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Marine Ally in Cancer Prevention: A Systematic Review on Antitumor Potential and Therapeutic Insights of Holothuroidea (Sea Cucumber)

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Abstract

Background: Sea cucumbers (Holothuroidea) are rich in bioactive metabolites, most notably triterpenoid glycosides (saponins), sulphated polysaccharides (fucoidans), and peptides with mounting evidence of anticancer activity.

Methods: Adhering to PRISMA 2020, we identified 40 records, assessed 13 full-texts for eligibility, and included eight studies in the synthesis. Risk of bias for animal/in

vivo evidence was evaluated using SYRCLE's Risk of Bias (RoB) tool, and reporting quality was summarized.

Results: Prominent effects across tumour models comprise suppression of migration/invasion, anti-angiogenesis, cell-cycle arrest (G0/G1 and G2/M), and intrinsic/extrinsic apoptosis induction. EGFR/PI3K/AKT, MAPK (including p38), and CDK-regulated checkpoints are often the targets of mechanistic modulation. Lead candidates such as Frondoside A and fucoidan fractions (e.g., Cf-Fuc) demonstrate consistent potency and early in-vivo tumor-growth inhibition with generally low observed toxicity; preliminary synergy with chemo-/radiotherapy is reported. However, heterogeneity of extracts, variable dosing/reporting, limited animal replication, and scarce pharmacokinetic/bioavailability data constrain inference.

Conclusions: Sea-cucumber-derived compounds exhibit multi-target anticancer potential and are promising as adjuncts or scaffolds for drug discovery. Translation will require standardized extract characterization, purified actives, rigorous dose–response and GLP toxicity studies, PK/PD profiling, and well-powered, registered clinical trials to establish efficacy, safety, and dosing and Sustainable sourcing, aquaculture ethics, and quality control are essential for scalable development.

Keywords: Sea cucumber; Holothuroidea; Frondoside A; fucoidan; triterpenoid glycosides; apoptosis.

Introduction

Cancer is an abnormality of body tissue cells that continues to grow and develop uncontrollably [1] and is the most infamous illness resulting in the highest number of fatalities in a year (an average of 10 million). According to the studies done by the World Health Organisation, lung cancer remains the number one cancer leading to the greatest number of deaths (1.8 million deaths), followed by colon and rectal cancer with 935,000 deaths, liver cancer with 830,000 deaths, stomach cancer and breast cancer with 769,000 and 685,000 deaths respectively remain the top five cancers that cause the greatest number of deaths per year. Despite the significant improvements in cancer treatments like chemotherapy, radiotherapy, and anticancer drug administration, other adverse effects remain part and parcel of the treatment process [2].

Aside from the general adverse reactions, other memory and cognitive disorders, like Alzheimer's and Parkinson's diseases, are also exhibiting an increase in mortality[3]. Coming up with alternative methods to kill or incapacitate the cancer cells has been made the paramount priority since the contemporary treatment procedures have umpteen undesirable effects on the people undergoing the latter treatments[4]. As of now, roughly 60% of the licensed cancer therapeutic drugs come from the environment. Natural substances found in plants and animals from the marine ecosystem possess anti-mutagenic and anti-carcinogenic properties. They hinder one or more phases of carcinogenesis by arresting or retarding the development of malignancy. Aquatic plants and animals have generated 14,000 pharmacologically active compounds, emphasizing this habitat's broad diversity spectrum. Hence, the incidence of discovering new lead molecules for the manufacture of chemotherapeutic drugs and nutraceuticals for cancer prophylaxis can increase in the marine environment. An extensive study performed by the U.S. National Cancer Institute for a period of 15 years revealed that antitumor chemicals were detected in 4% of all the marine species (largely animals) [5].

The fact that scientists are still facing challenges in developing new anticancer drugs that are efficient in treating a range of cancers is noteworthy. Novel anticancer from various sources, including sea

cucumbers, have been investigated since different kinds of medications with diverse anticancer processes may be required for therapies depending on the unique features of cancer cells [6]. As they are scientifically treated, Holothuroidea are sea creatures that survive on the ocean floor. It is well known that these animals have a vital role in maintaining the biological equilibrium of water bodies. Precisely, they are deposit feeders[7]. Cucumaria frondosa is a Cucumaria species, Cucumariidae family of the Dendrochirotida order of the Holothuroidea class. It is the most prevalent variety of sea cucumbers in and the biggest in New England, it also is broadly distributed in the oceans of the North Atlantic region and and Barents Sea in Russia. To acquire numerous ecologically beneficial substances, C. frondosa is collected, dehydrated, and treated using segmented chromatography. Many of which have been investigated for different possible pharmacological functions including anti-inflammatory, anti-bacterial, and immune-modulatory functions as well as the anticancer effects in different types of cancer. C. frondosa has been used as a dietary supplement and a traditional remedy in old Chinese medicine. There have been 14 biologically active glycosides extracted from it [8]. Its glycosides are important secondary metabolites and the building blocks of its chemical defense; their properties include antitumor, cytotoxin, viral, fungal resistance, good haemolysis, and immunoregulation [20]. Frondoside A is a triterpenoid glycoside extracted from the skin of *C.* frondosa. Certain types of sea cucumbers, notably Frondoside A2-2, Frondoside A4-2, and Frondoside A7-1 yield supplementary varieties of bioactive glycosides [8].

The previous research regarding the anticancer mechanism of the sea cucumber substances mainly focused on cytotoxic activity, induction of apoptosis, cell cycle arrest, inhibition of tumor growth, antimetastatic and anti-angiogenic properties, and inhibition of drug resistance. Previous reports of sea cucumber mainly focused on non-protein bioactive compounds and their various bioactivities. Recently, bioactive peptides have been considered one of the important potential therapeutic substrates in sea cucumber [10].

Most sea cucumbers have economic value as a food source, with anodising biological activities. Demand for sea cucumbers in the global food and pharmaceutical use market is increasing significantly. It has been recognized as a traditional treatment in Chinese and Malaysian literature for hypertension, asthma, rheumatism, wounds and burns, and impotence. The benefits of sea cucumbers as medicinal compounds can be attributed to several bioactive compounds, most notably triterpene glycosides[1].

Recent studies indicate that low concentrations of Frondoside A inhibit the growth and induce apoptosis of human pancreatic, leukaemia, and breast cancer cells via caspase activation [11]. A study found that Apigenin derivatives inhibited cervical cancer caused by human papillomaviruses and DNA polymerase theta receptors. This underscores the potential for targeted molecular interventions to reduce the progression of cervical cancer [19]. It is reported that the pancreatic tumor cell growth was suppressed by Frondanol-A5, a commercial product derived from the epithelial tissue of the edible sea cucumber Cucumaria frondosa[13]. Because of its beneficial therapeutic impact, sea cucumbers, which are members of the Holothuroidea class, are widely used in Asian countries as traditional tonic foods and medicinal materials. The sea cucumber, Acaudina molpadioides, is produced in large quantities and is found in sandy coastal areas of China and Southeast Asia [14]. The majority of studies on sea cucumbers in cancer prevention are still in the in-vitro or in-silico stages, with very few moving on

to animal or clinical research, which limits the body of literature on the subject. Global scientific output is limited because research is geographically limited to areas where sea cucumbers are traditionally used. Cross-study comparison is challenging due to the lack of standardized extraction, purification, and characterization techniques. Due to inadequate methodological quality or a lack of cancer-specific outcomes, many studies were excluded from consideration. Together, these elements produced a limited number of studies that qualified for this systematic review. The aim of this study is to assess the carcinopreventive competence of the Holothuroidea (class of marine organisms, generally used as an umbrella term encompassing a wide range of species colloquially addressed as sea cucumber) in cancer prevention.

Materials and Methods

The practical value of sea cucumber in foiling cancer was the subject of this systematic review. The PRISMA guidelines are taken into consideration while formatting this systematic review, with an emphasis on the role of sea cucumber in cancer suppression. The literature review was carried out systematically, including the following steps: the research question, formulating a strategy for conducting a literature search, searching the literature and retrieving articles, data extraction, interpretation, and evaluation of evidence gathered from the literature.

Research question

The research question is, "How effective is sea cucumber in the prevention of cancer?"

Information sources

PubMed, Scopus, Web of Science, Wiley Online Library, Grey literature.

Search strategy

ScienceDirect, Google Scholar, and PubMed were used in an electronic search. MeSH terms have been coupled alongside additional keywords particularly "sea cucumber", "Cucumaria frondosa", "sea cucumber in cancer prevention", "sea cucumber AND cancer"

Eligibility criteria:

The study's inclusion criteria are randomized control trials between 2018 till date that scientifically explored the impact of sea cucumbers on cancer prevention, with full-length articles compiled in English. The exclusion criteria were studies that did not involve animal studies, focused on non-cancer-related pathways, or were published in languages other than English, if language limitations applied.

Study selection

Preliminary review of titles & abstracts are conducted according to defined inclusion & exclusion criteria. Full-text review of selected articles was performed meticulously. Data extractions from eligible studies were done using a standardized form. Methodology: Studies that fulfilled eligibility parameters were listed. Data included citation (author/year), place of study, number and type of samples collected, intervention is provided, techniques and measurement methods, and results and inferences drawn from the study. Quality assessment was done using SYRCLE's Risk of Bias (RoB) tool [16].

Results

This research resulted in 40 articles, of which 13 were full-text articles having accessibility and were eligible for review. Ultimately, 8 articles were chosen for inclusion in this systematic review [Figure 1]. Table 1 displays the features of the intervention. Table 2 shows the intervention used in the study, including the outcome. Table 3 illustrates the risk of bias in all the included studies, utilizing SYRCLE's Risk of Bias (RoB) tool. This bias assessment uses the SYRCLE Risk of Bias framework to judge methodological quality across eight sea-cucumber anticancer studies, rating each domain with

"+" (low risk), "?" (unclear), or "–" (high risk). It focuses on random sequence generation, allocation concealment, random housing, blinding (personnel and outcome assessors), random outcome assessment, completeness of outcome data, selective reporting, baseline characteristics, and whether a primary outcome was specified. Overall, Ru et al., 2023 and Wargasetia et al., 2021 show comparatively low bias, reflecting stronger reporting and consistency, while Ding et al., 2024 and Arma et al., 2022 carry unclear/high risk in several domains due to missing details on randomization and blinding. An overview of the steps involved in the included studies according to PRISMA guidelines is depicted in the flowchart below.

Figure 1:

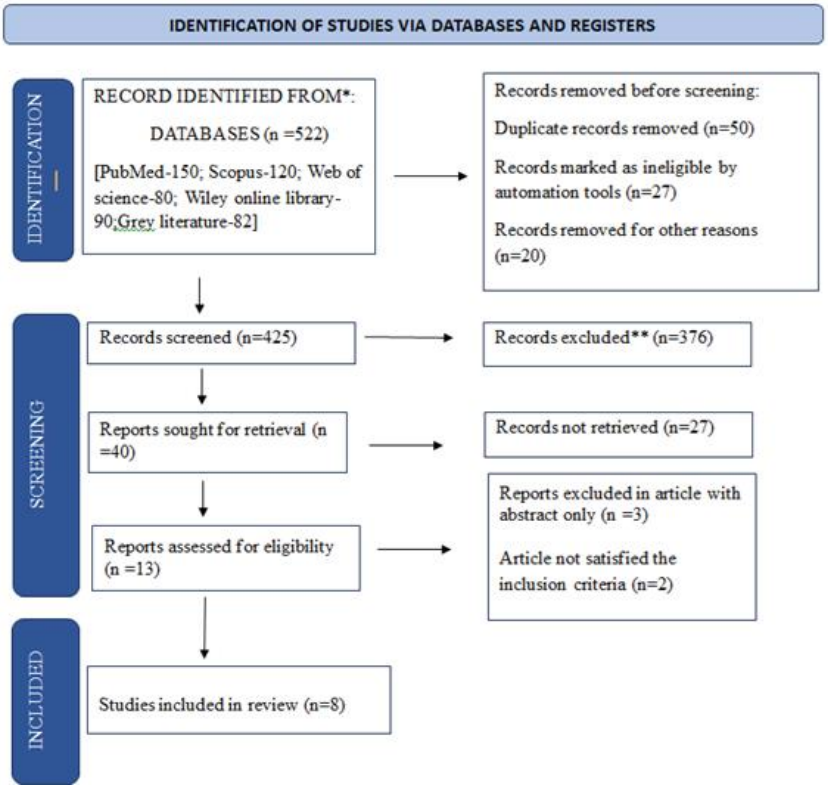

Table 1: Characteristics of the intervention of the studies included in the systematic review

Sn.	Author	Type of study	Assay	Type of sea cucumber	Type of cancer	Intervention
1	Kanta Pranweerapaiboon et al. 2021 [17]	In vitro experimental study on PC3 prostate cancer cells	MTT assay, Colony Formation, ROS assay, Flow Cytometry Hoechst 33342 staining, Annexin V-FITC/PI, Transwell assay,	Holothuria Scabra	Prostate cancer (PC3 cell line)	Control: Untreated U2OS cells showed normal adhesion and migration. Experimental: Cf-Fuc–treated cells (50–100 µg/ml) had reduced adhesion and migration.

			Western blot			Negative control: Cells without Cf-Fuc confirmed effects were treatment-specific.
2	Wargasetia TL et al. 2021 [18]	In silico (bioinformatics, molecular docking & dynamics simulation)	AutoDock Vina docking, Molecular Dynamics, Binding energy analysis, RMSD/RMSF	Cucumaria frondosa	Breast cancer (targets: EGFR, PI3K, AKT1, CDK4)	Control: Known inhibitors (Gefitinib, Wortmannin, AZD5363, Abemaciclib) of EGFR, PI3K, AKT1, CDK4. Experimental: Cucumaria frondosa peptides (WPPNYQW, YDWRF) tested for inhibition. Negative Control: Unbound EGFR, PI3K, AKT1, CDK4 without treatment.
3	Irena Ujianti et al. 2024 [19]	In vitro + in silico	LC-MS, MTT assay, SAR analysis, ADMET, STRING network, KEGG pathway	Stichopus herrmanni	Cervical cancer	Control Group: HeLa cells treated with vehicle. Experimental Group: HeLa cells treated with Stichopus herrmanni extract (ganoderic acid, 6-isoinosine). Negative Control: Untreated HeLa cells.
4	Chenhuan Ding et al. 2024 [20]	In vitro and in silico	MTT assay, Hoechst/PI staining, migration (scratch), invasion (Transwell), microarray, GO	Thelenota ananas	Ovarian cancer	Control Group: SKOV3 ovarian cancer cells treated with PBS. Experimental Group: SKOV3 cells treated with sea cucumber glycosides (47.66

			enrichment, STRING network			µg/ml). Negative Control: Untreated SKOV3 cells.
5	Utmi Arma et al. 2021 [21]	In vitro study	MTT cytotoxicity assay	Bohadschia marmorata	Tongue squamous cell carcinoma (SP-C1)	Control group: ethanol extract, hexane fraction, and butanol fraction Experimental group: ethyl acetate fraction showing strong cytotoxicity, Negative control: untreated SP-C1 tongue cancer cells.
6	Minglei Zhang et al. 2020 [22]	In vitro study	MTT assay, Cell adhesion assay, Transwell migration assay, U2OS migration tracking, F-actin staining, Rac1 activation, Western blotting	Cucumaria frondosa	Osteosarcoma (U2OS)	Control: Untreated U2OS cells showed normal adhesion and migration. Experimental group: Cf-Fuc–treated cells (50–100 µg/ml) had reduced adhesion and migration. Negative control: Cells without Cf-Fuc confirmed effects were treatment-specific.
7	Claudio Luparello et al. 2022 [23]	In vitro	MTT assay, wound healing, flow cytometry (apoptosis, ROS, MMP, AVO), proteomic analysis	Holothuria tubulosa	Hepatocellular carcinoma (HepG2 cells)	Control Group: HepG2 liver cancer cells treated with vehicle solution. Experimental Group: HepG2 cells treated with Holothuria tubulosa coelomic fluid extract. Negative Control: Untreated HepG2

						cells.
8	Ru et al. 2023 [24]	In vitro & In vivo	CCK-8 (viability), Flow cytometry, Wound healing (migration), qPCR, Xenograft model in nude mice	Cucumaria frondosa	Human Bladder cancer (UM-UC-3 cell line)	Control: Known inhibitors of EGFR, PI3K, AKT1, CDK4. Experimental: Cucumaria frondosa peptides (WPPNYQW, YDWRF). Negative Control: Untreated EGFR, PI3K, AKT1, CDK4.

Table 2: Characteristics of the primary outcome and the findings from the studies included in the systematic review

Sn.	Author	Type of cancer	Outcome	Result
1	Kanta Pranweerapaiboon et al. 2021 [17]	Prostate cancer (PC3 cell line)	Assessed cytotoxicity, ROS induction, cell cycle arrest, apoptosis, migration/invasion suppression	Methanolic extract from sea cucumber (BWMT) inhibited cell viability (IC50 ~28.47 µg/ml), increased ROS, induced apoptosis via JNK/p38, suppressed migration/invasion by downregulating MMP-2/-9 via ERK inhibition.
2	Wargasetia TL et al. 2021 [18]	Breast cancer (targets: EGFR, PI3K, AKT1, CDK4)	Assessed binding affinity, protein-ligand stability, interaction types	Sea cucumber peptide WPPNYQW showed stable and strong binding to all four proteins, outperforming known inhibitors. YDWRF also performed well, especially with PI3K and AKT1. WPPNYQW considered a more promising anti-breast cancer peptide.
3	Irena Ujianti et al. 2024 [19]	Cervical cancer	Modulated PI3K/AKT and p53 pathways, identified active compounds (ganoderic acid, isoinosine), low cytotoxicity to HeLa cells	Sea cucumber extract showed moderate inhibition of cervical cancer cell proliferation and bioinformatics support for anticancer potential via multiple pathways
4	Chenhuan Ding et al. 2024 [20]	Ovarian cancer	Induced apoptosis, inhibited proliferation, migration, and invasion; involved p38-MAPK pathway	Sea cucumber glycosides significantly induced apoptosis and reduced proliferation, invasion, and migration of SKOV3 cells via p38-MAPK cascade activation
5	Utmi Arma et al. 2022 [21]	Tongue squamous cell	Strong cytotoxic activity; IC_{50} = 18.833 µg/ml; decreased SP-C1 cell	Ethyl acetate fraction taken from sea cucumber exhibited potent anticancer

		carcinoma (SP-C1)	viability	activity against SP-C1 cells; potential for development as anticancer drug
6	Minglei Zhang et al. 2020 [22]	Osteosarcoma (U2OS)	Reduced adhesion and migration; inhibited FAK/paxillin phosphorylation and Rac1/PAK1/LIMK1/cofilin signaling	Cf-Fuc from sea cucumber significantly inhibited osteosarcoma cell adhesion and migration by disrupting cytoskeletal remodeling and suppressing key metastatic signaling pathways
7	Claudio Luparello et al. 2022 [23]	Hepatocellular carcinoma (HepG2 cells)	Reduced viability, G2/M cell cycle arrest, apoptosis induction, mitochondrial dysfunction, oxidative stress, autophagy inhibition, migration suppression	Sea cucumber's coelomic fluid extracts induced significant anti-cancer effects including decreased cell viability (IC50 = ~20.75 µg/mL), apoptosis, mitochondrial damage, and inhibition of cell migration
8	Ru et al. 2023 [24]	Human Bladder cancer (UM-UC-3 cell line)	↓ Cell viability, ↓ Migration, ↑ Apoptosis, Altered cell cycle, Inhibited tumor growth in vivo	Frondoside A from sea cucumber showed potent anti-cancer effects alone and synergistically with CpG-ODN; superior to Epirubicin in several assays; minimal side effects in vivo

Table 3: Risk of bias in all the included studies, utilizing SYRCLE's Risk of Bias (RoB) tool

Bias Domain	Ding et al.,2024	Wargasetia et al., 2021	Arma et al., 2022	Luparello etal.,2022	Ding et al.,2024	Pranweerapaiboon et al., 2021	Ru et al., 2023	Zhang et al., 2020
Random sequence generation	?	+	?	?	?	?	+	?
Baseline characteristics described	?	+	?	+	+	+	+	+
Allocation concealment	-	+	-	?	-	-	?	-
Random housing	-	+	-	?	-	-	?	?
Blinding of participants and personnel	-	+	-	?	-	-	?	-
Random outcome assessment	?	+	-	+	+	+	+	+
Blinding of outcome assessment	-	+	-	+	-	-	?	-

Incomplete outcome data	+	+	+	+	+	+	+	+
Selective outcome reporting	?	+	?	+	+	+	+	+
Primary outcome specified	+	+	+	+	+	+	+	+

Note:

Low risk of bias	+
Unclear risk of bias	?
High risk of bias	-

Discussion

This systematic review paper emphasizes the importance and wide range of scientific applications of sea cucumber, which were experimented in treating different types of cancers using the various species of sea cucumber, and were successful. There are manifold applications of assorted species of sea cucumber. Some of the anticancer traits of the above discussed sea cucumber species are as follows.

Holothuria scabra is one of the most rigorously scrutinized species of Sea cucumber. It is generally prevalent and traditionally bountiful in many shallow soft-bottom habitats all over the Indo-pacific region [25]. With an IC50 value of 152.98 µg/mL, the methanol extract of H. scabra demonstrated cytotoxic action through minimizing the proliferation of T47D cancer cells in a dose-associated manner; 99% of cancer cells underwent apoptosis as a result of the extract [26]. Cucumaria frondosa is widely disseminated throughout the North Pacific and North Atlantic areas [27]. One such salient compound extracted from Cucumaria frondosa is Frondoside A. Frondoside A is known to possess efficacy in stifling all solid malignancies, lymphoma, leukaemia cell types evaluated as of now by induction of growth hindrance, provoking apoptosis, obstructing distant metastasis and impeding vascular proliferation [28]. Stichopus hermanii is found to be present at the coastal regions of various Asian countries viz. Russia, Indonesia, Malaysia etc. The extract of Stichopus herrmanii exhibited bactericidal action against pathogenic bacteria like Escherichia coli, Pseudomonas sp., V.voinivica and Staphylococcus aureus to name a few [29]. Thelenota ananas is another species of the Holothuroidea class which is found in the surroundings of South China Sea namely Yongxing Island [30] and Woody Island of the Xisha Islands [31]. Triterpenoids, also known as steroids, are found in saponins and have a multitude of biological advantages, such as anticancer and hypolipidemic action, amelioration of non-alcoholic fatty liver, mitigation of lipid accumulation, antihyperuricemia, enhancement of bone marrow haematopoiesis, and antihypertension [31]. Natural resources are exceeding valuable to medicine and Stichoposide C(STC) is known to inhibit cell division by initiating apoptosis in leukemic and colorectal cancer cells by the formation of ceramide as demonstrated by prior research [31]. Yet another species of sea cucumber is Bohadschia marmorata which is collected largely from Red Sea coast of Hurghada. Its extract marmorata possesses shielding and remedial qualities in opposition to MTX-evoked hepatic and renal impairment, as measured utilizing biomarkers at the biochemical and histological levels [32]. Holothuria tubulosa is yet another species of Sea cucumber that is provided prominence in this article. It is found in the Mediterranean Sea [33] and

also Aegean Sea [34]. Analogous to the actions of the Sea cucumber species aforementioned, this species exhibits remarkable potent such as arresting cell division of the tumor cell under hypoxic and normoxic states [34].

This paper features eight research studies scientists conducted on curing different cancers. When experimented on the species Holothuria scabra, it is concluded that methanolic extract caused cell cycle arrest, suppression of migration of prostate cancer cells. Cucumaria frondosa upon research, showed that sea cucumber peptide WPPNYQW outperformed recognized inhibitors, showing stable and strong binding to all four proteins, which is also a more promising breast cancer peptide. Studies were conducted on Stichopus herrmanii and concluded that sea cucumber extract moderately inhibited cervical cancer cell proliferation. The species Thelenota ananas's glycosides significantly induced apoptosis and minimized proliferation, invasion, and migration of ovarian cancer cells. When the species Bohadschia marmorata was studied, it is deduced that the ethyl acetate fraction taken from sea cucumber exhibited effective anticancer activity against squamous cell carcinoma cells, which has potential for development as an anticancer drug. The sea cucumber Cucumaria frondosa was researched and the following results were provided stating that Cf-Fuc from sea cucumber significantly inhibited osteosarcoma cell adhesion and migration by disrupting cytoskeletal remodelling and suppressing key metastatic signalling pathways. Holothuria tubulosa's coelomic fluid extracts induced significant anticancer effects, including decreased cell viability, apoptosis, mitochondrial damage, and inhibited migration of hepatocellular carcinoma cells. Experiments on Cucumaria frondosa, concluded that Frondoside A from sea cucumber showed potent anticancer effects alone and synergistically with CpG-ODN against bladder cancer cells.

Kanta Pranweerapaiboon et al. [17] stated that the elevated mortality associated with prostate cancer is largely attributed to resistance to treatment and the spread of the disease. Holothuria scabra (BWMT)-derived triterpene glycosides have demonstrated promise as anticancer agents. This study shows that BWMT causes PC3 cells to produce reactive oxygen species (ROS), which prematurely ends the G0/G1 phase of the cell cycle. It also causes caspase-dependent apoptosis, which is marked by the downregulation of Bcl-2 and the upregulation of BAX and caspase-3. Additionally, it prevents metastasis by lowering MMP-2 and MMP-9 activity through p38/JNK pathway activation and ERK signalling pathway inhibition. In the battle against drug-resistant prostate cancer, BWMT is emphasized as a promising option.

Wargasetia et al. [18] declared that EGFR, PI3K, AKT1, and CDK4 are key proteins involved in the development of breast cancer by affecting pathways that regulate cell growth, survival, and metastasis. Targeting their ATP-binding sites can stop the growth of cancer cells, bring about apoptosis, and establish cell cycle arrest. This research illustrates that two sea cucumber- extracted peptides, WPPNYQW and YDWRF, display a strong affinity for these proteins' ATP-binding sites, outperforming current inhibitors in docking simulations. Inhibiting EGFR reduces cell invasion and levels of anti-apoptotic proteins, while inhibiting PI3K and AKT1 curtails proliferation and enhances pro-apoptotic activity; additionally, CDK4 inhibition stops the cell cycle in the G1 phase. Molecular dynamics simulations validated that stable interactions exist between peptides and proteins, most specifically with WPPNYQW. These findings suggest that both peptides can be useful potential multi-

target inhibitors for the treatment of breast cancer. Additional validation is required through other in vitro and in vivo studies.

Irena Ujianti et al. [19] reported that contemporary pharmacology is exploring the use of natural compounds as potential anticancer therapies. Extracts from the sea cucumber *Stichopus hermanii* show promise in treating cervical cancer, particularly against the HPV oncogenes E6 and E7. The E6 protein interferes with the p53 tumor suppressor, while the E7 protein promotes cancer growth through the PI3K/AKT/mTOR signalling pathway.LC-MS and in silico examinations have identified ganoderic acid and isoinosine as significant components. Ganoderic acid targets tyrosine kinase receptors that promote apoptosis, while isoinosine augments immune responses and may help in drug resistance. Both compounds interact with significant cancer-related proteins like TP53, EGFR, AKT, and CDK4. While less effective than doxorubicin, *S. hermanni* extract acts by alternate mechanisms and may act synergistically with standard therapies. This multi-target strategy could improve efficacy and decrease toxicity. Further studies and clinical trials must establish the therapeutic benefit, safety, and optimal use.

Chenhuan Ding et al.[20] added that Sea cucumber glycosides have great anticancer activity, particularly against ovarian cancer SKOV3 cells. This research is the first to show their potential to inhibit SKOV3 cell growth, migration, and invasion and their ability to induce apoptosis in a dose-dependent manner. Bioactive compounds like holothurin A, philinopsides, and frondoside A exhibited cytotoxic activity against different tumor cell lines. Gene set enrichment analysis indicates that sea cucumber glycosides trigger the p38-MAPK pathway, a key regulator of apoptosis, consistent with experimental results. Even multicellular SKOV3 spheroids, which are drug-resistant, responded well to the treatment. While individual active compounds remain to be determined, the effectiveness of the extract points to potential as a natural treatment. Additional studies using patient-derived cells are essential to confirm the involvement of p38-MAPK and to establish clinical significance in treating ovarian cancer.

Utmi Arma et al.[21] stated that, in contrast to the ethanol, hexane, and butanol fractions, the chempedak sea cucumber's (Bohadschia marmorata) ethyl acetate fraction exhibits strong anticancer properties. Triterpenoid substances, secondary metabolites produced from marine sources known as cytotoxic to various tumor cells, are accountable for this impact. In particular, sea cucumbers' triterpene glycosides, or saponins, can decrease angiogenesis and transcription signals, promote apoptosis, and block NF-κB activation. The ethyl acetate fraction also met the American National Cancer Institute's cell lethality standards (<20 µg/mL) with an IC_{50} value of 18.833%. The ethyl acetate extract is regarded as a possible anticancer medication because it effectively inhibits SP-C1 cancer cells.

As reported by Minglei Zhang et al. [22] contemporary treatment options for osteosarcoma (OS) are predominantly out of date, and the condition tends to metastasize early. Fucoidans and other marine-derived polysaccharides have the potential to forestall metastasis. Fucoidans sourced from Undaria pinnatifida impede tumor proliferation and metastasis through pathways including VEGFC/VEGFR3, c-MET, PI3K/AKT, ERK, and L-selectin, while they promote TIMPs and inhibit HIF-1α. This investigation revealed that Cf-Fuc, a sulphated polysaccharide obtained from Cucumaria frondosa, decreases the adhesion and migration of U2OS osteosarcoma cells, hinders F-actin polymerization, and disrupts integrin signalling by downregulating

phosphorylated FAK and paxillin. The Rac1/PAK1/LIMK1/cofilin signalling pathway, which is essential for the cytoskeletal remodelling involved in metastasis, is also inhibited by Cf-Fuc. These findings suggest that Cf-Fuc is probably an antimetastatic drug. Future research will concentrate on identifying functional motifs, confirming results with different OS cell lines, evaluating cscreening.

As stated by Claudio Luparello et al. [23] Holothuria tubulosa coelomic fluid extract (CFE) promotes G_2/M phase arrest, aggravates oxidative stress, interrupts mitochondrial activity, and induces apoptosis in hepatocellular carcinoma (HepG2) cells. These actions could be correlated with disrupting the actin cytoskeleton and blocking protective autophagy. A proteome characterization revealed several candidate proteins such as DMBT1, semaphorin-1A, and ficolin-2 that are involved in apoptosis, inhibition of migration, and antimetastatic. Exosome-associated proteins, histones H1 and H2B, and endoplasmic reticulum markers suggest that intact nanovesicles can mediate intracellular delivery of bioactive agents. Although the exact bioactive compounds have not yet been identified, possible candidates could be triterpenes, glycosaminoglycans, cerebrosides, and the synergy between these compounds. CFE was still bioactive even after lyophilization and freeze-thawing, showing that it is stable and can potentially be developed further. These results open the door for more investigation into the molecular mechanisms and active ingredients of H. tubulosa-derived CFE's potential as a marine-sourced, multidisciplinary therapeutic agent for liver cancer.

Chemotherapy is usually employed to combat bladder cancer, but its effectiveness can be compromised by drug resistance and side effects, as explained by Ru et al. [24] the sea cucumber Cucumaria frondosa is the source of frondoside A, a triterpenoid glycoside with strong anticancer effects and nominal toxicity. The effects of Frondoside A alone and in conjunction with CpG-ODN on UM-UC-3 bladder cancer cells were examined in this study. In comparison to epirubicin, the combination significantly reduced cell viability, induced apoptosis, and impeded cell cycle progression. Frondoside A influenced apoptosis-related genes like Bax and Bcl-2 through caspase- and TP53-independent mechanisms. Additionally, it decreased cell migration, exhibiting enhanced antimetastatic effects when paired with CpG-ODN. In animal models, Frondoside A slowed down tumor growth, under scoring its potential as a natural treatment option for bladder cancer.

However, the majority of the evidence base today consists of in-vitro/in-silico studies, with little animal testing and uneven reporting of risk of bias. Standardized extracts, purified active ingredients, thorough toxicity and dose-response profiling, and conclusive pharmacokinetics and bioavailability data are all necessary for translational advancement. Sturdy preclinical models ought to evaluate synergy with conventional radiotherapy and chemotherapy. In the end, establishing efficacy, safety, dosing, and target indications in humans requires carefully planned, registered clinical trials. For scalable, replicable treatments, parallel focus on ethical aquaculture, sustainable sourcing, and strict quality control will be essential. All things considered, compounds derived from sea cucumbers should be investigated more quickly and carefully in order to fully realize their multi-target anticancer potential.

Conclusion

Sea cucumbers are seldom taken into regard in the course of developing novel drugs against various kinds of cancer. Although, this is a field of limitless scope of

research, it has been overlooked for a long time and new researches are escalating in this domain. This systematic review paper sheds light on the myriads of Sea cucumber species and the biological importance of these elongated, soft, leathery bodied organisms in tackling tumours of different kinds.

Abbreviations: PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SYRCLE's RoB—Systematic Review Centre for Laboratory Animal Experimentation Risk-of-Bias tool; RoB—Risk of Bias; EGFR—Epidermal Growth Factor Receptor; PI3K—Phosphatidylinositol 3-Kinase; AKT—Protein Kinase B, MAPK—Mitogen-Activated Protein Kinase; CDK—Cyclin-Dependent Kinase; PK/PD—Pharmacokinetics/Pharmacodynamics; GLP—Good Laboratory Practice; Cf-Fuc—Cucumaria frondosa fucoidan ;BWMT – Body Wall Methanolic Extract; BAX – Bcl-2-associated protein X; MMP – Matrix Metalloproteinases; ERK – Extracellular signal-regulated kinase; EGFR –Epidermal Growth Factor Receptor; PI3K – Phosphatidylinositol-3 kinase; AKT1 – Serine/Threonine-Protein Kinase B1; CDK4 – Cyclin-Dependent Kinase 4; ATP – Adenosine Triphosphate; HPV – Human Papillomavirus; mTOR – Mechanistic Target of Rapamycin; LC-MS – Liquid Chromatography-Mass Spectrometry; TP53 – Tumor Protein p53; SKOV3 – human ovarian cancer cell line; p38MAPK – p38 Mitogen-Activated Protein Kinase; NF-**κB –** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **IC_{50} - h**alf-maximal inhibitory concentration; **SP-C1 – S**upri's Clone 1**;** VEGFC – Vascular Endothelial Growth Factor; VEGFR3 – Vascular Endothelial Growth Factor Receptor; cMET – cascade initiated by the Mesenchymal-Epithelial Transition; TIMPs – Tissue Inhibitors of Metalloproteinases; FAK – Focal Adhesion Kinase; PAK1 – p21-activated kinase 1; LIMK1 – LIM domain kinase 1; Cf-Fuc – Cucumaria frondosa fucoidan**;** **DMBT1 –** Deleted in Malignant Brain Tumours 1; CpG-ODN – Cytosine-phosphate-guanine Oligodeoxynucleotide; UM-UC-3 – **U**niversity of Michigan - Urothelial Carcinoma – 3

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