PHARMACIA

Pharmacia 68(3): 561–572
DOI 10.3897/pharmacia.68.e69140

Review Article

Current prospects of nutraceutical and pharmaceutical use of sea cucumbers

Abdullah Rasyid[1,2], Yasman Yasman[3], Masteria Yunovilsa Putra[2]

1 Magister Program of Marine Science, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, Depok, Indonesia
2 Research Center for Biotechnology, Indonesian Institute of Sciences, Bogor, Indonesia
3 Research Group of Metabolomics and Chemical Ecology, Department of Biology, Faculty Of Mathematics and Natural Sciences, Universitas Indonesia, Depok, Indonesia

Corresponding author: Masteria Yunovilsa Putra (masteria.yunovilsa@gmail.com, mast001@lipi.go.id)

Received 26 May 2021 ♦ **Accepted** 24 June 2021 ♦ **Published** 23 July 2021

Citation: Rasyid A, Yasman Y, Putra MY (2021) Current prospects of nutraceutical and pharmaceutical use of sea cucumbers. Pharmacia 68(3): 561–572. https://doi.org/10.3897/pharmacia.68.e69140

Abstract

Sea cucumbers are a group of marine invertebrates harvested throughout tropical and subtropical regions. In addition to their nutritional value, they have economic importance in the pharmaceutical and cosmetic industries. The most frequently consumed portion is the body wall, which also contains most of the active constituents known to have anticancer, anti-inflammatory, antimicrobial, antioxidant, and other bioactive properties. This review covers the literature from the last decade (2011–2020) regarding the bioprospecting of sea cucumbers to discover resources for pharmaceutical and cosmetic products.

Keywords

cosmetics, nutritional, pharmaceutical, sea cucumber

Introduction

Sea cucumbers are marine invertebrates distributed worldwide from shallow to deep-sea habitats (Rahman and Yusoff 2017; Gocer et al. 2018). At present, there are approximately 1250 species of sea cucumber (phylum: Echinodermata; class: Holothuroidea) (Kareh et al. 2018), of which 58 are considered commercially important. Sea cucumbers have been harvested and traded in more than 70 countries around the world. They are exploited in industrialized, semi-industrialized, and small-scale fisheries in arctic regions, temperate zones, and the tropics (Purcell et al. 2012). In the global market, sea cucumbers are typically processed as a dried product, known as beche-de-mer, trepang, or haisom (Sicuro and Levine 2011). While Asian countries are the predominant consumer market for sea cucumbers, they have gained in popularity around the world in recent years, resulting in a dramatic increase in demand (Aydin et al. 2011; Liu et al. 2017). Overfishing has depleted the wild stocks of sea cucumbers, with 70% of tropical sea cucumbers reported being fully exploited, over-exploited, or depleted (Purcell et al. 2012), encouraging the culturing of this economically valuable resource.

Sea cucumber is regarded as a delicacy in the Far East and Southeast Asia, where it is prepared locally in various traditional ways, both fresh and dried (Omran 2013). Along with their nutritional value, sea cucumbers are therapeutically and medically valuable as an important source of biological molecules with anticoagulant, antioxidant, anticancer, antimicrobial, and antiviral activities (Kareh et al. 2018). Over the past decades, the focus of research and industry has shifted to marine organisms for the discovery of bioactive substances due to shortages in terrestrial bioresources (Guo et al. 2020). Compounds isolated from

PENSOFT.

marine organisms are typically unique from those found in terrestrial organisms. At present, more than 40,000 natural products, many displaying pharmacological activities, have been isolated from marine organisms, including sponges, tunicates, mollusks, cnidarians, echinoderms, bryozoans, brown algae, red algae, green algae, and other microorganisms (Liu et al. 2017). Such biologically active compounds can be directly used as pharmaceutical substances or as prototypes for the development of compounds with a novel or improved pharmacological properties (Khotimchenko 2018). Additionally, sea cucumber components, such as polysaccharides, collagen, mycosporine-like amino acids, saponin, vitamins, and minerals(Siahaan et al. 2017), have the potential for use in the cosmetic industry.

Nutritional value of sea cucumbers

Sea cucumbers are extensively consumed in China and Japan (Ram et al. 2014). As such, the biochemical content of sea cucumber is largely explored in relation to its nutritional value (Al Azad et al. 2017). As a commercial product, sea cucumbers are graded based on parameters, such as species, odor, taste, body wall thickness, color, size, shape, texture, appearance, market demand, and moisture content appropriate to storage (Ram et al. 2014). The high-quality proteins, low level of fat, rich amino acid profile, and desirable trace minerals found in sea cucumbers contribute to their high nutritional value (Ceesay et al. 2019). Additionally, they are believed to have therapeutic efficacy for various diseases and conditions, such as hypertension, rheumatism, asthma, incisions, burns, and constipation, which can be traced to their biochemical composition (Kim et al. 2016).

Proximate composition of sea cucumbers

The proximate composition of sea cucumbers varies with species, feeding regimes, geographical location (Oh et al. 2017), and seasonal variation (Aydin et al. 2011) (Table 1). While sea cucumbers are known to have a high protein content, they are primarily consumed because of their flavor rather than nutritional value. Informing consumers on the nutritional composition of sea cucumbers may help them to appreciate the benefits of including this seafood in their diet (Barzkal et al. 2017).

The proximate moisture, ash, protein, and fat composition of fresh sea cucumbers varies from 67.93–93.01%, 2.01–7.86%, 3.40–8.86%, and 0.09–2.43%, respectively. Most fresh sea cucumbers have higher moisture content in their body wall than other seafood (Salarzadeh et al. 2012). Their high moisture content was considered as a tonic by fisheries when going to sea. Ash content varies with the mineral deposits and other inorganic matter in sea cucumber (Al Azad et al. 2017). The species, food, feeding patterns, environmental conditions, and reproductive activity may influence sea cucumber fat content (Lee et al. 2012).

The drying process alters the moisture, ash, protein, and fat content of fresh sea cucumber to 4.03–16.19%, 5.75–48.22%, 36.99–72.25%, and 0.55–8.19%, respectively. Fully dried sea cucumber material may contain high protein and is sold as a nutraceutical in capsule and tablet forms (Bordbar et al. 2011).

Mineral content of sea cucumbers

Minerals, such as calcium, sodium, magnesium, and phosphorus, are essential to humans. Unfortunately, information about mineral content in sea cucumbers is limited (Gocer et al. 2018). However, measurements of calcium (656–5700 mg/100 g dry weight (DW)), potassium (30–360 mg/100 g DW), and magnesium (155–4750 mg/100 g DW) suggest that sea cucumbers could be a viable alternative natural source of minerals (Table 2). Major mineral content appears to vary by sea cucumber species. Season, maturity, age, water temperature, availability of food, type of diet, and feeding system are reported to influence macro mineral levels in seafood (Oglunoglu and Oglunoglu 2017). For example, the phosphorus content is considerably high in *Holothuria scabra* (86.69 mg/100 g wet weight (WW)) (Table 2). In addition, sea cucumbers are reported to contain vitamins, including A, B1, B2, and B3 (Bordbar et al. 2011).

Table 1. Proximate content (%) of fresh and dried sea cucumbers (mean values + standard deviation).

Sea cucumbers	Moisture	Ash	Protein	Fat	References
Fresh sea cucumbers					
Apostichopus japonicus	90.72 + 0.35	3.20 + 0.40	3.40 + 0.18	0.14 + 0.05	Lee et al. (2012)
Holothuria arenicola	93.01 + 0.01	2.01 + 0.01	4.40 + 0.09	0.60 + 0.04	Barzkar et al. (2017)
Holothuria mammata	85.24 + 0.30	5.13 + 0.10	7.88 + 0.30	0.09 + 0.08	Aydin et al. (2011)
Holothuria tubulosa	84.30 + 0.20	6.13 + 0.60	8.02 + 0.30	0.18 + 0.05	Aydin et al. (2011)
Holothuria poli	81.24 + 0.40	7.85 + 0.90	8.66 + 1.20	0.15 + 0.04	Aydin et al. (2011)
Holothuria parva	67.92 + 3.81	32.74 + 1.17	17.61 + 0.95	2.43 + 0.53	Salarzadeh et al. (2012)
Holothuria scabra	84.55 + 001	7.38 + 0.07	6.95 + 0.04	0.78 + 0.02	Ardiansyah et al. (2020)
Stichopus horrens	92.88 + 0.03	5.41 + 0.06	3.47 + 0.15	0.41 + 0.01	Barzkar et al. (2017)
Dried sea cucumbers					
Actinopyga echinites	9.30 + 0.10	29.25 + 0.25	60.20 + 0.20	1.25 + 0.01	Ibrahim et al. (2015)
Holothuria atra	9.90 + 0.01	31.58 + 0.42	58.20 + 0.72	1.32 + 0.01	Ibrahim et al. (2015)
Holothuria lessoni	13.47 + 0.89	34.51 + 0.59	41.18 + 2.11	3.04 + 0.12	Andriamanamisata and Telesphore (2019)
Holothuria scabra	9.12 + 0.25	5.76 + 0.37	72.25 + 0.59	1.95 + 0.11	Sumarto et al. (2019)
Holothuria tubulosa	16.19 + 1.51	46.43 + 0.51	44.55 + 1.01	0.71 + 0.12	Sicuro et al. (2012)
Holothuria poli	22.03 + 3.07	48.22 + 1.09	36.99 + 0.62	0.55 + 0.12	Sicuro et al. (2012)
Parastichous californicus	4.03 + 0.19	25.73 + 0.25	47.04 + 0.53	8.19 + 0.27	Bechtel et al. (2013)

Table 2. Minerals content (mg/100 g) of fresh and dried sea cucumbers (mean values + standard deviation).

Mineral	*Actinopyga mauritiana*[a]	*Holothuria arenicola*[a]	*Holothuria poli*[a]	*Holothuria scabra*[b]	*Holothuria tubulosa*[a]	*Holothuria (pratyperona) sanctori*[a]	*Parastichopus californicus*[b]
Nickel	0.19 + 0.02	0.25 + 0.03	-	-	-	-	0.40 + 0.13
Manganese	5.23 + 0.04	5.85 + 0.07	-	-	-	-	4.36 + 0.43
Copper	0.95 + 0.01	5.11 + 0.10	-	-	-	-	0.35 + 0.02
Zinc	4.28 + 0.06	5.23 + 0.04	1.74 + 0.04	-	1.40 + 0.06	-	4.04 + 0.43
Sodium	4750 + 12.50	6220 + 9.10	-	380.79 + 2.21	-	552.39 + 0.29	8.80 + 0.02
Potassium	520 + 3.54	620 + 9.00	-	30.08 + 0.08	-	-	0.40 + 0.01
Calcium	5700 + 7.07	2610 + 8.54	-	1374.51 + 4.25	-	656.73 + 0.12	2.50 + 0.02
Magnesium	4750 + 2.86	1870 + 11.36	-	240.88 + 2.88	-	155.77 + 0.15	1.40 + 0.01
Iron	-	-	2.45 + 0.06	4.59 + 0.02	1.94 + 0.02	-	-
Phosphorus	-	-	-	86.69 + 2.00	-	10.91 + 0.19	0.50 + 0.01
Selenium	-	-	0.42 + 002	-	0.42 + 0.04	-	-
References	Haider et al. (2015)	Haider et al. (2015)	Sicuro et al. (2012)	Ardiansyah et al. (2020)	Sicuro et al. (2012)	Gocer et al. (2018)	Bechtel et al. (2012)

Note: [a] = dried sea cucumber; [b] = fresh sea cucumber.

Table 3. Amino acids profile (mg/100 g) of dried sea cucumbers (mean vaues + standard deviation).

Amino acids	*Actinopyga mauritiana*	*Bohadschia marmorata*	*Holothuria arenicola*	*Holothuria scabra*	*Holothuria leucospilota*	*Holothuria tubulosa*	*Holothuria poli*	*Parastichopus californicus*
Histidine	0.65 + 0.03	0.31 + 0.02	1.41 + 0.02	0.21 + 0.02	0.36 + 0.01	0.82 + 0.12	0.88 + 0.11	1.70 + 0.01
Threonine	2.19 + 0.09	0.37 + 0.03	4.59 + 0.07	1.98 + 0.02	2.73 + 0.02	2.74 + 0.28	1.89 + 0.19	5.70 + 0.01
Valine	2.13 + 0.10	2.00 + 0.02	2.94 + 0.03	1.79 + 0.20	1.51 + 0.01	1.23 + 0.12	1.37 + 0.21	4.80 + 0.01
Isoleucine	0.43 + 0.01	0.58 + 0.02	3.37 + 0.24	0.58 + 0.01	0.49 + 0.01	0.88 + 0.03	0.72 + 0.03	3.60 + 0.01
Phenylalanine	0.99 + 0.02	1.19 + 0.01	2.80 + 0.26	1.07 + 0.01	0.75 + 0.02	0.48 + 0.34	0.72 + 0.12	3.80 + 0.01
Leucine	1.58 + 0.02	1.73 + 0.03	5.19 + 0.06	1.89 + 0.02	1.86 + 0.01	1.56 + 0.03	1.37 + 0.16	5.30 + 0.01
Methionine	0.42 + 0.02	0.41 + 0.02	0.43 + 0.07	0.29 + 0.03	0.19 + 0.01	0.63 + 0.04	0.62 + 0.06	2.20 + 0.10
Cysteine	-	-	-	-	-	0.22 + 0.06	0.46 + 0.06	12.30 + 0.20
Lysine	3.52 + 0.01	1.53 + 0.01	2.06 + 0.06	0.75 + 0.01	0.73 + 0.02	1.11 + 0.15	0.77 + 0.07	4.10 + 0.10
Arginine	0.99 + 0.01	1.67 + 0.01	6.12 + 0.06	1.83 + 0.05	1.71 + 0.02	4.14 + 1.09	3.58 + 0.21	8.40 + 0.10
Alanine	6.45 + 1.02	6.53 + 1.07	11.72 + 0.04	6.52 + 1.05	5.80 + 1.03	4.60 + 0.41	3.71 + 0.23	5.60 + 0.10
Glutamic acid	5.25 + 0.10	5.16 + 0.10	11.77 + 0.02	4.97 + 0.10	5.64 + 0.12	8.03 + 0.34	6.18 + 0.38	13.10 + 0.20
Serine	2.11 + 0.10	2.31 + 0.10	4.54 + 0.11	2.35 + 0.01	2.33 + 0.30	1.81 + 0.13	1.46 + 0.08	3.10 + 0.10
Proline	0.24 + 0.02	2.21 + 0.01	7.56 + 0.17	0.23 + 0.01	0.14 + 0.01	4.53 + 1.09	4.90 + 1.33	6.70 + 0.10
Tyrosine	0.33 + 0.01	0.54 + 0.02	2.45 + 0.20	0.61 + 0.01	0.49 + 0.01	0.63 + 0.14	0.03 + 0.44	3.40 + 0.01
Aspartic acid	4.48 + 0.70	5.04 + 0.70	15.71 + 0.53	4.81 + 0.80	4.65 + 0.20	5.60 + 0.01	4.40 + 0.02	11.80 + 0.01
Glycine	18.79 + 1.01	18.80 + 1.10	17.33 + 0.02	18.38 + 1.10	19.17 + 1.30	10.96 + 2.72	7.41 + 0.19	12.30 + 0.20
References	Omran (2013)	Omran (2013)	Haider et al. (2015)	Omran (2013)	Omran (2013)	Sicuro et al. (2012)	Sicuor et al. (2012)	Bechtel et al. (2013)

Amino acid composition of sea cucumbers

The amino acid profiles of various sea cucumber species have been reported and are found to be influenced by species and geographic location (Table 3). As free amino acids can affect the quality of marine foods (Sicuro et al. 2012), it is important to measure their content as well. In their free form, amino acids give rise to sweetness, bitterness, sourness, and umami; in particular, glutamic acid imparts a distinctive flavor and taste. Glycine (7.41–19.17 mg/100 g DW) was the major free amino acid in almost all species, and glutamic acid (4.97–13.10 mg/100 g DW), aspartic acid (4.48–15.71 mg/100 g DW), and alanine (3.7–11.72 mg/100 g DW) were also prominently featured (Table 3). Notably, cysteine is the only amino acid not ubiquitously found in sea cucumbers but is one of the most prevalent free amino acids in *Parastichopus californicus* (Table 3).

Fatty acid composition of sea cucumbers

Fatty acid composition varied with species and habitat, with many species having a different dominant fatty acid (Table 4). However, arachidonic acid and *cis*-5,8,11,14,17-eicosapentaenoic acid were prominent components in most of the species. Surprisingly, palmitoleic acid was the major component in *P. californicus* but was absent in *Stichopus japonicus* and *Actinopyga mauritiana*. *cis*-10-Pentadecenoic acid, the major component in both *A. mauritiana* and *H. arenicola*, was not detected in *Apostichopus japonicus*, *Athyonidium chilensis*, *H. mammata*, *H. tubulosa*, *H. poli*, or *P. californicus*. Stearic acid has been detected in all species but is the major component only in *A. chilensis*.

Pharmaceutical properties of sea cucumbers

Over the past decades, marine natural products have attracted the attention of biologists, pharmacists, and chemists around the world. Marine organisms produce compounds that can be toxic or pharmaceutically useful (Ghadiri et al. 2018) (Table 5).

Table 4. Fatty acid profile (%) of dried sea cucumbers (mean value + standard deviation).

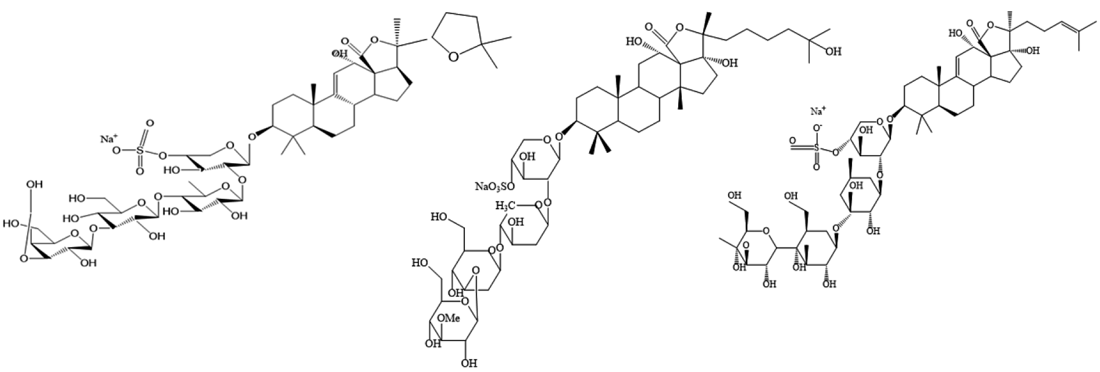
Fatty acid composition	*Apostichopus japonicus*	*Actinopyga mauritiana*	*Athyonidium chilensis*	*Holothuria arenicola*	*Holothuria mammata*	*Holothuria tubulosa*	*Holothuria poli*	*Parastichopus californicus*
Myristic acid	-	2.69 + 0.04	1.94 + 0.07	3.50 + 0.20	1.43 + 0.06	0.78 + 0.03	1.79 + 0.09	1.82 + 0.04
Myristoleic acid	-	1.42 + 0.04	-	2.50 + 0.26	0.72 + 0.08	0.28 + 0.40	0.62 + 0.09	-
Pentadecanoic acid	-	1.15 + 0.05	2.09 + 0.20	2.10 + 0.26	4.67 + 0.46	0.19 + 0.27	0.53 + 0.09	0.25 + 0.01
cis-10-Pentadecanoic acid	-	14.44 + 0.30	-	17.8 + 0.33	-	-	-	-
Palmitic acid	1.69 + 0.09	-	2.91 + 0.01	1.00 + 0.20	-	3.23 + 1.05	8.40 + 0.07	10.90 + 0.09
Palmitoleic acid	-	0.76 + 0.11	-	1.10 + 0.06	4.62 + 0.46	2.38 + 0.08	3.81 + 0.15	14.99 + 0.06
Heptadecanoic	-	2.49 + 0.26	1.83 + 0.10	3.90 + 0.10	0.91 + 0.05	0.43 + 0.04	0.57 + 0.10	-
cis-10-Heptadecanoic	-	0.53 + 0.01	-	0.60 + 0.04	0.20 + 0.20	-	-	-
Stearic acid	3.63 + 0.12	0.53 + 0.03	13.09 + 0.10	0.80 + 0.10	3.60 + 0.04	2.52 + 0.24	3.24 + 0.08	6.84 + 0.05
Oleic acid	4.34 + 0.27	5.55 + 0.15	8.08 + 0.05	6.60 + 0.26	3.16 + 0.23	2.67 + 0.15	2.49 + 0.24	4.96 + 0.10
Linoleic acid	2.03 + 0.11	3.04 + 0.03	1.80 + 0.04	2.30 + 0.01	3.81 + 0.69	2.30 + 0.34	4.88 + 0.17	-
Linolelaidic acid	-	1.64 + 0.01	-	2.60 + 0.05	-	2.30 + 34	4.97 + 0.17	-
γ-Linoleate acid	-	13.05 + 0.05	-	10.00 + 0.06	-	-	-	-
α-Linolenic acid	0.72 + 0.09	1.31 + 0.01	-	1.30 + 0.01	5.82 + 0.09	6.86 + 0.42	5.56 + 0.03	-
Arachidic acid	2.21 + 0.15	1.70 + 0.05	2.44 + 030	1.60 + 0.04	2.14 + 0.08	2.04 + 0.04	1.51 + 0.21	1.30 + 0.01
cis-11-Eicosatrienoic acid	4.30 + 0.27	0.45 + 0.05	3.85 + 0.30	0.60 + 0.07	1.43 + 0.04	1.05 + 0.04	1.14 + 0.20	2.49 + 0.10
cis-11,14-Eicosatrienoic acid	1.00 + 0.07	0.81 + 0.01	1.66 + 0.20	1.50 + 0.06	1.79 + 0.27	1.88 + 0.26	1.08 + 0.20	-
cis-11,14,17-Eicosatrienoic acid	-	-	-	0.40 + 0.10	2.35 + 0.47	0.17 + 0.24	0.96 + 0.15	-
cis-5,8,11,14,17-Eicosapentanoic acid	16.30 + 0.84	4.14 + 0.08	6.10 + 0.01	15.3 + 0.26	8.60 + 0.81	8.20 + 0.48	6.54 + 0.50	12.34 + 0.04
Arachidonic acid	14.62 + 0.91	6.86 + 0.03	10.24 + 0.04	14.60 + 0.36	16.41 + 0.19	20.36 + 0.35	11.20 + 0.36	7.05 + 0.03
Heneicosanoic acid	1.26 + 0.07	0.57 + 0.03	0.90 + 0.08	0.70 + 0.06	2.30 + 0.40	2.31 + 0.16	1.59 + 0.21	-
Erucic acid	3.36 + 0.25	1.77 + 0.01	0.33 + o.o2	1.70 + 0.02	2.36 + 0.47	2.95 + 0.26	1.66 + 0.27	1.30 + 0.02
cis-13,16-Docosadienoic acid	1.47 + 0.09	0.39 + 0.02	-	0.40 + 0.01	6.14 + 0.04	5.97 + 0.15	3.63 + 0.09	-
cis-4,7,10,13,16,19-Docosahexaenoic acid	4.71 + 0.51	-	-	1.80 + 0.05	7.24 + 0.04	5.00 + 0.05	7.72 + 0.23	6.19 + 0.06
Nervonic acid	1.40 + 0.07	2.69 + 0.02	2.44 + 0.10	1.90 + 0.02	3.89 + 0.04	4.98 + 0.38	2.64 + 0.24	1.67 + 0.01
References	Lou et al. (2012)	Haider et al. (2015)	Careaga et al. (2012)	Haider et al. (2015)	Aydin et al. (2011)	Aydin et al. (2011)	Aydin et al. (2011)	Bechtel et al. (2013)

Anticancer activities

Cancer remains a leading cause of death worldwide. Although high cure rates are achievable with currently available drugs, these produce a wide range of side effects (Sajwani 2019). As such, the identification of alternative, and potentially less toxic, anticancer agents derived from natural products is being pursued. Owing to their natural origin and inclusion in nutritional food products, bioactive compounds isolated from sea cucumbers are being investigated for use as anticancer agents. However, the mechanism of these compounds' anticancer activities is unclear and requires a comprehensive study (Eso et al. 2020).

Similar, noncytotoxic concentrations of an ethanolic extract and aqueous fraction of *H. poli* were reported to decrease the proliferation of MDA-MB-231 human breast cancer cells by more than 50% and arrest the treated cells in S-phase (Kareh et al. 2018). In this study, petroleum ether, chloroform, ethyl acetate, and *n*-butanol organic fractions showed no significant activity.

A chloroform extract of *H. nobilis* collected from Philippine sea waters was reported to contain an antitumor agent more potent and toxic (acute) than Taxol and etoposide. Hexane and chloroform extracts of *H. fuscopunctata* and a chloroform extract of *S. chloronotus* also exhibit weak antitumor activities in brine shrimp and are more toxic than standard anticancer drugs (Layson et al. 2014). Three triterpene glycosides, fuscocineroside C (**1**), scabraside D (**2**), and 24-dehydroechinoside A (**3**), were isolated from *H. scabra* and showed significant cytotoxicity compared to 10-hydroxycamptothecin against five human tumor cell lines, P-388, MKN-28, A549, HCT116, and MCF-7 (Han et al. 2012) (Fig. 1).



1 2 3

Figure 1. Structures of fuscocineroside C (**1**), scabraside D (**2**), and 24-dehydroechinoside (**3**).

Table 5. Pharmaceutical properties of sea cucumbers.

Sea cucumbers	Activities	References
Acaudina leucoprocta	Antitumor	Su et al. (2011)
Aposticopus japonicas	Anticancer	Park et al. (2011); Kim et al. (2017); Su et al. (2011)
	Anticoagulant	Luo et al. (2013)
	Antioxidant	Zhou et al. (2011); Guo et al. (2020)
	Anti-inflammatory	Lee et al. (2017)
Bohadschia argus	Antibacterial	Pringgenies (2013)
Bohadschia marmorata	Antibacterial	Pringgenies (2013)
Cucumaria frondosa	Anticancer	Hang et al. (2020)
Holothuria poli	Anticancer, anti-inflammatory	Kareh et al. 2018)
Holothuria parva	Antioxidant	Diba et al. (2016)
Holothuria nobilis	Antitumor, antibacterial	Layson et al. (2014)
	Anticoagulant	Luo et al. (2013)
Holothuria atra	Anticancer	Dhinakaran and Lipton (2014)
	Antioxidant	Pangestuti et al. (2016)
Holothuria axiologa	Antitumor, antibacterial	Layson et al. (2014)
Holothuria leucospilota	Antibacterial, antifouling	Darya et al. (2020)
	Anticancer	Bahroodi et al. (2014); Baharara et al. (2016)
	Antioxidant	Safari and Yaghoubzadeh 2020)
Holothuria edulis	Anticancer	Wijesinghe et al. (2013); Althunibat et al. (2013)
	Anticoagulant	Luo et al. (2013)
Holothuria scabra	Antitumor	Hua et al. (2012)
	Antioxidant	Nobsathian et al. (2017)
Holothuria forskali	Anti-inflammatory	Mena-Bueno et al. (2016)
Isostichopus badionothus	Antibacterial	Moguel-Salazar et al. (2013)
Pattalus mollis	Antiviral	Garcia-Candela et al. (2019)
Parastichopus tremulus	Anti-inflammatory	Mena-Bueno et al. (2016)
Pearsonothuria gareffei	Antiobesity, Anti-hyperlipidemia	Guo et al. (2015)
Stichopus chloronotus	Antitumor	Layson et al. (2014)
	Antibacterial	Layson et al. (2014); Pringgenies (2013)
Stichopus herrmanni	Antibacterial	Pringgenies (2013); Rasyid (2012)
	Antioxidant	Rasyid (2012)
Stichopus japonicus	Anticancer	Park et al. (2011; Kim et al.(2017); Su et al. (2011)
	Anticoagulant	Luo et al. (2013)
	Antioxidant	Zhou et al. (2011)
	Anti-inflammatory	Lee et al. (2017)
Stichopus horrens	Anticancer	Althunibat et al. (2013)

The activity of scabraside D, a sulfated triterpene glycoside extracted from *H. scabra*, against human cholangiocarcinoma (HC) was investigated both in vitro and in vivo for tumor growth inhibition using a xenograft mouse model (Assawasuparek et al. 2016). Scabraside D (12.5–100 μg/mL) significantly decreased the viability and migration of HC cells in a dose-dependent manner with an IC_{50} of 12.8 ± 0.05 μg/mL at 24 hours. Scabraside D (1 mg/kg/d for 21 days) also significantly reduced the growth of HC xenografts in mice without any adverse effects. Therefore, scabraside D may be a new therapeutic agent for cholangiocarcinoma treatment.

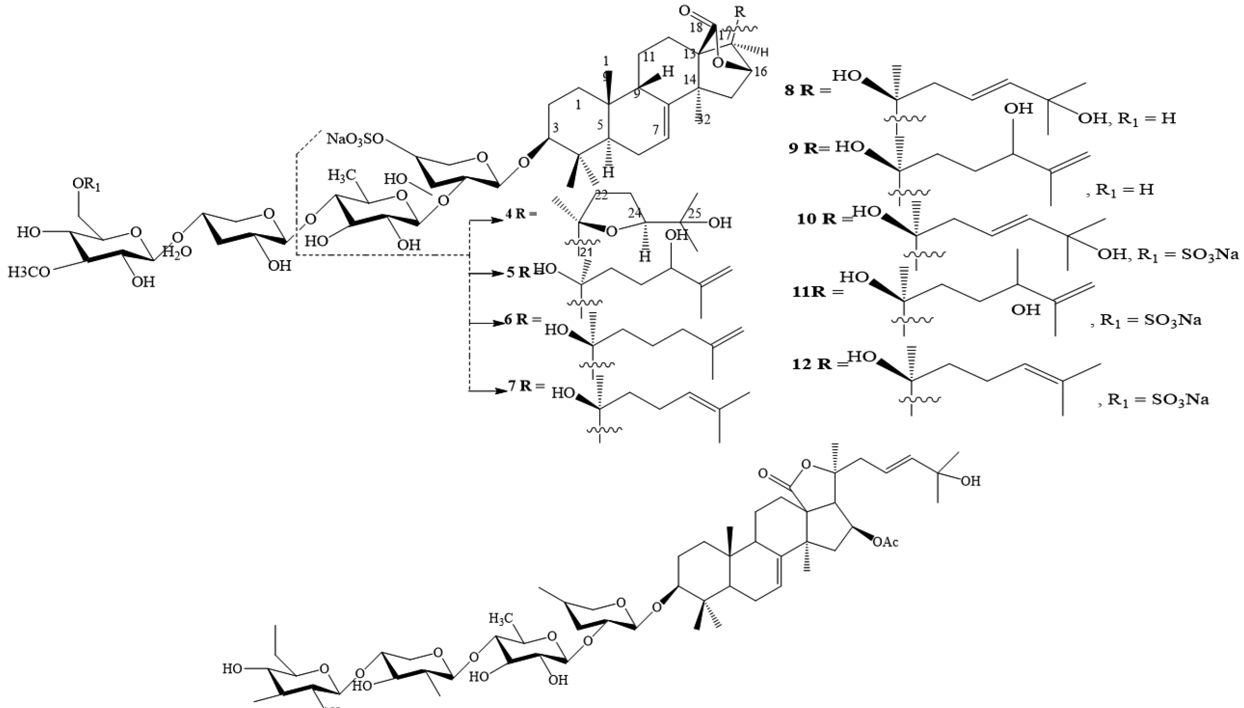
Various solvent extracts of the red sea cucumber, *A. japonicus*, were evaluated in colon cancer (HT-29), undifferentiated myeloid (HL-60), and hepatocarcinoma (Hep-G2) cells (Park et al. 2011). All fractions showed little cytotoxic activity against Hep-G2 cells, while the chloroform and ethyl acetate fractions showed more than 80% and 60% growth inhibition, respectively, in HL-60 and HT-29 cell lines. A comparison of canthaxanthin extraction methods from *A. japonicus* showed that ultrasonication extracted more canthaxanthin than either ethanol or water extraction and displayed higher inhibition (93.5%) against human malignant cell growth (Kim et al. 2017). The ultrasonication extract was found to inhibit both cancer cell proliferation and metastasis by downregulating skin tumor-promoting genes, such as B-cell lymphoma 2 (Bcl-2), matrix metalloproteinase-9 (MMP-9), and signal transducer and activator of transcription 3 (STAT3).

The antitumor activity of saponins and polysaccharides extracted from *A. japonicas* and *Acaudina leucoprocta* was investigated by testing the density gradient of S180 cells with various concentrations of saponin (S1 and S2) and polysaccharide (P1 and P2) extracts (Su et al. 2011). S1, P1, and P2 were extracted from *A. leucoprocta*, while S2 was extracted from a concentrated liquid of *A. japonicus*. The cytotoxic activities of S1 and S2 in S180 cells were dose and time-dependent based on MTT assays, in which saponin S2 exhibited the highest potency with an IC_{50} of 41.04 μg/mL at 44 hours. Additionally, Annexin V/P1 staining showed more viable cells with polysaccharide treatment than with saponins, indicating that saponins S1 and S2 have more potent in vitro antitumor activity than polysaccharides P1 and P2.

Holothuria edulis was reported to have in vitro anticancer potential, with an aqueous fraction showing strong cytotoxic effects against the human HL-60 leukemia cell lines (Wijesinghe et al. 2013). The anticancer and cytotoxic activities of a diethyl etheric extract from the *H. leucospilota* body wall were found to prevent the proliferation of human oral epidermoid carcinoma cells (KB) at a concentration of 500 μg/mL (Bahroodi et al. 2014). A methanolic extract was also effective at 100 μg/mL and 500 μg/mL. Overall, this work revealed that the body wall of *H. leucospilota* had a strong cytotoxic effect on normal cell lines (human embryonic kidney cells) and thus could be a potent cytotoxic; however, these extracts did not show significant therapeutic value against KB cells.

A methanolic extract of *H. atra* showed antiproliferative activities against HeLa and MCF-7 cell lines (Dhinakara and Lipton 2014). An ethanol extract of *H. atra* had strong anticancer activity (IC_{50} = 12.16 μL/mL) against Supris clone-1 (SP-C1) cells derived from a cloned lymphadenopathy of patients with oral squamous cell carcinoma (Satari et al. 2017). In contrast, hexane, ethyl acetate, and butanol fractions showed no cytotoxic activities in this study.

Organic extracts of *H. edulis* and *S. horrens* were tested for cytotoxic effects against two human cancer cell lines, esophageal carcinoma (TE-1) and non-small cell lung carcinoma (A549) (Althunibat et al. 2013). The organic extract of *H. edulis* exhibited cytotoxicity against TE-1 cancer cells (IC_{50} = 17 μg/mL), while the *S. horrens* organic extract was cytotoxic in TE-1 and A549 cancer cells (IC_{50} = 4.0 μg/mL and 15.5 μg/mL, respectively).



13

Figure 2. Structures of magnumosides A_1 (**4**), A_2 (**5**), A_3 (**6**), A_4 (**7**), B_1 (**8**), B_2 (**9**), C_1 (**10**), C_2 (**11**), C_4 (**12**), and colohiroside B_2 (**13**).

The anticancer potential of *H. leucospilota* saponin against the B16F10 melanoma cell line was investigated alone and in combination with the chemotherapy drug, dacarbazine (Baharara et al. 2016). The saponin, dacarbazine, and saponin-dacarbazine combination inhibited proliferation in a dose and time-dependent manner, with IC_{50} values of 10, 1400, and 4 + 1200 µg/mL respectively. Notably, the saponin extract induced intrinsic apoptosis via upregulation of caspase-3 and caspase-9, suggesting its potential as a new treatment modality for metastatic melanoma.

Osteosarcoma is the most common malignant bone cancer in children and adolescents (Kansara et al. 2014) and is particularly difficult to cure due to the incidence of malignant metastasis. New therapeutic approaches are urgently required to prevent metastasis and improve the outcomes for osteosarcoma patients. The anti-metastatic capacity of fucoidan isolated from *Cucumaria frondosa* against osteosarcoma cells (U2OS) has been investigated using cell adhesion, U2OS cell migration, and transwell migration assays(Zhang et al. 2020). The *C. frondosa* fucoidan was found to prevent U2OS cell adhesion to fibronectin and inhibit U2OS cell migration significantly, in particular, impairing the migration capacity, distance, and velocity. *C. frondosa* fucoidan impaired the dynamic remodeling of the cytoskeleton, possibly by suppressing the phosphorylation of focal adhesion kinase and paxillin and by activating the Rac1/PAK/UMK1/cofilin signaling axis.

Nine new sulfated triterpene glycosides, magnumosides A_1 (**4**), A_2 (**5**), A_3 (**6**), A_4 (**7**), B_1 (**8**), B_2 (**9**), C_1 (**10**), C_2 (**11**), and C_4 (**12**), and colohiroside B_2 (**13**) were successfully isolated from *Massinium magnum* collected from Vietnamese shallow waters (Fig. 2) (Silchenko et al. 2017). The cytotoxic activities of (**4**)–(**11**) were demonstrated against mouse spleen lymphocytes, the ascites form of mouse Ehrlich carcinoma cells, human colorectal carcinoma DLD-1 cells, and hemolytic cells. The erythrocytes were more sensitive to the glycosides than the splenocytes and cancer cells. Interestingly, (**6**) and (**10**) significantly inhibited colony formation and decreased the size of DLD-1 cancer cell colonies at non-cytotoxic concentrations. In addition, subtoxic doses of (**6**) and (**10**) – (**12**) manifested synergistic effects with radioactive irradiation on the proliferation of DLD-1 cells.

The presence of bioactive compounds with anticancer potential in sea cucumbers make them an important marine invertebrate for further exploration into the development of novel cytotoxics.

Antimicrobial activities

Bacteria are responsible for a vast number of human ailments and diseases, including diarrhea, cholera, pneumonia, tetanus, leprosy, typhus, tuberculosis, diphtheria, and dysentery. Antibiotics are useful against these microorganisms but their misuse and overuse have resulted in the evolution of multiple antibiotic-resistant bacterial strains. The failure of modern synthetic antibiotics has prompted the search for new compounds derived from natural resources.

An ethyl acetate extract of *H. leucospilota* body wall showed strong antibacterial activity against *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 0.250 mg/mL (Darya et al. 2020). A chloroform extract of *H. nobilis* was found to display antibacterial activity against *Escherichia coli* and was also a toxic (acute) and potent antitumor agent than several standard chemotherapeutics, such as Ara-C (Layson et al. 2014).

The antibiotic activity of four Indonesian sea cucumber species, *S. chloronotus*, *S. herrmanni*, *Bohadschia argus*, and *B. marmorata*, was tested against six bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* sp., *Vibrio vulnificus*, *V. anguillarum*, and *Bacillus subtilis*) (Pringgenies 2013). *Bohadschia argus* and *B. marmorata* were active against all the bacteria, while preliminary results with *S. herrmanni* and *S. chloronotus* suggested activity against *S. aureus*, *E. coli*, *Pseudomonas* sp., and *V. vulnificus*. A methanolic extract of *S. herrmanni* was found to display antibacterial activity against *S. aureus*, *B. subtilis*, and *V. eltor* (Rasyid 2012). *Stichopus herrmanni* has also shown significant antifungal activity against *Aspergillus niger*, with MICs ranging from 3–15 μg/mL. The most potent antifungal activity (18 μg/mL) against *A. niger* was found in a methanol extract of *S. herrmanni* body wall, resulting in a zone of inhibition of 38 mm (Sarhadizadeh et al. 2014).

The antibacterial activity of aqueous extracts from different tissues of *Isostichopus badionotus* was evaluated, with muscle and respiratory tract extracts displaying potent activity (Moguel-Salazar et al. 2013). In particular, high antibacterial activity against *V. cholera*, *E. coli*, *S. aureus*, and *P. aeruginosa* was observed from the membrane protein fraction, with MICs against *V. cholera* and *S. aureus* of 8.4 μg/mL and 37.4 μg/mL, respectively. Interestingly, this activity was resistant to both heat and proteinase K, indicating that the active compound is non-protein in origin and favors the use of *I. badionotus* as a potential source of novel antibiotics.

The antibacterial and antifungal activities of sea cucumber extracts suggest that this marine organism holds great potential for the discovery and development of future antibiotics.

Anti-inflammatory activities

The anti-inflammatory activities of *H. poli* have been investigated, with its aqueous fraction decreasing the levels of the inflammatory markers interleukin (IL)-6, nitric oxide, and MMP-9 in mouse mammary SCP2 cells (Kareh et al. 2018). The aqueous fraction of *H. poli* was also found to decrease IL-1 levels induced by phorbol-12-myristate-13-acetate–activated THP-1 human monocytes.

A methanolic extract of *H. leucospilota* muscular body wall was found to display anti-inflammatory activities in albino rats (Hadi et al. 2020). *Holothuria leucospilota* samples were dried and extracted with hexane, ethyl acetate, and methanol and examined in vitro via lipoxygenase enzyme inhibition, resulting in inhibition values of 9.74 ± 1.57%, 12.92 ± 1.22%, and 43.75 ± 2.83%, respectively. The methanol extract was notably potent, displaying anti-inflammatory effects superior to acetylsalicylic acid. The anti-inflammatory activities of *H. forskali* and *P. tremulus* extracts have also been investigated (Mena-Bueno et al. 2016). Bioavailable compounds in *H. forskali* decreased intercellular adhesion molecule expression in subcutaneous adipose tissue ($p < 0.05$) and those in *P. tremulus* reduced vascular cell adhesion protein ($p < 0.01$) and IL-6 ($p < 0.05$) expression levels in endothelial cells. It should be noted that this effect was observed in epicardial adipose tissue.

The in vitro anti-inflammatory potential of *H. edulis* was evaluated via the determination of a pro-inflammatory mediator (Wijesinghe et al. 2013). An ethyl acetate fraction exhibited profound anti-inflammatory potential in lipopolysaccharide-stimulated RAW 264.7 macrophages, dose-dependently inhibiting nitric oxide production and significantly downregulating inducible nitric oxide synthase and cyclooxygenase-2 expression, prostaglandin E2 release, and pro-inflammatory cytokine tumor necrosis factor-α, IL-1β and IL-6. These multiple activities suggest that the ethyl acetate fraction of *H. edulis* could contain functional ingredients for use in industrial applications.

Apostichopus japonicus extracts have been shown to ameliorate allergic airway inflammation via $CD4^{+}CD25^{+-}$ $Foxp3^{+}T$ cell activation and recruitment to the lung (Lee et al. 2017). This study investigated which components of *A. japonicus* contributed to the amelioration of airway inflammation using *n*-hexane fractionation to separate the components into three phases (*n*-hexane, alcohol, and solid). The three phases were evaluated the ability to elevate IL-10 expression in splenocytes and ameliorate symptoms in mice with ovalbumin/alum-induced asthma. The *n*-hexane treatment resulted in a significant increase in IL-10 expression and ameliorated asthma symptoms. Notably, approximately 47 fatty acids were identified in this phase.

Other properties

Sulfated polysaccharides were successfully isolated from *Holothuria nobilis*, *H. edulis*, and *Apostichopus japonicus* (Luo et al. 2013). Nuclear magnetic resonance analysis indicated that sulfated fucans and fucosylated chondroitin sulfates were present in all species, while neutral glycans were specific to *H. edulis*. The same polysaccharide type in different sea cucumber species had similar anticoagulant activities, while the different glycans functioned significantly different, likely due to differences in their average molecular weight, monosaccharide composition, and electric charge. The fucosylated chondroitin sulfates had stronger anticoagulant activities than the sulfated fucans, while the neutral glycan had no activity, which was expected owing to the absence of a sulfate.

Saponin-enriched *Pearsonothuria graeffei* Semper extract was found to exhibit antiobesity activity via inhibition of pancreatic lipase activity and upregulation of LXR-β signaling (Guo et al. 2015). Crude *P. graeffei* Semper extract inhibited pancreatic lipase activity by 36.44% of the control at 0.5 μg/mL. The optimal active extract (SC-3) and echinoside A inhibited pancreatic lipase with IC_{50} values of 2.86 μg/mL and 0.076 μM, respectively. Approximately 0.1% SC-3 reduced body weight (23.0 ± 62 versus 26.3 ± 0.76 g), serum total cholesterol (2.46 ± 0.04 versus 2.83 ± 0.12 mmol/L), serum triglyceride (0.19 ± 0.08 versus 0.03 ± 0.03 mmol/L), low-density lipoprotein cholesterol (0.48 ± 0.02 versus 0.51 ± 0.02 mmol/L), liver total cholesterol (1.19 ± 0.17 versus 1.85 ± 0.13 mmol/L), and triglyceride (6.18 ± 0.92 versus 10.87 ± 0.97 mmol/mg) contents of obese C57BL/6 mice on a high-fat diet. These results indicate that *P. graeffei* Semper may be useful for developing antiobesity and antihyperlipidemic drugs in the future.

There is growing interest in food components that may help prevent lifestyle-related diseases. The effects of *P. graeffei* saponins on high-fat diet-induced obesity, insulin resistance, and fatty liver in C57BL/6 mice have been investigated (Hu et al. 2012). The mice were fed a high-fat diet containing either 0.03% or 0.1% saponin sea cucumber for 8 weeks. Both doses exhibited weight-loss effects and significantly decreased adipose tissue weight in both visceral and subcutaneous depots. Moreover, 0.1% saponin sea cucumber dramatically decreased hepatic triglyceride and total cholesterol accumulation. Mice fed 0.1% saponin sea cucumber also showed significantly reduced serum glucose and insulin levels and a lower homeostatic model assessment for insulin resistance index (HOMA-IR). Dietary saponin sea cucumber also prevented adipokine imbalance by increasing adiponectin production and decreasing tumor necrosis factor-α levels associated with a high-fat diet.

Fucoidan extracted from *A. molpadioides* has been shown to significantly increase glucose consumption and improve insulin resistance both in vivo and in vitro (Xu et al. 2015). Insulin-resistant mouse models were established by feeding the mice a high-fat, high-fructose diet. Treatment with *A. molpadioides* fucoidan increased serum insulin levels, decreased HOMA-IR, reduced fasting blood glucose levels, and improved oral glucose tolerance, revealing that it could mitigate insulin resistance in vivo. Combination treatment with *A. molpadioides* fucoidan and rosiglitazone further reverted insulin resistance.

The antiviral activity of sea cucumbers against human rotavirus A was investigated in cell culture using an aqueous *Patallus mollis* extract (Garcia-Candela et al. 2019). *Patallus mollis* is endemic to the coasts of Chile and Peru. The mean extract cytotoxic concentration used in the antiviral assay was 27,042.10 µg/mL, with every concentration used resulting in 99.9% inhibition of antiviral activity. To determine its mode of action, cells were treated with the *P. mollis* extracts during different phases of the viral infection cycle. The extract was found to inhibit 99% of the virus during absorption and viral inactivation phases.

In vitro studies with *Stichopus* spp. extracts were performed to elucidate their effects on cell viability and function (Shahrulazua et al. 2013). An inverse relationship was observed between *Stichopus* spp. extract concentration and osteoblast cell viability ($p < 0.001$), with only 1 mg/mL significantly promoting cell viability at day 3 of incubation. Osteoblast cell function tended to increase with 50 mg/mL and 10 mg/mL *Stichopus* spp. extracts, although this varied with different incubation periods.

Although many marine-derived compounds have found use in the pharmaceutical industry, with some already on the market, their use in the development of natural cosmetics is underexplored compared to their terrestrial-derived counterparts. However, many cosmetic companies have recently begun turning their attention to the sea for compounds with potential for use in anti-aging, skin whitening, moisturizers, and photoprotection. With growing investigations of small molecules, enzymes, and biopolymers from the marine environment, it is expected that the era of "blue cosmetics" will soon dominate the sector (Alparslan et al. 2018). This expectation is not without reason, given the increasing public awareness of the importance of cosmetics in life. Additionally, the potential for the utilization of active compounds from marine organisms, particularly sea cucumbers is very promising.

Sea cucumbers for cosmetics

The cosmetics industry is one of the fastest-growing industries in the past decade. The demand for cosmetic products from marine resources has been rising rapidly due to their unique biological and chemical properties. The European Commission No. 1223/2009 regulation defines cosmetics as products intended for external application to the epidermis, hair, nails, lips, genital organs, teeth, mucous membranes of cavities, etc., with the exclusive or principal objective of cleaning, perfuming, protecting, altering appearance, or maintaining good condition. Cosmetics are not intended to affect the function or structure of the body. Cosmetics are required to be free of side effects and to be safe and show positive effects on well-being (Alves et al. 2020).

In the past few years, sea cucumber components have been considered for use as cosmetic ingredients in treating skin problems (Kim et al. 2016), particularly skin-moisturizing and wrinkle improvement. Owing to their effect on the appearance and condition of the skin, hyaluronic acid and collagen, such as that found in sea cucumbers, have been the subject of much anti-aging research and development (Li et al. 2019).

Antioxidant activities

Antioxidants are essential to preventing ultra violet-induced reactive oxygen species, such as hydroxyl radical, superoxide anion, and hydrogen peroxide, from attacking membrane lipids, DNA, and protein. The oxidation of membrane lipids is one of the primary causes of a reduced youthful appearance, therefore, preventing the formation of reactive oxygen species is essential to maintaining wrinkle-free skin. Antioxidants protect human skin from the pro-oxidative environment to which it is exposed in the form of ultraviolet radiation, air pollutants, and smoke (Alves et al. 2020).

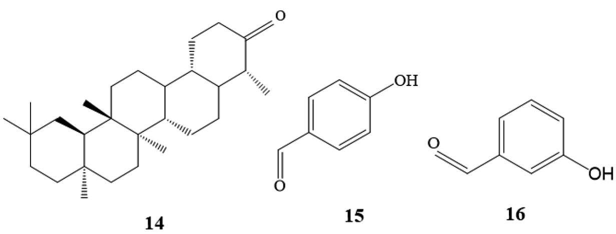
Sea cucumbers are reported to be a potential source of natural antioxidants. *Holothuria leucospilota* protein hydrolysate obtained using flavourzyme and alcalase enzymes showed concentration-dependent antioxidant activity. The flavourzyme preparation provided higher activity than the alcalase in the 2,2-diphenyl-1-picrylhydrazyl (DPPH)-free radical control, with concentrations of 5 mg/mL and 2 mg/mL (Safari and Yaghoudzadeh 2020). The antioxidant activities of aqueous and organic extracts of *S. horrens* and *H. edulis* were evaluated (Althunibat et al. 2013). *Stichopus horrens* aqueous and organic extracts inhibited 79.62% and 46.66% of ß-carotene oxidation by linoleate free radical, respectively. *H. edulis* aqueous and organic extracts exhibited DPPH radical scavenging with IC_{50} = 2.0 mg/mL and 8.73 mg/mL, respectively.

The antioxidant activities of fresh and rehydrated *H. parva* were equivalent to 0.063 and 0.060 mg vitamin C/g dry sample (IC_{50} = 5.26 µg/mL and 4.14 µg/mL), respectively. The flavonoid content of fresh and rehydrated samples was equivalent to 3.86 and 5.02 mg quercetin/g dry samples, respectively. The total phenolic content of the fresh and rehydrated sample was equivalent to 0.22 and 0.19 mg gallic acid/g dry sample, respectively (Diba et al. 2017).

Apostichopus japonicus was hydrolyzed by papain, trypsin, pepsin, acid protease, and neutral protease to obtain five peptide fractions, for which their antioxidant activities were evaluated by hydroxyl radical (•OH) and superoxide anion ($\bullet O_2^-$) scavenging (Zhou et al. 2011). The trypsinized peptides exhibited the highest antioxidant activity. *Apostichopus japonicas* hydrolysates increased survival rate, inhibited the accumulation of reactive oxygen species, upregulated total superoxide dismutase and catalase activities, and reduced lipid peroxidation malondialdehyde content in a C*aenorhabditis elegans* model undergoing increased oxidative stress (Guoet et al. 2020).

A methanolic extract of *S. herrmanni* collected from Indonesian waters was examined for antioxidant activity using DPPH giving an IC_{50} = 65.08 µg/mL (Rasyid 2012). *Stichopus vastus* collagen was successfully hydrolyzed by trypsin and was found to rich in alanine, glycine, proline, glutamine, and hydroxyproline residues and exhibited excellent radical-scavenging activity, indicating that collagen hydrolysates from *S. vastus* can be used as functional ingredients in nutraceutical and food products (Abedin et al. 2014).

Holothuria scabra is one of the most commercially valuable species. Its antioxidant activity was measured using DPPH and Folin-Ciocalteu reagent (Nobsathian et al. 2017). The crude methanol extract and purified friedelin (**14**), 3-hydroxybenzaldehyde (**15**), and 4-hydroxybenzaldehyde (**16**) (Fig. 3) isolated from this species strongly inhibit free radicals with effective concentrations (EC_{50}s) similar to ascorbic acid (14.90 ± 5.5 × 10^{-3}). The total phenolic content was 30.52 ± 0.21 GAE/g dry weight. These results indicate that *H. scabra* could be used to develop nutraceuticals for patients with cardiovascular symptoms. It may also support antioxidant substances involved in preventing free radical damage, such as quercetin, a flavonoid found in onions, as well as preserve blood pressure, vascular function, heart rate, and vascular responsiveness to stress.



14 15 16

Figure 3. Structures of friedelin (**14**), 3-hydroxybenzaldehyde (**15**), and 4-hydroxybenzaldehyde (**16**).

A comparison of the radical scavenging activity of *H. leucospilota*, *H. atra*, *H. fuscocinerea*, and *H. excellens* using DPPH found *H. atra* extract to have the strongest DPPH scavenging activity (13.14 ± 2.17%) at a concentration of 0.1 mg/mL. *H. atra* can be considered as a natural antioxidant source for pharmaceutical, food (Pangestuti et al. 2016), and cosmetic industries.

Antiaging activities

Research related to the treatment of aging and age-related diseases is a focus of public health. *A. japonicas* protein hydrolysate was found to increase age pigment and extend lifespan without reducing food intake, body length, or blood size of nematodes, demonstrating its capacity to delay physiological aging (Guo et al. 2020). The peptide profile and antiaging activity of purified *C. frondosa* hydrolysate prepared by enzymatic hydrolysis and ultrafiltration were examined in vivo in fruit flies and mice with age-related neurodegenerative disorders associated with D-galactose-induced aging (Lin et al. 2018). *California frondosa* hydrolysate significantly prolonged the lifespan of fruit flies and ameliorated learning and memory deficits in mice experiencing D-galactose-induced aging. The mechanism underlying these protective effects might be related to upregulation of Klotho expression, inhibition of lipid peroxidation and protein oxidation, increased superoxide dismutase and glutathione peroxidase activities, and downregulation of acetylcholinesterase activity. This work suggests that *C. frondosa* hydrolysate could contain health-promoting ingredients for combating aging and age-related diseases.

Other properties

The boiling process, one of the stages in the production of dried sea cucumbers, generates liquid extracts that are largely discarded without considering the therapeutic and economic value of their contents. In addition, this could contribute to environmental pollution.

Glycoprotein fractions from the liquid extract of boiled *S. japonicas* were investigated for their efficacy in skin whitening and wrinkle improvement and their effects on tyrosine and elastase inhibitory activities (Kim et al. 2016). Fractions greater and less than 50 kDa enhanced tyrosinase and elastase inhibitory activities by 50.84% and 28.79%, respectively, with the concentration of the > 50 kDa fractions showing a significant correlation with elastase inhibitory (R^2 = 0.983) and tyrosinase inhibitory (R^2 = 0.968) efficacy. This suggests that the glycoprotein fractions could be useful as cosmetic ingredients for skin whitening and wrinkle improvement.

The development of moisturizing cosmetic products from marine organisms, particularly sea cucumbers, continues to be pursued. Pepsin-solubilized collagen extracted from *H. cinerascens* has been compared with that from the skin of tilapia and pig, all of which exhibited better moisture absorption and moisture capacity than glycerol (Li et al. 2019). The dominant amino acids of the three collagens were proline (9–12%), glycine (31%), and alanine (10–12%). The collagen molecules of *H. cinerascens* were found to be rich in hydrophilic groups, which could prove useful in cosmetic formulations.

The exploitation of sea cucumbers must be carefully considered, as their numbers in the wild have been reduced. With the widespread dissemination and commercialization of their biological activity, a method guaranteeing sea cucumber availability, such as cultivation, is important.

Conclusion

Among other marine organisms, sea cucumbers are exploited for their unique bioactive compounds. Sea cucumbers have largely been used as food and pharmaceuticals, but have recently gained traction in the cosmetic industry, although it is used to a lesser extent than terrestrial organisms. Further research will provide important information about the potential uses of sea cucumbers in the cosmetic field.

References

Abedin MZ, Karima AA, Latiff AA, Gan CY, Ghazali FC, Barzideh Z, Ferdosh S, Akanda MJH, Zzaman W, Karim MR, Sarker MZI (2014) Biochemical and radical-scavenging properties of sea cucumber (*Stichopus vastus*) collagen hydrolysates. Natural Product Research 28(16): 1302–1305. https://doi.org/10.1080/14786419.2014.900617

Alparslan L, Sekeroglu N, Kijjoa A (2018) The potential of marine resources in cosmetics. Current Perspective on Medicinal & Aromatic Plants 2: 53–66. https://doi.org/10.38093/cupmap.488904

Althunibat OY, Ridzwan BH, Taher M, Daud JM, Ichwan SJA, Qaralleh, H (2013) Antioxidant and cytotoxic properties of two sea cucumbers, *Holothuria edulis* Lesson and *Stichopus horrens* Selenka. Acta Biologica Hungarica 64(1): 10–20. https://doi.org/10.1556/ABiol.64.2013.1.2

Al Azad S, Shaleh SRM, Siddique S (2017) Composition of fatty acid and approximate composition between *Holothuria edulis* and *Holothuria scabra* collected from coastal water of Sabah, Malaysia. Advances in Biosciences and Biotechnology 8: 91–103. https://doi.org/10.4236/abb.2017.83007

Alves A, Sousa E, Kijjoa A, Pinto M (2020) Marine-derived compounds with potential use as cosmeceuticals and nutricosmetics. Molecules 25(2536): 1–38. https://doi.org/10.3390/molecules25112536

Andriamanamisata VLR, Telesphore AF (2019) The nutritional values of two species of sea cucumbers (*Holothuria scabra* and *Holothuria lesson*) from Madagascar. African Journal of Food Science 13(11): 281–286.

Ardiansyah A, Rasyid A, Siahaan EA, Pangestuti R, Murniasih T (2020) Nutritional value and heavy metal content of sea cucumber *Holothuria scabra* commercially harvested in Indonesia. Current Research in Nutrition and Food Science 8(3): 765–773. https://doi.org/10.12944/CRNFSJ.8.3.09

Assawasuparerk K, Vanichviriyakit R, Chotwiwatthanakun C, Nobsathian S, Rawangchue T, Wittayachumnakul B (2016) Scabraside D extracted from *Holothuria scabra* induces apoptosis and inhibits the growth of human cholangiocarcinoma xenografts in mice. Asian Pacific Journal of Cancer Prevention 17: 511–517. https://doi.org/10.7314/APJCP.2016.17.2.511

Aydin M, Sevgili H, Turan B, Emre Y, Kose S (2011) Proximate composition and fatty acid profile of three different fresh and dried commercial sea cucumber from Turkey. International Journal of Food Sciences and Technology 46: 500–508. https://doi.org/10.1111/j.1365-2621.2010.02512.x

Baharara J, Amini E, Nikdel N, Abdollahi FS (2016) The cytotoxicity of dacarbazine potentiated by sea cucumber saponin in resistant B16F10 melanoma cells through apoptosis induction. Avicenna Journal of Medical Biotechnology 8(3): 112–119.

Bahroodi S, Nemathollahi MA, Aghasadeghi MR, Nazemi M, Behroz B (2014) In vitro cytotoxic and anticancer of body wall for sea cucumber (*Holothuria leucospilota*). Iranian Scientific Fisheries Journal 23(3): 11–20.

Barzkar N, Feriman GA, Taheri A (2017) Proximate composition and mineral content in the body wall of two species of sea cucumbers from Oman Sea. Environmental Sciences and Pollution Research 24: 18907–18911. https://doi.org/10.1007/s11356-017-9379-5

Bechtel PJ, Oliveira ACM, Demir N, Smiley S (2013) Chemical composition of the giant sea cucumber, *Parastichopus californicus*, commercially harvested in Alaska. Food Science & Nutrition 1(1): 63–73. https://doi.org/10.1002/fsn3.12

Bordbar S, Anwar F, Saari N (2011) High-value components and bioactives from sea cucumbers for functional foods – A review. Marine Drugs 9: 1761–1805. https://doi.org/10.3390/md9101761

Careaga VP, Munlain C, Maler MS (2013) Fatty acid composition of the edible sea cucumber *Athyonidium chilensis*. Natural Product Research 27(7): 638–646. https://doi.org/10.1080/14786419.2012.686909

Ceesay A, Shamsudin MN, Aliyu-Paiko M, Ismail IS, Nazarudin MF, Alipiah NM (2019) Extraction and characterization of organ components of the Malaysian sea cucumber *Hoothuria leucospilota* yielded bioactive exhibiting diverse properties. BioMed Research International 2019: 1–16. https://doi.org/10.1155/2019/2640684

Darya M, Sajjadi MM, Yousefzadi M, Sourinejad I, Zarei M (2020) Antifouling and antimicrobial activities of bioactive extracts from different organs of the sea cucumber *Holothuria leuospilota*. Helgoland Marine Research 74(4): 1–13. https://doi.org/10.1186/s10152-020-0536-8

Dhinakara DI, Lipton AP (2014) Bioactive compounds from *Holothuria atra* of Indian ocean. SpringerPlus 3: e673. [10 pp.] https://doi.org/10.1186/2193-1801-3-673

Diba G, Jamili S, Ramezani FE (2017) Evaluation of the antioxidant activity of dried (rehydrate) and fresh sea cucumber *Holothuria parva*. Iranian Scientific Fisheries Journal 25(4): 77–86.

Eso A, Uinarni H, Tommy T, Sitepu RK, Effendi IK, Ariestiyanto YC, Martamba HC, Arifin EM, Mawu FO, Sukmana BI (2020) A review on use of sea cucumber as a treatment for oral cancer. Systematic Review Pharmacy 11(5): 299–301. https://doi.org/10.31838/srp.2020.5.44

Garcia-Candela E, Pariona-Velarde C, Mandragon-Martinez A, Chumpitez-Cerrate V (2019) Antiviral activity of the sea cucumber tegument extract (*Pattalus mollis*) on human rotavirus A (RVA). Natural Product Research: 1–6. https://doi.org/10.1080/14786419.2019.1611807

Ghadiri M, Kazemi S, Heidari B, Rassa M (2018) Bioactivity of aqueous and organic extracts of sea cucumber *Holothuria leucospilota* (Brandt 1835) on pathogenic *Candida and Streptococci*. International Aquatic Research 10: 31–43. https://doi.org/10.1007/s40071-017-0186-x

Gocer M, Olgunoglu, IA, Oglunoglu MP (2018) A study on fatty acid profile and some major mineral contents of sea cucumber (*Holothuria* (*platyperona*) *sanctori*) from Mediterranean Sea (Turkey). Food Science and Quality Management 72: 1–5.

Guo K, Su L, Wang Y, Liu H, Lin J, Cheng P, Yin X, Liang M, Wang Q, Huang Z (2020) Antioxidant and anti-aging effect of sea cucumber protein hydrolysate and bioinformatics characterization of its composing peptides. Food & Function 11: 5004–5016. https://doi.org/10.1039/D0FO00560F

Guo L, Gao Z, Zhang L, Guo F, Chen Y, Li Y, Huang C (2015) Saponin-enriched sea cucumber extracts exhibit an antiobesity effect through inhibition of pancreatic lipase activity and upregulation of LXR-b signaling. Pharmaceutical Biology: 1–14. https://doi.org/10.3109/13880209.2015.1075047

Hadi G, Yazdan M, Melika N, Reza S (2020) Evaluation of anti-inflammatory effects of methanolic extract of Persian Gulf sea cucumber (*Holothuria leucospilota*) on rats (Rattus-ratrus). Journal of Fisheries [Iranian Journal of Natural Resources] 73(1): 91–100. https://doi.org/10.22059/JFISHERIES.2020.298396.1144

Haider MS, Sultana R, Jamil K, Lakhi-e-Zehra, Tarar OM, Shirin K, Afzal W (2015) A study on proximate composition, amino acid profile, fatty acid profile and some mineral contents in two species of sea cucumber. The Journal of Animal & Plant Sciences 25(1): 168–175.

Han H, Li L, Yi Y, Wang X, Pan M (2012) Triterpene glycosides from sea cucumber *Holothuria scabra* with cytotoxic activity. Chinese Herbal Medicines 4(3): 183–188. https://doi.org/10.3969/j.issn.1674-6384.2012.03.002

Hu X, Li Z, Xue Y, Xu J, Xue C, Wang J, Wang Y (2012) Dietary saponins of sea cucumber ameliorate obesity, hepatic steatosis and glucose intolerance in high-fat diet-fed mice. Journal of Medicinal Food 15(10): 909–916. https://doi.org/10.1089/jmf.2011.2042

Ibrahim MY, Elamin SM, Gideiri YBA, Ali SM (2015) The proximate composition and the nutritional value of some sea cucumber species inhabiting the Sudanese Red Sea. Food Science and Quality Management 41: 11–16.

Kansara M, Tang MW, Smyth MJ, Thomas DM (2014) Translational biology of osteosarcoma. Nature Reviews Cancer 14: 722–735. https://doi.org/10.1038/nrc3838

Kareh M, El Nahas R, Al-Aaraj L, Al-Ghadban S, Al Deen NN, Saliba N, El-Sabban M, Talh R (2018) Anti-proliferative and anti-inflammatory activities of the sea cucumber *Holothuria poli* aqueous extract. SAGE Open Medicine 6: 1–14. https://doi.org/10.1177/2050312118809541

Khotimchenko Y (2018) Pharmacological potential of sea cucumbers. International Journal Molecular Science 19(5): e1342. https://doi.org/10.3390/ijms19051342

Kim SJ, Park SY, Hong SM, Kwon E, Lee TK (2016) Skin whitening and anti-corrugation activities of glycoprotein fractions from liquid extracts od boiled sea cucumber. Asian Pacific Journal of Tropical Medicine 9(10): 1002–1006. https://doi.org/10.1016/j.apjtm.2016.08.001

Kim NY, Choi WY, Heo SJ, Kang DH, Lee HY (2017) Anti-skin cancer activities of *Apostichopus japonicus* extract from low-temperature ultrasonication process. Jounal of Healthcare Engineering 1: 1–6. https://doi.org/10.1155/2017/6504890

Layson RJ, Rodil MCA, Mojica EE, Deocaris CC (2014) Potential anticancer and antibacterial activities of Philippine echinoderm extracts. The Journal of Tropical Life Science 4(3): 175–181. https://doi.org/10.11594/jtls.04.03.03

Lee DI, Kang SA, Anisuzzaman M, Jeong UC, Jin F, Kang SJ, Lee JY, Yu HS (2017) Sea cucumber lipid-soluble extra fraction prevents ovalbumin-induced allergic airway inflammation. Journal of Medicinal Food 21(1): 1–9. https://doi.org/10.1089/jmf.2017.3994

Lee MH, Kim YK, Moon HS, Kim KD, Kim GG, Guo HA, Yoon NY, Sim KB, Park HY, Lee DS, Lim CW, Yoon HD, Han SK (2012) Comparison of proximate composition and nutritional profile of red and black sea cucumbers (*Apostichopus japonicas*) from Ulleungdo (Island) and Dokdo (Island), Korea. Food Science and Biotechnology 2(15): 1285–1291. https://doi.org/10.1007/s10068-012-0169-z

Lin L, Yang K, Zheng L, Zhao M, Sun W, Zhu Q, Liu, S (2018) Anti-aging effect of sea cucumber (*Cucumaria frondosa*) hydrolysate on fruit flies and D-galactose-induced aging mice. Journal of Functional Foods 47: 11–18. https://doi.org/10.1016/j.jff.2018.05.033

Li PH, Lu WC, Chan YJ, Ko WC, Jung CC, Huynh DTL, Ji YX (2019) Extraction and characterization of collagen from sea cucumber (*Holoturia cinerascens*) and its potential application in moisturizing cosmetics. Aquaculture 515: e734590. https://doi.org/10.1016/j.aquaculture.2019.734590

Liu L, Zheng YY, Shao CL, Wang CY (2019) Metabolites from marine invertebrates and their symbiotic microorganisms, molecular diversity discovery, mining, and application. Marine Life Science & Technology 1: 60–94. https://doi.org/10.1007/s42995-019-00021-2

Liu YX, Zhou DY, Ma DD, Liu ZQ, Liu YF, Song L, Dong XP, Li D, Zhu BW, Konno K, Shahidi F (2017) Effect of endogenous cysteine proteinases on structure of collagen fibers from dermis of sea cucumber (*Stichopus japonicus*). Food Chemistry 1232: 10–18. https://doi.org/10.1016/j.foodchem.2017.03.155

Lou QM, Wang YM, Liu XP, Xue CH (2012) Lipid profile and fatty acid compositions in body wall of *Apostichopus japonicas* (Selenka). Journal of Food Biochemistry 36(3): 317–321. https://doi.org/10.1111/j.1745-4514.2011.00544.x

Luo L, Wu M, Xu L, Lian W, Xiang J, Lu F, Gao N, Xiao C, Wang S, Zhao J (2013) Comparison of physicochemical characteristics and anticoagulant activities of polysaccharides from three sea cucumbers. Marine Drugs 11: 399–417. https://doi.org/10.3390/md11020399

Mena-Bueno S, Atanasova M, Fernandez-Trasancos A, Paradela-Dobarro B, Bravo SB, Alvarez E, Fernandez AL, Carrera I, Gonzalez-Juanateya JR, Eiras S (2016) Sea cucumber with an anti-inflammatory effect on endothelial cells nd subcutaneous but not on epicardial adipose tissue. Food & Function 7: 953–963. https://doi.org/10.1039/C5FO01246E

Moguel-Salazar F, Ortiz-Vazquez E, Rodriguez-Canul R, Olivers-Castillo L (2013) Antimicrobial activity of aqueous extracts of seacucumber (*Isosticopus badionotus*) from the coast of Yucatan, Mexico. African Journal of Microbilogy Research 7(28): 3621–3626.

Nobsathian S, Tuchinda P, Sobhon P, Tinikul Y, Poljaroen J, Tinikul R, Sroyraya M, Poomton T, Chaichotranunt S (2017) An Antioxidant activity of the whole body of *Holothuri scabra*. Chemical and Biological Technologies in Agriculture 4(4): 1–5. https://doi.org/10.1186/s40538-017-0087-7

Oglunoglu IA, Olgunoglu MP (2017) Major mineral (P, K, Ca) contents and proximate composition of the male and female blue swimming crab (*Portunus segnis* Fordkal, 1775) from Northeastern Mediterranean Sea, Mersin Bay, Turkey. Journal of Biology Agriculture and Healthcare 7(14): 50–54.

Oh GW, Ko SC, Lee DH, He SJ, Jung WK (2017) Biological activities and biomedical potential of sea cucumber (*Stichopus japonicus*): a review. Fisheries and Aquatic Sciences 20: e28. https://doi.org/10.1186/s41240-017-0071-y

Omran NEE (2013) Nutritional value of Egyptian sea cucumbers. African Journal of Biotechnology 23(35): 5466–5477. https://doi.org/10.5897/AJB2013.13020

Pangestuti R, Murniasih T, Putra MY, Rasyid A, Wibowo JT, Ardiansyah A, Untari F (2016) Free radical scavenging activity of selected sea cucumber species from Mataram-Lombok, Indonesia. Jurnal Teknologi (Science & Engineering) 78(4–2): 179–185. https://doi.org/10.11113/jt.v78.8202

Park SY, Lim HK, Lee S, Cho SK, Park S, Cho M (2011) Biological effects of various fractions derived from Jeju Island red sea cucumbers (*Stichopus japonicus*). Journal of the Korean Society for Applied Biological Chemistry 54: 718–724. https://doi.org/10.1007/BF03253150

Pringgenies D (2013) Antibacterial activity of sea cucumbers harvested from Karimunjawa. Squalene Bulletin of Marine & Fisheries Postharvest & Biotechnology 8(2): 87–94. https://doi.org/10.15578/squalen.v8i2.90

Purcell SW, Hair CA, Mills DJ (2012) Sea cucumber culture, farming and sea ranching in the tropics: Progress, problem and opportunities. Aquaculture 368–369: 68–81. https://doi.org/10.1016/j.aquaculture.2012.08.053

Rahman MA, Yusoff FM (2017) Sea cucumber fisheries: Market potential, trade, utilization and challenges for expanding the production in the South-East Asia. International Journal of Advances in Chemical Engineering & Biological Sciences 4(1): 26–30. https://doi.org/10.15242/IJACEBS.ER0117033

Ram R, Chand RV, Southgat PC (2014) Effects of harvest and post-harvest processing methods on quality of Beche-de-mer in Fiji Island. Journal of Marine Science: Research and Development 4(3): 1–6. https://doi.org/10.4172/2155-9910.1000153

Rasyid A (2012) Identification of secondary metabolites compounds, antibacterial and antioxidant activities on the methanol extract of sea cucumber *Stichopus herrmanni*. Jurnal Ilmu dan Teknologi Kelautan Tropis 4(2): 360–368. https://doi.org/10.29244/jitkt.v4i2.7799

Safari R, Yaghoubzadeh Z (2020) Antioxidant activity of bioactive peptides extracted from sea cucumber (*Holothuria leucospilota*). International Journal of Peptide Research and Therapeutics 26: 2393–2398. https://doi.org/10.1007/s10989-020-10031-9

Sajwani FH (2019) Frondoside A is a potential anticancer agent from sea cucumbers. Journal of Cancer Research and Therapeutics 15(5): 956–960. https://doi.org/10.4103/jcrt.JCRT_1427_16

Salarzadeh N, Afkhami M, Bastami KD, Ehsanpour M, Khazaali A, Mokhleei A (2012) Proximate composition of two sea cucumber species *Holothuria parva* and *Holothuria arenicola* in Persian Gulf. Annals of Biological Research 3(3): 1305–1311.

Sarhadizadeh N, Afkhami M, Ehsanpour M (2014) Evaluation bioactivity of a sea cucumber, *Stichopus hermanni* from Persian Gulf. European Journal Experimental Biology 4(1): 234–258

Satari MH, Arma U, llyas S, Handayani D (2017) Anticancer potency of black sea cucumber (*Holothuria atra*) from Mentawai Islands, Indonesia. Padjadjaran Journal of Dentistry 29(1): 54–57. https://doi.org/10.24198/pjd.vol29no1.11654

Shahrulazua A, Samsudin AR, Iskandar MA, Amran AS (2013) The in vitro effects of sea cucumber (*Stichopus sp1*) extract on human osteoblast cell line. Malaysian Orthopaedic Journal 7(1): 41–48. https://doi.org/10.5704/MOJ.1303.015

Siahaan EA, Pangestuti R, Munandar H, Kimi SK (2017) Cosmeceuticals properties of sea cucumbers : Prospects and trends. Cosmetics 4(26): 1–12. https://doi.org/10.3390/cosmetics4030026

Sicuro B, Levine J (2011) Sea cucumber in the Mediterranean: a potential species for aquaculture in the Mediterranean. Review of Fisheries Science 19: 299–304. https://doi.org/10.1080/10641262.2011.598249

Sicuro B, Piccinno M, Gai F, Abete MC, Danieli A, Dapra F, Mioletti M, Vilella S (2012) Food quality and safety of Mediterranian sea cucumber *Holothuria tubulosa* and *Holothuria poli* in Southern Adriatic sea. Asian Journal of Animal and Veterinary Advances 7(9): 851–859. https://doi.org/10.3923/ajava.2012.851.859

Silchenko AS, Kalinovsky A, Avilov S, Kalinin VI (2017) Nine new triterpene glycosides, magnumosides A1–A4, B1, B2, C1, C2 and C4, from the Vietnamese sea cucumber *Neothyonidium* (=*Massinium*) *magnum*: Structures and activities against tumor cells independently and in synergy with radioactive irradiation. Marine Drugs 15(8): e256. https://doi.org/10.3390/md15080256

Su X, Xu C, Li Y, Gao X, Lou Y, Ding J (2011) Antitumor activity of polysaccharides and saponins extracted from sea cucumber. Journal of Clinical & Cellular Immunology 2(1): 1–5. https://doi.org/10.4172/2155-9899.1000105

Sumarto, Hasan B, Karmila R, Sukmawati M (2019) Characteristics of chitosan Nanopartices extracted from sea cucumber (*holothurian scabra*) as source materials for glucosamine. Pertanika Journal of Science & Technology 27(4): 2409–2425.

Wijesinghe WAJP, Jeon YJ, Ramasamy P, Wahid MEA, Vairappan CS (2013) Anticancer activity and mediation of apoptosis in human HL-60 leukemia cells by edible sea cucumber (*Holothuria edulis*) extract. Food Chemistry 139: 326–331. https://doi.org/10.1016/j.foodchem.2013.01.058

Xu H, Xu J, Wang Y, Hu S, Wang Y, Wang J, Xue C (2015) Fucoidan isolated from the sea cucumber *Acaudina molpadioides* improves insulin resistance in adipocytes via activating PKB/GLUT4 pathway. European Food Research and Technology 240: 753–776. https://doi.org/10.1007/s00217-014-2380-z

Zhang M, Chen L, Liu Y, Chen M, Zhang S, Kong D (2020) Sea cucumber *Cucumaria frondosa* fucoidan inhibits osteosarcoma adhesion and migration by regulating cytoskeleton remodeling. Oncology Reports 44: 469–476. https://doi.org/10.3892/or.2020.7614

Zhou X, Wang C, Jiang A (2011) Antioxidant peptides isolated from sea cucumber *Stichopus japonicus*. European Food Research and Technology 234: 441–447. https://doi.org/10.1007/s00217-011-1610-x