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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

Functional foods and bioactive ingredients harnessed from the ocean: current status and future perspectives

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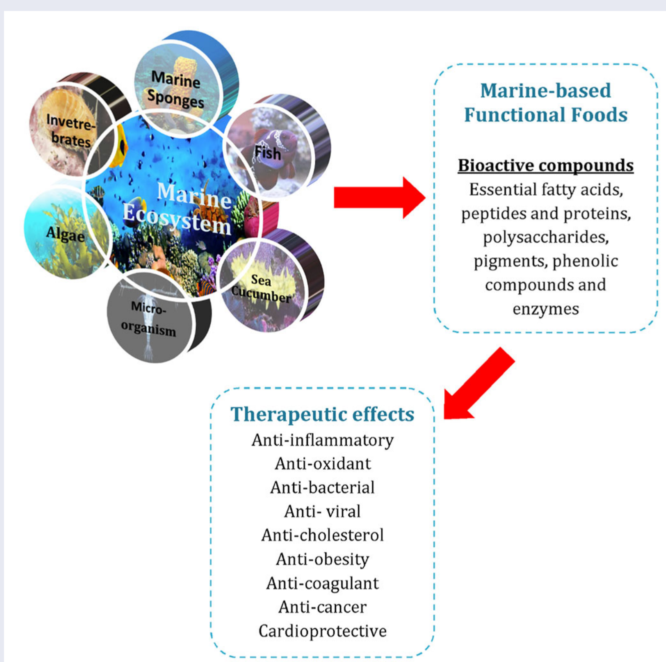
ABSTRACT

With an increase in life expectancy and decrease of quality-of-life couple with the high prevalence of diseases, diet is expected to play a key function in sustaining human health. Nutritionists, food technologists and medical experts are working in synergy to cater for the increasing demand of food with associated therapeutic benefits, commonly known as functional food, that may improve well-being and reduce the risk of diseases. Interestingly, the marine ecosystem, due to its abundant and phenomenal biodiversity of marine organisms, constitutes a vital source of a panoply of healthy foods supply for the thriving functional food industry. Marine organisms such as seaweeds, sea cucumbers, sponges, and mollusks amongst others are sources of thousands of biologically active metabolites with antioxidant, anti-parasitic, antiviral, anti-inflammatory and anticancer properties. Given the growing number of research and interest to probe into the therapeutic roles of marine products, this review was designed to provide a comprehensive summary of the therapeutic properties of marine organisms (macroalgae, sea cucumbers and fish among others) which are consumed worldwide, in addition to their potentials and as sources of functional ingredients for developing novel food and fostering wellness. The gap between research development and actual commercialization, and future prospects of marine-based products also summarized to some extent.

KEYWORDS
Marine foods; functional ingredients; therapeutic effects; nutritional supplements



Introduction

"*Let food be the medicine and medicine be the food*" was coined 2,500 years ago by Hippocrates, the father of modern western medicine. The conception that a close relationship exists between food and human health goes back to several centuries. However, this philosophy was largely neglected in

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the early 20th century, with the arrival of modern drug therapy (Admassu et al. 2015; Otles and Cagindi 2012; Sarkar 2007). Currently, there is a considerable change in consumer demands in food production sector, as the consumers are becoming increasingly health conscious. In this regard, functional foods play a vital role. These foods not only suppress the appetite and provides essential nutrients to human, but also help to control nutrition-related illnesses by improving the physical and mental health of consumers (Admassu et al. 2015; Rani et al. 2018).

The concept of functional food has emerged in Japan, in the 1980s, but was further developed in the Europe and United States and is now a vital part of the global food industry. In 2017, the revenue generated by global functional foods market was valued US$299.32 billion and is expected to increase to US$441.56 billion by 2022 (Tripathi et al. 2019). Japan, Europe and United States are the most dynamic markets leading the functional food industry (Suleria et al. 2015). Functional foods do not have an accepted formal definition since there is no legislation regarding these products in most countries worldwide (Tripathi et al. 2019). Generally, food can be considered as 'functional food', if it demonstrates health benefits beyond meeting basic nutrients, in a way that is relevant to either improve the state of health or well-being and/or reduce the risk of diseases (Admassu et al. 2015; Lordan, Ross, and Stanton 2011). Besides, it should be useful at normal consumption levels. Functional foods may consist of a single ingredient or a series of ingredients which are not present in similar conventional foods or in low doses. These are called functional ingredients (Figueiredo, Encarnação, and Campos 2016).

Functional foods include: (i) naturally occurring bioactive ingredients (e.g. dietary fibers and minerals) (ii) food enriched or enhanced or bioactive ingredients (e.g. probiotics, and antioxidants), and synthesized food ingredients incorporated into traditional foods (e.g. prebiotics). Probiotic and probiotics, phospholipids, omega-3 (ω-3)-polyunsaturated fatty acids (PUFAs), soluble fiber, conjugated linoleic acid, vitamins and minerals, herbal antioxidants, some proteins, peptides, and amino acids in general are commonly known functional components (Admassu et al. 2015; Grajek, Olejnik, and Sip 2005 Grimble et al., 2002; Ralston et al., 2018). Such active elements constitute the focus of contemporary science of human nutrition.

The marine environment, due to its phenomenal biodiversity, yields a wide spectrum of biologically active compounds in form of PUFAs, proteins, pigments, vitamins, and minerals amongst others that are being used to some extent, as components of functional foods. The industrial use of these compounds still faces technological and economic difficulties to enter and remain in the market. Despite of the strong scientific evidence on the biological activities of marine-derived ingredients, extensive research and development efforts are still required before these bioactives become a commercial reality in food formulation. The present paper attempts to review on the suitability of marine-derived bioactive compounds as functional food ingredients for the promising and dynamically developing segment of food industry, including the constraints and future prospects.

Potential use of marine organisms as functional foods

Oceans occupy the largest area of the biosphere which has been largely unexplored. Due to their diverse and extreme living environments such as varying temperature, salinity, pressure, light and nutrients, marine creatures have developed unique characteristics and biologically active metabolites as compared to terrestrial-based sources. The phenomenal biodiversity of the marine world makes it a logical target for searching natural products with diverse health benefits. Seaweeds, crustaceans, fish and fishery by-products, microorganisms, are most representative groups of organisms with prospective interest as healthy food or as a source of active ingredients such as polysaccharides, proteins, chitin, lipids, and vitamins among others. The last years have witnessed an incredible increasing interest in marine-derived constituents such as proteins, polysaccharides, lipids, and pigments for functional foods, due to their numerous health benefits (Hamed et al. 2015; Pangestuti and Arifin 2018; Shahidi and Ambigaipalan 2015). For instance, in the last decade, approximately 2500 peptides with anti-proliferative activity have been identified from a wide range of marine flora (Khalifa et al. 2019). However, proving that marine-derived biomolecules have defined health benefits poses a problem in nutritional research as it is difficult to assess preventive activity when it is modest. Although, the effect of bioactive compounds in the human body may be relatively low over short time, it can considerably contribute to health when they are consumed throughout life on a daily basis (Lordan, Ross, and Stanton 2011) Some major marine-derived functional ingredients and commercially available marine-based functional food or supplements are summarized in Tables 1 and 2, respectively. From this standpoint, the next sections describe, in a summarized way, the biological attributes of some marine organisms and their importance as functional foods.

Macroalgae

Macroalgae represent a large and diverse multicellular polyphyletic group of photosynthetic eukaryotic organisms. These organisms do possess roots or stems and extremely vary in morphology and size. Macroalgae are grouped into three categories, with a huge variety of species in each category, classified based on the presence of specific pigments other than chlorophyll: Phaeophyta (brown), Rhodophyta (red) and Chlorophyta (green) (Aryee, Agyei, and Akanbi 2018; Venkatesan, Anil, and Kim 2017; Wijesekara and Karunarathna 2017; Zhao et al. 2018). The pigment characteristics of macroalgae are related to their marine habitat because all algae do not require the same light intensity for photosynthesis. For instance, green algae that can absorb

Table 1. Main marine functional ingredients with potential food applications.

Category	Functional Ingredients	Marine Sources	Health Benefits	Potential Food Applications	References
Lipids	Omega-3 fatty acids	Fish and fish by-products, seaweeds and marine fungi	Numerous health benefits, for example: – Cardiovascular diseases reduction – Arthritis and hypertension disease reduction – Visual and neurological improvement	Used in bread and confectionary products – Fish oils capsules with potential use in other foods	(Hamed, Özogul, and Regenstein 2016; Kadam and Prabhasankar 2010)
Protein and Peptides	Collagen	Fish (Salmon, sardines, tuna, cod, mackerel) Sea cucumbers	– Antioxidant, antihypertensive/ angiotensin-converting-enzyme (ACE) inhibitory, anti-skin ageing activities – Reduction of lipid absorption.	Edible films and coatings.	(Felician et al. 2018; Gómez-Guillén et al. 2011; Hashim et al. 2015; Noitup, Garnjanagoonchorn, and Morrissey 2005)
	Gelatin	Cod, Atlantic salmon, haddock, Alaska pollack or hake; tropical or sub-tropical species such as red or black tilapia; giant squid	– Antioxidant and antimicrobial activities. Has shown to prevent and treat chronic atrophic gastritis	Stabilizing and thickness agents	(Gómez-Guillén et al. 2011; Gómez-Guillén et al. 2002)
	Albumin	Mollusks, crustaceans, low-fat fish	Anticoagulant and antioxidant properties	Whipping, suspending, or stabilizing agents	(Nicholson, Wolmarans, and Park 2000)
Polysaccharides	Carrageenan	Red algae (e.g. *Hypnea musciformis*	– Anticoagulant, Antimicrobial, anticancer and neuroprotective activities.	Stabilizers and thickeners, emulsifiers in foods (e.g. meat) and beverages	(Souza et al. 2018; Vlieghe et al. 2002)
	Agar Agar-agar	Red Alga is the main source of agar-agar *like Gracilaria* spp	– Anti-aggregation effect on red blood cells. – Antioxidant, antitumor, antiviral activities	Gelling agent and food gums	(Freitas et al. 2015)
	Fucans and fucanoids	Sea cucumbers and Cell walls of brown algae	– Anticancer, anticoagulant, anti-inflammatory, antithrombotic, antiviral and neuroprotective activities	Nutraceutical supplements	(Cui et al. 2016; Dore et al. 2013; Li et al. 2018; Tapon-Bretaudière et al. 2000; Vo and Kim 2013; Zhou, Xu, and Shen 2008)
	Chitin, chitosan, and derivatives	Shrimp, prawn, crab, squid, lobster and fish scales	– Prevention of inflammatory disorders – Antibacterial, anticancer and anticoagulant activities	– Gelling agents – Emulsifying agents – Food preservatives – Dietary fiber	(Azuma et al. 2015; Kadam and Prabhasankar 2010; Vikhoreva et al. 2005; Xia et al. 2011)
Phenolic Compounds and Pigments	Carotenoids (astaxanthin, lutein, fucoxanthin) and chlorophylls	Seaweeds	– Vitamin A precursors, – Antioxidants, anti-carcinogenic and anti-inflammatory activities – Prevent neurodegenerative disease	– Natural food colorings, – Food antioxidants – nutraceutical agents,	(Abu-Ghannam and Shannon 2017; Freitas et al. 2015; Maeda et al. 2005; Wells et al. 2017)
	Phlorotannins	Abundant polyphenols found in the marine brown algae	– Antioxidant, anti-allergic and anti-inflammation activities.	Nutraceutical supplements	(Barbosa et al. 2019; Barbosa et al. 2018; Li et al. 2017b; Sathya et al. 2017)
	Vitamins and Minerals	Present in almost all marine organisms. Seaweeds are rich sources of vitamins and minerals	– Involve in essential body functions	Food and nutraceutical supplements	(Admassu et al. 2015; Cofrades et al. 2017)
Enzymes	Gastric proteases (pepsin, Chymosin, gastricsins and chymosin	Various fish body viscera like Atlantic cod, sardine, carp, harp seals, and tuna etc.	–	In cold renneting milk and fish feed digestion aid	(Shahidi and Kamil 2001)
	Transglutaminase	in the muscle of red bream, rainbow trout, Atka mackerel, walleye, pollock liver and scallop	–	Responsible for creating cross-linkages in protein to improve rheological properties of gels, i.e., surimi, gelatin	(Shahidi and Kamil 2001)
	Lipases	Cod, salmon, seal, sardine, Indian mackerel and red sea bream	–	Several uses in the fats and oils industry	(Shahidi and Kamil 2001)

Table 2. Some commercially available marine-based functional food or supplements.

Products	Marine organism	Description/Health Claims	Company	Country
Hana Tsunomata	Seaweeds	Sea vegetables to be used with different salads, pasta, or other vegan dishes	Acadian Seaplants Limited	Canada
Seaweed biscuit		Nori salty flavor biscuit	Zhejiang Mizui Food Co., Ltd	China
Hawaiian Spirulina Pacifica		Available in two: powder and tablets. The powder is used as an ingredient in nutritional supplements and health beverages; tablets are consumed as a daily dietary supplement (rich in protein)	Cynotech	USA
BioAstin		Astaxanthin a red carotenoid to be consumed as natural antioxidant	Cynotech	USA
AstaFirst		Astaxanthin a red carotenoid to be consumed as a natural antioxidant	Wefirst Biotechnology Co.,Ltd	China
AstaPure		Astaxanthin a red carotenoid to be consumed as a natural antioxidant	Alga Technologies	Israel
FUCOIDAN		Fucoidan powder, capsule, and drink type	Umi No Shizuku	Japan
Swanson	Sea cucumbers	Capsule; for Joint health and mobility	Swanson Premium	USA
Deep Blue Health		Capsule; for joint health, immune system support and wellbeing	Deep Blue Health	New Zealand
CQ		Extract; for joint health	UltraHealth	New Zealand
SeaFit		Capsule; for Joint health	Vita Canyon	USA
Hawaii pharm.		Liquid; As a health supplement	HawaiiPharm	USA
Slim MED	Marine-derived Chitin	Capsule: Treatment of excess weight	Kitozyme	Belgium
Liposan Ultra	Marine derived Chitin	Capsule: for weight loss	Primex	Iceland
Aquatone	*Perna canalicus* (mollusk)	Extract; effective in maintaining healthy joints	Nature's Best	UK
Mussel 6000	*Perna canaliculus* (mollusk)	Capsules; for joint health; supporting joint flexibility and movement; naturally rich omega 3 for lubrication	Goodhealth	New Zealand
Abalone	*Haliotis* sp (mollusk)	Capsules; for eye health, general health, and vitality	Goodhealth	New Zealand
Oyster Plus	*Crassostrea sp.* (mollusk)	Capsules; for improving men's reproductive health; immune support; health and vitality	Goodhealth	New Zealand

large amounts of light energy grow in coastal waters, while red and brown algae prevail in deep waters where penetration of sunlight is limited (Bocanegra et al. 2009).

Edible macroalgae, commonly known as seaweeds, are one of the prominent primary producers in the food webs, which has traditionally been part of the human diet since ages. The use of seaweeds (also referred as sea vegetables) as a food source and medicine, has a long-standing history in Asian countries including China, Japan and Korea (Table 3). Seaweeds have been served as vegetables in these countries (Astorga-España et al. 2016; Pegg 2003; Zhao et al. 2018). It is documented that the Japanese consume 1.6 kg (DW) per capita of seaweeds annually (Fleurence, Morançais, and Dumay 2018). In the Hawaiian Islands, seaweeds were also the people's spices instead of pepper, oregano or mustard (McDermid and Stuercke 2003). Globally, 221 species of seaweeds: 125 Rhodophyta, 64 Phaeophyceae and 32 Chlorophyta are utilized commercially. Of these, 145 species are used in the food industry and 110 species for production of phycocolloids (Chung et al. 2011; Pereira 2011). Several edible seaweeds are known globally by their Japanese names such as Wakame (*Undaria pinnatifida*), Kombu (*Laminaria* spp.) and Nori (*Porphyra* spp.) (Gómez-Ordóñez, Jiménez-Escrig, and Rupérez 2010).

Macroalgae produce a myriad of bioactive molecules including carbohydrates, proteins, amino acids, lipids, fatty acids, sterols, vitamins, bioactive pigments and others which makes them potential candidate for wide range of food and pharmacological applications on industry scale (Zhao et al. 2018).

Food value and important nutrients

Seaweed is a rich source of micro- and macro-nutrients. The micronutrient compounds that are extensively used in beneficial health supplements include several vitamins (e.g. vitamin A, B, B_1, B_2, B_{12}, C, E and folic acid) (De Quirós et al. 2004; Ferraces-Casais et al. 2012; Kolb et al. 2004; Škrovánková 2011 Smith et al., 2014), minerals (e.g. iron, calcium, chloride, magnesium, phosphorus, potassium, sodium, zinc, cadmium and lead) (EEC 2008; Mišurcová, Machů, and Orsavová 2011; Peña-Rodríguez et al. 2011; Rao, Mantri, and Ganesan 2007; Rupérez 2002) and sterols (Lopes et al. 2013; Sánchez-Machado et al. 2004). Iodine is particularly abundant in seaweeds, with some of them having iodine content exceeds the dietary minimum requirement (150 mg/day). Brown seaweeds of genera *Sargassum*, *Laminaria*, *Macrocystis*, and *Undaria* are a particularly rich source of iodine (1500–8000 ppm) (Mišurcová, Machů, and Orsavová 2011; Rajapakse and Kim 2011). Since food derived from terrestrial plants have a low iodine content, seaweed is a cheaper food option to cater the iodine requirement of human (Rajapakse and Kim 2011). Seaweeds also contained calcium which may amount up to 7% of the dry weight (DW) in seaweeds. Thus, intake of a portion of seaweed (8 g DW) having 7% of calcium, provides substantial amount of calcium (560 mg) as compared to its

Table 3. Common seaweeds which is used for consumption and in tradition medicine in Asia countries. (Meenakshi et al. 2016)

Scientific Name	Common names	Usages/Country/Other details	References
Caulerpa spp. *C. lentillifera* and *C. racemosa* are most popular.	Sea grapes or Green caviar (Both spp have Grape-like appearance	It is consumed in the form of fresh vegetable or salad in most Asian countries.	(Nagappan and Vairappan 2014)
Codium fragile	shui-sung	Consumed in Korea, China and Japan	(Kasimala et al. 2015)
Gracilaria spp	–	It is used as laxative in Vietnamese traditional medicine	(Hong, Hien, and Son 2007)
Laminaria sp.		In Chinese traditional medicine, It is used for inducing labor or as an agent to enhance uterine contractions to induce placental detachment after birth	(Adams and Lien 2015)
Sargassum fusiforme	Hiziki or Hijiki	Widely consumed as vegetable and used as a medicinal herb in China, Japan, Korea and Southeast Asia. Known as 'Yang Xi Cai' in China, this alga is used against a number of diseases such as arteriosclerosis, skin disease, high blood pressure and neurosis.	(Liu, Heinrich, et al. 2012; Peng et al. 2012)
Sargassum naozhouense Tseng et Lu	–	It is consumed as a vegetable or as crude drugs for treating internal heat, infections, laryngitis and other ailments in locals (Guangdong province)	(Peng et al. 2012)
Ulva spp (e.g. *U. pertusa*, *U. lactuca*, and *U. compressa*)	Sea lettuce or Ao-Nori	It is eaten raw in salads and cooked. *U. lactuca* and *U. reticulata* are sold for use in traditional medicine	(Dominguez and Loret 2019; Kasimala et al. 2015)
Undaria pinnatifida	Wakame	Most popular edible seaweed in Japan. It used a remedy for fever and edema, and as a diuretic.	(Fitzgerald et al. 2011; Hong, Hien, and Son 2007)

recommended daily allowance (800–1000 mg) (Burtin 2003; Rajapakse and Kim 2011).

Besides micronutrients, seaweeds are rich reservoirs of macronutrients including bioactive peptides, amino acids and proteins, dietary fibers, polyunsaturated fatty acids (PUFAs) and polysaccharides (Astorga-España et al. 2016; Brown et al. 2014; Kadam et al. 2017). It is documented that seaweeds may contained 36–60% (DW) of dietary fiber and based on the daily dietary recommended allowance (24 g) of dietary fiber, a size of 8 g DW of seaweed fulfill about 12.5% of a person's daily fiber needs (MacArtain et al. 2007). However, the nutritional and metabolites profile of seaweeds varies due to many external factors such as species diversity, geographical location, environmental conditions (e.g. water temperature and depth), season and physiological variations (Lordan, Ross, and Stanton 2011).

High-value bio-actives and therapeutics

Epidemiological studies have revealed that regular consumption of seaweeds is associated with several health benefits (Brownlee et al. 2012; Sanjeewa, Lee, and Jeon 2018). Notably, the Japanese have the extended average life expectancy with low rate of coronary heart diseases and these scores are partly related to their diets, which include seaweeds as an important component (Cardoso et al. 2015; Yamori, Miura, and Taira 2001). These facts have an impact on Western culture to incorporate seaweeds in their diets to benefit from their potential health attributes and thus, food products containing seaweeds as functional ingredients are of increasing demand in the market. Many of the bioactive metabolites are well-known to exhibit noteworthy biological activities and have promising beneficial use in healthcare industry. Henceforth, seaweeds are presently under the spotlight of many investigations.

Polysaccharides. Seaweeds mainly consist of polysaccharides which represent up to 76% of dry weight. Generally, seaweed polysaccharides fall into two major groups, namely, structural cell-wall polysaccharides and storage polysaccharides (Holdt and Kraan 2011; Stiger-Pouvreau, Bourgougnon, and Deslandes 2016). Storage polysaccharide such as alginates, carrageenans and agar are the major commercial components and are widely used as emulsifiers, stabilizers and thickeners in the food industry (Freitas et al. 2015). A number of research has focused on the extraction and pharmacological evaluation of polysaccharides for potential commercial applications (Cui et al. 2018; Rioux, Turgeon, and Beaulieu 2007; Tian et al. 2015; Ye et al. 2008). These soluble fibers have been documented to promote the action of probiotics (Zaporozhets et al. 2014). In a study, Chen et al. (2018) have isolated polysaccharides from four Chinese seaweeds (*Grateloupia filicina*, *Eucheuma spinosum*, *Ulva pertusa*, and *Ascophyllum nodosum*), and characterized their structures and prebiotic effects in vitro. They observed that the seaweeds have carried total sugar and sulfate contents as well as monosaccharide composition and *G. filicina* and *E. spinosum* significantly enhanced bifidobacterium proliferation. Alginates have been predominantly known for their antiviral properties (Balboa et al. 2013; Xin et al. 2000). Vaugelade et al. (2000) have reported that alginates decreased intestinal absorption of glucose in pigs and modulate insulin response in pigs fed with a diet supplemented with 5% alginates from brown seaweed. Much similar observations have made in studies involving rat and humans. A study by Paxman et al. (2008), has demonstrated that daily intake of alginate reduced energy intake in free-living adults, suggesting that an alginate-containing formulation can potential be effective in the management of overweight and obesity. Agar is also extensively used in the pharmaceutical industry as a laxative or as an outer cover of capsules (Praseptiangga 2015). Seaweeds are known as a primary source of sulfated polysaccharides with numerous therapeutic properties that have potential applications in the biological and bio-medical areas due to their bio-compatibility and availability (Admassu et al. 2015; Wijesekara and Karunarathna 2017). The occurrence and structure of the sulfated polysaccharides vary according to seaweed species; for instance, sulfated galactan (e.g. agars and carrageenans) can be obtained from red algae, while fucoidans and laminarin are widely found in brown seaweeds and ulvans in green seaweeds (Jiao et al. 2011; Tanna and Mishra 2019). Li et al. (2017a) have reported the anti-coagulant properties of a rhamnan-type sulfated polysaccharide extracted from the widely consumed, green seaweed *Monostroma angicava*, collected from the coast of the Yellow Sea of China. The study carried by Wang et al. (2013) have showed that the degree of sulfation and a moderate molecular weight of sulfated polysaccharides extracted from *Monostroma angicava* is associated with highest anti-coagulant and antioxidant activities. Zha et al. (2012) reported that crude polysaccharides from *Laminaria japonica* at a dose of 400 mg/kg/day caused a decrease in total serum cholesterol, triglycerides, high density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol in serum.

Sulfated galactans are present in the intercellular matrix and cell wall of seaweeds. These macromolecules consist of galactose or modified galactose repeating units and the substituent of its main chain are sulfate and methoxyl groups, pyruvic acid acetals and glucosyl side chains. These groups can be unevenly distributed within the macromolecule (Chojnacka et al. 2012). *In-vitro* and *in-vivo* studies have showed that sulfated galactans possessed to display antitumor (Chojnacka et al. 2012; Delattre, Fenoradosoa, and Michaud 2011; Jiang and Shi 2018; Jin et al. 2019), anticoagulant (Farias et al. 2000; Magalhaes et al. 2011), antioxidant (Magalhaes et al. 2011), anti-inflammatory (Chaves et al. 2013) and antiviral properties (Talarico et al. 2004). A polysaccharides from *Sargassum fusiforme* significantly hindered the growth of human HepG2 cell-transplanted tumor in nude mice models (Fan et al. 2017). Carrageenan has been reported for its ability to lower lipid levels (Patil et al. 2018; Sokolova et al. 2014). Sulfated polysaccharide fraction from red alga *Porphyra haitanensis* have showed antioxidant effect in ageing mice (Zhang et al. 2003). Veena et al. (2007) have reported that sulfated polysaccharides from the edible seaweed *Fucus vesiculosus* hindered stone formation in experimental models by reducing oxidative stress and preventing crystal retention through averting membrane injury.

Sulfated galactans are commonly utilized in the food industry owing to their excellent jellifying and thickening properties (Yermak et al. 2017). Fucoidans contain α-1,3-linked sulfated L-fucose as main sugar unit and sulfate ester groups (Synytsya et al. 2010). The concentration of fucoidan in seaweeds is about 10% of dry mass. Fucoidan has shown significant antiviral activities against key viral pathogens such as human immunodeficiency viruses (HIV), herpes simplex virus (HSV) 1 and 2, dengue virus, and cytomegalovirus (Hidari et al. 2008; Witvrouw and De Clercq 1997). The key mechanism involved in the antiviral activities of these macromolecules is principally hindering the interaction of viruses to the cells, causing inhibition of viral-induced syncytium formation (Damonte, Matulewicz, and Cerezo 2004). In the study by Meenakshi et al. (2016) have demonstrated that fucoidans extracted the brown seaweed, *Turbinaria decurrens,* exerted neuroprotective effect in MPTP intoxicated Parkinsonic rat by reducing oxidative stress and upregulating proteins (tyrosine hydroxylase and dopamine transporter) expression. Xue et al. (2012) have reported that fucoidan exert anti-cancer effects by inducing cell death apoptosis, hindering angiogenesis and reducing lung metastasis of breast cancer in vitro and in vivo.

Another sulfated polysaccharide found in brown algae, laminaran, is well described for its therapeutic effects. Several *in-vitro* and *in-vivo* studies have evidenced on the prebiotic effects of laminarin (Devillé et al. 2007; Kuda et al. 2005; Walsh et al. 2013). The sulfated polysaccharide, porphyran, from the genus *Porphyra* (red algae) is used as a nutritional supplement antioxidant and gelling agent (O'Sullivan et al. 2010). Cao et al. (2016) have reported that porphyran from *Pyropia yezoensis* have displayed hypolipidemic and liver protecting effect in mice fed with high fatty acid diet. Recently, Tian et al. (2020) have reported that laminarin isolated from *L. japonica* Inhibits the proliferation of Bel-7404 and HepG2 cells and inhibited the growth of tumors in Hepa 1–6 tumor-bearing mice by upregulating senescence marker protein-30.

Extraction and purification of polysaccharides from algae include several steps that that are summarized in Figure 1 (Cunha and Grenha 2016; Xu, Huang, and Cheong 2017; Xue et al., 2012). While polysaccharides from algae are yet to be exploited, the shreds of evidence collectively amassed therein suggest that polysaccharides derived from seaweeds have potential applications in the food industry as novel functional food ingredients.

Protein, peptides and amino acids. Seaweed proteins represent a phenomenal and relatively unexplored resource, which is now increasingly gaining the attention of many researchers. The protein composition of seaweeds varies greatly (from 3% to 47%) from phylum to phylum and seasons (Harnedy and FitzGerald 2013); generally brown seaweeds possess low protein content (3 ± 15% DW), green seaweeds possess moderate (± 26% DW), red seaweeds possess high content (up to 47% DW) (Fleurence 1999; Fleurence, Morançais, and Dumay 2018; Lordan, Ross, and Stanton 2011). Among the numerous seaweeds' proteins, phycobiliproteins and lectins are of particular interest for the bioactivities they exhibit.

Lectins are proteins and glycoproteins which bind with carbohydrates reversibly with high specificity (Praseptiangga

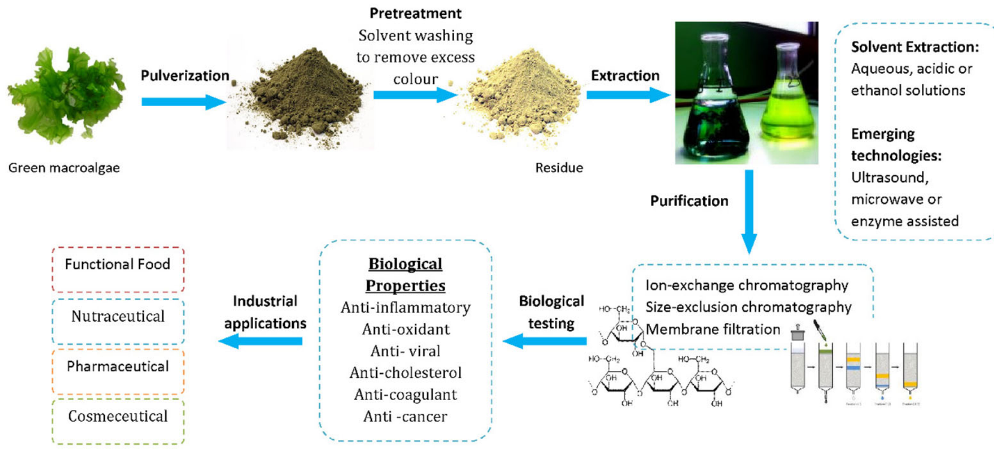

Figure 1. Systematic diagram of polysaccharide extraction and purification from macroalgae.

2015). They can recognize and bind to specific polysaccharides and are involved in crucial biological processes like intercellular communication (Chojnacka et al. 2012; Kim and Mendis 2006). Furthermore, these components from seaweeds have been documented to exert various biological properties including mitogenic, cytotoxic, antibiotic, antinociceptive, anti-inflammatory, anti-HIV, anti-adhesion, anti-HIV and inhibition of human platelet aggregation (de Queiroz et al. 2015; Fontenelle et al. 2018; Harnedy and FitzGerald 2013; Wu and Bao 2013). Teixeira et al. (2007) have reported on the ability of seaweed lectins to inhibit bacterial binding *in-vitro,* which is key characteristics for prevention of tooth decay.

Bioactive peptides are comprised of 3–20 amino acid residues and their pharmacological properties are primarily based on number and sequence of amino acids (Kim and Wijesekara 2010; Lordan, Ross, and Stanton 2011). Seaweed peptides are documented to display several pharmacological properties *in-vitro* including such as antioxidant, antimicrobial, anticancer, anti-hypertension, immunomodulatory and antithrombotic, besides its to nutrient utilization (Admassu et al. 2018; Admassu et al. 2015; Elias, Kellerby, and Decker 2008; Kim and Wijesekara 2010; Syed and Mehta 2018). Admassu et al. (2018) have reported on the *in-vitro* inhibitory potential of two novel bioactive peptides extracted from the red seaweed (*Porphyra* spp), against the key enzyme, α-amylase, involved in the pathology of diabetes. *Gracilariopsis lemaneiformis*, a red algae, is the main cultured seaweed in China, with commercial potentials. In 2017, Cao et al. (2017)have isolated a hydrolyzed bioactive peptide with high angiotensin-I-converting enzyme inhibitory effects from *G. lemaneiformis.*

The protein digestibility and amino acid profile are the two main factors determines the nutritive value of proteins. Besides, a protein with an excellent amino acid profile and low digestibility will have a reasonable nutritional value (Cheung et al. 2015; Fleurence, Morançais, and Dumay 2018). Reports have demonstrated that seaweed proteins have a significant capacity of in vitro digestibility (Galland-Irmouli et al. 1999; Marrion et al. 2005; Wong and Cheung 2001a; Wong and Cheung 2001b; Wu et al., 2020).

Lipids and polyunsaturated acids (PUFAs). The major class of lipids present in marine algae are phospholipids and glycolipids, representing 1-5% of cell composition, and thus are known as low-energy food (Chojnacka et al. 2012). As seaweeds can accumulate PUFAs at a lower environmental temperature, species found in cold regions has superior PUFAs content than species living in moderate or high temperatures (Holdt and Kraan 2011; Wall et al. 2010). Despite of the lower lipid content, PUFAs account for a significant part of the lipid content, with majority of it occurring in the form of omega-3 (ω-3) and omega-6 fatty acids (ω-6), for example arachidonic (AA) and eicosapentaenoic (EPA) acid, respectively (Lordan, Ross, and Stanton 2011; Plaza et al. 2009). The most noteworthy aspect of the lipid composition of seaweeds is the balance between the ω-3 and ω-6 fatty acids, which may improve their effectiveness as a nutritional supplement or as part of a stable diet (Bhattacharjee and Islam 2014; Dawczynski, Schubert, and Jahreis 2007). The recommended ratio of n-6/n-3 by world health organization for food to potentially lower risk of neurological, inflammatory, and cardiovascular diseases is below 10, while the European Nutritional Societies recommend an n-6/n-3 ratio of 5 (Tanna and Mishra 2019). A number of edible seaweeds have been reported to be nutritious, with an n6/n3 ratio within the recommended range (Dawczynski, Schubert, and Jahreis 2007; Fernandes et al. 2018; Schmid et al. 2018).

Red and brown seaweeds are predominantly rich in the ω-3 and ω-6 fatty acids including EPA, AA and α- linolenic acid, along with fairly high concentration of oleic and palmitic acids (Dawczynski, Schubert, and Jahreis 2007). In brown seaweeds, up to 5% of the lipid content is fucoxanthin and this lipid has been reported to exhibit anti-obesity effects and improve insulin resistance and decrease blood glucose level in vitro and in experimental animal models (Maeda et al. 2009; Maeda et al. 2005).

PUFAs are vital components of cell membranes and precursors of eicosanoids which regulate a range set of homeostatic and inflammatory processes (Dennis and Norris 2015). PUFAs are recognized to regulate a number of functions in the body including blood clotting, blood pressure, and the complete development and function of the brain and nervous system (Calder 2006; Wall et al. 2010). These bioactive compounds can effectively decrease the risk of attaining cardiovascular diseases, cancer, osteoporosis and diabetes (Mišurcová, Machů, and Orsavová 2011). Lipid extracts from the blue-green algae *Nostoc commune*, which is being used as a food delicacy as well as herbal medicine in many countries, has been documented to treat various medical conditions including antiviral and anticancer, burns and chronic fatigue (Rasmussen et al. 2008).

Commercially available PUFAs with reported therapeutic effects of specific attention are EPA, docosahexaenoic acid, palmitoleic acid, oleic acid, and linolenic acid and palmitic acid (Plaza et al. 2009; Stengel, Connan, and Popper 2011). Fish is one of the major commercial sources of ω-3 PUFAs, but they are not preferred due to unpleasant taste, fishy odor, and oxidative non-stability. Therefore, to cater the rising demand for food products with high PUFAs content, controlled batch culture of marine microalgae, especially *Thraustochytrium* and *Schizochytrium* strain, are being carried out to produce PUFAs (Mišurcová, Machů, and Orsavová 2011).

Pigments. Seaweeds are composed of three type of pigments namely (I) carotenoids, (ii) chlorophylls and (iii) phycobiliproteins with numerous applications in food and pharmaceutical industries. As bio-actives, these pigments are of great interest as they are known to exert therapeutic effects such as immune-modulatory, anti-cancer anti-diabetic, anti-angiogenic, anti-obesity, antioxidant, anti-inflammatory, and neuroprotective (Ganesan et al. 2011; Ina et al. 2007; Manivasagan et al. 2018; Pangestuti and Kim 2011) and sensorial properties (as food colorants) in food industry (Aryee, Agyei, and Akanbi 2018).

Carotenoids are naturally occurring pigments, belonging to tetraterpenoids group, with linear C40 molecular backbone (Boominathan and Mahesh 2015) and are regarded as accessory pigments. Carotenoids boost the light-harvesting properties of algae by passing on light excitation to chlorophyll (Aryee, Agyei, and Akanbi 2018; Larkum and Kühl 2005). Carotenoids can be broadly classified into carotenes (e.g. β-carotene and α-carotene), and xanthophylls (fucoxanthin, violaxanthin, astaxanthin, zeaxanthin, lutein and neoxanthin) (Figure 2) (Manivasagan et al. 2018; Miyashita and Hosokawa 2018; Pangestuti and Kim 2011). Carotenoids are documented to be effective antioxidants (Li and Kim 2011). Fucoxanthin are major carotenoids in seaweeds that contribute more than 10% of total carotenoid production in the marine ecosystem (Boominathan and Mahesh 2015). Several in vitro and *in-vivo* studies have highlighted on the effect of fucoxanthin and fucoxanthinol (decetylated derivative of fucoxanthin) as anti-cancer agents and are well known for other several health-benefits (Kumar, Hosokawa, and Miyashita 2013; Lopes-Costa et al. 2017; Mei et al. 2017; Satomi 2017; Takahashi et al. 2015). Fucoxanthin can be extracted from brown seaweeds such as *Undaria pinnatifida, Cladosiphon okamuranus, Hizikia fusiformis, Sargassum fulvellum* and several species of the genus *Ecklonia* and *Ascophyllum*. Similarly, other carotenoids have been documented for their anti-cancer effects. A study conducted in group of patients consuming a diet supplemented with carotenoids, including α-carotene and lycopene, has showed lowered lung cancer risk (Michaud et al. 2000).

Phycobiliproteins are another group of pigments with deep-colored and fluorescent water-soluble nature, are commonly presented in red algae, cyanobacteria and cryptomonads. There are three type of commercially important phycobiliproteins based on its color characteristics such as red algal pigment or phycoerythrin, blue pigment or phycocyanin and light blue pigment or allophycocyanin. Concisely, the phycobiliproteins are high-value pigments which are used in health foods as a potential nontoxic and non-carcinogenic natural colorants (C-phycocyanin), in the cosmetic industry (C-phycocyanin and R-phycoerythrin), in the biomedical research as a fluorescent marker (Christaki et al. 2016; Manirafasha et al. 2016).

Phenolic compounds. Phenolic compounds or polyphenols are found at a high level in algae, in particular, in those with potent antioxidant properties and other pharmacological properties. Among the polyphenols, phlorotannins have received much attention as functional food ingredients. Phlorotannins are tannin compounds formed by polymerization of phloroglucinol (1,3,5-trihydroxybenzene) units (Figure 2) via the acetate-malonate pathway. They are predominantly detected in brown algae (Catarino et al. 2019; Jormalainen and Honkanen 2004; Koivikko et al. 2007; Peng et al. 2015) and are secreted in the cell wall where they form complexes with different components such as alginic acid. Phlorotannins are vital for the physiological integrity of alga and are involved in several important secondary roles both at the cellular and organismal level (Generalić Mekinić et al. 2019; Li et al. 2017b). Phlorotannin composition in brown algae ranges between 1 to 10% of the dry weight (Admassu et al. 2015). The molecular weight of phlorotannins varies from low to high (molecular size up to 650 kDa), comprised of phenyl and phenoxy units. Based on the linkages, phlorotannins are grouped into fucols (phenly linkage), fuhalols and pholorethols (ether linkage), fucophloroethols (ether and phenyl linkage), and eckols (dibenzodioxin linkage). Fuhalols differ from phlorethols by the presence of additional hydroxyl groups. Some of the phlorotannins isolated from marine brown algae are phloroglucinol, eckol, fucodiphloroethol G, phlorofucofuroeckol A, 7-phloroeckol, dieckol, 6,6′-bieckol, 2,7-phloroglucinol-6,6-bieckol and pyrogallol-phloroglucinol-6,6-bieckol (Figure 3) (Li et al. 2011; Oh et al. 2018; Son et al. 2019).

The phlorotannins are highly hydrophilic in nature, with antioxidant, anti-inflammatory, anti-diabetic, anti-tumor, anti-hypertensive, anti-viral and anti-allergic activities (Barbosa et al. 2019; Besednova et al. 2019; Kannan et al. 2013; Ngo et al. 2011; Oh et al. 2018; Rengasamy et al. 2013; Rengasamy et al. 2014a; Rengasamy et al. 2014b; Sathya et al. 2017; Thomas and Kim 2011). The ability of phlorotannins to exhibit protective effects against hyper-glycaemia, hyper-lipidaemia, inflammation and oxidative stress makes them attractive candidates for developing functional food products, to reduce the risk of cardiovascular diseases and

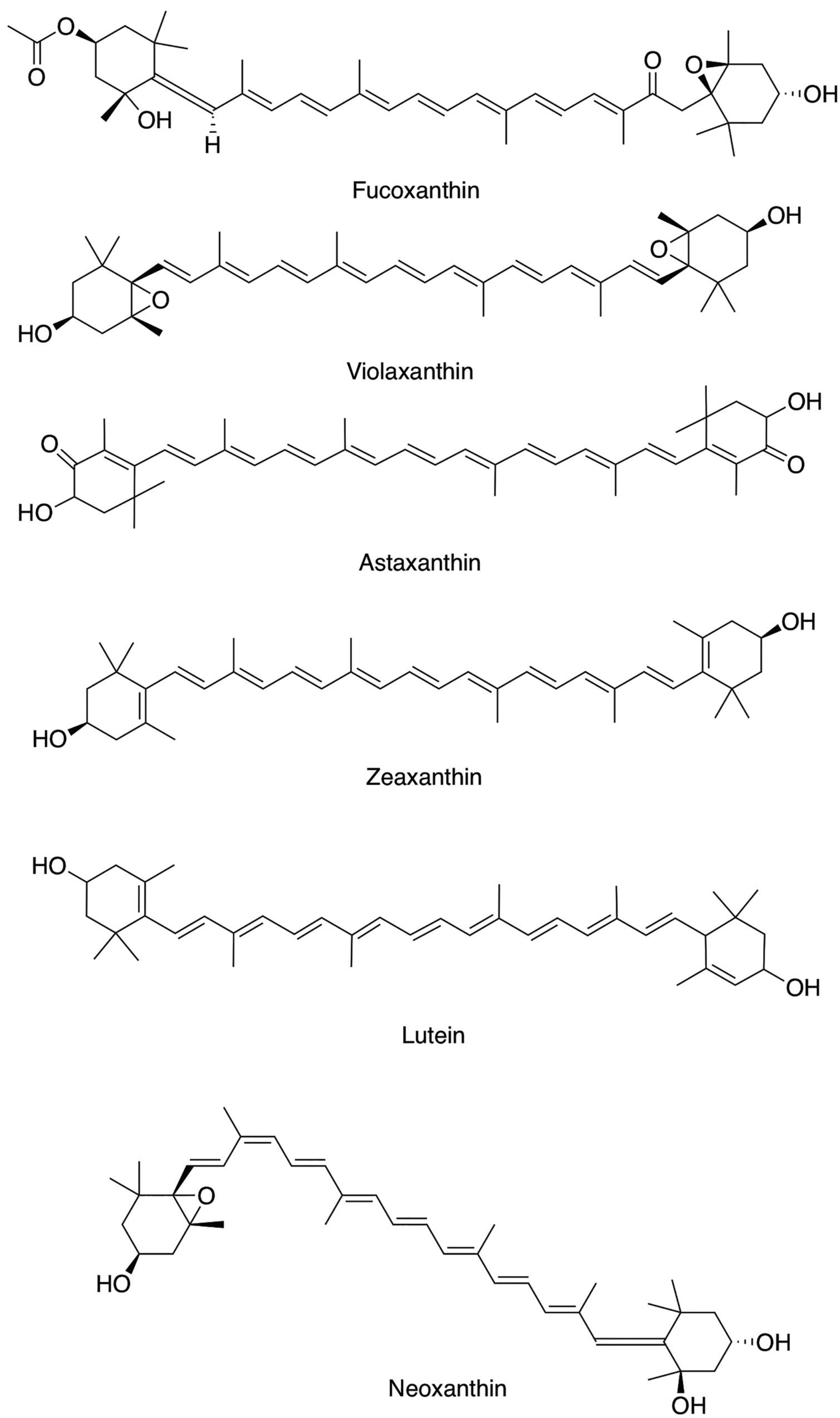

Figure 2. Chemical structure of some carotenoids in marine organisms.

type 2 diabetes (Murray et al. 2018a; Murray et al. 2018b). In human clinical trials, daily supplementation with *U. pinnatifida* and *Sacchariza polyschides* (as Gigantea bulbosa) was found to balance blood glucose levels, reduce serum triglyceride levels, and increase high-density lipoprotein cholesterol in patients with type 2 diabetes (Kim et al. 2008). Lee and Jeon, (Lee and Jeon 2015) have extracted antioxidant-rich phlorotannins from *Ecklonia cava* and administered the extract (1500 mg/day) to 80 pre-diabetic adults (aged 20–65). After three months, a significant

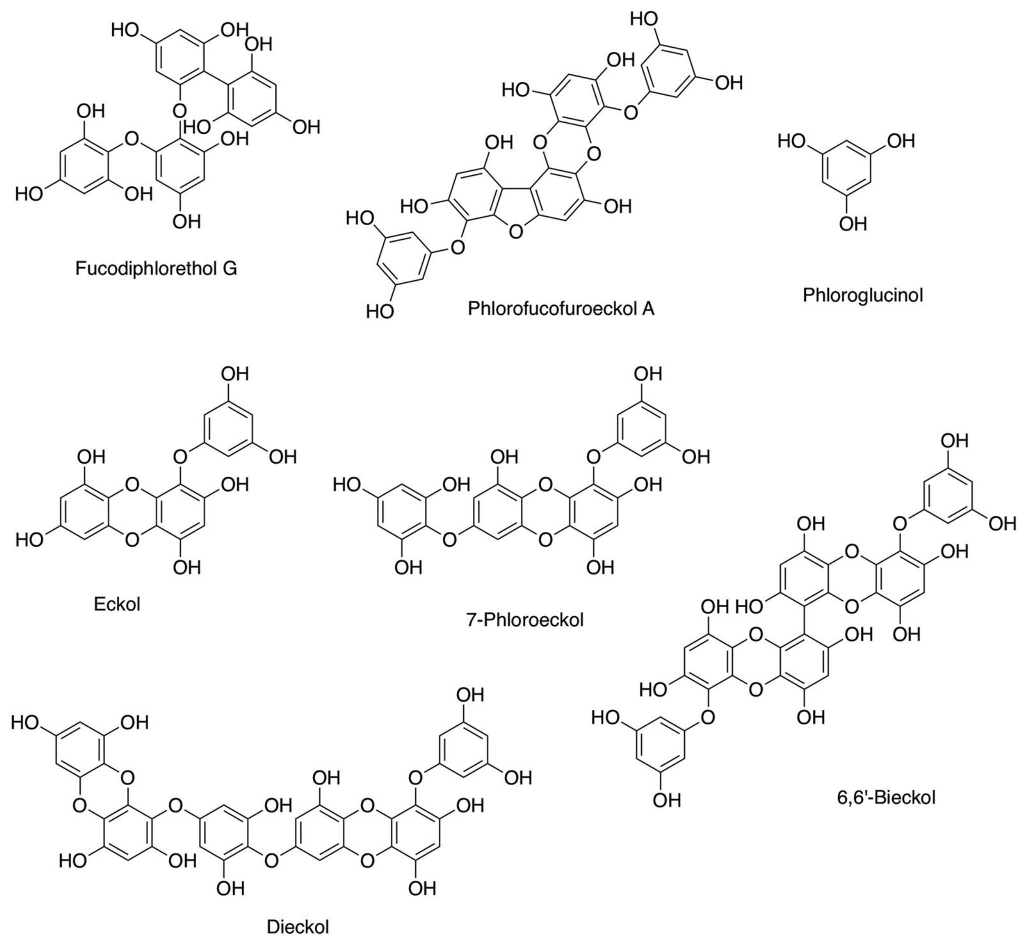

Figure 3. Chemical structure of phlorotannins isolated from marine brown algae.

reduction in postprandial glucose levels was noted in the phlorotannin extract group. It was postulated that the anti-diabetic effect was ascribed to the phlorotannin-rich (46%) extract, and the high content of the phlorotannin dieckol (10%).

Potential applications and future prospects

The seaweed industry is a multi-billion venture, owing to the myriad of high value-added ingredients or food products that can be harnessed from it, including hydrocolloids and food-grade pigments. In 2016, the global seaweed market amounted to $10.57 million and it is expected to reach approximately $26.1 million by 2025 (Transparent Market Research 2017). China and Indonesia are recognized as the main seaweed producers, with over 23 million tonnes of production in 2014 (Buschmann et al. 2017). Seaweeds are extensively used as nutritional health supplements, prebiotics cosmetics, plant growth regulators, thickening and gelling agent. The selection of seaweed for commercial uses mainly depends on the edible seaweed farming and hydrocolloid production; the most widely exploited seaweeds are *Eucheuma spp.* and *Kappaphycus alvarezii* for hydrocolloids and *Gracilaria* spp. for production of agar (Nayar and Bott 2014).

Seaweeds are sources of unique and therapeutically active molecules/nutrients essential for human nutrition. They are rich in dietary minerals (sodium, potassium and iodine), fibers and polyphenolic compounds and thus supplementing food with seaweeds or their extracts are of particular interest. There are various commercially available products which contain marine algae as their main ingredients (Table 2). Hana tsunomata is one of most popular products, which is be suitable for vegetarian and also recommended as macrobiotic diet. The high essential minerals content, free from gluten and low calorie makes Hana tsunomata a very good commercial product all over the world. Several algae-derived astaxanthin products are also commercially available (Tanna and Mishra 2019). Meat and meat products are an excellent source of dietary proteins and vitamins, but they have a low fibers content, which pave new avenue for seaweed industry to produce seaweed incorporated or seaweed fortified meat products in the commercial market. The supplementation of meat or meat products with seaweeds also help to overcome the technical problem linked with relatively low-salt meat products (Cofrades et al. 2017). Pasta and bakery products incorporating seaweeds have been developed (Kadam and Prabhasankar 2010; Prabhasankar et al. 2009). Soluble polysaccharides from seaweeds also have great potentials as dietary fiber for human nutrition and as prebiotics compounds (Chojnacka et al. 2012). For instance, the pasta supplemented with 10–20% of the Japanese edible seaweed wakame (*U. pinnatifida*) has not only received sensorial acceptance but has also resulted in a product with superior essential amino acid and PUFA content, strong antioxidant property, and relatively high fucosterol and fucoxanthin content (Prabhasankar et al. 2009).

Incorporation of seaweeds into human nutrition can be anticipated by an indirect way. The benefits, such as improved health and shelf life, nutritional compositions and shelf life, of feeding animals usually consumed by human, with diet supplemented seaweeds have been often described. Thus, seaweed supplemented diet for farmed animal can be easily included in the human food value chain (Fleurence et al. 2012; Michalak and Chojnacka 2018). Although, several studies have demonstrated health-benefits of seaweed based food products, low consumer awareness about health benefits of seaweeds, possible contamination of seaweeds with heavy metals, the fishy odor and sensory characteristics remain a challenge that need to overcome to make the product successful and sustain in the market (Roohinejad et al. 2017).

Sea cucumber

The marine invertebrate sea cucumbers also called as holothurians belongs to the class Holothuroidea (Echinodermata) and about 6000 species are available globally (El Barky et al. 2016). They have elongated tubular or flattened soft-body containing a single branched gonad, typically with leathery skin and many of them indeed look like a soft-bodied cucumber. Generally, they are considered essential parts of the marine ecosystem, distributed globally, in the tropical oceans, from the intertidal to the deep sea (Aminin et al. 2015; Mondol et al. 2017; Pangestuti and Arifin 2018).

Sea cucumbers are commonly known as 'trepang' in Indonesian; "bêche-de-mer" in French term which means marine food product and "balate" in Chamorro. In Asian and Middle East countries, sea cucumbers are widely used as food and in the traditional medicines. Sea cucumbers are the most commercially exploited species around the world, (52 and 36), particularly in Asia and Pacific regions, certainly due to known mega biodiversity in these areas (Bordbar, Anwar, and Saari 2011; Toral-Granda, Lovatelli, and Vasconcellos 2008). Indonesia is known as one of the oldest and top most sea cucumber exporting country in the world (Purwati 2005). However, there is a scarcity of information available on the chemical, pharmacological and diversity of the commercially important species. Besides, several sea cucumber species were marked without a clear taxonomic information especially in remote regions (Bordbar, Anwar, and Saari 2011; Toral-Granda, Lovatelli, and Vasconcellos 2008).

Commercially, the dried cucumbers are generally graded into low to high economic value depending on numerous factors such as species, appearance, abundance, color (such as red, green and black), odor, body wall thickness, and demands in the commercial market (Wen, Hu, and Fan 2010). The color variation influences the taste of the sea cucumber products, and eventually, the market price. Red sea cucumber is more pricey than the green or black one (Oh et al. 2018).

Food value and nutritional value

The edible sea cucumbers are regarded a culinary delicacy in many countries. Sea cucumbers are considered important dietary nutritional source for more than one billion consumers in Asian continent. Annually, around 10,000 tonnes of dried sea cucumber is traded worldwide, which roughly correspond to 200 million animals harvested from the marine ecosystems annually (Purcell et al. 2016).

As a food commodity, sea cucumbers are valued for their nutritional content. It possesses essential nutrients such as high protein content, vitamins (A, B_1, B_2 and B_3) and essential micro and macro elements required for health physiological functions (Bordbar, Anwar, and Saari 2011; Chen 2003; Kiew and Don 2012; Shi et al. 2016; Wen, Hu, and Fan 2010). The nutritional content of sea cucumbers varies greatly depending on the availability of species, variations in seasons and feeding regimes. Salarzadeh et al. (2012) reported that the proximate compositions of two fresh sea cucumbers (*H. parva* and *H. Arenicola*) harvested from Bandar-e-Lengeh coast of South Iran varies greatly; water (82–92.6%), carbohydrates (0–2.2%) protein content (2.5–13.8%), fat (0.1–0.9%) and ash (1.5–4:35%). Wensy and Rodrígeuz (Wensy and Adriana, 2016) have studied the nutritional content of *Isostichopus* sp. harvested during different seasons, and the results revealed that there were significant differences in the protein (2.74–6.63%), lipids (0.07–0.35%) and ash (3.16–3.81%) content. According to Chen (2003), a completely dried sea cucumber may have high protein content up to 83% and is commercialized as a nutritional supplement as tablet or capsules.

Sea cucumbers have also been documented to contain a considerable amount of valuable amino acids in almost all species identified. Several amino acids such as glutamic, glycine, aspartic leucine, histidine, lysine, threonine, arginine, valine and isoleucine have been identified in the studied species (Haider et al. 2015; Liu, Su, and Zeng 2011; Widianingsih et al. 2016; Zhong, Khan, and Shahidi 2007). Wen, Hu, and Fan (2010) reported that glycine (ca. 5.57–12.5 g/100 g WW) was the predominant amino acid in investigated eight species. It was also noted that the studied species exhibited minimum lysine: arginine ratio, along with maximum essential amino acid scores attributable to the occurrence of a substantial quantity of threonine, phenylalanine and tyrosine. A low lysine: arginine ratio is associated with lowered cholesterol level in the serum and aorta by exerting hypocholesterolemic effects (Rajamohan and Kurup 1997; Vallabha et al. 2016; Wen, Hu, and Fan 2010).

The fatty acid profile of sea cucumbers has also been portrayed. Fredalina et al. (Fredalina et al. 1999) have stated that fatty acids play a crucial role in tissue repair of sea cucumber. The fatty acid profile of lipid fractions extracted from *Stichopus chloronotus* using different solvent systems varied significantly and the major fatty acids were myristic (C14:0), palmitic (C16:0), stearic (C18:0), linoleic (C18:2), arachidic (C20:0), eicosapentaenoic (C20:5, EPA) and docosahexaenoic acid (C22:6, DHA) (Fredalina et al. 1999). In another work, arachidonic and eicosapentaenoic acids were observed as the main polyunsaturated fatty acids in the sea cucumber *Athyonidium chilensis* which make this species a valuable food for human consumption when considering its fatty acid contents (Careaga, Muniain, and Maier 2011).

High-value bio-actives and therapeutics

The olden Chinese medical records reveal that parts of sea cucumbers harbored the similar medicinal attributes as the herb ginseng and this is most likely why the popular Chinese name for sea cucumber is "haishen", which means "ginseng of the sea" (Bordbar, Anwar, and Saari 2011). Functional ingredients derived from holothurians have become promising components for developing new foods with health benefits, as well as biomedicine products. The main edible and medicinal parts of sea cucumber is the body walls, and it consists mainly of collagen and mucopolysaccharides. Besides, the body wall is rich in other bioactive compounds such as saponins, cerebrosides, gangliosides, peptides, polyunsaturated fatty acids, and chondroitin sulfates (Li et al. 2018; Sroyraya et al. 2017). The therapeutic effects of sea cucumbers-derived compounds are summarized in Table 4.

Triterpene glycosides or saponins. Triterpene glycosides also referred to as holothurins or sea cucumber saponins, are the major and most interesting bioactive metabolites in sea cucumbers that seem to defend them chemically. The glycosides of sea cucumber are amphiphilic in nature and have two moieties: aglycone (lipid-soluble) and glycone (water-soluble), both are vital for biological functions of the glycosides. Based on the presence of (18,20)-lactone in the triterpene structure, the sea cucumber glycosides grouped in two categories namely holostane and non-holostane (Figure 4). The sugar moieties mainly consisting of D-xylose, 3-*O*-methyl-D-xylose, D-glucose, 3-*O*-methyl-D-glucose, and D-quinovose (Figure 5) (Khotimchenko 2018; Mondol et al. 2017).

The most common biological property of sea cucumber glycosides is cytotoxicity which makes them one of the most investigated anticancer agents. To date, more than 300 triterpene glycosides with prominent pharmacological properties, have been identified from a range of sea cucumber species (Chludil et al. 2002; Khotimchenko 2018; Mondol et al. 2017). The triterpene glycosides, Argusides A-E isolated from *Bohadschia argus,* have exerted high in vitro cytotoxicity against several human tumor cell lines (Liu et al. 2008a; Liu et al. 2007). Han et al. (2010) reported the triterpene glycosides, pentactasides I-III, as well as philinopsides A -B, isolated from *Pentacta quadrangularis* elicited remarkable in vitro cytotoxicity effect against six different tumor cell lines (P-388, A-549, MCF-7, MKN-28, HCT-116, and U87MG) with an IC_{50} value ranging from 0.60 to 3.95 µM. Frondoside A, a triterpene glycoside isolated from the orange-footed sea cucumber, *Cucumaria frondosa*, has demonstrated anticancer effects in several models including pancreatic ductal adenocarcinoma, colon, prostate, cervix and bladder cancer cells (Adrian and Collin 2018). This glycoside is reported to exhibit anti-cancer activities through different mechanism of actions, including induction of cellular apoptosis, inhibition of cancer cell growth, migration, formation of metastases, invasion and angiogenesis (Adrian and Collin 2018; Al Shemaili et al. 2014; Attoub et al. 2013; Ma et al. 2012). The triterpene glycosides, fuscocinerosides A-C, pervicoside C and holothurin A isolated from the sea cucumber *Holothuria fuscocinerea* were observed to display significant cytotoxic effect on human leukemia HL-60 and human hepatoma BEL-7402 cells (Zhang, Yi, and Tang 2006). Three sulfated triterpene glycosides namely violaceusides I, II, and III isolated from the sea cucumber, *Pseudocolochirus violaceus,* have displayed noteworthy *in-vitro* cytotoxicity activity against stomach adenocarcinoma MKN-45 and CT-116 cells (Zhang, Yi, and Tang 2006). Although the detailed mechanism(s) of the anticancer activities of many triterpene glycosides remain largely unclear, based on the pieces of evidence, sea cucumber can potentially be used as a functional food to prevent cancer.

Holothurins have prominent biological activity against clinically important pathogens. Kumar et al. (2007), reported the antifungal activity of a novel triterpene gylcoside (the structure was elucidated as 3-*O*-β-D-xylopyranosyl-16β-acetoxyholost-7-ene), along two known glycosides holothurin A-B, isolated from *Actinopyga lecanora*. Holothurin B has shown antifungal activity against all the 20 fungal strains and was found to be more potent against *Trychophyton mentagrophytes* and *Sporothrix schenckii*, with a MIC value of 1.56 μg/ml. In another activity guided research by Han et al. (2009), the triterpene glycosides, scabraside A, echinoside A and holothurin A from *Holothuria scabra* were found to display antifungal properties. Maier et al. (2001) reported that the tri-sulfated triterpene glycosides, liouvillosides A-B, derived from the Antarctic sea cucumber, *Staurocucumis liouvillei*, have exerted remarkable antiviral activity against herpes simplex virus type 1 (HSV-1) at concentrations below 10 μg/mL. It is well documented that various bioactive metabolites including triterpene glycosides isolated from sea cucumbers could be an interesting reservoirs antifungal and antiviral compounds (Careaga, Muniain, and Maier 2011; Murray et al. 2002; Wang et al. 2012).

Polysaccharides. The most edible part of the sea cucumber is body wall which is composed of glycosaminoglycans fucosylated chondroitin sulfates (FCS) and sulfated fucans (Panagos et al. 2014; Ustyuzhanina et al. 2017). These sulfated polysaccharides are gaining much attention since they have been well documented for their anticancer, anticoagulant, anti-inflammatory, antithrombotic, antiviral and neuroprotective effects (Cui et al. 2016; Li et al. 2018; Tapon-Bretaudière et al. 2000; Zhou, Xu, and Shen 2008).

FCS of Holothuria are biopolymers, with structural characteristics similar to mammalian chondroitin sulfates, except the presence of unusual sulfated fucosyl branch *O*-linking to its carbon-3 in the region of the uronic acid residue (Myron, Siddiquee, and Al Azad 2014). The therapeutic effects of FCS principally depend on the degree of sulfation and position of sulfate in these branches, as well as on the distribution of branches along the polysaccharide backbone (Ustyuzhanina et al. 2017). Sulfated fucans usually possess

Table 4. Bioactive compounds of sea cucumbers and health functions.

Biological activities	Species	Experimental details	Bioactive compounds
Anti-viral	*Cucumaria frondosa*	*In-vitro*: EC_{50}=7.2–15.2 μg/mL	Enzymatic hydrolysates (Tripoteau et al. 2015)
Anti-obesity	*Pearsonothuria graeffei*	*In-vitro*: IC_{50} = 2.86 μg/mL In C57/BL6 mice 0.1 % of extract has reduced body weight, serum total cholesterol, thyroglobulin, low density lipoproteins and, liver total cholesterol and thyroglobulin	Saponin-enriched extract (Guo et al. 2016)
Antioxidant	*Apostichopus japonicus*	*In-vitro*: 0.5 mg/mL of FCS has inhibited DPPH radicals (39.63 %) and hydroxyl radicals (24.6 %)	Fucosylated chondroitin sulfate (Mou et al. 2018)
	Stichopus chloronotus	*In-vitro*: 0.5 mg/mL of FCS has inhibited DPPH radicals (35.33 %) and hydroxyl radicals (30 %)	Fucosylated chondroitin sulfate (Mou et al. 2018)
	Acaudina molpadioidea	1. 4 mg/mL of FCS has inhibited DPPH radicals (65.9 %), nitric oxide radicals (39.3 %) and lipid peroxides (39.3 %) 2. 400 µg/mL of cerebrosides has augmented superoxide dismutase activity by 79% in PC12 cells.	Fucosylated chondroitin sulfate (Mou et al. 2018; Scalbert, Johnson, and Saltmarsh 2005; Zou et al. 2016); cerebrosides (Wu et al. 2013)
	Holothuria nobilis	0.5 mg/mL of FCS has inhibited DPPH radicals (39.63 %) and hydroxyl radicals (24.6 %) *in-vitro*	Fucosylated chondroitin sulfate (Zou et al. 2016)
Anti-diabetic	*Acaudina molpadioides*	FCS has significantly reduced body weight, adipose tissue weight, and fasting blood glucose and serum insulin levels in experimental animal models. FCS treatment have enhanced glucose metabolism by regulating metabolic enzymes and upregulating the PI3K/PKB/GSK-3β signaling pathway mediated by insulin at the transcriptional level	Fucosylated chondroitin sulfate (Hu et al. 2014)
	Stichopus japonicas	IC_{50} = 4.45 and 14.87 μM for 1,3-Dipalmitolein and cis-9-octadecenoic acid, respectively	Fatty acids (Nguyen and Kim 2015)
	Holothuria thomasi	The extract has significantly inhibited α-amylase activity and lowered serum glucose, adiponectin, IL-6, TNF-α levels and liver L-MDA. Significant increase in serum insulin and liver glycogen levels as compared with the control groups were noted. The saponin extract has proved to decrease the degenerative change in β-cells.	Saponin extract (El Barky et al. 2016)
Anticoagulant	*Apostichopus japonicas*	Activated partial thromboplastin time (APTT) clotting assay. 13.30 and 2.20 µg/mL of SF and FCS have prolonged APPT, as compared to herparin (1.20 µg/mL)	Sulfated fucan and fucosylated chondroitin sulfate (Luo et al. 2013)
	Holothuria edulis	18.71 and 2.86 µg/mL of SF and FCS have prolonged APPT, as compared to herparin (1.20 µg/mL)	Sulfated fucan and fucosylated chondroitin sulfate (Luo et al. 2013)
	Holothuria nobilis	26.59 and 4.33 µg/mL of SF and FCS have prolonged APPT, as compared to herparin (1.20 µg/mL)	Sulfated fucan and fucosylated chondroitin sulfate (Luo et al. 2013)
	Isostichopus badionotus	APPT and TT (thrombin time) clotting assay: FS = 9 IU/mg (APTT) and 6 IU/mg (TT) FCS = 150 IU/mg (APTT) and 157 IU/mg in (TT) standard heparin= 150 IU/mg (APTT) and 150 IU/ mg (TT)	Sulfated fucan and Fucosylated chondroitin sulfate (Chen et al. 2012)
Anti -inflammatory	*Apostichopus japonicus*	Treatment with FCS (5–100 mg/kg) inhibited paw edema in carrageenan-induced inflammation model (31 – 48. 8 %)	Fucosylated chondroitin sulfate (Mou et al. 2018); Polysaccharides (Liu, Sun, et al. 2012)
	Stichopus japonicus	Suppressed NO release without cytotoxicity and levels of IL-6 and TNF-α mRNA in LPS-stimulated RAW 264.7 murine macrophages (IC_{50}= 48.48 μg/mL)	Aqueous extract (Song et al. 2013)
Anti-cancer	*Cucumaria frondosa*	LMWF induced p53/p21 cell cycle arrest, caspase-3 apoptosis, VEGF-mediated angiogenesis, and inhibited metastasis in mouse Lewis lung carcinoma	Low-Molecular-Weight Fucosylated Chondroitin Sulfate (Liu et al. 2016)
	Holothuria leucospilata	Treatment with saponin, dacarbazine, and combination of saponin-dacarbazine have inhibited proliferation of resistant B16F10 melanoma cells 10, 1400 and 4 + 1200 *µg/ml*, respectively	Saponin (Baharara et al. 2016)

(*continued*)

Table 4. Continued.

Biological activities	Species	Experimental details	Bioactive compounds
	Holothuria parva	Treatment with sub-fraction C1 (250 − 1000 μg/mL) and (Z)-2,3-diphenylacrylonitrile (10 − 40 μg/mL) have augmented ROS generation, stimulated collapse on the mitochondrial membrane potential, swelling in mitochondria and cytochrome c release on hepatocellular carcinoma liver mitochondria	Methanolic fraction and (Z)-2,3-diphenylacrylonitrile (Amidi et al. 2017)
Neuroprotective	*Stichopus variegatus*	EC_{50} = 5.18 μg/ml -Has promoted the proliferation of spinal astrocytes	Water extract (Patar et al. 2012)
	Cucumaria frondosa	• Pre-treatment with EPA-enriched PL (10 and 40 μg/mL for 24 h) has improved survival of H_2O_2 or t-BHP damaged PC12 cells • Improved the learning and memory deficits in SAMP8 mice	Eicosapentaenoic acid-enriched phospholipids (Wu et al. 2014)
	Stichopus japonicus	SP (400-500 μg/ml) has attenuated 6-OHDA-induced SH-SY5Y cell death, reversed morphological damage and suppressed ROS generation through inhibition of MAPK and NF-κB and activation of PI3K/Akt signaling pathways	Sulfated polysaccharide (Cui et al. 2016)
Anti-fatigue	*Stichopus japonicus*	Exhaustive swimming test: Rats treated with the peptide showed increased endurance capacity as compared to control group (P < 0.05)	Peptide (Ye et al. 2017)

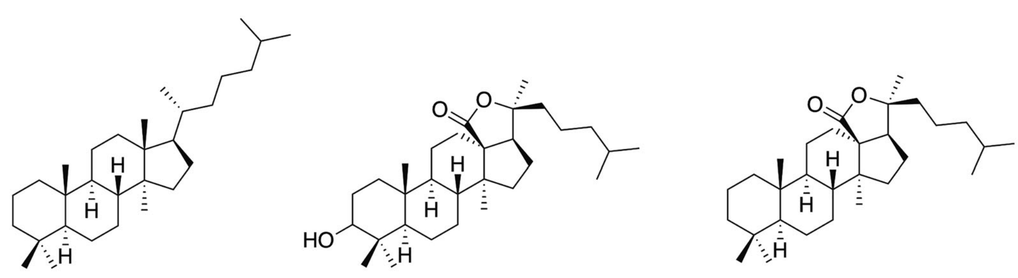

Figure 4. Chemical structure of lanostane, holostane (20S-dihydroxy-5_-lanostano-(18,20)-lactone) and holostanol (3β,20S-dihydroxy-5_-lanostano-(18,20)-lactone).

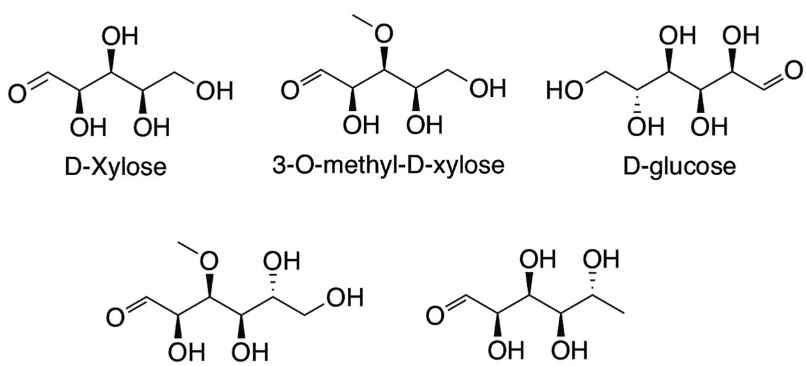

Figure 5. Common sugar moieties present in sea cucumber glycosides.

simple, unique structures of linear chains of L-fucose residues in a well-defined repetitive pattern. The biological properties of sulfated fucans depend on the structure of sulfation patterns. In contrast to the polysaccharides from marine algae, sulfated fucans from Holothurian are easily purified (Mourão 2015; Pomin and Mourão 2008; Ustyuzhanina et al. 2017).

People who suffer from arthritis and connective tissue disorders, often lack sulfated polysaccharides, mainly chondroitin sulfates. As such, holuthurian rich with chondroitin sulfate can be used as a functional food to ease joint pain and arthritis-like disorders (Imanari et al. 1999). It is reported that consumption of 3 g dried sea cucumber daily has an effect in reducing arthralgia considerably. The mechanism of action is considered to be similar to that of glucosamine sulfate, the main building block of chondroitin, which is useful for treating osteoarthritis (Chen et al. 2013; Ubani 2011). Mourao et al. (1998) suggested that fucosylated chondroitin is effective for preventing venous and arterial thrombosis, as it facilitates the proliferation of blood vessels.

Sulfated polysaccharides are also known to have promising antiviral properties; a holuthurian chondroitin sulfate has been patented in Japan for excellent HIV therapy (Chen et al. 2013). Masre et al. (2010) demonstrated that sulfated glycosaminoglycans isolated from *Stichopus hermanni* and *Stichopus vastus* had been found to accelerate the wound healing process in rats. Several authors have appraised the anticoagulant activities of FCS (Chen et al. 2011; Luo et al. 2013; Wu et al. 2012) and sulfated fucans (Chen et al. 2012; Wu et al. 2015).

Phenolic compounds. Sea cucumbers also reported to have considerable amounts of phenolics compounds with potential antioxidant activity. Mamelona et al. (2007) evaluated the total phenolics and total flavonoids contents, and antioxidant effect of various solvent extracts obtained from different part of *Cucumaria frondosa*. They noted that the phenols and flavonoid content varied greatly from 22.5 to 236.0 mg of gallic acid equivalents (GAE) and 2.9 to 59.8 mg of rutin equivalents per 100 g DW, respectively, depending on tissues and extracts involved. Of the tested extracts, the ethyl acetate extract prepared from digestive tract reported to have strong antioxidant activities. In another study, Esmat et al. (2013) reported that the extract of *Holothuria atra* body wall contained active phenolic compounds with antioxidant and chelating activities, which has possibly contributed to the significant hepatoprotective activity. Althunibat et al. (2009) reported that aqueous extract of *Holothuria leucospilota*, *Holothuria scabra* and *Stichopus chlorontus* contained relatively higher total phenolic contents (4.85–9.70 mg GAE/g DW) as compared to the solvent extracts (1.53–2.90 mg GAE/g DW) and have exhibited high antioxidant activities.

Potential applications and future prospects

In past decades, the commercial importance of sea cucumbers has bloomed in the invertebrate fishery, driven by a surge in demand worldwide. The growing international demand for "bêche-de-mer" has fueled the continuous processing, grading and sale of sea cucumbers in both dried and wet form. Up to now, China (Hong Kong and Guangzhou) and USA (New York) are dominating the sea cucumber marketing trade. Although sea cucumbers have been acknowledged as a reservoir of biologically active metabolites with pharmacological attributes, sea cucumber based functional food products is still in infancy stage and often considered as niche products (Pangestuti and Kim 2011).

While developing sea cucumber based functional foods, several factors such as the organoleptic property, bio-accessibility, bioavailability, and personally designed products, need to be considered. The organoleptic property, in particular, should be carefully assessed to ensure that sensory characteristics are aligned with consumers demand. In other hand, the oral bioavailability and bio-accessibility are two key factors which can be improved using micro-encapsulation and gastro-resistant tablets with well-equipped appropriate processing techniques.

Although it is expected to produce and promote sea cucumber as a health-based food product, there is growing concern that this organism is over-exploited. A decline in sea cucumber diversity from various coastal areas have been reported. Henceforth, it is imperative that once their therapeutic attributes and health benefits effects are evidenced, new aspects need to be address on the consumer interest and production, extraction and purification of active ingredients at a large scale (Kiew and Don 2012; Pangestuti and Kim 2011).

Fish and fish by-products

The fish industry represents a primary economic pillar for many countries globally. Over the fifty years, fish consumption underwent a major change; it is estimated that the intake per capita are higher than 20 kilograms, double the level of the 1960s. The global export of fish product was valued at $148 billion in 2014, up from $8 billion in 1976. China occupied topmost place among the world for exportation of fish and fishery by products. The global share of fish production destined for human consumption has increased considerably, from 67 per cent in the 1960s to 87 per cent, or more than 146 million tonnes, in 2014 (FAO 2016).

Growing demand for fish products for human consumption represents higher amount of fishery by-products are generated. It is reported that several million tonnes of fish and fishery by-products are dumped worldwide, as waste representing an economic loss and environmental problem. It has been estimated that more than 60% of fish tissues including fish heads, fins, viscera, trimmings and skin are dumped as they are considered "wastes" (Chalamaiah et al. 2012). The utilization of fish by-products represents a significant production opportunity for the fish industry, as it can potentially generate additional income as well as cut down disposal cost of these materials. The most common approach in utilizing fish-by products is by processing the unused fish parts into fishmeal, fish oil and fish protein hydrolysate (FPH) (Hosomi, Yoshida, and Fukunaga 2012). Fishmeal is the crude flour obtained after cooking, pressing, drying and milling fish or fish parts, while fish oil is a clear brown/yellow liquid extracted from whole fish, fish liver (mainly cod liver) and other fish by-products (FAO 2016). Generally, the chemical composition of fish oil varies widely between fish species, but also depends on the fish diets and the season in which the fish is caught (Butt and Salem 2016). Protein hydrolysates are fragments of peptides produced from the enzymatic conversion of proteins (da Rosa Zavareze et al. 2014).

Both randomized controlled clinical trials and observational studies have demonstrated that intake of diets composing of high fish content have showed cardio-protective effects in human. Based on these studies, the 2010 Dietary Guidelines for Americans have recommended the intake of two servings of seafood per week (4 oz per serving), to provide an average of 250 mg per day of long-chain omega-3 fatty acids, in persons with and without CVD

Nutritional value and functional ingredients

Fish and fish by-products are an important dietary constituent of several population groups, as it is a superior source of various nutrients which bring several benefits to the human organism. Fish provide high-quality protein, vitamins, minerals and essential fats (Al-Busaidi et al. 2015). Both observational and clinical intervention trials have demonstrated that intake of diets composing of high fish content is related to reduced risked of cardiovascular diseases (CVD) in human. Based on these studies, the 2010 Dietary Guidelines for Americans have recommended eating of at least two servings of seafood weekly (4 oz per serving), to provide an average of 250 mg per day of long-chain omega-3 fatty acids (EPA and DHA), in persons with and without CVD (Papanikolaou et al. 2014).

Globally, fish proteins are known to play a vital role in human nutrition and have been used as the key ingredient in processed seafood, for example, kamaboko (a kind of Japanese fish paste) and fish sausage (Hosomi, Yoshida, and Fukunaga 2012). Fish proteins possess a balanced amino acid composition and a high degree of digestibility. It is estimated that up to 10-20% (w/w) of total fish protein is found in its by-products. Several methods including acid and/or alkaline, enzymatic hydrolysis and autolysis are used to recover protein and peptides from fishery by-products (Zamora-Sillero, Gharsallaoui, and Prentice 2018). The enzymatic or chemical hydrolysis of fish wastes yields peptides called hydrolysates that contain 2 to 20 amino acids with desirable functional, biological and nutritional properties (Fernandes 2016).

Concerning human health, fish proteins are documented to influence lipid metabolism in human. Studies have shown that fish proteins have effectively reduced the serum cholesterol levels in animal models (Drotningsvik et al. 2018; Hosomi et al. 2011; Wergedahl et al. 2004). Hosomi et al. (2011) have reported that fish proteins reduce serum cholesterol content by hindering the cholesterol absorption and bile acid formation in experimental animals. Several prospective cohort studies have suggested that incorporating fish as a primary dietary source of protein, significantly reduces the incidence of cardiovascular diseases (Bernstein et al. 2010; Daviglus et al. 1997; Hu et al. 2002; Yuan et al. 2001). The dietary fish proteins also have other health beneficial effects such as antihypertensive (Girard et al. 2004; Jensen and Maehre 2016; Yahia et al. 2003), anti-obesity (Naqash and Nazeer 2011), antioxidant (Najafian and Babji 2012; Naqash and Nazeer 2011), and anti-cancer (Chakrabarti, Jahandideh, and Wu 2014; Nurdiani et al. 2017; Picot et al. 2006). Chakrabarti, Jahandideh, and Wu (2014) have reviewed the anti-inflammatory and antioxidants properties of foods derived from bioactive peptides, including those from fish hydrolysates. The composition, structure and hydrophobicity of peptides ascribe for their antioxidant properties. Amino acids such as tyrosine, tryptophan, methionine, lysine, cysteine, and histidine are examples that may act as antioxidants because they have aromatic residues that donate protons to free radicals (da Rosa Zavareze et al. 2014).

Fish oil is widely known to have higher amount of n-3 PUFAs such as EPA and DHA. Besides, clinically recommended level of fish oil (4 g/d of EPA and DHA) is reported to decrease high triglycerides content, which is essential for preventing cardiovascular diseases (Weitz et al. 2010). Fish oil has also been found to exert anti-inflammatory (Grimble et al., 2002), anti-depressive (Su 2009) and neuroprotective activities (Butt and Salem 2016; Denny Joseph 2013). Murphy et al. (Murphy et al. 2011) reported that supplementation of fish oil could increase chemotherapy efficacy in patients who have lung cancer.

Besides, being good source of collagen and gelatin, fish bones are an excellent source of calcium that can be used in food, feed or as supplements. Calcium phosphates such as hydroxyapatite present in fishbone can help rapid bone repair after major trauma or surgery. Fish also provides essential vitamins such as Vitamin A, B and minerals which include calcium, iodine, zinc, iron and selenium, among others (FAO 2016).

Potential application and future prospects

The functional properties of fish and fish products have attracted the attention of food biotechnologists, and a significant number of research has focused on evaluating possibilities to incorporate fish bioactive ingredients (such as peptides and fish oil) in human food. Fish protein hydrolysates possess water holding and oil immersion capacity, protein solubility, gelling activity, foaming and emulsification ability which make them suitable functional food ingredients (Chalamaiah et al. 2012; Chalamaiah et al. 2010; Nobile et al. 2016; Shaviklo 2015).

Fish protein powder is a functional value-added product intended for human consumption. This product contains concentrated protein than in the original fish flesh and, are currently used for food fortification and a binder, dispersing agent and emulsifier (Shaviklo 2015). Some of the commercially available nutraceuticals/functional food produced from FPH includes Seacure, Amizate, Protizen and Nutripeptin (Guérard et al. 2010; Marchbank et al. 2008; Nesse et al. 2011). The protein hydrolysates can also be used as antioxidants. Encapsulation of the protein hydrolysates can be used to protect the nutritional quality of food and to protect the body against chronic diseases related to ageing (da Rosa Zavareze et al. 2014).

Nowadays, it is recommended for higher consumptions of long-chain omega-3 PUFAs for reducing the risk of cardiovascular diseases; and the omega-3 fatty acids in fish oil, are increasingly being utilized for managing cardiovascular diseases (Weitz et al. 2010). In addition to lipids, fish oil contains other nutrients such as vitamins A, D, and E and these bio-actives exert several physiological functions in human, including neurological development, brain health and cognitive function. In Japan, there are more than 200 food products which contain fish oil; one example is formula milk products enriched with DHA, which is relevant for the development and functioning of the nervous system (Camacho, Macedo, and Malcata 2019; Ohshima 2002). There is evidence that increasing demand for fish oil is going into nutraceuticals for direct human consumption (Pike and Jackson 2010).

Crustacean exoskeletons

Chitin and chitosan are naturally occurring amino-polysaccharides with distinctive structures and multidimensional properties. As the second most abundant biopolymer on earth after cellulose, chitin is abundant in crustacean shell, fungi, insects, algae, and mushrooms (Manigandan et al. 2018; Shahidi and Ambigaipalan 2015; Yadav et al. 2019). Structurally chitin is similar to that of cellulose with 2-acetamido-2-deoxy-β-d-glucose (NAG) monomers attached via β (1-4) linkages. After deacetylation, chitin can be transformed to form several derivatives such as chitosan which comprises D-glucosamine chains, chitosan oligosaccharides (COS) and glucosamine (Mao et al. 2017; Shahidi and Ambigaipalan 2015). Chitosan is the only naturally occurring cationic polysaccharide known (Hamed, Özogul, and Regenstein 2016). The chemical structure of chitin and chitosan are illustrated in Figure 6.

Commercial product of chitin is widely retrieved, mainly from crustaceans processing industries and is usually sold in powder or as flakes form. Although the chitin in the crustacean shells greatly varies with species and seasonal changes, the exoskeletons contain reasonable amount of protein (30–40%) and minerals mainly in the form of calcium carbonate (30–50%), chitin (20–30%), carotenoid pigments including lutein, β-carotene, astaxanthin and canthaxanthin (Aranaz et al. 2009; Goy, Morais, and Assis 2016; Hayes 2012; Vani and Stanley 2013). Around 75% of the total weight of crustaceans end up as by-products which represent a practical challenge (Kuddus and Ahmad 2013). Therefore, the efficient utilization of crustacean shells is of utmost interest due to the high volumes being generated linked to their increased production and processing, and the slow biodegradation rate of shells. Thus, production of value-added products such as chitin, chitosan and their derivatives with remarkable pharmacological activities for vital application in different fields present a way to minimize the waste (FAO 2016; Shahidi, Arachchi, and Jeon 1999). However, the main limitation associated with the utilization of this biopolymer on a large-scale is its insolubility. Therefore, water-soluble derivatives have been produced and, of these, chitosan is the most important (Hamed, Özogul, and Regenstein 2016).

There is a growing interest for chitin and chitosan derivatives in various industrial and biomedical fields with applications including their use as biomaterials for tissue engineering (e.g. artificial skin, bones and cartilage regeneration) and pharmaceutical excipient or drug carrier, among others (Cheung et al. 2015; Manigandan et al. 2018; Ruiz and Corrales 2017). Chitin is also incorporated in animal food and nutrition by reducing lactose intolerance (Vani and Stanley 2013). In general, owing to their high-water solubility and multitude physiochemical properties including biodegradability, biocompatibility and nontoxicity, chitosan derivatives are more suitable as nutraceutical agents.

Chitin and chitosan derivatives are recognized for their numerous biological attributes, including antioxidant and antimicrobial effects that could be applied in the food industry to improve food safety, quality, and shelf-life. Several researchers have reported on the antioxidant effects of these biopolymers. (Hafsa et al. 2016; Ngo et al. 2011; Si Trung and Bao 2015) and this make them an effective ingredient for producing health and wellness food products which could prevent age-related and diet-related diseases. Chitinous materials also have their applications as food preservatives owing to their antioxidants and antimicrobial properties. The antibacterial activity of chitin and its derivatives has been associated to their positive charges which interact with the negatively charged bacterial cell walls leading to the lysis of the microorganisms (Goy, Morais, and Assis 2016; Khoushab and Yamabhai 2010). The film-forming and antimicrobial properties of chitosan make them promising edible packaging materials for long term storage of food products (Leceta, Guerrero, and De la Caba 2013; Muzzarelli and Muzzarelli 2005). Antimicrobial coating of food products such as vegetables, fruit and fish slow down microbial contamination and proliferation because chitosan acts as a protective barrier to improve the sensory and nutritional quality of the food (Hamed, Özogul, and Regenstein 2016; Sinha, Tripathi, and Chand 2012). The use

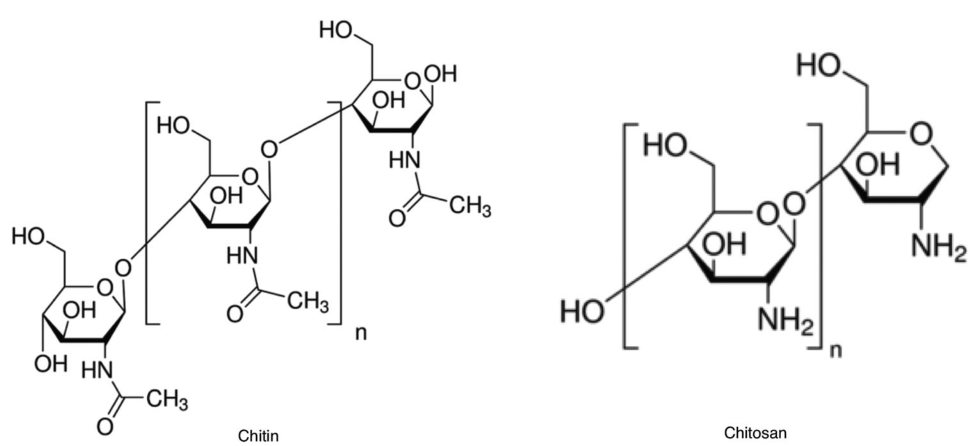

Figure 6. Chemical structure of Chitin and Chitosan.

of chitosan and chitosan oligosaccharides as dietary fibers has been documented (Xia et al. 2011). Lee et al. (2002) have reported that COS trigger the growth of beneficial bacteria in the gastrointestinal tract (*Bifidobacterium bifidium* and *Lactobacillus* sp.) and hence these biopolymers have potential use as prebiotic health–food.

A variety of currently available chitosan products are sold as fat reducers and cholesterol-lowering agents; however the clinical effectiveness of chitosan in blocking fat absorption remains controversial (Shahidi and Ambigaipalan 2015; Ylitalo et al. 2002), with work indicating that chitosan dietary supplementation had no significant effect on plasma cholesterol levels (Mhurchu et al. 2005; Tapola et al. 2008). In a assay guided work, Zhang et al. (2012) have noted that low molecular weight (LMW) chitosans lowered the total cholesterol, low-density lipoprotein (LDL) and liver triacylglycerol levels in rats fed with high-fat diets. Similarly, Liu, Zhang, and Xia (2008b) observed that rats fed meals supplemented with the highest amount of deacetylated chitosan had considerably reduced plasma cholesterol and low-density lipoprotein cholesterol and increased high-density lipoprotein cholesterol levels. Another study by Bokura and Kobayashi (Bokura and Kobayashi 2003), has demonstrated that chitosan was effective at lowering the total cholesterol in women with confirmed mild to moderate hypercholesterolemia. Numerous biological effects have been attributed to chitin and chitosan include anti-inflammatory (Azuma et al. 2015; Howard et al. 2009), anti-coagulant (Vikhoreva et al. 2005; Vongchan et al. 2003), anticancer (Azuma et al. 2015; Karagozlu and Kim 2014; Nam, Kim, and Shon 2007; Salah et al. 2013) and immuno-enhancing effects (Wu et al. 2020; Smith et al. 2014), which are supported by a number of in vitro and in vivo studies evaluating potential efficacy.

In Japan, several food products, (potato chips, soybean paste, and noodles) supplemented with chitosan are being sold as cholesterol-lowering functional foods (Freitas et al. 2015). Studies on the incorporation of chitosan in biscuits (Maezaki et al. 1993), in meat products (Jo et al. 2001; Lin and Chao 2001) and derivative products such as fish patties and sausages (Lopez-Caballero et al. 2005; López-Caballero et al. 2006) have been carried out.

The facts above indicated chitin, chitosan and their derivatives have an inherent variability due to their natural origin, which makes them a versatile biopolymer in food applications. However, their potential use as functional food ingredients need to be further investigated with a broader emphasis.

Other benthic species

Benthic species such as bryozoans, sponges, echinoderms, polychaetes, ascidians, mollusks and cnidarians have attracted attention of researchers globally since they are considered as exceptional reservoirs for new marine natural bioactive molecules. Research on these benthic species has discovered the majority of bioactive molecules which have known applications against cancer, inflammation, HIV-AIDS, infectious diseases and thrombotic disorders (Arizza 2013; Lordan, Ross, and Stanton 2011).

Mollusks and echinoderms have been extensively consumed and are regarded natural functional food (Suleria et al. 2015). Molluskan shells, soft tissue, basal parts, mucilage, and even entire organisms have been traditionally used to treat various ailments including gastrointestinal ailments, cancer, inflammations and dotage. These organisms, as part of the daily meal, have proven biological properties because are rich in essential nutrients and bioactive components. For instance, they have the ability to improve immune response. The possibility and ease of performing commercial breeding and farming and, the ease with which they can be caught, present mollusks as a suitable candidate for much industrial processing for nutraceuticals, functional foods, and food supplements (Celik et al. 2014; Khan and Liu 2019).

Biologically peptides purified from the fermented blue mussel and oyster sauces have reported to notably reduce hypertension (Je et al. 2005). Moreover, squid, octopus, and cuttlefish species are consumed for their health-benefit properties. Recently, Zaharah and Rabeta, (Fatimah and Rabeta 2018) have reported the antioxidant and antimicrobial activities of squid ink powder (Squid ink is a viscous, colorless medium produced at the end process of maturation). Salem et al. (2017) have demonstrated that octopus (*Octopus vulgaris*) protein hydrolysates possess significant free radical scavenging capacity and reducing power, making it a promising source of functional peptides that can be used to formulate functional foods.

The soft-bodied, sessile animals such as ascidians and sponges have been mostly valued for pharmaceutical studies. Most of the compounds that are in clinical and preclinical trials are sponges and ascidians-derived substances. These marine organisms produce a myriad of compounds that protect them from predators or from being infected and fouled by other marine organisms and also competing for space via allelopathic activities (Anjum et al. 2016; Arumugam et al. 2018). Bioactive molecules from ascidians and sponges or associated microorganisms have revealed broad-spectrum properties such as anticancer (Calcabrini et al. 2017; Palanisamy, Rajendran, and Marino 2017; Wyche et al. 2012), antibacterial, antifungal (Kossuga et al. 2004; Qaralleh et al. 2010; Wyche et al. 2012), antiviral (Chan et al. 2011; Sagar, Kaur, and Minneman 2010), anti-inflammatory (Chan et al. 2011; Keyzers and Davies-Coleman 2005), neurosuppressive and neuroprotective (Mehbub et al. 2014; Palanisamy, Rajendran, and Marino 2017).

Much interest is also being laid on marine bacteria and fungi, which have been investigated for their bioactive molecules. They live in close association with sessile organisms such as sponges and ascidians, and other marine invertebrates including corals. Many of the bioactive producing marine microorganisms can be easily cultured and manipulated in bioreactors and, thus, represent a notable renewable source of bioactive molecules (Figure 7). Bacteria from Polar Regions and deep seawater have been documented to produce high concentration of EPA and DHA, apparently to allow their membranes to be fluid and adapt to extreme

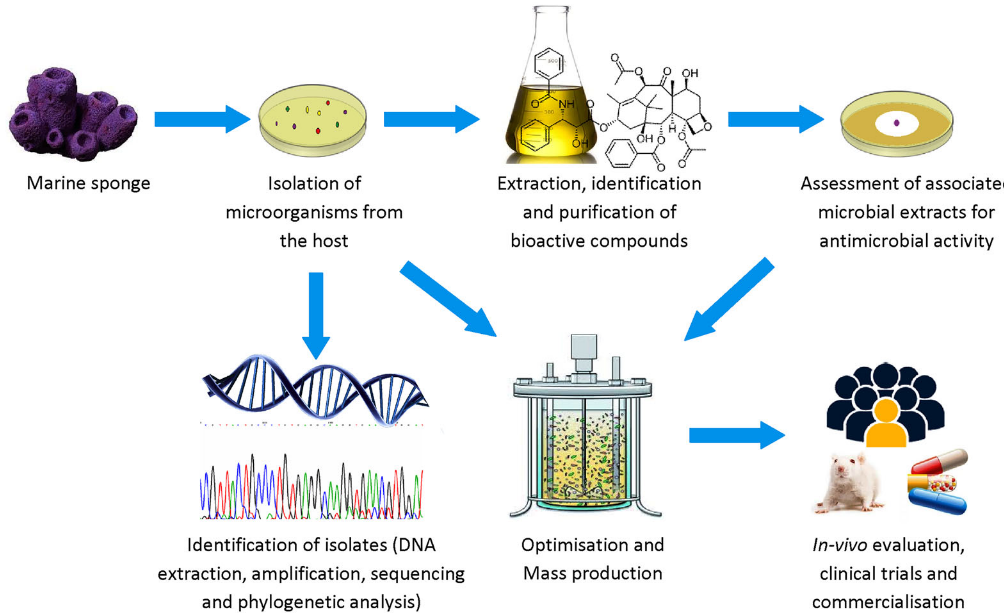

Figure 7. General procedure for recovery of bioactive metabolites, such as antimicrobials from microorganisms. The microorganisms are isolated from the host (e.g. marine sponge) and then antimicrobial activity screening and characterization of the organisms are performed. The biologically active compound is then purified, and the chemical structure is elucidated. Mass production and optimization of the extraction technique can be performed to obtain optimum yield of biologically active compound of interest, for further in vivo evaluation and clinical trials and product development.

temperatures and pressures (Lordan, Ross, and Stanton 2011; Yoshida et al. 2016). For example, the psychrotolerant piezophilic deep-sea bacterium, *Photobacterium profundum* SS9, produces EPA (8% of total fatty acids) and the EPA content rises when grown at a reduced temperature or elevated pressure (Allen, Facciotti, and Bartlett 1999). Extremophiles are of particular interest since they produce a diverse array of metabolites adapted to various extreme marine environments (Lordan, Ross, and Stanton 2011). The γ-proteobacterium, *Pseudoalteromonas tunicata*, acknowledged for the production of a number of biologically active molecules which is anticipated to play a role in defending the host against surface colonization by producing antimicrobial, anti-larval and antiprotozoal compounds (Egan et al. 2001; Egan et al. 2002; Franks et al. 2006; Holmatrom et al. 1998). Dharmaraj et al. (Dharmaraj, Ashokkumar, and Dhevendaran 2009) reported on the synthesis of food-grade pigments (carotenoids) by *Streptomyces* microbes isolated from the marine sponge *Callyspongia diffusa*.

Likewise, the oleaginous fungus *Mortierella alpina* can produce EPA as 15% of total extractable fatty acid at 12 °C (Bajpai and Bajpai 1993; Vadivelan and Venkateswaran 2014). A marine *Aspergillus* species isolated from the surface of *Sargassum horneri,* a marine brown seaweed, was found to yield a new polyoxygenated decalin derivative, dehydroxychlorofusarielin B along with two other fusarielins A and B. These compounds were observed to exert a mild antibacterial activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, and multidrug-resistant *S. aureus* (Nguyen et al. 2007). Masuda et al. (2008) reported about unicellular marine fungi collected from Pacific ocean, with high content of amino-butyric acid (GABA) of about 7–10 times higher than those of commercially available, for instance, bread yeast and other marine yeasts, which is a potential functional and healthy food ingredient. From the information amassed herein, it is quite pertinent that the benthic species mentioned above have capability to produce a panoply of biologically active molecules that can be used both in nutrition and pharmaceuticals.

Conclusion

As human life expectancy is increasing, diet plays a crucial role in sustaining health. This represent a challenge for the food sector as consumers not only demand tasty, convenient and high-quality food but also minimally processed, healthy and nutritious food (Camacho, Macedo, and Malcata 2019). There has been a combined effort among scientists to explore different sources to develop health-oriented food products to cater for the rapidly rising demand of consumers for health-promoting food. Marine organisms and marine by-products are, indeed, and incredible untapped reservoirs for novel value-added functional ingredients and bioactive compounds. Food products and supplements containing marine-derived biologically compounds are projected to occupy a huge market due to their numerous health benefits. Among the functional ingredients, omega-3 fatty acids have shown to be most effective against several health conditions; hence food products enriched with omega-3 fatty acids have been under the spotlight of many research and development programmes. Numerous researches are also focusing on seaweeds and their functional components with potential pharmacological properties mainly attributed to their omega-3 fatty acids, antioxidants and other biologically active components (Shahidi and Ambigaipalan 2015). Although numerous publications have demonstrated that seaweeds and sea cucumbers are valuable source of health-benefits compound, their consumption is adequate, and they are used in traditional Asian cuisine. Thus, more research is needed before seaweeds and sea cucumbers can used widely used in home cooking. Moreover, aquaculture should be extensively employed to produce large number of marine species of interest (e.g. seaweeds, sea cucumber and fish) for making these healthy foods readily available to the consumers. The biomass materials obtained during seafood processing is another source of functional constituents which can be exploited for useful marketable products.

However, the search and use of functional ingredients derived from the ocean continue to remain a challenge for scientists and food engineers, as it demands suitable and sustainable harvesting and extraction of the functional ingredients based on food-grade compatible, efficient, and sustainable procedures followed by purification of fractions or compounds in a controlled manner. An interdisciplinary approach is imperative to explore the potential of the marine ecosystem and produce value-added food for all (Boziaris 2014).

The legislation is another bottleneck in the functional food industry since it is constantly changing or being amended with the publication of new regulations and it often varies from country to country. Marketing health-related food ingredients now require substantial scientific evidence for the claims; for instance, in Europe, it is now obligatory to provide evidence for any health claim for a functional food product. Health claims entail extensive scientific validation via extensive human clinical trials which is expensive, and the targeted market niche may not be sufficient to recover the investment (Khan et al. 2014). Nonetheless, the ocean still offers numerous opportunities for future developments in the food industry.

Disclosure statement

The authors Devina Lobine, Kannan RR Rengasamy and Mohamad Fawzi Mahomoodally have no conflicts of interest.

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