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A Review over Sea cucumber (*Stichopus variegatus*): A Potential Candidate for Nutraceuticals

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Abstract

Sea cucumbers are marine animals that have been used as food and medicine. The complete nutritional content has been traditionally used as a nutraceutical ingredient for anti-inflammatory, anti-tumor, immunomodulatory, antimicrobial, and wound healing. One of the pharmaceutical companies in Indonesia that process sea cucumbers into nutraceuticals is PT. Natura Nuswantara Nirmala (Nucleus Farma) processes sea cucumbers into medicine, one of which is Onogate and Supahabu Beta capsules. This review reviews the chemical content and uses of sea cucumber extract.

Keywords: Sea cucumber; Onogate beta capsuls; Supahabu beta capsules; Nutraceutical

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Introduction

Natural foods are presently gaining wide significant popularity as a new and practical medical approach in lowering the dangers presented by several chronic ailments [1]. A typical example involves the use of sea cucumbers, predominantly found in deep seas and benthic areas. These marine animals are commonly echinoderms with soft bodies and comprise a broad group of elongated, flexible, leathery-skinned organisms resembling worms, albeit with single branched gonads and a cucumber-like gelatinous structure. The ability to reside in deep ocean floors appears as a major regular characteristic [2]. Sea cucumbers also belong to the class and phylum called Holothuroidea and Echinodermata, respectively. Widespread consumption of these species has been observed in Korea, Russia, China, Malaysia, Japan, and Indonesia, probably due to the various biological activities. Therefore, sea cucumbers serve as an important food source containing very minimal fat and cholesterol, but high protein.

Sea cucumber refers to an aquatic organism with an extensive occurrence across several Indonesian waters. Sea cucumber species that have important economic value so far are limited to the families of Holothuriidae and Stichopodidae, including Holothuria, Actinopyga, Bohadshia, Thelenota, and Scopus [3]. In 2001, Indonesia was the largest producer of dried sea cucumber exports reached 457 tons. About 40%-80% of smoked or dried sea cucumbers from Indonesia are exported to Hongkong, Japan, Korea, Singapore, Taiwan, Malaysia, and Australia. Local communities in Malaysia believe that sea cucumbers can cure various diseases such as cancer, asthma, hypertension, rheumatism, wound, and degenerative diseases. Sea cucumbers can be found in almost all coastal waters in Indonesia, from shallow tidal areas to deeper waters. Sea cucumbers prefer clear waters and relatively calm water. Generally, each type has a specific habitat, there are types of sea cucumbers that live in groups, and some live solitary (alone). Sea cucumbers generally occupy clear coral reef ecosystems, free from pollution, relatively calm water with fairly good water quality. The ideal habitat for sea cucumbers is seawater with a salinity of 29%-33% which has a pH range of 6.5-8.5; water brightness 50 cm-150 cm; dissolved oxygen content of 4 ppm-8 ppm and seawater temperature 20°C-25°C.

According to Nontji (2002), the body of sea cucumbers is usually cylindrical or elliptical and about 10 cm to 30 cm long, with a mouth located at one extremity, and an anus at the other. Because the general shape is like a cucumber, then in English this animal is called a sea cucumber which means sea cucumber. Based on Romimohtarto and Juwana's work, sea cucumbers have

a skin-like body and can be elongated and shriveled. In addition, Jasin in his study (1992) stated that the skin of the body consists of a cuticle that covers the epidermis which is not ciliated. The muscles possessed by the sea cucumber allow the sea cucumber to lengthen and shorten itself.

These marine organisms are extensively consumed in Japan and China. Al Azad et al., reported the biochemical content of sea cucumber is consequently largely explored concerning its nutritional value. As commodities, these organisms 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 [4,5]. The high-quality proteins, low levels of fat, rich amino acid profile, and desirable trace minerals found in sea cucumbers contribute to their high nutritional value [2]. A report by Zohdi et al., published in 2011, showed several studies have highlighted the pharmacological effects of these components, including antioxidant, antibacterial, and anti-inflammatory properties. Among many types of sea cucumbers, *Stichopus hermanni* possesses a higher content of glycosaminoglycan, as well as unsaturated fatty acids, including Eicosapentaenoic Acid (EPA) Arachidonic Acid (AA), and Docosahexaenoic Acid (DHA) but possesses lesser saponin content, compared to *Holothuriae scabra.*

In addition to serving as seafood, sea cucumbers have also exhibited potential medicinal value, consequently, gaining a wider consideration for the organisms. An increasing interest as a functional food ingredient was also observed, due to the presence of biologically active compounds which exhibit impressive therapeutic properties. This review will explain the chemical content of sea cucumber *S. variegatus* and its use for nutraceuticals as well as Onogate products containing *S. varietals* extract produced by PT. Nirmala Nuswantara (Nukleus Farma).

Systematics and Morphology of Sea Cucumbers

Sea Cucumber (*Stichopus variegatus*) is a member of thorn-skinned animals (Echinoderms). However, not all types of Sea Cucumber (*Stichopus variegatus*) have spines on their skin. Furthermore, there are several types of Sea Cucumber (*Stichopus variegatus*) that are not prickly. In addition to Sea Cucumber (*Stichopus variegatus*), sea stars that are included in the phylum Echinoderms are sea stars (Asteriodea) and sea urchins (Echinoidea). Among the four families of Sea Cucumber (*Stichopus variegatus*), only the family Holothuriidae is edible and has economic value. Of the three genera found as many as 23 species. In the international market, all types of *Stichopus variegatus* are known as teat fish. The names of Sea Cucumber (*Stichopus variegatus*) in each country are also different, in Indonesia, the local name is *Stichopus variegatus* (sea cucumber), Malaysia is called trepang, gamat, Hong Kong is called Haysom, sea cucumber, Thailand is the most chaotic, India is called attai, and the German name is seegueke (trepang). The classification of several types of Stichopus variegatus is as follows:

Phylum: Echinodermata

Class: Holothuroidea

Order : Aspidochirotacea

Family: Holothuriidae

Genus: 1. *Holothuria*

2. *Muelleria*

3. *Stichopus*

The body of the Sea Cucumber (*Stichopus variegatus*) is soft, fleshy, and elongated, with a cylindrical shape resembling a cucumber. Therefore, these animals are called sea cucumbers. The movement of Sea Cucumber (*Stichopus variegatus*) is so slow that almost all of its life is on the seabed. The body of these organisms can have various colours (*Stichopus variegatus*), ranging from black, gray, brownish, reddish, yellowish, to white [3]. Not all Sea Cucumber species found in Indonesian waters have important economic value. The species which are edible and have important economic value are limited to the family Holothuriidae in the genus Holothuria, Muelleria.

Chemical Composition of Sea Cucumbers and the Benefits

Sea cucumbers have a remarkable nutritional profile owing to the high contents of lipids (omega-6 and omega-3 fatty acids), protein (collagen), vitamins A, B1 (thiamine), B2 (riboflavin), and B3 (niacin), as well as certain minerals, including zinc, iron, calcium, and magnesium [6-10]. Furthermore, these organisms also contains a high proportion of compounds that exhibit bioactivity **(Figure 1)**, including lectins [11], fucoidan [12,13], saponins [14], chondroitin sulfate [15], peptides [16], sulfated polysaccharides [17,18], glycosaminoglycans [10], phenolics [19], cerebrosides [20], and sterols [21].

Mucopolysacarida is a form of cartilage and plays an important role in preventing joint disorders. Sea cucumbers not only contain Mucopolysaccharides (MPS) but also contain Glycosaminoglycans (GAGs). These substances can restore joint disease and rebuild cartilage. In addition, it can eliminate joint pain due to sitting too long. MPS together with GAGs exert a mucus effect on the cell wall. That is, sea cucumbers function as anti-thrombogenic to prevent clotting through blood thinning. Glycosaminoglycans (GAGs) also function to relieve arthritis and joint pain and help increase insulin levels. The body and skin of the sea cucumber *Stichopus variegatus* contain a lot of mucopolysaccharide acid which is useful for healing kidney disease, anemia, diabetes, wet lung, anti-tumor, anti-inflammatory, preventing aging of body tissues, and preventing arteriosclerosis. While the pure extract helps blood circulation, relieves pain, and helps reduce inflammation, and accelerates the wound healing process.

Anti-inflammatory

Inflammation is caused by the body's response to injury or disease entry and is a highly coordinated process which involves

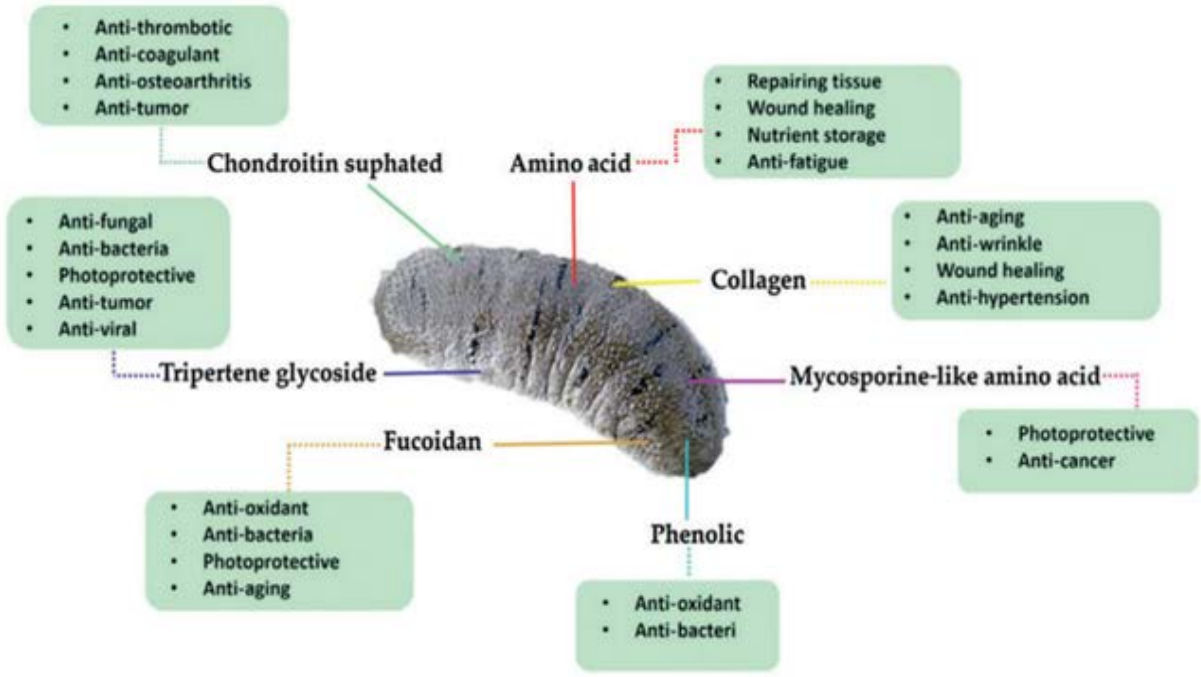

Figure 1 Bioactive compounds of sea cucumber and their beneficial actions on human health.

various types of cells [3]. A typical characteristic of inflammatory reactions is the infiltration of leukocytes as well as the release of other activated inflammatory mediators at the infection/injury sites. These reactions are ultimately regulated or resolved with the liberation of anti-inflammatory mediators. This is necessary for restricting current inflammation and tends to prevent its development into chronic conditions. Continuous inflammation possibly generates inflammatory diseases and ultimately, cancer [4,22]. Despite the availability of numerous anti-inflammatory pharmaceutics, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), their applications are constrained in terms of dosage or intervals. As a consequence, certain precautions ought to be taken to prevent cases of gastrointestinal toxicity [22]. Therefore, it is important to develop natural anti-inflammatory pharmaceutics with the potential to resolve or self-limit inflammatory cases before they progress into chronic states.

The active compounds in sea cucumber with anti-inflammatory potentials are saponins. Minale et al., described these compounds as complex amphipathic glycosides comprising a common steroid among sea stars or triterpenoid aglycone which possesses a carbohydrate moiety and is most prevalent in sea cucumbers [10]. Saponins also contain hydrophobic (aglycone) and hydrophilic (glycone) components. However, its sugar moiety content predominantly comprises Xylose (Xyl), Glucose (Glc), Glucuronic acid (Glu), Galactose (Gal), Methyl pentose, and/or Rhamnose (Rha), which connects to the hydrophobic component (sapogenin), through glycosidic bonds. In addition, the positions of various monosaccharide compositions or carbohydrate residues, as well as the nature of the side chains greatly influence saponin membranotropic activities and functional properties. Saponins tend to reduce the activity of COX-2 (Cyclooxygenase-2) that plays a significant role in stimulating inflammatory mediators. Wu in his work conducted in (2007), stated that the ability of these compounds as anti-inflammatory agents is achieved by inhibiting the cyclooxygenase enzyme action in converting arachidonic acid to prostaglandins as an inflammatory mediator. According to Valentine and Valentine's study in 2010, Arachidonic acid serves as the main n-6 PUFA in *S. variegatus*. Numerous studies on abyssal sea cucumber have been reported, however, high values were recorded for tropical species with similar contents of fatty acid. It has been also observed that the arachidonic acids (AA) plays a significant role in wound healing and growth, but disrupt the blood clotting process by attaching to the endothelial cells, due to the antithrombotic activity. *Stichopus hermanni* has a low lipid content (0.80% ± 0.02%), high protein content (47.00% ± 0.36%), and encompasses a significant quantity of sulfated glycosaminoglycans, which are unbranched, extensive polysaccharides comprising repeat disaccharide units of alternating amino sugars (D-glucosamine or D-galactosamine) and uronic acids (D-glucuronic or L-iduronic) **(Figure 2)**. Glycosaminoglycans (GS) are also categorized into sulfated and non-sulfated groups. A report by Masre et al., discovered the sulfated glycosaminoglycans obtained from *S. hermanni* exhibited various chemo-biological activities [9].

These glycosaminoglycan components inhibited the synthesis of proinflammatory mediators in HOC stimulated with IL-1β, through an NFκB-dependent mechanism. Several pro-inflammatory mediators, including Cyclooxygenase-2 (COX-2), interleukin-1 beta (IL-1β), and Tumor Necrosis Factor-alpha (TNF-α), were released during an inflammatory response. These mediators demonstrated important functions in initiating and amplifying inflammatory reactions [17]. The expression of Hemoxigenase-1

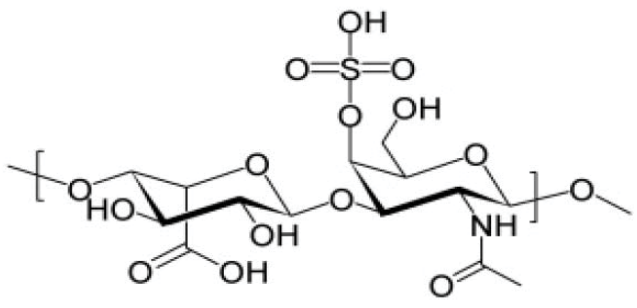

Figure 2 Glycosaminoglycan.

(HO-1) appears as a major mechanism in the inflammatory resolution. This enzyme catalyzes heme into biliverdin/bilirubin, Carbon Monoxide (CO), and free iron, known to decrease inflammation as well as prevent any inflammatory illnesses.

Immunomodulatory

Steroid aglycons or Triterpenes are common phytochemicals found in plants, however, saponin distributions in animals are rather sparse. Sea cucumbers belong to the class Holothurioidea, as well as the phylum Echinodermata, and are characterized by the presence of triterpene glycosides, which also occur in certain sponges. These mineral contents possess lanostane-type aglycons, however, the majority possess holostane-type aglycones, which have 18(20)-lactones. The carbohydrate structures of the glycosides in sea cucumbers are composed of 2 to 6 sugar residues, including quinovose, xylose, 3-O-methyl-glucose, glucose, and in rare cases, 3-O-methyl-xylose, as well as 1, 2, or 3 sulfate groups [23]. Based on the ability to undergo complexation with 5(6)-unsaturated sterols in cellular membranes, glycosides exhibit various biological activities, including antifungal, hemolytic, and cytotoxic properties, as well as several other membranotropic activities. In addition, these glycosides exhibit an impressive immunomodulatory effect at very minimal concentrations. Aminin et al., discovered the immunostimulatory impact exhibited by certain sea cucumber glycosides at sub-toxic, nanomolar concentrations [6]. The incubation of immune cells with glycosides was reported to induce activation, leading to a rise in immune cell adhesion on an extracellular matrix, improved cell motility and spreading, extended macrophage lysosomal activity, phagocytic activity, and ROS formation. Furthermore, the injection of certain glycosides in sub-toxic dosages stimulated the quantity of antibody-producing plaque-forming cells in mouse spleens, as well as caused an expansion in the acid, number, and size of lysosomes of peritoneal macrophages, as well as an extension of the phagocytic index. **Figure 3** shows glycosides were able to moderately induce the generation of certain cytokines, restore the lymphocytes CD-marker levels, increase the leucocyte bactericidal activity, and facilitate a rise in the resistance of mice to lethal doses of numerous pathogens, as well as radiation levels.

In addition, a tubular immune-stimulating complex, a novel nanoparticulate antigen delivery system comprising glycolipid monogalactosyldiacylglycerol obtained from marine macrophytes, as well as triterpene glycoside cucumarioside A2-2, and cholesterol, were produced. Tubular immune-stimulating complex influenced the cytokine mechanisms of immunological regulation, however, the adjuvant effect was observed to vary based on the components. Furthermore, the use of proteomic methods showed the immunomodulatory activity exhibited by certain sea cucumber glycosides on immune cells tends to regulate how particular proteins are expressed in the formation of immune responses. Also, these have the ability to synchronize the proteins associated with lysosome phagocytosis, activation, merging, maturation, cell adhesion, cytoskeletal reorganization, motility as well as immune cell proliferation.

Anti-tumor

Sea cucumbers have been reported to contain various anti-tumor agents which play significant roles in the different stages of tumor development, progression, and metastasis. These active components must, therefore, be explored to create various opportunities in the discovery of novel antitumor agents from more marine sources for cancer treatment [24]. Several studies reported diverse compounds to play an important role as anticancer, such as triterpene glycosides, saponins, holothurin A, stichoposides, frondoside A, cucumariosides, dsechinosides, fucoidan, triterpenoid aglycones (philinopgeni), nonglycosaminoglycan, sulfated glycans, non-sulphated triterpene glycosides (variegatuside), and sphingoid [22,25-27]. Based on the literature studies, the beneficial search of sea cucumber for human health is still required to be done more deeply.

A previous *in vitro* study reported the profound cytotoxic activity exhibited by isolated sphingoid bases of sea cucumbers (*Stichopus variegatus*) which led to a reduction in cell viability and induced apoptosis with caspase 3 activity within WiDr, DLD-1, and Caco-2 human colon cancer cells. These studies suggest sea cucumber glycosides possess possible anti-tumor activity for the treatment and prevention of colon cancer in humans. According to a previous study, sphingoid bases, including 4, 8-sphingadienine (d18:2), d17:1, d19:3, and d18:3 exhibited profound strong cytotoxicity against particular cell lines of colon cancer, through apoptosis induction [22]. Meanwhile, a novel compound identified as glycosphingolipid, ophidiacerebroside C was isolated from ophidiaster, ophidiamus. The main components of cerebrosides were (2S, 3R, 4E, 8E, 10E-1-(β-D-glucopyranosyloxy)-2-hudrocy-2-®-2-hydroxydocosanoy) amino)-9-methyl-4, 8, 10-octadecatriene. Furthermore, this exhibited significant cytotoxicity against L1210 leukemia cells during in vitro studies [28]. Also, marine-derived cerebrosides and derivative sphingoid bases demonstrated profound anti-tumor activities, mainly dependent on the sphingoid base structure. Anti-cancer effects were generated due to the ability of cucumarioside A2-2 **(Figure 4)** to capture the cell cycle during the phase of DNA synthesis (S). This compound tends to induce programmed

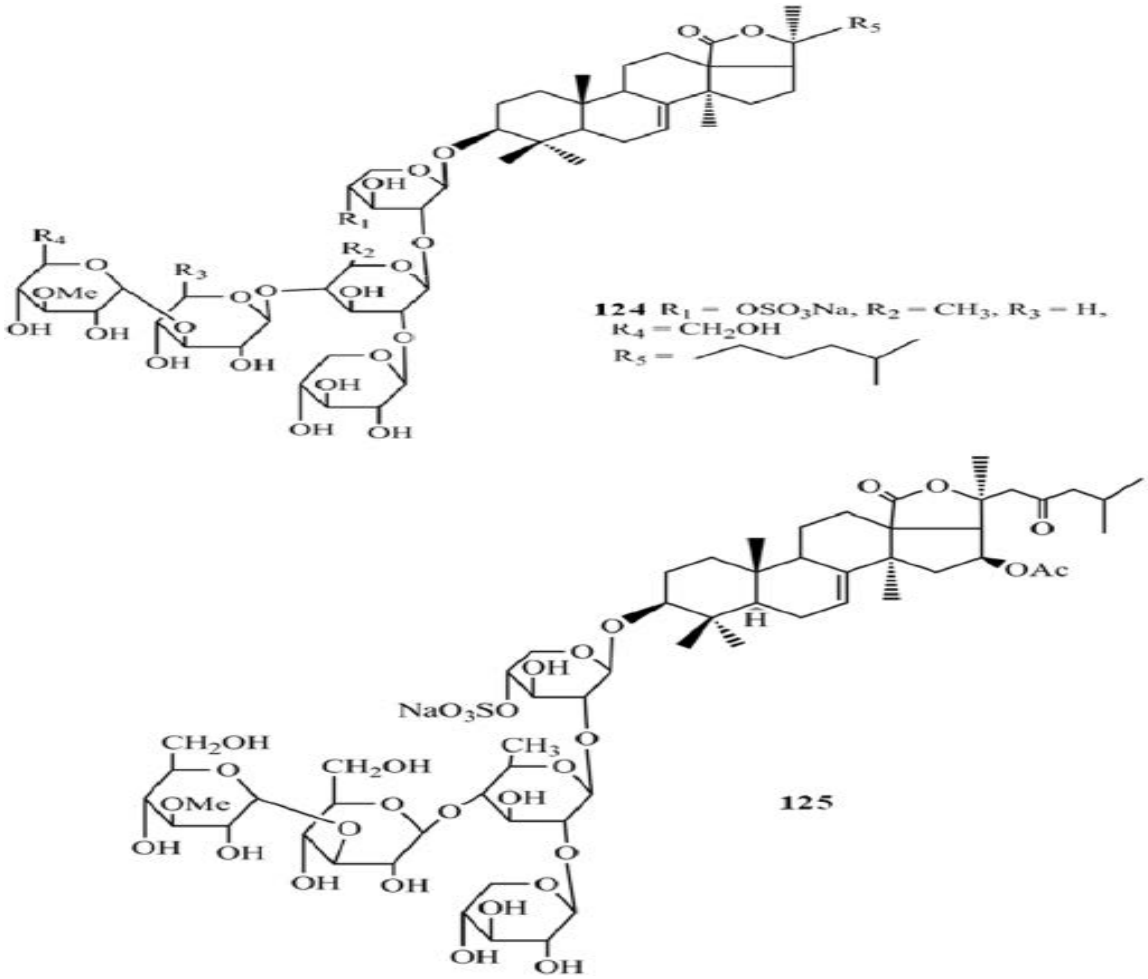

Figure 3 Triterpenoid glycosides: frondoside A and cucumarioside A2-2, obtained from sea cucumbers [21].

destruction in the tumor cells of mice with Ehrlich carcinoma [7]. Based on another study, the cell cycle arrest during the G0/G1 phases in hepatocellular liver carcinoma cells (HepG2), was triggered by Ds-echinoside A, Echinoside A and the triterpenoid glycosides obtained from *Peasonothuria graeffe*. Meanwhile, a reverse transcriptase-polymerase chain reaction evaluation confirmed both triterpenoid glycosides were responsible for the increase in the cell cycle-related genes, including p21, c-myc, and p16, as well as the decrease in cyclin D1 [29].

Anti-oxidant

Sea cucumbers as an alternative source of natural dietary antioxidants plays a very significant role in countering the harmful consequences of oxygen-free radicals caused by normal metabolism as well as external factors, including pollution and radiation. This outcome is implicated in the development of regular illnesses, such as cancer (gene damage), premature aging, cardiovascular and other degenerative diseases. Fawzya et al. reported an assay of the DPPH radical scavenging activity of collagen hydrolysate from the golden sea cucumber at concentrations of 1 mg/mL, 2 mg/mL, 4 mg/mL, and 8 mg/mL, using ascorbic acid was used as a positive control at concentrations of 0.004 mg/mL, 0.006 mg/mL, 0.008 mg/mL and 0.010 mg/mL [30]. The results showed a significant increase in samples' antioxidant activities which was concentration-dependent. An additional evaluation of the IC50 values showed the least value (5.25 mg/mL ± 0.15 mg/mL) was recorded for the hydrolysate from the 60 min hydrolysis, indicating this hydrolysate exhibited maximum antioxidant activity. However, this value appeared much greater, compared to ascorbic acid as control (0.0082 mg/mL ± 0.0001 mg/mL). The antioxidant activity of ascorbic acid with an equivalent of 46.5 µM (MW of 176.12 Da) was between 4.5 times to 8 times higher, compared to the collagen hydrolysate (375 µM and 210 µM, respectively), and with estimated molecular weights of 14 kDa and 25 kDa, respectively.

Anti-microbial

Ridzuan, et al. described *Stichopus variegatus* or *Stichopus hermanni* as the species with the most value, not merely a source of food, but because the species provide numerous therapeutic benefits [31]. Meanwhile, Shakouri, et al. recorded a growth inhibition on *A. niger* and *E. coli* by aqueous methanol and methanolic extracts of the body wall of *S. variegatus* using concentrations of 1 mg/mL to 8 mg/mL [18]. In addition, the

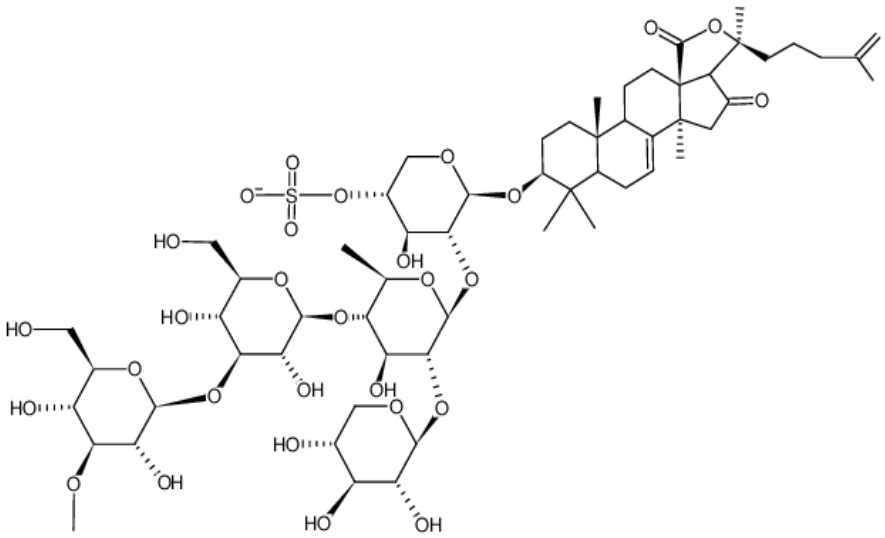

Figure 4 Cucumarioside A2-2.

aqueous methanol and chloroform extracts of sea cucumber also hindered *S. aureus* growth. Maximum inhibition zones of 12.26 mm, 11.13 mm, and 11.6 mm, were recorded against *E. coli*, *S. aureus*, and *A. niger*, respectively, using 8 mg/mL of the aqueous methanol extract. Therefore several sea cucumber species exhibit various antimicrobial properties, and this is probably due to variations in the extracted peptides' molecular masses and amino acid sequences. However, the methanol extract from *Stichopus hermanni* obtained from the Persian Gulf was unable to inhibit growth in Pseudomonas aeruginosa at a concentration of 18 g/mL even though at that concentration it could inhibit *Aspergillus niger* microbes with a 38 mm inhibition zone diameter and also tested antibacterial activity of methanol extract against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both did not produce an inhibition zone. The methanol extract of *Stichopus hermanni* from South Lampung waters had an inhibition zone against Staphylococcus aureus of 7 mm or 24.14% against ampicillin positive control.

The antifungal property of *S. hermanni* extracts is believed to demonstrate an extensive effect against fungal pathogens, compared to bacterial. This capacity is possibly attributed to the fungal presence that tends to induce the production of antifungal compounds. The value of *S. hermanni* in the export market is considered very minimal, due to the easy disintegration of its body walls on exposure to air after harvesting and during boiling. Therefore, sea cucumbers are ostensibly recommended as potential sources of antimicrobial agents [16].

Wound healing

The ability of sea cucumbers to regenerate cells is the main basis that sea cucumbers can heal wounds. Living in a harsh environment often causes the sea cucumber's body wall to break or injuries to its organs. But sea cucumbers can regenerate themselves in 10 days-90 days to make it whole again. This is due to the presence of a cell regeneration factor (cell growth factor), which is able to stimulate regeneration for the recovery of damaged cells or body tissues. The high protein content of sea cucumbers can increase the regeneration of dead cells due to wounds so that they can heal wounds. In addition, protein can also function to strengthen the immune system and produce hormones and enzymes to launch metabolism. Collagen which is a connective tissue in bones and skin can be used for skin beauty and can increase the regeneration of dead cells due to wounds so that it can accelerate healing. Therefore, sea cucumbers can be used as cosmetics and ointments to heal wounds. In bone growth, calcium, phosphate, and collagen supplements are needed as filler tissue, so without collagen, the bones will be brittle and break easily. Collagen together with chondroitin sulfate forms a new cartilage mass, so it can reduce pain due to arthritis.

Sea Cucumber as a Nutraceutical Product

Stichopus variegatus also serves as a protein source, with the body wall which comprises mainly mucopolysaccharides and collagen, serving as the major edible portion [16]. According to Liu, et al. this high collagen composition requires an extensive value for pharmaceutical or nutraceutical applications [13]. Previous research reported a more significant protein content, compared to the raw material, as well as minimal moisture content, compared to the flesh [14]. Meanwhile, two separately processed tissues of *Cucumaria frondosa* products were sources of bioactive ingredients [32].

The use of functional ingredients from sea cucumbers is fast becoming an interesting method in the development of new foods and biomedical products. These species contain high

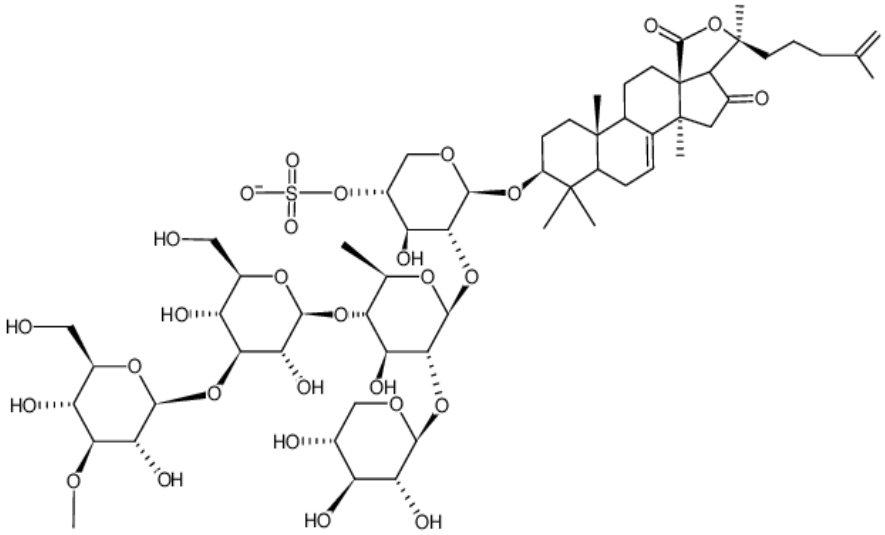

Figure 5 Some products from PT Natura Nuswantara Nirmala which contain sea cucumber.

valuable compounds with several health benefits. Typical examples of sea cucumber-derived functional ingredients possibly introduced at various production stages of foods and biomedicines include vitamins, bioactive peptides, amino acids, fatty acids, minerals, gelatins, carotenoids, saponins, collagens, chondroitin sulfates, and other bioactive compounds [8]. The active compounds contained in *Stichopus variegatus* possess a lot of medicinal and nutritional values. The polysaccharide condroition sulphate is capable of reducing athritic pain. In addition, its glycoprotein, fucans and lectins content are also useful for the development of therapeutic drugs **(Figure 5)** for arthritis, cancer, or HFV treatments. The active compounds help enhance blood circulation, reduce high blood pressure, soothe joint inflammation, reduce weariness, and provide other therapeutic effects.

Conclusion

Stichopus variegatus has the potential to be developed into nutraceutical products because it has anticancer, anti-inflammatory, antibacterial, antioxidant and immunomodulatory effects. PT. Natura Nuswantara Nirmala (PT. Nucleus Farma) is a traditional medicine company that produces many nutraceutical products containing *S. variegatus* extract, including: Onogate capsules and Supahabu Beta capsules.

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