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The Bioactive Compound and Mechanism of Action of Sea Cucumber (Holothuridae) As Anticancer: A Review

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ABSTRACT

The extreme development and resistance towards cancer drugs, and also the high toxicity, drug resistance and side effects of cancer chemotherapy drug triggers us to develop new drugs as one of the alternative substitutes or combinations of cancer drugs, one of the resources come from marine biodiversity especially sea cucumber. The bioactive compound from sea cucumber can inhibit cancer cell growth with the various mechanism. This study aims to analyze chemical composition, bioactive compound from sea cucumber to inhibit cancer cell line and to analyze mechanism of action of sea cucumber as anticancer with the most recent research studies. The result shows sea cucumber contained protein 44-82%, amino acid, fatty acid, collagen, peptide, micro essential. Each sea cucumber species produced the different secondary metabolites that can use as anticancer. Sea cucumbers contain triterpene glycosides, saponins, holothurin A, stichoposides, frondoside, cucumariosides, dsechinoside, fucoidan, triterpenoid aglycones (philinopgeni), non-glycosaminoglycan, sulfated glycans, sulfated polysaccharides, non-glycosaminosides) that can inhibit cancer cell line. Those bioactive compounds have a various mechanism such as apoptosis in cell line and mitochondria, antioxidative mechanism and membranolytic.

Keywords: anticancer, bioprospecting, holothuridae, mechanism of action, sea cucumber

INTRODUCTION

The increasing of research publications on discovery and development of cancer-related drugs in this decade correlate with the expansion in new cases of cancer in the world, both in developed and developing countries. Global cancer case in 2018 estimated 1.8 million new cases with the total number of 9.6 million deaths [1], while Riskesdas 2018 reported, the inflation of cancer case in Indonesia from 1.4/1000 in 2013 to 1.79/1000 of population. The highest number was in Special Region of Yogyakarta Province with 4.86/1000, West Sumatera 2.47/1000 and Gorontalo 2.44/1000 of population. Major cancer with dead cause 18.4% of the total were lung cancer, colorectal cancer 881,000 deaths, and breast cancer 627,000 deaths [2]. This condition has triggered various academics to conduct the research in discovery and development of new drugs in order to reduce the growth of cancer rates in Indonesia and the World.

Cancer treatment has three main pillars of implementation starting with surgery, radiotherapy, and chemotherapy. These three types of therapy do not compete but complement each other. Most of cancer patient need two or three combination of therapies. The availability of various cancer drugs in chemotherapy, required having long-term efficacy with low side effect of drugs, moreover targeted where only inhibit the development of cancer cells thereby

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compressing side effects on healthy cells. One alternative offered is by using herbal medicines derived from natural resources, especially marine products for reducing drug resistance by semi-synthesis or modification to increase bioactivity and minimize the side effect.

Indonesia is an archipelago consisting of 17,500 islands with 70% of marine territory. The potential of Indonesia as maritime country is very wide, marine resources are not optimally utilized in pharmaceutical field whereas active compounds derived from marine ecosystems have their own uniqueness compared to organisms from terrestrial ecosystems. Often found chemical compounds with unique functional groups, such as the presence of isonitrile and multi-halogenation, also the existence of carbon skeletons. Active compounds derived from the sea can be further explored to be used as a cancer drug [3]. National Cancer Institute in United States of America has tested various raw materials for cancer drugs and found that 4% of active ingredients as anti-cancer originated from the sea, one of marine potential known as sea cucumber [4].

Sea cucumber is marine commodity widely distributed throughout Indonesian waters. Sea cucumber species that have important economic value so far are limited to the famillies of *Holothuriidae* and *Stichopodidae,* including *Holothuria, Actinopyga, Bohadshia, Thelenota,* and *Sticopus* [5]. In 2001, Indonesia was the largest producer of dried sea cucumber exports reached 457 tons. About 40-80% smoked or dried sea cucumbers from Indonesia exported to Hongkong, Japan, Korea, Singapore, Taiwan, Malaysia, and Australia [6]. Local communities in Malaysia believes that sea cucumbers can cure various diseases such as cancer, asthma, hypertension, rheumatism, wound, and degenerative diseases [7]. Nutrient content of sea cucumber consists of 86% protein, 3-5% carbohydrates and 1-2% fat [8]. Sea cucumber contain EPA and DHA which play a role in the development of brain nerves, wound healing agents and antithrombotic. Furthermore, sea cucumber also contains bioactive ingredients as antihypertensive [9], antibacterial and anti-fungal [10], anti-cancer [11], and anticoagulant [12].

Several studies reported diverse compounds play an important role as anticancer, such as; triterpene glycosides, saponins, holothurin A, stichoposides [13], frondoside A [14], cucumariosides, dsechinosides, fucoidan, triterpenoid aglycones (philinopgeni) [15], non-glycosaminoglycan [16], sulfated glycans [17], non-sulphated triterpene glycosides (variegatuside) [18], and sphingoid [19]. Based on the literature studies, the beneficial search of sea cucumber for human health still required to be done more deeply.

The aim of this review is to get into detail analysis more about the chemical composition, active compounds including chemical substances and peptides from sea cucumber of *Holothuridae* as anticancer. And also, to figure out the mechanisms of action of sea cucumbers in inhibiting various cancer cells. Through this study, hoped that sea cucumbers can be utilized as one of the candidates for new drugs in overcoming the problem of cancer in Indonesia.

Sea cucumber (*Holothuridae*)

Sea cucumbers are a group of marine invertebrates in the class Holothurioidea, Phylum Echinoderms, and consist of 1,200 species scattered in tropical shallow waters [20]. The types of commercial sea cucumbers traded include: *Holothuria, Actinopyga, Bohadschia, Thelenota* and *Stichopus*. There are 29 types of sea cucumbers in trading commodities both on local and international market (Table 1) [21]. Sea cucumbers have a round shape and elongated with rough surface. The body of *Holothuria scabra* is similar to cucumber with two main body part from the mouth to the anus (oral-aboral). The oral consists of modified tube feet tentacles with 10 to 30 of tentacles used as a touch. The touch or mouth found at the interior while anus at the

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posterior. This animal moves with ambulacral water vascular system hydraulically. The center of water vascular system has calcareous ring that regulates hydraulic pressure than the tentacles can be moved. Endoskeleton of sea cucumber called a spicula as an identification of sea cucumbers species. Spicula is an endoskeleton that has been reduced to a microscopic size embedded in the dermis layer. The main substance is calcium carbonate dissolved in acidic solutions.

Table 1. Types of sea cucumber in International trade [21]

Spesies	Common name	Distribution
Actinopyga echinites	Brownfish	Pacific Ocean
A. lecanora	Stonefish	Pacific Ocean
A. mauritiana	Surf red fish	Pacific Ocean
A. miliaris	Black fish	Pacific Ocean
Athyonidium chilensis		Peru, Chili
Bohadschia argus	Leopard fish	Pacific Ocean, Southeast Asia
B. graffei	Orange fish	Pacific Ocean, Southeast Asia
B.marmorata marmorata	Chalky fish	Pacific Ocean, Southeast Asia, Red sea
B.marmorata vitensis	Brown sandfish	Pacific Ocean, Southeast Asia, Red sea
B.vitensis	Brown sandfish	Pacific Ocean
Cucumaria frondosa	Pumpkins: orange footed cucumber	West Atlantic
Holothuria atra	Lolly fish	Pacific Ocean
H. edulis	Pink fish	Pacific Ocean
H. fuscogilva	White teafish	Pacific Ocean, Southeast Asia, Indian Ocean.
H. impatient	Elephant trunkfish	Pacific Ocean, Southeast Asia
H. mexicana	Slender sea cucumber	Caribbean
H. nobilis	Donkey dung	Caribbean
H. scabra	Black teafish	Pacific Ocean, Southeast Asia
H. scabra versicolor	Sandfish	Pacific Ocean, Southeast Asia, Indian Ocean
Stichopus badionatus	Golden sandfish	Pacific Ocean, Southeast Asia
S. fucus	Three rowed sea cucumber	Caribbean,
S. californicus	Giant red sea cucumber	East pacific
S. parfimensis	Warty sea cucumber	East pacific
S. chloronatus	Green fish	East pacific
S. hermanii	Curry fish	Pacific Ocean, Indian Ocean
S. japonicus		Southeast Asia, Pacific Ocean, Japan
S. mollis	New Zealand sea cucumber	NZ, Australia, Tasmania
Theleontha ananas	Prickly redfish	Pacific Ocean
T. anax	Amberfish	Pacific Ocean

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Mostly, sea cucumber found in shallow marine waters, but some are found up to a depth of 10,000 meters with temperatures of 28-31°C and salinity of 30-34 ‰ [23]. The main source of food is organic substances found in mud, detritus, and plankton. Other food sources are microorganism, protozoa, filament algae, seaweed, and small pieces of animals, marine plants and sand particles [24], sea cucumber morphology can be seen in Figure 1.

Figure 1. Sea cucumber morphology found from Indonesian's waters: (a) *Holothuria Scabra*, (b) *Holothuria atra*, and (c) *Holothuria (Metriatyla) albiventer* and *Stichopus sp* (©author)

Chemical composition and bioactive compound of sea cucumbers

Sea cucumbers have high nutrition and important for the body. It contains of 44-55% protein, 3-5% carbohydrate and 1.5% fat in wet matter. Whereas in dry matter consist of 82% protein, 1.7 fat, 4.8% carbohydrate, 455 µg vitamin A dan vitamin B (0.04% thiamine, 0.07% riboflavin and 0.4% niacin). The total calories of 100 grams of dried sea cucumbers is 385 calories [26] (Table 2).

Table 2. Chemical composition of sea cucumbers

Composition	Fresh sea cucumber	Dried Sea cucumber
Protein	44-55%	82%
Carbohydrate	3-5%	4.8%
Fat	1.5%	1.7%
Ash	8.6%	8.6%
Energy	385 Kcal	
Calcium	308 mg	
Phosphor	23 mg	
Iron	41.7 mg	
Sodium	770 mg	
Potassium	91 mg	
Vitamin A	455 mg	
Vitamin B2	0.04 mg	
Vitamin B1	0.07 mg	
Riboflavin	0.4 mg	

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Sea cucumbers contains unsaturated fatty acid such as EPA, oleic, DHA, linoleic and arachidonic acid also essential for heart and brain health. Linoleic fatty acid, EPA and DHA included in omega 3 group, while linolenic and arachidonic fatty acid in omega 6 group [27]. Fatty acid component in sea cucumbers are presented in Table 3.

Table 3. Fatty acid of dried sea cucumbers [26]

Fatty Acid	Total (%w/d)
Lauric Acid	0.05
Myristic Acid	0.19
Pentadeconoic Acid	0.16
Palmitic Acid	1.18
Palmitoleic Acid	0.33
Heptadecanoic Acid	0.28
Cis-10 Heptadecanoic Acid	0.03
Stearic Acid	1.27
Oleic Acid	0.17
Linoleic Acid	0.17
Arachidic Acid	0.68
Cis-11 Eicosanoic Acid	0.12
Linolenic Acid	0.15
Heneicosanoic Acid	0.68
Cis-11,14 Eicosanoic Acid	0.20
Behenic Acid	0.83
Cis-8,11,14 Eicosanoic Acid	0.00
Erucic Acid	0.08
Cis-11,14,17 Eicosanoic Acid	0.80
Arachidonic Acid	1.11
Tricosanoic Acid	0.30
Cis-13,16 docosadienoic Acid	0.69
Lignoceric Acid	0.23
Cis-5,8,11,14,17 Eicosapentaenoic Acid	0.44
Nervonic Acid	0.80
Cis-4,7,10,13,16,19 Docosahexaenoic Acid	0.00
Total Fatty Acid	**11.52**

The highest content of fatty acids in dried sea cucumbers are palmitic acid, (1.18%), followed by Arachidonic acid 1.11%, and docosadienoic acid. Similar result obtained in research [27] that the content of fatty acids in stewed sea cucumbers include palmitic acid 1.27%, arachidonic acid 3.20%, and docosadienoic acid 1.31%. These results were not significantly different with the fatty acid content of dried sea cucumbers. In addition, sea cucumbers have amino acids consist of essential and non-essential amino acids. Essential amino acid of sea cucumber is glycine 8.09%, glutamate acid 7.18%, alanine 4.18%, Leucine 1.34%, aspartic acid 4.27% [28], apart that containing of 80% collagen [29]. Collagen is substance from protein with fiber form. Collagen often used as biomedical for connective tissue in the growth of bones and joints. It also contains of chondroitin sulfate and glucosamine in pain reduction causes by arthritis and inhibit the development of HIV [30].

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Sea cucumbers contain bioactive compound as functional food and drugs. The research results [31] showed the presence of bioactive compounds from flavonoid and saponin group in *Holothuria atra*, *Stichopus horrens*, and *Holothuria hilla*. Saponin are found in the Cuvierian tubules, body walls and internal organs also produced as a form of chemical self-defense mechanism for sea cucumbers in nature. Moreover, it may have self-defence from predators, having biological effects, including antifungal, cytotoxic against tumor cells, hemolysis, immunomodulator effect, and anticancer [32].

Active compound as anticancer

Each type of sea cucumber produces different secondary metabolites that can be used as anticancer. Several studies of active compounds from sea cucumber as anticancer showed that holothurin A3 and A4 produced from *Holothuria scabra* exhibit cytotoxicity through blocking of growth of cancer cells with toxic effect in carcinoma [34], epidermoid (KB) dan hepatocellular (Hep-G2) [35]. Similarly, philinopside E sulfated triterpene glycoside derived from *Pentacta quadrangularis*, exhibit strong cytotoxicity with IC_{50} of 0.75-3.50 μg/mL that can inhibit the growth of leukimia cells-HL-60, lymphocytic leukemia cells- P388, lung cancer cells A549, gastric cancer cells-MKN28, lung adenocarcinoma cells-SPC-A4, gastric cancer cells-SGC7901, human epithelial carcinoma cells-A431, hepatoma cells-BEL7402, human ovarian carcinoma HO8901, and fibroblast -W138 [36]. Additionally, the complex compound of cucumariosides monosulfated isolated from *Cucumaria japonica* also showed immuno-modulatory effect in low doses of C57Bl6 mice. Study on [38] displayed frondoside A 0.2 μg increases the innate immune response where the host immune response was inhibited by cytotoxic agents against antigens or tumor growth. Moreover, triterpene glycoside isolated from *Mensamaria intercedens* showed anti-tumorigenic properties in sarcoma cells-S180 and rat lung cancer cells [39]. *Stichopus japonicas* extract also reported to inhibit proliferation of human colon cancer cells (Caco-2 cells) [40].

Research on sea cucumber as anticancer in Indonesia is still limited, some studies on review of the potential of sea cucumbers as an anticancer include [41] *Holothuria atra* originated from Lampung Bay contains saponin (triterpene glycosides) of holothurin A, holothurin A2, holothurin B, holothurin B1 and holothurin B2. *H. atra* has IC_{50} values of 21.39 and 21.05 μg/mL for T47D cells and WiDr cells [42]. Other studies also reported that *H. atra* originated from Halmahera had an IC_{50} value of 12.99 μg/mL for WiDr cells, 13.42 μg/mL in MCF-7 cells and 44.51 μg/mL in vero cells [43]. Several active compounds of sea cucumber as anticancer are summarized in Table 4.

Each species of sea cucumber produces different active compounds, depend on metabolism and environmental conditions. Active compounds are generated as self-defense form of dangerous thing or the enemies. Some of active substance obtained such as phiinopside A and B from *Pentacta quadrangularis* (Figure 2), patagonicosides from *Pentacta quadrangularis* (Figure 3), holothurin A and echinosides from *Holothuria scabra* (Figure 4), colohiroside A from *Colochirus anceps* (Figure 5), intercedensides A (Figure 6), Okhotosides and Frondosides A from *Curcumaria okhtensis* (Figure 7), sticoposides from *Thelenota anax* (Figure 8), bivittosides A and holothurinoside A from *Holothuria* sp. (Figure 9), holotoxin from *Holothuria* sp. (Figure 10), cucumariosides from *Cucumaria japonica* (Figure 11). The chemical structure of the active compound produced by sea cucumbers is as depicted in (Figure 2-11) [44].

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Table 4. Active compound of sea cucumber and mechanisms as anticancer

Sea cucumber types	Active compound	Cancer types
Mensamaria intercedens	Triterpene glycosides	Carcoma cells- S180 in mice, lung cancer cell lines,
Stichopus japonicas	Water extract	Colon cancer CaCo2 cell lines
Holothuria leucospilota	Organic solvent extract	Cancer cells-A549, lung cancer, Cervical cancer C33A
H. scabra, *S. chloronotus*		
Pearsonothuria graeffei	sulfated triterpene glycosides	Hepatocellular carcinoma (HepG2) and endothelial cells (ECV-304)
Cucumaria frondosa	Frondanol A5, Frondoside A and B, Frondoside A Gemcitabine	Pancreatic cancer xenografts, lung cancer xenografts, breast cancer xenografts, breast cancer, pancreatic cancer cells, colon cancer HCT116, colon cancer $Apc^{Min/+}$
C. frondosa *H. Arenicola*	Water extract	CT26
Bohadschia argus	Arguside A-E	HCT-116, A549, HCT-116, HepG2, MCF-7
H. polii	Bivittoside	Cancer cell HCT116, MCF7
Colochirus anceps	Colochiroside A	p388, HL60, A-549, SpC-A4, MKN28
H. leucospilota	Crude saponin	B16F10
C. japonica	Cucumarioside A2–2	Carcinoma cancer cells, HL-60
P. graeffei	Ds-echinoside A	Hep G2
H. nobilis	Echinoside A	26 human cell line
P. graeffei	Echinoside A	Hep G2, HCT116, AsPC-1, S2013
C. okhotensis	Frondoside A	THP-1, HeLa, RT112, RT4, HT-1197
H. grisea	Griseaside A	HL-60, BEL-7402, Molt-4, A549
H. hilla lesson	Hillasides A-B	A549, MCF7, IA9, CAKI-1, PC-3, KB
H. scabra	Holothurin A3-A4	KB, Hep-G2
C. okhotensis	Okhotoside B1-2, B3	HeLa cells
S. chloronotus	Organic/water extract	C33A, A549, P-388, A-549, MCF-7, MKN-28,
Pentacta quadrangularis	Pentactasides I-III, Philinopsides A-B	HCT-116, U87MG P388, HL60, A549, SPC-A4, MKN28
S. variegates	Sphingoid	Caco-2, DLD-1, WiDr
Thelenota anax	Stichoposide D	HL-60, K562
Pseudocolochirus violaceus	Violaceusides A-B	HL-60, BEL-7402
S. horrens	Stichorrenoside C-B	Hep-G2, KB, LNCaP, MCF7, SK-Mel2

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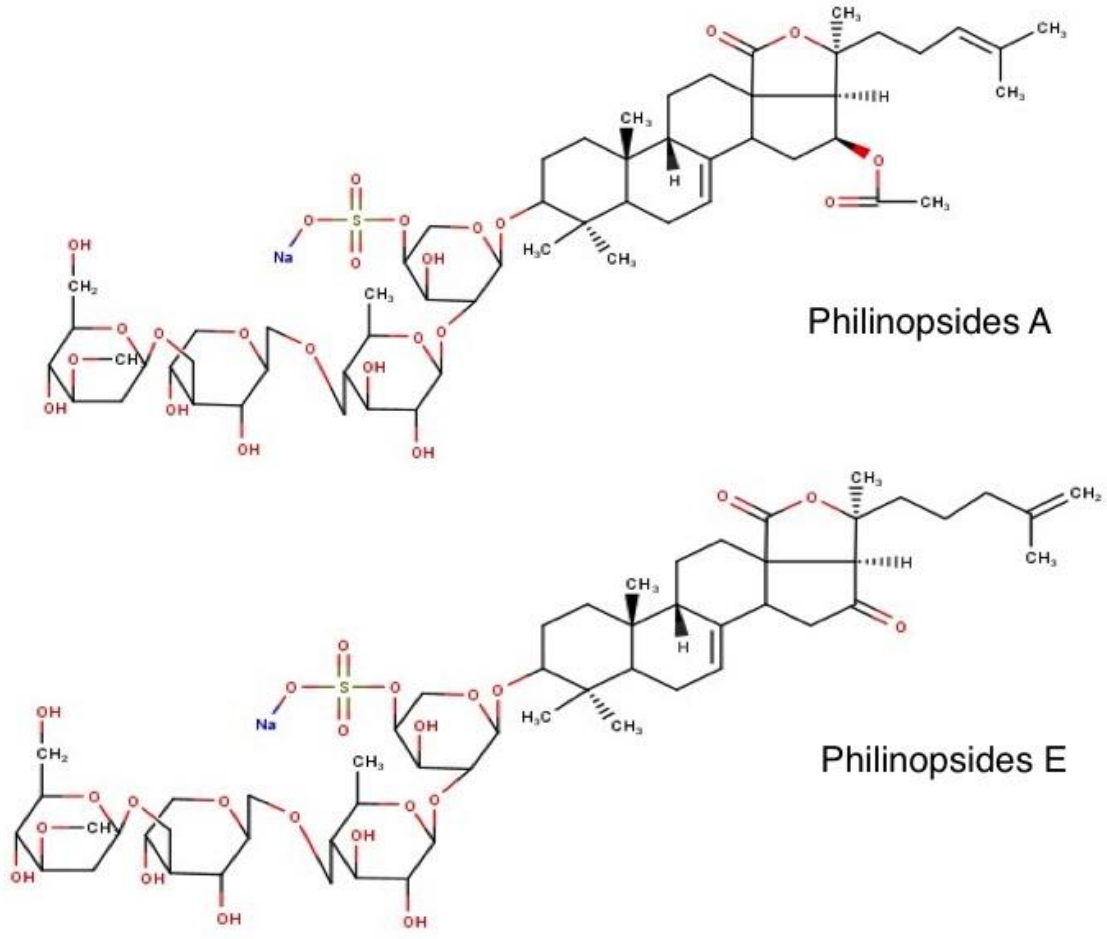

Figure 2. Chemical structure of Philinopsides

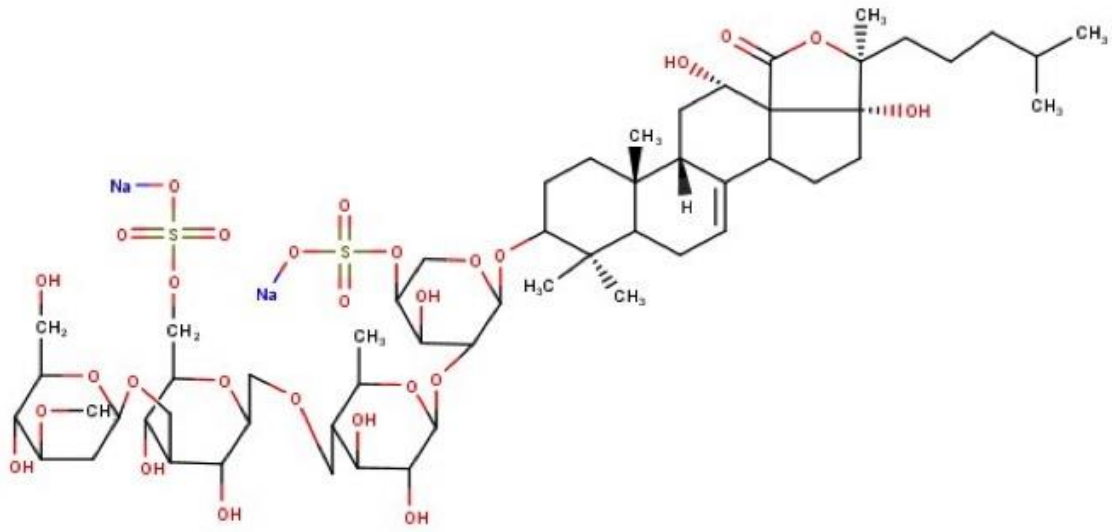

Figure 3. Chemical structure of Patagonicoside

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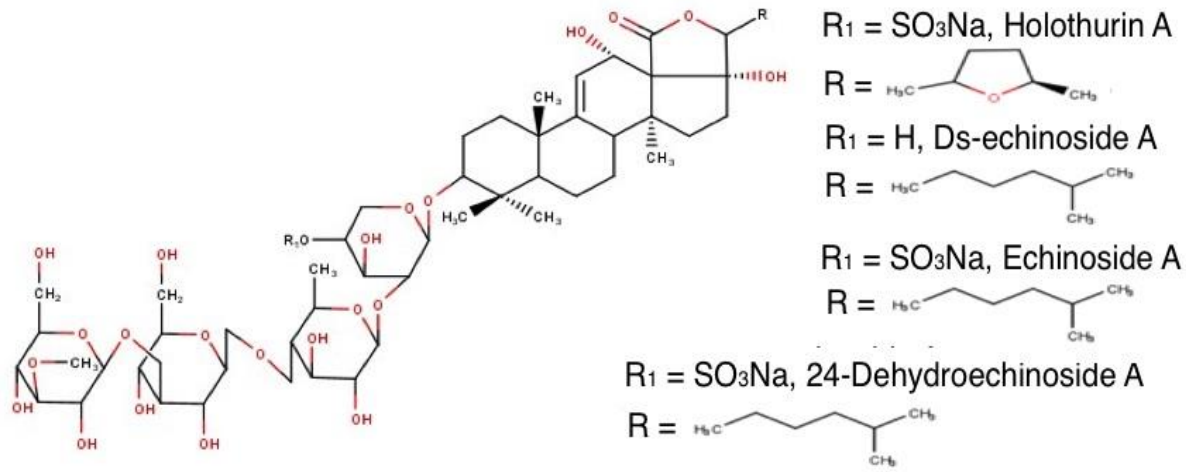

Figure 4. Chemical structure of holothurin A and Echinoside

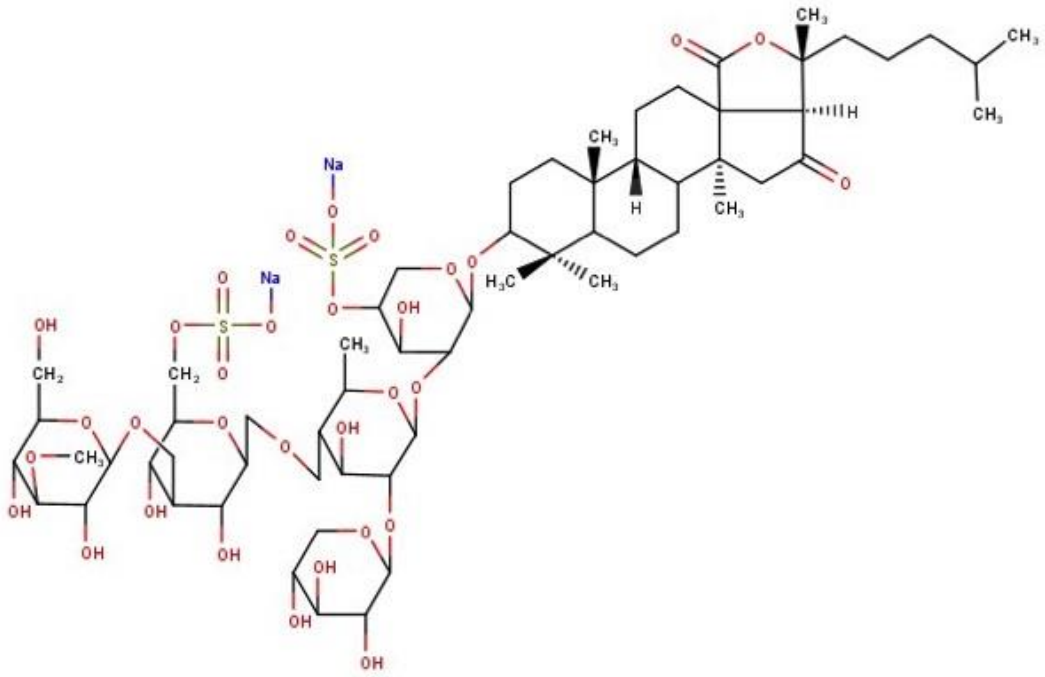

Figure 5. Chemical structure of colohiroside A

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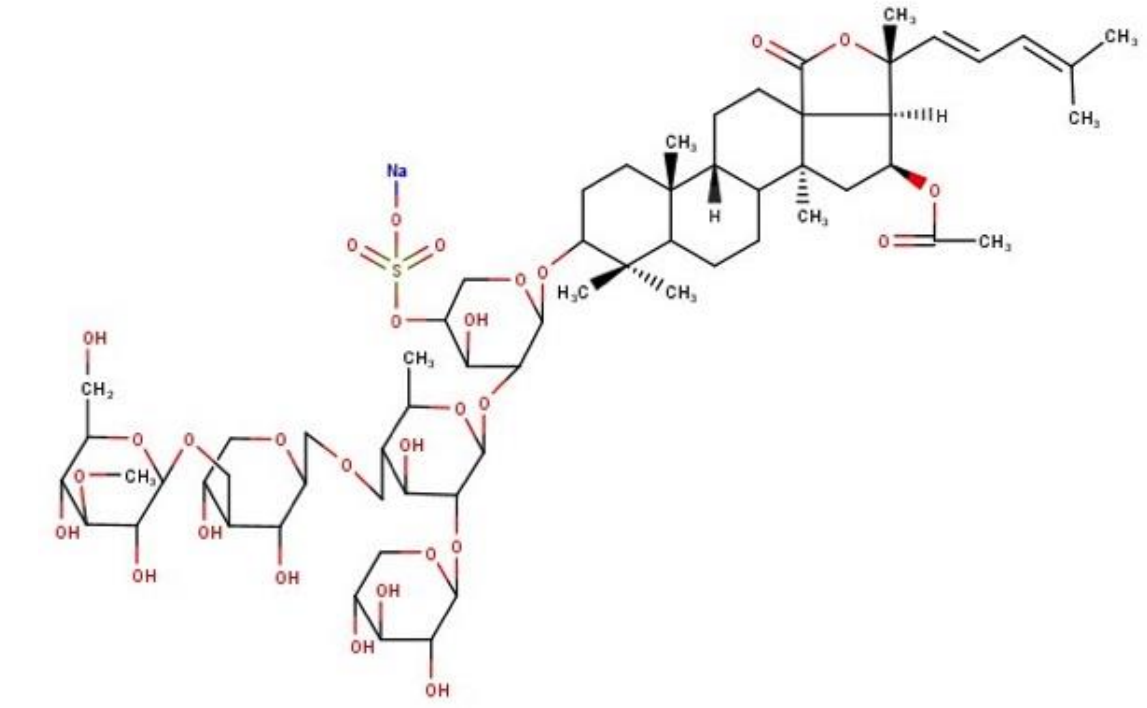

Figure 6. Chemical structure of intercedenside A

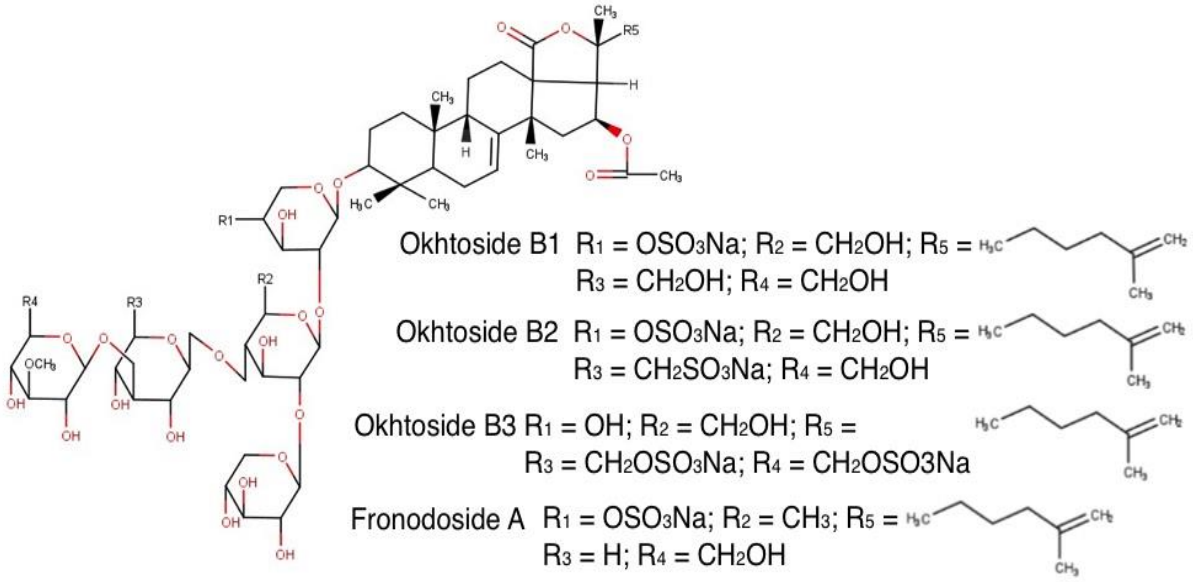

Figure 7. Chemical structure of okhotoside B1-3 and frondoside A

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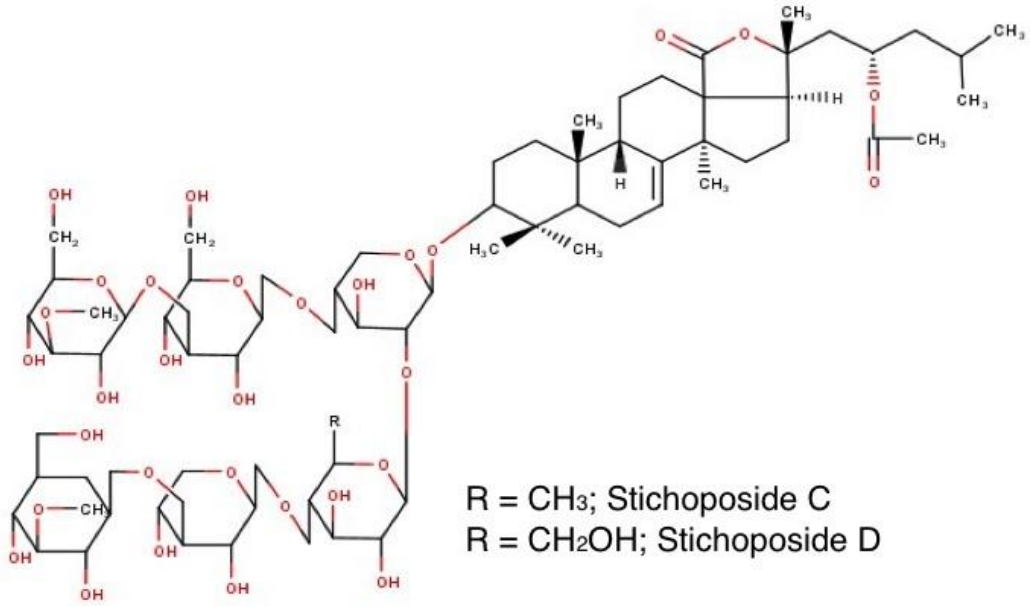

Figure 8. Chemical structure of stichoposide C-D

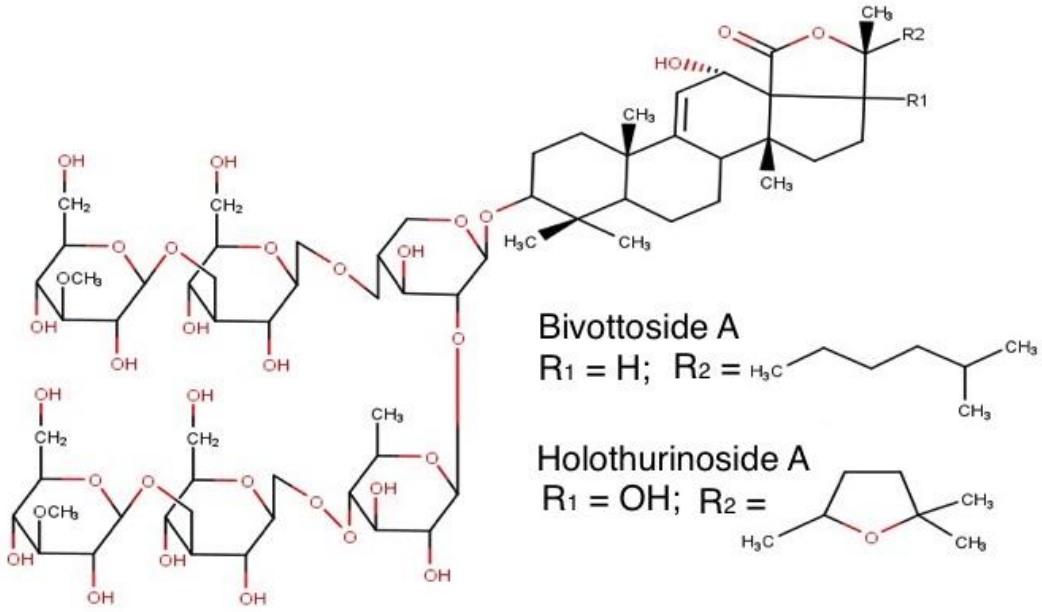

Figure 9. Chemical Structure of bivittoside A and holothurinoside A

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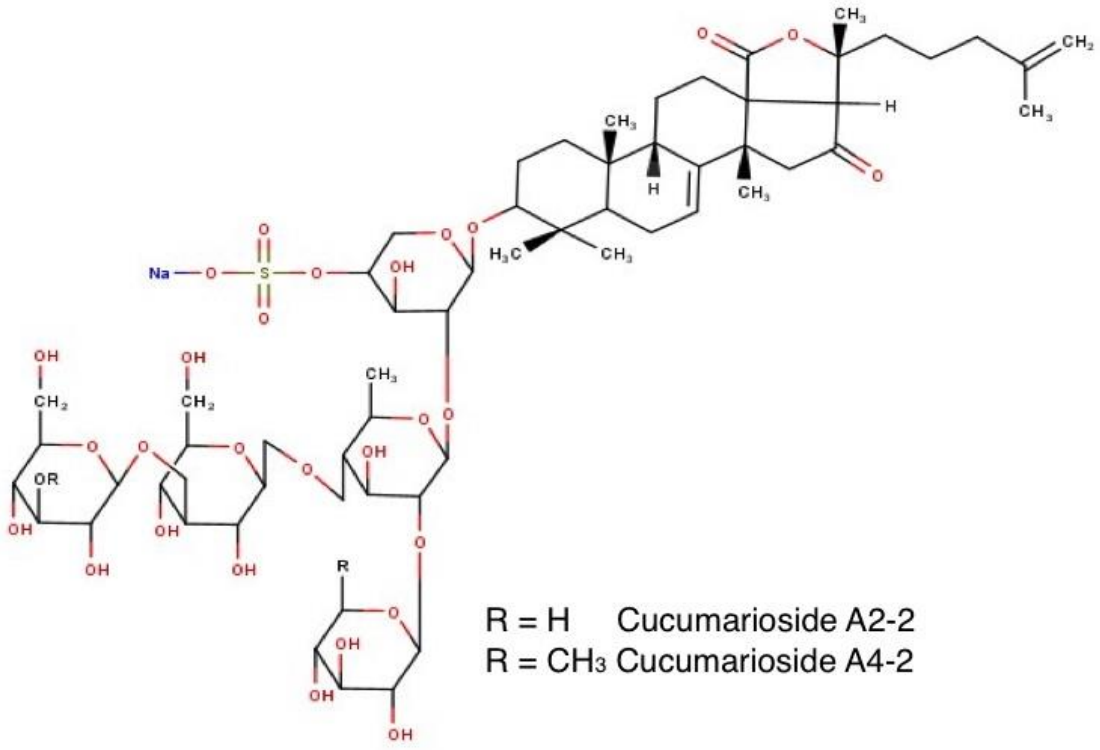

Figure 10. Chemical structure of cucumarioside

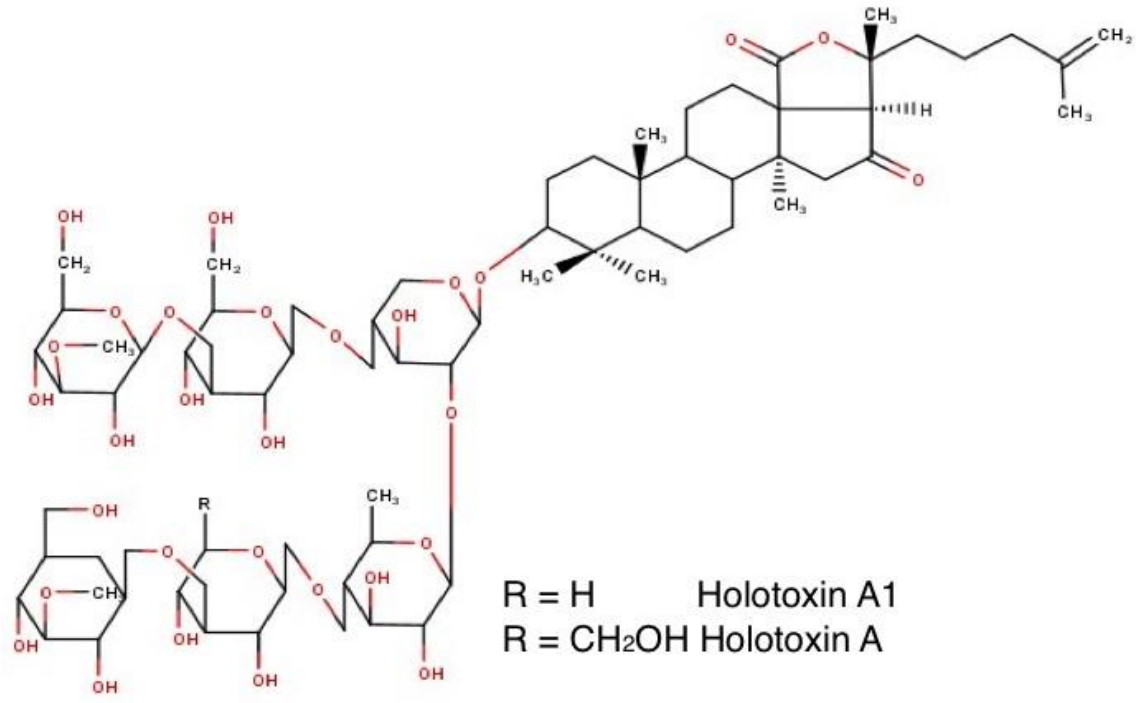

Figure 11. Chemical structure of holotoxin.

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Peptide potential of sea cucumber as anticancer

Bioactive peptides are generally composed of 2 - 20 amino acids that have activities based on the composition of the amino acid sequences. In the recent years, marine derived bioactive peptides have attracted much interest in research of pharmaceutical, cosmeceutical, and nutraceutical products with their biological potential. Bioactive peptide from marine organism reported have wide biological potential as antihypertensive, antioxidant, antidiabetic, and anticancer. It was also recorded that bioactive peptides highly potential as therapeutic drugs in the treatment of heart, blood vessel disease and diabetes, formulated in functional food [45]. Some bioactive peptides have been reviewed as anticancer found in several marine organisms such as sponges, mollusks, fish and other marine organisms including sea cucumbers.

Marine derived bioactive peptides as anticancer including peptide from tuna with molecular weight of 400-1400 Da. There are two types of most active bioactive peptides namely LPHVLTPEAGAT amino acid composition hydrolyzed using papain and PTAEGVYMVT hydrolyzed with protease XXIII [46]. Other organisms with bioactive peptide as anticancer are *Dysidea arenaria* from sponge species produced arenastatin A, *Geodia* sp. produced geodiamolide H. Bioactive peptides that have been traced from the mollusk group is *Dollabella auricularia*, where the presence of linear pentapeptide has antiproliferative activity [47]. Sea cucumber is marine organism candidates as anticancer agents. Peptides from sea cucumbers have activity to inhibit Hela cells, AGS and DLD-1 from gelatin hydrolyzed with flavourzyme or called low-molecular-weight gelatin hydrolysate (LMW-GH) with molecular weight of 700-1700 Da as an inhibitor of melanin fusion and tyrosinase activity in B16 cells [48]. Some peptide compounds from protein hydrolysate of sea cucumbers also have potential as anticancer with enzymatic hydrolysis namely collagen can be a cancer inhibitor agent in the gastrointestinal [49,50], moreover according to [51] amino acids of alcalase, trypsin, pepsin, chymotrypsin, pancreatin and thermolysin can also inhibit cancer cells growth.

The mechanism of action of sea cucumber as anticancer

Sea cucumbers as anticancer have been proven by various studies. It has quite strong anticancer activity when compared with Doxorubicin as cancer drugs in the market. Study [52] reported that doxorubicin can inhibit the growth of Hela cells and MCF-7 with IC_{50} value of 2.23 and 2.60 μg/mL while *Holothuria atra* inhibit the growth of Hela cells and MCF-7 with IC_{50} value of 12.48 and 17.90 μg/mL.

The mechanism of cancer cells inhibition in sea cucumber can be seen from the formazan crystal indicator. Formazan crystals are like sharp prickly crystals shape with black colour which indicate apoptosis or cells death by necrosis [53]. Apoptosis is an active process that requires the transcription and translation of certain specific gene and also needs the use of intracellular energy sources, while necrosis is cell death. The fundamental differences in the two mechanisms of cell death include; death through the apoptosis mechanism has decreased cytoplasmic volume, the cell nucleus shrinks, membranes and organelles remain united, otherwise cell death caused by necrosis, cells appear to be swollen, lysis occurs in the cell nucleus, the plasma membrane and core membrane are damaged and undergo disintegration of cell organelles [55].

Sea cucumbers also have antioxidant of saponin glycosides. The compound has a similar structure to ginseng and ganoderma. Anticancer substances such as terpenoid, protein, saponin and polysaccharides were also present in sea cucumbers. The results showed that sea cucumbers contained the active compound of triterpene glycoside could inhibit tumor growth in lymphoid cells, human lung tumor cells, cervical tumor cells, and melanoma of rat in the

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concentration of 0.38–0.46 mg/mL through antioxidant mechanisms [56]. The mechanism of several types of sea cucumbers in inhibiting cancer cells presented in Table 5.

Table 5. The Mechanisms of anticancer on sea cucumber [57]

Sea cucumber types	Active compound	Mechanism
P. graeffei	24-dehydroechino-side A (DHEA)	Inhibit migration and invasion of HepG2 cells, upgrade MMP-9, reduce TIMP-1, VEGF, & NF-κB (by HA1)
H. arenicola	Water extract	Apoptosis
C. anceps	Colochiroside A	Inhibit of tumor cells
H. leucospilota	Saponin	Apoptosis
C. japonica	Cucumarioside A_2–2	Prevent tumor cell growth with apoptosis
P. graeffei	Ds-echinoside A	Decrease MMP-9, and VEGF; increase p16, p21, and c-myc; decrease cyclin D1), induction of apoptosis by reducing Bcl-2, NF-κB, and enhance TIMP-1 & caspase-3
H. nobilis	Echinoside A	Induction of apoptosis
P. graeffei	Frondanol A5	Increase p21, GiLT expression, and Apoptosis
C. frondosa	Polar extract of frondanol A5	throwdown cyclin A, cyclin B, and cdc25c, and intensify p21
C. frondosa	Frondoside A	Anti-metastatic (by antagonize EP4, TPA-induced MMP-9 activation via NF-κB and AP-1 signaling), avoid tumor cells multidrug resistance, induce apoptosis (via caspase-3, −8, and −9, PARP, Bax, p21, p53), blocking pro-survival autophagy
P. patagonicus	Glycosides 1 & 2	Activate NF-kappaB and droped Ikappa B alpha in A549 tumor cell lines (cytotoxic activity)
M. intercedens	Intercedensides A, B, and C	Avert the activity of anti-neoplastic
H. parva	Methanol extract	Antioxidant, increase ROS
P. quadrangularius	Philinopside A	Inhibit poliferation, migration and angiogenesis in cell lines
P. quadrangulariu	Philinopside E	Apoptosis, prevent tumor cell growth, anti-angiogenesis through inhibition of KDR-αvβ3
Sea cucumber	Sea cucumber active fraction	The mechanism of antioxidant, anti-angiogenesis
Stichopus variegates	Sphingoid bases	Apoptosis
Thelenota anax	Stichoposide C and D	Apoptosis

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The mechanism of action of peptide as an anticancer classified into two pathways; membranolytic and non-membranolytic. The principle of **membranolytic mechanism** is break down the cancer cell membranes in order to kill cancer cells. Bioactive peptides used as antimicrobials can kill cancer cells by entering the cancer cell membrane. Specifically, cancer cell membranes are more negatively charged due to the presence of phosphatidylserine, sialic acid or heparan sulfate, whereas normal cells have neutral charged membranes, this technique should be carried out so that bioactive peptides are more targeted for inhibiting cancer cells. Induction of bioactive peptides on the target membrane can interfere the membrane with several techniques: (1) interaction with the pores that exist between the lipids in the membrane, (2) depletion of the bilayer membrane layer, (3) randomization / destruction of the lipid membrane, and (4) and the formation of macromolecules between peptides and lipids in the membrane layer [58,59].

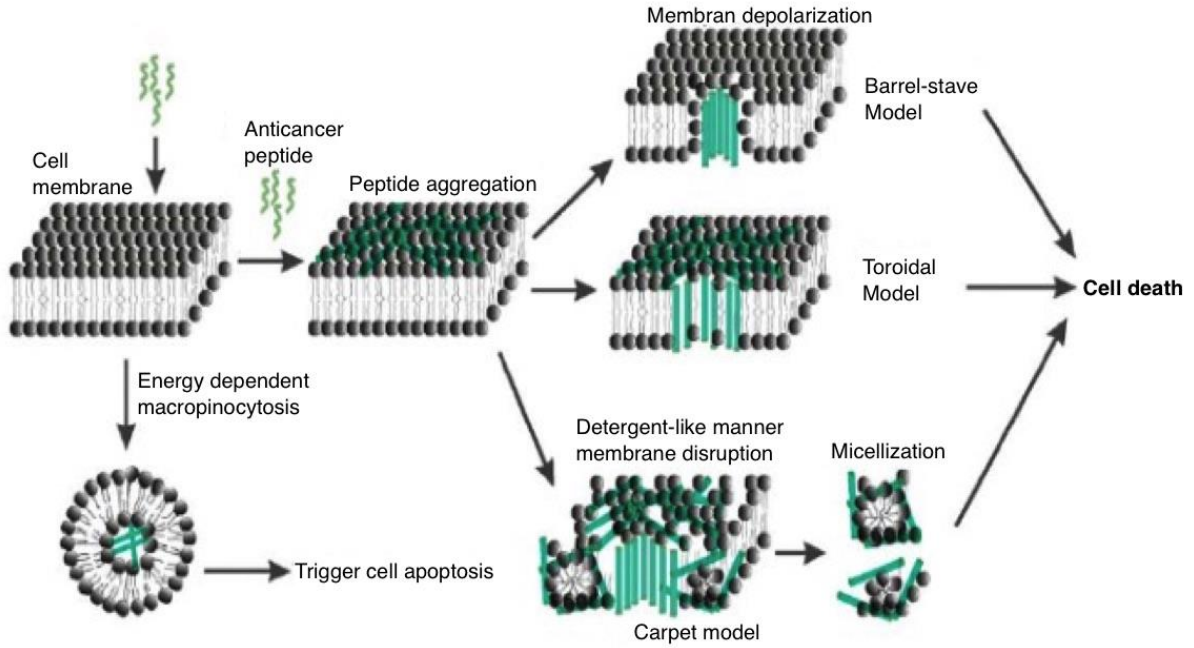

Figure 12. Schematic illustration of the mechanism of bioactive peptides as anticancer in cells (Membranolytic) [60]

Besides of cell death induction by disrupting the plasma membrane, some anticancer peptides induce apoptosis through the mitochondrial pathway or known as **the mechanism of mitochondrial apoptosis.** Apoptosis induction through the mitochondrial pathway has a role in carcinogenesis. Establishment of mitochondrial Permeability Transition Pore (mPTP) in the Inner Mitochondrial Membrane (IMM) which the main part of primary necrosis. This process will interfere ATP synthesis so that large amount of solution enters the matrix with the cell electrochemical system.

CONCLUSION

Sea cucumbers are marine invertebrates that have potential as anticancer. Large amount of protein, collagen, essential and non-essential amino acids, fatty acids, vitamins, minerals contained in sea cucumber that possess health benefit for the body. Active compound as

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anticancer such as philinopside A and B, patagonicosides, holothurin A and echinosides, colohiroside A, Intercedenside A, Okhotosides and Frondoside A sticoposide originating from *Thelenota anax*, sticoposide, bivittoside A, Holocosinos A and Holotox, cucumariosides produced from different types of sea cucumbers. Each active compound has a different mechanism of action to inhibit cancer cells. In general, inhibition of cancer cell growth from sea cucumber active compound through the mechanism of apoptosis in cells and mitochondria.

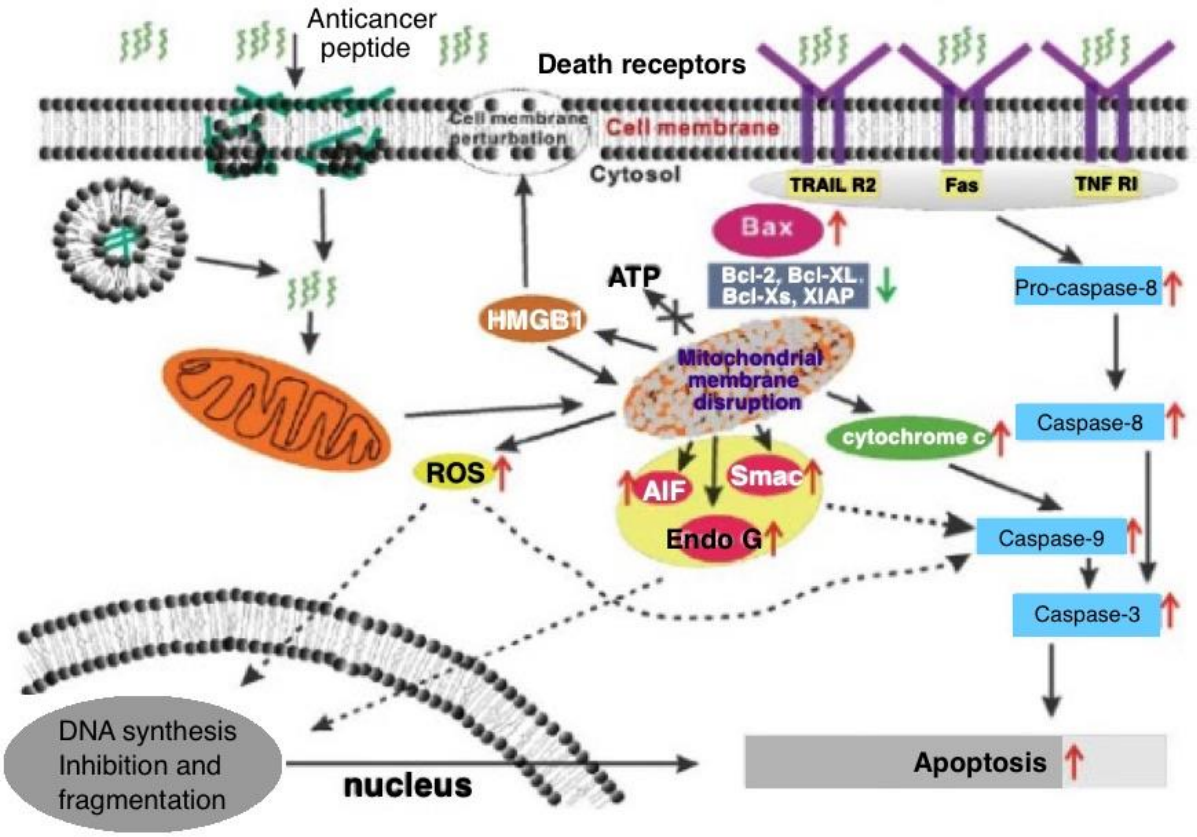

Figure 13. Schematic illustration of apoptosis mechanism in mitochondrial pathway [60]

CONFLICT OF INTERETS

Authors declare that there is no competing interest up on submission the manuscript.

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