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IN-VITRO ANTI-CANCER ACTIVITY OF TWO BRITTLE STAR SPECIES: *OPHIOCOMA ERINACEUS* AND *OPHIOMASTRIX ANNULOSA*

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Keywords:

Anticancer, HepG2, MCF7, *Ophiocoma erinaceus* and *Ophiomastrix annulosa*

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ABSTRACT: Marine organisms are excellent sources of structurally diverse molecules that are potentially valuable as drugs. The brittle starfish was shown to contain the bioactive components which exhibit various biological activities including cytotoxicity effects. Hence, the present study was carried out to determine the cytotoxicity of the extracts of two different starfish species like *Ophiocoma erinaceus* and *Ophiomastrix annulosa.* The homogenized fresh body component of brittle starfish was extracted and concentrated. The cytotoxic effect of EtOH extract of *Ophiocoma erinaceus* and *Ophiomastrix annulosa* against cancer cell lines was determined by MTT assay. In this study, it was observed that the extracts induce a concentration-dependent inhibition of cells against MCF -7, VERO and HELA cell line at a lower concentration. Based on abundance, the top three major compounds present in the *O. erinaceus* were n-Nonadecanol-1 (24.643), Ethyl 9-hexadecenoate (26.437) and hexadecanoic acid, ethyl ester (26.868). The starfish extract exhibited strong cytotoxicity against cancer cells. Overall, these findings confirmed the utility of clinical investigations of the efficacy of starfish extracts in preventing in cancer chemotherapy.

INTRODUCTION: Marine natural products have attracted the attention to biologists and chemists all over the world for the last five decades. Approximately 16,000 marine natural products have been isolated from marine organisms and reported in approximately 6,800 publications as of date. In addition to these publications, there are approximately another 9,000 reports, which cover syntheses, reviews, biological activity studies, ecological studies, *etc*. on the subject of marine natural products [1].

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Many new drugs derived from secondary metabolites have been applied in the treatment and prevention of various diseases. However, these drugs have various and severe adverse effects such as nausea, vomiting, edema, and diarrhea. Therefore, naturally occurring agents with high effectiveness and no side-effects are desirable chemical therapeutics. Medicinal marine natural products have been intensively proposed as diverse chemotherapeutic agents. Therefore there is an affinity to find efficient modality to overwhelm ovarian cancer chemoresistance complication. Hence, introducing of valuable marine antitumor agents can suggest attractive insight into fighting cancer. One critical approach to discover new chemotherapeutic agents is the evaluation of anticancer effects of total natural extracts to obtain biomedicinal properties [2].

Brittle stars (Ophiuroidea) are marine invertebrates belonging to Echinodermata, and one of their more prominent features is their capacity for arm regeneration that has received little attention in the literature for its biomedical application [3]. Brittle stars are extensive marine invertebrates and possess some bioactive metabolites, including glycosides, terpenes, naphthoquinone and cerebrosides which may be appreciable n anti-cancer therapy [4].

Among the echinoderms, many cancer compounds are extracted from sea cucumbers, and starfish and the anticancer effects of the brittle star are less studied [5]. To date, the presence of some bioactive substances such as terpenes, sulfated sterols, carotenoid sulfate, phenylpropanoid and naphthoquinone in brittle stars has been proved which may have an important role in anticancer therapy [6]. Hence, this study aimed to prepare extracts of two brittle star namely *Ophiocoma erinaceus a*nd *Ophiomastrix annulosa* collected from Andaman island and evaluate the anti-cancer inhibitory effect of *Ophiocoma erinaceus a*nd *Ophiomastrix annulosa* against human cancer cell line, and compounds of its species were identified by mass spectrometry.

MATERIALS AND METHODS:

Sample Collection: Brittle stars (*Ophiocoma erinaceus* and *Ophiomastrix annulosa*) were gathered in Andaman Island, from the shallow up to deeper parts of the sea. Each sample was washed with water to remove dirt and sand. Samples were individually packed in polypropylene bags.

Extraction: Air-dried samples were cut into small pieces and soaked in 95% ethanol (1 g: 4 mL) for one week. The crude extract was centrifuged, and the centrifuged was concentrated under reduced pressure at 40 °C using rotary evaporator (Buchi R-124).

In-vitro Anticancer Activity:

Cell Lines and Culture Conditions for the Study Anticancer Property: Cell lines were obtained from the National center for cell sciences Pune (NCCS). The cells were maintained in Minimal Essential Media supplemented with 10% FBS, penicillin (100 U/ml), and streptomycin (100 µg/ml) in a humidified atmosphere of 50 µg/ml CO_2 at 37 °C.

Reagents: MEM, Fetal bovine serum (FBS), Trypsin, methyl thiazolyl diphenyl- tetrazolium bromide (MTT), Dimethyl sulfoxide (DMSO) were purchased from Hi-media & Sigma Aldrich Mumbai.

***In-vitro* Assay for Cytotoxicity Activity (MTT Assay):** MTT assay was performed to determine the cytotoxic property of extract of BSF 1 and BSF 2 samples against HELA, MCF-7, and VERO cell line [5]. Stock solutions of BSF 1 and BSF 2 samples were prepared in sterile distilled water and diluted to the required concentrations (100, 50, 25, 12.5, 6.25, 3.12, 1.56 µg/ml) using the cell culture medium. Cells (1×10^5/well) were plated in 0.2 ml of medium/well in 96-well plates. Incubate at 5% CO_2 incubator for 72 h. Then, add various concentrations of the samples in 0.1% DMSO for 24 h at 5% CO_2 incubator. After removal of the sample solution and 20µl/well (5mg/ml) of 0.5% 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-tetrazolium bromide (MTT) in phosphate- buffered saline solution was added. After 4 h incubation, 1ml of DMSO was added. Viable cells were determined by the absorbance at 540 nm. Measurements were performed, and the concentration required for a 50% inhibition of viability (IC_{50}) was determined graphically. The effect of the samples on the proliferation of HELA, MCF-7 and VERO cell was expressed as the % cell viability, using the following formula:

Calculation:

% Cell viability = A540 of treated cells / A540 of control cells × 100%

GC MS Analysis: The compounds were identified through GC/MS analysis using a GC 7890A system equipped with a quadrupole MS 5975C detector and an HP-35 column (30 m × 0.25 mm i.d., 0.25 µm film thickness) (Agilent Technologies, Waldbronn, Germany). The injection volume and port temperatures were 2 µL and 250 °C, respectively. The temperature of the column was started at 100 °C for 2 min, raised to 300 °C at 20°C/min and held for 6 min. Helium was used as the carrier gas, delivered at a linear flow rate of 1 mL/min. All of the spectra were scanned within the range of 33-600 m/z. The structures of the metabolites were deduced by comparing their

spectroscopic data with those reported in the library.

RESULT: The cytotoxic effects of the brittle star extracts of macrophages were evaluated using the MTT assay. The plates were observed under an inverted microscope to detect morphological changes. The result showed that HELA cells proliferation was significantly inhibited by BFS 1 and BFS 2 with an IC_{50} value of 6.25 µg/ml and 12.5 µg/ml of the concentration compare with normal cell inhibition. Thus, the active compounds were found to be potently cytotoxic agent against HeLa cell lines these results indicate that the sensitivity of human cancer cell line for cytotoxic drugs is higher than that of Vero cell line for the same cytotoxic agent's **Table 1** and **2**.

Fig. 1 and **Fig. 2** showed that plates were observed under an inverted microscope to detect morphological changes caused by extracts from two different species.

TABLE 1: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF HELA CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOCOMA ERINACEUS*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.00	0.0
2	50	1:1	0.02	2.2 ± 0.4
3	25	1:2	0.06	6.8 ± 1.4
4	12.5	1:4	0.11	12.6 ± 1.3
5	6.25	1:8	0.55	57.4 ± 1.41*
6	3.12	1:16	0.61	62.1 ± 1.54
7	Control	-	0.87	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

TABLE 2: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF HELA CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOMASTRIX ANNULOSA*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.00	0.0
2	50	1:1	0.02	3.2 ± 0.53
3	25	1:2	0.06	18.61 ± 2.61
4	12.5	1:4	0.16	50.13 ± 2.3*
5	6.25	1:8	0.49	61.6 ± 3.91
6	3.12	1:16	0.65	68.1 ± 2.51
7	Control	-	0.85	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

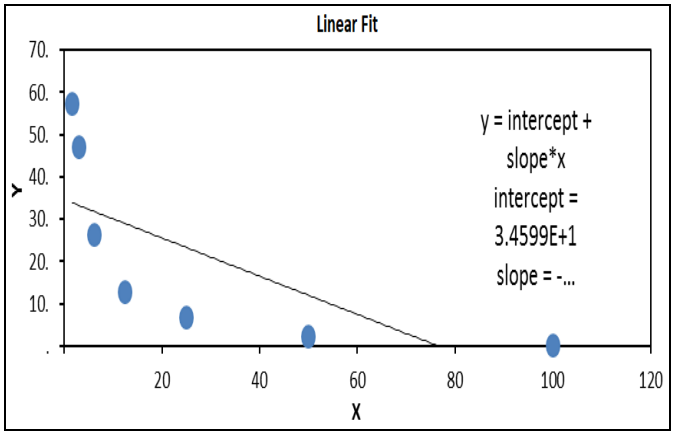

FIG. 1: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON HELA CELL LINE AT VARIOUS CONCENTRATIONS

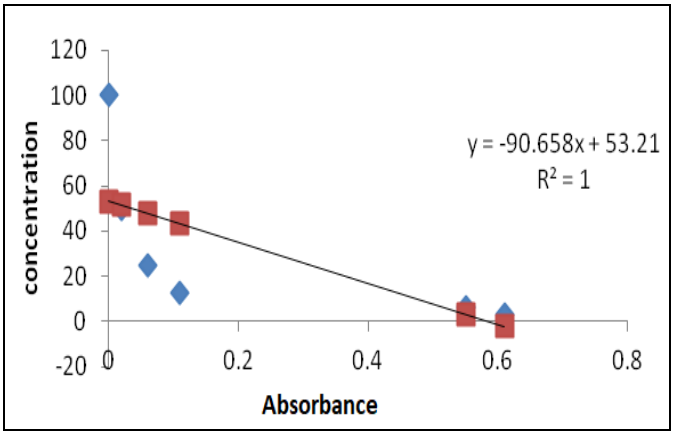

FIG. 2: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON HELA CELL LINE AT VARIOUS CONCENTRATIONS

The results given in **Table 3** and **Table 4** showed that MCF-7 cells proliferation was significantly inhibited by BSF 1 and 2 extracts with an IC_{50} value of 6.25 µg/ml of the lower concentration with higher inhibition effect of MCF 7 Cell and compare with normal control **Fig. 3** and **Fig. 4**. Thus, the bioactive compounds were found to be potently cytotoxic agent against MCF7 cell lines.

TABLE 3: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF MCF-7 CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOCOMA ERINACEUS*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.00	0.0
2	50	1:1	0.05	6.2 ± 0.53
3	25	1:2	0.23	10.61 ± 2.61
4	12.5	1:4	0.41	32.01 ± 3.81
5	6.25	1:8	0.52	51.16 ± 4.61*
6	3.12	1:16	0.64	68.4 ± 1.76
7	Control	-	0.84	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

TABLE 4: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF MCF-7 CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOMASTRIX ANNULOSA*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.00	0.0
2	50	1:1	0.11	8.2 ± 0.17
3	25	1:2	0.23	12.1 ± 1.40
4	12.5	1:4	0.38	38.6 ± 2,17
5	6.25	1:8	0.50	50.03 ± 3.27*
6	3.12	1:16	0.66	67.6 ± 4.91
7	Control	-	0.91	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

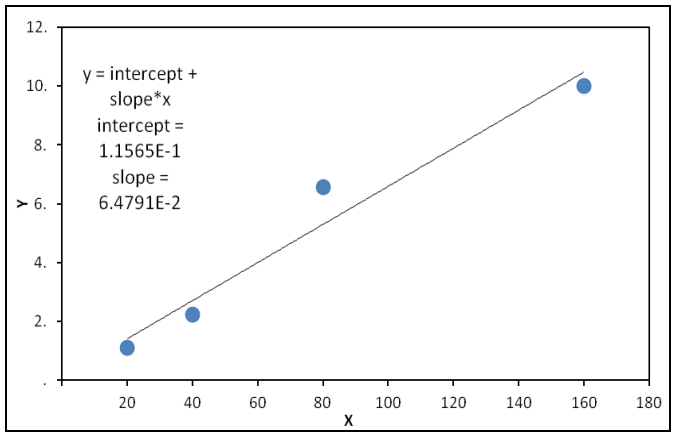

FIG. 3: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON MCF-7 CELL LINE AT VARIOUS CONCENTRATIONS

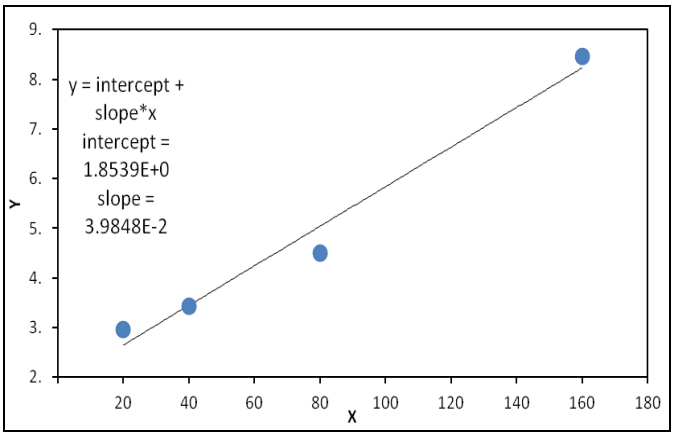

FIG. 4: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON MCF-7 CELL LINE AT VARIOUS CONCENTRATIONS

Table 5 and **6** showed cytotoxic results indicate that the sensitivity of human cancer cell line for cytotoxic drugs is higher than that of Vero cell line for the same cytotoxic agents. The analysis showed that the exposure of VERO cells to BSF1 and BSF 2 the various concentrations for 72 h reduced the cell viability in a concentration-dependent manner. However, the cell viability at the higher concentration of 12.5 µg/ml was not significant. As the concentration increases the cell viability decreases significantly.

TABLE 5: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF VERO (NORMAL CELL-MONKEY KIDNEY) CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOCOMA ERINACEUS*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.13	9.60 ± 1.0
2	50	1:1	0.22	20.72 ± 1.51
3	25	1:2	0.32	37.6 ± 2.2
4	12.5	1:4	0.50	49.92 ± 2.61*
5	6.25	1:8	0.55	58.2 ± 2.81
6	3.12	1:16	0.71	66.9 ± 3.51
7	Control	-	1.91	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

TABLE 6: *IN-VITRO* GROWTH INHIBITORY ACTIVITY (IC_{50} µg/ml) OF VERO (NORMAL CELL-MONKEY KIDNEY) CELL LINES AFTER TREATMENT WITH CONCENTRATIONS OF EXTRACT OF *OPHIOMASTRIX ANNULOSA*

S. no.	Concentration µg/ml	Dilution	Absorbance 540 nm	IC_{50} (µg/ml) cell Viability
1	100	Neat	0.21	10.6 ± 1.5
2	50	1:1	0.28	20.3 ± 1.21
3	25	1:2	0.35	33.9 ± 2.8
4	12.5	1:4	0.56	51.5 ± 2.12*
5	6.25	1:8	0.63	68.7 ± 3.1
6	3.12	1:16	0.71	71.9 ± 3.81
7	Control	-	1.03	100

*Data presented are the mean ± SEM of three independent experiments p<0.05

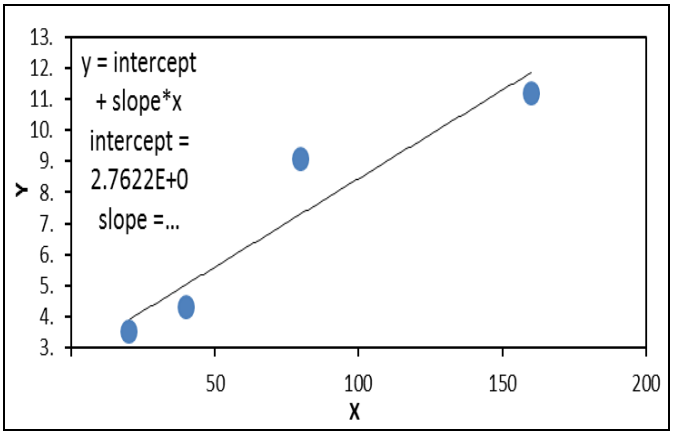

FIG. 5: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON VERO CELL LINE AT VARIOUS CONCENTRATIONS

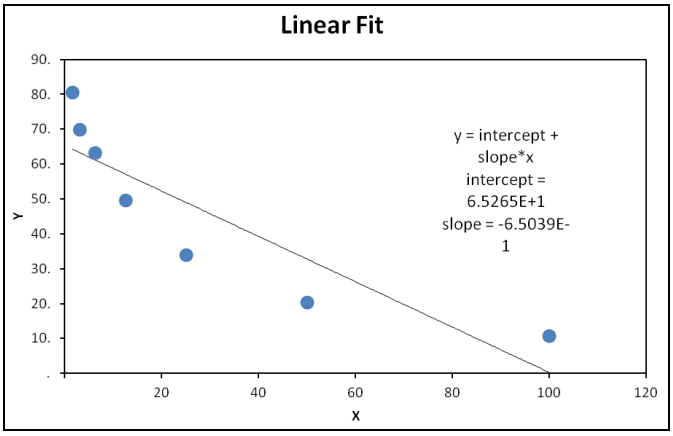

FIG. 6: IC_{50} VALUES OF CELL VIABILITY PERCENTAGE ON VERO CELL LINE AT VARIOUS CONCENTRATIONS

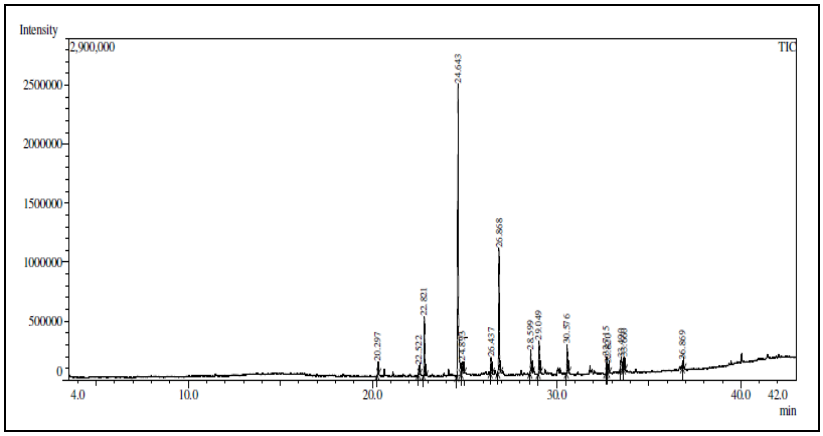

FIG. 7: GC MS ANALYSIS OF *OPHIOCOMA ERINACEUS*

TABLE 7: COMPOUND IDENTIFIED FROM *OPHIOCOMA ERINACEUS*

Peak	R. Time	Area	Area%	Name of compounds
1	20.29	252075	1.53	1-Tetradecanol
2	22.522	198946	1.21	n-Pentadecanol
3	22.821	1283414	7.77	Tetradecanoic acid, ethyl ester
4	24.643	7565780	45.83	n-Nonadecanol-1
5	24.893	474608	2.87	Ethyl 13-methyl-tetradecanoate
6	26.437	380456	2.30	Ethyl 9-hexadecenoate
7	26.868	2811325	17.03	Hexadecanoic acid, ethyl ester

The bioactive compounds present in methanol extracts obtained from *O. erinaceus* are shown in **Table 7** and **Fig. 7**. Their identification and characterization were based on their elution order in the column. The elution time, molecular formula and the amount of these bioactive compounds were also presented. Based on abundance, the top three major compounds present in the *O. erinaceus* were

n-Nonadecanol-1 (24.643), Ethyl 9-hexadecenoate (26.437) and Hexadecanoic Acid, Ethyl Ester (26.868). The GCMS chromatogram of the *O. annulosa* extract presented in **Table 8** and **Fig. 8** show major compounds like ascorbic acid 2,6-dihexadecanoate (26.213), ethyl 9-hexadecenoate (26.437), hexadecanoic acid, ethyl ester (26.870), E, E, Z-1,3,12-Nonadecatriene-5,14-diol (30.074) and Octadecanoic acid, ethyl ester (30.575) show the retention time in the column and the detected peaks which correspond to the bioactive compounds present in the extract.

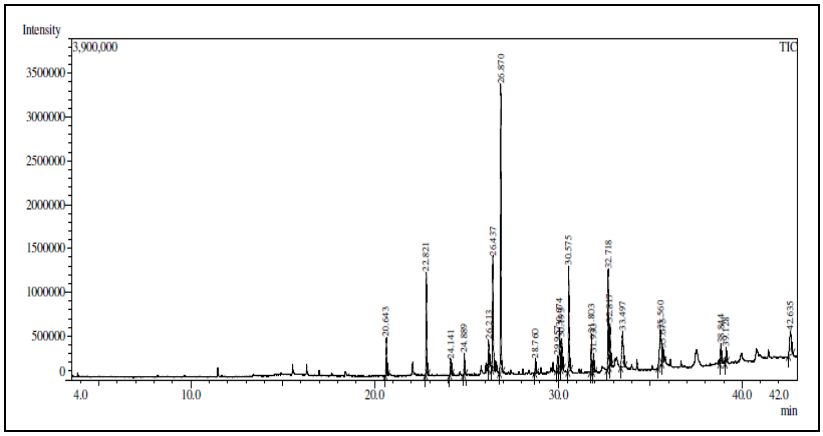

FIG. 8: GC MS ANALYSIS OF *OPHIOCOMA ANNULOSA*

TABLE 8: COMPOUND IDENTIFIED FROM *OPHIOCOMA ANNULOSA*

Peak	R. Time	Area	Area%	Name of compounds
1	20.643	1075733	2.64	1-Tetradecanol
3	22.821	2968768	7.29	Tetradecanoic Acid, Ethyl Ester
4	24.141	566808	1.39	Ethyl 13-Methyl-Tetradecanoate
5	26.213	944019	9.50	Ethyl 9-Hexadecenoate
6	26.870	8712326	21.38	Hexadecanoic Acid
7	26.868	2811325	17.03	Hexadecanoic Acid, Ethyl Ester
8	28.760	414893	1.02	Ethyl 15-Methyl-Hexadecanoate
9	29.957	442664	1.09	N-Propyl 9,12-Octadecadienoate
10	30.074	1720293	4.22	E,E,Z-1,3,12-Nonadecatriene-5,14-Diol
11	30.575	3309387	8.12	Octadecanoic Acid, Ethyl Ester
1	20.643	1075733	2.64	1-Tetradecanol

DISCUSSION: The Ocean is considered to be a source of potential drugs and some of these bioactive compounds or secondary metabolites have biomedical potential. Oceans comprise 70% of the earth area, and the marine ecosystems represent 95% of the biosphere. 33-34% of animal phyla live in a marine environment. Marine life constitutes almost 80% of the world biota. The diversity of the species is extraordinary, and in the tropical zones, there are almost 1000 different species per square meter [7].

It was previously reported that polyhydroxy-steroidal glycosides from the starfish *Anthenea chinensis* exhibited significant activity against the promotion of tubulin polymerization *in-vitro*, inhibiting the proliferation of human leukemia K-562, hepatoma BEL-7402, and spongioblastoma U87MG cell lines. Recently, we demonstrated that some anthenosides from *Anthenea sibogae* slightly inhibited the proliferation and decreased the colony size of human breast cancer T-47D cells [8]. More recently, compounds exerting antimicrobial, antiviral, and antitumor activity, mainly from sea cucumbers and starfish, have been isolated, leading to a growing interest for the discovery of immunostimulatory activities useful for human health [9].

The anti-proliferative activity of marine sponge organic extracts (hexane, ethyl acetate, and n-butanol) in human cancer cell lines demonstrated the high cytotoxicity of extracts in HL-60 cells. Also, their findings showed that the ethyl acetate extract of *Jaspis sp.* with a significant increase of cells in the sub-G1 phase, induced apoptosis in KB cells. In contrast, our results exhibited that methanol extract of brittle star exerted a pro-

apoptotic effect on HeLa cells *via* translocation of phosphatidylserine to extrinsic leaflet, sub-G1 increment and caspase activation [10].

In the present study, *O. erinaceus* and *O. annulosa* were extracted from Andaman brittle star, and its anticancer effect was evaluated. The result showed that MCF-7 cells proliferation was significantly inhibited by *O. erinaceus* and *O. annulosa* extracts with an IC_{50} value of 6.25µg/ml of the lower concentration with higher inhibition effect of MCF 7 Cell and compare with normal control. Moreover, this is the study related to extracted from brittle stars which postulated therapeutic potency against breast cancer (MCF-7). These findings are in agreement with other studies revealing the potential in cancer therapy. A few studies devoted to the proapoptotic activity of steroidal glycosides from starfishes have been reported anthenosides from *Anthenea sibogae* slightly inhibited the proliferation and decreased the colony size of human breast cancer T-47D cells [11].

Many researchers have reported that starfishes contain steroids, including sterols, polyhydroxy-steroids, and saponins remarkably prevented cancer invasion and migration associated with down-regulation of matrix metalloproteinase expression. Therefore, saponins could be suggested as an anti-invasive candidate against cancer cells [12-13]. Two polyhydroxysteroids of *A. pectinifera* starfish were also cytotoxic to the HL-60 cells, with IC_{50} values of 80.3 and 40.5 µM. Moreover, we found derived fatty acid like nonadecanol-1 (24.643), ethyl 9-hexadecenoate (26.437) and hexadecanoic acid, ethyl ester from *O. erinaceus* and *O. annulosa.*

In the present study, the starfish extract exhibited strong cytotoxicity against cancer cells. Overall, these findings confirmed the utility of clinical investigations of the efficacy of *O. erinaceus* and *O. annulosa* extracts in preventing in cancer chemotherapy. These data can be considered an important basis for proceeding to patient studies or to the formulation of drug products. However, further *in-vivo* studies using animal models and human patients are necessary to develop and exploit this nascent promise.

CONCLUSION: The anticancer effects of starfish extracts were evaluated to identify the beneficial effects of this species under conditions related to cancer prevention. The brittle star extracts exhibited strong anticancer activities against human cancer cells. These biological activities of the brittle star extracts could be partially explained by the presence of nonadecanol-1 ethyl 9-hexadecenoate and hexadecanoic acid, ethyl ester like compounds. Based on the biofunctional activities of the brittle star extracts, *O. erinaceus* and *O. annulosa* could be utilized as a functional ingredient in food or pharmaceutical products to promote human health.

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CONFLICT OF INTEREST: The authors declare nil conflict of interest.

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