraceutical products have been introduced to the nutraceuticals and functional foods markets.

This paper examines the current state of the marine nutraceuticals and ingredients industry from an international perspective, with a focus on the available marine bio-resources for nutraceutical products and functional ingredients in global markets and their claimed health benefits. Also discussed are emerging products, production methods, ongoing R&D activities, and challenges in marine nutraceuticals and ingredients markets in different parts of the world, along with future developments in marine nutraceuticals and ingredients industry and research.

The main sources and products of primary interest for marine nutraceuticals and ingredients include omega-3 fish/algal oil, phospholipids (bound omega-3 fatty acids), micro/macro algal nutrition supplements, fish proteins and peptides, hydrolysates, shellfish chitin, fish collagen, and mineral supplements.

Omega-3 Polyunsaturated Oils

Omega-3 polyunsaturated oils offer several health benefits, including cardiovascular disease risk reduction, immune function improvement, brain health, and rheumatoid arthritis inflammation reduction. The oils are currently produced from fish, algal, krill, seal, and recently from squid. Fish oil with omega-3 fatty acids (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) experienced a sales increase of 35–40% in 2005–2006 (Hjaltason, 2007). The combined sale of consumer products fortified with omega-3 fatty acids is estimated to be $19 billion globally, according to the Global Organization for EPA and DHA Omega-3 (GOED Omega-3) (Moloughney, 2011).

Fish oil is produced from various sources, including anchovy, menhaden, herring, mackerel, salmon, and cod liver, and marketed in various forms, most commonly as concentrated omega-3 oil in soft gel capsules and microencapsulated powder. In order to improve yield and oxidative stability, enzymatic concentration and microencapsulation of omega-3 fish oil have been carried out based on a complex coacervation technology at Ocean Nutrition Canada (Kralovec et al., 2009). The delivery of omega-3 oil in beverage products is being sought through a sophisticated microemulsion technology (Moloughney, 2011).

Unlike other fish oil, farmed Atlantic salmon oil contains a 2:1 ratio of DHA and EPA, together with astaxanthin. The key producers of omega-3 oil are Ocean Nutrition Canada, Dartmouth, Nova Scotia, Canada; Epax AS, Aalesund, Norway; and Napro Pharma AS, Brattvaag, Norway, from anchovy and sardine; and Omega Protein, Houston, Texas, from menhaden. Other producers include Nissui, Tokyo, Japan, and Pronova BioPharma, Lysaker, Norway, for omega-3 oil-derived pharmaceuticals, and Croda, Goole, UK.

Antarctic krill and squid oils contain mostly phospholipid-bound omega-3 fatty acids; krill oil also offers a potent antioxidant, astaxanthin (Beer, 2011). Neptune Technologies & Bioresources, Laval, Quebec, teamed with
Each 240-ml serving of Stonyfield Organic Whole Milk provides 50 g of omega-3 EPA/DHA for heart, brain, and eye health. Ocean Nutrition Canada supplies the omega-3 ingredients, which are derived from fish oil.

Marine Life Sciences, Salt Lake City, Utah, to market a blend of Antarctic krill oil and concentrated marine algae for dual benefits. Aker BioMarine, Oslo, Norway, the world largest krill oil producer, is the exclusive supplier for Valensa International, Eustis, Fla., which markets a krill oil-based supplement for joint and eye health. The two companies are also performing joint clinical studies of krill oil. Enzymotec, Migdal, Israel, is another global supplier of refined krill oil.

Parma Marine, Terøy, Norway, markets phospholipid-bound omega-3 fatty acid-containing oil from squid byproducts. Phospholipids of marine origin are a good source of more bioavailable omega-3 fatty acids, particularly for brain health. These phospholipids have been used for memory treatments (Louis-Sylvestre, 1999) and are an important ingredient in larval fish feed (Lian et al., 2008). Currently, marine phospholipids are produced from krill and squid in commercial quantities.

Algal oil with DHA is currently produced by DSM-Martek Biosciences, Columbia, Md., through heterotrophic culture of Cryptophycodinium cohnii (DHA > 30%) for infant nutrition formula in combination with fungal arachidonic acid (ARA) and Schizochytrium sp. (DHA > 33% with 13.5% docosapentaenoic acid, DPA: 22:5n-6, osbond acid) for general nutrition supplements. Lonza Group, Basel, Switzerland, produces microalgal oil (DHA > 43%) from Ulkenia sp. (Kiy et al., 2005). Photonz Corp., Auckland, New Zealand, has developed pharmaceutical-grade EPA omega-3 oil from cultured diatom Nitzschia laevis.

New entries to the algal oil market are Algae Bioscience Corp., Overgaard, Ariz., (EPA and DHA) and Aurora Algae, Hayward, Calif. (EPA only). Recently, Solazyme Roquette Nutritional, South San Francisco, Calif., has developed an egg and butter replacement ingredient, algal flour, from microalgae for fat reduction.

Mussel oil produced from New Zealand green-lipped mussel (Perna canaliculus) contains eicosapentaenoic acid (ETA: 20:5n-3) and octacosapentaenoic acid (OOA: 28:5n-3) in addition to EPA and DHA. It is used for inflammatory arthritis relief. Supercritical fluid extraction (SFE) based on pressurized CO₂ (liquid at 31°C and 7.38 MPa) is used in mussel oil extraction. The bioactive marker for anti-inflammatory activity has not been isolated, but such activity is believed to be from the synergistic function of various omega-3 fatty acids (EPA, DHA, and ETA) (Sankaran and Mouly, 2007) along with glycosaminoglycans.

Seal oil, which contains DHA, EPA, and docosapentaenoic acid (DPA: 22:5n-3, elupanodonic acid), is anti-atherogenic (Nakhla, 1998) and is more stable than fish oil (Shahidi, 1994). It is currently produced in Newfoundland and Labrador, Canada.

Shark liver oil contains squalamine (aminosterols) and squalene (alkylglycerols), which deliver potential immune enhancement, anti-angiogenic activity, and skin conditioning (Newman and Cragg, 2004).

Industry analysts estimated global consumption of marine and algal omega-3 ingredients in 2008 at 71,452 tons, with North America being the largest consumer at 26,948 tons, followed by Asia-Pacific at 21,145 tons, European Union (EU) at 13,596 tons, and the remainder of the world at 5,762 tons (Real, 2009). Currently, there is about 85,000 tons, according to GOED Omega-3 (Moloughney, 2011). In an effort to implement quality standards and also to increase consumer awareness and regulatory approval, GOED Omega-3 was established in 2006.

Other than capsules and microencapsulated forms, omega-3 fish oil can be consumed in the form of microemulsion in beverage products, oily fish such as mackerel and salmon, or processed seafood such as nugget, patty, and sausage formulated from high omega-3 oil-containing fish as well as omega-3 oil added surimi products, if fatty acids can be adequately protected from oxidation (Lee et al., 2007; Tolasa et al., 2010).

Microalgae of Commercial Importance

A commercial, large-scale microalgal culture started in the early 1960s in Japan with the culture of Chlorella. In the following 40 years, the microalgal industry has grown and diversified significantly. Currently, the microalgal biomass market produces about 5,000 tons of dry matter/year and generates a turnover of approximately U.S.$1.25 billion/year (Pulz and Gross, 2004; Spolaore et al., 2006).

Chlorella (Chlorella vulgaris and Chlorella pyrenoidosa) is rich in chlorophyll, protein (40–60%), and carotenoids. It exhibits putative anti-carcinogenic, immunomodulatory, hypolipidemic, gastric mucosal-protective, and detoxification activities. Producers of Chlorella include Cyanotech, Kailua-Kona, Hawaii, and Earthrise Nutritional, Ishigaki Island, Japan.

Spirulina (Spirulina platensis) is one of the few plant sources of vitamin B12. It provides immune enhancement, protein supplementation (65–71% by weight), and has putative health benefits including anemia prevention, hypcholesterolemic, antioxidant, hepatoprotective, and anti-allergic activities. Producers of Spirulina include Cyanotech; Earthrise Nutritional, Irvine, Calif.; and Parry Nutraceuticals, Chennai, India.

Dunaliella salina is a primary algal source of β-carotene (antioxidant) with putative aging retardant and immune enhancement. It is capable of producing bioglycerol. Cognis Nutrition and Health, Tullamarine, Australia (now part of BASE) manufactures and markets Dunaliella salina.
Cryptothecodinium cohnii produces DHA (> 30%), which is being used primarily for infant formula with arachidonic acid (ARA). DSM-Martek Biosciences is a supplier of Cryptothecodinium cohnii.

Schizochytrium sp. produces DHA (> 35%) plus 13.5% DPA and is used as a nutritional supplement and active ingredient in poultry feed. DSM-Martek Biosciences is a supplier of Schizochytrium sp.

Nitzchia laevis produces EPA. Photozont Corp. has developed a pharmaceutical-grade EPA omega-3 manufacturing process from microalgal biomass along with SFE technology from Separex S.A., Champigneulles, France. Its application is aimed at cardiovascular disease.

Haematococcus pluvialis produces astaxanthin (7% of dried weight), a dietary antioxidant (500x vitamin E). Producers of Haematococcus pluvialis include Cyantech; Mera Pharmaceuticals, Kailua Kona, Hawaii; Valensa International; Parry Nutraceuticals; Astareal, Gustavsberg, Sweden; and Algatechtechnologies, Kibbutz Ketura, Israel.

Seaweeds
In recent years, seaweed has gained much attention due to interest in its nutraceutical potential and development of seaweed-based functional foods and nutraceuticals worldwide, the most actively in China, Japan, and Korea. For instance, Marine Bioprocess Co., Busan, Korea, focuses exclusively on seaweed-derived functional drinks, foods, and cosmetics. The company employs fermentation technology. There are several known seaweeds that offer nutraceutical properties and can be developed into functional foods. They include Laminaria japonica, Undaria pinnatifida, Ecklonia cava, Fucus ceranoides, Ascosyphum nodosum, Ulva lactuca, Carposphyllum flexuosum, and Cladosiphon sp. Seaweed may possess nutraceutical and cosmeceutical properties, including antioxidant, fat cell thermogenesis, retarding fat absorption, hypocholesterolemic, immune enhancement, type 2 diabetes control, anti-hypertensive (ACE inhibition), anti-inflammatory, and anti-cancer activities. In addition, seaweed may provide UV-protective function, natural sunscreen, and skin care potential (Lee and Apostolidis, 2009).

Potential bioactive components in seaweeds responsible for nutraceutical activities include fucoidan (sulfated polysaccharide), fucoxanthin (carotenoid), fucosterol, phloroglucinol-based polyphenols (phlorotannins and simple phenolics), glycoproteins, and peptides.

Fucoids are sulfated polysaccharides (> 40% of the dry weight of the algal cell walls) and have demonstrated beneficial effects on cardiovascular, joint, and digestive systems in experimental studies. They are also known to boost the immune system, help protect against thyroid cancer and other cancers (Itoh et al., 1993; Zhuang et al., 1995), moderate blood sugar and cholesterol levels (Murata et al., 1999), and detoxify the body from heavy metals (Morris et al., 1999) and radioactive elements (Carlson and Erlandsson, 1991). A comprehensive review discussed the therapeutic role of fucoidan in the control of acute and chronic inflammation (Fittton, 2011).

Fucoxanthin, a carotenoid with formula C_{42}H_{58}O_{6}, is reported to promote fat burning within fat cells (thermogenic) by increasing the expression of thermogenin (uncoupling protein 1, UCP1) (Miyashita, 2009).

Fucosterol has demonstrated hypocholesterolemic activity, antioxidant activity (Lee et al., 2003), and anti-diabetic activity (Lee et al., 2004) when brown seaweed (Pelvetia siliquosa) was tested.

Phloroglucinol-based polyphenols (phlorotannins) have exhibited antioxidant activity (Smith and McLean, 2006; Hwang et al., 2010), inhibitory effect on α-glucosidase and α-amylase linked to type 2 diabetes (Apostolidis et al., 2008), and UV-protective function as a potential natural sunscreen (Heo et al., 2009).

Chitosan oligosaccharide is an oligomer of D-glucosamine and obtained by an enzymatic hydrolysis of chitosan using chitosanase (Kim and Rajapakse, 2005). It may offer several benefits, including binding excess fat and inhibiting fat absorption, lowering LDL, boosting HDL cholesterol, anti-cancer, antimicrobial, immune enhancement, lowering blood sugar, controlling blood pressure, enhanced absorption of calcium, reduced risk of cardiovascular disease, and reduced level of uric acid in the blood, thus preventing the occurrence of gout.

Other Sources of Marine Nutraceuticals
Bioactive peptides from hydrolyzed bonito (Sarda orientalis) show anti-ACE (angiotensin-I-converting enzyme). ACE is a key enzyme in the regulation of peripheral blood pressure which converts angiotensin I into angiotensin II, a highly potent vasoconstrictor molecule. This enzyme causes a reaction that increases both the volume of blood flowing through arteries and the degree of constriction of the blood vessels. These peptides lower blood pressure by inhibiting ACE (Fujita et al., 2001) and help maintain healthy blood pressure. Commercial products made from hydrolyzed bonito include Levenorm from Ocean Nutrition Canada, Pept.ACE from Natural Factors, and Bonito Peptide from Ortho Molecular Products.

Fish protein hydrolysate produced from lean white fish through microbial fermentation, a technology developed...
by Proper Nutrition, Reading, Pa., is shown to promote intestinal health and maintain healthy bowel function. Commercial products containing fish protein hydrolysate include Seacure and Intestive from Proper Nutrition.

Collagen for skin care has been produced mainly from cold water fish skins such as cod, haddock, and salmon. However, recently, collagen is being commercially produced from fish scale, such as tilapia, by decalcification and enzymatic hydrolysis (Nagai et al., 2004). The uniqueness of scale collagen is its molecular weight, which is lower (~ 1,000) than skin collagen.

Since 1991, Imedeen has been a leading internal skin care product for dry, mature, or sun-damaged skin. It was developed by Ferrosan, a Danish healthcare company, which uses a patented fish extract that contains properties similar to those found in the dermis (notably collagen and elastin).

The development of a salmon-based skin cream has been aided by researchers at Norway’s University of Science and Technology, who discovered the skin softening enzyme, zonase, from the hatching fluid of the salmon eggs. Zonase helps dead skin flake off and stimulates the growth of healthy, new skin cells. It has also been proven helpful in healing wounds. The skin cream is sold under the brand name Aquabeautine XL from Aqua Bio Technology, Bergen, Norway.

Marine nutraceuticals-related research is being conducted in the U.S. at various marine biotechnology research centers. They include Marine Biotechnology Center (MBC) (Univ. of California-Santa Barbara); Center for Marine Biotechnology and Biomedicine (CMBB)/Scripps Institution of Oceanography (Univ. of California-San Diego); Center of Marine Biotechnology (COMB) (Univ. of Maryland-Baltimore); The Center of Excellence in Biomedical and Marine Biotechnology (Harbor Branch Oceanographic and Florida Atlantic University); Marine Bioproducts Engineering Center (MarBEC), Hawaii-Manoa; and recently Food Science and Nutrition Research Center (Univ. of Rhode Island, Kingston). Their common interests are in marine biotechnology and marine organisms-derived bioactive, pharmaceutical, and nutraceutical products.

**Industry and R&D**

Ocean Nutrition Canada is in the business of discovery, manufacturing, and marketing marine-based ingredients, which improve human health and are used for dietary supplements and functional foods. It is a world-leading producer of concentrated omega-3 fish oil, along with microencapsulated omega-3 oil powder as a food ingredient for functional food and dietary supplement applications. Production and delivery technologies for omega-3 fatty acid concentrates have also been developed (Kralovec et al., 2009).

Copalis, Portel, France, is a global supplier of marine-based natural ingredients for nutraceutical, functional food, animal nutrition, and skin care products utilizing fish processing byproducts for marine bioactives through hydrolysis and fractionation. It formed a research alliance with Ifremer (French Research Institute for Exploitation of the Sea), Aquimer (National cluster for aquatic products), Nausicaä (The French National Sea Experience Centre), Nutrition Healthcare Longevity Cluster, and SEAFOODplus. SEAFOODplus is an integrated seafood research program supported by the European Union.

NutraMara (Marine Functional Food Research Initiative), Dublin, Ireland, focuses on fish processing waste streams, underutilized raw materials, and underutilized species of fish and seaweed with an interest in the development of value-added marine functional foods while fostering collaboration between higher education research institutions and the food and pharmaceutical industries. “Our seas are a huge reservoir for bioactive compounds that can be incorporated into food additives, which can be harnessed for human health,” said Maria Hayes, Scientific Project Manager of the NutraMara project.
Bioconversion of Marine Biomaterials and Processing Byproducts

Bioconversion is a process by which raw materials or substrates are converted into useful, value-added products by biological means, most commonly done with aid of endogenous or exogenous enzymes. On a global scale, directly accessible marine biomass represents up to 100 million tons of fish/year, crustacean and mollusks from fisheries, and aquaculture. It is estimated that more than 50% becomes waste or is underutilized (European Science Foundation Marine Board, 2001). This poorly utilized biomass is an important source of biologically active molecules possessing unusual properties.

Various research projects are being actively carried out under SEAFOODplus, an integrated umbrella research program supported by the EU. One of the main objectives is to screen, map, and recover new, health beneficial compounds from seafood byproducts and underutilized species by advanced bioconversion processes in order to develop new bioactive, functional seafood ingredients (www.seafoodplus.org).

According to SEAFOODplus studies, all fish hydrolysates exerted a weak to moderate in vitro inhibition of angiotensin-I-converting enzyme (ACE), suggesting that hydrolysis of fish proteins yields hypotensive peptides. Fish protein hydrolysates exhibited CT (calcitonin)-like activities for calcium and phosphorus metabolism for the treatment of hypocalcaemia or osteoporosis; and gastrin and CCK (cholecystokinin)-like activities for stimulation of digestive enzyme secretion, which restrict stomach emptying, thus giving a false sense of fullness. Gastrin stimulates secretion of gastric acid, while CCK causes the release of digestive enzymes and bile to stimulate the digestion of fat and protein.

Hydrolysate peptides also exhibit antioxidative and free radical scavenging properties. Matis (Iceland Food and Biotechnology Research) Reykjavik, Iceland, employs alkaline protein recovery prior to enzymatic hydrolysis for production of superior quality peptides. Marine Bioproducts, Storebø, Norway, is a production and research company focusing on gentle and natural processing of fresh raw materials of marine origin. Enzymatic hydrolysis at low temperatures is the basic concept, followed by separation steps that yield high-quality protein-, lipid-, and bone-derived products. The current product line includes hydrolysates, peptides, amino acids, digested protein meals, minerals, and oil from salmon.

Products yielded by bioconversion need to be further refined to separate target bioactives using fractionation techniques such as ultrafiltration (UF) membrane for continuous operation (Jeon and Kim, 2000; Park et al., 2008) (Figure 1) or fractionation by centrifugation at selected g forces (Lee, 2009).

Production of bioactives by fermentation with probiotic cultures was done by fermenting
squid processing byproduct with *L. rhamnosus* and *P. acidilactici*, yielding good DPPH scavenging activities and IL-6 and TNF-α activities (Xu et al., 2009). A similar process was used by Proper Nutrition to produce fish protein hydrolysate for intestinal health.

**Marine Nutraceuticals Today & Tomorrow**

Marine nutraceuticals take a small share of the $22 billion global nutraceuticals market projected in 2013 (Moloughney, 2009). Global interests in marine bio-resources have spurred several international conferences, including “Marine Ingredients Conference,” held in Oslo, Norway in September 2010, and “Biomarine Business Convention,” held in Nantes/Saint-Nazaire, France this past September.

The marine nutraceuticals market will grow steadily as the global nutraceuticals and functional foods markets continue to expand. Aging Baby Boomers will help enlarge the marine nutraceuticals market.

Developers and marketers of marine nutraceuticals and bioingredients should focus on identifying products for domestic or global markets; exploring indigenous bio-resources for domestic markets, building on the existing infrastructure, and expanding to overseas markets; securing sustainable resources through aquaculture and cell culture; and establishing high-throughput screening tests for candidates based on biomarkers and nutrigenomic approaches (Lee, 2009).

Development of marine nutraceutical products and ingredients is highly market driven and requires good marketing strategies. Special attention should be given to types of products (i.e., marine nutraceutical ingredients or functional foods) and to the most suitable form of product in terms of compatibility, stability, consumer acceptability, and regional preference. To succeed in the marketplace, products require good science-based clinical evidence. Marine omega-3 oil will enjoy continuous growth, while algae-based products will find expanding opportunities. **FT**
REFERENCES


