Molecular Science

AIMS Molecular Science, 13(3): 251–292.
DOI: 10.3934/molsci.2026013
Received: 05 December 2025
Revised: 03 April 2026
Accepted: 06 May 2026
Published: 01 June 2026

https://www.aimspress.com/journal/Molecular

Review

Potential use of sea cucumber compounds in cancer treatment

Lyudmila S. Dolmatova*

Laboratory of biochemistry, V.I. Il'ichev Pacific Oceanological Institute, Far Eastern Branch of the Russian Academy of Sciences, Vladivostok, Russia

* **Correspondence:** Email: dolmatova@poi.dvo.ru; Tel: +7-4232-312580; Fax: +7-4232-312573.

Abstract: New effective tumor-specific and patient-safe drugs are in demand for cancer treatment. Various classes of substances from holothurians (sea cucumbers) have a number of unique structural properties that provide their high cytotoxicity and other anticancer activities. Until recently, the main attention of researchers was focused on triterpene glycosides (TGs), primarily isolated from commercially used species of sea cucumbers. TGs have pronounced anticancer activity, but in many cases cause side effects. The aim of this review was to analyze data on the anticancer effects of the most studied classes of compounds isolated from sea cucumbers (TGs, proteins and peptides, sphingolipids, polysaccharides), including species that are not used, their mechanisms of action, and approaches to ensuring their safe use in anticancer therapy. The analysis revealed high anticancer activity of the studied compounds against a wide range of tumors, which is performed largely through different mechanisms. The safety of using TGs increases when combined with some compounds of other chemical classes, which is manifested in the absence of a significant side effect on healthy cells. High efficacy and safety of experiments using a wide range of compounds isolated from sea cucumbers demonstrate that they are promising candidates for anticancer drugs.

Keywords: cancer therapy; holothurians; polysaccharides; proteins; sphingolipids; triterpene glycosides

1. Introduction

Cancer, a major health problem causing a high mortality worldwide, continues to be one of the most pressing challenges to modern medicine [1]. Knowledge about the mechanisms of onset and progression for different types of cancer is insufficient [2]. In addition, cancer treatment is complicated

by the rapid development of drug resistance by cancer cells and the high toxicity of drugs administered, often with severe side effects [1]. Hence, there is an urgent need for novel drugs with different mechanisms of action, combining efficacy with low toxicity.

Marine invertebrates are a source of many compounds with unique toxicity [3,4], and their bioprospection is a tool for developing potential anticancer drugs. In particular, attention to anticancer properties of holothurians (Echinodermata, Holothuroidea), commonly referred to as sea cucumbers, has increased enormously over the past 20 years. As evidenced by a large-scale study of literary sources conducted by Zare and co-authors [5], the number of publications on this topic increased more than 4-fold in 2021 compared to 2006.

According to the latest data, there are 1,762 living species of holothurians in the world [6]. The number of new species is increasing, partly due to the exploration of previously inaccessible deep-sea and polar habitats [7].

Sea cucumbers are widely distributed across the world's oceans, with the greatest diversity of species and stocks recorded from the Asia-Pacific region. These animals make up a significant share in the macrozoobenthos biomass in ocean waters. Many sea cucumber species are of high commercial value and are used as food and a source of valuable biologically active substances. Nevertheless, only about 70 holothurian species are known that have been commercially exploited worldwide until 2016 [8]. Historically, sea cucumbers have been used for traditional medicine in South East and East Asia, primarily in China, Japan, North Korea, and South Korea, for many centuries. Due to over-demand and decline in abundance of the most valuable species, the number of harvested species, which were not previously exploited, is continuously increasing [9–11]. Interest in the sea cucumbers is also growing in other countries [12–14]. Thus, the species that are not harvested but have the potential to be used in the food and pharmaceutical industry have received attention from researchers in recent years [15–17].

Biocompounds isolated from sea cucumbers include triterpene glycosides, sphingolipids, polysaccharides, proteins and peptides, amino acids, polyunsaturated fatty acids, phenolic compounds, and carotenoids [12,13]. The first four groups include some unique compounds, and anticancer activity of these groups is the most studied.

The review summarizes and analyzes findings regarding the anticancer effects of triterpene glycosides, sphingolipids, polysaccharides, and proteins from sea cucumbers, the mechanisms of their action, and the feasibility of using them as agents in anticancer therapy.

2. Triterpene glycosides

Triterpene glycosides are characterized by structural diversity, primarily, of aglycones (triterpene derivatives of lanostane) and carbohydrate chains. These compounds may contain up to four sulfate groups in their carbohydrate backbone. The generic and species specificity enable using these glycosides as a taxonomic important character [18].

The anticancer effects of drugs are mainly based on their ability to directly kill cancer cells, reduce their invasiveness, and inhibit their proliferation, metastasis, and angioplasticity of tumors [2]. Triterpene glycosides are known as multi-target agents.

2.1. Cytotoxic activity

Triterpene glycosides (saponins), being the best-studied of all substances derived from sea cucumbers, considered in 72% of studies [19], have shown the greatest cytotoxicity [20]. More than 100 sea cucumber-derived saponins have been identified [21], with their number continuously growing. Different types of cancer cells are distinguished by their characteristics, and, therefore, their treatment requires a vast number of compounds with different anticancer mechanisms [22]. The structural diversity of glycosides provides broad opportunities for their potential use. As known, tumor cell lines exhibit different sensitivities to cytotoxic glycosides derived from sea cucumbers [23,24], which are, consequently, of certain therapeutic interest. Table 1 presents the best studied triterpene glycosides with low-dose cytotoxic effect [4,25–61]. Many sea cucumber-derived triterpene glycosides have shown a cytotoxic effect on a number of cell lines of various tumor types. The cytostatic activity of glycosides has most frequently been shown for colon, lung, liver, and breast cancer cells: 18 glycosides have shown an effect on six cell lines of colon cancer [4,25-27,31,34–37]; 23 glycosides on three cell lines of lung cancer [4,25–34]; 27 glycosides on four cell lines of liver cancer [4,25,28,30,31,33,36,38–44]; and 26 glycosides on eight cell lines of breast cancer [4, 25–27,31,32,36,37,41,42,45–49].

In other cancer types studied (stomach, blood, skin, pancreas, cervix, throat, bladder, kidney, prostate, brain, ovarian, nasopharynx, muscle), glycosides are also effective, but cancer cell sensitivity to different glycosides was less comprehensively studied in these cases [4,26–31,34,40–44,46,50–54, 56–61].

A number of glycosides have shown efficacy in many cancer types. For example, they include argusides B, C, D, E, isolated from *B. argus* [25,36], intercedensides D–H from *M. intercedens* (non-exploited species) [34], pentactasides I, II, III and philinopsides A and B from *C. quadrangularis* (unaccepted name *P. quadrangularis*) [26,27], griseaside A from *H. grisea* [28], frondoside A from *C. frondosa* [4,46,57,59,60] and from *C. okhotensis* (a non-commercial species) [54,58], colochiroside A from *C. anceps* (formerly name *C. anceps*) [29], hillasides A and B from *H. hilla* [30], echinoside A from *H. nobilis* [31], stichorrenosides C and B from *S. horrens* [42], and thelenotoside B from *S. horrens* [42].

Notably, among the 27 sea cucumber species listed in the Table 1, 11 are either of no commercial value or barely exploited.

Table 1. Cytotoxicity of triterpene glycosides against cancer cell lines.

Cancer type	Cell line	Glycoside	Sea cucumber species	Ref
Lung	A549 human non-small lung carcinoma	Frondoside A	*Cucumaria frondosa*	[4]
		Argusides B, C, D, E	*Bohadschia argus*	[25]
		Philinopsides A, B, E	*Colochirus quadrangularis* (obsolete name *Pentacta quadrangularis*)	[26]
		Pentactasides I, II, III	*Colochirus quadrangularis*	[27]
		Griseaside A	*Holothuria grisea*	[28]
		Colochiroside A	*Cercodemas anceps* (obsolete name *Colochirus anceps*)	[29]
		Hillasides A, B	*Holothuria hilla*	[30]
		Echinoside A	*Holothuria nobilis*	[31]
		Nobiliside D	*Holothuria nobilis*	[32]
		Impatienside A	*Holothuria impatiens*	[33]
	SpC-A4 lung adenocarcinoma	Intercedensides D-H	**Mensamaria intercedens*	[34]
	LNM35 large cell lung cancer	Philinopside E	*Colochirus quadrangularis*	[26,27]
Colon	HCT-116 colon cancer	Frondoside A	*Cucumaria frondosa*	[4]
		Argusides A, B, C, D, E	*Bohadschia argus*	[25,35,36]
		Bivittoside	*Holothuria polii*	[37]
		Pentactasides I, II, III	*Colochirus quadrangularis*	[27]
		Philinopsides A and B	*Colochirus quadrangularis*	[26]
		Echinoside A	*Holothuria nobilis*	[31]
	DLD-1 colorectal adenocarcinoma	Frondoside A	*Cucumaria frondosa*	[4]
		Intercedensides D-H	**Mensamaria intercedens*	[34]
	HT-29 colorectal adenocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
	LoVo colorectal adenocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
	Caco-2 human colorectal adenocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
	HCT-8 human colon carcinoma	Intercedensides D-H	**Mensamaria intercedens*	[34]

Continued on next page

Cancer type	Cell line	Glycoside	Sea cucumber species	Ref
Liver	SMMC-7721 hepatocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
	HepG2 human hepatocellular carcinoma	Argusides B, C, D, E	*Bohadschia argus*	[25,36]
		Holothurin A_1	*Peasonothuria graeffei*	[38]
		Dehydroechinoside A (DHEA)	*Peasonothuria graeffei*	[38]
		Ds-echinoside A	*Peasonothuria graeffei*	[39]
		Echinoside A	*Holothuria nobilis*	[31]
		Frondoside A	*Cucumaria frondosa*	[4]
		Holothurins A3 and A4	*Holothuria scabra*	[40]
		Stichorrenosides C, B	*Stichopus horrens*	[41]
		Stichorrenoside E	*Stichopus horrens*	[42]
		Deacetylated thelenotoside B	*Stichopus horrens*	[42]
		Thelenotoside B	*Stichopus horrens*	[42]
		Impatienside A	*Holothuria impatiens*	[33]
	H22 hepatoma	Echinoside A	*Holothuria nobilis*	[31]
	BEL-7402 human hepatocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
		Griseaside A	*Holothuria grisea*	[28]
		Violaceusides A, B	**Pseudocolochirus violaceus*	[43]
		Fuscocinerosides A, B, C	**Holothuria fuscocinerea*	[44]
		Pervicoside	**Holothuria fuscocinerea*	[44]
		Holothurin A	**Holothuria fuscocinerea*	[44]
		Hillasides A, B	*Holothuria hilla*	[30]
Breast	MCF-7 human breast adenocarcinoma	Argusides B, C, D, E	*Bohadschia argus*	[25,36]
		Bivittoside	*Holothuria polii*	[37]
		Djakonovioside E_1	**Cucumaria djakonovi*	[45]
		Frondosides A, B	*Cucumaria frondosa*	[46]
		Pentactasides I, II, III	*Colochirus quadrangularis*	[27]
		Philinopsides A, B	*Colochirus quadrangularis*	[41]
		Stichorrenosides C, B	*Stichopus horrens*	[32]

Continued on next page

Cancer type	Cell line	Glycoside	Sea cucumber species	Ref
Breast	MCF-7 human breast adenocarcinoma	Nobiliside D	*Holothuria nobilis*	[26]
		Thelenotoside B	*Stichopus horrens*	[42]
		Psolusosides A, L	*Psolus peronii*	[47]
	MDA-MB-231 triple-negative breast cancer	Frondosides A, B	*Cucumaria frondosa*	[46]
		Echinoside A	*Holothuria nobilis*	[31]
		Djakonovioside E_1	**Cucumaria djakonovi*	[45]
		Psolusoside A	**Psolus peronii*	[47]
	SK-BR-3 human breast adenocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
		Frondoside A	*Cucumaria frondosa*	[4]
	MDB-MA-435 human breast carcinoma	Frondoside A	*Cucumaria frondosa*	[4]
		Echinoside A	*Holothuria nobilis*	[31]
	MDB-MA-468 human breast adenocarcinoma	Echinoside A	*Holothuria nobilis*	[31]
	66.1 triple-negative murine breast cancer	Frondoside A	*Cucumaria frondosa*	[4]
	Mouse Ehrlich carcinoma	Cucumariosides A1, A6	**Eupentacta fraudatrix*	[48]
		Typicosides A1, A2, B1, C2	**Actinocucumis typica*	[49]
	T-47D human breast cancer	Psolusoside L	**Psolus peronii*	[47]
Stomach	MKN28 gastric carcinoma cells	Colochiroside A	*Cercodemas anceps*	[29]
		Pentactasides I, II, III	*Colochirus quadrangularis*	[27]
		Philinopsides A, B, E	*Colochirus quadrangularis*	[26]
		Echinoside A	*Holothuria nobilis*	[31]
	MKN-45 human gastric cancer	Echinoside A	*Holothuria nobilis*	[31]
	SGC-7901 human gastric cancer	Echinoside A	*Holothuria nobilis*	[31]
Blood	HL60 human leukaemia	Colochiroside A	*Cercodemas anceps*	[29]
		Fuscocinerosides A, B, C	**Holothuria fuscocinerea*	[44]
		Cucumarioside A2–2	*Cucumaria japonica*	[46,50]
		Frondoside A	*Cucumaria frondosa*	[4]
		Griseaside A	*Holothuria grisea*	[28]
		Philinopside E	*Colochirus quadrangularis*	[26]

Continued on next page

Cancer type	Cell line	Glycoside	Sea cucumber species	Ref
Blood	HL60 human leukaemia	Stichoposide D	*Thelenota anax*	[51]
		Violaceusides A, B	**Pseudocolochirus violaceus*	[43]
		Echinoside A	*Holothuria nobilis*	[31]
		Chilensosides A1, B, C	**Paracaudina chilensis*	[52]
		Chitonoidosides E, K, L	**Psolus chitonoides*	[53]
	THP-1 human monocytic leukemia	Frondoside A	**Cucumaria okhotensis*	[54]
	K562 human erythroleukemic cell	Stichoposide D	*Thelenota anax*	[55]
		Echinoside A	*Holothuria nobilis*	[31]
Skin	B16F10 murine melanoma	Crude saponin	*Holothuria leucospilota*	[56]
	MDA-MB-435 melanoma	Frondoside A	*Cucumaria frondosa*	[46]
		Stichorrenosides C, B	*Stichopus horrens*	[41]
	SK-Mel2 melanoma	Intercedensides D-H	**Mensamaria intercedens*	[34]
		Thelenotoside B	*Stichopus horrens*	[42]
	A431 human skin cancer (epidermoid carcinoma)	Echinoside A	*Holothuria nobilis*	[31]
Pancreas	AsPC-1 human pancreatic adenocarcinoma	Frondoside A	*Cucumaria frondosa*	[57]
	S2013 human pancreatic cancer	Frondoside A	*Cucumaria frondosa*	[57]
	MiaPaca-2 human pancreatic carcinoma	Frondoside A	*Cucumaria frondosa*	[4]
Cervix	HeLa cervical cancer	Frondoside A	**Cucumaria okhotensis*	[54]
		Echinoside A	*Holothuria nobilis*	[31]
		Chitonoidosides E, K, L	**Psolus chitonoides*	[53]
		Okhotosides B1, B2, B3	**Cucumaria okhotensis*	[54]
Throat	KB human epidermoid carcinoma	Hillasides A, B	*Holothuria hilla*	[30]
		Echinoside A	*Holothuria nobilis*	[31]
		Holothurins A3, A4	*Holothuria scabra*	[40]
		Thelenotoside B	*Stichopus horrens*	[41,42]
		Stichorrenosides C, B	*Stichopus horrens*	[41,42]
Bladder	RT112 human bladder cancer	Frondoside A	**Cucumaria okhotensis*	[58]
	RT4 human bladder cancer	Frondoside A	**Cucumaria okhotensis*	[58]

Continued on next page

Cancer type	Cell line	Glycoside	Sea cucumber species	Ref
Bladder	HT-1197 human bladder carcinoma	Frondoside A	**Cucumaria okhotensis*	[58]
	T24 human bladder carcinoma	Frondoside A	**Cucumaria okhotensis*	[58]
	486p human bladder carcinoma	Frondoside A	**Cucumaria okhotensis*	[58]
	TCC-SUP human bladder transitional cell carcinoma	Frondoside A	**Cucumaria okhotensis*	[58]
	UM-UC-3 bladder cancer cells	Frondoside A	*Cucumaria frondosa*	[59]
Kidney	CAKI-1 kidney carcinoma	Hillasides A, B	*Holothuria hilla*	[30]
		Intercedensides D-H	**Mensamaria intercedens*	[34]
Prostate	PC-1 human prostate cancer	Frondoside A	*Cucumaria frondosa*	[4]
	PC-3 human prostatic carcinoma	Hillasides A, B	*Holothuria hilla*	[30]
		Echinoside A	*Holothuria nobilis*	[31]
		Frondoside A	*Cucumaria frondosa*	[4]
		Thelenotoside B	*Stichopus horrens*	[42]
	LNCaP human prostatic adenocarcinoma	Stichorrenosides C, B	*Stichopus horrens*	[42]
		Frondoside A	*Cucumaria frondosa*	[4]
	DU145 human prostatic carcinoma	Frondoside A	*Cucumaria frondosa*	[4]
	VCaP human prostatic carcinoma	Frondoside A	*Cucumaria frondosa*	[60]
	22Rv1 human prostatic carcinoma	Frondoside A	*Cucumaria frondosa*	[60]
Brain	U87MG human brain glioblastoma	Pentactasides I, II, III	*Colochirus quadrangularis*	[27]
		Philinopsides A, B, E	*Colochirus quadrangularis*	[26]
	Neuro 2A neuroblastoma	Psolusoside L	**Psolus fabricii*	[61]
Ovarian	SK-OV-3 ovarian cancer	Intercedensides D-H	**Mensamaria intercedens*	[34]
		Echinoside A	*Holothuria nobilis*	[31]
	HO-8910 ovarian carcinoma	Echinoside A	*Holothuria nobilis*	[31]
	1A9 ovarian cancer	Intercedensides D-H	**Mensamaria intercedens*	[34]
Muscle	RH30 rhabdomyosarcoma	Echinoside A	*Holothuria nobilis*	[31]
	S180 mouse sarcoma	Echinoside A	*Holothuria nobilis*	[31]
Nasopharynx	KB-VIN epidermoid carcinoma of the nasopharynx	Intercedensides D-H	**Mensamaria intercedens*	[34]

Note: *–species non-exploited or of little commercial importance.

It should be noted that sulfated glycosides are the most active compounds. Of them, monosulfated glycosides are more active than disulfated or trisulfated glycosides, as shown, for example, by comparing cytotoxicities of the monosulfated frondoside A (Figure 1A) with the disulfated frondoside B (Figure 1B) and the trisulfated frondoside C in AsPC-1 and S2103 human pancreatic cancer cells [4]. On the contrary, tri- and tetrasulfated glycosides compared to di-sulfated compounds display a great potential to be used as anticancer agents in cases of promyeloblast HL-60 and monocytic THP-1 cell lines (trisulfated chilensoside C, but not tetrasulfated chilensoside D, Figure 2) [52] and HeLa, DLD-1, and HL-60 cell lines (tetrasulfated chitonoidosides K and L, Figure 3) [53]. Nonetheless, membranolytic activity of disulfated cucumarioside A3-2 from *E. fraudatrix* is stronger than that of trisulfated koreoside A [45]. Hence, there is no direct cytotoxicity dependence on the degree of sulfation. The sensitivity of the cancer cell lines to the cytotoxic action of sea cucumber-derived glycosides depends on the glycoside's chemical structures and the composition of the cellular membrane [46]. Furthemore, the presence of acetyl group at C-16 in the structure is essential for the cytotoxic activity of glycosides, which is manifested as a higher activity of frondoside A compared to cucumarioside A2–2 (Figure 4) [50]. The quantitative structure–activity relationship (QSAR) method displays the complex nature of the relationships between the structure of glycosides and their membranolytic action, with considerable effect of numerous weak predictors in combination with each other [45].

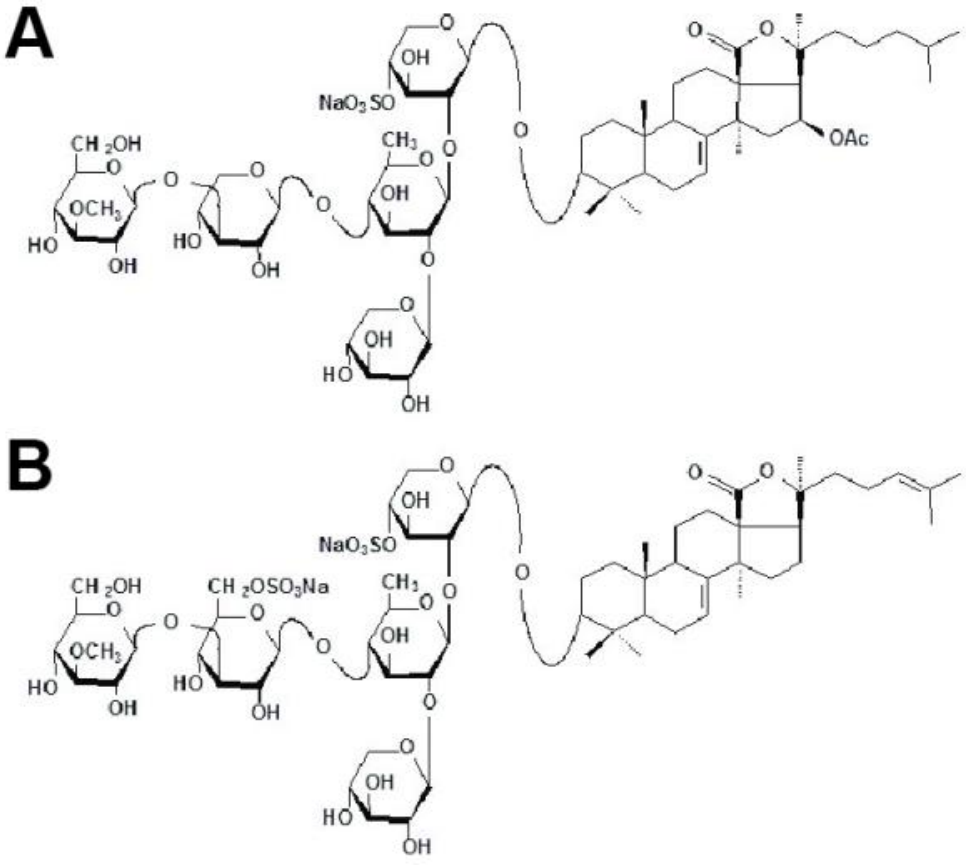

Figure 1. Structure of frondosides A (A) and B (B).

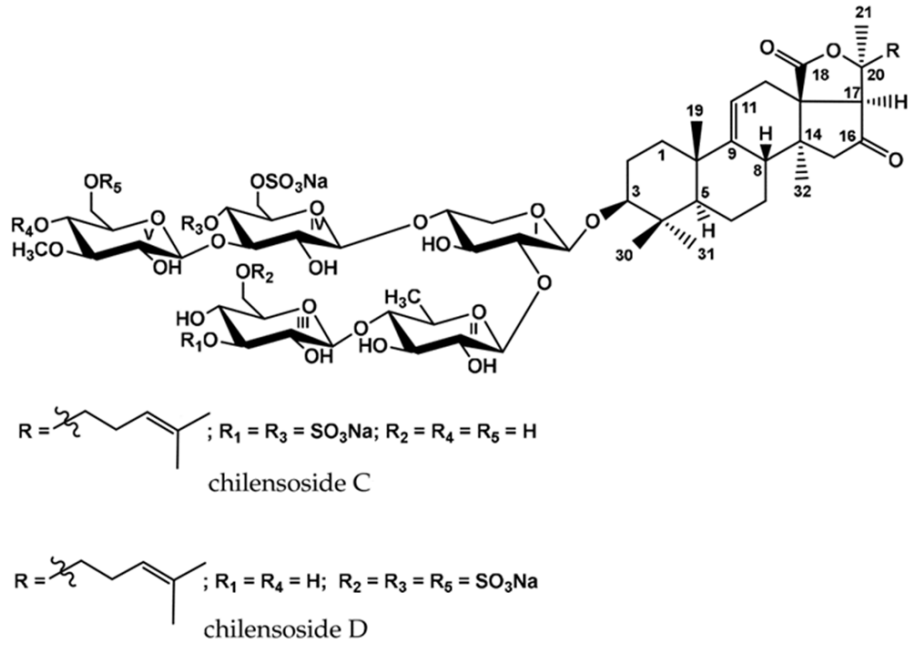

Figure 2. Structure of chilensosides C and D.

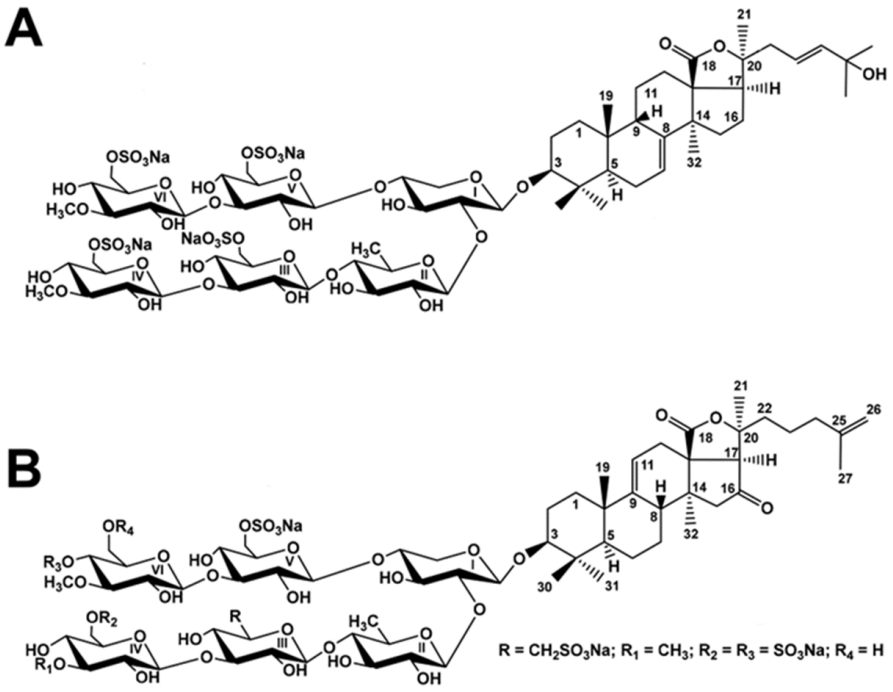

Figure 3. Structure of chitonoidosides K (A) and L (B).

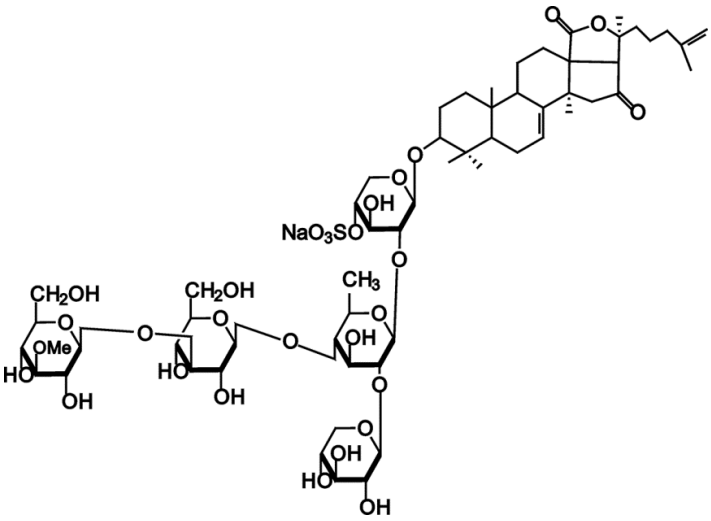

Figure 4. Structure of cucumarioside A2–2.

Mechanisms of cytotoxicity and other anticancer activities of some triterpene glycosides are displayed in Table 2. As the results of studies on cytotoxicity of triterpene glycosides show, they induce apoptosis of cancer cells [1], often through different signaling pathways. Apoptosis is a programmed cell death characterized by morphological and metabolic features, of which the most significant are chromatin condensation and fragmentation of nuclear DNA. It is a homeostatic mode of cell death [62]. Philinopsides A and E from *C. quadrangularis* (former name *P. quadrangularis*) stimulate apoptosis of sarcoma-180 cells [1]. The cytotoxic activity of nobiliside D from *H. nobilis* associated with its apoptotic effect deserves a special mention here. The level of induced apoptosis varies between cancer cell lines, with the maximum recorded for 45.8% of K562 myelogenous leukemia cells and for 58.7% of MCF-7 breast cancer cells (half maximal inhibitory concentration (IC50) of 0.83 ± 0.14 and 0.82 ± 0.11 μg/mL for K562 and MCF-7, respectively) [32]. The mechanisms of apoptosis in these cases were not identified.

For a limited number of triterpene glycosides, studies have been conducted on the mechanisms of their apoptotic action. Moebioside A, which was first described from *Holothuria moebii*, induces apoptosis in human glioblastoma U87-MG cells. This glycoside does not have a significant effect on the expression of pro- and antiapoptotic genes, as analyzed by Western blot, but reduces the expression levels of glycolytic and glutaminolytic enzymes, which indicates a new mechanism of glioma suppression [63]. Frondoside A and cucumarioside A2–2 induced apoptosis in HL60, THP-1, and NB4 human leukemia cells, and frondoside A is more toxic to leukemic cells compared to cucumarioside A2–2. Using caspase inhibitors shows that frondoside A induces apoptosis independently of caspase activation, but apoptosis triggered by cucumarioside A2–2 is caspase-3-dependent [50]. Stichoposide C, isolated from *T. anax*, induces apoptosis in human K562 and HL-60 leukemia cells through a Fas death receptor clastering, activation of caspase-3 and caspase-8 (enzymes involved in apoptosis induction), and Bid (pro-apoptotic protein of the Bcl-2 family). In addition, activation of ceramide synthase (CerS)6 and ceramide generation followed by p38 kinase activation takes place, which is known to induce apoptosis by an intrinsic pathway [51]. A crude saponin isolated from *Holothuria leucospilota* up-regulates caspase-3 and caspase-9 and causes morphological characteristics of apoptotic cell death in B16F10 melanoma cells [56]. Frondoside A from *C. frondosa* induces apoptosis

through an increase in expression of the p53 protein (a transcription factor that regulates the cell cycle) and by stimulating caspases 3, 7, and 9 in MDA-MB-231 breast cancer cells [64]. In human urothelial carcinoma RT112 cells, frondoside A from *C. okhotensis* also induces apoptosis by stimulating caspase-3, -8, and -9, as well as poly (ADP ribose) polymerase (PARP), nuclear enzyme involved in DNA repair, Bax, and cyclin-dependent kinase inhibitor p21 (a target of the transcription factor p53) expressions. However, in the cells with suppressed p53, frondoside A is more effective. As Dyshlovoy et al. emphasized, apoptosis in cancer cells is often independent of caspase- and p53-activities [58]. Furthemore, frondoside A increases the expression of p21 in PC-3 and DU145 cells, and suppresses its expression in LNCaP [4], indicating a different sensitivity of tumor types to frondoside A anticancer effects.

Several hypotheses have been advanced to explain the phenomenon of caspase-independent apoptosis in cancer cells, including the possible involvement of non-caspase proteases, the increased production of reactive oxygen species (ROS) in mitochondria, and the incomplete inhibition of caspases by caspase inhibitors in model experiments [4]. In this regard, the assumption that the apoptosis regulation by glycosides occurs at a higher level seems most plausible [58]. Nuclear factor kappa-B (NF-κB) is a family of dimeric transcription factors taking part in a number of physiological conditions, including apoptosis. In the cytoplasm, NF-κB is associated with protein inhibitor (IκB), and after activation by several receptors and some factors, followed by proteasomal degradation of IκB protein, NF-κB translocates to the nucleus and attaches to target genes [22]. Apparently, NF-κB may play a certain role in caspase-independent apoptosis, in particular by stimulating antioxidant defense and inactivation of caspases, and inhibiting p53 activity [22]. Moreover, NF-κB is important for tumor progression in non-small cell lung cancer [65]. NF-κB activation in mutated Kras-induced lung cancer and pancreatic cancer cells causes tumor initiation and progression [66]. NF-κB is also involved in the tumor progression through activation of cyclooxygenase (COX)-2. In addition, NF-κB increases angiogenesis by stimulating genes of pro-inflammatory cytokines, for example, interleukine (IL)-8 and inducible nitric oxide synthase (iNOS) expression, as reported in studies on colorectal cancer and breast cancer cells [67,68], and triggers invasion and metastasis through epithelial-mesenchymal transition (EMT) in colon cancer [68]. Stichoposide D and more potent stichoposide C from *S. chloronotus* induce apoptosis in HL-60 and THP-1 cells. Taking into account the results of the study of the effect of stichoposide D on the transcriptional activity of activating protein-1 (AP-1) nuclear transcription factor, which is involved in the regulation of proliferation and apoptosis, and on the NF-κB expression, the apoptotic effect of this stichoposide may be associated with the inhibition of the activity of these transcription factors [69]. Ds-echinoside A from *P. graeffei* has an apoptosis-stimulating effect, reducing the expression of the apoptosis regulator Bcl-2 and NF-κB, increasing the expression of caspase-3, and cleaving PARP [39,70].

Moreover, frondoside A was shown to inhibit p21 protein (Rac/Cdc42)-activated p21-kinase (PAK1) *in vitro*. This kinase is upstream of several other signal transduction mechanisms including NF-κB expression, which explains such a wide range of anticancer effects of the compound [4].

Table 2. Mechanisms of the anticancer activity of triterpene glycosides.

Activity	Triterpene glycoside	Cancer type/cell line/model	Mechanism	Ref
Cytotoxic (apoptotic)	Philinopsides A, E	Sarcoma-180	N/d	[1]
	Nobiliside D	K562; MCF-7	N/d	[32]
	Moebioside A	U87-MG	Reduction in the expression levels of some glycolysis and glutaminolysis enzymes	[63]
	Frondoside A	HL60, THP-1, and NB4	Caspase-independent	[50]
	Cucumarioside A2–2	HL60, THP-1, and NB4	Caspase-3-dependent	[50]
	Stichoposide C	K562; HL-60	Activation of Fas clastering, caspase-3, caspase-8, and Bid, activation of CerS6 and p38 kinase, and ceramide generation	[51]
	Crude saponin from *H. leucospilota*	B16F10	Up-regulation of caspase-3 and caspase-9	[56]
	Frondoside A	MDA-MB-231	Increase in expression of p53 protein and in activity of caspases 3, 7, and 9	[64]
	Frondoside A	RT112	Stimulation of caspase-3, -8, and -9, PARP, Bax, p21; Activation of JNK1/2, and inhibition of p38 and ERK1/2	[58]
	Frondoside A	PC-3, DU145	Increase in the expression of p21	[4]
	Frondoside A	LNCaP	Decrease in the expression of p21	[4]
	Stichoposide C	HL-60, THP-1	N/d	[69]
	Stichoposide D	HL-60	Suppression of NF-κB and AP-1 activity	[39,70]
	Ds-echinoside A	Hep G2	Reducing the expression of Bcl-2, NF-κB, and increasing the expression of caspase-3, cleavage of PARP	[39,70]

Continued on next page

Activity	Triterpene glycoside	Cancer type/cell line/model	Mechanism	Ref
Overcoming chemotherapy resistance	Frondoside A	RT112	Autophagy inhibition simultaneously with apoptosis inducing; Activation of JNK1/2, and inhibition of p38 and ERK1/2	[58]
	Frondoside A	Ehrlich carcinoma	Formation of complexes with cell membrane cholesterol and inhibition of the activity of the membrane transport protein P-glycoprotein	[46,76]
	Cucumarioside A2–2	Ehrlich carcinoma	Formation of complexes with cell membrane cholesterol and inhibition of the activity of the membrane transport protein P-glycoprotein	[46,76]
Anti-proliferative effects	Cucumarioside A2–2	Ehrlich carcinoma	Cell cycle arrest in the (S) phase	[77]
	Echinoside A	HepG2	Cell cycle arrest in the G0/G1 phase; An increase in p16, p21, and c-Myc expression; Decrease in cyclin D1 expression; Inhibition of Bcl-2 expression and increased cytochrome c release from mitochondria, caspase-3 activation, and PARP cleavage	[70]
	Ds-echinoside A	HepG2	Cell cycle arrest in the G0/G1 phase; Increase in p16 and p21, and c-Myc expression; Decrease in cyclin D1 expression; Inhibition of the expression of Bcl-2, and increase in cytochrome c release from mitochondria, caspase-3 activation, and PARP cleavage; Decrease in the NF-κB expression	[70]
	Frondoside A	PC-3	Cell cycle arrest in the G2/M phase and a reduction in the proportion of cells in the G0/G1 phase	[4]
	Frondoside A	Burkitt lymphoma cell lines	Cell cycle arrest in the G1 phase	[78]

Continued on next page

Activity	Triterpene glycoside	Cancer type/cell line/model	Mechanism	Ref
Inhibition of angiogenesis	Ds-echinoside A	ECV-304	Decrease in the tube-forming ability in matrigel. Suppression of MMP-9 expression, increased TIMP-1 expression, and reduced NF-κB and VEGF expression	[39]
	24-dehydroechinoside A	ECV-304	Reduced tube formation on matrigel, suppressed VEGF expression, and increased TIMP-1 expression	[38]
	Holothurin A	ECV-304	Reduced tube formation on matrigel, suppression of VEGF expression, and increased TIMP-1 expression; Decrease in NF-κB expression	[38]
	Philinopside A	Model human microvascular endothelial cells	Reducing tube formation on the Matrigel; Inhibition of the proliferation and migration	[79]
		Cultured rat aortas	Suppression of new microvessel formation	[79]
		Chick embryo chorioallantoic membranes	Inhibition of angiogenesis	[79]
		S180-associated endothelial cells	Inducing apoptosis	[79]
	Frondoside A	Chick chorioallentoic membrane	Inhibition of basal and FGF-stimulated angiogenesis	[4]
		Human umbilical vein endothelial cells	Reducing vascular tube formation	[4]
		LNM35 xenograft	Reducing microvessel density	[4]
Anti-metastatic activity	Okhotoside A1-1	MDA-MB-231	Inhibition of the formation and growth of colonies and the migration of cells	[18]
	Cucumarioside A0-1	MDA-MB-231	Inhibition of the formation and growth of colonies and the migration of cells	[18]
	Frondoside A	UM-UC-3	Inhibition of the migration of cells	[59]

Continued on next page

Activity	Triterpene glycoside	Cancer type/cell line/model	Mechanism	Ref
Anti-metastatic activity	Frondoside A	MDA-MB-231	Antagonizing EP2 and EP4 receptors, reduction of cAMP-mediated intracellular signaling; Suppression of NF-κB and AP-1 expression, inhibition of PI3K/Akt, ERK1/2, and MAPK; Increase in TIMP-1 expression and reduced MMP-9 expression	[80,81]
	Holothurin A	PC3	Antagonizing the EMT program and downregulating MMP-2 and MMP-9 via the Akt/P38/JNK-MAPK signaling pathway	[83]
	Holothurin A1	HepG2	Downregulation of MMP-9, decreased expression of VEGF and NF-κB, and upregulation of TIMP-1	[38]
	24-dehydroechinoside A	HepG2	Downregulation of MMP-9, decreased VEGF expression, and upregulation of TIMP-1	[39]
Immunomodulation	Cucumarioside A2-2	Macrophages	Stimulation of NO and ROS generation	[86]
	Frondoside A	Macrophages	Stimulation of spreading, lysosomal activity, and ROS generation	[4]
	Frondoside A	NK cells	Prevention of NK cells from PGE2 mediated suppression	[4]

Note: N/d - not determined.

2.2. Overcoming chemotherapy resistance

Another advantage of using glycosides is that they help overcome tumor resistance to chemotherapy. This resistance is largely related to autophagy of cancer cells, a type of programmed cell death through self-digestion. Autophagy is an earlier response to stress compared to apoptosis and can maintain cell survival. The two death types can occur simultaneously and independently in the same cell, affecting one another [71,72]. As Li et al. [72] emphasized in their review, tumors can disrupt the normal regulation of autophagy and use its mechanisms to restructure their metabolism for adapting to unfavorable impact. However, the role of autophagy in the mechanisms of drug resistance of cancer cells is not clear, since it can promote cancer cell death and protect cells from chemotherapy [73]. It was also shown that the outcome may depend on the cancer cell line [74,75]. For example, protection against autophagy was reported for frondoside A isolated from *C. okhotensis* and tested on the RT112 cell line. The protection is associated with apoptosis. Furthermore, c-Jun N-terminal kinase (JNK) 1/2 is activated, and extracellular signal-regulated kinase (ERK) 1/2 is inhibited. According to Dyshlovoy et al., since JNK1/2 can activate and reduce apoptosis, this multidirectional effect of frondoside A on both kinases explains its unique ability to simultaneously induce apoptosis and inhibit autophagy [58].

On the other hand, frondoside A and cucumarioside A2–2 from *C. japonica* form a complex with cell-membrane cholesterol. In the Ehrlich ascites carcinoma mouse tumor model, this ability leads to decreased activity of the transport P-glycoprotein responsible for the transmembrane transport of drugs and linked to multidrug resistance in tumor cells [46,76]. Apparently, the ability of frondoside A and cucumarioside A2–2 to potentiate effects of a number of antitumor drugs [57,58,77] is also based on their impact on transmembrane transport.

2.3. Anti-proliferative effects

Another mechanism of anticancer action reported for a number of glycosides is the delay of cell division, thus inhibiting tumor growth [1]. Cucumarioside A2–2 from *C. japonica* induces cell arrest in the S phase in Ehrlich carcinoma cells [77]. Echinoside A and, to a greater extent, ds-echinoside A from *P. graeffei* affect the G0/G1 phases in HepG2 cells. These echinosides also inhibit cell proliferation through an increase in the expression of cyclin-dependent kinase inhibitors, such as p16, p21, and the c-myc oncogene, and decrease the expression of protein cyclin D1. However, only ds-echinoside A, but not echinoside A, significantly decreases NF-κB expression [70]. Frondoside A increases the proportion in cells arrested in the G2/M phase of the cell cycle and reduces the proportion of cells in the G0/G1 phase [4]. In Burkitt lymphoma cell lines (BL-2, CA46, Namalwa, and Ramos), frondoside A increases the proportion of cells only in the G1 phase [78]. This indicates different mechanisms of action of individual compounds on proliferative activity and different sensitivities of tumors to the same substance.

2.4 Inhibition of angiogenesis

Glycosides can also inhibit angiogenesis. Thus, ds-echinoside A from *P. graeffei* decreases the tube-forming ability of the human urinary bladder carcinoma cell line ECV-304 in matrigel. This action is considered to be associated with the suppression of matrix metalloproteinase-9 (MMP-9), which is

a marker of chronic inflammation, expression, and activation of tissue inhibitors of metalloproteinase-1 (TIMP-1), regulating MMP-9, and with reducing vascular endothelial growth factor (VEGF), having a mitogenic and an anti-apoptotic effect on endothelial cell receptors, and with NF-κB expression [39].

Holothurin A and 24-dehydroechinoside A from *P. graeffei* also suppress the expression of MMP-9 and VEGF and enhance the level of TIMP-1 expression. Holothurin A, but not 24-dehydroechinoside A, also reduces NF-κB expression. Both compounds reduce tube formation of ECV-304 cells on the matrigel *in vitro* and decrease neovascularization in the chick embryo using the chorioallantoic membrane (CAM) assay *in vivo* [38]. This indicates that their antiangiogenic potential may be NF-κB-independent.

Philinopside A from *C. quadrangularis* (former name *P. quandrangularis*) also exhibits potential anti-angiogenic activity that manifested itself through inhibition of the proliferation, migration, and tube formation of human microvascular endothelial cells, inhibition of angiogenesis in chick embryo chorioallantoic membrane assay, and suppression of new microvessel formations in cultured rat aortas. Philinopside A also inhibits many angiogenesis-related receptor tyrosine kinases (RTKs), such as fibroblast growth factor (FGF) receptor-1, platelet-derived growth factor (PDGF) receptor-beta and epithelial growth factor (EGF) receptor, and reduced VEGF expression. In addition, philinopside A induces apoptosis of S180-associated endothelial cells [79].

Frondoside A displays antiangiogenic capacities in the model experiments on the chick chorioallentoic membrane (inhibition of basal and FGF-stimulated angiogenesis) and human umbilical vein endothelial cells (HUVEC), where frondoside A abolishes vascular tube formation, as well as in xenografts of LNM35 lung cancer cells (reducing microvessel density) [4]. However, the mechanisms of its antiangiogenic effects have not been studied.

2.5. Anti-metastatic activity

Anti-metastatic effects were reported for some holothurian's glycosides. It should be noted that glycosides can inhibit the adhesion and migration of tumors, thereby preventing their metastasis. Okhotoside A1-1 and cucumarioside A0-1 from *C. djakonovi* have demonstrated effective inhibition of the formation and growth of colonies and the migration of cells of the most aggressive triple-negative MDA-MB-231 cell line of breast cancer [18].

Frondoside A inhibits the migration of UM-UC-3 bladder cancer cells [59]. This glycoside also supresses the migration and invasion of MDA-MB-231 *in vitro* and *in vivo* [80–82]. The mechanism of inhibition is at the level of the antagonizing prostaglandin E receptors EP2 and EP4, thus, reducing the cyclic adenosine monophosphate (cAMP) mediating intracellular signaling, indicating the COX-2-dependent mechanism of antimetastatic effect [80]. At the downstream level, frondoside A reduces the expression of NF-κB and transcription factor AP-1 and inhibits tissue plasminogen activator-induced activation of phosphatidylinositol 3-kinase (PI3K)/RAC-alpha serine-threonine-protein kinase (Akt), ERK1/2, and p38 mitogen-activated protein kinase (MAPK) [81]. This is important because, when over-activated, the PI3K signaling pathway is involved in carcinogenesis. These effects are associated with the increased expression of TIMP-1 [80] and significantly reduced expression of MMP-9 [80,81].

The mechanism of suppression of MMP activity is also manifested as the anti-metastatic action of holothurin A from *H. scabra* on PC3 cancer cells. This glycoside demonstrates anti-metastatic ability by antagonizing the EMT program and downregulating MMP-2 and MMP-9 via the

Akt/P38/JNK-MAPK signaling pathway [83]. Holothurin A1 and 24-dehydroechinoside A from *P. graeffei* also display anti-metastatic effects on HepG2 cancer cells through downregulation of MMP-9 and increasing expression of TIMP-1. They also prevent the expression of VEGF. However, only holothurin A1 inhibits the expression of NF-κB, which indicates that the antimetastatic activity of not all triterpene glycosides is NF-κB-dependent [38]. Another compound from *P. graeffei*, ds-echinoside A, exhibits anti-metastatic activity in HepG2 cancer cells by suppressing NF-κB expression, followed by inhibiting MMP-9 and VEGF expressions [39].

2.6. Immunomodulating mechanisms

In addition to their direct effect on cancer cells, glycosides are supposed to influence the cell microenvironment, in particular immune cells. The most common among them are tumor-associated macrophages (TAMs). The latter play a key role in the interaction between tumor and the microenvironment. Macrophages are divided into the two major types, M1 and M2, differing in their metabolism and morphology. The presence of iNOS that catalyzes nitric oxide (NO) production and high levels of NO are typical for the M1 type, and high activity of arginase is a marker of M2 macrophages. TAMs are represented mainly by M2 macrophages [84]. There are several anti-cancer agents derived from marine organisms (synthetic analogues of substances from mollusks, ascidians, and some other invertebrates) that combine efficacy in killing cancer cells and immunoregulation. Most of them can repolarize macrophages into the M1 phenotype [17]. The potential of anti-cancer agents from sea cucumbers to influence macrophage polarization is poorly studied. In particular, cucumarioside A2-2 stimulates NO and ROS production in spleen macrophages, which indicates the promotion of M2 to M1 polarization. Furthermore, studies on RAW 264.7 macrophages treated with drivers of macrophage polarization showed that cucumarioside A2-2 stimulates polarization toward the M1-phenotype [85]. Frondoside A from *C. frondosa* also stimulates spreading, lysosomal activity, and the generation of ROS in macrophages. Moreover, frondoside A, being a blocker for EP4 prostaglandin receptors, protects natural killer (NK) cells from PGE2 mediated suppression and inhibits breast cancer metastases in an NK cell-dependent manner [4]. However, there is no data on the effect of sea cucumber-derived glycosides on TAMs in cancer. Thus, the immunomodulatory effect of glycosides in cancer should be given more attention in the future.

3. Proteins and peptides

Proteins make up more than 70% of holothurian's body wall [86] and represent another class of compounds with anticancer properties. As shown in the Table 3, total body-wall protein from *H. leucospilota* has a cytotoxic effect on HepG2, A549, and pancreatic adenocarcinoma Panc02 cancer cell lines through the induction of apoptosis. In addition, the total body-wall protein can selectively block phases of the cell cycle depending on the cell line; for example, it triggers G0/G1 phase arrest in HepG2 cells, increases the proportion of cells in the G0/G1 phase in A549 cells, and reduces the G0/G1 phase of Panc02 cells. Furthemore, the protein treatment reduces the proportion of cells in the G2/M phase in HepG2 cells and A549 cells, and increases the G2/M phase of Panc02 cells. Notably, the protein targets tumor, but not normal, cells [87]. The potential of *C. frondose*-derived peptides in suppressing breast cancer growth was demonstrated using a molecular docking analysis based on peptide binding to overexpressed EGFR, PI3K, AKT1, and cyclin dependent kinase 4 (CDK4) proteins [88]. In

particular, EGFR and CDK4 regulate cell proliferation, and their activation through the estrogen receptor ER+ is often involved in the development of breast cancer.

Table 3. Anticancer activity of sea cucumber-derived proteins.

Cancer type/line/model	Protein/peptide	Species	Effect	Ref
HepG2	Total body-wall	*H. leucospilota*	Cytotoxic, inducing the G0/G1 phase arrest, reducing the proportion of cells in the G2/M phase	[87]
A549	Total body-wall	*H. leucospilota*	Cytotoxic, increasing the G0/G1 phase, reducing the proportion of cells in the G2/M phase	[87]
Panc02	Total body-wall	*H. leucospilota*	Cytotoxic, reducing the proportion of cells in G0/G1 phase, and increasing the proportion in G2/M phase	[87]
Molecular docking analysis	Peptides	*C. frondosa*	Suppressing breast cancer growth via peptide binding to overexpressed EGFR, PI3K, AKT1, and CDK4 proteins	[88]
MCF-7	Peptides	*A. japonicus*	Triggering apoptosis by upregulating caspase-9, caspase-3, and cytochrome *c* expression. Inhibiting PI3K/Akt pathway	[89]
Lewis lung carcinoma	Protein	*A. japonicus*	Apoptosis, inhibition of the adhesion, migration, and invasion	[90]
A549	Protein	*A. japonicus*	Inhibition of the proliferation, migration and invasion	[91]

Peptides with a relative molecular weight <2,000 Da isolated from intestine of *Apostichopus japonicus* induces apoptosis of MCF-7 cells *in vitro*. The peptides increase the expression of cleaved caspase-9 and cleaved caspase-3, but not caspase-8, and enhances the cytochrome c expression in MCF-7 cells. Thus, apoptosis occurs via the intrinsic apoptosis pathway, including the inhibition of the PI3K/Akt pathway [89]. Moreover, ADAMTS13 human protease-like protein is isolated from *A. japonicus*. This protein contains 10 TSP1 domains, one of which (the third), named Aj-Tspin, contains an arginine–glycine–aspartate (RGD) motif characteristic of disintegrins. Its theoretical molecular weight is 6.976 kDa. Aj-Tspin suppresses the proliferation of Lewis lung carcinoma cells through apoptosis and inhibits the adhesion, migration, and invasion of tumor cells [90]. The holothurian-derived peptide also effectively inhibits the proliferation, migration, and invasion of A549 cells. The tumor suppressor gene TUSC2 targeted by miR-378a-5p is involved in the inhibition [91].

Studies of the anticancer action of proteins and peptides isolated from sea cucumbers have been mainly developed in the last five years and they demonstrate the high potential of these compounds for cancer treatment.

4. Sphingoid-based substances

Another type of compounds from sea cucumbers is sphingolipids, including, in particular, sphingosides (Table 4). For example, cerebrosides and gangliosides contain long chain amino alcohol sphingosine (Figure 5) or its derivative, an amide-linked fatty acid and a polar head group such as carbohydrates. Additionally, gangliosides contain sialic acids. The composition of gangliosides in sea cucumbers differs from that in mammals, particularly by the direct binding of sialic acid to the glucose component and the sandwich-like interlayer of two or three sialic acids between sugar chains. Moreover, sialic acids play an important role in the bioactivity [92]. Sphingoid bases from *Stichopus variegatus* has a cytotoxic effect on colorectal cancer cell lines DLD-1, WiDr, and Caco-2 and induce apoptosis through the activation of caspase-3 and regulation of the Bcl-2 gene family. Notably, the cytotoxic doses of sphingolipids used have little impact on normal cells. However, these substances, derived from mammals, are digested in the intestine [92] and, therefore, the oral administration of sphingolipids as drugs is in question.

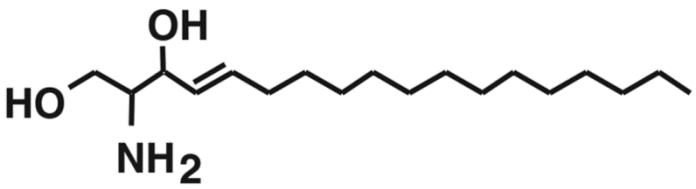

Figure 5. Structure of sphingosine.

In their study on the anti-HepG2 activity of structural variants of sphingolipids from *C. frondosa*, Jia et al. [93] found that all glucocerebrosides (cerebrosides in which the monosaccharide group is glucose), ceramides (sphingoid base linked to a fatty acid, Figure 6), and long-chain bases inhibit cancer cell proliferation, with ceramide being the most effective.

Ceramides induce apoptosis through a special mechanism. They directly increase mitochondrial outer membrane permeabilization, which is a key event in apoptotic signaling, by forming ceramide channels, followed by the release of cytochrome c from the mitochondria into the cytosol. Moreover, activation of CerS5 and the increase in ceramide level can induce lethal autophagy in cancer cells. However, the studies on the outcome of colorectal patients highlighted that overexpression of CerS5 and the increase in ceramide level correlate with a more aggressive cancer by unknown mechanisms [94]. The sea cucumber ceramides were not used in these studies. Moreover, a study by Du et al. [95] showed that the effect of glucocerebroside depends on the chemical structure of its sphingoid base and the fatty acid composition, though there is a need to further study the mechanisms of action of sphingoid-based compounds isolated from sea cucumbers.

Table 4. Anticancer activity of sphingoid-based substances from sea-cucumbers.

Cancer cell line	Sphingoid base	Species	Effect	Ref
WiDr	Sphingoid bases	*S. variegatus*	Cytotoxic, inducing apoptosis through activation of caspase-3 and regulation of Bcl-2	[92]
DLD-1	Sphingoid bases	*S. variegatus*	Cytotoxic, inducing apoptosis through activation of caspase-3 and regulation of Bcl-2	[92]
Caco-2	Sphingoid bases	*S. variegatus*	Cytotoxic, inducing apoptosis through activation of caspase-3 and regulation of Bcl-2	[92]
HepG2	Ceramides	*C. frondosa*	Apoptosis through formation of ceramide channels and increased mitochondrial outer membrane permeabilization	[93,94]

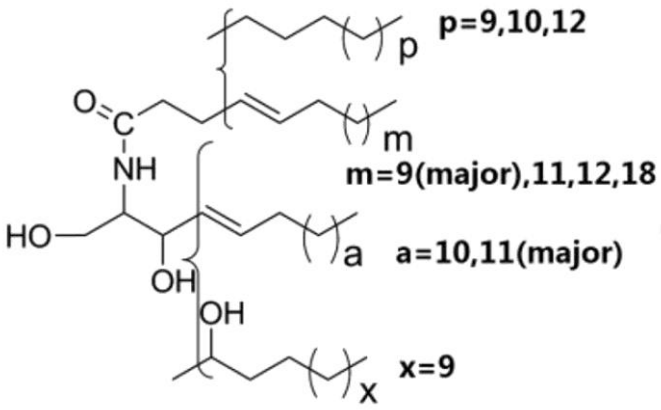

Figure 6. Structure of ceramide from *C. frondosa*.

5. Polysaccharides

There are two major types of polysaccharides in holothurians: Fucoidans (sulfated fucans), containing sulfated carbohydrate, mainly fucose, residues [96], and mucopolysaccharides, or glycosaminoglycans (GAGs), consisting of D-glucuronic acid, N-acetyl-D-galactosamine residues, and sulfate ester groups [97]. It was shown (Table 5) that SvF3 (Figure 7), a fucoidan, isolated from the body wall of *S. variegatus*, does not exhibit cytotoxicity toward T47D and MDA-MB-231 cancer cell lines, but inhibits their growth in the colony and migration of MDA-MB-231 cells *in vitro* [98]. A fucoidan from *C. frondosa* has significant cytotoxic and antimetastatic effects on U2OS human osteosarcoma. The latter effect is due to the influence on the metastasis mechanisms associated with rearrangements of the cytoskeleton [99], the regulation of which is performed with the involvement of the Rho small guanosine triphosphatase (GTPase) family, in particular, Rac1 [100]. Fucoidan decreases

the F-actin content and disrupts the Rac1 activation and the subsequent signaling pathway for cytoskeletal rearrangement [99]. In addition, the purified fraction F2 from the water-soluble protein-sulfated fucan (PSF) complex from *A. japonicus* (former name *Stichopus japonicus*) is effective in stimulating the cytotoxicity of NK against HeLa, HepG2, and HT-29 cancer cell lines [101]. The PSF also displays a potential to stimulate macrophage programming into M1 cells [96].

Table 5. Anticancer activity of polysaccharides from sea-cucumbers.

Cancer cell line	Polysaccharides	Species	Effect	Ref
	Fucoidans			
T47D	SvF3	*S. variegatus*	Inhibition of the growth in colony	[98]
MDA-MB-231	SvF3	*S. variegatus*	Inhibition of the growth in colony and cell migration *in vitro*	[98]
U2OS	Fucoidan	*C. frondosa*	Cytotoxic and antimetastatic effects through reduced F-actin production and inhibition of Rac1 activation, resulting in cytoskeletal rearrangement	[99]
HeLa, HepG2, and HT-29	Purified fraction F2 from the water-soluble PSF	*A. japonicus*	Stimulation of NK cell cytotoxicity against tumor cells	[101]
	Glycosaminoglycans (GAGs)			
YAC-1	GAG	*A. japonicus*	Cytotoxicity through activation of NK cell–mediated antitumor activity	[97]
B16	GAG	*A. japonicus*	Cytotoxic, through activation of antineoplastic activity of CTLs	[97]
B16F10	GAG	Sea cucumber	Inhibition of tumor cell adhesion and migration by regulating the protein levels of integrins, focal adhesion kinase, and MMP-2/9	[102]
HepG2	SJAMP	*A. japonicus*	Inhibition of proliferation by upregulating nm23-H1 and inducing apoptosis by downregulating Bcl-2	[104]

Continued on next page

Cancer cell line	Polysaccharides	Species	Effect	Ref
HepG2	HfFucCS	*Holothuria floridana*	Preventing carcinogenesis by disrupting the interaction of Sulf-2 with cell-surface heparan sulfate	[105]
4T1	Oligosaccharides	*H. floridana* *H. fuscopunctata*	Inhibition of heparan sulfate degradation and preventing tumor angiogenesis and metastasis	[104, 106]
A549	GAG	*A. japonicus*	Inhibition of proliferation by inducing cell cycle arrest in the G1 and G2 phases. Enhancement of the inhibitory effect of DDP on A549 cells by downregulating Bcl-2 and survivin and upregulating Bax and caspase-3	[107]
A549	GAG	*C. frondosa*	Cytotoxicity, promotion of apoptosis. Enhancement of the sensitivity of A549 cells to hematoporphyrin derivative-photodynamic therapy	[108]

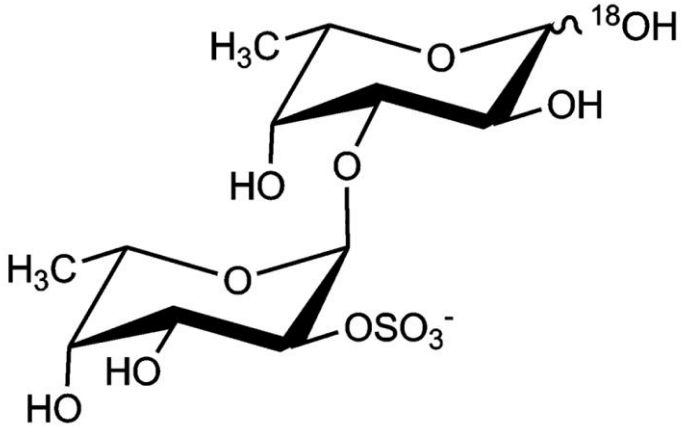

Figure 7. Proposed structural basis of monosulfated SVF3 from *S. variegatus*.

GAGs of marine animals differ from those of terrestrial organisms, mostly in terms of molecular weight and sulfation degree [102]. Moreover, fucosylated glycosaminoglycans (Figure 8), which are GAG derivatives, are exclusively in sea cucumbers [103]. In their native state, these compounds are part

of proteoglycans. GAG from *A. japonicus* promote antineoplastic activity of NK cells against YAC-1 lymphoma cells and specific-cytotoxic T lymphocytes (CTLs) against B16 melanoma cells [97]. GAG from the sea cucumber inhibits P-selectin-mediated B16F10 tumor cell adhesion and migration *in vitro* through the regulation of protein levels of integrins, focal adhesion kinase, and MMP-2/9 [102]. The acid mucopolysaccharide SJAMP from the sea cucumber *A. japonicus* (*S. japonicus*) inhibits the proliferation and induces apoptosis of HepG2 cells, decreasing the expression of Bcl-2 and increasing the expression of nm23-H1 (an inhibitor of tumor cell proliferation) [104].

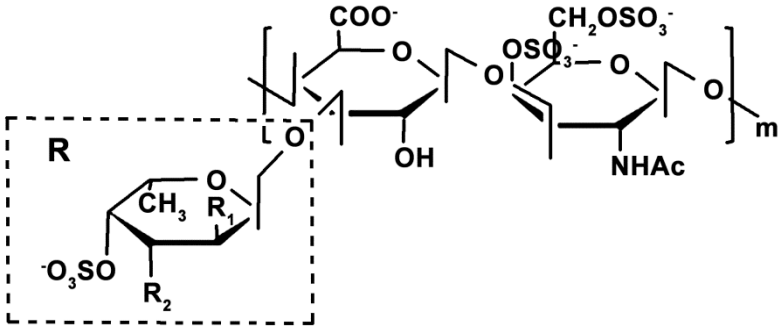

Figure 8. Proposed structural unit for glycosaminoglycan from *A. japonicus*.

A unique glycosaminoglycan, fucosylated chondroitin sulfate HfFucCS, with 3,4-disulfated fucose structural motif, from the sea cucumber *Holothuria floridana* disrupts the interaction of heparan-6-O-endosulfatase 2 (Sulf-2) and surface heparan sulfate. Sulf-2 plays an important role in physiological modification of the cell surface and extracellular matrix, and its dysregulation contributes to carcinogenesis. The targeted inhibitory effect of HfFucCS on Sulf-2-associated damage to cell surface indicates the prospects for further studies of its anticancer action [105].

Oligosaccharides derived from fucosylated GAG from *H. floridana* [104] and *Holothuria fuscopunctata* [106] act as heparanase inhibitors, preventing degradation of heparan sulfate, a critical process for tumor angiogenesis and metastasis. The antimetastatic effect has been demonstrated for 4T1 mammary carcinoma cells [106].

In addition, GAG increases the sensitivity of lung cancer cells to chemotherapy. A combined administration of GAG from *A. japonicus* and cisplatin (cis-diamminedichloroplatinum(II)) (DDP) enhances the inhibitory effect of DDP on A549 cells through an apoptosis mechanism, including the reduction in Bcl-2 and survivin, and the increase in Bax and caspase-3 expression. GAG can also promote cell cycle arrest in the G1 and G2 phases [107]. Studies have also been conducted on the combined anticancer effects of GAG and phototherapy. A GAG from *C. frondosa* inhibits proliferation and promotes apoptosis of A549 cells. This compound also enhances the sensitivity of A549 cells to hematoporphyrin derivative-photodynamic therapy [108].

Thus, both types of polysaccharides exhibit cytostatic, antimetastatic, immunomodulatory, and anticoagulant activities [99,102,109]. However, their cytostatic activity is observed only at high concentrations. For example, only a concentration of fucoidan from *C. frondosa* ≥400 μg/mL exhibits a cytotoxic effect on U2OS cells after 24 h of incubation [99], while a 100 μg/mL concentration of GAG from *A. japonicus* induces apoptosis in the A549 cells after 24 h, comparable to the effect of

DDP (3 μg/mL) [107]. In contrast, the complete inhibition of HepG2 cells is achieved within 12 h upon treatment with echinoside A from *H. scabra* at a concentration of 3 μg/mL [20]. Available data on the antimetastatic activity of GAGs and their potentiating effects on known cytostatic agents suggest their higher potential as drug candidates for cancer therapy compared to fucoidans.

However, it should be noted that the anticancer activity of polysaccharides derived from holothurians, as well as their mechanisms of action, especially *in vivo,* remain poorly studied. In addition, since GAGs are part of proteoglycans, their activity may depend on the protein moiety, which can, for example, influence the binding of molecules to the membranes of immune cells and, consequently, the regulation of their activity [96]. Similarly, the activity of fucoidans is influenced by bound proteins and by the degree of sulfation [101]. This is important for the immunomodulatory component of these substances and requires further investigation to determine the significance of the protein component of glycoproteins. Furthermore, the efficacy of GAGs [96] and fucoidans [101] is influenced by the degree of sulfation of the molecules, which affects their binding to cells and requires further study to better understand their mechanisms of action and to enable the development of standardized preparations. In addition, the anticoagulant properties of GAGs depend on their concentration. At low doses, a procoagulant tendency has been observed [109], which may contribute to thrombosis. In contrast, at doses that produce an anticoagulant effect of polysaccharides, there is a risk of bleeding. This highlights the need for careful dose selection when developing drug candidates. Further, it was found that depolymerized holothurian glycosaminoglycan is partially absorbed in the gastrointestinal tract with metabolic degradation, including the loss of groups important for activity such as the sulfate group [110]. This suggests that intravenous administration of GAG is preferable.

6. Effects of sea cucumber-isolated compounds *in vivo*

Most studies on compounds isolated from sea cucumbers have been carried out *in vitro*. Anticancer effects of some substances have been confirmed in *in vivo* models. Glycosides proved to reduce tumor growth *in vivo*. For example, in a xenograft model in mice, frondoside A, administered intraperitoneally, inhibited the growth of AsPC-1 [57], MDA-MB-231 [80], and UM-UC-3 cancer cells [59]. Frondoside A also inhibits angiogenesis and metastasis of LNM35 xenografts [4]. In contrast to the parenteral administration, the oral administration (100 μg/kg/day) of frondoside A for 30 days does not affect the growth of AsPC-1 xenografts. However, when frondoside A is taken orally, metastasis of a number of cancers, including lung, breast, and prostate, declines. Frondoside A also displays activity when administered orally in combination with known drugs (DDP, gemcitabine), increasing their efficacy [19].

In the Balb/c mice model, saponins from *H. moebii* showed antitumor activity against colorectal CT-26 tumor, but at a dose that had a significant effect (120 mg/kg), several side effects were observed related to the liver and spleen [77]. In a mouse model, philinopsides A and E effectively reduced the growth of sarcoma 180, while philinopside E inhibited the growth of hepatoma [1,22]. The effects of echinoside A have also been studied in nude mouse and human prostate carcinoma models. Its anticancer activity is assumed to be associated with the ability to inhibit topoisomerase 2α by a unique mechanism: preventing the enzyme from binding to DNA, disrupting the DNA cleavage and religation. However, the intensity of echinoside A effect varies between cancer cell lines in the same organ [19]. Despite these encouraging results, glycosides have neither been approved as anticancer agents nor been put to clinical trials [59].

Data on *in vivo* antitumor effects of other holothurian-derived compounds are rare. It is known that peptides from *A. japonicus* suppress the growth of MCF-7 xenografts in a dose-dependent manner [89]. Glucocerebrosides from *Acaudina molpadioides* inhibited the growth of S180 tumors in a mouse model. These compounds induced apoptosis by reducing the expression of Bcl-2, Bcl-xL, while up-regulating the Bax, cytochrome c, caspase-9, and caspase-3 mRNA levels of tumor cells [95].

The SJAMP from *A. japonicus* at doses 17.5 mg/kg, 35 mg/kg, and 70 mg/kg, administered 5 days/week *per os*, suppresses the growth of experimental HCC hepatocellular carcinoma in rats, improves biochemical indices, improves the phagocytic activity of macrophages and cytotoxic activity of NK cells, and normalizes the CD4+/CD8+ T cell ratio [111]. Moreover, fucosylated chondroitin sulfate from *Ludwigothurea grisea* inhibits the metastasis of murine colon adenocarcinoma MC-38 cells to the lungs *in vivo* [112]. In addition to their effects *in vitro*, oligosaccharides from fucosylated glycosaminoglycans exhibit antimetastatic effects on 4T1 mammary carcinoma cells in a mouse model [106].

To summarize, the targets of anticancer activity of different classes of compounds from sea cucumbers are presented in Figure 9.

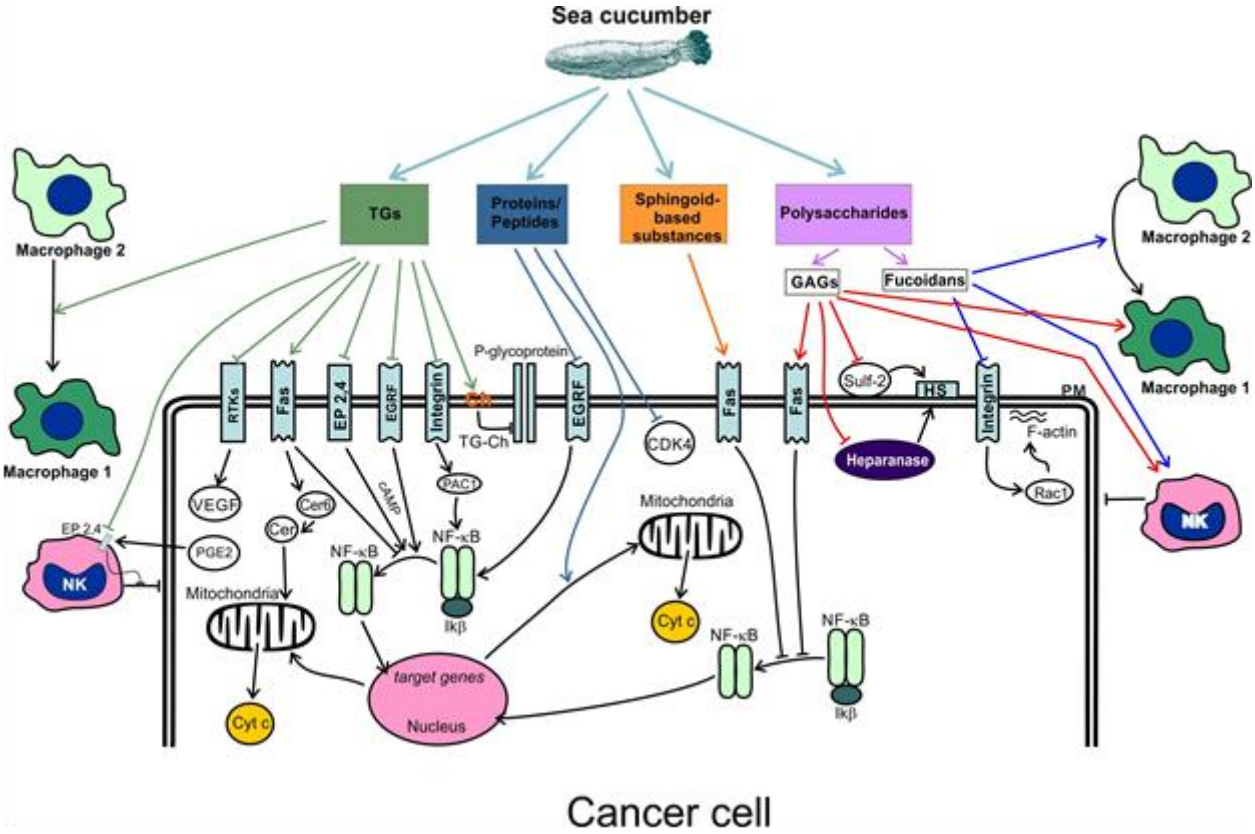

Figure 9. Scheme of modern concepts on the types and targets of the anticancer effects of compounds isolated from sea cucumbers. Individual TGs generally affect cancer cells by binding to receptors on the cell surface, followed by the induction of apoptosis and a decrease in proliferation through inhibition of NF-κB activity and its downstream signaling pathways. The intrinsic pathway of apoptosis is also activated. Moreover, a number of TGs have been shown to form complexes with cell membrane cholesterol and to decrease the activity of the transport protein P-glycoprotein, thereby inhibiting the efflux of substances

from the cell through the PM and reducing multidrug resistance in tumor cells. Inhibition of EPs and EGFR via COX-2-dependent mechanisms contributes to the antimetastatic effects of TGs. Inhibition of EGFR tyrosine kinases, as well as other TRKs, contributes to their anti-angiogenic effects. TGs can additionally reprogram M2 macrophages into M1 type and reduce cancer-induced immunosuppression. For other types of compounds, data on the mechanisms underlying their anticancer effects remain limited. Peptides induce apoptosis via the intrinsic pathway and are thought to inhibit cell proliferation by binding to CDK4 or EGFR, as well as some other cellular receptors. Sphingoid-based substances induce apoptosis through an NF-κB-dependent pathway. GAGs influence cancer cells through modulation of NF-κB activity, as well as by inhibiting Sulf-2 and heparanase, thereby preventing HS degradation and cell surface damage. Fucoidans exhibit the ability to reduce F-actin levels and cytoskeletal rearrangements. Both types of polysaccharides can activate immune cells. Moreover, fucoidans can promote the reprogramming of M2 macrophages toward the M1 phenotype. Abbreviations: cAMP, cyclic adenosine monophosphate; CerS, ceramide synthase; Ch, cholesterol; Cyt c, cytochrome c; EGFR, epidermal growth factor receptor; EP2,4, prostaglandin E receptors EP2 and EP4; CDK4, cyclin dependent kinase 4; Fas, Fas death receptor; GAG, glycosaminoglycan; HS, heparan sulfate; NF-κB, nuclear factor kappa B; NK, natural killer; PAK1, p21 protein (Rac/Cdc42)-activated p21-kinase; PM, plasma membrane; Sulf-2, Heparan-6-O-endosulfatase 2; TGs, triterpene glycosides; TRKs, receptor tyrosine kinases; VEGF, vascular endothelial growth factor.

7. Safety of use

One of the challenges of using glycosides in cancer therapy is the high sensitivity of erythrocytes to them, often exceeding the sensitivity of cancer cells [52,53]. However, no significant side effects have been reported in some cases. Thus, frondoside A induces an anticancer effect against UM-UC-3 cancer cells in a mouse xenograft model without any significant toxic side-effects [57]. Additionally, the *in situ* treatment with saponins from *H. moebii* has antiglioblastoma effects without side effects on hemolytic activity [113]. Moreover, stichoposide D, inducing apoptosis through increased ceramide levels, displays anti-tumor activity without any toxicity in K562 and HL-60 cell xenograft models used [51].

F2 fraction of PSF complex isolated from the *A. japonicus* (former *S. japonicus*) combined with TNF-related apoptosis-inducing ligand (TRAIL), a member of the tumor necrosis factor (TNF) family of death ligands, selectively induces the apoptosis of DLD-1 and HCT116 colorectal cancer cells but not normal primary colon cells CCD18Co, while F2 or TRAIL alone do not influence apoposis in cancer cells [114]. The mechanisms of selective anticancer effects of the compounds from sea cucumbers remain unclear.

A search for approaches to reduce the toxic side effects of glycosides shows promising results when some substances are added to glycosides. A decrease in the hemolytic activity of glycosides from *C. japonica* is achieved by combining cucumarioside A2-2 as a basic substance of lead Cumaside with cholesterol. A 10-fold decrease in hemolytic activity compared to glycosides has been demonstrated, while the lead is active in suppressing different forms of experimental mouse Ehrlich carcinoma *in vivo* [115].

In the context of reduction in toxicity of glycosides, their use in combination with other substances in extracts seems promising. New studies of sea cucumber extracts support this idea (Table 6).

Table 6. Anticancer effects of the extracts from sea cucumbers.

Species/solvent	Cancer (line)/anticancer effect	Mechanism	Ref
H. tubulosa/cell-free coelomic fluid	HepG2/ cytotoxic effect, suppression of migration	Suppression of autophagy	[116]
C. frondosa /isopropyl alcohol/water (Frondanol A5)	S2013 and AsPC-1/ inhibition of proliferation and inducing G2/M phase cell cycle arrest	Induction of phosphorylation of SAPK/JAK and MAPK, increase in expression of p21, activation of caspase-3. Decrease in expression of cyclin A, cyclin B, and cdc25c	[119]
C. frondosa /isopropyl alcohol/water (Frondanol A5)	HCT116/ inhibition of growth	Apoptosis via histone *H2AX* phosphorylation, increase in p21 expression and activation of caspase-2	[120,121]
A. japonicus/water 98 ℃ 1 h	Caco-2/ inhibition of viability and proliferation	N/d	[122]
Sea cucumber/water (TBL-12)	LNCaP, 22RV1, PC-3, and DU145/ inhibition of the proliferation, colony formation, migration, and invasiveness *in vitro* and inhibition of tumor growth in xenograft PCa mice	Suppression of MMP-2 and MMP-9 and decrease in surviving by activating caspase-9, caspase-7, and PARP. Inhibition of the secretion of angiogenic factors, including VEGF	[123]
H. edulis / water or water/MeOH–CH_2Cl_2/MeOH	A549, TE1/ cytotoxic effect, inhibition of growth	High antioxidant activity	[124]
S. horrens/ water or water/MeOH–CH_2Cl_2/MeOH	A549, TE1/ cytotoxic effect, inhibition of growth	High antioxidant activity.	[124]
H. leucospilota/ water/MeOH–CH_2Cl_2 or MeOH	A549, C33A/ antiproliferative effect	N/d	[125]
H. leucospilota/ MeOH	SK-BR-3/ cytotoxic and antiproliferative effect, arrest of the cells in G2/M phase	Apoptosis through the downregulation of Bcl-2 and upregulation of Bax, caspase-3, and caspase-7 proteins	[126]
H. scabra/ MeOH–CH_2Cl_2/MeOH	A549, C33A/ antiproliferative effect	N/d	[125]
S. chloronotus/ water	A549, C33A/ antiproliferative effect	N/d	[125]

Continued on next page

Species/solvent	Cancer (line)/anticancer effect	Mechanism	Ref
S. chloronotus/ MeOH–CH_2Cl_2/ MeOH	A549, C33A/ antiproliferative effect	N/d	[125]
H. parva/ MeOH	HCC/apoptosis	ROS generation, releasing cytochrome c, degradation of MMP, and inducing caspase-3 cleavage	[127]
H. parva/ MeOH	CCL/ cytotoxicity	Apoptosis through the increase in the level of ROS and the release of cytochrome c from mitochondria, and the degradation of MMP	[128]
H. scabra/ MeOH	PC3/cytotoxicity and inhibition of the invasion	Apoptosis through upregulation of JNK and p38 signaling pathways; downregulating MMP-2/-9 expression via the ERK pathway	[129]
H. polii/water	MDA-MB-231/ cytotoxic and anti-proliferative properties, arrest in the S-phase	N/d	[131]
	SCp2	Suppressing levels of MMT-9, NO, IL-6	[131]
	THP-1	Suppressing level of IL-1β	[131]

Note: N/d- mechanisms have not been determined.

As shown by Luparello et al. [116], cell-free coelomic fluid from *Holothuria tubulosa* has a cytotoxic effect on HepG2 cells, which is associated with the suppression of autophagy. In addition, such an extract (presumably its protein components) suppresses the migration of cancer cells. However, a more detailed study of individual proteins has not been carried out.

Frondanol A5, which is an isopropyl alcohol/water extract of the enzymatically hydrolyzed epithelium from *C. frondosa*, contains a complex of sulfated glycosides, including frondoside A, unsaturated fatty acids, fucosylated chondroitin sulfate, and carotenoids [117,118]. Frondanol A5 causes apoptosis in pancreatic cancer cells S2013 and AsPC-1 [119] and the HCT116 colon cancer cell line [120]. In pancreatic cancer cell lines, Frondanol A5 also induces G2/M phase cell cycle arrest. The mechanisms of apoptosis and inhibition of proliferation include the induction of phosphorylation of stress-activated protein kinase and Janus kinase (SAPK/JAK) and MAPK, increase in the expression of p21, activation of caspase-3, and the decrease in expressions of cyclin A, cyclin B, and cdc25c [119]. In HCT116 cells, the extract induces apoptosis via histone H2AX phosphorylation followed by the activation of caspase-2. Caspase-2 is known to play a role in early apoptosis or to increase cell survival depending on the cell type and/or stimulus [121]. Therefore, the caspase-2-inducing effect of Frondanol A5 needs to be further elucidated. In a rat model of colon cancer, the extract increased the p21 expression and apoptosis, and proved to be effective against tumor growth (aberrant crypt foci) [120].

Aqueous extract (98 °C, 1 h) of *A. japonicus* (former *S. japonicus*) significantly inhibits proliferation and induces cytotoxicity in Caco-2 cells. Hot water extraction makes it possible to collect high molecular weight compounds, such as glycosaminoglycans and collagen [122]. The holothurian extract TBL-12 induces apoptosis, inhibits the proliferation, colony formation, migration, and invasiveness of prostate cancer cells (LNCaP, 22RV1, PC-3, and DU145) *in vitro*, and significantly inhibits tumor growth in xenograft prostate cancer mice *in vivo*. The extract also suppresses MMP-2 and MMP-9 and reduces cell viability by activating caspase-9, caspase-7, and PARP. In addition, it inhibits the secretion of angiogenic factors [123]. Moreover, aqueous and organic extracts of *Holothuria edulis* and *S. horrens* show high antioxidant activity, but water non-soluble compounds obtained by re-extraction with methanol (MeOH)–CH_2Cl_2 (1:1 v/v), followed by MeOH (100%), exhibit significantly higher cytotoxic activity against A549 cells and an even more pronounced effect against TE1 human esophageal squamous cell carcinoma. The organic extracts are suggested to be rich with sphingoid bases [124].

Similarly, the water-insoluble substances from *H. leucospilota*, *H. scabra*, and *S. chloronotus* re-extracted with organic solvents exert anti-proliferative effects on human A549 cells and C33A cervical cancer cells, with the *H. scabra* extract being the most effective. However, of the aqueous extracts, only that of *S. chloronotus* is active against these cancer cells. It is hypothesized that the aqueous fractions are enriched in TGs, whereas the organic fractions are enriched in hydrophobic sphingoid bases. No correlation has been found between antioxidant and antiproliferative activity levels [125].

Methanolic extracts are abundant in TGs but also contain other compounds. A methanolic extract of *H. leucospilota*, containing over 30 substances of different molecular classes, demonstrates cytotoxic activity against SK-BR-3. The effect is associated with apoptosis through the downregulation of Bcl-2 and the upregulation of Bax, caspase-3, and caspase-7 proteins. The extract also arrests the cell growth in G2/M phase and inhibits the proliferation of cancer cells [126]. A methanolic extract of *Holothuria parva* induces apoptosis in mouse HCC cells but not in non-cancerous hepatocytes by releasing cytochrome c from mitochondria and inducing caspase-3 cleavage [127]. It also induces apoptosis, stimulates caspase-3, and increases the level of ROS, the release of cytochrome c from mitochondria, and the degradation of MMP in CLL cells, but not in normal lymphocytes [128]. In PC3 cells, the methanolic extract of *H. scabra* induces apoptosis, reduces cell viability by upregulation of JNK and p38 signaling pathways, and inhibits the invasion of PC3 cells by downregulating the MMP 2/9 expression via the ERK pathway [129].

It is worth noting that the extracts, similarly to the mixtures of glycosides with other compounds [115,130], can be less toxic compared to a single compound. Ethanolic extract and the aqueous, but not organic, fractions of *H. polii* demonstrate anti-proliferative effects on MDA-MB-231 cells, causing an arrest in their S-phase at noncytotoxic concentrations. As shown for mammary epithelial cells and THP-1 human monocytic cells, the mechanism of the aqueous fraction activity may include the suppression of generating the inflammatory markers, such as MMT-9, NO, IL-6, and IL-1β [131].

As Liang et al. [19] noted, 72 *in vivo* tests of sea cucumber-derived compounds were carried out during 2012–2021. The substances tested were mostly glycosides (16%), extracts (13%), and glycosaminoglycans (10%). However, no clinical studies on anticancer activity of compounds isolated from holothurians have been conducted to date, with the exception of TBL12 Sea Cucumber Extract NCT01302366. In the latter case, the researchers focused on asymptomatic (smouldering) myeloma MM. Unfortunately, stage 2 was interrupted independently of results [132].

The introduction of the extracts into clinical practice is also hampered by the poor knowledge of

pharmacological effects of its constituent substances. Among other reasons is also the limited natural resource that cannot provide industrial production [6,8]. This problem can be addressed by creating mariculture and/or developing synthetic or semisynthetic analogues, as it has been done for a number of anti-cancer drugs based on a synthetic derivative of dolastatin 10 pentapeptide from the sea slug *Dolabella auricularia* [17].

It is also known that the content of saponins and other biologically active substances in sea cucumber tissues may vary depending on the region and season. Moreover, external factors such as ambient temperature, light, and salinity may influence the metabolism in sea cucumbers [133]. Therefore, the effect of the environment on holothurian's metabolism could be a promising subject of further studies to standardize pharmaceutical raw material.

The accumulated material on the safety of sea cucumber extracts and on the selective effect of individual substances on cancer cells, reducing the toxicity of glycosides when combined with some other substances, provide the basis for further research in these areas to obtain effective and safe anticancer drugs and, consequently, to perform their dedicated clinical trials.

8. Conclusions

Sea cucumber tissues contain many compounds with anticancer activity, with triterpene glycosides being the best studied. Their sulfated forms exhibit the greatest cytotoxicity to many tumors, causing apoptosis or autophagy of cancer cells. However, most triterpene glycosides *in vivo* also cause a toxic effect on the body, and this limits their use in clinical practice as monotherapy. Nevertheless, for some of the glycoside-based leads, for example, frondoside A and Cumaside, sufficiently encouraging results for anticancer therapy have been obtained: They are toxic toward cancer cells and not healthy cells.

In addition, some other classes of compounds such as proteins, cerebrosides, and polysaccharides have also shown high anticancer activity: They often kill cancer cells through mechanisms other than those of glycosides, and have a much milder effect on healthy cells. Thus, the use of triterpene glycosides in combination with other substances appears to be a novel and promising approach, reducing the concentration and toxicity of the glycosides while maintaining therapeutic efficacy. It is also important to further study the immunomodulatory properties of these agents and identify those contributing to inhibiting TAMs activity, in addition to exhibiting toxicity to cancer cells. In general, the high anticancer activity of compounds from holothurians enables them to be promising drug candidates for effective treatment of cancer.

Use of Generative-AI tools declaration

The author declares that Artificial Intelligence (AI) tools have not been used in the creation of this article.

Acknowledgments

The study was performed as part of the state assignment of the Ministry of Science and Higher Education of the Russian Federation (no. 121021500052-9).

Conflict of interest

The author declares no conflicts of interest in this paper.

References

1. Wargasetia TL, Widodo (2017) Mechanisms of cancer cell killing by sea cucumber-derived compounds. *Invest New Drugs* 35: 820–826. https://doi.org/10.1007/s10637-017-0505-5
2. Schulz WA, Ribarska T (2011) Insights into cancer mechanisms from genomic research on urological cancers. *Genome Med* 3: 20. https://doi.org/10.1186/gm234
3. Kumar MS, Adki KM (2018) Marine natural products for multi-targeted cancer treatment: A future insight. *Biomed Pharmacother* 105: 233–245. https://doi.org/10.1016/j.biopha.2018.05.142
4. Adrian TE, Collin P (2018) The anti-cancer effects of Frondoside A. *Mar Drugs* 16: 64. https://doi.org/10.3390/md16020064
5. Zare A, Izanloo S, Khaledi S, et al. (2023) A bibliometric and in silico-based analysis of anti-lung cancer compounds from sea cucumber. *Mar Drugs* 21: 283. https://doi.org/10.3390/md21050283
6. Mariyatib JT, Tuwo A (2021) Species composition and density of sea cucumbers in Buru Regency, Maluku province, Indonesia. *IOP Conf Ser Earth Environ Sci* 860: 012004. https://doi.org/10.1088/1755-1315/860/1/012004
7. Mackenzie M, O'Loughlin PM, Griffiths H, et al. (2021) Sea cucumbers (Echinodermata, Holothuroidea) from the JR275 expedition to the eastern Weddell Sea, Antarctica. *Zookeys* 1054: 155–172. https://doi.org/10.3897/zookeys.1054.59584
8. Purcell SW, Conand C, Uthicke S, Byrne M (2016) Ecological roles of exploited sea cucumbers. *Oceanogr Mar Biol* 54: 367–386.
9. Patar A, Jamalullail SMS, Jaafar H, et al. (2012) The effect of water extract of sea cucumber *Stichopus variegatus* on rat spinalastrocytes cell lines. *Curr Neurobiol* 3: 11–16.
10. Zhao YC, Xue CH, Zhang TT, et al. (2018) Saponins from sea cucumber and their biological activities. *J Agric Food Chem* 66: 7222–7237. https://doi.org/10.1021/acs.jafc.8b01770
11. Tolon MT, Engin S (2019) Gonadal development of the holothurian *Holothuria polii* (Delle Chiaje, 1823) in spawning period at the Aegean Sea (Mediterranean Sea). *EgeJFAS* 36: 379–385. https://doi.org/10.12714/egejfas.36.4.09
12. Choo PS (2008) Population status, fisheries and trade of sea cucumbers in Asia, In: Toral- Granda V, Lovatelli A, Vasconcellos M, Eds., *Sea cucumbers. A global review of fisheries and trade. FAO Fisheries and Aquaculture Technical Paper*, Rome: FAO, 81–118. Available from: https://openknowledge.fao.org/handle/20.500.14283/i0375e.
13. Ahmad SI, Ahmad R, Khan MS, et al. (2020) Chitin and its derivatives: Structural properties and biomedical applications. *Int J Biol Macromol* 164: 526–539. https://doi.org/10.1016/j.ijbiomac.2020.07.098
14. Salindeho N, Nurkolis F, Gunawan WB, et al. (2022) Anticancer and anticholesterol attributes of sea cucumbers: An opinion in terms of functional food applications. *Front Nutr* 9: 986986. https://doi.org/10.3389/fnut.2022.986986

15. González-Wangüemert M, Domínguez-Godino JA, Cánovas F (2018) The fast development of sea cucumber fisheries in the Mediterranean and NE Atlantic waters: From a new marine resource to its over-exploitation. *Ocean Coast Manage* 151: 165–177. https://doi.org/10.1016/j.ocecoaman.2017.10.002
16. Mukhortova AM, Uzbekova OR, Lyzhov II, et al. (2018) Comparative technical and chemical properties and promising ways of processing for holothurians *Molpadia arctica*, *Molpadia borealis* and *Cucumaria frondosa* from the Barents and the Kara Seas. *Rybnoe Khozyaystvo* (Fisheries) 1: 36–40.
17. Dolmatova LS, Dolmatov IY (2021) Tumor-associated macrophages as potential targets for anti-cancer activity of marine invertebrate-derived compounds. *Curr Pharm Des* 27: 3139–3160. https://doi.org/10.2174/1381612827666210319125652
18. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2023). Djakonoviosides A, A_1, A_2, B_1–B_4—ttriterpene monosulfated tetra- and pentaosides from the sea cucumber *Cucumaria djakonovi*: The first finding of a hemiketal fragment in the aglycones; activity against human breast cancer cell lines. *Int J Mol Sci* 24: 11128. https://doi.org/10.3390/ijms241311128
19. Liang Q, Ahmed F, Zhang M, et al. (2022) *In vivo* and clinical studies of sea cucumber-derived bioactives for human health and nutrition from 2012-2021. *Front Mar Sci* 9: 917857. https://doi.org/10.3389/fmars.2022.917857
20. Wang J, Han H, Chen X, et al. (2014) Cytotoxic and apoptosis-inducing activity of triterpene glycosides from *Holothuria scabra* and *Cucumaria frondosa* against HepG2 cells. *Mar Drugs* 12: 4274–4290. https://doi.org/10.3390/md12084274
21. Kim SK, Himaya SW (2012) Triterpene glycosides from sea cucumbers and their biological activities. In: *Advances in food and nutrition research.* 65: 297–319. http://doi.org/10.1016/B978-0-12-416003-3.00020-2
22. Wargasetia TL, Ratnawati H, Widodo N (2022) Sea cucumber compounds targeting NF-κB in cancer treatment. *Bioinform Biol Insights* 16: 1–7. https://doi.org/10.1177/11779322221091740
23. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2021) Triterpene glycosides from the Far Eastern sea cucumber *Psolus chitonoides*: chemical structures and cytotoxicities of Chitonoidosides E_1, F, G, and H. *Mar Drugs* 19: 696. https://doi.org/10.3390/md19120696
24. Chawla S, Rockstroh A, Lehman, et al. (2022) Gene expression based inference of cancer drug sensitivity. *Nat Commun* 13: 5680. https://doi.org/10.1038/s41467-022-33291-z
25. Liu BS, Yi YH, Li L (2008) Argusides B and C, two new cytotoxic triterpene glycosides from the sea cucumber *Bohadschia argus* Jaeger. *Chem Biodivers* 5: 1288–1297. https://doi.org/10.1002/cbdv.200890115
26. Zhang SL, Li L, Yi YH, et al. (2006) Philinopsides E and F, two new sulfated triterpene glycosides from the sea cucumber *Pentacta quadrangularis*. *Nat Prod Res* 20: 399–407. https://doi.org/10.1080/14786410500185584
27. Han H, Xu QZ, Tang HF, et al. (2010) Cytotoxic holostane-type triterpene glycosides from the sea cucumber *Pentacta quadrangularis*. *Planta Med* 76: 1900–1904. https://doi.org/10.1055/s-0030-1249854
28. Sun GQ, Li L, Yi YH, et al. (2008) Two new cytotoxic nonsulfated pentasaccharide holostane (=20-Hydroxylanostan-18-oic acid γ-lactone) glycosides from the sea cucumber *Holothuria grisea*. *Helv Chim Acta* 91: 1453–1460. https://doi.org/10.1002/hlca.200890158

29. Zhang Y, Yi Y (2011) Studies on antitumor activities of triterpene glycoside colochiroside A from sea cucumber *Colochirus anceps*. *Zhongguo Zhong Yao Za Zhi* 36: 504–550.
30. Wu J, Yi YH, Tang HF, et al. (2007) Hillasides A and B, two new cytotoxic triterpene glycosides from the sea cucumber *Holothuria hilla* Lesson. *J Asian Nat Prod Res* 9: 609–615. https://doi.org/10.1080/10286020600882676
31. Li M, Miao ZH, Chen Z, et al. (2010) Echinoside A, a new marine derived anticancer saponin, targets topoisomerase 2α by unique interference with its DNA binding and catalytic cycle. *Ann Oncol* 21: 597–607. https://doi.org/10.1093/annonc/mdp335
32. Zhang JJ, Zhu KQ (2017) A novel antitumor compound nobiliside D isolated from sea cucumber (*Holothuria nobilis* Selenka). *Exp Ther Med* 14: 1653–1658. https://doi.org/10.3892/etm.2017.4656
33. Mohsen M, Yang H (2021) *Sea cucumbers: Aquaculture, biology and ecology*. London: Acad Press. https://doi.org/10.1016/C2020-0-01035-2
34. Zou Z, Yi Y, Wu H, et al. (2005) Intercedensides D-I, cytotoxic triterpene glycosides from the sea cucumber *Mensamaria intercedens* Lampert. *J Nat Prod* 68: 540–546. https://doi.org/10.1021/np040205b
35. Liu BS, Yi YH, Li L (2007) Arguside A: A new cytotoxic triterpene glycoside from the sea cucumber *Bohadschia argus* Jaeger. *Chem Biodivers* 4: 2845–2851. https://doi.org/10.1002/cbdv.200790234
36. Liu BS, Yi YH, Li L, et al. (2008) Argusides D and E, two new cytotoxic triterpene glycosides from the sea cucumber *Bohadschia argus* Jaeger. *Chem Biodivers* 5: 1425–1433. https://doi.org/10.1002/cbdv.200890131
37. Omran NEE, Khedr AM (2015) Structure elucidation, protein profile and the antitumor effect of the biological active substance extracted from sea cucumber *Holothuria polii*. *Toxicol Ind Health* 31: 1–8. https://doi.org/10.1177/0748233712466135
38. Zhao Q, Xue Y, Liu ZD, et al. (2010) Differential effects of sulfated triterpene glycosides, holothurin A1, and 24-dehydroechinoside A, on antimetastasic activity via regulation of the MMP-9 signal pathway. *J Food Sci* 75: H280–H288. https://doi.org/10.1111/j.1750-3841.2010.01837.x
39. Zhao Q, Liu ZD, XueY, et al. (2011) Ds-echinoside A, a new triterpene glycoside derived from sea cucumber, exhibits antimetastatic activity via the inhibition of NF-κB-dependent MMP-9 and VEGF expressions. *J Zhejiang Univ Sci B* 12: 534–544. https://doi.org/10.1631/jzus.B1000217
40. Dang NH, Thanh NV, Kiem PV, et al. (2007) Two new triterpene glycosides from the vietnamese sea cucumber *Holothuria scabra*. *Arch Pharm Res* 30: 1387–1391. https://doi.org/10.1007/BF02977361
41. Cuong NX, Vien LT, Hoang L, et al. (2017) Cytotoxic triterpene diglycosides from the sea cucumber *Stichopus horrens*. *Bioorg Med Chem Lett* 27: 2939–2942. https://doi.org/10.1016/j.bmcl.2017.05.003
42. Vien LT, Hoang L, Hanh TTH, et al. (2018) Triterpene tetraglycosides from the sea cucumber *Stichopus horrens*. *Nat Prod Res* 32: 1039–1043. https://doi.org/10.1080/14786419.2017.1378206
43. Zhang SY, Yi YH, Tang HF, et al. (2006) Two new bioactive triterpene glycosides from the sea cucumber *Pseudocolochirus violaceus*. *J Asian Nat Prod Res* 8: 1–8. https://doi.org/10.1080/10286020500034972

44. Zhang SY, Yi YH, Tang HF (2006) Bioactive triterpene glycosides from the sea cucumber *Holothuria fuscocinerea*. *J Nat Prod* 69: 1492–1495. https://doi.org/10.1021/np060106t
45. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2023) Sulfated triterpene glycosides from the Far Eastern sea cucumber *Cucumaria djakonovi*: Djakonoviosides C_1, D_1, E_1, and F_1; cytotoxicity against human breast cancer cell lines; quantitative structure–activity relationships. *Mar Drugs* 21: 602. https://doi.org/10.3390/md21120602
46. Aminin DL, Menchinskaya ES, Pislyagin EA, et al. (2016) Sea cucumber triterpene glycosides as anticancer agents. *Stud Nat Prod Chem* 49: 55–105. https://doi.org/10.1016/B978-0-444-63601-0.00002-8
47. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2024) The composition of triterpene glycosides in the sea cucumber *Psolus peronii*: anticancer activity of the glycosides against three human breast cancer cell lines and quantitative structure-activity relationships (QSAR). *Mar Drugs* 22: 292. https://doi.org/10.3390/md22070292
48. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2012) Triterpene glycosides from the sea cucumber *Eupentacta fraudatrix*. Structure and biological action of cucumariosides A_1, A_3, A_4, A_5, A_6, A_{12} and A_{15}, seven new minor non-sulfated tetraosides and unprecedented 25-keto, 27-norholostane aglycone. *Nat Prod Commun* 7: 517–525.
49. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2013) Structures and biological activities of typicosides A1, A2, B1, C1 and C2, triterpene glycosides from the sea cucumber *Actinocucumis typica*. *Nat Prod Commun* 8: 301–310. https://doi.org/10.1177/1934578X1300800307
50. Jin JO, Shastina VV, Shin SW, et al. (2009) Differential effects of triterpene glycosides, frondoside A and cucumarioside A_2–2 isolated from sea cucumbers on caspase activation and apoptosis of human leukemia cells. *FEBS Lett* 583: 697–702. https://doi.org/10.1016/j.febslet.2009.01.010
51. Yun SH, Park ES, Shin SW, et al. (2015) By activating Fas/ceramide synthase 6/p38 kinase in lipid rafts, Stichoposide D inhibits growth of leukemia xenografts. *Oncotarget* 6: 27596–27612. https://doi.org/10.18632/oncotarget.4820
52. Silchenko AS, Avilov SA, Andrijaschenko PV, et al. (2022) The isolation, structure elucidation and bioactivity study of chilensosides A, A_1, B, C, and D, holostane triterpene di-, tri- and tetrasulfated pentaosides from the sea cucumber *Paracaudina chilensis* (Caudinidae, Molpadida). *Molecules* 27: 7655. https://doi.org/10.3390/molecules27217655
53. Silchenko AS, Avilov SA, Andrijaschenko PV, et al. (2022) Structures and biologic activity of chitonoidosides I, J, K, K_1 and L-triterpene di-, tri- and tetrasulfated hexaosides from the sea cucumber *Psolus chitonoides*. *Mar Drugs* 20: 369. https://doi.org/10.3390/md20060369
54. Silchenko AS, Avilov SA, Kalinin VI, et al. (2008) Constituents of the sea cucumber *Cucumaria okhotensis*. Structures of okhotosides B1–B3 and cytotoxic activities of some glycosides from this species. *J Nat Prod* 71: 351–356. https://doi.org/10.1021/np0705413
55. Park ES, Yun SH, Shin SW, et al. (2012) Induction of apoptosis and antitumor activity by stichoposide D through the generation of ceramide in human leukemia cells. *J Life Sci* 22: 760–771. http://doi.org/10.5352/JLS.2012.22.6.760
56. Baharara J, Amini E, Nikdel N, et al. (2016) The cytotoxicity of dacarbazine potentiated by sea cucumber saponin in resistant B16F10 melanoma cells through apoptosis induction. *Avicenna J Med Biotechnol* 8: 112–119.

57. Al Shemaili J, Mensah-Brown E, Parekh K, et al. (2014) Frondoside A enhances the antiproliferative effects of gemcitabine in pancreatic cancer. *Eur J Cancer* 50: 1391–1398. https://doi.org/10.1016/j.ejca.2014.01.002
58. Dyshlovoy SA, Madanchi R, Hauschild J, et al. (2017) The marine triterpene glycoside frondoside A induces p53-independent apoptosis and inhibits autophagy in urothelial carcinoma cells. *BMC Central* 17: 93. https://doi.org/10.1186/s12885-017-3085-z
59. Ru R, Chen G, Liang X, et al. (2023) Sea cucumber derived triterpenoid glycoside Frondoside A: a potential anti-bladder cancer drug. *Nutrients* 15: 378. https://doi.org/10.3390/nu15020378
60. Dyshlovoy SA, Menchinskaya ES, Venz S, et al. (2016) The marine triterpene glycoside frondoside A exhibits activity *in vitro* and *in vivo* in prostate cancer. *Int J Cancer* 138: 2450–2465. https://doi.org/10.1002/ijc.29977
61. Silchenko AS, Kalinovsky AI, Avilov SA, et al. (2019) Structures and bioactivities of psolusosides B_1, B_2, J, K, L, M, N, O, P, and Q from the sea cucumber *Psolus fabricii*. The first finding of tetrasulfated marine low molecular weight metabolites. *Mar Drugs* 17: 631. https://doi.org/10.3390/md17110631
62. Obeng E (2021) Apoptosis (programmed cell death) and its signals—A review. *Braz J Biol* 81: 1133–1143. https://doi.org/10.1590/1519-6984.228437
63. Yu S, Ye X, Huang H, et al. (2015) Bioactive sulfated saponins from sea cucumber *Holothuria moebii. Planta Med* 81: 152–159. https://doi.org/10.1055/s-0034-1383404
64. Al Marzouqi N, Iratni R, Nemmar A, et al. (2011) Frondoside A inhibits human breast cancer cell survival, migration, invasion and the growth of breast tumor xenografts. *Eur J Pharmacol* 668: 25–34. https://doi.org/10.1016/j.ejphar.2011.06.023
65. Yueh PF, Lee YH, Chiang IT, et al. (2021) Suppression of EGFR/PKC-δ/NF-κB signaling associated with imipramine-inhibited progression of non-small cell lung cancer. *Front Oncol* 11: 735183. https://doi.org/10.3389/fonc.2021.735183
66. Xia Y, Shen S, Verma IM (2014) NF-κB, an active player in human cancers. *Cancer Immunol Res* 2: 823–830. https://doi.org/10.1158/2326-6066.CIR-14-0112
67. Luo C, Zhang H (2017) The role of proinflammatory pathways in the pathogenesis of colitis-associated colorectal cancer. *Mediators Inflamm* 2017: 5126048. https://doi.org/10.1155/2017/5126048
68. Chattopadhyay I, Ambati R, Gundamaraju R (2021) Exploring the crosstalk between inflammation and epithelial-mesenchymal transition in cancer. *Mediators Inflam* 2021: 9918379. https://doi.org/10.1155/2021/9918379
69. Fedorov SN, Dyshlovoy SA, Kuzmich AS, et al. (2016) *In vitro* anticancer activities of some triterpene glycosides from holothurians of cucumariidae, stichopodidae, psolidae, holothuriidae and synaptidae families. *Nat Prod Commun* 11: 1239–1242. https://doi.org/10.1177/1934578x1601100911
70. Zhao Q, Xue Y, Wang JF, et al. (2012) *In vitro* and *in vivo* anti-tumour activities of echinoside A and ds-echinoside A from *Pearsonothuria graeffei*. *J Sci Food Agric* 92: 965–974. https://doi.org/10.1002/jsfa.4678
71. Wang K (2015) Autophagy and apoptosis in liver injury. *Cell Cycle* 14: 1631–1642. https://doi.org/10.1080/15384101.2015.1038685
72. Li C, Wei C, Zhao G, et al. (2023) Cancer cells remodeling and quality control are inextricably linked to autophagy. *AIMS Mol Sci* 10: 109–126. https://doi.org/10.3934/molsci.2023009

73. Yun CW, Lee SH (2018) The roles of autophagy in cancer. *Int J Mol Sci* 19: 3466. https://doi.org/10.3390/ijms19113466
74. Zheng Y, Rodrik V, Toschi A, et al. (2006) Phospholipase D couples survival and migration signals in stress response of human cancer cells. *J Biol Chem* 281: 15862–15868. https://doi.org/10.1074/jbc.M600660200
75. Gurtner A, Starace G, Norelli G, et al. (2010) Mutant p53-induced up-regulation of mitogen-activated protein kinase kinase 3 contributes to gain of function. *J Biol Chem* 285: 14160–14169. https://doi.org/10.1074/jbc.M109.094813
76. Menchinskaya E, Gorpenchenko T, Silchenko A, et al. (2019) Modulation of doxorubicin intracellular accumulation and anticancer activity by triterpene glycoside cucumarioside A_2-2. *Mar Drugs* 17: 597. https://doi.org/10.3390/md17110597
77. Menchinskaya ES, Pislyagin EA, Kovalchyk SN, et al. (2013) Antitumor activity of cucumarioside A_2–2. *Chemotherapy* 59: 181–191. https://doi.org/10.1159/000354156
78. Dyshlovoy SA, Rast S, Hauschild J, et al. (2017) Frondoside A induces AIF-associated caspase-independent apoptosis in Burkitt lymphoma cells. *Leuk Lymphoma* 58: 2905–2915. https://doi.org/10.1080/10428194.2017.1317091
79. Tong Y, Zhang X, Tian F, et al. (2005) Philinopside A, a novel marine-derived compound possessing dual anti-angiogenic and anti-tumor effects. *Int J Cancer* 114: 843–853. https://doi.org/10.1002/ijc.20804
80. Ma X, Kundu N, Collin PD, et al. (2012) Frondoside A inhibits breast cancer metastasis and antagonizes prostaglandin E receptors EP4 and EP2. *Breast Cancer Res Treat* 132: 1001–1008. https://doi.org/10.1007/s10549-011-1675-z
81. Park SY, Kim YH, Kim Y, et al. (2012) Frondoside A has an anti-invasive effect by inhibiting TPA-induced MMP-9 activation via NF-κB and AP-1 signaling in human breast cancer cells. *Int J Oncol* 41: 933–940. https://doi.org/10.3892/ijo.2012.1518
82. Melincovici CS, Boşca AB, Şuşman S, et al. (2018) Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol* 59: 455–467.
83. Janta S, Pranweerapaiboon K, Vivithanaporn P, et al. (2023) Holothurin A inhibits RUNX1-enhanced EMT in metastasis prostate cancer via the Akt/JNK and P38 MAPK signaling pathway. *Mar Drugs* 21: 345. https://doi.org/10.3390/md21060345
84. Vinogradov S, Warren G, Wei X (2014) Macrophages associated with tumors as potential targets and therapeutic intermediates. *Nanomedicine* 9: 695–707. https://doi.org/10.2217/nnm.14.13
85. Pislyagin EA, Manzhulo IV, Gorpenchenko TY, et al. (2017) Cucumarioside A_2-2 causes macrophage activation in mouse spleen. *Mar Drugs* 15: 341. https://doi.org/10.3390/md15110341
86. Yu Y, Wu G, Jiang Y, et al. (2020) Sea cucumber peptides improved the mitochondrial capacity of mice: a potential mechanism to enhance gluconeogenesis and fat catabolism during exercise for improved antifatigue property. *Oxidative Med Cell Longev* 2020: 4604387. https://doi.org/10.1155/2020/4604387
87. Ru R, Guo Y, Mao J, et al. (2022) Cancer cell inhibiting sea cucumber (*Holothuria leucospilota*) protein as a novel anti-cancer drug. *Nutrients* 14: 786. https://doi.org/10.3390/nu14040786
88. Wargasetia TL, Ratnawati H, Widodo N, et al. (2021) Bioinformatics study of sea cucumber peptides as antibreast cancer through inhibiting the activity of overexpressed protein (EGFR, PI3K, AKT1, and CDK4). *Cancer Inform* 20: 1–11. https://doi.org/10.1177/11769351211031864

89. Wei W, Fan XM, Jia SH, et al. (2021) Sea cucumber intestinal peptide induces the apoptosis of MCF-7 cells by inhibiting PI3K/AKT pathway. *Front Nutr* 8: 763692. https://doi.org/10.3389/fnut.2021.763692
90. Qiao R, Xiao R, Chen Z, et al. (2021) Cloning, expression and inhibitory effects on Lewis lung carcinoma cells of rAj-Tspin from sea cucumber (*Apostichopus japonicus*). *Molecules* 27: 229. https://doi.org/10.3390/molecules27010229
91. Mao J, Zhang Z, Chen Y, et al. (2021) Sea cucumber peptides inhibit the malignancy of NSCLC by regulating miR-378a-5p targeted TUSC2. *Food Funct* 12: 12362–12371. https://doi.org/10.1039/d1fo02267a
92. Sugawara T, Zaima N, Yamamoto A, et al. (2006) Isolation of sphingoid bases of sea cucumber cerebrosides and their cytotoxicity against human colon cancer cells. *Biosci Biotechnol Biochem* 70: 2906–2912. https://doi.org/10.1271/bbb.60318
93. Jia Z, Song Y, Tao S, et al. (2016) Structure of sphingolipids from sea cucumber *Cucumaria frondosa* and structure-specific cytotoxicity against human HepG2 cells. *Lipids* 51: 321–334. https://doi.org/10.1007/s11745-016-4128-y
94. Alizadeh J, da Silva Rosa SC, Weng X, et al. (2023) Ceramides and ceramide synthases in cancer: focus on apoptosis and autophagy. *Eur J Cell Biol* 102: 151337. https://doi.org/10.1016/j.ejcb.2023.151337
95. Du L, Li ZJ, Xu J, et al. (2012) The anti-tumor activities of cerebrosides derived from sea cucumber *Acaudina molpadioides* and starfish *Asterias amurensis in vitro* and *in vivo*. *J Oleo Sci* 61: 321–330. https://doi.org/10.5650/jos.61.321
96. Cao RA, Lee SH, You S (2014) Structural effects of sulfated-glycoproteins from *Stichopus japonicus* on the nitric oxide secretion ability of RAW 264.7 cells. *Prev Nutr Food Sci* 19: 307–313. https://doi.org/10.3746/pnf.2014.19.4.307
97. Wang H, Yang S, Wang Y, et al. (2017) Immunoenhancement effects of glycosaminoglycan from *Apostichopus japonicus*: *In vitro* and in cyclophosphamide-induced immunosuppressed mice studies *Mar Drugs* 15: 347. https://doi.org/10.3390/md15110347
98. Thinh PD, Ly BM, Usoltseva RV, et al. (2018) A novel sulfated fucan from Vietnamese sea cucumber *Stichopus variegatus*: Isolation, structure and anticancer activity *in vitro. Int J Biol Macromol* 117: 1101–1109. https://doi.org/10.1016/j.ijbiomac.2018.06.017
99. Zhang M, Chen L, Liu Y, et al. (2020) Sea cucumber *Cucumaria frondosa* fucoidan inhibits osteosarcoma adhesion and migration by regulating cytoskeleton remodeling. *Oncol Rep* 44: 469–476. https://doi.org/10.3892/or.2020.7614
100. Mizuno K (2013) Signaling mechanisms and functional roles of cofilin phosphorylation and dephosphorylation. *Cell Signal* 25: 457–469. https://doi.org/10.1016/j.cellsig.2012.11.001
101. Surayot U, Lee S, You S (2018) Effects of sulfated fucan from the sea cucumber *Stichopus japonicus* on natural killer cell activation and cytotoxicity. *Int J Biol Macromol* 108: 177–184. https://doi.org/10.1016/j.ijbiomac.2017.11.102
102. Yue Z, Wang A, Zhu Z, et al. (2015) Holothurian glycosaminoglycan inhibits metastasis via inhibition of P-selectin in B16F10 melanoma cells. *Mol Cell Biochem* 410: 143–154. https://doi.org/10.1007/s11010-015-2546-4
103. Shi X, Guan R, Zhou L, et al. (2021) Structural characterization and heparanase inhibitory activity of fucosylated glycosaminoglycan from *Holothuria floridana. Mar Drugs* 19: 162. https://doi.org/10.3390/md19030162

104. Lu Y, Zhang BY, Wand BL, et al. (2010) The effects of *Stichopus japonicus* acid mucopolysaccharide on the apoptosis of the human hepatocellular carcinoma cell line HepG2. *Am J Med Sci* 339: 141–144. https://doi.org/10.1097/MAJ.0b013e3181c20d01
105. Farrag M, Aljuhani R, Benicky J, et al. (2025) Heparan-6-O-endosulfatase 2, a cancer-related proteoglycan enzyme, is effectively inhibited by a specific sea cucumber fucosylated glycosaminoglycan. *Glycobiology* 35: cwaf025. https://doi.org/10.1093/glycob/cwaf025
106. Zhou L, Yin R, Gao N, et al. (2021) Oligosaccharides from fucosylated glycosaminoglycan prevent breast cancer metastasis in mice by inhibiting heparanase activity and angiogenesis. *Pharmacol Res* 166: 105527. https://doi.org/10.1016/j.phrs.2021.105527
107. Lin C, Zhu X, Jin Q, et al. (2020) Effects of holothurian glycosaminoglycan on the sensitivity of lung cancer to chemotherapy. *Integr Cancer Ther* 19: 1–10. https://doi.org/10.1177/1534735420911430
108. Hao-Yu D, Ding-Yi Y, Bao-Hong X, et al. (2023) Two molecular weights holothurian glycosaminoglycan and hematoporphyrin derivative-photodynamic therapy inhibit proliferation and promote apoptosis of human lung adenocarcinoma cells. *Integr Cancer Ther* 22: 1–8. https://doi.org/10.1177/15347354221144310
109. Ben Mansour M, Balti R, Ollivier V, et al. (2017) Characterization and anticoagulant activity of a fucosylated chondroitin sulfate with unusually procoagulant effect from sea cucumber. *Carbohydr Polym* 174: 760–771. https://doi.org/10.1016/j.carbpol.2017.06.128
110. Manan WZWA, Mahalingam SR, Arshad K, et al. (2016) Safety and efficacy of sea cucumber containing products. *Arch Pharma Pract* 7: S48–S52. https://doi.org/10.4103/2045-080X.183038
111. Song Y, Jin SJ, Cui LH, et al. (2013) Immunomodulatory effect of *Stichopus japonicus* acid mucopolysaccharide on experimental hepatocellular carcinoma in rats. *Molecules* 18: 7179-7193. https://doi.org/10.3390/molecules18067179
112. Borsig L, Wang L, Cavalcante MCM, et al. (2007) Selectin blocking activity of a fucosylated chondroitin sulfate glycosaminoglycan from sea cucumber: Effect on tumor metastasis and neutrophil recruitment. *J Biol Chem* 282: 14984–14991. https://doi.org/10.1074/jbc.M610560200
113. Tian X, Tang H, Lin H, et al. (2013) Saponins: The potential chemotherapeutic agents in pursuing new anti-glioblastoma drugs. *Med. Chem* 13: 1709–1724. https://doi.org/10.2174/13895575113136660083
114. Kim JL, Park SH, Jeong S, et al. (2019) Sea cucumber (*Stichopus japonicus*) F2 enhanced TRAIL-induced apoptosis via XIAP ubiquitination and ER stress in colorectal cancer cells. *Nutrients* 11: 1061. https://doi.org/10.3390/nu11051061
115. Aminin DL, Chaykina EL, Agafonova IG, et al. (2010) Antitumor activity of the immunomodulatory lead Cumaside. *Int Immunopharmacol* 10: 648–654. https://doi.org/10.1016/j.intimp.2010.03.003
116. Luparello C, Branni R, Abruscato G, et al. (2022) Cytotoxic capability and the associated proteomic profile of cell-free coelomic fluid extracts from the edible sea cucumber *Holothuria tubulosa* on HepG2 liver cancer cells. *EXCLI J* 21: 722–743. https://doi.org/10.17179/excli2022-4825
117. Janakiram NB, Mohammed A, Rao CV (2015) Sea cucumbers metabolites as potent anti-cancer agents. *Mar Drugs* 13: 2909–2923. https://doi.org/10.3390/md13052909

118. Subramanya SB, Chandran S, Almarzooqi S, et al. (2018) Frondanol, a nutraceutical extract from *Cucumaria frondosa*, attenuates colonic inflammation in a DSS-induced colitis model in mice. *Mar Drugs* 16: 148. https://doi.org/10.3390/md16050148
119. Roginsky AB, Ding XZ, Woodward C, et al. (2010) Anti-pancreatic cancer effects of a polar extract from the edible sea cucumber, *Cucumaria frondosa*. *Pancreas* 39: 646–652. https://doi.org/10.1097/MPA.0b013e3181c72baf
120. Janakiram NB, Mohammed A, Zhang Y, et al. (2010) Chemopreventive effects of Frondanol A5, a *Cucumaria frondosa* extract, against rat colon carcinogenesis and inhibition of human colon cancer cell growth. *Cancer Prev Res* 3: 82–91. https://doi.org/10.1158/1940-6207.CAPR-09-0112
121. Vigneswara V, Ahmed Z (2020) The role of caspase-2 in regulating cell fate. *Cells* 9: 1259. https://doi.org/10.3390/cells9051259
122. Ogushi M, Yoshie-Stark Y, Suzuki T (2005) Cytostatic activity of hot water extracts from the sea cucumber in Caco-2. *Food Sci Technol Res* 11: 202–206. https://doi.org/10.3136/fstr.11.202
123. Yuan L, Huang X, Zhou K, et al. (2019) Sea cucumber extract TBL-12 inhibits the proliferation, migration, and invasion of human prostate cancer cells through the p38 mitogen-activated protein kinase and intrinsic caspase apoptosis pathway. *Prostate* 79: 826–839. https://doi.org/10.1002/pros.23788
124. Althunibat O, Ridzwan B, Taher M, et al. (2013) Antioxidant and cytotoxic properties of two sea cucumbers, *Holothuria edulis* Lesson and *Stichopus horrens* Selenka. *Acta Biol Hung* 64: 10–20. https://doi.org/10.1556/ABiol.64.2013.1.2
125. Althunibat OY, Hashim RB, Taher M, et al. (2009) *In vitro* antioxidant and antiproliferative activities of three Malaysian sea cucumber species. *Eur J Sci Res* 37: 376–387.
126. Khaledi M, Moradipoodeh B, Moradi R, et al. (2022) Antiproliferative and proapoptotic activities of sea cucumber *H. leucospilota* extract on breast carcinoma cell line (SK-BR-3). *Mol Biol Rep* 49: 1191–1200. https://doi.org/10.1007/s11033-021-06947-0
127. Seydi E, Motallebi A, Dastbaz M, et al. (2015) Selective toxicity of Persian Gulf sea cucumber (*Holothuria parva*) and sponge (*Haliclona oculata*) methanolic extracts on liver mitochondria isolated from an animal model of hepatocellular carcinoma. *Hepat Mon* 15: e33073. https://doi.org/10.5812/hepatmon.33073
128. Salimi A, Motallebi A, Ayatollahi M, et al. (2017) Selective toxicity of Persian gulf sea cucumber *Holothuria parva* on human chronic lymphocytic leukemia b lymphocytes by direct mitochondrial targeting. *Environ Toxicol* 32: 1158–1169. https://doi.org/10.1002/tox.22312
129. Pranweerapaiboon K, Noonong K, Apisawetakan S, et al. (2021) Methanolic extract from sea cucumber, *Holothuria scabra*, induces apoptosis and suppresses metastasis of PC3 prostate cancer cells modulated by MAPK signaling pathway. *J Microbiol Biotechnol* 31: 775–783. https://doi.org/10.4014/jmb.2103.03034
130. Nigam M, Suleria HAR, Farzaei MH, et al. (2019) Marine anticancer drugs and their relevant targets: A treasure from the ocean. *DARU J Pharm Sci* 27: 491–515. https://doi.org/10.1007/s40199-019-00273-4
131. Kareh M, El Nahas R, Al-Aaraj L, et al. (2018) Anti-proliferative and anti-inflammatory activities of the sea cucumber *Holothuria polii* aqueous extract. *SAGE Open Med* 6: 1–14. https://doi.org/10.1177/2050312118809541

132. Chari A, Mazumder A, Lau K, et al. (2018) A phase II trial of TBL-12 sea cucumber extract in patients with untreated asymptomatic myeloma. *Br J Haematol* 180: 296–298. https://doi.org/10.1111/bjh.14314
133. Dolmatova LS, Slinko EN, Kolosova LF (2020) Variations in the heavy metal contents in tissues of the sea cucumber *Eupentacta fraudatrix* in the coastal waters of the sea of Japan: the influence of physiological and anthropogenic factors. Oceanology 4: 446–457. https://doi.org/10.1134/S0001437020040050

AIMS Press