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Sea cucumber as a therapeutic aquatic resource for human health

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Abstract

Sea cucumbers are worm-like, leathery bodied, benthic, marine organisms with a branched gonad. There are over 900 species, and these organisms are capable of changing their mechanical state, regenerating their small appendages, and digestive tract. Additionally, sea cucumbers possess both commercial and therapeutical value. Furthermore, it is thought that the metabolites these organisms possess may give rise to their therapeutical value. The use of sea cucumbers in therapy can be traced back to the Ming dynasty, where they were eaten for their tonic properties against constipation, hypertension, and rheumatism. A plethora of studies have been conducted, whereby different metabolites were extracted from sea cucumbers and tested for different therapeutic properties. Herein, we review and discuss the anti-cancer, anti-microbial, anti-coagulant, anti-diabetic, antioxidant, and anti-inflammatory properties of the sea cucumber by assessing literature on PubMed and Google Scholar. Furthermore, the genome and epigenome of these remarkable species is discussed. With the immense data supporting the therapeutic properties of sea cucumbers, further studies are warranted, in order to develop novel and innovative therapeutic compounds for the benefit of human health from these fascinating marine organisms.

Keywords: Echinodermata, Holothuroidea, Anti-thrombotic, Metabolites, Drug discovery

Introduction

Sea cucumbers are soft bodied, worm-like, leathery bodied, benthic, marine organisms with a branched gonad, and belong to the Echinodermata phylum and class Holothuroidea (Dolmatov, 2021; Hossain et al., 2020; Senadheera et al., 2020). Interestingly, sea cucumbers have been utilized over the years as a form of therapy in traditional Chinese medicine (TCM) (Adrian & Collin, 2018; Attoub et al., 2013; Janakiram et al., 2015; Pangestuti & Arifin, 2017). As various diseases are on a rise, large effort is needed in the development of therapeutic compounds, and species that reside in environments which would be detrimental to humans such as marine organisms, whereby they come across pollution and heavy metals for example, may be an untapped resource which can be utilized to develop novel therapeutic compounds (Adrian & Collin, 2018; Correia-da-Silva et

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al., 2017; Jeyamogan et al., 2017; Wargasetia & Widodo, 2017).

Infectious diseases, and cancer are on the rise (Akbar et al., 2019; Liu et al., 2016; Siddiqui et al., 2016). Infectious diseases are responsible for the death of approximately fourteen million individuals per annum (Akbar et al., 2019). This is coupled with increase in cases of cancer which are expected to double to 21.4 million cases and 13.2 million deaths by the next eight years (Siddiqui et al., 2016). Additionally, thrombotic diseases are believed to account for approximately 30% of early deaths worldwide (Liu et al., 2016). Yet, each of these diseases face obstacles with their current treatments; for example, the treatment for infectious diseases is hampered due to the global problem of antibiotic/antimicrobial resistance, especially with the emergence of several superbugs (Akbar et al., 2020; Davies & Davies, 2010; Khan & Siddiqui, 2014). Antithrombotic drugs may result in unwanted bleeding, and limiting the usage of the drugs and cancer treatments have severe side-effects (Liu et al., 2016). Thus, the search for novel compounds in various diverse and rich environments is suggested, including the marine environment in which sea cucumbers are found (Alves et al., 2020; Choudhary et al., 2017).

These leathery organisms belong to the marine world; a world which is part of nature, hence it can impact the flow of diseases, as the environment, humans and animals are all interconnected and affected by one another: a system known as one health (Hossain et al., 2020; Senadheera et al., 2020; Solis & Nunn, 2021). Over the years, various studies have shown that sea cucumbers, have both commercial and pharmaceutical benefits, including their tonic properties against hypertension and constipation (Hossain et al., 2020; Mondol et al., 2017). Herein, the recent discovery of various metabolites and chemicals released by the sea cucumbers is reviewed, as well as their anti-cancer, anti-microbial, anti-thrombotic, anti-coagulant, antioxidant, anti-inflammatory, and antidiabetic therapeutic properties (Table 1). Present knowledge coupled with future studies in the precise structure, doses, and concentrations of the sea cucumber metabolites may serve as therapeutical drugs found in the medical industry for the benefit of human health.

What are sea cucumbers?

Sea cucumbers are marine organisms belonging to the Echinodermata phylum and class Holothuroidea, with more than 900 species identified worldwide (Gu et al., 2022; Shikov et al., 2020). These organisms have worm-like, elongated bodies (Dolmatov, 2021; Gajdosechova et al., 2020). In fact, they are soft bodied, with leathery skins and a branched gonad (Hossain et al., 2020; Pangestuti & Arifin, 2017; Senadheera et al., 2020; Wargasetia & Widodo, 2017). Moreover, they can extend from a few millimeters up to a meter in length (Hossain et al., 2020; Mondol et al., 2017). Additionally, they can change their mechanical state very fast, since they contain collagen in their skin (Hossain et al., 2020; Pangestuti & Arifin, 2017). Additionally, they have the ability to alter the stiffness within their inner dermis (Capadona et al., 2008). Also, using their tiny tube-like feet they can control their movement. Furthermore, they can communicate with one another through their transmission of various hormone signals in the water. They also have good regenerative abilities, with a capability to regenerate small appendages such as their tentacles and tube feet as well as their digestive tract (Dolmatov, 2021). Moreover, they can also restore their internal organs such as their gonads; this is important, as sea cucumbers tend to undergo evisceration: a possible defense mechanism against predators, hence, their ability to regenerate is crucial (Dolmatov, 2021; García-Arrarás & Greenberg, 2001; Weigel, 2020). Additionally, it was found that upon regeneration of the visceral organs of the digestive system, the gut microbiome was also regenerated, resulting in the upregulation of genes responsible for cell proliferation, carbohydrate metabolism, and immune system in the sea cucumber *Apostichopus japonicus* (Weigel, 2020).

These marine invertebrates are found in all the world's oceans in varying depths reaching more than 5,000 m deep; as they are benthic organisms, living on the ocean floor (Chen et al., 2021; Dolmatov, 2021; Pierrat et al., 2022). Yet, in South-East Asia and Australia they are found in greater abundance (Dolmatov, 2021). Furthermore, in Indonesia itself, around 350 sea cucumber species have been found, some of which are observed to have economic value (Pangestuti & Arifin, 2017). Sea cucumbers of great commercial value, like: *Holothuria poli*, *Holothuria tubulosa*, *Holothuria mammata*, and *Parastichopus regalis*, have led to the placement of fishing regulations and regulatory measured to ensure the restoration of their populations (Montero et al., 2021; Pierrat et al., 2022). Thinking of it on a global scale, Southeast Asia is the market hotspot for sea cucumber trade, with the dried body wall of the sea cucumber being part of the Asian dried seafood market for long periods of time (Eriksson et al., 2012; Pangestuti & Arifin, 2017; Pierrat et al., 2022).

Furthermore, they are divided into three subclasses Aspidochirotacea, Apodacea, and Dendrochirotacea (Chen et al., 2021; Mondol et al., 2017; Pawson et al., 2010). These three

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Table 1. Therapeutic effects of sea cucumbers

Properties	Description	References
Anti-cancer	– Triterpenoids exhibited cytotoxic activity was exhibited against human leukemia HL-60 and human hepatoma BEL-7402 cells – Frondoside A resulted in inhibition of lung cancer cells LNM 35 in xenografts, reduction of AsPC-1 pancreatic cancer cell lines growth, induction of apoptosis in pancreatic cells, and inhibited the migration of MBA-MD-231 breast cancer cells – Frondoside A inhibited cell viability in Burkitt's lymphoma cell lines	Adrian & Collin, 2018 Li et al., 2013 Sajwani, 2019
Anti-viral	– FUCS-1 blocked entry and replication of HIV_{IIIB} laboratory strain – FUCS-1 reduced p24 antigens in $HIV\text{-}1_{KM018}$ and $HIV\text{-}1_{TC2}$ clinical isolates – Cytopathic effect of HSV-1 virus prevented up to 98.3% *in vitro* through treatment with crude water extract of sea cucumber – Liuouvilloside A reduced HSV-1 infectivity to 24% – Liuouvilloside B reduced HSV-1 infectivity to 2.5%	Farshadpour et al., 2014 Maier et al., 2001 Pangestuti & Arifin, 2017
Anti-bacterial	– Proteases bromelain and papain exhibited antibacterial effects against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Pseudomonas* sp. – Cuvierian organs, and coelomic fluid of sea cucumber exhibited antibacterial effects against *E. coli*, *Salmonella typhi*, *P. aeruginosa*, and *Staphylococcus aureus*	Adibpour et al., 2014 Ghanbari et al., 2012
Anti-fungal	– Body wall and coelomic fluid of sea cucumber inhibited growth of *Candida albicans*, *Aspergillus brasiliensis*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus fumigatus* – Variegatuside D, and variegatuside E exhibited significant inhibition of *C. albicans, Candida parapsilosis, Candida neoformans, Candida tropicalis*, *Candida pseudotropicalis*, *Nannizzia gypsea*	Adibpour et al., 2014 Cardoso et al., 2020
Anti-coagulant/ anti-thrombotic	– Lower molecular weight of FCS diminished factor XII in rats – Novel FCS from *Holothuria mexicana* sea cucumber accelerated inhibition of thrombin – Sulfated fucans activated factors IIa and Xa	Khotimchenko, 2018 Mou et al., 2017 Pangestuti & Arifin, 2017
Antioxidant	– High-scavenging activity towards NO radicals – Inhibition of lipid peroxidation processes – Moderate iron-chleating activity – Increase in glucathione peroxidase and superoxide dismutase activities *in vivo* – Reduction in hydrogen peroxide induced apoptosis upon treatment of macrophage cell line J774A.1 with lysoplatelet activating factory and lysophosphatidylcholine – Eicosapentaenoic acid-enriched phospholipids within triterpene glycosides reduced oxidative damage in rat adrenal pheochromocytoma cell line PC12	Esmat et al., 2013 Khotimchenko, 2018 Nishikawa et al., 2015 Wu et al., 2014
Anti-inflammatory	– Downregulation of inflammation induced genes – NO production decrease within lipopolysaccharide stimulated RAW 264.7 cells	Olivera-Castillo et al., 2018 Song et al., 2013
Antidiabetic	– Sea cucumber hydrolysates resulted in hypoglycemic, hypolipidemic, and insulin-sensitizing effects within streptozotocin induced diabetic rats FCS promotes glucose uptake and consumption	Gong et al., 2021 Wang et al., 2020

FUCS-1, fucosylated chondroitin sulfate-1; FCS, fucosylated chondroitin sulfate; HIV, human immunodeficiency virus; HSV, herpes simplex virus; NO, nitric oxide.

subclasses are divided into six orders which are Apodida, Dactylochirotida, Dendrochirotida, Elasipodida, Aspidochirotida, and Molpadida (Chen et al., 2021). Some of the commercially important are *Cucumaria japonica*, *Holothuria forskali*, *Holothuria nobilis*, *H. poli*, *Acaudina molpadioides*, *A. japonicus*, *H. tubulosa*, *Pearsonothuria graeffei*, and *Isostichopus badionotus* (Hossain et al., 2020). One reason as to why they are commercially important is because of their perceived ability to cure various diseases (Janakiram et al., 2015; Khotimchenko, 2018; Sajwani, 2019). In fact, because of their various benefits, East Asians consider them to be a nutritious and luxurious type of food (Janakiram et al., 2015; Khotimchenko, 2018; Sajwani, 2019; Senadheera et al., 2020). Some of the diseases they may cure include asthma, hypertension, cuts, burns, rheumatism, back pain, joint pain, kidney problems, wound injuries, constipation, impotence, and reproductive disorders (Hossain et al., 2020). Additionally, they are believed to hold a high nutritional value, as they contain vitamin A, vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_3 (niacin), calcium, magnesium, iron, and zinc (Bordbar et al., 2011). Furthermore, sea cucumbers are characterized by their low lipid and high protein composition, which is of nutritional value, with proteins constituting 40–60 percentage by weight (wt%) of sea cucumber dry matter (Xu et al., 2018). The proteins within the sea cucumber are usually in the form of collagen, moreover, the proteins within the body wall are mostly insoluble collagen fiber matter (Xu et al., 2018). The collagens in sea cucumbers usually consists of three polypeptide chains, with repeating Glycine-X-Y motifs, X and Y

represent amino acids; the two dominant amino acids within sea cucumbers are glutamic acid and glycine, glycine is the most abundant matter (Xu et al., 2018). On the other hand, fatty acids are small in amount, with only 2 to 8 wt% of sea cucumber dry matter (Xu et al., 2018). Furthermore, 15 wt% of carbohydrates is found in the body wall, whereas 8 wt% is found in muscle bands matter (Xu et al., 2018). Moreover, sugars bound to one another via glycosidic bonds are referred to as glycosides. Within sea cucumbers, triterpene glycosides are one of the most abundant secondary metabolites (Xu et al., 2018). They are composed of carbohydrate chains commonly containing glucose, xylose, quinovose, 3-O-methyglucose, and sometimes 3-O-methyxylose, 3-O-methylquinovose, 3-O-methylglucoronic acid, and 6-O-acetyl-glucose matter (Xu et al., 2018).

Furthermore, fucan, fucoidan, and fucosylated chondroitin sulfate (FCS) are all polysaccharides found within sea cucumbers. Fucoidan contains a backbone built by (1–3)-linked tetrafucose repeated units, each fucose unit containing either one or two HSO_4 substitution. Whereas FCS contains a chondroitin sulfate backbone with either sulfated or non-sulfated fucose on the side chain matter (Myron et al., 2014; Xu et al., 2018). Fucan constitutes of 1 → 3 and/or 1 → 2 linked tetrasaccharide repeating units with either sulfated or non-sulfated fucose residues on it backbone chain matter (Xu et al., 2018).

The genome and epigenome of sea cucumbers

As mentioned earlier, sea cucumbers are organisms that share a common ancestry with chordates, and have the ability to regenerate; this is an outstanding feature, which still needs further research to comprehend the mechanisms involved (Medina-Feliciano et al., 2021; Zhang et al., 2017). This species is capable of regrowing their body parts in a much greater scale compared to sea urchins and sea stars, hence, they are considered to being prime regeneration models (Zhang et al., 2017). Unfortunately, not many studies have been accomplished examining the genome and epigenome of sea cucumbers at present (Medina-Feliciano et al., 2021). However, various research has been conducted on different species of sea cucumbers such as *A. japonicus* and *Holothuria glaberrima* in relation to their genome (Medina-Feliciano et al., 2021; Zhang et al., 2017). If enough genomic and epigenomic resources are available, then further understanding of the sea cucumbers regenerative abilities will be possible. Additionally, research on the genome may provide the framework for future research of potential medicinal use, as well as aid in establishing a breeding program for sea cucumbers, which is of commercial value (Zhang et al., 2017).

A. japonicus is a commercially important sea cucumber whose genome has been sequenced (Zhang et al., 2017). The genome of *A. japonicus* was sequenced at an assembly of 805 Mb and 30,350 protein coding genes using Illumina and PacBio platforms. This led to the conduction of various phylogenetic and comparative analyses revealing the presence of marker genes. The marker genes were found to be associated with the gill slits and notochord, indicating that these features may have possibly been part of the ancestral echinoderms. Additionally, biomineralization genes were found which explained the unique shape and weak mineralization properties the sea cucumber possesses (Zhang et al., 2017).

Recently, the genome of the sea cucumber *Holothuria glaberrima* was assembled using only short sequencing reads (Medina-Feliciano et al., 2021). The genome was constructed in 89,105 scaffolds. Additionally, 894 complete and partial genes were queried. Within *H. glaberrima*, four types of melanotransferrin (*Mtf*) genes were found (Hg*MTF1*, Hg*MTF2*, Hg*MTF3*, and Hg*MTF4*): these are membrane-bound molecules involved in the development of cancer, Alzheimer's diseases and various other, whereas in other echinoderms, only one melanotransferrin was reported (Hernández-Pasos et al., 2017; Medina-Feliciano et al., 2021). By conducting further studies, and obtaining more knowledge regarding the genes, and genomic sequence of the types of sea cucumbers, an understanding of the different regenerative abilities and therapeutic activities may be established. Furthermore, work on the epigenome of these remarkable species will be essential, as unlike the genome, which remains mostly static, the epigenome is involved in regulating gene expression, development, tissue differentiation, and may be altered by various environmental conditions.

Sea cucumbers and their anti-cancer activity

Over the years much effort has been put into finding therapeutic compounds in marine organisms, as these organisms are believed to be untapped sources with a potential of possessing compounds with anti-cancer effects (Adrian & Collin, 2018; Correia-da-Silva et al., 2017; Wargasetia & Widodo, 2017). Sea cucumbers, for almost hundreds of years have been used to treat cancer in Chinese medicine (Adrian & Collin, 2018; Attoub et al., 2013; Janakiram et al., 2015; Pangestuti & Arifin, 2017). Sea cucumbers are part of TCM with a history capable of being traced back to the Ming dynasty (Chen, 2003; Fu et al., 2016). Historically, sea cucumbers were eaten by the Chinese for their

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tonic properties and effectiveness against rheumatism, constipation, hypertension, and much more (Fu et al., 2016; Guo et al., 2015; Mondol et al., 2017; Tang, 1987). However, only in the year 1952 in an article authored by Nigelli, the possession of biologically active compounds in the sea cucumber was suggested (Khotimchenko, 2018). A characteristic secondary metabolite of sea cucumbers is triterpene glycosides (Aminin et al., 2015; Claereboudt et al., 2019; Park et al., 2014). Triterpene glycosides are also known as saponins, and not only do they have important pharmaceutical properties, but they also play an enormous role in the holothurians self-defense (Claereboudt et al., 2019; Hossain et al., 2020). These secondary metabolites possess a carbohydrate chain of up to six monosaccharides such as D-glucose, D-xylose, 3-O-methyl-D-xylose, 3-O-methyl-D-glucose, and D-quinovose. Furthermore, almost 60% of the triterpene glycosides which have been identified contain sulfate groups attached to the monosaccharide's groups in the carbohydrate chain. One type of triterpene glycoside which is extracted from the skin of *Cucumaria frondosa* is frondoside A (Li et al., 2008; Sajwani, 2019). This is a well-known saponin which is typically isolated from the sea cucumbers (Hossain et al., 2020). In addition, frondoside B and frondoside C are also derived from sea cucumbers, with only minor structural differences in comparison to frondoside A (Adrian & Collin, 2018). Frondoside A is a pentaoside with its third monosaccharide residue being xylose and its terminal monosaccharide residue being a 3-O-methylglucose (Adrian & Collin, 2018). Moreover, it possesses an acetoxy group at C-16 aglycone and has a sulphate group on its first residue.

A good anticancer compound should be able to either reverse, inhibit or delay the progression of cancer (Li et al., 2013). Although this can be done in various ways, such as exhibiting antiproliferation effects, showcasing pro-apoptosis, anti-invasive, and antimetastatic properties (Sajwani, 2019). One general way for a compound to prove to be an anticancer agent, is by it simply being toxic to the cancer cells (Li et al., 2013).Various triterpenoids from the sea cucumber have shown potent cytotoxicity against human leukemia HL-60 and human hepatoma BEL-7402 cells (Li et al., 2013). Moreover, various compounds within sea cucumbers have shown antiproliferative effects thus impacting cancer (Bordbar et al., 2011). For example, frondoside A has been studied to understand its effect against cell viability and proliferation (Adrian & Collin, 2018). Various studies using methods such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay, thymidine incorporation, and cell counts, were used on pancreatic ductal adenocarcinoma, breast, colon, prostate, cervix, and bladder cells as well as acute leukemias. Furthermore, a suppression in lung cancer growth using frondoside A in a dose-dependent manner was found (Attoub et al., 2013; Sajwani, 2019). Upon the injection of frondoside A at an intraperitoneal dose of 10 μg/kg/day, the growth of lung cancer cells LNM35 in xenografts were inhibited (Adrian & Collin, 2018). At the end of the ten-day treatment period, there was a reduction in more than 40% of the tumor growth. Similarly, an intraperitoneal dose of 10 μg/kg/day of frondoside A led to a significant reduction in the growth of AsPC-1 pancreatic cancer cell lines in a 32-day period. Additionally, frondoside A inhibited the cell viability of Burkitt's lymphoma cell lines after a 48-hour treatment with a range of concentrations from 0.3–0.6 μM (Sajwani, 2019).

Frondoside A was shown to induce apoptosis through annexin V binding (Adrian & Collin, 2018). This binding implies the exteriorization of phosphatidylserine, and DNA fragmentation through the conduction of terminal deoxynucleotidyl triphosphate nick-end labeling assay. Additionally, there was an increase in the pro-apoptosis proteins and decrease in anti-apoptosis proteins. Likewise, in pancreatic cells, it is shown that frondoside A induces apoptosis via the mitochondrial pathway. This is because, frondoside A has led to an increase in the expression of cyclin-dependent kinase inhibitor, p21.

Additionally, frondoside A is also capable of inhibiting the invasion and migration of lung and breast cancer cells (Adrian & Collin, 2018). This conclusion has been made by studying and measuring the migration microscopically in a wound healing model. In this model, a 1 mm scrape is made through a confluent monolayer of cells; the cells are then to move and fill in the gap. Frondoside A was found to inhibit the migration of MBA-MD-231 breast cancer cells and LNM35 lung cancer cells (Adrian & Collin, 2018).

Further studies are necessary to ensure frondoside A to be a good anticancer compound capable of being used in patients. For instance, it is important to determine and optimize the necessary concentrations and doses of the compound (Janakiram et al., 2015; Sajwani, 2019). Additionally, it is crucial to understand the exact mechanisms of action of the compound and be able to administer the drug orally in patients (Aminin et al., 2015). Intraperitoneal administration of the compound poses procedure risks for the patients (Sajwani, 2019). Moreover, it is important to ensure the safety of this compound towards humans and understand the adverse effects the sea cucumber may pose on

humans and the environment through the conduction of cytotoxicity assays (Hossain et al., 2020; Li et al., 2013).

Antimicrobial activities

Sea cucumbers are believed to be nutritionally valuable due to their high protein and low-fat content and have been used as a food source in many Asian countries as mentioned earlier (Ghanbari et al., 2012; Senadheera et al., 2020). Additionally, these organisms due to the various bioactive compounds may possess a variety of therapeutic/pharmacological properties (Ghanbari et al., 2012; Kamyab et al., 2020). Previously, their possession of anti-cancer properties was described. However, this species also possesses various antimicrobial properties (Adibpour et al., 2014; Senadheera et al., 2020). They have been found to exhibit antibacterial, antifungal, and antiviral activity (Adibpour et al., 2014; Farshadpour et al., 2014; Senadheera et al., 2020).

With viral diseases always being a major health issue humans face, the need to continuously find new antiviral drugs is consistent (Farshadpour et al., 2014). The metabolic compounds of sea cucumbers have been looked at for various antimicrobial properties. In fact, the triterpenoid compounds of sea cucumbers have been examined against the human immunodeficiency virus (HIV) and the herpes simplex virus type 1 (HSV-1) (Maier et al., 2001).

One major virus responsible for the infection of 33.3 million people worldwide is the HIV type-1 (HIV-1) (Huang et al., 2013). Although millions of people acquire this infection, many individuals are unable to use the present drugs due to their severe adverse effects, as well as the continuous mutation of the virus. Hence, with the hope of finding new and effective treatment options, studies have been conducted on the sea cucumber. A species of sea cucumber in which novel antivirals were investigated is *Thelenota ananas*. From the body wall of this sea cucumber, FCS was isolated (Huang et al., 2013; Vessella et al., 2020). FCS is a water-soluble depolymerized glycosaminoglycan, which contains *N*-acetylgalactosamine, glucuronic acid, fucose, and ester sulfate in 1:1:1:3.7 respectively (Pangestuti & Arifin, 2017).

To determine the effect FCS has against this virus, its lower molecular weight fragment (fucosylated chondroitin sulfate-1, FUCS-1) was prepared through free radical depolymerization (Huang et al., 2013). The FUCS-1 was then tested against different strains of HIV-1 including clinical isolates. The results obtained indicated the ability of FUCS-1 to block the entry and replication of HIV-1_{IIIB} a laboratory strain (Pangestuti & Arifin, 2017). It was found that FUCS-1 can inhibit the production of p24 antigen with an EC_{50} at 0.73 μg/mL (Huang et al., 2013). The researchers determined this through their conduction of a p24 assay, where cells were inoculated with HIV-1_{IIIB}. Moreover, FUCS-1 was also found to reduce the p24 antigen in clinical isolates HIV-1_{KM018} and HIV-1_{TC-2}, with their EC_{50} values being 23.75 μg/mL and 31.86 μg/mL respectively. With these finding in place, it is believed that the isolate from the sea cucumber can be further developed as a novel HIV-1 treatment of infected patients (Pangestuti & Arifin, 2017). This is of particular interest since FUSC-1 is also capable of inhibiting the p24 antigen in drug resistant strains, protease inhibitor resistant strains and nonnucleoside reverse transcriptase inhibitors resistant strains (Huang et al., 2013).

Furthermore, various studies have been conducted on the antiviral properties of the sea cucumber against the HSV-1. This virus belongs to the Herpesviridae family and is a DNA enveloped virus (Farshadpour et al., 2014). With most drugs showing severe side effects, studies looking at the effects of marine organisms against this virus have been conducted. In a study conducted, the crude water extract of the sea cucumber was taken and tested against the HSV-1 replication and virus adsorption to the cells in an *in vitro* study (Farshadpour et al., 2014). Sea cucumbers from the Bushehr port in the Persian Gulf were harvested to understand its antiviral effect. To study the antiviral effect of the sea cucumber crude extracts, researchers used human epithelial-2 cells containing HSV-1. The goal was to see how the sea cucumber extract will affect the replication of the virus intracellularly. To do so different concentrations of the extract were added to the virus inoculated cells. The study conducted indicated that with a concentration of 400 μg/mL, the cytopathic effect of the virus could be prevented up to 98.3% (Farshadpour et al., 2014).

Moreover, in another independent study the effect of two new trisulfated triterpene glycosides, liouvillosides A and B isolated from *Staurocucumis liouvillei*, a sea cucumber from the Antarctic, was studied for its virucidal effects against the same virus HSV-1 (Maier et al., 2001). The two new trisulfated triterpene glycosides were found to be virucidal against HSV-1 at concentrations as low as 10 μg/mL. Liouvilloside A was found to weakly inactivate the virus at a maximum concentration, reducing the virus's infectivity to 24%; while liouvilloside B was found to lower the infectivity of the virus 10 times more, bringing it to 2.5%.

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Furthermore, these compounds are also capable of exhibiting antibacterial and antifungal activities (Adibpour et al., 2014). There are various compounds aside from the saponins which exhibit these antimicrobial effects. These include steroidal glycosides, naphthoquinone pigments, polyhydroxylated sterols, lysozymes, complement substances, and antimicrobial peptides. Due to its ability to defend itself against predators, such as fish or different starfish like *Patiria pectinifera*; it is believed that these organisms possess various chemical defenses as well as defense organs (Kamyab et al., 2020; Popov et al., 2014).

Certain peptides from sea cucumbers upon hydrolysis have shown antibacterial properties (Ghanbari et al., 2012). For example, the sea cucumber *Actinopyga lecanora* when hydrolyzed for 24 hours via different proteases such as bromelain and papain, exhibited antibacterial properties. The hydrolysates produced by these two proteases were shown to have antibacterial properties against gram-negative bacteria. In fact, a 30%, 30.7%, and 51.85% inhibition in the growth of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Pseudomonas* sp. respectively was recorded (Ghanbari et al., 2012).

Also, the bioactive molecules found in sea cucumbers such as saponins contain defense molecules which have exhibited various antimicrobial properties (Kamyab et al., 2020). In a study conducted, the crude extracts from the sea cucumber were used against a range of pathogenic and non-pathogenic bacteria. The results of this study proved the antibacterial activity of sea cucumbers with a display of inhibition potential. In fact, sea cucumbers *Holothuria fuscopunctata*, *Bohadschia argus*, *Holothuria coronopertusa*, *Stichopus chloronotus*, *Actinopyga mauritiana*, *Bohadschia vitiensis* all exhibited a 50% inhibition potential. Moreover, the crude extracts from *Actinopyga echinites*, *Holothuria whitmaei*, *Holothuria hilla*, and *H. coronopertusa* exhibited extremely potent antibacterial activity of almost 75% inhibition potential. It is believed the composition and amount of saponins present in the sea cucumber plays a role in its antibacterial properties. This is because sea cucumbers such as *Holothuria atra* and *H. whitmaei* have low saponin concentrations and yet they were able to show antibacterial activity (Kamyab et al., 2020).

Moreover, the various organs of the sea cucumbers were tested for their antibacterial and antifungal properties (Adibpour et al., 2014). It was found through the conduction of antibacterial assays that the body wall, Cuvierian organs and coelomic fluid of the sea cucumber showed the highest antibacterial activity against *E. coli*, *Salmonella typhi*, *P. aeruginosa*, and *Staphylococcus aureus* (Adibpour et al., 2014).

Additionally, the body wall and coelomic fluid of the sea cucumber through the conduction of an antifungal assay was confirmed to inhibit the growth of *Candida albicans*, *Aspergillus brasiliensis*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus fumigatus* fungi. It is important to keep in mind the main cause of fungal infections, responsible for approximately 50 to 70 percent of the infections is *C. albicans*; against which the sea cucumber has exhibited antifungal effects (Adibpour et al., 2014; Cardoso et al., 2020).

Fungal infections are an extreme threat to public health as they account to almost 1.5 million deaths annually: showcasing a mortality rate of 90% (Cardoso et al., 2020). Further studies conducted looked at other compounds isolated from the sea cucumber *Stichopus variegates*. These compounds include variegatusides A, B, C, D, E, and F, holothurin B, and triterpene glycosides, which when tested for antifungal activity showed selective activity. However, variegatuside D and variegatuside E showed significant fungal growth inhibition against *C. albicans*, *Candida parapsilosis*, *Candida neoformans*, *Candida tropicalis*, *Candida pseudotropicalis*, and *Nannizzia gypsea* (Cardoso et al., 2020). Variegatuside D was shown to exhibit activity with MIC_{80} values at 3.4, 3.4, 6.8, 13.6, 3.4, and 3.4 mg/L respectively. Whereas variegatuside E has MIC_{80} value of 25 mg/L against *C. albicans* and 12.5 mg/L against the remaining fungi (Cardoso et al., 2020).

With the increase in various infectious diseases worldwide, the marine environment, a rich and chemically diverse source is being studied (Alves et al., 2020; Choudhary et al., 2017). In the case of the sea cucumbers further studies are needed to further develop the compounds into drugs applicable for human use. For instance, additional chemical analyses is necessary to be taken against all isolated and purified compounds obtained from the sea cucumber (Adibpour et al., 2014; Kamyab et al., 2020). Additionally, the various mechanisms of action being exerted by the compounds should be known (Farshadpour et al., 2014). Moreover, the doses and strengths of the compounds are to be determined, along with a several clinical trials to determine the safety and appropriate dosage concentration of the compounds (Adibpour et al., 2014; Pangestuti & Arifin, 2017).

Although the process of developing a drug from marine organisms is lengthy and time consuming, there are few drugs in the market coming from marine origins (Cardoso et al., 2020). Two examples of drugs derived from marine origins are cephalosporin C and vidarabine (Malve, 2016). Cephalosporin C is an

antimicrobial derived from the marine fungus *Cephalosporium acremonium*, while vidarabine is a synthetic purine nucleoside derived from the sponge *Tethya crypta* to use against recurrent epithelial keratitis due to HSV-1 (Malve, 2016). Yet, the marine environment when compared to the terrestrial environment remains under-investigated, hence more research needs to be done to learn about the various habitats in the marine world which may be extremely beneficial to human health (Festa et al., 2020).

Anticoagulant and antithrombotic properties

Anti-coagulants are essential as they aid in the prevention of blood clots and help in the treatment of thromboembolic disorders (Hirsh et al., 2005). Hence, the sulfated polysaccharide: FCS obtained from sea cucumbers is of importance as it provides anti-thrombotic, and heparin-like anticoagulant properties (Mou et al., 2017; Pomin, 2014). FCS is highly sulfated with large amounts of sulfated fucose branches. It has shown anti-coagulant activity, similar to that of heparin, however, with less of a bleeding risk (Liu et al., 2016; Vessella et al., 2020). With thrombotic diseases being responsible for almost 30% of deaths worldwide, many antithrombotic drugs have come to the market, such as anticoagulants. However, these drugs like heparin may cause unwanted bleeding hence limiting their use; this is why different resources are being observed such as sea cucumbers.

In order to understand the anticoagulant activity presented by sea cucumbers, *T. ananas*, a type of sea cucumber was studied (Pangestuti & Arifin, 2017). The anticoagulant activity of *T. ananas* was studied through activated partial thromboplastin time (APTT) assays. It is believed, the molecular weight of the FCS affected the anticoagulant activity. When FCS was injected intravenously in rats, it activated factor XII which in turn led to hypotension. However, when injecting FCS of a lower molecular weight, the activation of factor XII seemed to diminish (Pangestuti & Arifin, 2017).

Additionally, studies were conducted on *Holothuria mexicana* from which a novel FCS (HmG) was isolated (Mou et al., 2017). Through the conduction of anticoagulant assays, it was found that HmG tends to accelerate the inhibition of thrombin through the heparin cofactor II (HCII), inhibit the activation of factor VIII and inhibit the activation of factor X through an intrinsic tenase complex (Mou et al., 2017). Furthermore, the major side effect of anticoagulant drugs: unwanted bleeding was found to be decreased upon comparison to heparin.

Moreover, using APTT, thrombin time and prothrombin time the anticoagulant effects of FCS was studied (Khotimchenko, 2018). In the study conducted, from the body wall of the sea cucumber, fucans and FCS were isolated. Fucans are sulfated polysaccharides found in the body wall of various marine organisms, in this case, sea cucumbers (Chollet et al., 2016). It was found that both the fucans and FCS possess heparin-like anticoagulant activities. Through *in vitro* conditions, the weight and length of the thrombus generated within an artificial blood vessel is measured. The sulfated fucans which are generally of a lower molecular weight showed lower anticoagulant activity compared to FCS. They are believed to activate factors IIa and Xa while FCS activated HCII as mentioned earlier (Khotimchenko, 2018).

Furthermore, studies were conducted *in vivo* to understand the anticoagulant properties of FCS isolated from *C. frondosa* and *T. ananas* (Liu et al., 2016). To understand the effects of thrombosis *in vivo*, male Wistar rats were used. The Wistar rats were electrically induced for arterial thrombosis. It was found that FCS from *T. ananas* (FCSt) and FCS from *C. frondosa* (FCSc) showed significantly higher inhibitory effects at 0.1 mg/kg compared to heparin. Furthermore, to understand whether the molecular weight has an effect on FCS action, lower molecular weight fragments were prepared using Cu^{2+} catalytic free radical polymerization; the modified FCS is referred to as dFCS. Yet again, the antithrombotic activity was found to be reduced as the molecular weight of the polysaccharide reduced (Liu et al., 2016).

Yet, additional studies should be conducted in order to further understand the structure of FCS and HmG (Liu et al., 2016; Mou et al., 2017; Pangestuti & Arifin, 2017). Furthermore, the mechanisms of action being exerted by these compounds is to be further studied and understood (Mou et al., 2017). One major limitation is the isolation of new compounds which could possibly showcase different effects (Pangestuti & Arifin, 2017). Additionally, when studies are to move forward, and clinical trials have been completed the ability to produce the functional ingredients of the sea cucumber on an industrial level may be difficult. However, for now, researchers are to focus on the structure, mechanism, and safety of the current effective compounds.

Additionally, to address the major side effect of unwanted bleeding most antithrombotic drugs possess, the bleeding time after the administration of drugs was measured (Liu et al., 2016). The tails of Kunming male mice were cut 5 mm from the tip; using a tissue paper they were blotted every 30 s. Both FCS and dFCS showed dose-dependent bleeding in mice. The

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controls Heparin and low-molecular-weight heparins had a bleeding time of 350 s while FCSt, FCSc, dFCSt, and dFCSc prolonged the bleeding time 441, 502, 326, and 316 s respectively (Liu et al., 2016).

Anti-inflammatory and anti-diabetic properties

Inflammation is an integral part of many diseases such as autoimmune diseases, and chronic metabolic diseases both of which are a global problem due to their rise in cases, hence, anti-inflammatory drugs are in need (Olivera-Castillo et al., 2018). The sea cucumber *I. badionotus* was harvested from the Yucatan coast, and their body walls were prepared, freeze dried, and grounded. Anti-inflammatory effects were evaluated via chorioallantoic membrane assay, rat small intestine/diet trial, and mouse ear inflammation model. *I. badionotus* was found to possess anti-inflammatory properties, down-regulating inflammation induced genes in the rat intestine and enhancing the expression of pathways essential for gut barrier integrity and homeostasis (Olivera-Castillo et al., 2018). Moreover, in a different study conducted, the anti-inflammatory effects of *S. japonicus* sea cucumber extracts were examined against lipopolysaccharide-stimulated RAW 264.7 cells, by evaluating nitric oxide (NO) production, as excess NO production initiates allergic inflammatory diseases (Song et al., 2013). It was found that upon treatment with *S. japonicus* fractions, NO production level drastically decreased, and *S. japonicus* water extract inhibited NO release (Song et al., 2013).

Another disease against which sea cucumbers are found to have effect is diabetes mellitus, a chronic metabolic disorder characterized by the elevation of blood glucose levels due to defective insulin resistance and/or insulin secretion (Wang et al., 2020). This disease is believed to affect approximately 629 million individuals by the year 2040 according to the International Diabetes Federation; hence, there is a search for drugs of natural substance origin, proving to be safe, non-toxic, and effective against patients (Wang et al., 2020). In a study conducted, the impact of sea cucumber hydrolysates (SCH) on glucose metabolism, insulin resistance, and lipid metabolism were studied on streptozotocin induced diabetic rats, it was found that SCH exerts effectively potent hypoglycemic, hypolipidemic, and insulin-sensitizing effects (Wang et al., 2020). Moreover, in another study conducted, FCS was isolated from the body wall of *S. japonicus* (FCS*sj*) and was tested *in vitro* using glucosamine induced insulin resistant HEP G2 cells (Gong et al., 2021). It was found that FCS*sj* is capable of promoting glucose uptake and consumption, alleviating cell damage (Gong et al., 2021).

Antioxidant properties

Antioxidants are protective systems scavenging free-radicals and reducing their effects, free-radicals include reactive oxygen species and reactive nitrogen species (Khotimchenko, 2018). Endogenously, antioxidants regulating the redox balance through chemical buffering, as well as enzyme-catalyzed free-radical detoxification is present; however, if the protective systems fail to withstand the influence of free radicals, resulting in oxidative stress, then administration of antioxidants through food, supplements or pharmaceuticals will take place (Khotimchenko, 2018).

Through the analytical technique of high-performance liquid chromatography, it has been determined that sea cucumber extracts contain chlorogenic acid, pyrogallol, coumaric acid, rutin, ascorbic acid, and catechin all of which are phenolic compounds and potential antioxidants (Khotimchenko, 2018). The compounds were found to possess high scavenging activity for NO radicals, inhibition of lipid peroxidation processes, and moderate iron-chelating activity *in vitro* (Esmat et al., 2013; Khotimchenko, 2018). Furthermore, *in vivo* studies were conducted, rats serving as the animal models were administered with sea cucumber extracts, ultimately leading to increased glutathione peroxidase, and superoxide dismutase activities (Esmat et al., 2013; Khotimchenko, 2018).

Additionally, lysoplatelet activating factor and lysophosphatidylcholine isolated from sea cucumber *H. atra* were used to treat macrophage cell line J774A.1 with, resulting in a reducing in hydrogen peroxide induced apoptosis (Khotimchenko, 2018; Nishikawa et al., 2015). Moreover, triterpene glycosides from *C. frondosa* sea cucumber were found to possess eicosapentaenoic acid-enriched phospholipids exhibiting remarkable reduction in oxidative damage induced by hydrogen peroxide and tert-butylhydroperoxide within rat adrenal pheochromocytoma cell line PC12 (Khotimchenko, 2018; Wu et al., 2014).

Concluding remarks and future perspectives

The sea cucumber is a leathery organism used thousands of years ago, as a part of TCM. For almost hundreds of years, these benthic organisms were part of TCM to help treat rheumatism, constipation, and hypertension (Fu et al., 2016; Guo et al., 2015; Mondol et al., 2017; Tang, 1987). The discovery of their possession of biologically active compounds was first published in an article by Nigelli in the year 1952 (Khotimchenko, 2018). This

species possesses metabolites capable of various therapeutic properties such as: anti-cancer, anti-bacterial, anti-fungal, anti-viral, anti-thrombotic properties, antioxidant, antidiabetic, and anti-inflammatory properties. They were found to possess various anti-viral properties against viruses such as HIV-1 and HSV-1 (Farshadpour et al., 2014; Huang et al., 2013; Maier et al., 2001; Pangestuti & Arifin, 2017; Vessella et al., 2020). In addition, sea cucumbers are of economic value, due to their pharmacologically active compounds, and are often used as a food delicacy (Khotimchenko, 2018). For example, Indonesia is the largest producer of dried sea cucumbers in the world, however, export value obtained from the sea cucumbers in Indonesia is not high, due to the low quality (Aprianto et al., 2019). Hence, it is crucial to study and develop better processes to care for the sea cucumbers and process them into trepang (dry sea cucumber) without damaging their quality. Additionally, as sea cucumbers are in high demand, over-exploitation rates are increasing, resulting in high value sea cucumbers like *H. fuscogilva* becoming scarce (Ochiewo et al., 2010). The establishment of policies, regulating sea cucumber catches to prevent overexploitation, and allow for the healthy development of sea cucumbers are needed.

Nonetheless, much work is still needed to be accomplished to develop these metabolites into approved pharmaceutical compounds for the treatment of diseases. Initially, the structures of the metabolites must be well clarified. Later, the concentration doses of the metabolites should be determined and adjusted to ensure both safety and efficacy. Currently, there are various drugs in the industry isolated from marine organisms, such as cephalosporin C and vidarabine (Malve, 2016). Furthermore, once appropriate concentrations are determined, clinical trials may follow, to utilise the sea cucumber for the benefit of human health.

Competing interests

No potential conflict of interest relevant to this article was reported.

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Availability of data and materials

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics approval and consent to participate

This article does not require IRB/IACUC approval because there are no human and animal participants.

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