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Sea Food Bioactives for Health and Wellness

Babita .S[1], Krishan Datt .S[2], Caresma .C[3]

Department of Food Science and Technology, Y.S. Parmar University of Horticulture and Forestry, Nauni, India
Email: *babitasharma9419[at]gmail.com*

Abstract: ***Health is a state of complete physical, mental and social well-being and not simply the absence of disease or illness. The importance of seafood having a unique and different type of bioactive compounds is increasing. Organisms in shellfish make up nearly half of the world's biodiversity and are the largest reservoir of beneficial natural molecules that could be used as functional components. The main functional compounds in crustaceans are proteins, peptides, amino acids, fatty acids, sterols, polysaccharides, oligosaccharides, phenolic compounds, photosynthetic pigments, vitamins and minerals that have health benefits. The demand for new substances for the treatment of human diseases such as cancer, microbial infections and inflammatory processes has increased the exploration of new bioactive compounds. Peptides isolated from fish and algae polysaccharides have been reported to have antitumor, anticoagulant and antihypercholesterolemic activity. Marine bacteria and fish oils contain a large amount of omega-3 fatty acids, while algae and shellfish, such as crustaceans, have powerful antioxidants which include carotenoids and phenolic compounds. This review gives information about uses and types of bioactives compounds in sea foods. Marine resources offer important benefits for the human body and can be applied in many fields, like pharmaceutical, cosmetic and food industries. Functional foods can be easily developed from seafood as they are widely available and have the ability to prevent some diseases and cure some of them. Various types of shellfish and sea foods offer a huge resource for finding new compounds and are considered the largest remaining reservoir of natural molecules that can be used as functional ingredients in the food industry.***

Keywords: Seafood, Bioactive, Marine, Peptides

1. Introduction

As we know, in recent years people have become aware of health and importance of marine creatures as a source of bioactive compounds is running out and these bioactive compounds are the additional nutritional components found in small amounts in food. These compounds vary widely in chemical structure. A bioactive compound is any compound found in foods such as animals; plants and seafood, etc. Commercial seafood includes shells, shrimp, crabs, fish, and scales. There is a lot of scope for using these products, as they are rich in liquids, PFAs, chitin and proteins. The ocean occupies approximately 71% of the earth's surface and 80% of all life on earth is found below the ocean's surface, and two-thirds of the phyla are exclusively marine (Maripandi*et al.*, 2010).

The marine world is a rich resource of biologically active compounds. Marine organisms live in complex habitats and are exposed to extreme conditions, producing a wide variety of specific and potent active substances that cannot be found anywhere else. These products are also effective in the prevention of certain diseases for the treatment of human diseases such as cancer, microbial infections and inflammatory processes which have increased the exploration of new bioactive compounds. Marine organisms are considered as the best potential reservoir for these compounds. Many marine compounds have been found to have different biological activities: peptides isolated from fish and polysaccharides from algae have been reported to have anticancer, anticoagulant and antihypercholesterolemic activities (Lordan*et al.*,2011). Marine bacteria and fish oils contain large amounts of omega-3 fatty acids, while algae and shellfish such as crustaceans have powerful antioxidants including carotenoids and phenolic compounds (Rasmussen & Morrissey, 2007).

2. Bioactive Compounds

Bioactive compounds refer to any chemical that affects a specific physiological function of any organism. The invertebrate phyla, so extensively studied, are due to the abundance of a myriad of bioactive compounds. The passion for biologically active marine substances was born in 1969 with the discovery of 15-ear-PGA2, a prostaglandin. The molecule was isolated from the Caribbean gorgon, *Plexaurahomomalla* (Weinheimer&Spraggins, 1969). About 5,000 species of sponges, 11,000 species of corals, jellyfish and sea anemones, 9,000 species of segmented worms, 100,000 species of annelids, polychaetes, snails, clams and octopuses, 6,000 species of starfish and sea cucumbers are present in the marine environment (Ruggeri,1976). From the groups mentioned above, more than 6,500 biologically active compounds have been isolated (Kamboj, 1999). Marine invertebrates offer a source of potential antimicrobial drugs (Bansemir*et al.*, 2006; Mayer *et al.*, 2007 and Jayaraj*et al.*, 2008). Studies on antimicrobial mechanisms and compounds in marine invertebrates can provide valuable information for new antibiotic discoveries and provide new information on bioactive compounds in farmed aquaculture molluscs.

In the last decade there has been a lot of help in the search for natural products of marine origin. Scientists from all over the world have discovered new bioactive compounds from macro and microorganisms. So far, 300 patents on bioactive marine natural products have been issued, with 134 patents relating to applications in the field of human health. Since the beginning, the number of compounds isolated from various marine organisms has practically increased rapidly and now exceeds 10,000, with hundreds of new compounds still being discovered every year (Faulkner,2002). Among the various phyla represented in the marine environment, Mollusca are the second largest phylum after Arthropod consisting of about 100,000 species worldwide in almost all habitat types. Most shellfish are very delicious seafood for their nutritional value, along with fish and shellfish. The pearls produced by molluscs, especially the oriental ones, have been the object of a recognized position of the kings and wealthy since ancient times and still constitute an important charm today. They are also excellent sources of biomedically important products (Shenoy,1988). Antitumor (48%, immunoregulatory (4%), antiviral (20%), anti-inflammatory (5%), antibacterial (8%), antifungal (7%), anthelmintic (3%), others (5%) Many types of shellfish exhibit bioactive compounds such as anticancer, antileucymic, antibacterial and antiviral properties worldwide (Rajaganapathy*et al.*,2000).

3. Importance of Crustaceans

Molluscs are any form of marine life considered food by humans. Fish includes fish and shellfish. The latter include shellfish: bivalves (mussels, oysters and scallops), univalves (abalone and snail) and cephalopods (squid, cuttlefish and octopus); crustaceans (shrimp, crab and lobster) and echinoderms. Most people would also include algae and microalgae. The fish is tasty, nutritious and rich in proteins containing all essential amino acids, polyunsaturated fatty acids (PUFA), calcium, iodine, vitamins and many other nutrients (Venugopal, 2005). Recently, natural bioactive compounds have received more attention, including those obtained from marine organisms (Kim &Wijesekara,2013). Marine bioactive components can be obtained from various marine animals, plants and lower organisms. Each is unique as a species and, due to its life in different conditions, such as salinity, pressure, temperature and lighting (Lordan*et al.*, 2011 and Kulawik*et al.*,2013), potentially contain several natural products.

Seafood and health benefits

Seafood plays an essential role in the human diet and is not only a consistent source of protein but also has a nutritional impact to its lipid, vitamin and mineral constituents. Shellfish proteins are highly digestible and easily absorbed by the body. Lys and Met are 2 of the most important essential amino acids. These are generally found in high concentrations in fish proteins.

Health benefits of shellfish as a source of antioxidants

Synthetic antioxidants such as butylated hydroxyl anisole (BHA), butylated hydroxyl toluene (BHT), tertiary butyl hydroquinone (TBH), and propyl gallate (PG) have been widely used to retard lipid oxidation. However, these synthetic compounds are subject to strict regulation in most countries due to their potential health risks (Park *et al.*,2001). Antioxidant activity has been reported for fish protein hydrolyzates (FPH) prepared from various marine species such as tuna, mackerel, yellowfin sole and Alaskan cod (Je *et al.*, 2005 and Je *et al.*,2007). Peptides isolated from fish can be derived from muscles, skin, scales, bones and other tissues. Although all free amino acids can generally interact with free radicals, the most effective are those that can easily donate hydrogen atoms. These are amino acids that contain nucleophilicsulfur-containing side chains (Cys and Met) or aromatic side chains (Trp, Tyr and Phe). The antioxidant nature of FPH mainly depends on the size of the peptide and the composition of the amino acids (Kim &Wijesekara, 2013).

Anti-cardiovascular effects

Consumption of fish is known to have a beneficial effect on quality of life due to the PUFAs in fatty fish. Many studies have been conducted to demonstrate the relationship between fish consumption and decreased quality of life and coronary heart disease. Populations that consume more seafood, such as Alaskans and the Japanese, have been shown to suffer from less heart disease (Kinsella,1989). Another study showed that Mediterranean people who consumed large amounts of shellfish (as part of a Mediterranean diet) showed a reduction in coronary heart disease mortality because omega-3 fatty acids reduce the risk factors associated with triglyceride concentrations, blood pressure, platelet accumulation and cardiac arrhythmias (Juturu, 2008 and Chan &Cho, 2009). Furthermore, fish intake in the Mediterranean has also been associated with less severe symptoms of depression in adults and fewer asthma and respiratory allergies in children (Lloret, 2010). Omega-3 PUFAs also protect against the development of certain cancers such as breast (Zheng*et al.*, 2013) and prostate cancer (Berquin*et al.*,2007).

Impact on prebiotics

Macroalgae contain various polysaccharides that could be used as prebiotic compounds for sanitary applications. Different polysaccharides are found in all species. Chlorophyte contains highly complex sulphatedheteropolysaccharides. Alginates and Fucani arefound in brown algae. Agar and carrageenan are also extracted from red algae. The benefits of macroalgae polysaccharides have been demonstrated in vitro and in vivo.

The results were promising, as laboratory animals were shown to have higher numbers of *Bifobacterium*and *Lactobacillus* (Wang *et al.*,2006). Other parameters that indicate a prebiotic activity are the pH of the caecal content, the concentrations of organic acids and the fecal weight (Ishihara *et al.*, 2010). To be considered a prebiotic, a compound must meet 3 criteria:

1) It must not be digested in the upper gastrointestinal tract (GIT).
2) It must be a selective substrate for the growth of beneficial bacteria; and
3) It must have a beneficial effect on the health of the host. Pathogenic and beneficial bacteria coexist in GIT, but research focuses on changing this composition towards a more beneficial balance, reducing potentially harmful bacteria and promoting the development of other species that have beneficial results in the organism (increased resistance to infections, reduce the risk of colon cancer and reduce the risk of obesity). Furthermore, prebiotics have been shown to increase the absorption of Ca and Mg, influence blood glucose levels and improve plasma lipids (Zheng*et al.*, 2013).

Influences on anti-inflammatory activity

The anti-inflammatory effects of crustaceans are due to the fact that PUFAs, in particular omega-3s, can inhibit some inflammatory mediators (Calder, 2009). Several studies indicate that increasing the ratio of omega-3 to omega-6 fatty acids in the diet reduces inflammation. In fact, eicosanoids derived from omega-6 PUFAs (such as AA) have active proinflammatory and immune functions, while eicosanoids derived from omega-3 PUFAs (EPA and DHA) have anti-inflammatory properties. Unfortunately, Western food has a much higher percentage of omega-6 PUFAs than omega-3 PUFAs (Wall *et al.*, 2010). Preclinical and clinical research has shown that consuming fish oils, which contain EPA and DHA, has an effect on inflammation. Prostaglandins and leukotrienes that are formed from EPA from cyclooxygenases (COX) and lipoxygenases (LOX) are less pro-inflammatory than those derived from AA (omega-6) (Moreillon et al., 2012). For this reason, increasing the (DHA + EPA) / AA ratio decreases inflammatory mediators. Omega-3 fatty acids are also known to inhibit the activity of the proinflammatory nuclear factor transcription factor kb (nf-kb), which induces the expression of many pro-inflammatory genes that encode adhesion molecules (e.g., the molecule of intercellular adhesion, cytokines, chemokines and other effectors of the innate immune response (Zwart*et al*, 2010 and Rahman&McFadden, 2011). Additionally, fish oils have been tested as alternatives to non-steroidal anti-inflammatory drugs (NSAIDs).

Health benefits related to obesity prevention

Obesity is a chronic metabolic disorder caused by an imbalance between energy intake and expenditure. Excessive accumulation of fat leads to too many health problems such as hypertension, type 2 diabetes, high blood cholesterol levels, coronary heart disease and sleeping disorder (Must *et al.*,1999). Obesity also has a negative social effect. Obese people have to tolerate discrimination due to their weight (Puhl&Heuer,2009). The growing incidence of obesity has become a medical problem around the world. Fish oil has been shown to help you lose weight. Although human studies are relatively few and have generally been conducted for short periods of time (Buckley &Howe, 2009), the results obtained can be used to conclude that fish consumption can help with obesity. Gunnarsdottir*et al.*,(2008) conducted a study on 324 men and women, aged 20 to 40, from different countries (Spain, Iceland and Ireland). They were given a diet with sunflower oil or fish oil. Various measurements were made: total cholesterol (TC), high density lipoprotein (HDL), LDL, cholesterol, triacylglycerol (TG) and anthropometric measurements. The fish oil weight loss diet led to a greater reduction in TG and TC. HDL remained stable.

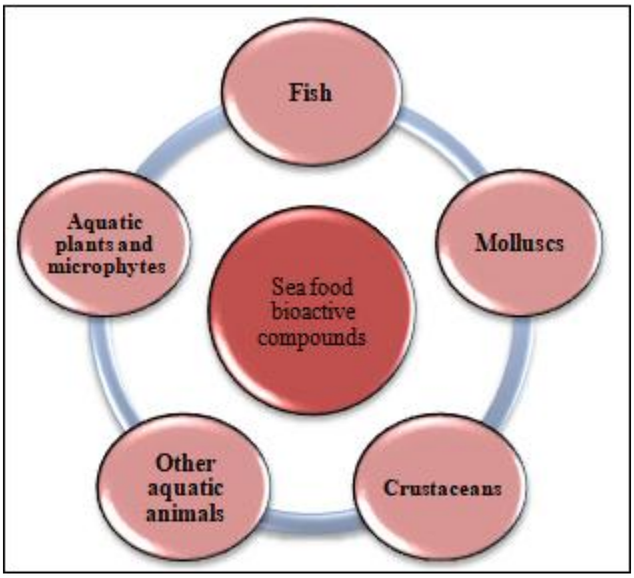
Neuroprotective effects of crustaceans

Neurodegenerative diseases are considered one of the most common causes of death among the elderly (Bjarkam*et al.*,2001). For this reason, scientists have looked for new neuroprotective agents to prevent apoptosis, damage to neuronal cells, central nervous system (CNS) dysfunction and deterioration (Zarros, 2009). Although synthetic compounds have been used to act as neuroprotectors, there are side effects that include anxiety, nervousness, drowsiness, dry mouth or fatigue (Pangestuti&Kim, 2011a). There is a low incidence of neurodegenerative diseases in East Asia, which has been linked to its high consumption of fish and algae. Most studies involve animal or in vitro models. However, there are currently insufficient data from clinical trials. Calon&Cole (2007) reported the association between consumption of DHA or high levels of DHA in the blood and a lower risk of developing Alzheimer's disease (AD) later in life. The work demonstrated that animal models of AD are more vulnerable to DHA depletion than controls and that DHA exerts a beneficial effect against pathological signs of AD, including amyloid peptide β (Aβ) accumulation, cognitive impairment, loss of synaptic markers and hyperphosphorylation of tau. Another study by Cole*et al.* (2009) confirmed the results. A reduced intake of omega-3 fatty acids or consumption of fish was related to an increased risk of age-related cognitive decline or dementia diseases such as AD. DHA can protect against AD using several mechanisms, such as limiting the production and accumulation of peptidotoxin Aβ, which is widely believed to be the cause of the disease. Omega-3 fatty acids have been shown to be effective in rats with epilepsy in preventing damage to the hippocampus (Ferrari *et al.*, 2008). To demonstrate neuroprotective activity, an immunological cytochemical study was performed in animals using the distribution of parvalbumin (PV) and calretinin (CR) as markers. The results were positive for the group that received omega-3 PUFA, as more PV-positive and CR-positive neurons (Ferrari *et al.*,2008).

Health benefits to prevent cancer

Tumours can be defined as diseases in which cells stop responding normally to chemical signals from other cells. Instead of stopping, they keep growing and dividing. These abnormal cells can kill by invading and subverting normal tissues (Silverstein *et al.*,2006). It is important to look for molecules capable of triggering apoptosis (programmed cell death). Cellular dysregulation, whether it is a loss of pro-apoptotic signals or an increase in anti-apoptotic signals (or both), can lead to a variety of pathological conditions such as cancer. Therefore, stimulating apoptosis is an important goal for cancer therapy. Several studies have been conducted to test the relationship between cancer prevention and fish consumption. Picot *et al.*(2006) investigated the antiproliferative activity of FPH in vitro in 2 human breast cancer cell lines. An inhibition of proliferation was observed and a composition analysis of the hydrolysates showed that they contained a complex mixture of free amino acids and peptides of various molecular weights up to 7 kDa along with minor amounts of lipids and NaCl. The anticancer and anti-metastasis activities of omega-3 fatty acids present in fish oil were tested in mice carrying Lewis 3LL lung cancer. The mice were fed a diet rich in omega-3 fatty acids and few parameters such as tumour growth, body weight, and lung metastases were followed. The control diets contained soybean oil. These diets were tested in combination with the conventional cytotoxic agent cisplatin. Fish oil suppressed tumour growth and reduced metastatic burden. In the same study, it was observed that the effects of omega-3 polyunsaturated fatty acids can be enhanced by adding vitamins E and C (Yam *et al.*,2001). Other authors have reported the same positive results from diets containing fish oil using other markers, such as decreased growth of DU-145 human prostate cancer cells in nude mice.

4. Sources of bioactive compounds of seafood



1) Major bioactive compounds in fish

a) Proteins

Proteins are complex polymers made up of a combination of 20 different amino acids encoded by the genetic code (DNA) along with many other amino acids. In addition to being nutritionally necessary, proteins have several important roles in biological and food systems acting as hormones (insulin, growth factors and more), transport proteins (transferrin, hemoglobin and others) and antibodies (immunoglobulins) (Goodb,2002). Fish is an excellent source of protein and contains all essential amino acids in proportions suitable for humans. The essential amino acids for humans are His, Phe, Val, Thr,Trp, Leu, Ile, Met and Lys (Driskell,1999). Fish proteins compare favourably with proteins such as milk and soy proteins (Tahergorabi*et al.*,2002).

The high protein content of several microalgae species and their amino acid patterns compare favourably with that of other dietary proteins, suggesting that they could become a potential source of protein. Spirulina, for example, is rich in proteins (from 60% to 70%), with an excellent balance of essential amino acids and bioavailability. Spirulina appears to be one of the most important microalgae used by man. It has been used as food by many civilizations (including Aztecs and Maya) and by African populations near the alkaline lakes in Chad and Niger. Among its bioactivities are the reduction of potential brain damage and anti-inflammatory activity. A daily spirulina supplement is believed to reduce allergy symptoms (Rasmussen &Morrissey, 2007).

b) Peptides

The hydrolysis of proteins leading to bioactive peptides has been the subject of intense research, including peptides derived from marine proteins. These peptides have been isolated from marine sources, for example algae, crustaceans and fish species. Bioactive peptides often have 3 to 20 amino acid residues depending on the composition and sequence of the amino acids (Ibanez *et al.*,2011). They are indicated to have biological functions, for example antioxidant, antithrombotic, antihypertensive, immunomodulatory, antitumor and antimicrobial effects. Several studies have also shown that peptides derived from different marine protein hydrolysates can act as potential antioxidants and have been isolated from marine organisms such as giant squid, tuna and scal(Kim &Wijesekara, 2010). Furthermore, several studies have suggested that peptides derived from marine fish proteins may be more potent antioxidants than α-tocopherol (vitamin E) in some oxidative systems (Jun *et al.*,2004).

c) Amino acids

Among the water-soluble components, the muscles of crustaceans are rich in amino acids, mainly taurine, Gln, Pro, Gly, Ala and Arg. Cooking or thermal processing causes the loss of water-soluble components and therefore its positive properties are likely to be greater when molluscs are processed to a minimum (Luten,2009). Lys, amino acids that contain sulphur, and are often not present in sufficient quantities in children's diets, especially when they are based on cereals. Therefore, the consumption of fish muscle proteins, generally rich in these amino acids, is recommended to increase the nutritional value of foods and improve their nutritional status for humans. The protein content differs significantly from phylum to phylum in macroalgae and has all essential amino acids in reasonable proportions, although their content varies greatly depending on the species. The red alga *Palmariapalmata* is rich in Leu, Val and Met (Bocanegra*et al.*,2009), and its average levels are similar to those observed mainly in ovalbumin. However, the concentrations of Ile and Thr are similar to those found with legume proteins. According to Taboada*et al.* (2009), the green alga *Ulvarigida* contains Leu, Phe and Val as the main essential amino acids. Theirs, which is an essential amino acid for babies, is found at levels close to those of legumes and eggs.

d) Lipids and fatty acids

The fatty acid composition of crustaceans is generally characterized by a relatively low content of saturated fatty acids (SFA). A low intake of AGS is recommended as a link between AGS consumption and the development of cardiovascular disease (CVD). However, recent research questions this hypothesis as carbohydrates are considered a possible culprit. Crustaceans also contain PUFA and substantial amounts of monounsaturated fatty acids (Larsen *et al.*,2011) which are considered beneficial as long as they are not oxidized.

Polyunsaturated fatty acids

The lipid fraction of shellfish consists mainly of PUFA which have been well documented as essential for human health (Zheng*et al.*,2013). Humans are unable to synthesize PUFAs with more than 18 carbon atoms; therefore, they must get them from food. Molluscs are the main sources of long-chain PUFA, although synthesis occurs in algae consumed by fish. Long-chain omega-3 fatty acids such as Eicosapentaenoic acid (EPA, C20: 5) or Docosahexaenoic acid (DHA, C22: 6) are useful in protecting against CVD (Kris-Etherton*et al.*,2003). The composition and extraction of PUFA from algae, fish and other marine sources has been extensively studied (Sanchez-Machado et al.,2004). A major commercial source of omega-3 polyunsaturated fatty acids, including DHA and EPA, are fatty fish such as herring, mackerel, sardines, and salmon. The quantity and composition of these oils depend on the species, the season and the location of the catch sites (Sijtsma&de Swaaf,2004).

e) Sterols

Another class of lipids of marine origin are the sterol compounds. They are membrane lipids produced by Eukaryotes and by some bacteria (June *et al.*, 2004). Research has focused on the composition of sterols extracted from macro and microalgae, fish and other marine invertebrates (Ozyurt*et al.*, 2013). Sterols and some of their derivatives have been shown to be involved in lowering low-density lipoprotein (LDL) cholesterol levels in vivo. Another bioactivity related to sterols is the anti-inflammatory effect. Furthermore, phytosterols (sterols C28 and C29) are essential precursors of some vitamins. For example, ergosterol is a precursor of vitamin D2 and cortisone. Spirulina has been reported to contain sterols, including clionasterol, associated with increased formation of plasminogen activating factor in vascular endothelial cells (Lordan*et al.*,2011). Fucosterol, chondrillasterol and sargasterol are found in brown algae and cholesterol in red algae (Kayama *et al.*,1989).

f) Vitamins

Vitamins are necessary for the human body for various chemical and physiological functions. Seaweed is generally a good source of B vitamins (B1, B 2 and B12) (Kim &Taylor,2011). Vitamin composition varies with many factors, including species, geographic area, season and environmental parameters (Norziah&Ching, 2000). Ortiz *et al.*(2006) reported that 100 g of seaweed provides more than the daily requirement of vitamins A, B2, B 12 and two thirds of the vitamin C requirement. Vitamin B12 exists in red macroalgae (such as *Palmarialongat* and *Porphyratenera*) and in particular in green algae, while vitamins C and E are both found in *U. pinnatifida* and *Laminariadigitata*. Microalgae are crucial sources of almost all other essential vitamins like A, B1, B 2, B 6, B12, C, E, etc. They are also abundant in chlorophylls (Lordan*et al.*,2011).

Fatty fish are one of the few dietary sources of vitamin D. Vitamin D deficiency causes many problems including rickets in infants and children and osteomalacia in adults (Luten,2009). Vitamin B12 (cobalamin) is found widely in algae in higher concentrations in green and red algae than in brown algae. Vitamin B12 is a cobalt-containing tetrapyrrole related to chlorophyll and heme. Cobalaminisa cofactor of enzymes.Cobalamin deficiency can cause serious health disorders such as megaloblasticanaemia and neuropsychiatric disorders (Misurcova,2011). The highest vitamin B12 content in algae measured to date is found in *Porphyra sp.* (134 µgB12 / 100 g dry weight). It has been reported that a high content of this vitamin is also found in green algae (*Enteromorpha sp.*, Dulse and Spirulina) (Kim &Taylor, 2011). Vitamin B12 is recommended for the treatment of the effects of aging, chronic fatigue syndrome and anemia(Ravishankar*et al.*,2005). Vitamin C (ascorbic acid) is present in all red, brown and green algae. Historically, a red seaweed (*Porphyra*) has been used to prevent scurvy caused by vitamin C deficiency. Additionally, this vitamin has other health benefits such as radical elimination, strengthening the immune system and anti-aging activity (Haidara*et al.*, 2006).

g) Minerals

Algae are also very rich in essential minerals and trace elements. This is associated with its ability to retain inorganic atoms from seawater. Most of these essential minerals are found in higher levels in algae than in native foods. All the essential minerals and trace elements necessary for the human diet exist in macroalgae (Ito &Hori,1989), so it is considered an important functional food for this reason. The mineral composition of algae can vary depending on the phylum, season, environment, geography and physiology (Mabeau and Fleurence,1993). Some phaeophytes (*U. pinnatifida* and *Sargassum*) and some rhodophyta (*Chondruscrispus* and *Gracilariopsis*) can be considered a dietary supplement to find the daily intake of some important minerals (Na, K, Ca and Mg), as well as trace elements (Fe, Zn, Mn and Cu). Furthermore, the analysis of Ulva(*Ulvalactuca*)rigid showed a balanced content of Na and K from a nutritional point of view. Elevated Na/K ratios have been associated with the incidence of hypertension (Taboada*et al.*,2009). Furthermore, algae are one of the most important plant sources of Ca. Therefore; Seaweed intake may be a useful risk for Ca deficiency risk, particularly pregnant women, adolescents and the elderly. The most important feature of marine plants is their high content of Iodine and important nutrient in metabolic regulation and growth patterns. It is abundant in most algae (MacArtain*et al.*, 2007).

2) Major bioactive compounds in mussels

Biological activity-Name of bioactive protein/peptide		Mussel species	Origin/product
Antioxidant	Mussel-derived radical scavenging peptide (MRSP)	ME (*M. edulis*)	Fermented sauce
	N.g.	MC (*M coruscus*)	*In vitro* gastrointestinal digest
Antimicrobial	Mytilusdefensin A	ME	Blood
	Mytilusdefensin B	ME	Blood
	MGD-1	MG (*M galloprovincialis*)	Hemocytes
	Myticin C	MG	Hemocytes
Anti-inflammatory	-	MG	Proteic extract
Antihypertensive	N.g.	ME	Fermented sauce
Antifungal	Mytimycin	ME	Blood
Anticoagulant	N.g.	ME	Edible part
Anti-thrombin	Pernin	PC (*P. canaliculus*)	Byssus
Anti-inflammatory	-	MG	Proteic extract
Antihypertensive	N.g.	ME	Fermented sauce
Antifungal	Mytimycin	ME	Blood

(Silve*et al.*,1992; Marie *et al.*, 2009; Benkendorff*et al.*, 2010 and Grienke*et al.*, 2014);

a) **Mollusca**

The phylum Mollusca is comprised of eight distinct classes and is highly diverse, although <1% of species have so far been studied for secondary metabolites, while evidence for other compounds / molecules is equally limited. Within this, proteins, lipids and carbohydrates have received a particular research focus, with mussel lipids being a well-established treatment for rheumatoid arthritis. In terms of osteogenicbioactives, a new activity has been found, such as that of the gastrointestinal digest of abalone from Haliotis*discus hannai*(Benkendorff*et al.*,2010). These partially digested extracts were studied using an osteoblast-like cell line (MG-63) and were subsequently shown to increase alkaline phosphatase (ALP) levels and mineralization. RT-PCR and Western blot analysis revealed an increase in BMP-2 expression, which is believed to be the result of activation of the MAPK pathway. However, with the exception of this example, mother-of-pearl tests constitute the majority of studies reporting the osteogenic activity of mollusc derived material (Grienke*et al.*,2014).

b) Mother of pearl(Nacre)

Mother-of-pearl, often in powder form, features in a considerable body of research. Also known as nacre, nacre is the glossy aragonite inner layer found in the shells of molluscs in taxa such as mussels and abalone. Like bone, nacre has both inorganic and organic components, with an organic shell matrix consisting of proteins, glycoproteins and polysaccharides that serve as a template for calcium carbonate mineralization. It is this similarity that has fuelled the idea that mother of pearl may contain a factor capable of stimulating mineralization and keeping human bone healthy. Research on nacre has been conducted since the early 1990s and initial in vitro work has demonstrated its ability to stimulate the mineralization of human osteoblasts (Marie *et al.*, 2009). Since this initial work, there has been an increase in research efforts, including in vitro and in vivo studies, as well as those that specifically focus on the proteins and mechanisms involved in enhancing cellular activity, making mother-of-pearl into an excellent case study of bioactive research (Silve*et al.*,1992).

c) Main bioactive compounds of crustaceans

Chitin and chitosan: chitin (β- (1-4) -poly-N-acetyl-D-glucosamine) is widely distributed in nature and is the second most abundant polysaccharide after cellulose (Aider, 2010). Chitin, which occurs naturally as ordered macro fibrils, is the main structural component in the exoskeletons of crustaceans, crabs and shrimps, as well as in the cell walls of fungi. For biomedical applications, chitin is generally converted to its deacetylated derivative, chitosan. Chitin and chitosan are biocompatible, biodegradable and non-toxic biopolymers. They are also antimicrobial and moisturizing agents (Bhale*et al.*, 2003). Depending on the source of the chitin, it occurs as two allomorphs, namely the α and β forms, which can be characterized by both infrared and solid-state NMR spectroscopy, along with X-ray diffraction which has also been described. Allomorphs differ in the orientation of the microfibrils. The biosynthesis of chitin is catalyzed by a widely preserved enzyme in nature called chitin synthase. This enzyme exists in all organisms that synthesize chitin. Chitin synthase remains attached to the growing polymer chain through many polymerization steps that sequentially add the individual GlcNAc units to the non-reducing end of the extended chain(Atiba*et al.*, 2011). The linear chitin polymers that are obtained first and then spontaneously assemble into microfibrils of different diameter and length. After polymer synthesis, the completed fibrils are transported into the extracellular space. Glycosyl hydrolases (GH) are a broad class of enzymes that degrade polysaccharides; they are currently classified into 130 families based on similarities in their amino acid sequences. Chitinases are mainly classified into the GH-18 and GH-19 families and have been found to be present in a wide range of organisms, including bacteria, fungi, insects, plants and animals. Chitin and chitosan are used in a wide range of biomedical applications, including tissue engineering, drug and gene release, wound healing, and stem cell technology(Bhale*et al.*, 2003). These biopolymers can be easily transformed into various products, including hydrogels, membranes, nanofibers, beads, micro / nanoparticles, scaffolds and sponges. Tissue engineering is one of the most studied fields in which chitin and chitosan have been successfully used to produce polymer scaffolds for tissue repair and regeneration(Bhaskara*et al.*, 2000).

d) Bioactive compounds of microphytes

One group of promising marine invertebrates as a source of bioactives are algae, especially macroalgae. Seaweed has much greater bioactive diversity than nacre, including limestone extracts, sulfated polysaccharides and raw seaweed extracts.

3) Aquamin

Aquamin is a food supplement derived from the red alga *Lithothamnioncorallioides*and contains calcium, magnesium and 72 other trace elements (Gorman *et al.*,2011). L. corallioides is quite unique in that it is one of the few species of algae that produces a calcareous skeleton. It is normally found on muddy or sandy substrates less than 20 m deep, in loose algal aggregations known as maerl beds (Wilson *et al.*, 2004). It is from these beds, with wide distribution in Europe (including the western coasts of Ireland and Great Britain) and further north, that maerl is harvested before being ground into the commercial product known as Aquamin. Aquamin is currently licensed and manufactured only by Marigot Limited (Marigot, Cork, Ireland).

a) Fucoidan

Within the algae group, fucoidan is one of the best studied extracts. Fucoidans are highly sulfated and fucose-rich polymers, found as a highly branched and relatively high-yielding form in brown macroalgae and a more linear form in echinoderms (Fitton,2011). These marine polymers are multifunctional, with a variety of therapeutic uses, from anti-inflammatory to antiviral ones (Fitton,2011). In terms of effects on bone, the extract appears to have both antiresorptive and osteogenic potential. Fucoidan extracted from sea cucumber *Apostichopus japonicas* has been shown to inhibit osteoclastogenesis, while the work of Kim *et al.* (2014) demonstrated the same effect with brown algae extracts added to cultures of bone marrow macrophages. This reduction in osteoclast differentiation was attributed to inhibition of RANKL-dependent MAPKs and down regulation of transcription factors c-Fos and NFATc1.

However, the precise molecular mechanism by which this inhibition occurs has not yet been elucidated, which is a common limitation to studies on this polysaccharide. Fucoidan is hypothesized to bind to RANKL or RANK to inhibit intracellular signaling, an action that can be facilitated by its sulfated regions (Kim *et al.*,2014).

b) *Sargassumhorneri*

While fucoidan is one of the best known bioactives, there are other seaweed extracts that also have an effect on bone homeostasis. *Sargassumhorneri* brown seaweed extracts are known to stimulate osteoblastogenesis and inhibit osteoclastogenesis in vitro in preosteoblastic and monocytic cell lines (Yamaguchi &Matsumoto,2012). Similar in vitro and in vivo work was conducted using rat femoral tissues, which demonstrated the ability of *S. horneri* extracts to increase bone calcium content and inhibit bone desorption(Uchiyama &Yamaguchi, 2002). This work complements the in vivo tests, which indicate that *S. horneri* extracts have a preventive effect on bone loss in streptozotocin diabetic rats. In addition, a basic human study was even conducted to investigate the effect of oral algae ingestion on bone metabolic markers. Although limited by very small sample sizes, this study reported an inhibitory effect of the extract on bone resorption, determined by reduced levels of circulating resorption markers such as TRAP, and is one of the few trial studies in progress for any compound of marine origin. As for fucoidan, the main limitation of *S. horneri's* work lies in the identification of the active component of the extract, which appears to be different for bone stimulation and suppression of resorption (Uchiyama *et al.,* 2004).

c) *Hizikia fusiform*

Another brown algae extract that has been tested both in vitro and in vivo is *Hizikiafusiforme* (Jeong*et al.*,2016). In particular, a hot water by-product from algae containing high levels of polysaccharides has been shown to stimulate ALP activity and BMP-2 levels in mouse C2C12 myoblast cells. Furthermore, the in vivo stimulation of skeletal activity has been confirmed in zebra fish, ovariectomized mice and mouse calvaria bones (Jeong*et al.,* 2016).

d) *Sargassumthunbergii*

This is also an important alga similarly; a study based on brown algae examined quinone derivatives of *Sargassumthunbergii* and found that treatment with a crude extract containing these derivatives could improve osteoblast differentiation (Kim *et al.*,2016). Finally, fucoxanthin, a marine carotenoid found in brown algae, was also tested for its osteogenic activity. Fucoxanthin administered to rats has been shown to significantly reduce the oxidative stress index, but has no significant effect on ALP levels and causes only a limited reduction in alveolar bone resorption, despite the significant reduction in RANKL levels. Similarly, a related study found that fucoxanthin had no effect on the viability of MC3T3-E1 (anosteoblastic cell line), but did stimulate apoptosis in osteoclasts (Das *et al.*, 2010). So far, research on this carotenoid is limited and therefore it is difficult to determine its effects in vitro, although it initially appears to inhibit osteoclast resorption rather than stimulate osteoblast activity.

e) *Cladophorarupestris and Plocamiumcartilagineum and Ceramiumsecundatum*

Similarly, extracts from two red algae, *Plocamiumcartilagineum* and *Ceramiumsecundatum*, increased human bone marrow stromal cell (hBMSC) activity and caused significant increases in opercular bone size in juvenile zebrafish. Another osteogenic bioactive derived from red algae is fl oridoside, a glycosidic metabolite of the glycerol of *Laurenciaundulata* (among other red algae). Floridoside is known to promote the differentiation of D1 osteoblast cells, as well as the increase in ALP levels, mineralization and the expression of factors including type I collagen, Runx-2 and Osterix.

Bioactive compounds from marine bacteria

Source	Compound	Activity	Bacteria
Bacillus licheniformis	a-D-galactopyranosyl-(1/2)glycerol-phosphate	Antibiofilm	*Escherichia coli* and *Pseudomonas fluorescens*
Acinetobactersp	6-bromoindole-3-carboxaldehyde	Antifouling	Larval settlement of barnacle *Balanus Amphitrite*
Pseudomonas sp	Phenazine-1-carboxylic acid	Antifouling	Larval settlement under laboratory and field experiment assays
Streptomyces praecox	Diketopiperazines	Antifouling	Larval settlement under laboratory and field experiment assays
Streptomyces violaceorube	3-octa-1′-enyl-4-methylfuran-2(5H)one	Antifouling	Zoospores of *Ulvapertusa*, the diatom*Naviculaannexa*, and the mussel *Mytilusedulis*
Letendraeahelminthicola	3-methyl-N-(2-phenylethyl) butanamide	Antifouling	Larval settlement of barnacle *Balanus Amphitrite*
Cochlioboluslunatus	Resorcyclic acid lactones	Antifouling	Larval settlement of barnacle *Balanus Amphitrite*
Emericellavariecolor	Ophiobolin K	Antibiofilm	*Mycobacterium bovis*
Unidentified marine fungus	Mevalonolactone	Antibiofilm	*Staphylococcus epidermidis*
(Desjardine*et al.*,2007; Greve*et al.*, 2008; Trisuwan*et al.*, 2008 and Trisuwan*et al.*,2009;)			

Risk associated with the consumption of fish

It benefits from CVD health to the reduction of CVD risk triggered by the consumption of massive fish (FAO, 2010). However, eating fish includes some risks associated with exposure to environmental toxins. On the other hand, the only exposure to methylmercury is through edible marine products. Released mercury rapidly metabolizes methylmercury by the microorganism and if it accumulates and infests the upper part of the food chain. Exposure to methylmercury affects the highly sensitive nervous system. The developing fetal and infantile nervous systems were also highly sensitive to methylmercury. Methylmercury induces damage in the central nervous system that depends on ingested quantity (Clarkson *et al.*,2003).

The recommendations on the consumption of fish for pregnant women and children are accompanied by warnings of the quantity and type of fish to eat. Furthermore, dioxins and polychlorinated bipenyls contained in molluscs have raised concerns in relation to the health effects of the consumer of molluscs (Arisawa*et al.,* 2005). Balancing the health benefits and risks of fish intake is an important issue (He 2009). Some researchers have reported that the consumption of seafood provides benefits that outweigh the risks, with the exception of sharks, fish and edible animals and plants from areas with high levels of environmental pollutants (Dewailly*et al.*,2007).

5. Conclusion

People have understood the importance of seafood in our diet. Numerous studies have shown that some of the best sources of excellent health-promoting fats, proteins, vitamins and minerals are found in seafood. It is a shame that it took so many years before the health benefits of shellfish materialized. In the future, an increase in lifestyle-related diseases is expected, most of which are the result of eating habits, in both developed and developing countries. It has been shown that increased consumption of shellfish and bioactive components derived from fish, shellfish and algae could have a positive impact on the health of people around the world. Therefore, the role of shellfish in maintaining and improving health can be strengthened, given the problem of diseases related to the food environment and local lifestyle. In summary, it is of utmost importance to promote the consumption of seafood and the reduction of foods that are high in sugar and fat, including fast foods and soft drinks (sugar, in particular), saturated fatty acids and n-6 PUFAs. This is currently excessive.Marine resources offer important bioactive molecules that have benefits for the human body. They can be applied in many fields, such as the pharmaceutical, cosmetic and food industries. Functional foods can be easily developed from seafood as they are widely available and have the ability to prevent some diseases and cure some of them. Various types of shellfish are consumed as a nutritionally beneficial food. The sea offers a huge resource for finding new compounds and is considered the largest remaining reservoir of natural molecules that can be used as functional ingredients in the food industry. As a result, efforts should be made to develop functional marine foods responsibly, as their consumption could result in a decrease in the occurrence and severity of chronic diseases.

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