Sys Rev Pharm 2020; 11(6): 761 – 770
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

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

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*Article History:* *Submitted: 10.04.2020* *Revised: 14.05.2020* *Accepted: 22.06.2020*

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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**DOI:** 10.31838/srp.2020.6.112



## 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. ß-carotene is an antioxidant and may have a role in catching peroxy free radicals in tissues with low oxygen partial pressure. ß-carotene acting as an antioxidant is caused by its ability to stabilize peroxide free radicals in conjugated alkyl structure. Because ß-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 ergocalsifol, 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 : Aspidochirotacea
Order : Aspidochirotide
Family : Holothuriidae
Genus : Holothuria, Muelleria, Stichopus

Table 1: Sea cucumber's classification[8]

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

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 alkoloid, 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 *Stichopuschioronatus*, *S. Hermanii, S. Varigeatus* 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 $10^6$ bacteria and $10^9$ 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 species[15] 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 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 fucosylatedchondroitin 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*is 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-1IIIB strains and their replications, and also inhibits infection by isolating HIV-1KM018 and HIV-1TC-2.

Fucosylatedchondroitin 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 fucosylatedchondroitin 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 (Holothuriale ucospilata) (Reza Safari, Zahra Yaghoubzade h) | 10 sea cucumbers( *H. leucospilata* ) | *H. leucospilata*andso me additional ingredients stored frozen, and then chopped. Analysis of antioxidant activity using DPPH radical-scavenging assay and FRAP | Concentration of *H. leucospilata*: DPPH / FRAP<br>2: 35.3 ± 0.2 / 0.34 ± 0.03<br>3: 43.25 ± 0.2 / 0.39 ± 0.02<br>4: 54.7 ± 0.8 / 0.66 ± 0.02<br>5: 68.27 ± 0.2 / 0.75 ± 0.09<br>Conclusion: Hydrolyzed protein extract with a molecular weight of less than 30 KDa from *H. leucospilata* has antioxidant activity and can be used as a natural additive in drugs and foods. |
| 2 | In Vitro Antioxidant and Antiproliferati ve Activities of Three Malaysian Sea Cucumber Species (Osama Y. Althunibat et al) | 3 species of sea cucumber: *Holothurias cabra, Holothurial eucospilota*aa nd *Stichopuschl oronotus.* The sea cucumberw ere dissected for internal organs removal and stored at -80 degrees Celsius. | Liquid extracts of subjectsare made in aqueos extract and organic extract. Antioxidant activity was analyzed using DPPH assay and beta carotene bleacing. | Species / DPPH Assay (IC50) / Beta carotene bleacing (% antioxidant activity)<br>*Holothuria scabra* – Fluid: > 10 / 77.46 ± 5.16<br>*Holothuria scabra* – Organic: > 10 / 35.92 ± 2.87<br>*Holothuria leucospilota* – Fluid: 3.91 ± 0.12 / 64.03 ± 6.24<br>*Holothuria leucospilota* – Organic: 5.44 ± 0.15 / 55.85 ± 3.38<br>*Stichopus chloronotus* – Fluid: 2.13 ± 0.05 / 80.58 ± 4.92<br>*Stichopus chloronotus* – Organic: > 10 / 73.87 ± 3.04<br>Conclusion: Each sea cucumber species may have different levels of antioxidant activity. In this study the highest value was found in *Stichopuschloronotus* species compared to the two other species. |
| 3 | Antioxidant And Cytotoxic Properties Of Two Sea Cucumbers, HolothuriaEd ulis | Two species of sea cucumber (*H. edulis*and *S. horrens*) are dissected to remove | Extracts of both sea cucumber species are made in aqueos extract and organic extract. Antioxidant activity was | Species / DPPH Assay / Beta carotene bleaching<br>*H. edulis* – Organic: 8.73 ± 0.13 / 28.52 ± 1.31<br>*H. edulis* – 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 bleacing. | *S. horrens* | Organic | > 10 | 79.62 ± 1.91 |
| | | | | | Fluid | > 10 | 46.66 ± 1.13 |
| | | | | Conclusion:<br>Each sea cucumber species may have different levels of antioxidant activity. In this study the highest antioxidant activity was found inaqueos extract of*S. horrens* species. | | | |
| 4 | Structure characterization, antioxidant and immunoregulatory properties of a fucoidan novel from the sea cucumber Stichopuschloronotus (Qiang Li, ShuxinJianga, Weiwei Shia, XiaohuiQia, WeiguoSonga, b, JiaojiaoMoua, Jie Yang) | Dried *S. chloronotus* species | Antioxidant analysis was performed to the isolated fucoidan from *S. chloronotus*species. | Results:<br>The maximum fat peroxidation inhibition was reached by using 0.2-1.0 mg/mL concentrationof*S. chloronotus*(32.5% at a concentration of 0.8 mg/mL). | | | |
| | | | | Conclusion:<br>Fucoidanof *S. chloronotus* 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 | | | |
|---|---|---|---|---|---|---|---|
| 1 | Antioxidant and antihyperlipidemic activities of polysaccharides from sea cucumber Apostichopusjaponicus (XinLiua, ZhenliangSunc, MiansongZhangb, XiumeiMenga, XuekuiXiab, WenpengYuana, FengXuec, Changheng Liu) | Polysaccharides of *Apostichopusjaponicus* (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 | Group | TC | TG | HDL-C |
| | | | | 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 |

<table>
<tr><td></td><td></td><td>mg/kg as standard treatment.</td><td></td><td></td><td>± 0.25</td><td>± 0.16</td><td>± 0.33</td></tr>
<tr><td colspan="5"></td><td colspan="3">Conclusion:<br>AJP can uses as natural antioxidant resource and treats hyperlipidemia condition.</td></tr>
<tr><td>2</td><td>Bioactive compounds, antioxidant potential, and hepatoprotective activity of sea cucumber (Holothuriaatra) against thioacetamide intoxication in rats (Amr Y. Esmat, Mahmoud M. Said, Amel A. Soliman, Khaled SH El-Masry, Elham Abdel Badiea)</td><td>62 Swiss albino female rats were divided into 4 groups: normal, given orally H. atra extract,thioacetamide intoxicated, thioacetamide intoxicatedand given AJP extract.</td><td>Two groups of mice were injected with thioacetamidein traperitoneally. One of the groups was given H. atra sea cucumber extract. Mortality rates were observed between the groups.</td><td colspan="2">Group</td><td colspan="3">Mortality after 8 weeks (%)</td></tr>
<tr><td colspan="4"></td><td colspan="2">Control (normal)</td><td colspan="3">0</td></tr>
<tr><td colspan="4"></td><td colspan="2">Only given orallyAJP extract</td><td colspan="3">0</td></tr>
<tr><td colspan="4"></td><td colspan="2">Thioacetamideintoxicated</td><td colspan="3">65</td></tr>
<tr><td colspan="4"></td><td colspan="2">Thiacetamideintoxicated + given orally AJP extract</td><td colspan="3">35</td></tr>
<tr><td colspan="4"></td><td colspan="5">Conclusion:<br>Antioxidants in H. atra extract increases hepatic superoxide dismutase which prevents cell damage and increases glutathione peroxidase activity that protects organs from oxidative damage, microscopic results showesthe regression of fibrosis and hepatocyte necrosis, thereby reducing mortality due to thioacetamide intoxication.</td></tr>
<tr><td>3</td><td>Antioxidant And Cytotoxic Properties Of Two Sea Cucumbers, HolothuriaEdulis Lesson And StichopusHorrensSelenka (OY AlthunibAt, et al)</td><td>Two species of sea cucumber (H. edulisand S. horrens) were dissected for removal of internal organs and stored at -80 degrees Celsius.</td><td>Fluid extracts from both sea cucumber species are made in aqueos extract and organic extract, then analyzed their cytotoxic activity against esophageal cancer cells (TEI1) and non-small cell lung cancer (A549) by observed the inhibitory concentration of extract levels needed to reduce 50% cell viability .</td><td colspan="2">Species</td><td colspan="2">TEI1</td><td>A549</td></tr>
<tr><td colspan="4"></td><td rowspan="2">S. horrens</td><td>Fluid</td><td colspan="2">not detected</td><td>not detected</td></tr>
<tr><td colspan="4"></td><td>Organic</td><td colspan="2">4.0 ± 0.5</td><td>15.5 ± 2.0</td></tr>
<tr><td colspan="4"></td><td rowspan="2">H. edulis</td><td>Fluid</td><td colspan="2">78.0 ± 3.0</td><td>132.0 ± 9.0</td></tr>
<tr><td colspan="4"></td><td>Organic</td><td colspan="2">17.0 ± 1.5</td><td>22.5 ± 1.0</td></tr>
<tr><td colspan="4"></td><td colspan="5">Conclusion:<br>Esophageal cancer cells (TE1) are more sensitive than non-small-cell lung cancer cells (A549) to sea cucumber extract.</td></tr>
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<td>4</td>
<td>Antiviral Activity Of Holothuria 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)</td>
<td>Fresh cucumber sea (Holothuria sp.) dissected for internal organs removal.</td>
<td>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.</td>
<td>● 50 micrograms/mL of sea cucumber extract is not enough to produce anti-replication effect against the virus.<br>● 400 micrograms/mL of sea cucumber extract suppressed the virus up to 98.3% compared to those not treated.<br><br>Conclusion:<br>Sea cucumber extract Holothuria sp. in certain doses has significant antiHSV-1activity.</td>
</tr>
<tr>
<td>5</td>
<td>Radioprotective Properties of Cumaside, a Complex of Triterpene Glycosides from the Sea Cucumber Cucumaria Japonica and Cholesterol (Aminin D, Zaporozhets TA, Adryjashchenko PV, Avilov SA, Kalinin VI, Stonik VA)</td>
<td>CD-1 strain female rats were divided into 5 groups: control 1, control 2 (given radiation), and 3 groups given cumasidein differentdoses: 0.01, 0.1 and 1.0 microgram/kg, respectively.</td>
<td>Mice underwent radiation exposure intervention and were given C. japonicacumaside in different doses.</td>
<td>
<table>
<tr><td>Group</td><td colspan="2">Leukocytes</td><td colspan="2">Neutrophils</td></tr>
<tr><td>Day</td><td>4th</td><td>9th</td><td>4th</td><td>9th</td></tr>
<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>
<tr><td colspan="5">Conclusion:<br>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</td></tr>
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## 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]

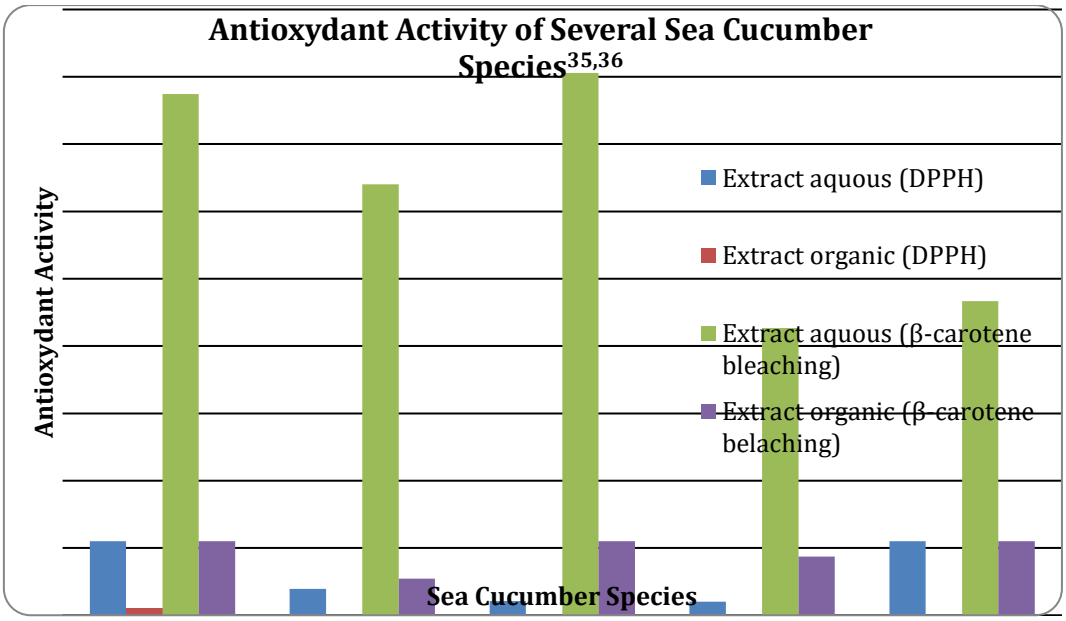
High vitamin A in sea cucumber provides a significant inhibition effect of norovirus replication. Where a similar inhibitory effect was observed for replication of the norovirus genome in human cells containing norovirus replication at 24, 48, and 72 hours after retinol treatment, number of copies of the human norovirus gene had decreased significantly in the presence of 100 U/ml retinol compared to negative controls.[27]Another 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 showsdecreased 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*Srichopushorrens*. 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 *Holothuriaatra*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.

## REFERENCES


1. ViviTriana. Various kinds of vitamins and their functions in the human body. Journal of Public Health. 2006; 1 (1): 40-47
2. Zinder R, Cooley R, Vlad LG & Molnar JA. Vitamin A and Wound Healing. Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition. 2019; 34 (6): 839–849. DOI: https://doi.org/10.1002/ncp.10420
3. Ana Fitriana. A description of the intake of vitamins as an antioxidant agent of soccer athletes in the Central Java education and training center for students in Salatiga. Unimus Nutrition Journal. 2014; 3 (1)
4. Makayadhaha, WeningDamayanti. An overview of the interpretation of total 25-OH vitamin D results in patients in ProdiaSalatiga [Thesis]. Semarang. Muhamadiyah University Semarang; 2017
5. Helde-Frankling M &Björkhem-Bergman L. Vitamin D in Pain Management. International journal of molecular sciences. 2017; 18 (10), 2170. DOI: https://doi.org/10.3390/ijms18102170
6. Sonny RieldoDamanik, BambangYulianto, Subagiyo. Potential of Coarse sea cucumber extract Holothuriaatra, Jaeger, from PulauPanjang, Jepara. Journal of Marine Research. 2019; 8 (3): 262-268
7. BintRumiyati. Effect of water depth on behavior and length of life of local sea cucumbers during the adaptation period in the rearing tank. Surabaya: Airlangga University; 2014
8. AminuddinEso, HerlinaUinarni, Thomas Tommy, RyantoKarobuanaSitepu, IwanKurnia Effendi, Justin Charles Ariestiyanto, Hutasot Charles Martamba, EviMustikawatiArifin, Ferrea Olivia Mawu, BayuIndraSukmana, Huldani. A Reviews on Use of sea cucumber as a treatment for oral cancer. SRP. 2020; 11 (5): 299-307. doi: 10.31838 / srp.2020.5.44
9. Xue Z, Li H, Wang X, Li X, Liu Y, Sun J & Liu C. A review of the immune molecules in the sea cucumber. Fish & shellfish immunology. 2015; 44 (1), 1–11. DOI: https://doi.org/10.1016/j.fsi.2015.01.026
10. HaryoTriajie. The sea cucumber extract activity test which has been formulated on the ability of sex reversal and survival of giant prawns. Indonesian Journal of Marine Science and Technology. 2010; 3 (1) .41-47
11. Pranoto, E., N Widodo FM, Denialis P. Study of the bioactive activity of extracts of sea cucumber sand (Holothuriascabra) against the fungus Candida albicans. Journal of Fisheries. 2012; 1 (2): 1-8
12. TheresiaDwiSuryaningrum. Sea cucumbers: Potential as a nutraceutical food and its processing technology. 2008; 3 (2) .63-69
13. MY Zhou, Chen XL, Zhao HL, Dang HY, Luan XW, Zhang XY, et al. Diversity of both the cultivable protease-producing bacteria and their extracellular proteases in the sediments of the south China sea. Microb Ecol. 2009; 58: 582-90. DOI:10.1007 / s00248-009-9506-z
14. Darmananda, S. Sea Cucumber. Institute for Traditional Medicine. 2006.2 pp
15. Yu L, Xue C, Chang Y, et al. Elucidation structure of fucoidan structure of an tetrafucose repeating unit from sea cucumber Thelenotaananas. Food Chem. 2014; 146 (0): 113e119.
16. Wu M, Xu S, Zhao J, Kang H, Ding H. Physicochemical characteristics and anticoagulant activities of low molecular weight fractions by free-radical depolymerization of a fucosylated chondroitin sulphate from sea cucumber Thelenataananas. Food Chem. 2010; 122 (3): 716e723.
17. Wu M, Xu S, Zhao J, Kang H, Ding H. Free-radical depolymerization of glycosaminoglycan from sea cucumber Thelenataananas by hydrogen peroxide and copper ions. CarbohydrPolym. 2010; 80 (4): 1116e1124.
18. Huang N, Wu MY, Zheng CB, Zhu L, Zhao JH, Zheng YT. The depolymerized fucosylated chondroitin sulfate from sea cucumber potently inhibits HIV replication via interfering with virus entry. Carbohydr Res. 2013; 380: 64e69.
19. Luo L, Wu M, Xu L, et al. Comparison of physicochemical characteristics and anticoagulant activities of polysaccharides from three sea cucumbers. MarDrugs. 2013; 11 (2): 399-417. DOI:10.3390 / md11020399
20. Gao N, Lu F, Xiao C, et al. B-Eliminative depolymerization of the fucosylated chondroitin sulfate and anticoagulant activities of resulting fragments. CarbohydrPolym. 2015; 127: 427-437. DOI:https://doi.org/10.1016/j.carbpol.2015.04.002
21. Pangestuti R, Arifin Z. Medical and health benefit effects of functional sea cucumber. Journal of Traditional and Complementary Medicine. 2017. DOI:https://doi.org/10.1016/j.jtcme.2017.06.007
22. Huang N, Wu MY, Zheng CB, Zhu L, Zhao JH, Zheng YT. The depolymerized fucosylated chondroitin sulfate from sea cucumber potently inhibits HIV replication via interfering with virus entry. Carbohydr Res. 2013; 380: 64-69. DOI:https://doi.org/10.1016/j.carres.2013.07.010
23. Mayer A, Guerrero AJ, Rodríguez AD, Taglialatela-Scafati O, Nakamura F, &Fusetani N. Marine Pharmacology in 2014-2015: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis, Antituberculosis, Antiviral and Anthratic ; Affecting the Immune and Nervous Systems, and Other Miscellaneous Mechanisms of Action. Marine drugs.

2019; 18 (1): 5. DOI:https://doi.org/10.3390/md18010005

24. Mondol M, Shin HJ, Rahman MA, & Islam MT. Sea Cucumber Glycosides: Chemical Structures, Producing Species and Important Biological Properties. Marine drugs. 2017; 15 (10): 317. DOI:https://doi.org/10.3390/md15100317
25. Maier MS, Roccatagliata AJ, Kuriss A, Chludil H, Seldes AM, Pujol CA, Damonte EB. Two new cytotoxic and virucidaltrisulfatedtriterpene glycosides from the Antarctic sea cucumber Staurocucumisliouvillei. J. Nat. Prod. 2001: 64; 732-736. DOI : 10,1021 / np000584i
26. F. Farshadpour, S. Gharibi, M. Taherzadeh et al. Antiviral activity of Holothuria sp. A sea cucumber against herpes simplex virus type 1 (HSV-1). European Review for Medical and Pharmacological Sciences. 2014; 18: 333-337
27. Heetae Lee, GwangPyoKo. Antiviral effects of vitamin A on norovirus infection via modulation of the gut microbiome. 2016; 6: 25835. doi: 10.1038 / srep25835
28. Enrique Garcia Candela, Carlos ParionaVelarde, Aaron Mondragon Martinez, Victor ChumpitazCerrate. Antiviral activity of the sea cucumber tegument extract (Patallusmollis) on human rotavirus A (RVA). Natural Product Research. 2019; doi: 10.1080 / 14786419.2019.1611807
29. Safari R &Yaghoubzadeh Z. Antioxidant Activity of Bioactive Peptides Extracted from Sea Cucumber (Holothurialeucospilata). International Journal of Peptide Research and Therapeutics. 2020; 1-6 DOI:https://doi.org/10.1007/s10989-020-10031-9
30. Li Q, Jiang S, Shi W, Qi X, Song W, Mou J & Yang J. Structure characterization, antioxidant and immunoregulatory properties of a fucoidan novel from the sea cucumber Stichopuschloronotus. Carbohydrate polymers. 2020; 231: 115767. DOI:https://doi.org/10.1016/j.carbpol.2019.115767
31. Liu X, Sun Z, Zhang M, Meng X, Xia X, Yuan W, Xue F & Liu C. Antioxidant and antihyperlipidemic activities of polysaccharides from sea cucumber Apostichopusjaponicus. Carbohydrate polymers. 2012; 90 (4): 1664–1670. DOI: https://doi.org/10.1016/j.carbpol.2012.07.047
32. Sheng J & Sun Y. Antioxidant properties of different molecular weight polysaccharides from athyriummultidentatum (doll.) Ching. Carbohydrate Polymers. 2014; 108: 41–45.DOI: 10.1016 / j.carbpol.2014.03.011
33. Mou J, Wang C, Li Q, Qi X, & Yang J. Preparation and antioxidant properties of low molecular holothurian glycosaminoglycans by H2O2 / ascorbic acid degradation. International Journal of Biological Macromolecules. 2018; 107: 1339–1347.DOI: 10.1016 / j.ijbiomac.2017.10.161
34. Mou J, Li Q, Shi W, Qi X, Song W & Yang J. Chain conformation, physicochemical properties of fucosylated chondroitin sulfate from sea cucumber Stichopuschloronotus and its in vitro fermentation by human gut microbiota. Carbohydrate polymers. 2020; 228: 115359. DOI:https://doi.org/10.1016/j.carbpol.2019.115359
35. Althunibat OY, Hashim RB, Taher M, Daud JM, Ikeda MA &Zali BI. In vitro antioxidant and antiproliferative activities of three Malaysian sea cucumber species. Eur J Sci Res. 2009; 37 (3): 376-87.
36. Althunibat OY, Ridzwan BH, Taher M, Daud JM, Ichwan SJA &Qaralleh H. Antioxidant and cytotoxic properties of two sea cucumbers, Holothuriaedulis Lesson and StichopushorrensSelenka. ActaBiologicaHungarica. 2013; 64 (1): 10-20.DOI: 10.1556 / ABiol.64.2013.1.2
37. Zhang, M., Chen, L., Liu, Y., Chen, M., Zhang, S., & Kong, D. (2020). Sea cucumber Cucumariafrondosafucoidan inhibits osteosarcoma adhesion and migration by regulating cytoskeleton remodeling. Oncology reports, 10.3892 / or.2020.7614. Advance online publication. DOI:https://doi.org/10.3892/or.2020.7614
38. Esmat AY, Said MM, Soliman AA, El-Masry KS &Badiea EA. Bioactive compounds, antioxidant potential, and hepatoprotective activity of sea cucumber (Holothuriaatra) against thioacetamide intoxication in rats. Nutrition (Burbank, Los Angeles County, Calif.). 2013; 29 (1): 258-267. DOI:https://doi.org/10.1016/j.nut.2012.06.004
39. Wallach D, Varfolomeev EE, Malinin NL, Goltsev YV, Kovalenko AV, Boldin MP. Tumor necrosis factor receptor and Fas signaling mechanisms. Annu Rev. Immunol. 1999; 17: 331–367. DOI:https: //doi.org/10.1146/annurev.immunol.17.1.331
40. Zhao Y, Guo M, Lv Z, Zhang W, Shao Y, Zhao X & Li C. Fasdied death domain (FADD) in sea cucumber (Apostichopusjaponicus): Molecular cloning, characterization and pro-apoptotic function analysis. Developmental and comparative immunology. 2020; 108: 103673. DOI:https://doi.org/10.1016/j.dci.2020.103673
41. Yuan SC, Huang SF, Zhang W, Wu T, Dong ML, Yu YH. An amphioxus TLR with dynamic embryonic expression pattern responses to pathogens and activates the NF-kB pathway via MyD88. MolImmunol 2009; 46 (11-12): 2348-56. DOI:https://doi.org/10.1016/j.molimm.2009.03.022
42. Huldani, Sukmana BI, Rahmiati, Pujiningtyas A &Savitri E, Fauziah, Nihayah U. Cellular Immunity of River Water Consuments and Bandarmasih Municipal Waterworks Consuments. Indian Journal of Public Health Research & Development. 2019; 10 (7): 823. DOI: 10.5958 / 09765506.2019.01674.7
43. Suhermanto A, Andayani S &Maftuch M. Provision of total phenol of sea cucumber sand (holothuriascabra) to increase leukocytes and differential leukocytes of carp (cyprinuscarpio) infected with AeromonasHydrophila bacteria. Marine Journal: Indonesian Journal of Marine Science and Technology. 2011; 4 (2), 150-157. The Center Hotel
44. Aminin D, Zaporozhets TA, Adryjashchenko PV, Avilov SA, Kalinin VI, Stonik VA. Radioprotective Properties of Cumaside, a Complex of Triterpene

Ahmad H. Horax S, Ramadhany S, et.al. 2019. Resistivity of Ant Nest (*Myrmecodia pendans)* On Ethanol Fraction Burkitt's Lymphoma Cancer Cells (Invitro) Through Interleukin 8 Angiogenesis Obstacles (Il-8). Journal of International Dental and Medical Research ,. ISSN 1309-100X. Vol 12 No. (2) pp.516-523 Glycosides from the Sea Cucumber Cucumaria Japonica and Cholesterol. Natural product communications. 2011; 6: 587-92. DOI: 10.1177 / 1934578X1100600503.

45. Hendrastuti H, Achmad H , Andam Dewi, Marhamah Firman, Surijana Mappangara, Sri Ramadhany, Rini Pratiwi, Dwi Putri W. 2018. Analysis of Antibacterial Effectiveness of Red Ginger Extract (Zingiber Officinale Var Rubrum) Compared to White Ginger Extract (Zingiber Officinale Var. Amarum) In Mouth Cavity Bacterial Streptococcus Mutans (In-Vitro) Journal of International Dental and Medical Research, April. ISSN 1309-100X. Vol 11 No. (2) pp.676-681.
46. Achmad H , Sherly Horax, Sri Ramadhany, Irene Edith Rieuwpassa, Melyanti Sari, Hendrastuti Handayani, Marhamah F. Singgih, Sumintarti Sugiharto. 2019 . Anti-Cancer and Anti-Proliferation Activity of Ethyl Acetate Extract From Ant Nest (Myrmecodia pendans) in Burkitt's Lymphoma Cancer Cells. Pesquisa Brasileira em Odontopediatria e Clinica Integrada. ISSN 1519-0501, 19 (1): e4325.
47. Achmad H, Sri Ramadhany, Philip Eric Suryajaya. 2019. Streptococcus Colonial Growth of Dental Plaque Inhibition Using Flavonoid Extract of Ants Nest (*Myrmecodia pendans*): An in Vitro Study. Pesquisa Brasileira em Odontopediatria e Clinica Integrada. ISSN 1519-0501, 19 (1): e4250