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An Overview of the Potential of Sea Cucumbers with Antioxidant and Antiviral Contents as Nutritional Supplements

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ABSTRACT

Sea cucumber is one of the marine biotas and used as drugs composition or as an additional component of foods. Its complete nutritional compositions, antioxidant and antiviral activities have been widely studied and are known useful for human health. Each sea cucumber species, may have different antioxidant activity values, also depends on its forms, organic or aqueous extract. In the right dose and duration of consumption of sea cucumber extract, it has significant therapeutic effect in several medical problems. Not only as an antioxidant and antiviral, but sea cucumber has also been known

contain antifungal, antimetastase, cytotoxic, and various other roles that can be supplied for medical treatment

Keywords: sea cucumber, antioxidant, antiviral

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INTRODUCTION

Vitamins are organic nutrients that needed in small amounts for various biochemical functions in human body.¹ Vitamin A or retinal is a polyisoprenoid compound containing cyclohexenyl ring. Vitamin A deficiency is commonly found in people with infection. Consumption of vitamin A helps reduce the level of morbidity and death due to infection.² Retinoic acid involved in glycoprotein synthesis and also plays a role in tissue growth and its differentiation. Retinoids and carotenoids have anti-cancer activity. Many human cancer cells in the human body are arise in epithelial tissue that are dependent on retinoids for normal cellular differentiation. β -carotene is an antioxidant and may have a role in catching peroxy free radicals in tissues with low oxygen partial pressure. β -carotene acting as an antioxidant is caused by its ability to stabilize peroxide free radicals in conjugated alkyl structure. Because β -carotene works effectively at low oxygen concentration, this provitamin supplement complements the effects of antioxidant properties of vitamin E with higher oxygen concentration.¹ Vitamin C is one of natural antioxidants to ward off various extracellular free radicals. Vitamin C acts as a coenzyme and in certain circumstances is a reducing agent

and antioxidant.³ Vitamin D known as ergocalciferol, this compound have anti-inflammatory effects on the vascular system as a cardioprotective agent. In addition, vitamin D is also a natural immune modulator.⁴ Vitamin E is fat-soluble antioxidant and easily gives hydrogen and hydroxyl (OH) groups in the ring structure to free radicals.³ Research reveals that people with vitamin D deficiency will experience more severe pain. And vitamin D is very helpful in reducing pain in people with vitamin D deficiency (25-OHD levels <30 nmol / L).⁵

Sea cucumber is one of the marine biotas that belong to the *Echinoderms* group that grows in sandy habitats or muddy sand habitats as well as coral reefs. The sea cucumber's body is generally elliptical and cylindrical about 10-30 cm, with the mouth at one end.^{6,7}

Below is the sea cucumber taxonomy:^{8,9}

Phylum	: Echinoderms
Subfilum	: Echinozoa
Class	: Holothuroidea
Subclass	: Aspidochirotea
Order	: Aspidochirotide
Family	: Holothuriidae
Genus	: Holothuria, Muellieria, Stichopus

Table 1: Sea cucumber's classification⁸

Family	Order	Genus	Species	Local's name			
Aspidochirotida	Holothuriidae	Actinopyga	<i>A. miliaris</i>	Teripang lotong			
			<i>A. lecanora</i>	Teripang batu			
			<i>A. echinites</i>	Teripang batu			
				Holothuria	<i>A. mauritiana</i>	Teripang bilalo	
					<i>H. scabra</i>	Teripang pasir, teripang hitam	
					<i>H. nobilis</i>	Teripang susuan putih	
					<i>H. fuscogilva</i>	Teripang susuan putih	
					<i>H. atra</i>	Teripang dada merah	
					<i>H. edulis</i>	Teripang keling	
					<i>H. coluber</i>	Teripang tali jangkar	
					<i>H. leucospilota</i>	Teripang hitam	
					<i>H. pervicas</i>	Teripang karang	
					<i>H. fuscocimirea</i>	Teripang karang	
					<i>H. gyvifer</i>	Teripang karang	
					<i>H. hilla</i>	Teripang karang	
					<i>H. impatiens</i>	Teripang karang	
					<i>H. pardalis</i>	Teripang karang	
				Bohadschia	<i>B. argus</i>	Teripang mata kucing	
					<i>B. graeffei</i>		
					<i>B. marmorata</i>	Teripang getah putih	
			Stichopodiae	Stichopus	<i>S. chloronotus</i>	Teripang belimbing	
						<i>S. horrens</i>	
						<i>S. variegates</i>	Teripang kasur
				Thelenota	<i>T. ananas</i>	Teripang nenas	
					<i>T. anax</i>		

Sea cucumber is one of the marine commodities of domestic and international value of fisheries sub-sector that is quite potential so that Indonesia is the largest country that exports sea cucumber whole the world.¹⁰ Secondary metabolite of sea cucumber have bioactive compounds, they are alkaloid, saponin, triterpenoid, flavonoid and steroids.¹¹ Sea cucumber contains a variety of compounds depending on its species. The types of sea cucumber that are consumed as medicine and food are *Stichopus chloronotus*, *S. Hermanii*, *S. Variegatus* and *S. Japonicus*. According to US Department of Medicine and Food (USDA) states, sea cucumber contains complete nutritional compositions, including 9 types of carbohydrates, 59 types of fatty acids, 19 types of amino acids, 25 components of vitamins, 10 types of minerals, and 5 sterols. The nutritional compositions of dried sea cucumber are 8.60% water, 82.0% protein, 1.70% fat, 8.60% ash, 4.80% carbohydrates, 455 µg% of vitamin A, 0.04 mg% vitamin B (thiamine), 0.4 mg% niacin, 0.07 mg% riboflavin and 365 calories per 100 grams.¹² Water research revealed that per milliliter of sea water contains up to 10⁶ bacteria and 10⁹ viruses. Every animals that lives in the sea has a strong ability of immunity, including sea cucumber.¹³ There are many benefits of sea cucumber that are not widely known, one of them is as antiviral. The studies reveals that lectins have a therapeutic effect on Human Immunodeficiency Virus (HIV). Laboratory test results using lymphoid cells shows that lectins perfectly can block the HIV virus.¹⁴ *T. ananas* and *T. anax* are two species of sea cucumbers from the family *Stichopodidae* that lives in the tropical waters. *T. ananas* is known as a pineapple or thorny redfish. This species is one of the most popular sea cucumber species consumed in China and Southeast Asian countries and a

commercial sea cucumber species¹⁵ Due to excessive commercial consumption, this species availability has decreased by 80-90% and put as an endangered species by the International Union for Conservation of Nature. The therapeutic effects of *T. ananas* including antioxidant, anti-inflammatory, antitumor, antiproliferative, anticoagulant and antiviral effects has been established. Wu et al. have isolated novel fucosylated chondroitin sulfate from the body wall of *T. ananas* which consists of N-acetylgalactosamine (GalNAc), glucuronic acid (GlcUA), fucose and esters of sulfate by approximate ratio 1:1:1:3:7, respectively.^{16,17} Fucosylated chondroitin sulfate soluble in depolymerized glycosaminoglycan water isolated from echinoderm.¹⁸ The physicochemistry of the fucose branches differs based on sea cucumber species.¹⁹ The anticoagulant activity of fucosylated chondroitin sulfate from *T. ananas* measured by the partially activated thromboplastin time test variety according to the proportion of molecular weight following a logarithmic function.²⁰ The molar ratio for the type of fucose branch found in *T. ananas* 25:22:53 for 3-monosulfate, 4-monosulfate and 2,4-disulfate, respectively. The compositions are correlated with the anticoagulant activity of fucosylated chondroitin sulfate. Recently, the activity of oscillating sulfate anticoagulant from *T. ananas* is mediated by inhibiting the intrinsic tenase.²⁰ However, difucosylated chondroitin sulfate from *T. ananas* also activates factor XII which subsequently causes hypotension when injected intravenously in mice. Besides, activation of factor XII may be reduced by a low molecular weight sulfate, fucosylated chondroitin; this revealed that molecular weight played an important role in anticoagulant effect of fucosylated chondroitin sulfate as well.²¹ Not only anticoagulant activity,

low molecular weight fragments of chondroitin sulfate phosphorylated from *T. ananas* prepared by depolymerization of free radicals had shown functions to inhibit the Human Immunodeficiency Virus (HIV) replication.²² Fucosylated chondroitin sulfate is effectively impedes the entry of HIV-111B strains and their

replications, and also inhibits infection by isolating HIV-1KM018 and HIV-1TC-2. Fucosylated chondroitin sulfate may be potential as a new HIV-1 entry inhibitor for the treatment of HIV/AIDS, especially for patients that infected by resistant T-20 virus. However, further research to explain the fucosylated chondroitin sulfate and its activity will be carried out in the further study.

RESEARCHES IN ANTIOXIDANT ACTIVITY OF SEA CUCUMBER

Table 2: Below are some research comparisons of antioxidant activities of sea cucumber extract based on its species.

No	Title (Author)	Subject	Method	Results			
1	Antioxidant Activity of Bioactive Peptides Extracted from Sea Cucumber (Holothurialeucospilata) (Reza Safari, Zahra Yaghoubzadeh)	10 sea cucumbers (<i>H. leucospilata</i>)	<i>H. leucospilata</i> and some additional ingredients stored frozen, and then chopped. Analysis of antioxidant activity using DPPH radical-scavenging assay and FRAP	Concentration of <i>H. leucospilata</i>	DPPH	FRAP	
				2	35.3 ± 0.2	0.34 ± 0.03	
				3	43.25 ± 0.2	0.39 ± 0.02	
				4	54.7 ± 0.8	0.66 ± 0.02	
				5	68.27 ± 0.2	0.75 ± 0.09	
				Conclusion: Hydrolyzed protein extract with a molecular weight of less than 30 KDa from <i>H. leucospilata</i> has antioxidant activity and can be used as a natural additive in drugs and foods.			
2	In Vitro Antioxidant and Antiproliferative Activities of Three Malaysian Sea Cucumber Species (Osama Y. Althunibat et al)	3 species of sea cucumber: <i>Holothuria cabra</i> , <i>Holothurialeucospilata</i> and <i>Stichopus chloronotus</i> . The sea cucumber were dissected for internal organs removal and stored at -80 degrees Celsius.	Liquid extracts of subjects are made in aqueous extract and organic extract. Antioxidant activity was analyzed using DPPH assay and beta carotene bleaching.	Species	DPPH Assay (IC50)	Beta carotene bleaching (% antioxidant activity)	
				<i>Holothuria scabra</i>	Fluid	> 10	77.46 ± 5.16
					Organic	> 10	35.92 ± 2.87
				<i>Holothurialeucospilata</i>	Fluid	3.91 ± 0.12	64.03 ± 6.24
					Organic	5.44 ± 0.15	55.85 ± 3.38
				<i>Stichopus chloronotus</i>	Fluid	2.13 ± 0.05	80.58 ± 4.92
					Organic	> 10	73.87 ± 3.04
				Conclusion: Each sea cucumber species may have different levels of antioxidant activity. In this study the highest value was found in <i>Stichopus chloronotus</i> species compared to the two other species.			
3	Antioxidant And Cytotoxic Properties Of Two Sea Cucumbers, <i>Holothuria edulis</i>	Two species of sea cucumber (<i>H. edulis</i> and <i>S. horrens</i>) are dissected to remove	Extracts of both sea cucumber species are made in aqueous extract and organic extract. Antioxidant activity was	Species	DPPH Assay	Beta carotene bleaching	
				<i>H. edulis</i>	Organic	8.73 ± 0.13	28.52 ± 1.31
					Fluid	2.03 ± 0.06	42.69 ± 1.25

	Lesson And StichopusHorrensSelenka (OY Althunibat, et al)	their internal organs, then stored at -80 degrees Celsius.	analyzed using DPPH assay and beta carotene bleaching.	<i>S. horrens</i>	Organic	> 10	79.62 ± 1.91
					Fluid	> 10	46.66 ± 1.13
				Conclusion: Each sea cucumber species may have different levels of antioxidant activity. In this study the highest antioxidant activity was found in aqueous extract of <i>S. horrens</i> species.			
4	Structure characterization, antioxidant and immunoregulatory properties of a fucoidan novel from the sea cucumber <i>Stichopus chloronotus</i> (Qiang Li, Shuxin Jianga, Weiwei Shia, Xiaohui Qia, Weiguo Songa, b, Jiaojiao Moua, Jie Yang)	Dried <i>S. chloronotus</i> species	Antioxidant analysis was performed to the isolated fucoidan from <i>S. chloronotus</i> species.	Results: The maximum fat peroxidation inhibition was reached by using 0.2-1.0 mg/mL concentration of <i>S. chloronotus</i> (32.5% at a concentration of 0.8 mg/mL).			
				Conclusion: Fucoidan of <i>S. chloronotus</i> has significant antioxidant activity.			

RESEARCHES IN ANOTHER USEFULL ACTIVITIES OF SEA CUCUMBER

Table 3: Below are some research comparisons of another sea cucumber activities (antiviral, hepatoprotector, antimetastatic, cytotoxic) and sea cucumber contents based on subjects (animals and growth medium), species and methods.

No	Title (Author)	Subject	Method	Results			
				Group	TC	TG	HDL-C
1	Antioxidant and antihyperlipidemic activities of polysaccharides from sea cucumber <i>Apostichopus japonicus</i> (XinLiua, ZhenliangSun c, MiansongZhangb, XiumeiXiab, WenpengYuan, FengXuec, ChanghengLiu)	Polysaccharides of <i>Apostichopus japonicus</i> (AJP) were extracted and 72 albino male wistar rats were divided into 6 groups: normal controls, hyperlipidemia control, and another 3 groups received AJP extract in different doses (200, 400, and 800 mg/kg) and the last group received atorvastatin 10	Rats were given interventions according to grouping, then observed total serum cholesterol, triglyceride, and HDL-C levels	Normal control	1.74 ± 0.22	0.49 ± 0.05	1.51 ± 0.21
				Hyperlipidemia control	2.38 ± 0.23	0.77 ± 0.31	1.21 ± 0.26
				AJP 200 mg/kg	2.18 ± 0.22	0.74 ± 0.19	1.43 ± 0.21
				AJP 400 mg/kg	1.97 ± 0.33	0.61 ± 0.33	1.54 ± 0.25
				AJP 800 mg/kg	2.01 ± 0.31	0.62 ± 0.16a	1.35 ± 0.21a
				Atorvastatin	1.87	0.51	1.24

		mg/kg as standard treatment.			± 0.25	± 0.16	± 0.33
				Conclusion: AJP can uses as natural antioxidant resource and treats hyperlipidemia condition.			
2	Bioactive compounds, antioxidant potential, and hepatoprotective activity of sea cucumber (Holothuria atra) against thioacetamide intoxication in rats (Amr Y. Esmat, Mahmoud M. Said, Amel A. Soliman, Khaled SH El-Masry, Elham Abdel Badiea)	62 Swiss albino female rats were divided into 4 groups: normal, given orally <i>H. atra</i> extract, thioacetamide intoxicated, thioacetamide intoxicated and given AJP extract.	Two groups of mice were injected with thioacetamide intraperitoneally. One of the groups was given <i>H. atra</i> sea cucumber extract. Mortality rates were observed between the groups.	Group	Mortality after 8 weeks (%)		
				Control (normal)	0		
				Only given orally AJP extract	0		
				Thioacetamide intoxicated	65		
				Thioacetamide intoxicated + given orally AJP extract	35		
				Conclusion: Antioxidants in <i>H. atra</i> extract increases hepatic superoxide dismutase which prevents cell damage and increases glutathione peroxidase activity that protects organs from oxidative damage, microscopic results show the regression of fibrosis and hepatocyte necrosis, thereby reducing mortality due to thioacetamide intoxication.			
3	Antioxidant And Cytotoxic Properties Of Two Sea Cucumbers, <i>Holothuria edulis</i> Lesson And <i>Stichopus horrens</i> Selenka (OY Althunibat, et al)	Two species of sea cucumber (<i>H. edulis</i> and <i>S. horrens</i>) were dissected for removal of internal organs and stored at -80 degrees Celsius.	Fluid extracts from both sea cucumber species are made in aqueous extract and organic extract, then analyzed their cytotoxic activity against esophageal cancer cells (TE11) and non-small cell lung cancer (A549) by observed the inhibitory concentration of extract levels needed to reduce 50% cell viability.	Species	TE11	A549	
				<i>S. horrens</i>	Fluid	not detected	not detected
					Organic	4.0 ± 0.5	15.5 ± 2.0
				<i>H. edulis</i>	Fluid	78.0 ± 3.0	132.0 ± 9.0
					Organic	17.0 ± 1.5	22.5 ± 1.0
				Conclusion: Esophageal cancer cells (TE1) are more sensitive than non-small-cell lung cancer cells (A549) to sea cucumber extract.			

4	Antiviral Activity Of <i>Holothuria</i> Sp. A Sea Cucumber Against Herpes Simplex Virus Type 1 (Hsv-1) (F. Farshadpour, S. Gharibi, M. Taherzadeh, R. Amirinejad, R. Taherkhani, A. Habibian, K. Zandi)	Fresh cucumber sea (<i>Holothuria</i> sp.) dissected for internal organs removal.	Sea cucumber was extracted and sterilized. Then, the herpes simplex 1 virus is placed in Dulbeccos's minimum essential medium and used HEp-2 as human cells. Antiviral activity was analyzed using CPE inhibition assay.	<ul style="list-style-type: none"> 50 micrograms/mL of sea cucumber extract is not enough to produce anti-replication effect against the virus. 400 micrograms/mL of sea cucumber extract suppressed the virus up to 98.3% compared to those not treated. <p>Conclusion: Sea cucumber extract <i>Holothuria</i> sp. in certain doses has significant antiHSV-1 activity.</p>																																		
5	Radioprotective Properties of Cumaside, a Complex of Triterpene Glycosides from the Sea Cucumber <i>Cucumaria japonica</i> and Cholesterol (Aminin D, Zaporozhets TA, Adryjashchenko PV, Avilov SA, Kalinin VI, Stonik VA)	CD-1 strain female rats were divided into 5 groups: control 1, control 2 (given radiation), and 3 groups given cumaside in different doses: 0.01, 0.1 and 1.0 microgram/kg, respectively.	Mice underwent radiation exposure intervention and were given <i>C. japonica</i> cumaside in different doses.	<table border="1"> <thead> <tr> <th rowspan="2">Group</th> <th colspan="2">Leukocytes</th> <th colspan="2">Neutrophils</th> </tr> <tr> <th>4th</th> <th>9th</th> <th>4th</th> <th>9th</th> </tr> </thead> <tbody> <tr> <td>Control 1</td> <td colspan="2">5.0 ± 1.0</td> <td colspan="2">56 ± 2.1</td> </tr> <tr> <td>Control 2</td> <td>0.9 ± 0.1</td> <td>0.8 ± 0.4</td> <td>34 ± 4.7</td> <td>35 ± 3.5</td> </tr> <tr> <td>cumaside 0.01</td> <td>1.0 ± 0.2</td> <td>1.8 ± 0.5</td> <td>40 ± 3.5</td> <td>39 ± 4.8</td> </tr> <tr> <td>cumaside 0.1</td> <td>1.3 ± 0.3</td> <td>2.5 ± 0.6</td> <td>32 ± 2.8</td> <td>40 ± 3.1</td> </tr> <tr> <td>cumaside 1.0</td> <td>0.9 ± 0.2</td> <td>0.6 ± 0.2</td> <td>37 ± 3.4</td> <td>28 ± 3.1</td> </tr> </tbody> </table> <p>Conclusion: Cumaside helpsto accelerate the neutrophil levels recovery to normal after radiation exposure. The most effective dose of cumaside for this effect is 0.1 micrograms/kg</p>	Group	Leukocytes		Neutrophils		4th	9th	4th	9th	Control 1	5.0 ± 1.0		56 ± 2.1		Control 2	0.9 ± 0.1	0.8 ± 0.4	34 ± 4.7	35 ± 3.5	cumaside 0.01	1.0 ± 0.2	1.8 ± 0.5	40 ± 3.5	39 ± 4.8	cumaside 0.1	1.3 ± 0.3	2.5 ± 0.6	32 ± 2.8	40 ± 3.1	cumaside 1.0	0.9 ± 0.2	0.6 ± 0.2	37 ± 3.4	28 ± 3.1
Group	Leukocytes		Neutrophils																																			
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Control 1	5.0 ± 1.0		56 ± 2.1																																			
Control 2	0.9 ± 0.1	0.8 ± 0.4	34 ± 4.7	35 ± 3.5																																		
cumaside 0.01	1.0 ± 0.2	1.8 ± 0.5	40 ± 3.5	39 ± 4.8																																		
cumaside 0.1	1.3 ± 0.3	2.5 ± 0.6	32 ± 2.8	40 ± 3.1																																		
cumaside 1.0	0.9 ± 0.2	0.6 ± 0.2	37 ± 3.4	28 ± 3.1																																		

DISCUSSION

Studies shows that triterpene glycosides are the primary bioactive compounds possessed by sea cucumbers. This compound has many useful natural activities, i.e. antiviral, cytostatic, and immunomodulator. Anti fungal activity in sea cucumber is played by variegatuside D and coustesides C and D which contain terpenoid glycosides. This compound works to inhibit *Candida albicans* and several other *Candida* sp.²³ From triterpen glycosides isolation of sea cucumber, we also knows that it only works oneukariotic biotas, not on prokaryotes.²⁴

Virucidal ability is carried out by a component of sea cucumber glycoside called Liouvilloside A that fights the herpes simplex virus.²⁵ Other studies of intracellular antiviral activity to HSV-1 viruses have found that sea cucumber extract in HSV-1 intracellular replication on HEp-2 cells in 50 micrograms/ml extractdoes not significantly inhibit virus

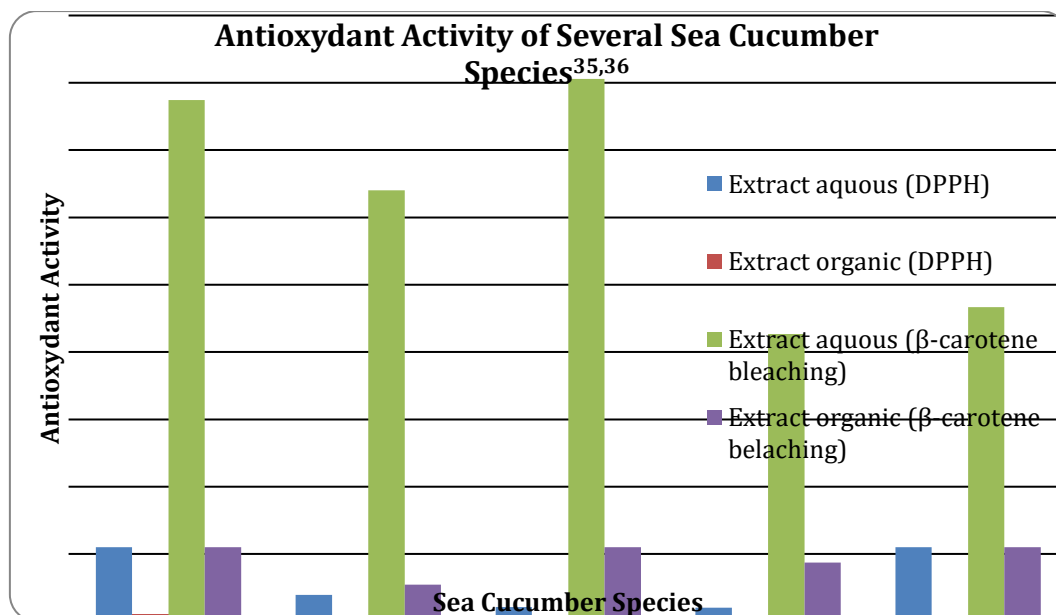
replication in host cells. However at 400 micrograms/ mL the extract can prevent the presentation of the virus.²⁶

High vitamin A in sea cucumber provides a significant inhibition effect of norovirus replication. Where a similar inhibitory effect was observed for replication of the norovirus genome in human cells containing norovirus replication at 24, 48, and 72 hours after retinol treatment, number of copies of the human norovirus gene had decreased significantly in the presence of 100 U/ml retinol compared to negative controls.²⁷Another study found further evidence of *Pattalusmollis* extract potential use, the results shows that the extract could inhibit 99% of Human Rotavirus A (RVA) during the virus absorption and its inactivity phases.²⁸

A research by Safari et al shows that a hydrolyzed protein extract with a molecular weight of less than 30 KDa from *H. leucospilata* has antioxidant activity that can be used as a natural additive in drugs and foods.²⁹ Li et al conducted a study of fucoidan extracts of *Stichopuschloronotus*. The

results shows the maximum antioxidant activity was 32.5% by using 0.8 mg/mL fucoidan extract concentration.³⁰ In addition to its antioxidant and antiviral activity, sea cucumber also has other benefits. Research by Liu et al was conducted on wistar rats which were contained hydrolyzed polysaccharides from *Apostichopusjaponicus* (AJP). The results shows decreased levels of total serum cholesterol, triglycerides and LDL-C. So their concluded that AJP could be a natural antioxidant resource in treatment for people with hyperlipidemia.³¹ The high or low polysaccharide activity in sea cucumbers is dependsto its molecular size,^{32,33} monosaccharide composition, glycoside patterns, and other aspects.³⁴ Although the antioxidant of sea cucumbers is already known, their activity will still differ between species. In addition, in medicinal purposes, the forms of sea cucumber extract consumed will also affect the antioxidant effect. Research by Althunibat et al shows differences in antioxidant and

antiproliferative activity of three marine cucumber species:*Holothuriascabra*, *Holothurialeucospilota*and*Stichopuschloronotus*. The results shows the antioxidant activity of *Stichopuschloronotus* was the highest level (80.58%) compared to the other two species. And only this species has antiproliferative activity by inhibiting the growth of human cervical cancer and human non-small lung carcinoma.³⁵ He has also conducted similar studies to find out the comparison of antioxidant and cytotoxic activities between liquid and organic preparations from the sea cucumber species *Holothuriaedulis*and*Srichopuschorrens*. The evaluation using beta carotene bleaching assay shows that the highest antioxidant activity was found inaqueos extract of*S. horrens* and the lowest activity in organic extract of *H. edulis*.³⁶



Cytotoxic activity only found in *H. edulis* species to against cancer cells in both form extracts, aqueos and organic. Esophageal cancer cells (TE1) are more sensitive than non-small-cell lung cancer cells (A549) to the sea cucumber extract.³⁶ Beside the cytotoxic activity, it is also known that fucoidan in *Cucumariafrondosa*species has antimetastatic activity in bone cancer cells malignant, known as osteosarcoma. Fucoidan works by inhibiting adhesion and signaling migration of cancer cells, it has potential as an antimetastasis in osteosarcoma.³⁷ Research by Said et al to Swiss female albino rats was conducted to analyzeactive phenolisactivity in *Holothuriaatrae*extract as a hepatoprotector from liver injury induced by thioacetamide. The results shows that sea cucumber extract is safe to use even for a relatively long period. Antioxidants in this sea cucumber extract produce an increase in hepatic superoxida dismutase which prevents cell damage and increased glutathione peroxidase activity which protects the organ from oxidative damage. Laboratory results of liver function tests were normal and microscopically

regressed the process of fibrosis and hepatocyte necrosis due to thioacetamide. This intervention reduces mortality in subjects who have thioacetamide-induced liver damage.³⁸ It is known that in mammals there is a Fas-associated death domain (FADD) which is a protein adapter in the process of sending apoptotic signals by death receptors.³⁹ In *A. japonicus*, FADD is important as a defense against bacteria and viruses. However, if its expression is excessive it will cause apoptosis in human renal embryonic cells and have received transfusion of adenovirus DNA 5 (HEK293 cells).⁴⁰ In this species also identified two toll-like receptor (TLR) genes, known as TLR3 and Toll protein. Both are plays an important role in the immune response to infections caused by gram-negative bacteria and viral dsRNA.⁴¹ An increase in leukocytes is a sign of infection in the body.⁴² Leukocytes components such neutrophils will be increases rapidly due to infection, but it is cannot last long.⁴³ Research by Aminin et al on female rats given radiation intervention to determine the effect of cumaside (a triterpenmonosulfate glycoside compounds of *Cucumaria japonica*) to neutrophil

levels. The results shows that cumaside can help speed up the recovery of neutrophil levels to normal after radiation exposure. The most effective dose of cumaside for this effect is 0.1 micrograms/kg.^{44,45,46,47}

CONCLUSION

Sea cucumber has antioxidant and antiviral activity that significantly proven to use as treatment in various conditions that have been studied.

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