

## Review Article

## Medicinal bioactive compounds to functional foods from geochemical signatures marine biomasses: sea cucumbers, macroalgae and crown of thorns biomasses

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**Abstract**

Recognition of health benefits associated with consumption of marine derived biomasses is one of the most promising developments in human nutrition and disease-prevention research. This endeavor for bioactives and functional ingredients discovery from marine sources is “experience driven,” as such the search for therapeutically useful synthetic drugs, and functional components is like “looking for a needle in a haystack,” thus a daunting task. Zoonotic infection, adulteration, global warming and religious belief can be the star-gate barrier: - For example, the outsourcing for Glycosaminoglycans (GAGs), a pharmacologically bioactive compound have emerged as novel biomarkers and molecular players both within tumor cells and their microenvironment, as they integrate signals from growth factors, chemokines, integrins, and cell-cell matrix adhesion. As such, worldwide initiatives in outsourcing from geochemical signatures marine biomasses are flourishing. Most of these scientific interests are related to marketable compounds optimised via biotechnology applications. Approximately 50% of the US FDA approved drugs during 1981–2002 consist of either marine metabolites or their synthetic analogs. These bioactive compounds acts as antioxidant, peptides, chitoligosaccharides derivatives, sulfated polysaccharides, phlorotannins and carotenoids. Highlights from works to harness and provide scientific support to folk medicine much claimed legacy, pertaining to geochemical signatures vouchered sea cucumbers, macroalgae and crown of thorns starfish will be extrapolated.

*Keywords: Bioactive compounds; marine invertebrates; functional foods and therapeutic agents.*

**1.0 Introduction**

Globally, there is an increasing interest for availability of tangible, novel, added value, sustainable commercial exploitable therapeutic compounds of naturally geochemical signatures derived resources. Earth’s oceans are probably the most valuable natural products resource. However, the Census of Marine Life, evaluating marine biodiversity, ascertained that at least 50% and potentially more than 90% of marine species are undescribed by science (Census of Marine Life, 2017). Evolved over millions of years, and living in a highly competitive environment, many of these organisms have perfected the technique of survival through chemical defense. As such, these marine organisms constitute nearly half of the worldwide biodiversity; thus, oceans and sea present a vast resource for new substances and it is considered the largest remaining reservoir of beneficial natural molecules that might be used as functional constituents in the food sector. This endeavor for bioactive compounds and functional ingredients discovery from marine sources is “experience driven,” the search for a therapeutically useful synthetic drug, and functional components is like “looking for a needle in a haystack,” thus it is seems as a daunting task. Zoonotic infection, adulteration, global warming and religious belief can be the star-gate barrier.

Marine invertebrates utilize a ‘plethora of substances,’ in their natural immunity ranging from peptides, to alkaloids, terpenoids to steroids for defense and preservation of their natural integrity. Many marine compounds have been detected as having various biological activities: peptides isolated from fish as well as algal polysaccharides have been reported to have anticancer, anticoagulant, and antihypercholesterolemic activities (Lordan, *et al.*, 2013). Various literatures survey revealed that the bioactive compounds isolated in recent past from the marine poriferans, cnidarians, annelids, arthropods, molluscs and echinoderms could be rich sources of therapeutic agents having antibacterial, anti-inflammatory and anticarcinogenic properties. While marine bacteria and fish oils contain great amount of omega-3 fatty acids, whereas seaweeds and shellfish such as crustaceans have potent antioxidants including carotenoids and phenolic compounds (Rasmussen and Morrissey 2007).

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The importance of marine metabolites in modern day drug research is revealed by the fact that around 50% of the US FDA approved drugs during 1981–2002 consist of either marine metabolites or their synthetic analogs. Their low effective dosage, better selectivity against target malignant tissues and relative non-vulnerability to resistance development as compared to compounds of terrestrial origin, render them as useful target molecules. As such the challenge in this scientific area is to identify bioactive compounds and their associated health effects as well as their underlying biological mechanism of action. Impressive and growing numbers of bioactive compounds have been identified and outsourced at various geochemical areas that have potentially important health benefits. As such, acknowledging this integral historical dynamics of the outsourcing relationship between humankind and the Earth is basically an essential health care issue finger print agenda so as our future descendants are left with considerable terms of natural product resources. *Per se*, among these bioactives compounds include resources that can act as antioxidants, enzyme inhibitors and inducers, of gene expression. While marine bacteria and fish oils contain great amount of omega-3 fatty acids, seaweeds and shellfish such as crustaceans have potent antioxidants including carotenoids and phenolic compounds (Rasmussen and Morrissey 2007).

Naturally occurring antioxidants can be found in a variety of marine organisms including marine algae, invertebrates, fish, shellfish, and marine bacteria. Antioxidants manifest a positive effect on human health as they protect the human anatomy against detrimental damage by reactive oxygen species (ROS), which attack macromolecules structures such as membrane lipids, proteins and DNA, lead to many health disorders such as cancer, diabetes mellitus, neurodegenerative and inflammatory diseases with severe tissue injuries (Yang, Landau, Huang, & Newmark, 2001; Frlich & Riederer, 1995). Marine-derived bioactive peptides have been obtained widely by enzymatic hydrolysis of marine proteins (Kim and Wijesekara, 2010) and have shown to possess many physiological functions, including antioxidant (Kim, Je, and Kim, 2007). Radical scavenging compounds such as bioactive peptides, COS, SPs, phlorotannins, and carotenoids pigments including fucoxanthin and astaxanthin from marine foods and their by-products can also be used indirectly as functional ingredients to reduce cancer formation in human bodily tissues and organs. As such the search for effective and safe antioxidants from natural sources is of great interest to researchers, producers, and consumers alike. So, antioxidants from marine sources may be used as substitutes for plant antioxidants such as those from rosemary and sage.

In this milenia, there is a great potential in marine bioprocess industry to convert and utilize most of marine food products and marine food by-products as valuable functional ingredients. The components of proteins in marine foods have been extrapolated to contained sequences of bioactive peptides. These peptides could exert a beneficial physiological effect in the human body. Moreover, some of these bioactive peptides have also been identified to possess nutraceutical potentials that are of wellness beneficial towards global human health promotion (Defelice, 1995). This is so as functional food is defined “as food which is demonstrated to positively affect one or more physiological functions so that it is able to increase the well-being and/or to reduce the risk to suffer a disease” (Diplock, *et al*, 1999). Thus functional foods can improve the general conditions of the body (such as pre and probiotics), decrease the risk of some diseases (cholesterol lowering products), and can even be used for curing cardiovascular disease and osteoporosis illnesses (Siro *et al*, 2008). However at present further in-depth understanding of the relationship between nutritional value and its level, stock density and global dilemmas especially from outsourced marine biomass and its health benefits need to be better action lines, optimized and sustainably exploited with green approaches. This is to ensure the legacy and future development of functional foods from exploitable geochemical signatures marine biomasses can be a marketable without endangering its wild population.

## 2.0 Bioactive and functional food compounds from sea cucumbers

Sea cucumbers are echinoderms with soft, elongated, worm-like organisms. The invertebrates possesses a flexible cylindrical-gelatinous -body with a leathery skin and used their delicate tentacles for feeding on microscopic algae, absorbing sedimented nutrients from the marine intertidal zone organic matter [Conand, 1990, Fell, *et al*, 1972]. They are commonly known as trepang (in Indonesia) and *beche-de-mer* (in France). The friendly intertidal marine invertebrates which have been much exploited and utilized as a culinary delicacy, particularly in some parts of Asia [Huizeng, 2001]. Sea cucumbers, also known as *Gamat* in Malay are marine invertebrates from the phylum Echinodermata (Kamarul, *et al*, 2010) and can be found throughout the worlds’ ocean intertidal beds (Fredalina, *et al*, 1999). Throughout the world there are more than 2500 sea cucumbers species (Ibrahim. 2003). Among the most popular species are *Stichopus hermanni*, *Stichopus vastus*, *Stichopus badionotus*, *Stichopus chloronotus*, *Holothuria atra*, *Holothuria edulis*, and *Holothuria scabra* (Ridzwan, *et al*, 1995). These sea cucumbers are involved in sustaining geochemical marine ecosystem ecological functions such as in nutrient recycling by excretion of inorganic nitrogen and phosphorus, thus enhancing the productivity of benthic biota and its bioturbation (Steven Purcell *et al*, 2016). Another ecological function of these sea cucumbers is to buffer coral reefs from ocean acidification. Feeding on reef sand these tropical sea cucumbers increases the alkalinity in surrounding seawater. This may help to protect corals and other reef organisms from ocean acidification.

A profile of tangible important bioactive compounds and functional food natural products of nutritional and medicinal values have been isolated from geochemical vouchered sea cucumbers (Nurul ‘Izzah Ibrahim, *et al*, 2018) . Nutritionally, sea cucumbers have an impressive profile of valuable nutrients such as Vitamin A, Vitamin B1 (thiamine), Vitamin B2 (riboflavin), Vitamin B3 (niacin), and minerals, especially calcium, magnesium, iron and zinc. A number of unique biological and pharmacological activities including anti-angiogenic, anti-cancer, anti-coagulant, anti-hypertension, anti-inflammatory, anti-microbial, anti-oxidant, anti-thrombotic, anti-tumor and wound healing have been ascribed to various species of sea cucumbers invertebrates.

Literatures have indicated that this bioactive compounds and functional food ingredients that have long been purported in folk medicine may be due to sulfated polysaccharide representatives. The sulfated polysaccharide is a semi-synthetic chemical compound and contains sulfate groups of natural polysaccharide derivatives. Sulfated polysaccharides (SPs), from other natural resources have exhibit various biological activities such as anticoagulant, antiviral, antioxidative, and anticancer activities with potential health benefits: may enhance the immune system and biological activities (Zaidi *et al*, 2017).

*Stichopus hermanni* and *Stichopus vastus* sea cucumber species that are friendly intertidal marine invertebrates (light weighted, easily undergoes eviscerated-self death) from the *Stichopodidae* family within the coastal waters of Malaysia have been outsourced for N-, O- sulphated and total sulphated glycosaminoglycans (GAGs). The invertebrate integument tissues revealed the highest content of total, O- and N-sulphated GAGs, followed by the internal organs and the coelomic fluid for both species of sea cucumbers [Siti Fathiah Masre, *et al*, 2011]. This data is in congruent with nutrient analyses that show the body wall of sea cucumbers to have higher nutrient value (Chen, 2004). The total sulfated GAGs from *Stichopus vastus* coelomic fluid thus have showed a significantly acceleration on wound healing process dynamics especially in pertinent to epithelial migration, fibroblasts proliferation, new vessels formation and collagen reorganization of the wound.

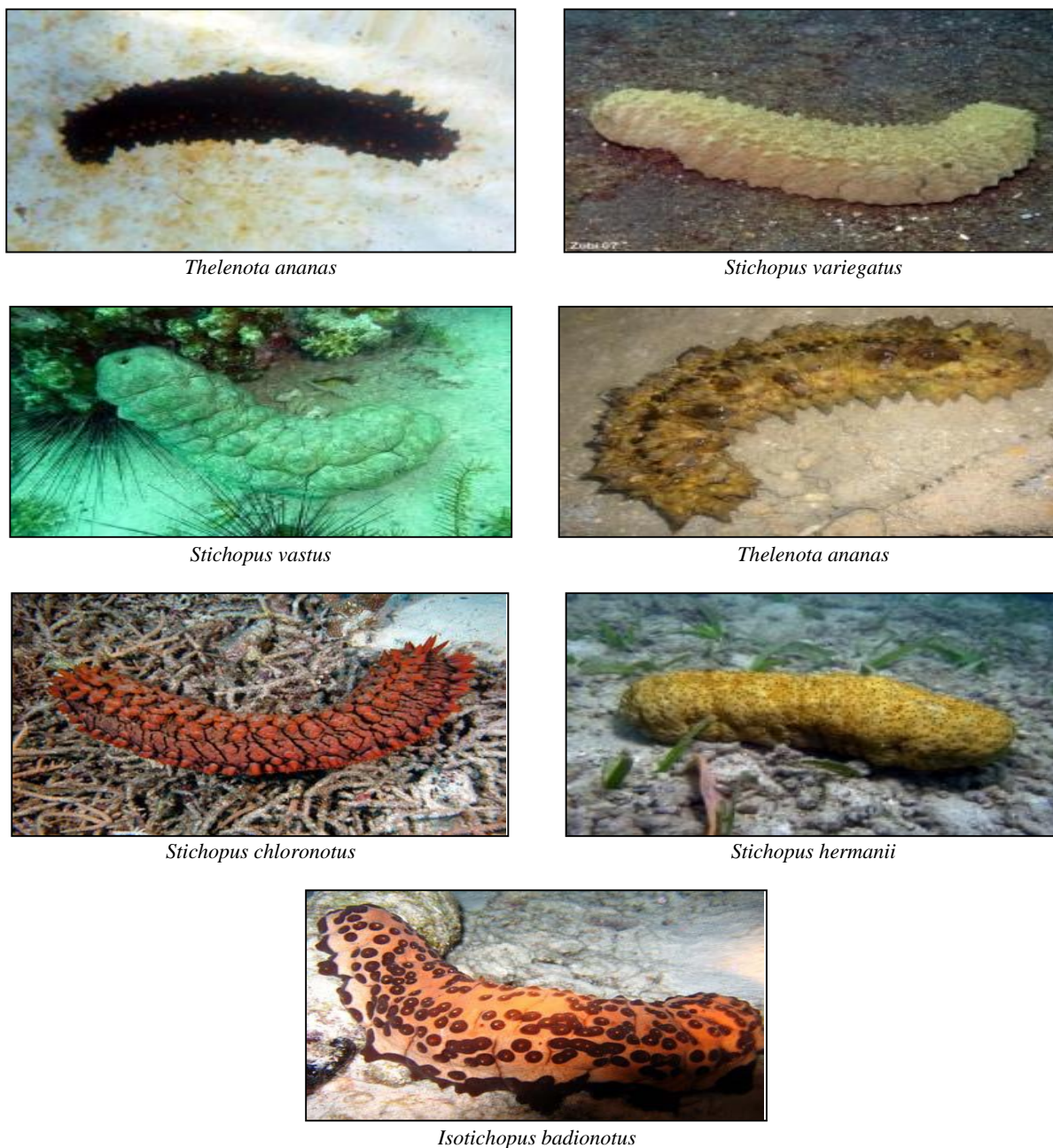
Sea cucumbers are soft bodies’ organisms; these marine creatures are protein-rich marine invertebrate. A new immunomodulatory lead Cumaside a complex of monosulfated triterpene glycosides from the sea cucumber *Cucumaria japonica* possesses cytotoxic activity against Ehrlich carcinoma cells (Aminin, *et al*. 2004). Globally biological and pharmacological activities biocompounds namely anti-angiogenic (Tian, *et al*, 2005), anti-cancer (Roginsky, *et al*, 2004), anti-coagulant (Nagase, *et al*, 1995 and Chen, *et al*, 2011), anti-

hypertension (Hamaguchi, *et al.*, 2010), anti-inflammatory (Collin, 1999 and Collin, 2004), anti-microbial (Beauregard, *et al.*, 2001 and Hing, *et al.*, 2007), antioxidant (Althunibat, *et al.*, 2009), anti-thrombotic (Mourao, *et al.*, 1998 and Pacheco, *et al.*, 2000), antitumor (Zou, *et al.*, 2003 and Tong, *et al.*, 2005), and wound healing (Kerr, *et al.*, 1995) have been ascribed to chemical compounds extracted from different geochemical vouchered sea cucumber species. These medicinal benefits and health functions of sea cucumbers can be attributed to the presence of appreciable amounts of bioactive compounds, especially the triterpene glycosides (Miyamoto, *et al.*, 1990, Aminin *et al.*, 2010 and Vieira, *et al.*, 1991), chondroitin sulfates (Mourao, *et al.*, 1999), glycosaminoglycan [(Nagase, *et al.*, 1995 and Pacheco, *et al.*, 2000), sulfated polysaccharides (Goad, *et al.*, 1985), sterols: glycosides and sulfates (Mamelona, *et al.*, 2007), phenolics (Rafiuddin, *et al.*, 2004), peptides (Sugawara, *et al.*, 2006), cerebrosides (Mojica & Merca, 2004) and lectins (Mojica & Merca, 2005, and Mojica, *et al.*, 2005).

**Table 1.** A tabulated reflective of important bioactive compounds and functional food natural products isolated (cited in articles in the field selected) from geochemical signatures sea cucumbers, macroalgae, and Crown of Thorns origin.

Bioactive compounds and functional food natural products from geochemical signatures: Sea cucumbers, macroalgae, and Crown of Thorns origin.				
Marine sources (Major phylum)	Bioactive compounds	Disease prevention	Functional food	References
Sea Cucumbers: <i>Cucumaria</i> , <i>Stichopus chloronotus</i> , <i>Stichopus vastus</i> , <i>Stichopus horrens</i> , <i>Actinopyga lecanora</i> , <i>Stichopus hermanni</i> , <i>Holothuria glaberrima</i>	Triterpenoid glycoside sulfates Saponins, sterol derivatives, terpenoids, glycoproteins, cerebrosides, pyrimidine nucleosides, thymine deoxyriboside and uracil deoxyribose, polysaccharides, $\beta$ -carotene ACE-inhibitory biopeptides	Hemolytic, antibacterial, antifungal, antineoplastic, antitumor, antiviral especially anti HIV activity, anti-inflammatory, anti cancer, anti allergy Wound healing Wound healing and organ regeneration	Fatty acid, Pepsin Solubilised Collagen Collagen hydrolysates Total Sulfated Glycosaminoglycan (GAG)	Fredalina, <i>et al.</i> , 1999, Miyamoto, <i>et al.</i> , 1990. Ridzwan, <i>et al.</i> , 1995. Linhardt, <i>et al.</i> , 1990, Bita Forghani, <i>et al.</i> , 2012 Yasser, Chim Chi, <i>et al.</i> , 2017, Md Zainul Abedin, <i>et al.</i> , 2013, Md Zainul Abedin, <i>et al.</i> , 2014, Siti Fathiah Masre, <i>et al.</i> , 2010. Siti Fathiah Masre, <i>et al.</i> , 2011.
Macroalgae: Sargassum horneri Large brown seaweeds, such as Laminaria hyperborea, Ascophyllum nodosum, and Macrocytis spp. Macroalgae genus Ulva (Ulvales, Chlorophyta)	Protein hydrolysates Lipoxigenase/hydroperoxide lyase Biocatalyst products - Polyunsaturated aldehydes: 2,4,7-decatrinal and 2,4- decadienal	Antioxidant, Strengthening of the immune system, Antirickets, Anti-osteomalacia, Anticoagulant, $\alpha$ -amylase and $\alpha$ -glucosidase inhibitory effect Anti-obesity agents	Vitamins [B12, C, E and D], Chlorophylls, Alginate and Alginic acid, High content in essential minerals namely Na, K, Mg, P, I, Zn and Fe	Harnedy and FitzGerald, 2011, Marquez and Sinnecker, 2007, Packer, 1997, Witting and Stocker 2003, Haidara and others 2006, Anantharaman, <i>et al.</i> , 2011, Lordan, <i>et al.</i> , 2013, Vazhiyil., 2011a. 2011b, Bocanegra, <i>et al.</i> , 2009. Dawczynski, <i>et al.</i> , 2007, Chu Wan-Loy and Phang Siew-Moi, 2016.
Crown of Thorns: <i>Acanthaster planci</i> <i>Asterias amurensis</i>	Collagens Saponins	Anti-cancer	Sulfated polysaccharides	Ahmed Faisal Mutee, <i>et al.</i> , 2012, Farhana Sharmin, <i>et al.</i> , 2017

Linhardt, *et al.*, (1990) have reported that low molecular weight sulphated polysaccharides were noted from sea cucumbers with efficient anticoagulant activities and several pharmacological properties. The chondroitin and glucosamine components of holothurian were reported to be important cartilage building blocks and other bio activities including anti-inflammatory and antitumor activity properties (Herecia and Ubeda, 1998). Total sulfated glycosaminoglycan (GAGs) from sea cucumber *Stichopus hermanni* and *Stichopus vastus* integumental tissue were investigated for evaluation of wound healing potential in rats. Three groups of female Sprague-Dawley rats each consist of 6 animals were assigned. Normal saline was applied as a control to group 1 rat while group 2 and group 3 rats were treated topically with total sulfated GAGs from both sea cucumber species' integumental tissue to 6 mm diameter of full thickness wound from day 0-12. The effects on the contraction rate percentage of wound healing were assessed. In that experiments, wounds treated with total sulfated GAGs from sea cucumbers *Stichopus hermanni* and *Stichopus vastus* integumental tissue preparations showed significantly ( $p < 0.05$ ) improvement in its wound contraction rate percentage as compared to those wounds not treated with the sulfated GAGs in control group. The study results seems to suggest the beneficial effects of total sulfated GAGs particularly from the integument body wall of sea cucumbers *Stichopus hermanni* and *Stichopus* for the positive enhancement of wound healing process dynamics especially in rats model (Siti Fathiah Masre, *et al.*, 2010). The study also is in support of other previous reported research that also seems to confirm that holothurians glycosaminoglycan (HG) and holothurians fucan (HF) present in other species of sea cucumbers can be found in higher levels in the sea cucumber integument.



**Figure 1:** The *Stichopodidae* sea cucumbers known as ‘Gamat’ in Malaysia.

Source: Farid Che Ghazali. (2012). Ekstrak Gamat Untuk Penyembuhan Luka. Journal: *Dewan Kosmik Majalah Sains Dan Teknologi*. March 2012. 9-14. Koperasi Dewan Bahasa Dan Pustaka (M) Berhad. ISSN 0128-6579.

Numerous Angiotensin-converting enzyme (ACE) is an - inhibitory biopeptides that has been generated and characterized from different species of *sea cucumber* such as *Stichopus horrens* (Bita Forghani, *et al.*, 2012);, *Actinopyga lecanora* tissue proteins (Raheleh Ghanbari, *et al.*, 2012), *Isostichopus badionotus* (Yasser Chim-Chi, *et al.*, 2017), and *Acaudina malpadioidea* wall protein. The ACE is an exopeptidase (peptidyl-dipeptidase ACE) that catalyses removal of dipetidyl residues from the COOH ends of peptide substrates. The ACE-inhibitory biopeptides derived from marine invertebrates were reported to exhibit *in vitro* inhibitory effect through both competitive and noncompetitive mechanisms on ACE. Additionally, *in vivo* studies in hypertensive rats have shown the ACE-inhibitory potential of marine-derived antihypertensive peptides

### 3.0 Bioactive and functional food compounds from photosynthetic marine macroalgae biomasses

Marine macroalgae are sea weeds that have been consumed as food since ancient times in East Asia. These photosynthetic-like plants form the basic biomass in the intertidal zone. Marine macroalgae have been recognized as the plant-based food of the future (Winterman, 2012), as research have noted that these macroalgae are rich source of health-promoting compounds capable of acting on a wide spectrum of disorders and diseases (Lordan, *et al.*, 2011, Fitzgerald, *et al.*, 2011 and Cardoso, *et al.*, 2014). Although macroalgae do not compete with food crops for the use of arable land and fresh water resources. *Sargassum* brown macroalgae, aquatic ‘plants’, pose a large disposal problem for beaches worldwide, and this macroalgae bio-oil cannot be directly used as a result of a high oxygen content and low heating values. However evidence based research have revealed that these photosynthetic biomasses are a good supply of essential nutrients including carbohydrates, protein and minerals (Lordan, *et al.*, 2011 and Bocanegra, *et al.*, 2009).



**Common Name (Leafless Bladder Wort)**

A close-up of a small mass of *Sargassum* weed shows the numerous small round spheres are floats filled with carbon dioxide. These provide buoyancy to the algae.

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Scientific classification of *Sargassum* spp.

Empire	Eukaryotic
Kingdom	Chromista
Super Phylum	Heterokonta
Phylum	Ochrophyta
Class	Phaeophyceae
Subclass	Fucophycidae
Order	Fucales
Family	Sargassaceae
Genus	<i>Sargassum</i>

**Figure 2:** Macroalgae: *Sargassum* spp. Source: Aroyehun AbdulQudus Bola, Shariza Abdul Razak, Farid Che Ghazali. The Perspective of Macro Algae as Functional Food. *Health and the Environment Journal*, 2017 Vol 8, Supplement 1.

These seaweeds also lack many of the distinct organs found in terrestrial plants. In this millennia, these marine macrophytic algae ‘seaweeds’ represent one of the important living renewable resources of the marine ecosystem. This macroalgae biomass are purportedly enriched and contain many types of bioactive compound such as omega-3 PUFAs, fucoxanthin, fucosterol and polyphenol, sulfated polysaccharides, dietary fiber, essential amino acids, minerals and vitamins (Plaza, *et al.*, 2008). As such geochemical vouchered macroalgae lipids have potential applications for a marketable exploitation of human wellness benefits.

Macroalgae seaweeds are marine photosynthetic biomasses in intertidal zones. Of approximately, 9000 seaweed species that have been identified, these biomasses have been documented to be rich in chemical compounds that possess biological applications with numerous health benefits. Marine macroalgae represent one of the richest sources of natural antioxidants (Mayer and Hamann, 2002; Ruperez, 2001). It is believed that marine macroalgae are protected against oxidative deterioration by certain antioxidant systems. On the basis of their pigmentation, these species have been broadly classified into three main groups of brown (Phaeophyta), red (Rhodophyta), and green (Chlorophyta) seaweeds (Miyashita, *et al.*, 2013). The marine seaweeds lack distinct organs found in terrestrial plants, as such the entire plant is available as a biomass source. Geochemical signatures macroalgae contain various polysaccharides that could be used as prebiotic compounds for health applications. Different polysaccharides are found in all the species. Alginates, fucans, and laminarins are found in brown algae. Agar and carrageenans are also extracted from red algae. The benefits of macroalgae polysaccharides have been shown *in vitro* and *in vivo*. The results were promising as laboratory animals have been shown to have increased numbers of *Bifidobacterium* and *Lactobacillus* (Kuda *et al.*, 2005; Wang *et al.*, 2006). *Chlorophyta* contains highly complex sulfated heteropolysaccharides. *Chlorophyta* also contains non-steroidal anti-inflammatory drugs (NSAID). Research have been conducted to reveal its potency as observed on patients with rheumatoid arthritis (RA), which is an autoimmune diseases characterized by flare-ups of arthritis involving small and large joints. In that clinical trial, it was revealed that anti inflammatory effect was mediated by an exaggerated production of eicosanoids and cytokines (Adam, *et al.*, 2003).

Macroalgae seaweed contains a wide range of bioactive compounds with potential antioxidant activity. The antioxidant sources of macroalgae seaweeds are related mainly to their polyphenols content, particularly phlorotannins, which are the largest group of polyphenols in brown seaweed (Eom, *et al.*, 2012). Polyphenols derived from seaweeds may be more potent than analogous polyphenols derived from terrestrial plant sources due to presence of up to eight interconnected phenol rings (Hemat, 2007). Meanwhile phlorotannins purified from marine brown algae have been shown to exert antioxidant activities. These protective effects is against hydrogen peroxide-induced cell damage (Kang, *et al.*, 2005; Kang *et al.*, 2006). Phlorotannins act as free radical scavengers, reducing agents and metal chelators, and thus able to regulate lipid oxidation pathway. Phlorotannins are phenolic compounds formed by the polymerization of phloroglucinol defined as 1, 3, 5-trihydroxybenzene monomer units and biosynthesized through the acetate–malonate pathway. These phenolic compounds are highly hydrophilic components with a wide range of molecular sizes ranging between 126 and 650,000 Da (Ragan and Glombitza, 1986). Marine

brown algae accumulate a variety of phloroglucinol-based polyphenols, as phlorotannins could be used as functional ingredients in nutraceutical with potential health effects (Wijesekara, Yoon, & Kim, 2010). Among the marine macroalgae, *Ecklonia cava*; an edible brown algae is a rich source of phlorotannins (Soo-Jin Heo, *et al.*, 2005). These phlorotannins have several health beneficial biological activities including, antioxidant (Li, *et al.*, 2009), anti-HIV (Artan, *et al.*, 2008), anti-proliferative (Kong, Kim, Yoon, & Kim, 2009), anti-inflammatory (Jung, *et al.*, 2009), radioprotective (Zhang *et al.*, 2008), ant-diabetic (Lee, Li, Karadeniz, Kim, & Kim, 2009), acetyl cholinesterase inhibitory effects as in anti- Alzheimer's disease (Yoon, Lee, Li, & Kim, 2009), anti-microbial (Nagayama, Iwamura, Shibata, Hirayama, & Nakamura, 2002) and anti-hypertensive (Jung, Hyun, Kim, & Choi, 2006) pathophysiology.

Macroalgae lipids have scientifically marketable applications potential. These macroalgae lipids have drawn increased scientific interest due to their purported health benefit and as plant-based food of the future. Macroalage lipids represent only 1%–5% of seaweed's dried weight (DW), whereby almost half of that fraction is in polyunsaturated form. Omega-3 and omega-6 fatty acids like eicosapentanoic acid and arachidonic acid are found in abundant. This is revealed by studies on Brown macroalgae lipids that were found to contain many types of bioactive compounds such as omega-3, omega-6, arachidonic acid, fucoxanthin, fucosterol, and some polyphenols. Among these compounds, fucoxanthin, major carotenoids in brown seaweed, is regarded as a nutraceutical compound specific to brown seaweed lipids because it shows several physiological effects based on unique molecular mechanisms (Miyashita, *et al.*, 2011). Nutrigenomic studies reveal that fucoxanthin induces uncoupling protein 1 [UCP1] in abdominal white adipose tissue [WAT] mitochondria, leading to the oxidation of fatty acids and heat production in WAT. Fucoxanthin also improves insulin resistance and decreases blood glucose levels through the regulation of cytokine secretions from WAT. Fucoidan is a fucose-containing sulfated polysaccharide derived from brown seaweed such as *Laminaria* and *Fucus*. Studies have demonstrated antiproliferative, antiangiogenic, and anticancer properties of fucoidan *in vitro* by targeting multiple receptors or signaling molecules in various cell types of tumor cells [as an antiangiogenic agent] and immune cells. VO, *et al.*, 2012, have also showed that the marine algae derived fucoidan is effective as an anticoagulant agent similar to that of heparin, which has been used as the anticoagulant drug of choice for many years. However, due to heparin's side effects such as excessive bleeding, thrombocytopenia, mild transaminase elevation, and hyperkalemia, there is a need for alternatives.

Dietary iodine is essential for the production of the thyroid hormones thyroxine and triiodothyronine, which regulate many important physiological processes in humans. A dietary iodine deficiency can cause several problems including an effect on growth and development due to insufficient formation of the thyroid hormones leading to spontaneous abortion, stillbirth, cretinism, goiter, and mental defects. Iodine is ubiquitous in seawater. In fact, kelp, a type of macroalgae, is a rich source of iodine and is used as a functional food and nutritional supplement (Li, *et al.*, 2009; Catarina Guedes *et al.*, 2013). At present the development of beverages products with macroalgae revealed that these beverages containing water-insoluble algal dietary fibers (of 0.01% to 20%), citric acid, sugar, fruit juice, plant thickeners and water, which can prevent and ameliorate distinct diseases, that include cardiovascular disorders (Fu, *et al.*, 2009). Meanwhile a *Hizikia fusiforme* macroalgae fortified drink with antihypertensive effects has been formulated (Kim, 2008). This latter product contained a purified form of polymannuronic acid from the macroalgae kelp *Undaria*.

Macroalgae seaweed-derived sulfated polysaccharides including agar and alginate, have found widespread applications in biomedical research and medical therapeutic applications including wound healing, drug delivery, and tissue engineering. Given the recent increases in the incidence of diabetes, obesity and hyperlipidemia, there is a pressing need for low cost therapeutics that can economically and effectively slow the progression of atherosclerosis (Nikita, *et al.*, 2018). Marine sulfated polysaccharides have been consumed by humans for millennia and are available in large quantities at low cost. Sulfated polysaccharides representatives from macroalgae such as ulvans, carrageenans and fucoidans, are now regards as exploitable bioactives compounds which have protective effects on atherosclerotic-plaque formation and its related progression. These carrageenans, are typically present in red macroalgae, were recently used in a clinical trial study. Patients with ischemic heart disease (IHD) were reported to exhibit a significant effect on lipid profile by a short-term carrageenans supplement. In fact, the prophylactic administration of the carrageenans food supplement in the complex therapy of IHD patients could significantly decrease the plasmatic TC levels by 16.5% and LDL-C by 33.5% as compared with the baseline measurements [Sokolova, *et al.*, 2014]

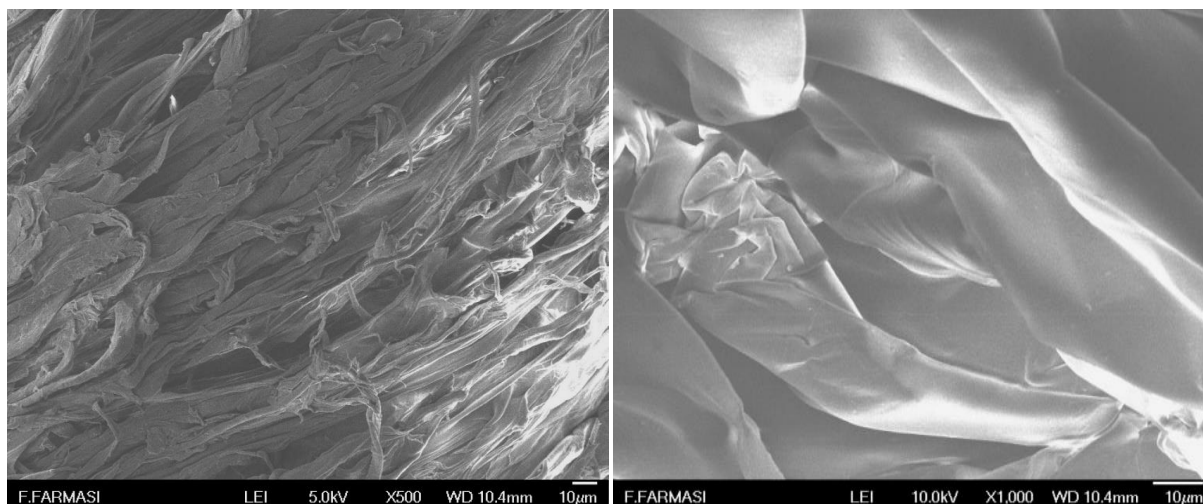
Obesity is a major epidemic that poses a worldwide threat to human health. Macroalgae are also been documented to have anti-obesity activity, especially the brown macroalgae *Undaria Pinnatifida*, *Hizikia fusiformis*, and *Sargassum fulvellum*. Fucoxanthin isolated from edible seaweeds, and its metabolite fucoxanthinol, have been shown to inhibit pancreatic lipase activity in the gastrointestinal lumen. The inhibitory action leads to suppressed triacylglycerol absorption within the lymph-duct (Matsumoto, *et al.*, 2010). In addition, fucoxanthin and fucoxanthinol were found to significantly inhibit pancreatic lipase activity, assayed based on inhibition of the hydrolysis of triolein. The inhibitory activities (IC<sub>50</sub>) of fucoxanthin and fucoxanthinol were similar but were much lower than orlistat. Fucoxanthin has also been reported to have an antidiabetic effect (Maeda, *et al.*, 2009), which has a unique structure containing an allenic bond and a 5, 6-monoepoxide (Løvdal Holdt and Kraan 2011), whose structure has been linked to the anti-obesity effect (Miyashita, 2009).

#### 4.0 Bioactive and functional food compounds from predatory *Crown-of-Thorns* starfish

*Crown-of-Thorns* starfish (COTs) or *Acanthaster planci* (Linnaeus, 1758) belongs to the phylum Echinodermata. It is a radial marine invertebrate (Kosarek, 2000), that feed solely on coral reef tissue as such, will devastate coral reefs vegetation. These marine starfish are *Asteroidea*, and is the second largest starfish that propagates sexually and asexually (Harriott, *et al.*, 2003). *Asteroidea* represent the second most diverse group within the phylum *Echinodermata*, with an estimated number of 1900 living species (Mah and Blake 2012, Mah, 2013). Over the years our research activities have indicate that indigenous *Crown-of-Thorns* (COTs) biomass are potentially prolific sources of highly bioactive components that might represent useful leads in the development of new pharmaceutical agents, nutraceutical functional foods and cosmeceutical applications. Among these compounds/components are the sulfated polysaccharides. Sulfated polysaccharides (SPs) glycosaminoglycans can now be extracted from geochemical taxonomied *Acanthaster planci*. This sulfated polysaccharides (SPs) glycosaminoglycans are also rich in fucoidans, carrageenans, and ulvans. The sulphated polysaccharides possesses a molecular mass of <30 kDa. This molecular mass measurement has been shown to be its most biologically active mass weight. *Vis a Vis*, the sulphated polysaccharides of 26–35 kDa have been shown to be able to block carcinogens and display antiviral properties. With these properties (molecular biology, biochemistry, and enzymology) it seems very indicative that indigenous *Acanthaster planci* biomass is an industrial technology-able applications biomass.

Antiviral compounds, AP-I and AP-II was successfully purified from COTs by Shimizu, (1971). The extracted biological active compounds were found to inhibit the multiplication of influenza virus in chicken embryos. The said study also support similar antiviral compounds found present in two other species of starfish, i.e. *Asterias forbesi* and *Asterina pectinifera*. In addition to that, COTs integument cellular and visceral tissues level characterization have been examined microscopically (optical and scanning electron microscopy) and was found to be rich in mutable dense collagenous bundles (Bahrom, *et al.*, 2012). Our study has successfully extracted collagen (as also reported by O'Neil, 1989) from the body wall of local indigenous coral reef associated COTs (Tan *et al.*, 2013). Pepsin-solubilized collagen (PSC) was

isolated from the inert body wall of COTs using pepsin digestion in 0.5 M acetic acid (conventional method). The electrophoretic pattern of PSC showed that it contained two main  $\alpha$ - chains components ( $\alpha 1$  and  $\alpha 2$  chains), suggesting that it might be a type I collagen. While the amino acid composition analysis showed that the said PSC contained high content of glycine, proline and hydroxyproline, Fourier transform infrared spectroscopy (FTIR) investigation also revealed the existence of triple helix structure of the isolated collagen. The study seems in agreement that the collagen molecules from echinoderm collagenous tissues are similar to mammalian fibrillar collagens in the length of their triple helices and in their quarter-staggered association to form fibrils with a characteristic D-period and gap/overlap ratio.



**Figure 3:** SEM photomicrograph of pepsin solubilized collagen from *Crown-of-Thorns* starfish (COTs) revealed a homogenous soft surface that is easily folded. Secondary electron mode. Gold coated. Source: Tan *et al.*, 2013 and Bahrom, *et al.*, 2012.

These starfish are coral predatory marine invertebrates that feed solely on coral reef tissue as such, will devastate coral reefs vegetation. There is a long documented history of research into *Crown-of-Thorns* starfish biology, ecology, and the causes of their outbreak. These marine starfish are *Astroidea* that represent the second most diverse group within the phylum *Echinodermata* used as traditional medicine for thousands of years in China and North-eastern Brazil (Ventura, *et al.* 2012). Taxonomically, the *Crown-of-Thorns starfish* (COTs) is the second largest starfish categorized under the phylum. It is a carnivorous starfish that preys on the polyps of reef-building corals. The species is widely distributed across the Indo-Pacific in tropical and subtropical latitudes and occurs in most locations where scleractinian corals, the primary food of adult *Crown-of-Thorns* are common. Indigenous population in northeastern Brazil have utilized dried whole starfish such as *Oreaster reticulatus*, *Luidia senegalensis* and *Echinaster* sp. as traditional medicine component to treat diseases such as asthma, bronchitis, diabetes and heart diseases (Alves and Rosa, 2007; Alves and Alves, 2011). Presently more than 1900 species of starfish's are recognized.

Various biologically active compounds and molecules have recently been identified in starfish such as glucosylceramides, steroidal glycosides, ceramide, and cerebroside (Farhana Sharmin, *et al.*, 2017, and Ishii, *et al.*, 2006). In pertinent to this, the biological actives metabolites from starfish could be subdivided into three main groups: i.e., asterosaponins, cyclic steroidal glycosides and glycosides of polyhydroxylated steroids. Steroidal glycosides, are composed of a polyhydroxylated steroidal aglycone and a carbohydrate portion containing only one or two monosaccharide units, are a growing subgroup of the active glycoside compounds that have been isolated from starfishes (Iorizzi, *et al.*, 1986). Steroidal glycosides are the main metabolites of starfish and possess most toxicity. Meanwhile, glycoside that belongs to the asterosaponins, are reported to exhibit various biological activities, including hemolytic, cytotoxic, antifungal, antibacterial and antiviral activities (Lee, *et al.*, 2014). In tandem to this, Luo, *et al.*, 2011, reported that the *Crown-of-Thorns* starfish chemical constituent results showed that its protein content of was 19.8 to 22.0% of its dry weight and the amino acid composition was similar to that of fish meal.

The venomous *Crown-of-Thorns* starfish possesses many useful pharmacological and biological characteristics. Among them are anticancer properties (Lee, *et al.*, 2014). *Vis a Vis*, purified cytotoxic toxin from *Crown-of-Thorns* starfish venom has been identified. These cytotoxic toxin have been identified as plancitoxin I protein by mass spectrum analyses. The Plancitoxin I showed characteristics to be able to inhibits the proliferation of A375.S2 cells through induction of oxidative stress, mitochondrial dysfunction and ER stress associated apoptosis pathway. At times whereby, breast cancer remains the most common cancer among women all over the world, Many new drugs derived from secondary metabolites have been applied in the treatment and/or prevention of cancer. Current chemotherapeutic drugs for breast cancer such as tamoxifen show severe side effects. Therefore, there is a focus toward new chemotherapeutic agents (such as revealed by plancitoxin 1) to be obtained from marine biomasses such as *Crown-of-Thorns* starfish biomass or byproducts. Study have been conducted to evaluate cytotoxic and apoptotic effects of geochemical vouchered *Acanthaster planci* starfish extract compared to tamoxifen in human breast cancer MCF-7 cell line. The extract was obtained using phosphate buffered saline. MTS assay and Annexin V assay were performed to evaluate the cytotoxic effect and apoptotic effect, respectively. The extract was found to inhibit the growth of MCF-7 cells ( $IC_{50}=15.6 \mu\text{g/ml}$ ) and induced apoptosis (52.9% after 1 hour treatment and 63.9% after 2 ours treatment). This apoptotic effect was more potent and earlier than the apoptotic effect induced by tamoxifen. This study seems to suggest that *Crown-of-Thorns* starfish extract may be utilized as potential chemotherapeutic agents to be used in the treatment of human breast cancer (Ahmed Faisal Mutee, *et al.*, 2012).

## 5.0 Conclusion

Entering into the industrial 4 eras of these millennia, marine geochemical signature organisms such as *Crown of Thorns* COTs, macroalgae and sea cucumbers are excellent sources of structurally diverse molecules that are potentially valuable as formulation of drug products. Among the structurally diverse molecules is sulfated polysaccharides and its representatives especially glycosaminoglycan. Further scientific advances in marine exploration strategies, natural products chemistry, genomic and bioassays characterizations studies will lead to greater surge in the search for marine based novel biomolecules. However the importance of correct taxonomic characterization and identification during outsourcing is a must do.

Optimised with green approaches, well vouchered marine biomasses and its by products are tangible exploitable resources. As such, these marine biomass and byproducts seems to offer many possibilities that do have advantages towards human wellness and can be considered to be of a safer alternative to some existing biotechnological derived synthetic drugs.

The review and its literatures seem very indicative that functional marine derived compounds: proteins, peptides, amino acids, fatty acids, sterols, polysaccharides, oligosaccharides, phenolic compounds, photosynthetic pigments, vitamins, and minerals) are of significant finding within the marine biomasses. As such these compounds can be applied and optimised as therapeutic drugs, nutraceutical products and as cosmetic solutions products (especially in anti-aging process).

## 6.0 Declaration

The authors declare no conflicts of interest in this work.

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