

Review

# Therapeutic Application of Diverse Marine-derived Natural Products in Cancer Therapy

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**Abstract.** *Natural products (NPs) are useful sources of bioactive compounds and play important roles in the development and discovery of new drugs for diverse human diseases. Most natural products originate from terrestrial species, but diverse marine organisms are another source of new agents for cancer therapy. Natural products derived from marine organisms show diverse pharmacological activities via bioactive secondary metabolites. They regulate biological activities, such as cell proliferation, cell viability, induction of ROS production, ER stress, and apoptosis via modulation of cellular mechanisms in many cancers. Many natural products isolated from marine species require further study to elucidate the efficacy of their biological activity and anticancer effects. In this review, we summarize the biological properties and anticancer effects of diverse natural products extracted from marine organisms and their roles in tumor therapy.*

Cancer is one of the leading causes of death and an economic burden worldwide (1). Cancer involves an abnormal proliferation of cells and tissues, and is affected by various risk factors such as age, diet, genetics, and environmental factors (2, 3). It is also caused by the mutation of several cancer-related genes called tumor suppressors and oncogenes (4). Cancer also presents the ability of metastasis and recurrence, which are difficult to treat (5). Although conventional anticancer therapy includes both chemotherapy to induce apoptosis of target cancer cells and surgical

therapy to remove tumors, these methods are limited by issues of therapeutic efficacy, safety, and side effects. Thus, it is necessary to develop novel strategies for cancer therapy, and natural products (NPs) are a promising source for novel drug development because they show diverse biological activities and anticancer effects via inhibition of tumor growth by interacting with several signaling pathways (6, 7).

NPs have been a useful source of bioactive compounds and play an important role in the discovery and development of drugs. Most NPs, originated from terrestrial microbes, fungi, and plants, have been discovered to possess many pharmacologically active factors and used to treat several human diseases. Some of these are utilized as clinically valuable drugs for anticancer therapy (8-10). However, marine organisms have recently attracted substantial attention because 70% of the earth is covered by water, representing 95% of biodiversity (11-13). NPs derived from marine organisms have been researched for novel bioactive secondary metabolites due to their diverse pharmacological activities. Marine environments are estimated to harbor more than one million species and one billion different types of marine microbes (14). Today, around 28,000 new compounds isolated from marine species, such as algae, seaweed, sponges, and starfish, have been reported, and this species diversity provides a diverse array of secondary metabolic products (15, 16).

In this review, we present NPs derived from marine environments, and summarize their anticancer activities, such as inhibition of tumor growth, cancer drug resistance, and metastasis. Finally, we discuss NPs as therapeutic agents for safe and efficient cancer treatment.

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## The Potential Therapeutic Effects of Marine Seaweed- and Algae-derived Natural Products for Cancer Therapy

Marine algae or seaweeds are plants living in marine or brackish water and are autotrophic organisms that contain chlorophyll for oxygenic photosynthesis (17, 18). These

plants demonstrate metabolic plasticity and produce several compounds that can be used for drug development (19). Moreover, they can be easily cultivated in bioreactors to obtain high amounts of biomass and provide diverse marine compounds for drug discovery (20).

*Inhibition of cancer cell proliferation and survival by Carotenoids derived from marine seaweed and algae.* *Chlorella* species can be used to extract diverse carotenoids, such as lutein,  $\beta$ -carotene, zeaxanthin, and astaxanthin. One study showed that carotenoids extracted from the green algae *Chlorella ellipsoidea* and *C. vulgaris* inhibited the proliferation of human colon cancer cells (21). The carotenoid extract of *C. ellipsoidea* contains violaxanthin and two other xanthophylls, such as antheraxanthin and zeaxanthin, whereas the extract from *C. vulgaris* mainly contains lutein. The anti-cancer activity of carotenoid extracts was measured using the MTT assay after 24 h exposure to the two compounds. To confirm the apoptotic effects linked to the anti-proliferative effects, the authors also performed an annexin V-fluorescein assay and reported that the two extracts have an apoptotic effect (21). Fucoxanthin is a marine carotenoid that is mainly isolated from brown seaweeds and some microalgae (22, 23). Fucoxanthinol is the deacetylated derivative of fucoxanthin, and is an active form of fucoxanthin (24). One study has shown that fucoxanthin inhibits proliferation in colorectal cancer. The NMR analysis of fucoxanthin following degradation *via* ozonolysis showed that fucoxanthin divides into two types of cyclohexyl derivatives, and the treatment of degraded fucoxanthin induced antiproliferative effects in colon cancer (25). Another study has confirmed that fucoxanthin and fucoxanthinol have anticancer effects in colorectal cancer (26). The treatment with the two compounds induced an increase in dose dependent drug sensitivity, inhibited cancer cell growth, and induced apoptosis in colorectal cancer (26). Other study has indicated that fucoxanthinol reduced cell viability of breast cancer cells *via* modulation of the NF-kappa B pathway. Fucoxanthin and fucoxanthinol decreased cell viability and induced apoptosis. Fucoxanthinol was more potent in inducing apoptosis compared to fucoxanthin (27). These results suggest that fucoxanthinol and fucoxanthin might be potential therapeutic reagents against different types of cancers, including colon and breast cancer.

*Therapeutic effects on cancer of Polysaccharides from marine seaweed and algae.* Polysaccharides, polymers of monosaccharides, are natural products that are present in a large amount in marine algae and are found intracellularly and in the cell wall. Some of them exert diverse pharmacological and anticancer effects: alginic acid fucoidan from brown algae and carrageenans from red algae (28, 29).

Carrageenans isolated from *Kappaphycus alvarezii* have been evaluated for their anticancer effects *in vitro*. The

carrageenans suppressed the growth of breast, colon, liver, and osteosarcoma cell lines (30). In addition, carrageenan extracted from red seaweed of the Rhodophyceae family and *L. papillosa* showed cytotoxicity *via* inhibition of cell proliferation and induction of apoptosis in human intestinal cancer, breast cancer, and liver cancer cells (31, 32). Consistent with the anticancer activity, the administration of  $\lambda$ -carrageenan stimulated the immune system *via* up-regulation of proinflammatory IL17A and TNF- $\alpha$ , thereby stimulating the activities of tumor infiltrating M1 macrophages, dendritic cells, and T lymphocytes (33). Furthermore, a recent study has confirmed that the extracted sulfated carrageenan (ESC) consists of  $\iota$ -carrageenan, which infers a direct damage to DNA by modulating nuclear condensation and DNA fragmentation in breast cancer MDA-MB-231 cells. ESC induced cell death *via* the apoptotic caspase 8 pathway (34).

The fucoidan isolated from the brown seaweeds *Cladosiphon okamuranus* and *Fucus evanescens* consists of fucose and galactose, mannose, and xylose (35). Fucoidan treatment suppressed cell proliferation, apoptosis, and migration *via* down-regulation of prion in colon cancers (36) and modulation of PI3K-AKT-GSK3b axis in breast cancer (37). In addition, administration of fucoidan for 28 days inhibited tumor growth and angiogenesis *via* modulation of JAK and STAT3 phosphorylation in animal studies (38). Furthermore, the administration of fucoidan suppressed endothelial mesenchymal transition (EMT) and induced apoptosis in breast cancer cells. Fucoidan inhibited cell migration and invasion *via* up-regulation of E-cadherin and down-regulation of MMP-9, and promoted apoptosis in breast cancer cells (39). In addition, fucoidan inhibited tumorigenesis and tumor growth *via* induction of ER stress, which resulted in apoptosis *in vitro* and in a lung cancer animal model. Fucoidan treatment increased the levels of reactive oxygen species (ROS), and induced an increase in ATF4, CHOP, and ER stress *via* modulation of Toll-like receptor 4 in lung cancer cells, leading to apoptosis and inhibition of cell proliferation (40).

Some studies confirmed successful applications of the complex of fucoidan and multiple nanoparticles in cancer therapy. One study employed the complex of fucoidan (Fu) and synthetic rutin (Ru) in anticancer therapy. Treatment with the Ru-Fu complex, which has no adverse effects on normal cells, resulted in disruption of cell cycle regulation and apoptosis *via* nuclear fragmentation, production of ROS, and induction of mitochondrial damage (41). Another study synthesized fucoidan-coated copper sulfide nanoparticles (F-CuS) as a candidate in chemo-photothermal cancer therapy. F-CuS, which acts as a nanocarrier promoting intracellular delivery of fucoidan, was applied as a photothermal agent in cancer cells. The administration of F-CuS induced cellular apoptosis following 808 nm diode laser irradiation in diverse cancer cells *in vitro* and *in vivo* (42).

**Anticancer activity of extracts of *Ulva lactuca*.** Many studies indicated that a variety of *Ulva lactuca* extracts possess biological and pharmacological properties, including anticoagulant, antiviral, antioxidant, and anti-inflammatory properties (43-46). Extracts from the sea lettuce *U. lactuca* may have chemopreventive properties. Treatment of an DMBA-induced breast cancer rat model with ulvan polysaccharides for 10 weeks showed chemopreventive effects *via* prevention of histological alterations and carcinogenic lesions (47). Furthermore, ulvan polysaccharides have demonstrated cytotoxic effects against hepatocellular carcinoma (HCC), human breast cancer, and HeLa cells (48). In addition, administration of sulfated polysaccharides extracted from *U. lactuca* showed chemopreventive effects of DENA-induced hepatocarcinogenesis *via* suppression of cell proliferation and apoptosis induction. Treatment with these products improved hepatic damage and regulated antioxidant mechanisms, indicating their potential as novel chemopreventive and therapeutic agents for HCC (49).

These results indicate that diverse natural products derived from marine algae and seaweed show cytotoxic effects and could be novel agents for cancer therapy (Table I).

### The Anticancer Activity of Natural Products Isolated from Sea Cucumber

Sea cucumbers belong to the class Holothuroidea, phylum Echinodermata, and are marine invertebrates that are phylogenetically associated with starfish, sea urchins, and sea lilies (50, 51). Sea cucumbers contain many nutrients and natural products, such as vitamins, calcium, triterpene glycosides, fucoidan, and sphingoid bases (51-55). Natural compounds extracted from sea cucumber have been reported to exhibit strong cytotoxic activity in human cancer cell lines (Table II).

**The anticancer activity of Frondoside A and Cucumarioside A2-2.** Frondoside A, isolated from *Cucumaria frondosa* exhibited enhanced apoptosis through increased expression of p53, p21 and caspase 3/7, 9 genes when used in the treatment of human breast and pancreatic cancer (56, 57). Frondoside A has been shown to enhance the therapeutic effects of the anti-cancer drugs oxaliplatin and 5-fluorouracil in colon cancer cells. Use of frondoside A enabled reduction in dosage of oxaliplatin or 5-fluorouracil. The combination treatment inhibited cell colony growth *via* inactivation of ERK 1/2 phosphorylation and induction of apoptosis (58). Another study has found that frondoside A extracted from sea cucumber *Cucumaria okhotensis* shows high anticancer activity in human prostate cancer, while normal cells were less affected. The mode of action included inhibition of cell proliferation and colony formation *via* induction of cell-cycle arrest and apoptosis and reduction of pro-survival autophagy

in drug-resistant prostate cancer cells. Frondoside A has been shown to inhibit metastasis and bring about immunomodulatory effects by increasing in lymphocyte concentration (59). It also exhibited high cytotoxicity in urothelial carcinoma cells through induction of apoptosis by modulation of diverse apoptosis-related proteins, such as caspase 3, 8, and 9, PARP, and through DNA fragmentation. It inhibited pro-survival autophagy and exhibited synergistic effects with cisplatin and gemcitabine (60). In addition, cucumarioside A2-2, isolated from the sea cucumber, *Cucumaria japonica* has been shown to exhibit cytotoxic effects in ehrlich carcinoma cells and to inhibit cell viability, cell proliferation, and DNA biosynthesis and to induce apoptosis *via* the caspase dependent pathway (61, 62).

**The inhibitory effects of Echinaside A, Ds-echinaside A, Frondanol A5 on cancer cell proliferation.** Echinaside A and Ds-echinaside A are triterpenoid glycosides, isolated from *Pearsonothuria graeffei*, and cause cell cycle arrest in hepatocellular carcinoma cells (63). Ds-echinaside A has been shown to inhibit the mouse double minute 2 homolog (MDM2) and C-X-C chemokine receptor type 4 (CXCR4), thereby enhancing apoptosis *via* modulation of p53, and to reduce cell proliferation and growth *via* protein tyrosine kinase 2 regulation (64). In addition, Ds-echinaside A has also been shown to inhibit proliferation of human hepatocellular carcinoma cells, and to suppress cell adhesion, migration, invasion, and angiogenesis *via* regulation of MMP9, TIMP-1, and VEGF expression (65). Frondanol A5 is an isopropyl alcohol/water extract derived from *Cucumaria frondosa* and its application has been shown to inhibit cell growth *via* modulation of p21WAF1/CIP and Cdc25c, thus inducing apoptosis of human colon cancer cells (66), as well as innate immune responses and inhibiting the growth of intestinal tumors in mice model (67). Frondanol A5P, a polar extract isolated from *Cucumaria frondosa*, has been shown to suppress cell proliferation and to induce cell cycle arrest *via* decrease in cell cycle-related proteins, such as cyclin A and cyclin B. It up-regulated stress-activated protein kinase, janus kinase, and p38 mitogen-activated protein kinase, resulting in enhanced apoptosis in pancreatic cancer cells (68).

**The inhibitory effects of Philinopsides on cancer cell proliferation, migration, and angiogenesis.** Philinopside A is isolated from the sea cucumber *Pentacta quadrangularis* and has been shown to inhibit cell proliferation, migration, and tube formation in human microvascular endothelial cells and animal models. Philinopside A also reduced tumor volume *via* induction of apoptosis and inhibited angiogenesis-related receptor tyrosine kinases, such as vascular endothelial growth factor (VEGF) receptor, fibroblast growth factor (FGF) receptor-1, platelet-derived growth factor (PDGF)

Table I. The anticancer effects of marine seaweed- and algae-derived compounds.

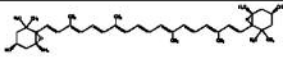
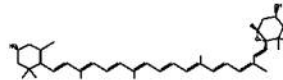
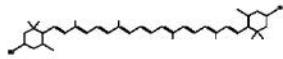
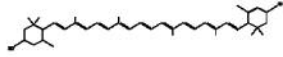
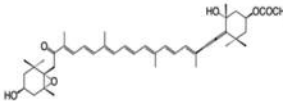
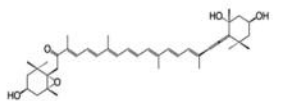
Compounds	Type of source	Findings	Reference
 Violaxanthin  Antheraxanthin  zeaxanthin  lutein	<i>Chlorella ellipsoidea</i>  <i>Chlorella vulgaris</i>	Inhibition of cell proliferation, induction of apoptosis in human colon cancer	(21)
 Fucoxanthin  Fucoxanthinol	brown seaweeds <i>Phaeophyceae</i>  <i>Fucus</i> , <i>Dictyota</i> , and <i>Laminaria</i>	Inhibition of cell proliferation, increased drug sensitivity, induction of apoptosis in colon and breast cancer	(22-27)
	<i>Kappaphycus alvarezii</i>	Suppression of cell growth, induction of immune response in breast, colon, liver cancer, and osteosarcoma cell lines.	(30)
	Rhodophyceae family	Inhibition of cell proliferation and viability, induction of apoptosis in human intestinal, liver, and breast cancer	(31, 32)
	<i>Laurencia papillosa</i>	Stimulation of immune system via regulation of proinflammatory cytokines and immune cells	(33)

Table I. Continued

Table I. *Continued*

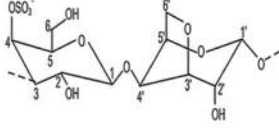
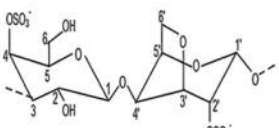
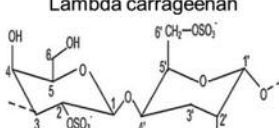
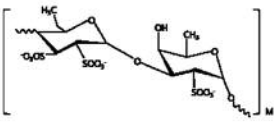
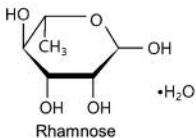
Compounds	Type of source	Findings	Reference
<p>Kappa carrageenan</p>  <p>Iota carrageenan</p>  <p>Lambda carrageenan</p>  <p>Carrageenans</p>		Induction of DNA damage via nuclear condensation and DNA fragmentation, enhancement of apoptosis in breast cancer	(34)
<p>Fucoidan</p> 	<p><i>Fucus vesiculosus</i></p> <p><i>Cladosiphon okamuranus</i></p>	Inhibition of cell growth, reduction of cell cycle related proteins by modulating of prion expression in human colon cancer, induction of apoptosis	(36)
		Inhibition of cell proliferation, induction of apoptosis via regulation of PI3K-AKT-GSK3b in breast cancer	(37)
		Inhibition of cell proliferation and viability, cell migration and tube formation in human prostate cancer, modulation of JAK/STAT3 pathway, inhibition of tumor growth, and angiogenesis <i>in vivo</i>	(38)
		Suppression of EMT, induction of apoptosis in breast cancer, inhibition of migration and invasion via modulation of E-cadherin and MMP9	(39)

Table I. *Continued*

Table I. *Continued*

Compounds	Type of source	Findings	Reference
		Inhibition of tumorigenesis and tumor growth, induction of ROS production, ER stress, and apoptosis in breast cancer	(40)
		Complex of fucoidan and synthetic rutin, disruption of cell cycle regulation, induction of apoptosis via nuclear fragmentation, production of ROS, and increase of mitochondrial damage	(41)
		Synthetic fucoidan-coated copper sulfide nanoparticles, induction of the cellular apoptosis	(42)
 <p>Ulvian polysaccharides</p>	<i>Ulva lactuca</i>	Prevention of histological alterations and carcinogenic lesions in breast cancer rat model, cytotoxic effects in hepatocellular carcinoma, human breast cancer, and in HeLa cells	(47, 48)

receptor-beta and epithelial growth factor (EGF) receptor (69). Philinopside E has been shown to interact with the extracellular domain of kinase domain containing receptor KDR and block the interaction between KDR and VEGF, thus inhibiting further downstream signalling pathway. These results indicated that philinopside E could inhibit cancer angiogenesis (70).

### The Potential Anticancer Activity of Starfish and Sea Urchin Extracted NPs

*The potential usage of NPs isolated from Starfish as anticancer reagent.* Starfish contain diverse polar steroid, mono- and biglycosides of polyhydroxysteroids, as well as oligoglycosides. Starfish-derived steroid glycosides exert cytotoxic, neuritogenic, hemolytic, antiviral, antibacterial, antitumor, and cancer-preventive effects (71-73). One study

has reported that two asterosaponins and six glycosylated polyhydroxysteroids were isolated from the starfish *Culcita novaeguineae*. Among extracted products, four glycosylated polyhydroxysteroids has shown slight cytotoxic effects against human hepatoma, epidermoid carcinoma, prostate cancer, breast cancer, and melanoma (74). Another study has confirmed the cytotoxic activity of six new polyhydroxysteroidal glycosides and two previously known glycosides, which were isolated from starfish *Anthena sibogae*. The mixture of two known glycosides has been shown to exert slightly inhibitory effects on cell proliferation in human breast cancer and to decrease colony size *in vitro* (75). Plancitoxin I derived from the venom of the crown-of-thorns starfish *Acanthaster planci*, has been reported to exert strong cytotoxic effects in human malignant melanoma cells (76, 77). Plancitoxin I decreased cell viability *via* induction of ROS, nitric oxide production, and reduction of mitochondrial

Table II. Mode of action of anticancer activity of compounds extracted from marine sea cucumber.

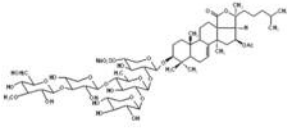
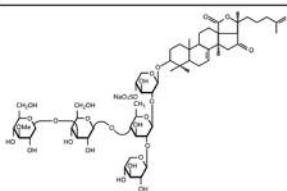
Compounds	Source	Findings	Reference
 Frondoside A	<i>Cucumaria frondosa</i>	Increased apoptosis via induction of p53 and p21 expression,	(56, 57)
		Synergetic effects with oxaliplatin and 5-fluorouracil, inhibition of tumor growth, induction of apoptosis	(58)
	<i>Cucumaria okhotensis</i>	Inhibition of cell proliferation and colony formation, induction of cell cycle arrest and apoptosis, reduction of pro-survival autophagy, inhibition of metastasis, regulation of immunomodulation	(59)
		Induction of apoptosis, modulation of apoptosis related proteins and DNA fragmentation, inhibition of pro-survival autophagy, synergistic effects with anticancer drugs	(60)
 cucumarioside A <sub>2</sub> -2	<i>Cucumaria japonica</i>	Inhibition of cell viability, proliferation, and DNA biosynthesis, induction of apoptosis	(61, 62)
	<i>Pearsonothuria graeffei</i>	Induction of cell cycle arrest	(63)

Table II. Continued

membrane potential, inducing apoptosis (77). Another study has confirmed that pancitoxin I reduced antioxidant enzymes such as SOD and catalase, and induced mitochondrial dysfunction. Moreover, pancitoxin I increased  $\text{Ca}^{2+}$

concentrations and induced ER stress, subsequently elevating apoptosis *via* an increase in apoptosis related proteins such as caspase 3, 8, and 9 (76). In addition, cyclic steroid glycosides isolated from starfish *Echinaster luzonicus*, such as

Table II. Continued

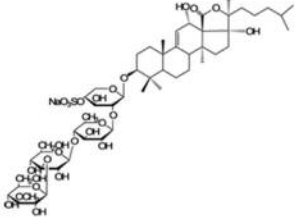
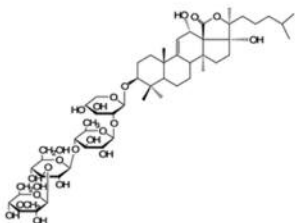
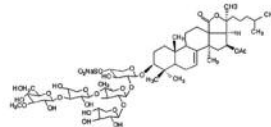
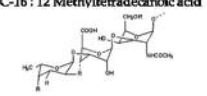
Compounds	Source	Findings	Reference
 <p>Echinoid A</p>		Inhibition of MDM2 and CXCR4, enhancement of apoptosis, reduction in cell proliferation and tumor growth	(64)
 <p>Ds-echinoid A</p>		Inhibition of cell proliferation, suppression of cell adhesion, migration, invasion, and angiogenesis, regulation of MMP9, TIMP-1, and VEGF expression	(65)
 <p>Frondoid A</p> <p>C-16 : 12 Methyltetradecanoic acid</p>  <p>Fucosylated Chondroitin Sulfate R=OSO<sub>3</sub><sup>-</sup> or OH</p> <p>Frondanol A5</p>	<i>Cucumaria frondosa</i>	Inhibition of cell growth, modulation of p21WAF1/CIP and Cdc25c, induction of apoptosis	(66)
		Induction of innate immune response, inhibition of tumor growth	(67)
		Suppression of cell proliferation, induction of cell cycle arrest, activation of stress-activated protein kinase, janus kinase, and p38 mitogen-activated protein kinase, induction of apoptosis	(68)

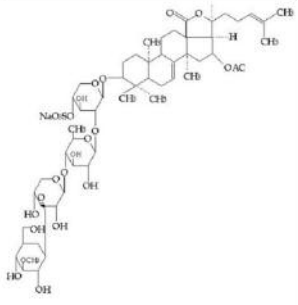
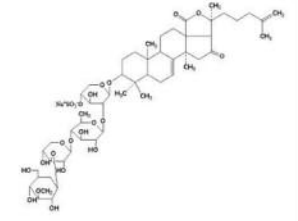
Table II. Continued

luzonicoside A and D, have been shown to have anticancer activity in human melanoma. Luzonicoside A and D inhibited cell proliferation, colony formation, and migration *via* regulation of cell cycle and apoptosis induction (78).

*The potential anticancer activity of NPs extracted from sea urchin.* Sea urchins belong to echinoderms and are part of the same group of invertebrates, such as starfish, brittle stars, and sponges (79). Extracts derived from sea urchins have



Table II. *Continued*

Compounds	Source	Findings	Reference
 Philinopside A	<i>Pentacta quadrangularis</i>	Inhibition of cell proliferation, migration, and tube formation, reduction of tumor growth, induction of apoptosis, suppression of angiogenesis related receptor tyrosine kinases	(69)
 Philinopside E		Anti-angiogenic effects, inhibition of KDR and downstream signaling pathway	(70)

been shown to exhibit diverse biological properties such as anti-tumor activity and immunomodulation. The steroidal components from sea urchin *Diadema savignyi* Michelin were isolated and their cytotoxic activity was confirmed in human cancer cell lines, including human promyelocytic leukemia, prostate cancer, and embryonic lung cells. The steroidal components inhibited cell proliferation and viability and induced apoptosis *via* modulation of apoptosis-related protein expression, inactivation of MAPK pathway, and decrease in c-Myc expression (80). Ovothiols, extracted from eggs of the sea urchin *Paracentrotus lividus*, have been shown to play an important role in the protection of cells *via* modulation of the cellular redox balance and recycling of oxidized glutathione. In addition, one study has suggested that ovothiols may decrease cell proliferation *via* activation of autophagy in human liver carcinoma cells, without affecting normal lung cells (81). In another study, treatment with *strongylocentrotus nudus* egg polysaccharide (SEP), isolated from the eggs of sea urchins, was found to exhibit immunomodulatory activity *via* enhancement of splenocyte proliferation and stimulation of B and T cell proliferation. However, SEP treatment did not directly affect cancer cells, and the anticancer effects of SEP were associated with modulation of immune system functions (82). During

investigation of the anti-cancer activity of four glycolipids extracted from the intestine of the sea urchin *Strongylocentrotus intermedius*, only one glycolipid (sulphonoquinovosyl-lysoglyceride) was found to exhibit significant cytotoxic effect in human lung adenocarcinoma. The application of the extract inhibited tumor growth and induced necrosis in mouse model (83). These results indicate that starfish and sea urchin derived extracts need to be further studied to establish their anticancer activity against different types of cancer (Table III).

### The Therapeutic Effects of NPs Derived from Marine Sponges and Tunicate and Clinical Trials of Cancer Therapy

Marine sponges belong to the phylum Porifera and are the richest source of natural marine compounds (84). Diverse molecules derived from marine sponges, such as nucleosides, sterols, alkaloids, and amino acid derivatives have been discovered and at least 60 of them have been shown to have potential chemopreventive and anticancer activities (85, 86). These properties of marine sponge-derived natural products are affected by multiple cellular and molecular processes, such as cell cycle, apoptosis, and inflammation (Table IV).

Table III. Mode of action of anticancer activity of marine starfish and sea urchin derived compounds.

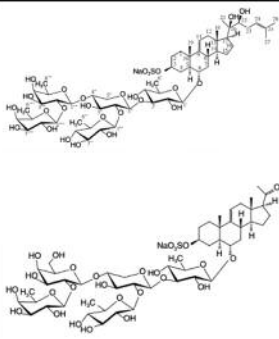
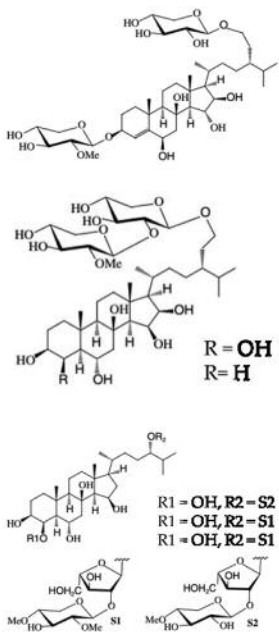
Compounds	Type of source	Findings	Reference
 <p>Two asterosaponins</p>  <p>six glycosylated polyhydroxysteroids</p>	<p><i>Culcita novaeguineae</i></p>	<p>Slight cytotoxic effects against human hepatoma, epidermoid carcinoma, prostate, breast cancer, and melanoma</p>	<p>(74)</p>

Table III. Continued

The preclinical and clinical trials of cancer therapy using *Renieramycin M* and its derivatives. Renieramycin M (RM) isolated from the blue sponge *Xestospongia* sp. is a tetrahydroisoquinoline, and is the first marine anticancer drug approved by the European Union and the Food and Drug Administration (FDA) for the treatment of advanced soft tissue sarcomas (87). These products have shown

cytotoxic activity in human colon, lung, prostate, brain, and breast cancer cells (88-90). Treatment with RM isolated from the sponge *Xestospongia* species showed cytotoxic effects against lung cancer stem cells (CSC), reduced colony and spheroid formation, as well as CSC markers, such as CD133, CD44, and ALDH1A (90). Moreover, RM treatment has shown a therapeutic effect by resensitizing anoikis in anoikis-resistant lung cancer cells. Anoikis resistance is

Table III. *Continued*

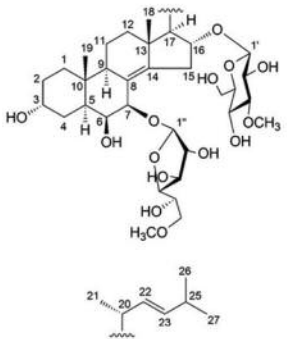
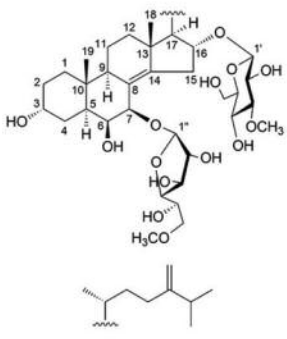
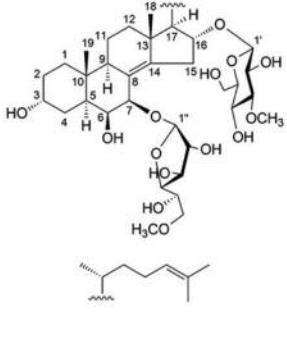
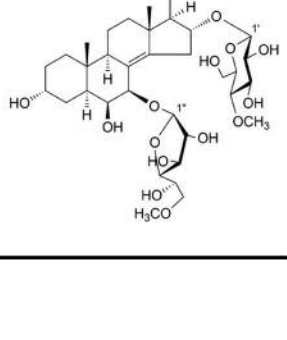
Compounds	Source	Findings	Reference
	<i>Anthenea sibogae</i>	Slight inhibitory effects on cell proliferation and colony formation in human breast cancer	(75)
			
			
			

Table III. *Continued*

Table III. *Continued*

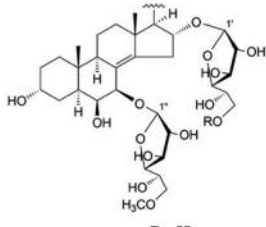
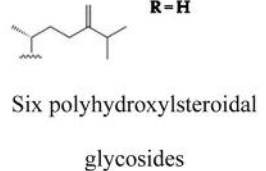
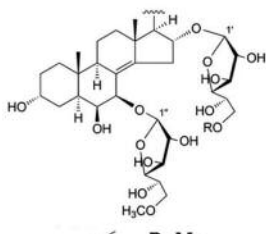
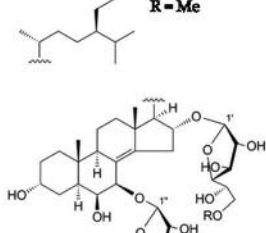
Compounds	Source	Findings	Reference
 <p><b>R = H</b></p>  <p>Six polyhydroxysteroidal glycosides</p>  <p><b>R = Me</b></p>  <p><b>R = Me</b></p> <p>Two known glycosides</p>			
<p>Plancitoxin I (GenBank: BAD13432)</p>	<p><i>Acanthaster planci</i></p>	<p>Decrease in cell viability, induction of ROS and nitric oxide production, reduction of mitochondrial membrane potential, induction of apoptosis</p>	(77)
		<p>Reduction in antioxidant enzymes, induction of mitochondrial dysfunction, ER stress, and apoptosis</p>	(76)

Table III. *Continued*

Table III. *Continued*

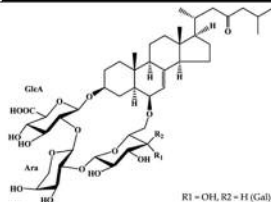
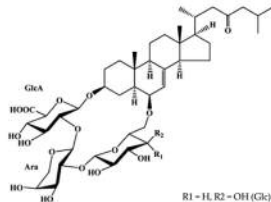
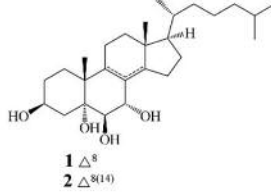
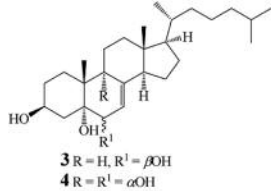
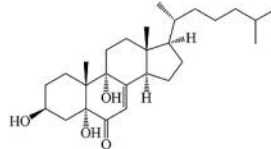
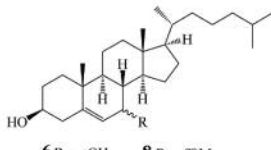
Compounds	Source	Findings	Reference
 <p>luzonicoside A</p> <p>R1 = OH, R2 = H (Gal)</p>  <p>luzonicoside D</p> <p>R1 = H, R2 = OH (Glc)</p> <p>Cyclic steroid glycosides</p>	<i>Echinaster luzonicus</i>	Inhibition of cell proliferation, colony formation, and migration, regulation of cell cycle, induction of apoptosis	(78)
 <p>1 <math>\Delta^8</math> 2 <math>\Delta^{8(14)}</math></p>  <p>3 R = H, R<sup>1</sup> = <math>\beta</math>OH 4 R = R<sup>1</sup> = <math>\alpha</math>OH</p>  <p>6 R = <math>\alpha</math>OH 7 R = <math>\beta</math>OH</p>  <p>8 R = <math>\beta</math>OMe 12 R = H</p>	<i>Diadema savignyi</i> Michelin	Suppression of cell proliferation and viability, induction of apoptosis, modulation of apoptosis related proteins, modulation of MAPK pathway	(80)

Table III. *Continued*

Table III. Continued

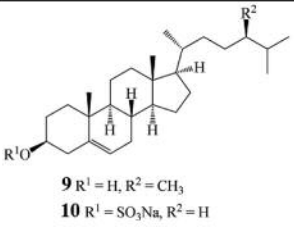
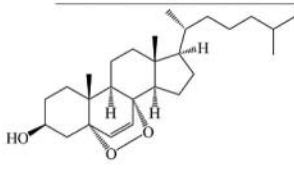
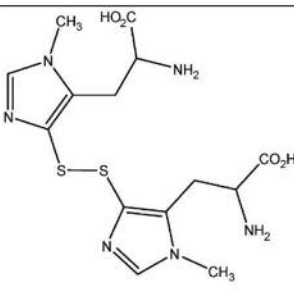
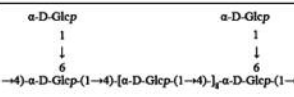
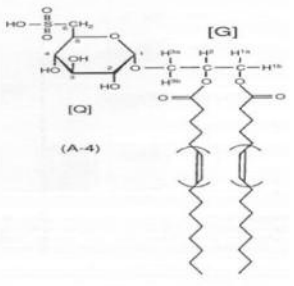
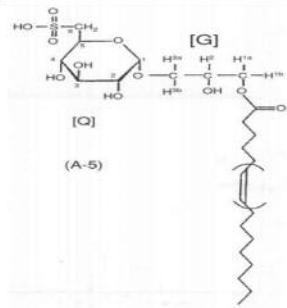
Compounds	Source	Findings	Reference
 <p> <b>9</b> R<sup>1</sup> = H, R<sup>2</sup> = CH<sub>3</sub>  <b>10</b> R<sup>1</sup> = SO<sub>3</sub>Na, R<sup>2</sup> = H                 </p>  <p>steroidal components</p>			
 <p>Ovothiols</p>	<i>Paracentrotus lividus</i>	Modulation of cellular redox balance, recycling of oxidized glutathione in normal cells, suppression of cell proliferation, activation of autophagy	(81)
 <p>Strongylocentrotus nudus egg polysaccharide (SEP)</p>	<i>Strongylocentrotus nudus</i>	Immunomodulatory activity, enhancement of solenocyte proliferation, stimulation of B and T cells	(82)
 <p>(A-4)</p>	<i>Strongylocentrotus intermedius</i>	Inhibition of cell growth, induction of necrosis	(83)

Table III. Continued

Table III. *Continued*

Compounds	Source	Findings	Reference
 <p>sulphonosulphoglycosyl- lysoglyceride</p>			

induced by modulating the up-regulation of survival and anti-apoptotic proteins, such as phosphorylated extracellular signal-regulated kinase (p-ERK), phosphorylated ATP-dependent tyrosine kinase (p-AKT), and B-cell lymphoma-2 (BCL2). RM significantly suppressed cell viability and the expression of p-ERK, p-AKT, and BCL2 (91). Further, hydroquinone 5-O-cinnamoyl ester (CIN-RM), a newly-synthesized derivative of RM, has been shown to be more cytotoxic against non-small cell lung cancer cells compared to RM. CIN-RM treatment induced apoptosis by increasing apoptosis inducing factor and by activating of caspase 3 and 9 through a p53-dependent mechanism (92). Another study has reported the formation of bishydroquinone renieramycin M (HQ-RM) by modifying the quinone ring of RM. HQ-RM treatment has been shown to have stronger cytotoxic effects compared to RM. HQ-RM reduced the viability of lung cancer cells and induced apoptosis by increasing pro-apoptotic proteins, such as BAX, and decreasing the anti-apoptotic proteins BCL2 and MCL *via* mitochondrial apoptosis (93).

*The clinical trials and therapeutic effects of Cytarabine and Zalypsis.* Werner Bergmann's group isolated arabino nucleoside spongothymidine and spongouridine from the Caribbean sponge *Cryptotethya crypta* (94). Cytarabine (Ara-C) is the synthetic analog of natural arabino nucleosides and cytosine arabinose and has been used as an anti-metabolite drug in cancer therapy. An anti-metabolite drug is similar to the structure of a natural metabolite and blocks normal cell metabolism (95). Cytarabine has been shown to interrupt DNA synthesis (96, 97) and approved for clinical use in

1969 and is still widely used in the treatment of various types of leukemia. Cytarabine is commonly used for the treatment of acute leukemia therapy. Treatment with cytarabine has been shown to induce apoptosis *via* phosphatidylserine exposure, caspase activation, and inhibition of RNA synthesis in B-chronic lymphocytic leukemia (98). In acute myeloid leukemia therapy, cytarabine is also used as one of the important drugs. Treatment with cytarabine has been shown to inhibit cell growth and to induce apoptosis *via* regulation of autophagy pathway in human leukemia cell lines (99).

Zalypsis<sup>®</sup> is a newly synthetic dimeric isoquinoline alkaloid structurally related to renieramycin J isolated from the species of marine sponge, *Netropsia*. The molecular pharmacology of this compound has been reported to be similar to that of ET743, but it does not activate the DNA damage checkpoint response (100). Treatment of Zalypsis<sup>®</sup> has been shown to increase double strand breaks (DSBs), inhibit transcription and cell cycle, and then increase apoptosis in human cancer cells (100). In addition, Zalypsis<sup>®</sup> has shown potent anti-leukemic activity and synergetic effect with conventional antileukemic drugs, including cytarabine, fludarabine and daunorubicin. Treatment of Zalypsis<sup>®</sup> has been shown to induce apoptosis *via* modulation of DSBs related pathway in leukemia cells and patients samples (101). Zalypsis<sup>®</sup> has been tested three Phase I/II clinical trials. One clinical trial, aimed at developing novel treatments for advanced malignant solid tumors or lymphoma, was terminated (NCT00359294). This Phase I study investigated the safety, tolerability, dose limiting toxicity and recommended dose of Zalypsis<sup>®</sup>. Another clinical trial,

Table IV. The anticancer effects of compounds extracted from marine sponges.

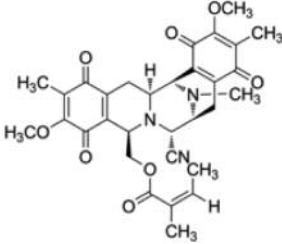
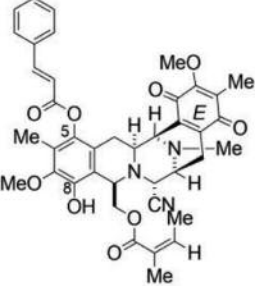
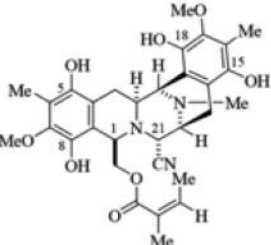
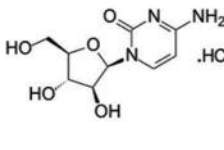
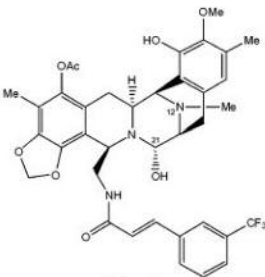
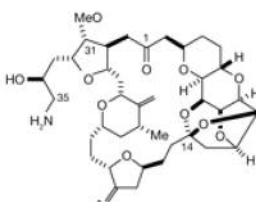
Compounds	Type of source	Findings	Reference
 <p>Renieramycin M</p>	<i>Xestospongia</i> sp	Reduction of colony and spheroid formation, and CSC markers in lung cancer stem cells	(90)
		Resensitizing and anoikis in resistant lung cancer, inhibition of cell viability and related protein expression	(91)
 <p>hydroquinone 5-O-cinnamoyl ester (CIN-RM)</p>	Derivative of Renieramycin M	Induction of apoptosis by increase and activation of apoptosis related proteins in non-small cell lung cancer	(92)
 <p>Bishydroquinone renieramycin M (HQ-RM)</p>	Derivative of Renieramycin M	Reduction of cell viability, induction of apoptosis and pro-apoptotic proteins in lung cancer	(93)
		Anti-metabolic drug, inhibition of DNA synthesis in acute leukemia	(95-97)

Table VI. Continued



Table VI. *Continued*

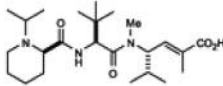
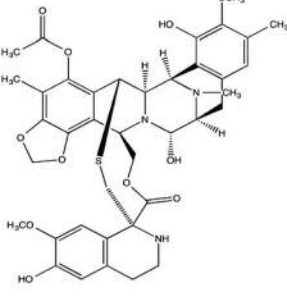
Compounds	Type of source	Findings	Reference
 Cytarabine	<i>Cryptotethya crypta</i>	Induction of apoptosis, interruption of RNA synthesis in B-chronic lymphocytic leukemia	(98)
		Inhibition of cell growth, induction of apoptosis via modulation of autophagy pathway in leukemia	(99)
 Zalypsis®	Netropsia	Induction of double strand breaks (DSBs) and apoptosis, inhibition of transcription and cell cycle in human cancer	(100)
		Induction of apoptosis via regulation of DSBs in leukemia	(101)
		Clinical trials for safety, tolerability, dose limiting toxicity, pharmacokinetic profile, pharmacogenomics profile, evaluation of antitumor activity	NCT00359294 NCT00900562 NCT01222767
 Eribulin mesylate	Porifera <i>Halichondria okadai</i>	Synthetic product of halichondrin B, induction of microtubule destabilization and mitotic arrest	(103)

aimed at developing novel treatments for advanced and/or metastatic endometrial or cervical cancer, was also terminated (NCT00900562). This Phase II study evaluated the antitumor activity, safety profile, pharmacokinetic profile and pharmacogenomic profile of Zalypsis®. The third clinical trial, aimed at developing novel treatments for

unresectable locally advanced and/or metastatic Ewing family of tumors, has been completed (NCT01222767). This Phase II study evaluated the antitumor activity of Zalypsis®.

*The clinical trials and therapeutic effects Eribulin mesylate and E7974 on cancer.* Eribulin mesylate is a synthetic

Table VI. Continued

Compounds	Type of source	Findings	Reference
 E7974	<i>Hemiasterella minor</i>	Synthetic product of hemiasterlin, suppression of microtubule polymerization binding, induction of cell cycle arrest and apoptosis	(109, 111) (NCT00165802, NCT00130169, NCT00121732)
 Trabectedin	<i>Ecteinascidia turbinata</i>	Treatment for soft tissue sarcomas, evaluation of safety, toleration, and antitumor activity of combination therapy	(113-115) NCT01426633 NCT00102609 NCT02247544 NCT00113607

product of halichondrin B isolated from the Poriferan *Halichondria okadai*, and it is the only commercial anticancer drug derived from marine sponges available for the treatment of breast cancer (102). Eribulin mesylate has been shown to induce microtubule destabilization, which leads to irreversible mitotic arrest *via* the formation of abnormal mitotic spindles (103). In addition, eribulin mesylate has been shown to reverse the epithelial-to-mesenchymal transition in cancer (104). Eribulin mesylate has shown anticancer activity against diverse cancers, including breast, ovarian, colon, and pancreatic cancer (105-107). In a clinical study, administration of eribulin mesylate has shown anticancer effects with manageable side effects including neutropenia and fatigue (108). E7974 is a synthetic product of hemiasterlin, which is extracted from the marine sponge *Hemiasterella minor* (109, 110). E7974 has been found to suppress microtubule polymerization and to alter the mitotic spindle, thus inducing cell cycle arrest and apoptosis. E7974 has shown an inhibitory effect on cell proliferation in several cancer cell lines (111). Three Phase I clinical trials with E7974 have been completed (NCT00165802, NCT00130169, NCT00121732). These clinical trials have been performed in patients with refractory solid tumors and therapeutic effects of E7974 were observed. Administration of E7974 has shown reversible and manageable side-effects.

*The clinical trials and therapeutic effects of NPs isolated from Tunicate as anticancer agents.* Trabectedin is a synthetic marine-derived alkylating agent extracted from the Caribbean tunicate, *Ecteinascidia turbinata* (112). Trabectedin has succeeded in the treatment of soft tissue sarcomas in preliminary clinical trials and approved in the EU for treatment of advanced soft tissue sarcoma and recurrent platinum-sensitive ovarian cancer. Currently, large, randomized phase III clinical trials proceed in many countries. One clinical trial, aimed at developing combination therapy of gemcitabine and trabectedin for L-sarcomas, has been completed (NCT01426633) (113). This Phase I study evaluated the antitumor activity of combination therapy and provided negative results for the treatment of advanced and/or metastatic leiomyosarcoma or liposarcoma. Another clinical trial, aimed at developing combination therapy with doxorubicin and trabectedin for soft tissue sarcoma, has also been completed (NCT00102609) (114). This Phase I study evaluated the safety and toleration, and antitumor activity of the combination therapy, and the results showed that the combination therapy is safe and well tolerated, and exerts anticancer activity. A phase II clinical trial, aimed at confirming the therapeutic effect of trabectedin for retroperitoneal leiomyosarcoma and well differentiated/dedifferentiated liposarcoma, has also been completed (NCT02247544). This Phase II study assessed the

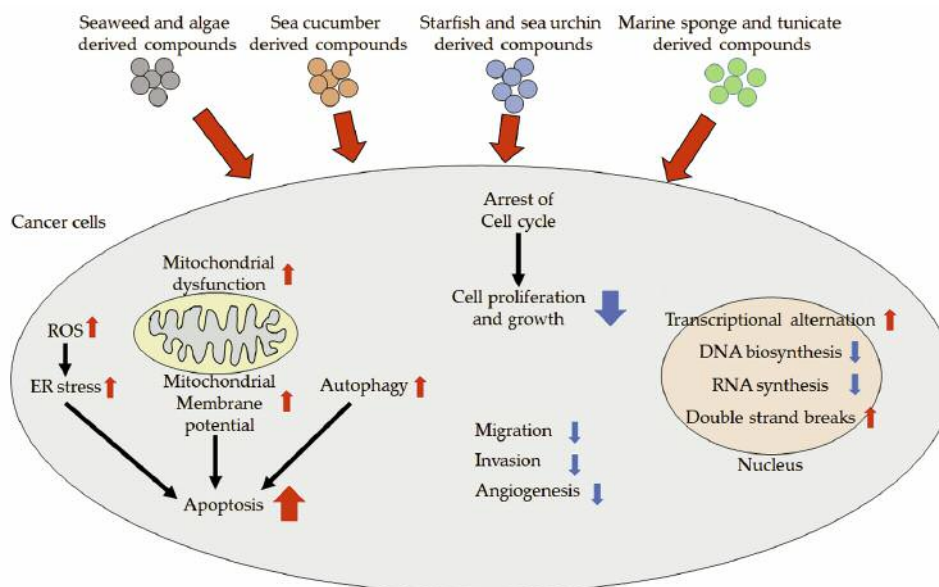


Figure 1. A schema illustrating the overview of anticancer activity of marine-derived compounds in diverse cancers.

activity of trabectedin as a secondary treatment. This clinical study is completed, but the results are not yet published. A phase III trial clinical, aimed at confirming the therapeutic efficacy and safety of trabectedin for advanced relapsed ovarian cancer, has also been completed (NCT00113607) (115). This Phase III study assessed the effect of combination of trabectedin and pegylated liposomal doxorubicin. The results showed that the combination treatment has little or no decrement in patient-reported functional status and symptoms, and led to manageable and non-cumulative toxicity with fewer adverse events and a significant improvement in progression-free survival and overall response rate.

## Conclusion

Marine organisms have provided a promising source of useful natural products, molecules, and drugs for therapeutic use. The results of numerous studies, summarized in this review, suggest that natural products derived from marine organisms are novel candidate therapeutic agents for the prevention and treatment of cancer. Marine extracts possess cytotoxic activity against many cancers, including breast and colon cancer, *via* inhibition of cell proliferation and cell viability, induction of ROS production, mitochondrial dysfunction, ER stress, and apoptosis. In addition, many marine organisms are promising sources of anticancer compounds and have shown beneficial effects upon combination with traditional

anticancer drugs (Figure 1). However, it is still necessary to further study the natural products isolated from a large number of marine species.

The therapeutic and commercial usage of promising marine natural product is dependent on the results of preclinical and clinical studies. Many studies have reported that marine isolated natural products and its derivatives show potential therapeutic efficacy for cancer therapy. Cytarabine and Zalypsis have been studied in many preclinical and clinical trials and are used to treat various leukemias and cancer. Also, eribulin mesylate and E7974 have proceeded to clinical trials to investigate their therapeutic effects on several cancers. Currently, many marine derived compounds have been reported to be in the process of development into drugs. Therefore, it is necessary to study the anticancer activities of marine extracted natural products in order to develop novel anticancer drugs for diverse cancers.

## Conflicts of Interest

The Authors have no conflicts of interest to declare with regards to this study.

## Authors' Contributions

Chul Won Yun: Data collection and drafting of manuscript; Hyung Joo Kim: drafting of manuscript; Sang Hun Lee: organizing the structure of the manuscript, drafting and editing of the manuscript, procurement of funding.

# Acknowledgements

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