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Review article

Medicinal and health benefit effects of functional sea cucumbers

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ABSTRACT

Sea cucumbers have long been used as food and traditional medicine in Asian countries with *Stichopus hermanni*, *Thelenota ananas*, *Thelenota anax*, *Holothuria fuccogilva*, and *Actinopyga mauritiana* as most highly-valued species. These organisms are potential source of high value-added compounds with therapeutic properties such as triterpene glycosides, carotenoids, bioactive peptides, vitamins, minerals, fatty acids, collagens, gelatins, chondroitin sulfates, amino acids. In the recent years, health benefit effects of sea cucumbers have been validated through scientific research and have shown medicinal value such as wound healing, neuroprotective, antitumor, anticoagulant, antimicrobial, and antioxidant. These functional materials lead to potential development in various foods and biomedicine industries. In this review, we have presented a general view of major medicinal and health benefit effects of functional sea cucumbers from Asia region. The structural significance and the potential application of sea cucumber-derived functional materials as well as their nutritional value are also discussed.

1. Introduction

The increasing number of scientific papers published in the last few decades correlating functional materials derived from natural resources and some chronic diseases has shown the extraordinary possibilities of functional foods and nutraceuticals as well as biomedicine products to support, or even to improve, our health beyond the provision of basic nutritional requirements.[1,2] As a consequence, consumer's interest in the relationship between health, diseases prevention, and well-being has grown substantially worldwide. The sources of functional foods, nutraceuticals and biomedicine products are exist in many reservoirs and may be found in terrestrial and marine environments. Terrestrial resources such as fruits, vegetables, cereals, probiotics, and mushrooms; however, is by far more explored than the marine resources.[2] Even though the majority of those products in the marketplace are of terrestrial origin, marine organisms-based products are gaining attention due to their unique features, which are not found in terrestrial-based resources.[3]

Among marine organisms, sea cucumber is an interesting natural source of novel functional materials with biological activities that could be used in food as well as biomecicine industries. Sea cucumbers are soft bodied marine invertebrate from the class Holothuroidea. Sea cucumbers have a leathery skin and an elongated body containing a single branched gonad. These organisms constitute 1716 species, with the greatest biodiversity being in the Asia Pacific region. Sea cucumber is also known as "*teripang* or *trepang*" in Indonesian; "*beche-de-mer*", a French term that means marine food product, and "*balate*" in Chamorro. Sea cucumbers are organisms that live in complex environments submitted to extreme conditions, therefore, they must adapt to the new environmental conditions to survive, and produce secondary biologically active metabolites which cannot be found in other organisms. According to the Ming dynasty report (1368–1644 BC), the sea cucumber harbored the same medicinal properties as the herb ginseng, therefore, it also called as "haishen" which means "ocean ginseng".[4] Indonesia is well known as mega biodiversity country located in the center of Coral Triangle (the earth's storehouse of biological diversity), and also one of the largest sovereign nation in the worlds. It has been reported that Indonesia is the oldest and major sea cucumber exporter in the world.[5] Approximately, 350 sea cucumber species from Indonesian waters have been recorded with more than half were collected from the depth of more than 3000 m. Of the 350 sea cucumber species, at least 26 with economic value have

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been reported, these economic value sea cucumbers which bring benefits to fishers for centuries were called as trepan or teripang in Indonesia.[6] Not only, Indonesia, Malaysia and Philippines are also an important exporter of the sea cucumber and their products.[7] Globally, The Southeast Asia represents the global market hot-spots for sea cucumbers trade due to their known mega biodiversity. Many of sea cucumber is gathered for human consumption and some are cultivated in aquaculture systems.

Hence, the objectives of this article are first to present the results obtained of a detailed bibliographical search about the composition of sea cucumbers from tropical regions especially Asia and secondly, to discuss their biological activities and possibilities as new sources of functional ingredients. The information provided on the various species of sea cucumbers does not refer in many cases to the same constituents since it has been taken from different research papers with different objectives. However, we believe the information provided can be useful to many research groups considering a huge interest in the search for nutritional and medicinal value of sea cucumbers.

Fig. 1. *Stichopus hermanni* from Lembeh strait, Indonesia.

2. Chemical composition of various sea cucumbers

Functional ingredients from sea cucumbers have become an increasingly interesting way to develop new foods as well as biomedicine products. Sea cucumbers are a source of high value-added compounds with health benefit effects to be used as functional ingredients. Bioactive peptides, vitamins, minerals, fatty acids, saponins, carotenoids, collagens, gelatins, chondroitin sulfates, amino acids, fatty acids and other bioactive compounds are example of such sea cucumber derived functional ingredients that can be added at different stages of the food and biomedisine production process.[8] The sea cucumber species (*Stichopus hermanni, Thelenota ananas, Thelenota anax, Holothuria fuscogilva, Holothuria leucospilota, Holothuria atra, Holothuria scabra* and *Actinopyga mauritiana)* described in this article has been selected considering edible species, medicinal effects, and low toxicity. The aforementioned selected varieties are some of high-value sea cucumbers in Asia. Assuming that any new functional ingredient obtained from sea cucumbers could be used for further development of new products in food and pharmaceuticals industries. Another important factor is their nutritional value and potential as new sources of functional ingredients.

2.1. S. hermanni (local name in Indonesia: gamat emas, gamat kacang, taikongkong)

Sea cucumber *S. hermanni* (curryfish, golden sea cucumbers) belongs to the genus Stichopus; these species were formerly known as *Stichopus variegatus*. In Indonesia and Malaysia, sea cucumber *S. hermanni* (Fig. 1) has long been used for the preparation of traditional medicinal products like gamat water and gamat oil.[9] These species are gaining much recognition among consumers, medical and biomedical researchers due to their potential health benefits. In Asian region communities, *S. hermanni* have been exploited for medicinal purposes; however such applications needs to be proven on a scientific basis using some clinical models.

As shown in Table 1, *S. hermanni* contains high amount of protein (47.00% ± 0.36%) and low percentage of lipid (0.80% ± 0.02%). This sea cucumber contain significant amount of sulfated glycosaminoglycan. Glycosaminoglycan are long, unbranched polysaccharides composed of repeating disaccharide units consisting of alternating uronic acids (D-glucuronic acid or L-iduronic acid) and amino sugars (D-galactosamine or D-glucosamine) Glycosaminoglycan are divided into non-sulfated and sulfated glycosaminoglycan. Sulfated glycosaminoglycan extracted from *S. hermanni* possess various chemico-biological functions.[10] Compared to other parts such as internal organs and coelomic fluid; integument body wall of *S. hermanni* contain highest glycosaminoglycan, both sulfated and non-sulfated. Further, sulfated glycosamioglican from integument has been demonstrated to accelerate wound healing process in rats.[11] More than 60% of wound heal area in rats was observed after daily treatment with sulfated glycosaminoglycan (20 μL of 1 μg/mL) for 12 days. The healing activity of sulfated glycosaminoglycan was mediated through acceleration of wound contraction in wound healing phase I. In addition, 40% of *Stichopus hermanii* extract were able increase the number of lymphocytes during the healing process of traumatic ulcer on Wistar rat's oral mucous.[12] Most recently, Arundina et al. (2016) extracted *S. hermanni* from Kalimantan, Indonesia and demonstrated their growth stimulating effects in mesenchymal stem cells.[13] Mesenchymal stem cells are self-renewing cells that have the capacity to differentiate into adipocytes, chondrocytes, myocytes, and osteoblast. Following treatment with *S. hermanni* extract and osteogenic induction medium for 4 weeks, mesenchymal stem cells were differentiated into osteoblast. Collectively, it can be assumed that sea cucumber *S. hermanni* is able to accelerate wound healing process. Further, these sea cucumber species can be used to prepare lotion or a topical ointment for wound healing management.

Neuroprotection may defined as mechanisms and strategies used in order to protect neuronal cells against injury, apoptosis, dysfunction and or degeneration in the central nervous system (CNS).[3] In the CNS, there are two classes of cells, including neuron, and glia (microglia, astrocytes and the related Schwann cells and oligodendrocytes). Astrocytes plays an important structures that provide housekeeping functions necessary to maintain neuronal function, actively shape synaptic function, and act as neural precursors in adult neurogenic regions. In addition, astrocytes also preserve the host integrity following injury. Recently, Patar et al. (2012) prepared water extract of *S. hermanni* from Malaysia and showed their growth promoting effect to promote proliferation of spinal astrocytes.[14] In pathological cases like spinal cord injury, proliferating reactive astrocytes are proven essential for early regeneration process, provide neuroprotective effects and preserve motor function after acute injury. Further, it was demonstrated by GC-MS results that 37% of the total *S. hermanni* water extracts were comprised of amino acids (37%) followed by hydrocarbon (21%), ester compounds (16%), the orther remaining compounds consisted of phenols, alcohol groups and unidentified compounds. The 2-carbamoyl-3-methylquinoaxaline was found to be the most abundant compounds in *S. hermanni* extracts.[15] Interestingly,

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Table 1
Proximate composition (%) of sea cucumbers (mean values ± standard deviation).

Spesies	Moisture	Protein	Lipid	Ash	Carbohydrates	Ref
Stichopus hermanni (dried)	10.20 ± 0.32	47.00 ± 0.36	0.80 ± 0.02	37.90 ± 0.33	–	27
Thelonata ananas (dried)	15.10 ± 0.29	55.20 ± 0.38	1.90 ± 0.01	25.10 ± 0.30	–	27
Thelonata anax (dried)	1.20 ± 0.06	40.70 ± 0.33	9.90 ± 0.27	39.20 ± 0.28	–	27
Holothuria fuscogilva (fresh)	84.34 ± 0.72	63.64 ± 4.56	1.12 ± 0.28	30.45 ± 6.79		73
Holothuria leucospilota (fresh)	81.41 ± 0.60	45.71 ± 0.20	4.60 ± 0.30	4.30 ± 0.20	44.96 ± 0.30	74
Holothuria scabra (fresh)	85.76 ± 0.30	43.43 ± 0.20	5.66 ± 0.09	2.26 ± 0.15	48.65 ± 0.20	74
Holothuria atra (dried)	9.90 ± 0.01	58.20 ± 0.72	1.32 ± 0.00	31.58 ± 0.42	–	75
Actinopyga mauritiana (dried)	11.60 ± 0.31	63.30 ± 0.43	1.40 ± 0.02	15.40 ± 0.18	–	27

quinoxaline derivatives has been reported to involved in reducing neurological deficits and glia loss after spinal cord injury. These, quinoxaline may contribute to the neuroprotective effects of *S. hermanni*.

Based on several findings it may conclude that *S. hermanni* are valuable source of functional materials and could be introduced for the preparation of novel functional ingredients in food and biomedicine as a good approach for the treatment and or prevention of many diseases. Furthermore, it can be suggested that *S. hermanni* is an alternative source to synthetic ingredients that can contribute in wound healing and neuroprotection. Until now, wound healing as well as neuroprotective activities of *S. hermanni* have been observed in vitro. Therefore, further research studies are needed in order to investigate *S. hermanni* biological activities in vivo as well as human subject.

2.2. T. ananas (local Indonesian name: teripang nanas) and T. anax (local Indonesian name: teripang babi, teripang donga, teripang duyung)

T. ananas and *T. anax* are two sea cucumber species belong to the Stichopodidae family which found in tropical waters. *T. ananas* (Fig. 2) are known as pineapple sea cucumber or prickly redfish. These species is considered as commercial sea cucumber species and one of the most popular edible sea cucumber species consumed in China and Southeast Asian countries.[16] Due to intense commercially exploitation population, these sea cucumber species declined by 80–90% in at least 50% of its range and listed as endangered species by the *International Union for Conservation of Nature*. Medicinal value of *T. ananas* including antioxidant, antiinflammatory, antitumor, antiproliferative, anticoagulant and antiviral effects have been established.

Fig. 2. *Thelenota ananas* from Kupang, Indonesia.

Wu et al. (2010) have isolated novel fucosylated chondroitin sulfate (Fig. 3) from the body wall of the sea cucumber *T. ananas*, which consisted of *N*-acetylgalactosamine (GalNAc), glucuronic acid (GlcUA), fucose and ester sulfate with about 1:1:1:3.7, respectively.[17,18] Fucosylated chondroitin sulfate is a water-soluble depolymerized glycosaminoglycan isolated from echinoderm sea cucumber.[19] Physicochemical of the fucose branch are differ according to the sea cucumber species. Anticoagulant activity of the fucosylated chondroitin sulfate from *T. ananas* as measured by the activated partial thromboplastin time assay varies in proportion to the molecular weight follows a logarithmic-like function.[20] The molar ratio for types of fucose branch found in *T. ananas* is 25:22:53 for 3-monosulfate, 4-monosulfate and 2,4-disulfate, respectively. Fucose content and composition correlate with anticoagulant activities of fucosylated chondroitin sulfate; in addition to the composition. More recently, it was demonstrated that anticoagulant activity of fucosylated chondroitin sulfate from *T. ananas* was mediated by inhibition of intrinsic tenase.[21] However, fucosylated chondroitin sulfate from sea cucumber *T. ananas* also activated factor XII which further lead to hypotension when injected intravenously in rats. Interestingly, the activation of factor XII could be diminished by the low molecular weight fucosylated chondroitin sulfate; suggesting that molecular weight also plays an important role in anticoagulant effect of fucosylated chondroitin sulfate. Not only anticoagulant activity, low molecular weight fragment of fucosylated chondroitin sulfate from sea cucumber *T. ananas* which prepared by free radical depolymerization has been demonstrated to inhibit virus HIV replication.[19] Fucosylated chondroitin sulfate was effective in blocking laboratory strain HIV-1IIIB entry and replication, and inhibiting infection by clinic isolate HIV-1_{KM018} and HIV-$_{1TC-2}$. Fucosylated chondroitin sulfate might possess potential to be further developed as a novel HIV-1 entry inhibitor for treatment of HIV/AIDS patients, particularly for those infected by T-20-resistant variants. However, further study to elucidate fucosylated chondroitin sulfate structure and activity relationship will be required in the near future.

Fucoidan (Fig. 3) is sulfated polysaccharide found in brown algae and sea cucumbers. In sea cucumbers, it was first isolated from *Ludwigothurea grisea*. Recently, low molecular weight fucoidan which composed of a novel tetrafucose repeating units has been isolated from sea cucumber *T. ananas* by enzymatic degradation. Fucoidan from *T. ananas* was proven to possess a significant superoxide radical scavenging activity with an IC_{50} value of 17.46 ± 0.14 μg/mL.[16] The radical scavenging effect of fucoidan on superoxide radicals improved along with the increasing sulfate content. However, additional 2-O-sulphation in a specific residue increase the radical scavenging effect; suggesting that antioxidant activity of fucoidan derived from *T. ananas* depends on the sulfation pattern not simply on sulfate content.

Triterpene glycosides or also referred as saponins are substances consisting of a sugar moiety attached to a triterpene or steroid aglycone. These substances are widely distributed in plants, marine

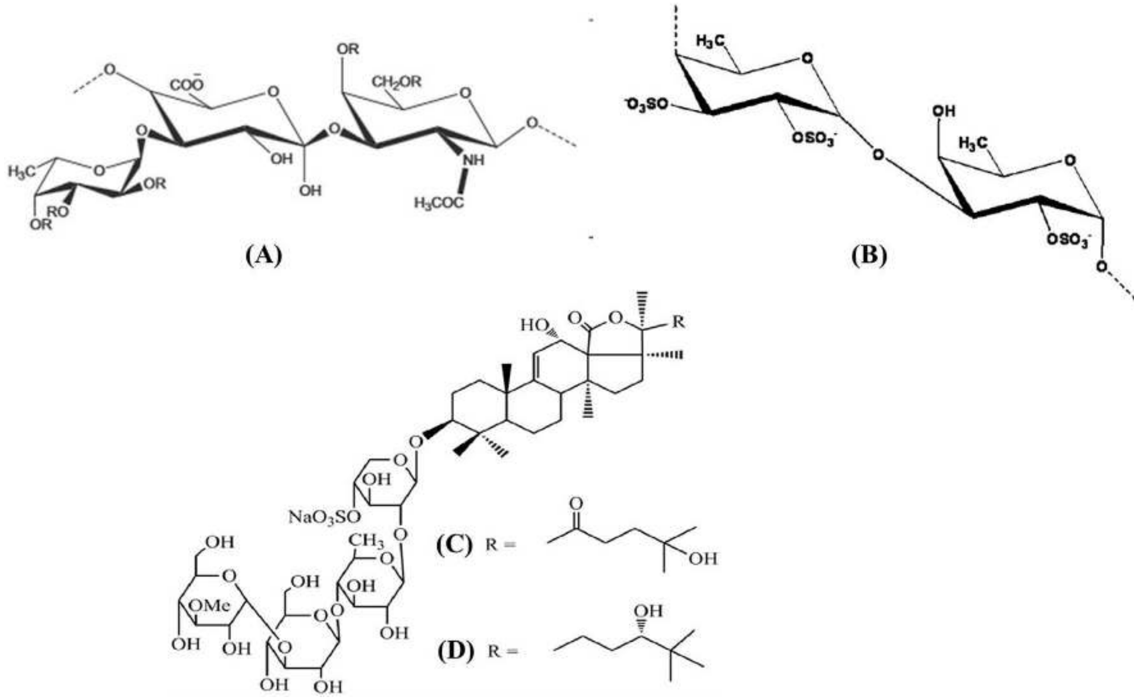

Fig. 3. Functional materials-derived from sea cucumbers. Fucosylated chondroitin sulfate (A); Fucoidan (B); Holothurin A_3 (C); and Holothurin A_4 (D).

invertebrates and are characteristic secondary metabolites of echinoderms, octocorals, and sponges Two triterpene glycosides (stichoposide C and stichoposide D) have been isolated from the *T. ananas* and *T. anax*.[22] The structural differences between stichoposide C and stichoposide D are sugar residue; where stichoposide C has quinovose, and stichoposide D has glucose as the second monosaccharide unit. Stichoposide C showed potent anticancer activity in leukemia cells (HL-60) and mouse subcutaneous tumor cells (CT-26) by inducing apoptosis through the activation of both intrinsic and extrinxic pathway.[23] Further, these compounds also showed antitumor activity in vivo which appears to be related to its membranotropic effects.[24] Antifungal activity of stichoposide C from sea cucumber *T. anax* has also been reported.[25] Guo et al (2016) has investigated antiobesity effect of triterpene glycosides-enriched extracts from 10 sea cucumbers (including *T. ananas*). Among them, *T. ananas* showed potent antiobesity effect through inhibition of pancreatic lipase activity.[26]

Nutritional value of *T. ananas* and *T. anax* (Fig. 4) were characterized by high protein with low lipid content (Table 1). Eicosapentaenoic acid (EPA, C20: 5n-3) was the primary n-3 polyunsaturated fatty acids (PUFA) in *T. ananas* (3.92%) and *T. anax* (3.10%); however, docosahexaenoic acid (DHA, C22: 6n-3) was not detected in both species.[25] EPA is the major n3-PUFA in sea cucumber. Consumption of EPA are associated with decreased risk of coronary heart disease, cancer and wound healing activity.[27]

2.3. H. fuscogilva (local Indonesian name: teripang susu)

The popular name for *H. fuscogilva* (Fig. 5) is white teatfish.[5] *H. fuscogilva* is one of the most prized of the commercially sea cucumber species in the world.[28] These species distributed throughout the Indo-Pacific and has a patchy distribution on reef

Fig. 4. *Thelenota anax* from Halmahera, Indonesia.

Fig. 5. *Holothuria fuccogilva* from Kupang, Indonesia.

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slopes, seagrass, and lagoons at depth of 3–40 m. Due to their ease of capture, strong demand, improved fishing technologies; *H. fuscogilva* wild populations have been depleted by overfishing. In the recent years, stock enhancement and restocking of these species have been practiced successfully in Japan and Republic of Kiribati. For commercial purposes, once *H. fuscogilva* are caught, they usually are gutted, boiled and then dried. In China, *H. fuscogilva* are highly valued for their reputed effects as an aphrodisiac.

The contents of saturated fatty acids, monounsaturated fatty acids (MUFA) and PUFA of *H. fuscogilva* were 59.50 %, 32.19 %, 8.32 %, respectively (Table 2). *H. fuscogilva* have shown higher amounts of SFA and MUFA but lower contents of PUFA. *H. fuscogilva* extracts possess cytotoxic activity against *Candida* sp, *Leishmania* sp, and human supraclavicular lymph node metastasis cells (LoVo).[29] Due to the high content of triterpene glycosides, it is assumed that biological activity of *H. fuscogilva* was due to the presence of triterpene glycosides. In the nature, sea cucumbers are produced triterpene glycosides to protect them against predators, fungi and other protists. These cytotoxic effects of *H. fuscogilva* open the potential of *H. fuscogilva* as antiinfective agents.

2.4. Holothuria atra (local Indonesian name: teripang susu)

H. atra (Fig. 6) is commonly referred as black sea cucumber or lollyfish. Recently, their importance as a source of novel bioactive substances is growing rapidly and researchers have revealed that *H. atra* originated compounds exhibit various biological activities. As an example, phosphate-buffered saline extract of *H. atra* from Malaysia, exhibited significant antimicrobial activity and inhibited the growth of gram-negative and gram-positive bacteria. Interestingly, extracts obtained from the inner part of *H. atra*, showed

Fig. 6. *Holothuria atra* from Lembeh strait, Indonesia.

Table 2
Fatty acid profiles (%) of sea cucumbers (mean values ± standard deviation).

Fatty acids	*S. hermanni*	*T. ananas*	*T. anax*	*H. fuscogilva*	*H.leucospilota*	*H. scabra*	*H. atra*	*A. mauritiana*
C8:0	n.d	n.d	0.03 ± 0.01	n.d	–	–	–	n.d
C10:0	n.d	n.d	0.04 ± 0.01	n.d	–	–	–	25.07 ± 0.04
C12:0	0.12 ± 0.01	0.07 ± 0.01	0.33 ± 0.01	0.06 ± 0.01	–	–	–	n.d
C13:0	0.34 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.18 ± 0.01	–	–	–	0.79 ± 0.06
C14:0	2.29 ± 0.09	7.00 ± 0.12	7.97 ± 0.21	5.53 ± 0.21	11.88 ± 0.27	18.16 ± 0.11	19.44 ± 0.09	2.69 ± 0.04
C15:0	2.46 ± 0.06	4.86 ± 0.09	4.27 ± 0.11	4.56 ± 0.01	–	–	–	1.15 ± 0.05
C16:0	13.77 ± 0.44	22.08 ± 0.41	31.60 ± 0.91	31.86 ± 0.82	35.63 ± 0.10	52.66 ± 0.06	34.21 ± 0.03	n.d
C17:0	3.23 ± 0.04	3.12 ± 0.02	2.68 ± 0.06	2.60 ± 0.06	–	–	–	2.49 ± 0.26
C18:0	10.26 ± 0.12	10.09 ± 0.11	8.93 ± 0.41	9.29 ± 0.12	22.06 ± 0.11	0.44 ± 0.02	3.39 ± 0.03	0.53 ± 0.03
C19:0	2.68 ± 0.03	1.82 ± 0.02	1.14 ± 0.02	1.12 ± 0.02	–	–	–	–
C20:0	4.79 ± 0.16	2.10 ± 0.04	1.67 ± 0.04	1.44 ± 0.03	–	–	–	1.70 ± 0.00
C21:0	4.07 ± 0.10	1.98 ± 0.02	1.33 ± 0.02	1.33 ± 0.02	–	–	–	0.57 ± 0.03
C22:0	2.32 ± 0.08	1.05 ± 0.01	1.05 ± 0.01	1.05 ± 0.01	–	–	–	0.87 ± 0.02
C23:0	0.48 ± 0.01	0.14 ± 0.01	0.09 ± 0.01	0.28 ± 0.01	–	–	–	–
C24:0	0.37 ± 0.01	0.24 ± 0.01	0.29 ± 0.01	0.20 ± 0.01	–	–	–	–
ΣSFA	47.20 ± 1.26	54.70 ± 0.88	61.60 ± 1.85	59.50 ± 1.26	–	–	–	39.62
C14:1	0.27 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.18 ± 0.01	–	–	–	1.42 ± 0.04
C16:1 n-7	4.50 ± 0.23	12.46 ± 0.10	12.77 ± 0.11	21.03 ± 0.22	4.79 ± 0.27	7.57 ± 0.15	4.02 ± 0.18	0.76 ± 0.11
C17:1	n.d	0.18 ± 0.01	0.04 ± 0.01	0.04 ± 0.01				0.53 ± 0.01
C18:1 n-9	3.78 ± 0.31	3.16 ± 0.12	3.15 ± 0.21	3.77 ± 0.12	0.38 ± 0.07	0.12 ± 0.02	0.29 ± 0.02	5.55 ± 0.15
C20:1 n-9	16.93 ± 0.32	6.11 ± 0.09	5.38 ± 0.12	4.36 ± 0.12	–	–	–	0.45 ± 0.05
C22:1 n-9	1.50 ± 0.02	1.72 ± 0.01	1.35 ± 0.01	0.28 ± 0.01	–	–	–	1.77 ± 0.01
C23:1 n-9	5.27 ± 0.21	3.52 ± 0.02	1.67 ± 0.01	1.17 ± 0.01	–	–	–	–
C24:1 n-9	5.47 ± 0.18	2.61 ± 0.06	2.55 ± 0.08	1.36 ± 0.01	–	–	–	–
ΣMUFA	37.70 ± 1.28	29.80 ± 0.42	27.00 ± 0.56	32.19 ± 0.40	–	–	–	28.27
C16:2 n-6	0.17 ± 0.01	0.45 ± 0.01	0.60 ± 0.01	0.64 ± 0.01	–	–	–	–
C16:3 n-3	0.24 ± 0.01	0.04 ± 0.01	0.10 ± 0.01	0.16 ± 0.01	–	–	–	–
C18:2 n-6	2.02 ± 0.04	1.08 ± 0.02	1.21 ± 0.02	1.23 ± 0.02	–	–	13.71 ± 0.04	3.04 ± 0.03
C18:3 n-3	1.56 ± 0.03	0.89 ± 0.01	0.41 ± 0.01	0.59 ± 0.01	0.69 ± 0.04	0.31 ± 0.03	–	1.31 ± 0.0
C18:3 n-6	–	–	–	–	–	–	–	13.05 ± 0.05
C18:4 n-3	0.57 ± 0.01	0.88 ± 0.01	0.33 ± 0.01	0.33 ± 0.01	–	–	–	–
C20:2 n-6	1.32 ± 0.02	0.64 ± 0.01	0.65 ± 0.01	0.37 ± 0.01	–	–	–	0.81 ± 0.01
C20:4 n-6 AA	7.90 ± 0.36	7.54 ± 0.21	5.03 ± 0.22	3.76 ± 0.04	23.23 ± 0.08	19.63 ± 0.04	24.76 ± 0.07	6.86 ± 0.03
C20:5 n-3 EPA	1.31 ± 0.09	3.92 ± 0.04	3.10 ± 0.09	1.24 ± 0.01	1.34 ± 0.13	1.12 ± 0.02	0.17 ± 0.02	4.14 ± 0.04
C22:6n-3 DHA	–	–	–	–	–	–	-	–
ΣPUFA	15.10 ± 0.57	15.40 ± 0.32	11.40 ± 0.38	8.32 ± 0.28	25.26	21.06	38.64	32.12
Σn-6	11.20 ± 0.43	9.26 ± 0.25	6.89 ± 0.26	6.00 ± 0.24	–	–	–	–
Σn-3	3.44 ± 0.14	5.69 ± 0.07	3.84 ± 0.12	2.32 ± 0.11	–	–	–	–
n-6/n-3	3.26 ± 0.14	1.63 ± 0.09	1.79 ± 0.07	2.59 ± 0.11	–	–	–	–
n-3/n-6	0.31 ± 0.14	0.61 ± 0.09	0.56 ± 0.07	0.39 ± 0.11	–	–	–	0.21
References	27	27	27	27	76	76	76	77

stronger antimicrobial action compared to outer part extracts.[30] The higher antimicrobial activity of inner part may correlate to the presences of microorganisms which are taken in together with the food substances. Antifungal activity of *H. atra* from Indonesia has also been reported. The antifungal activity of the above sea cucumber has been determined in *Candida albicans* by agar well diffusion assays. *H. atra* extract were not cytotoxic togingiva-derived mesenchymal stem cell in the concentration of $\leq$ 0.5%; suggesting the extract safety and can be develop for further phase of clinical trial.[31] The use of human cells could increase the correlation between safety studies and clinical trials, an important benefit since conventional animal models of toxicity are not always predictive of human responses. Extract of *H. atra* were also effective against the *Malassezia furfur* fungus that causes tinea versicolor.[32] More recently, antifungal activity of *H. atra* extracts against various fungal strains such as *Trichoderma viride, Aspergillus niger, Aspergillus flavis, C. albicans* and *Penicillium chrysogenum* has also been reported.[33] Antifungal activity of *H. atra* has opened the potency of sea cucumber as antifungal agent and could become the novel alternative solution as oral therapy of candidiasis and others.

Dhinakaran and his colleagues studied pharmacological effect of *H. atra* from the Indian ocean.[34] They demonstrated antiinflammatory, analgesic activity, as well as antipyretic activity of *H. atra* extracts. *H. atra* extract showed potent inhibitory activity against tumor growth in human cervical cancer cells (HeLa) as well as human breast cancer cells (MCF-7).[35] Extract from *H. atra* also showed hepatoprotective activity against thioacetamide-induced liver fibrosis in rats. Subchronic administration of *H. atra* extract at the 200 mg/kg to normal rats showed no toxic side effects on the host as evident by the insignificant changes in the relative weights of the liver, heart, kidneys, and spleen, favorable growth rate, and survival rate (100%) of the animals.[36] Hepatoprotective and curative effects of the *H. atra* extract against 7,12-dimethylbenz [a]anthracene (DMBA)-induced hepatorenal diseases in rats has also reported.[37] DMBA intake produced oxidative stress in liver of rats. The increased malondialdehyde concentration level suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanisms to prevent formation of excessive free radicals. Treatment with *H. atra* extract prior to or after DMBA intoxication significantly reversed these changes, suggesting that the mechanism of *H. atra* extract hepatoprotection may be due to its antioxidant effect.

High-performance liquid chromatographic (HPLC) analysis of the *H. atra* extract revealed the presence of phenolic components, such as chlorogenic acid, pyrogallol, rutin, coumaric acid, catechin, and ascorbic acid.[36] Supporting HPLC analysis, GC-MS results showed that the presence of 59 compounds belongs to the groups of flavonoids, phenolic, terpenoids, saponins, and alkaloids.[35] It was also reported that epidermal tissues, ovaries, viscera, gut contents of *H. atra* contained carotenoid pigments, mycosporine-like amino acids (MAAs) and other bioactive compouns such as gadusol.[38] The presence of the active phenolic and carotenoids compounds in the body wall of the *H. atra* may be due to phenolic and carotenoid-rich materials such as phytoplankton and particles derived from degrading seaweeds which are the main food sources for sea cucumbers. Collectively, scientific evidence provides information that *H. atra* could be explored as a potential source of high-value bioactive metabolites and could be used in the food as well as pharmaceutical industry.

2.5. *Holothuria leucospilota (local Indonesian name: getah, cera, jepun, keeling, talengko)*

Sea cucumber *H. leucospilota* (Fig. 7) is a tropical holothurian species that is widely distributed in shallow reef areas (e.g. reef flats, shallow costal lagoons, seagrass beds) of the tropical and subtropical Indo-Pacific region, including the Red Sea.[39] These sea cucumber species contain significant amount of carotenoids including β-carotene, β-echinenone, canthaxanthin, phoenicoxanthin, astaxanthin, lutein, zeaxanthin, diatoxanthin, alloxanthin, ketozeaxanthin, fucoxanthin, fucoxanthinol and idoxanthin.[40] Carotenoids are linear polyenes that function as light energy harvesters and antioxidants that inactivate reactive oxygen species (ROS) formed by exposure to light and air.[3] Antioxidants may have a positive effect on human health as they can protect human body against damage by ROS, which attack macromolecules such as membrane lipids, proteins and DNA, lead to many health disorders such as diabetes mellitus, neurodegenerative and inflammatory diseases with severe tissue injuries.[41] It has been demonstrated that *Holothuria leucospiota* extract and their bioactive compounds have potential antioxidant activity. Antioxidant activity of *H. leucospilota*-derived carotenoids have been determined by various methods such as 1,1-diphenyl-2-picrylhydrazyl (DPPH), linoleic acid free radical scavenging, as well as β-carotene bleaching assays.[42,43]

Fig. 7. *Holothuria leucospilota.*

Many bioactive metabolites have been characterized for the protection against some form of cancer cells. Sea cucumber *H. leucospilota* have also been considered as potential sources of cytotoxic compounds for such observations and much research have been conducted. Organic extract of *H. leucospilota* were found to be cytotoxic against Hela cells with IC_{50} values of 50 μg/ml.[44] Further, crude triterpene glycosides from *H. leucospilota* found to be cytotoxic against human lung carcinomana cells (A549) and skin melanoma cells (B16F10) with an IC_{50} values of 6 μg/ml and 10 μg/ml, respectively.[45–47] In addition, triterpene glycosides from the sea cucumber *H. leucospilota* has been isolated, namely leucospilotaside A, leucospilotaside B, leucospilotaside C, echinoside B, holothurin A, holothurin B, holothurin B_2.[48–51] It was reported that, sea cucumber triterpene glycosides exhibit pronounced anticancer effects by direct interaction with tumor cells in the sub-cytotoxic range of concentration.[52]

2.6. *Holothuria scabra (local Indonesian name: teripang pasir, putih, gosok, kamboa)*

H. scabra (Fig. 8) is also known as sandfish.[5] Several numbers of studies have reported antimicrobial effect of *H. scabra* extracts. Extracts of *H. scabra* were active against bacteria such as *Aeromonas hydrophila*, *Escherichia coli*, *Enterococcus* sp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus* and *Vibrio harveyi*, and fish-borne mold, *Aspergillus* sp.[53] Later, the possible involvement of T-antigen binding lectin in *H. scabra*

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Fig. 8. *Holothuria scabra.*

antibacterial activity was demonstrated.[54] The expression of defensive lectin is induced by bacterial challenge, wherein cell wall glycoconjugates of bacteria are involved in lectin induction. Further, lectin also showed strong broad spectrum antibacterial activity.

Two new triterpene glycosides isolated from *H. scabra* collected from the South China Sea, scabraside A and B showed strong cytotoxicity against HL-60, MOLT-4, A549, and BEL-7402 cells. Scabraside A and B exhibit the same common structural features, i.e., the presence of 12- and 17-hydroxy groups in the holostane-type triterpene aglycone with a 9 (11)-ene bond, but are different in the side chains of the triterpene aglycone.[55] Scabraside D which also a novel triterpene glycosides from *H. scabra* showed potent inhibitory activity against P-388, A549, gastric cancer (MKN-28), human colon cancer (HCT116), and MCF-7 cells with an IC_{50} values of 0.96 μmol/l, 1.72 μmol/l, 1.27 μmol/l, 1.63 μmol/l, and 1.80 μmol/l, respectively.[56] Subsequently, it was demonstrated that Scabraside D induced disruption in mitochondria through the alteration of Bax/Bcl-2 ratio which stimulates the intrinsic apoptotic pathway. Disruption of mitochondria lead to release of cytochrome C and further stimulates caspase-9 and induced caspase-3 activation.[57]

In addition, two other new triterpene glycosides, namely holothurin A_3 and A_4 (Fig. 3) were isolated from the methanol extract of *H. scabra* from Vietnam. Both saponins were found to be strongly cytotoxic to human epidermoid carcinoma and human hepatoma (HepG2) cells with IC_{50} of 0.87 and 0.32 μg/mL (for holothurin A_3) and of 1.12 and 0.57 μg/mL (for holothurin A_4), respectively.[58] Aqueous extract of *H. scabra* were not active against in human cervical cancer (C33 A) and A549 cells.[59] Several reviews suggested that the bioactivity of sea cucumber triterpene glycosides is a resultant of its strong membranolytic activity. The membranolytic activity is a function of the structural feature of the glycoside.[60]

2.7. *A. mauritiana (Indonesia local name: teripang buntal, teripang ballang ulu)*

A. mauritiana commonly known as Surf Redfish, the body of this sea cucumber is arched on the upper side and flat on the lower side. *A. mauritiana* is found in sandy ares, sea grasses, and sand lagoons in the coral reefs. These species is distributed up to 30 m deep, but abundantly found in between 5–10 m deep. *A. mauritiana* can grow to a length of 25 cm.[61] These species is amongst the most widespread holothurians, highly valued, in great demand and harvest in large number. Adults' *A. mauritiana* are dried and processesed for their meat which is exported primarily to East Asia countries. The meat of *A. mauritiana* is high in protein, low in fat and believed to be aphrodisiac.[62]

According to the study carried by Wen *et al.* (2010) on the chemical composition of composition of *A. mauritiana*, the major components is protein (63.30% ± 0.43%) with low percentage of lipid (1.40% ± 0.02%). High protein content of *A. mauritiana* can be hydrolized to obtain bioactive peptides.[63] The content of essential amino acids (EAA) in *A. mauritiana* was lower than non-essential amino acids (NEAA) with the ratio of EAA: NEAA are 0.44 ± 0.01.[27] Glycine is the most abundant amino acids in these species which constituted around 11 % of the total amino acids, followed by glutamic acid and proline. Glycine is used to help create muscle tissue and convert glucose into energy, it is also essential to maintain healthy central nervous and digestive systems, and recently has been shown to provide protection from some types of cancer and antioxidant activities.[64] It has been found also that glycine reduced serum total cholesterol level. On the other side lysine: arginine ratio was low; it has been reported that this low ratio reduced concentrations of cholesterol in the serum and aorta and provide hypocholesterolemic effects.[65]

3. Potential of sea cucumbers as functional ingredients in pharmaceuticals and foods industry

The latest trend in food and pharmaceutical sector has been the recovery of functional ingredients from marine resources. It is well known that consumption of marine foods rich in functional ingredients beyond meeting basic nutritional needs, is also fundamental for diseases risk reduction and health promotion (Fig. 9). The composition of different sea cucumbers described in the previous section showed that these organisms can be interesting natural sources of functional ingredients. In general, sea cucumber represents good nutritional values which make them good candidates as source of amino acids, triterpene glycosides, PUFA, polysaccharides, carotenoids, vitamin, minerals, collagen, gelatin, phenolic, flavonoids, and bioactive peptides. Additionally, sea cucumber presents low contents in lipids.

Sea cucumbers are manly used in Asian cuisines for centuries. Following a complicated process of preparation, the sea cucumber dried meat can be used in soups, stir-fried dishes, and also be pickled. A traditional Chinese preparation is to poach the sea cucumber, and cover with a thick sauce of garlic, ginger, onion and soy sauce. These marine organisms have also been used for traditional medicinal purposes since ancient times and recently, many studies provide scientific evidences that sea cucumber contain multitude biologically active materials that provide health benefit effects such as antioxidant, antibacterial, antifungal, antiviral, antiinflammatory activities, neuroprotective activities, etc.

Sea cucumber, from a nutritional point of view, is an ideal tonic food with medicinal value, as it contains a higher level of protein and a lower level of lipid than most other foods. The main part of the described sea cucumber presents a high collagen and gelatin contents. The body wall of sea cucumber, which consists of insoluble collagen, has been used as a nutrient supplement of hematogenesis. The use of commercial enzymes to produce collagen from sea cucumbers appears to be a feasible process to convert an underutilized species to a more useful product that contains a functional ingredient for the food and pharmaceutical industry. However, further studies are needed to isolate and identify the specific peptides and or amino acid sequences in sea cucumber collagen hydrolysates with functional activity for potential utilization in food and pharmaceutical production. Bioactive peptides are specific protein fragments that have a positive impact on a body's function or condition and may ultimately influence human health. Bioactive peptides must be provided by a safe, reliable, and consistent oral

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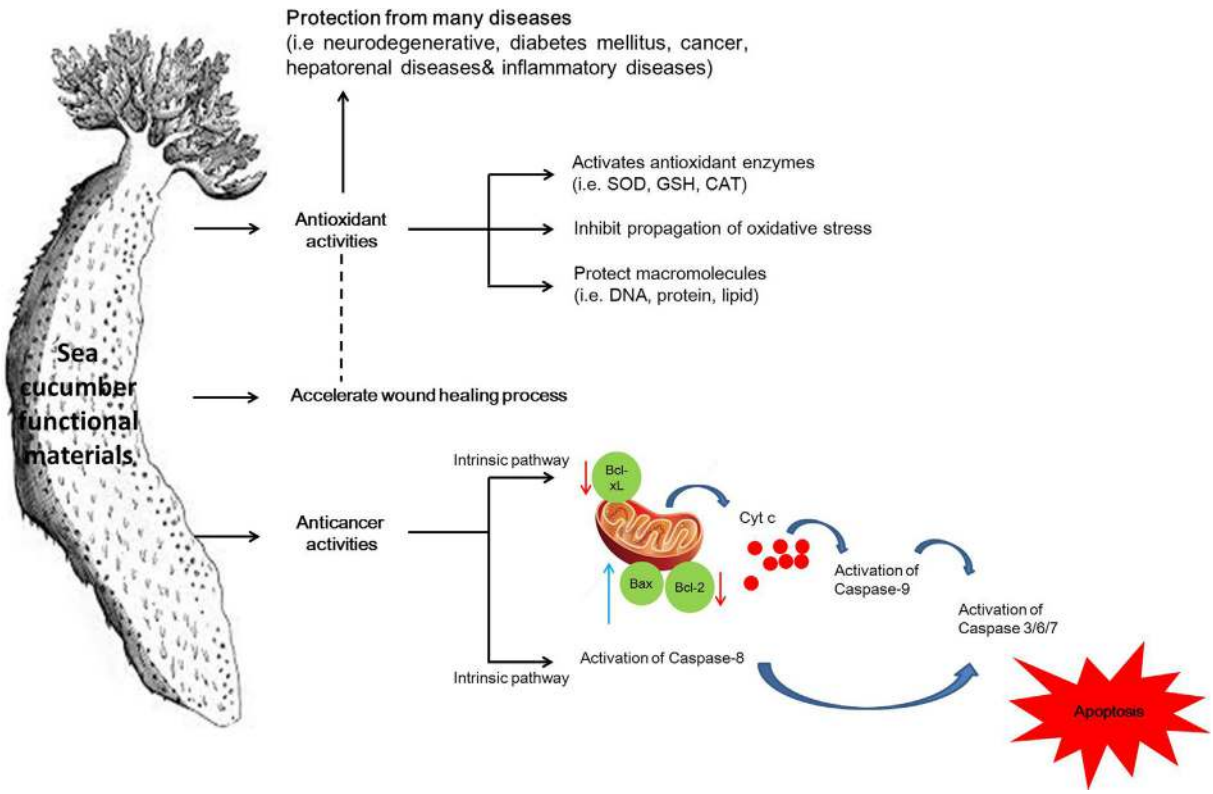

Fig. 9. Biological activities of sea cucumber-derived bioactive materials.

delivery system.[66] Marine-derived bioactive peptides have been shown to possess many physiological functions, including antihypertensive or angiotensin-I-converting enzyme inhibition, antioxidant, anticoagulant, and antimicrobial activities. Some of these bioactive peptides may have potential for human health promotion and disease risk reduction. Bioactive peptides may be produced by several methods, including solvent extraction, enzymatic hydrolysis, and microbial fermentation. Gelatin from sea cucumber is considered to be more valuable than gelatins from others organisms because of its characteristic amino acid composition, especially the essential amino acids.[67]

Another class of compounds of great interest that are common in sea cucumbers described in this article is sulfated polysaccharides. As an example, *T. ananas* contains fucoidan, and fucosylated chondroitin sulfate, whereas *S. hermanni* contain significant amount of sulfated glycosaminoglycan. In the further study, novel extraction and separation techniques, such as supercritical CO_2 extraction, ultrasonic-aided extraction and membrane separation technology can be applied in development of sulfated polysaccharides from sea cucumbers. In addition, PUFA probably the substances that have attracted major interest since PUFA content in sea cucumber are varied. As an example, sea cucumber species from abyssal have shown higher amounts of SFA and MUFA but lower contents of PUFA compared to the tropical and temperate regions. Variations of fatty acid components among species of different sea cucumbers as well as from different regions might be linked to factors such as diet, natural habitat climatic conditions and post-harvest processing regimes, especially the drying temperature.

The other compounds of great importance derived from sea cucumber described in this work are triterpene glycosides. Extensive research has revealed that the sea cucumbers gain healing power due to the presence of triterpene glycosides. These compounds exhibit wide spectrum of biological activities such as antifungal, cytotoxic, hemolytic, and immunomodulatory effects. Linear with the increased understanding of the health beneficial properties of sea cucumbers-derived compounds, considerable efforts have been exerted in discovering more direct therapeutic-related food and pharmaceutical applications, but, despite high expectations, no commercially successful product ranges have yet been developed utilizing sea cucumber derived compounds targeting optimum health and nutrition for human. Up to now, there is very few sea cucumbers-based products can be seen covering food and pharmaceuticals market. However, as a functional food product in the market, sea cucumber is not up to the expectation. Fortification of food products having higher consumer acceptance with sea cucumber health benefit effects and natural sources would provide an opportune approach to popularize sea cucumbers based products among consumers. Sea cucumber based-functional foods present major challenges in the food industry as they appear to be a new and unfamiliar territory for product developers in marketing and developing business strategies. Translating scientific advances and nutritional innovations into consumer products is a costly and complex process. Sound science must underlie the development, marketing, and regulation of these new functional foods to gain success.[68] The increasing awareness of problems is the skepticism of consumers of sea cucumbers. Hence, successful functional foods development is therefore a question of combining nutritional/medical insight, technological capabilities, and a thorough understanding of consumers.

Importantly, when considering sea cucumbers sustainability for foods and pharmaceuticals commercialization, these organisms are susceptible to overexploitation due to their late maturity, density-dependent reproduction, and low rates of recruitment. Furthermore, the high value of some species, the ease with which such shallow water forms can be harvested, and their vulnerable nature due to their biology, population dynamics and habitat preferences

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Table 3
Heavy metals content in sea cucumber.

Sea cucumber species	Mean concentration of heavy metals						
	Pb	Cd	Zn	Cu	Cr	Mn	Ref
S. hermanni	0.52 mg/kg	0.03 mg/kg	33.00 mg/kg	3.00 mg/kg	1.60 mg/kg	9.10 mg/kg	78
T. ananas	0.24 mg/g	2.43 mg/g	15.22 mg/g	1.34 mg/g	3.33 mg/g	5.65 mg/g	79
T. anax	0.19 mg/g	0.04 mg/g	9.98 mg/g	0.95 mg/g	1.46 mg/g	4.04 mg/g	79
H. fuscogilva	0.69 mg/kg	1.10 mg/kg	11.00 mg/kg	57.00 mg/kg	1.30 mg/kg	9.40 mg/kg	78
H. leucospilota	0.3 mg/g	0.05 mg/g	16.27 mg/g	0.87 mg/g	1.55 mg/g	2.24 mg/g	79
A. mauritiana	n.d	n.d	52.30 mg/kg	51.10 mg/kg	n.d	58.5 mg/kg	77

all contribute to the overexploitation and collapse of fisheries that have been reported in several areas in Indonesia. During these years, the shortage of sea cucumber seed was a bottleneck for developing aquaculture. The potential area for sea farming of sea cucumber in Indonesia is around 720.500 ha; however, only a few areas are used, e.g. in East Java, West Nusa Tenggara, North Sulawesi, Central Sulawesi, South-East Sulawesi, Molucca and Papua. Supporting aquaculture for sea cucumber based functional foods development, Research Center for Oceanography-LIPI currently developing research on sea cucumber aquaculture in Marine Bio-industry Implementation Unit, Research Center of Oceanography LIPI Mataram.[69]

4. Toxic materials in sea cucumbers

The ocean is vulnerable to human influences such as pollutions and toxic chemicals. Toxic chemicals released to the environment from point sources such as industrial and municipal discharges and from nonpoint sources such as agricultural runoff and atmospheric deposition have contaminated surface waters and their sediments and then flow to the ocean.[70] One of the greatest problems with many of these contaminants is their tendency to build up in the bodies of aquatic organisms in increasingly high levels. Uptake of a toxin from the water and from eating other contaminated organisms is called bioaccumulation. Bioaccumulation of heavy metals in sea food poses a significant human health concern.

Increased levels of heavy metals in seafood may constitute a food safety risk. Several cases of human disease, disorders, malfunction and malformation of organs due to metal toxicity have been reported. Heavy metals are accumulated in vital organs in the human body such as the kidneys, bones and liver and are associated with numerous serious health disorders. In addition, individual metals exhibit specific signs of their toxicity.[71] For example, Arsenic (As), is best known as a poison and can generate both acute and chronic toxicity. Ingestion of As may induce peripheral vascular diseases and skin disease such as hyperkeratosis. Intake of lead (Pb) and cadmium (Cd) can cause kidney damage; with long-term exposure to Cd may cause skeletal damage, which may result in fractures.[72] Therefore, safety of seafood is becoming of great concern in seafood consumption. In order to develop sea cucumber as functional foods, it is very important to estimate the potential and real risk for human health derived from sea cucumber consumption, heavy metals concentrations must be characterized. Table 3 summarized heavy metals content in sea cucumber.

Up to now, there are no international (Codex Alimentarius 1995) as well as local standards (Ministry of Health, Republic of Indonesia) set as limits of Pb, Cd, Zn, Cu, Cr, Mn, As, Hg and Al specifically for Echinodermata. However, considering the maximum limit for Pb in other marine products (i.e.fish, molluscs, shellfish and crustaceans) is 0.3 mg/kg; Pb concentrations in some sea cucumber are acceptable. European Comission set the lowest maximum limit set for Cd is 0.05 mg/kg for unspecified fish (EC 2006). Cd levels obtained in sea cucumbers presented in this study were below that value. In comparison with the level of concern set for similar marine products, the concentration of heavy metals in sea cucumber were generally below the level of concern of international standards; however, continuous care must be taken to monitor the heavy metal levels in sea cucumber.

5. Conclusions

Sea cucumbers showed high potential as natural ingredients in foods as well as pharmaceutical industry; hence, these marine organisms can be used maximally in the research areas of new drug development. However, understanding the specific structures and bioactivities relationship of marine algal fibers is still a great challenge, further there is considerable gap in this area compared with isolation rate of new compounds. Adequate clinical trials are needed in drug development of sea cucumber-derived bioactive materials. More importantly, once their biological activities and health benefit effects are demonstrated, new aspects needs to be address such as culture of sea cucumber, production of functional ingredients at industrial scale, extraction and purification of functional ingredients, and scientifically demonstrated health properties.

Conflict of interest

The authors declares no conflict of interest.

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