International Journal of
Translational Medicine

MDPI

Review

Recent Advances in Marine-Derived Bioactives Towards Cancer Therapy

Nafisa Nawar Tamzi [1], Md Motiur Rahman [2,3] and Subhadeep Das [4,5,*]

[1] Department of Fishing and Post-Harvest Technology, Chattogram Veterinary and Animal Sciences University, Chattogram 4202, Bangladesh; nafisa@cvasu.ac.bd
[2] School of Engineering Technology, Purdue University, West Lafayette, IN 47907, USA; rahma112@purdue.edu
[3] Department of Physical and Mathematical Sciences, Chattogram Veterinary and Animal Sciences University, Chattogram 4202, Bangladesh
[4] Department of Biochemistry, Purdue University, BCHM A343, 175 S. University Street, West Lafayette, IN 47907-2063, USA
[5] Purdue University Institute for Cancer Research, Purdue University, Hansen Life Sciences Research Building, Room 141, 201 S. University Street, West Lafayette, IN 47907-2064, USA
* Correspondence: das193@purdue.edu; Tel.: +1-(765)-409-6394

Abstract: The increase in cancer incidence in recent years necessitates urgent exploration of novel and alternative sources of natural bioactives for targeted cancer therapy. Approximately 75% of the Earth's surface is covered by oceans, which are thought to harbor untapped physiologically active compounds with potential efficacy against cancer. Recently, a growing focus has been on isolating and investigating novel bioactive compounds derived from marine sources. Bioactive metabolites with diverse chemical structures, isolated from various marine species such as algae, mollusks, and actinomycetes, demonstrate potential efficacy against a wide range of cancers. To our knowledge, this is one of the articles that has reviewed recent papers on the application of marine-derived bioactives in targeted cancer therapy. This study aims to showcase some of the most current developments in targeted cancer therapy with various bioactives that have been identified from marine sources.

Keywords: marine bioactives; cancer therapy; drug discovery; targeted therapy

Citation: Tamzi, N.N.; Rahman, M.M.; Das, S. Recent Advances in Marine-Derived Bioactives Towards Cancer Therapy. *Int. J. Transl. Med.* **2024**, *4*, 740–781. https://doi.org/10.3390/ijtm4040051

Academic Editor: Caterina Cinti

Received: 31 October 2024
Revised: 28 November 2024
Accepted: 3 December 2024
Published: 6 December 2024

1. Introduction

Cancer remains a significant global health challenge, accounting for nearly 10 million deaths annually, with projections indicating an increase in prevalence in the coming decades [1–3]. Despite advancements in treatment modalities such as surgery, chemotherapy, radiotherapy, and immunotherapy, the prognosis for many cancer patients remains poor due to severe side effects, drug resistance, and the inability of conventional therapies to specifically target cancer cells without harming healthy tissues [4,5]. These limitations highlight the urgent need for more effective and less harmful therapeutic approaches.

In recent years, marine-derived bioactive compounds have emerged as promising alternatives or complements to conventional cancer therapies. The marine environment, which covers over 70% of the Earth's surface, is a largely untapped reservoir of bioactive molecules [5,6]. Marine organisms have evolved in extreme environments, developing sophisticated biochemical defense mechanisms against predators and environmental stressors, which has led to the production of bioactive compounds that are often not found in terrestrial organisms [5,7]. Consequently, marine compounds represent a largely unexplored resource for drug discovery, particularly in oncology [8–10]. Organisms such as algae, sponges, fungi, bacteria, etc., produce a diverse array of secondary metabolites with unique chemical structures and potent biological activities, many of which exhibit significant anticancer potential [11,12]. These bioactive compounds, including alkaloids, peptides, polysaccharides, terpenoids, and other metabolites, have shown promising results

in modulating cancer-related pathways [13,14]. For instance, trabectedin, derived from the tunicate *Ecteinascidia turbinata*, has been approved by the FDA (NDA 207953) for the treatment of soft tissue sarcoma and ovarian cancer due to its ability to disrupt cancer cell DNA repair mechanisms [15]. Another notable compound, eribulin, a synthetic derivative of the sponge metabolite halichondrin B, is FDA-approved (NDA 201532) for treating metastatic breast cancer, demonstrating its effectiveness in inhibiting microtubule dynamics [16].

Recent advancements in drug delivery systems have enhanced the therapeutic potential of marine-derived compounds. For example, liposomal formulations of fucoidan, a sulfated polysaccharide from brown algae, have shown improved bioavailability and targeted delivery, amplifying its antitumor effects [17]. In addition, salinosporamide A, produced by marine actinomycetes, is currently undergoing Phase II clinical trials for its potential to treat multiple myeloma (NCT00891280) [18]. Advances in nanotechnology, such as nanoparticle-based carriers, have further refined the delivery of marine-derived bioactives, minimizing off-target effects while enhancing therapeutic efficiency [19]. Meanwhile, bryostatins, sourced from the bryozoan *Bugula neritina*, are under investigation for their potential as cancer immunomodulators [20].

Among marine organisms, macroalgae stand out for their ability to produce bioactive compounds that interfere with cancer progression through multiple mechanisms [21]. For instance, fucoidan, a sulfated polysaccharide from brown algae, has demonstrated antitumor properties by inhibiting angiogenesis and inducing apoptosis. Other compounds from red and green algae have also been shown to block cell-cycle progression and enhance immune responses, further supporting their potential in cancer therapy [22,23]. Additionally, sponges are another rich source of bioactive compounds, yielding molecules such as halichondrin B, which inhibits cancer cell proliferation and has led to the development of drugs like eribulin for treating breast cancer [1]. Marine fungi contribute significantly to the pool of bioactives, particularly through the production of secondary metabolites with immunomodulatory and cytotoxic effects on cancer cells [1].

Marine invertebrates, including mollusks, tunicates, and echinoderms, are known for producing bioactive peptides and alkaloids. For example, tunicates produce compounds like trabectedin, which has shown promising anticancer activity and is approved for treating soft tissue sarcoma and ovarian cancer [2,24]. Marine bacteria and actinomycetes are also prolific sources of bioactive compounds, with actinomycetes yielding molecules like salinosporamide A currently undergoing clinical trials for its potential to treat multiple myeloma [6,8]. Despite the vast potential of these marine-derived compounds, the marine environment remains largely underexplored compared to terrestrial ecosystems, with over 70% of marine species yet to be discovered or fully understood [25]. As research into marine organisms expands, bioactive compounds are being identified with structural properties and mechanisms of action that are often distinct from terrestrial sources, adding to their therapeutic appeal [13,26,27].

The motivation for exploring marine-derived bioactives in cancer therapy arises from the inadequacies of current treatments, which often result in recurrence, drug resistance, and significant toxicity [28,29]. Chemotherapy, for instance, can be highly toxic, damaging healthy tissues while not always effectively eradicating cancer [30]. Furthermore, the high economic burden of cancer treatments, combined with the limitations of conventional therapies, necessitates the search for alternative solutions. Marine bioactives, with their unique modes of action, present an attractive option by offering potent anticancer activity with fewer side effects.

Recent reports indicate that marine bioactives target novel mechanisms, including DNA repair, autophagy, and apoptosis, along with the modulation of the tumor microenvironment [3,31–33].

Metachromin C isolated from the marine sponge *Hippospongia metachromia* may disrupt the association of Topoisomerase I (TOPO I) to DNA, hinder TOPO I activity, impede DNA relaxation, induce DNA damage, and subsequently trigger the DNA repair pathway in four pancreatic cancer cell lines: PANC-1, BxPC-3, MiaPaCa-2, and AsPC-1. In addition, it

concurrently functions as an anti-angiogenic molecule [32]. A separate report highlighted the impact of non-small cell lung cancer (NSCLC) cells treated with Cycloheptylprodigiosin, which was isolated from the marine bacterium *Spartinivicinus ruber* MCCC 1K03745T. The compound may interfere with autophagic flow by promoting autophagy initiation as well as lysosomal degradation of autophagic cargo. Interestingly, the processes by which autophagy is disrupted vary throughout NSCLC cell lines. The secretion of cathepsin D showed a notable increase, likely due to the breakdown of the trans-Golgi network, suggesting a disturbance in the secretory pathway [33]. A separate report indicates that curdepsidone A, a derivative of depsidone isolated from *Curvularia* sp. IFB-Z10 can inhibit the growth of cervical cancer HeLa cells through the induction of G0/G1-phase cell-cycle arrest and apoptosis. Curdepsidone A induced apoptosis through the activation of ROS production, the suppression of the *PI3K/AKT* pathway, and the inhibition of protective autophagy [34]. Piscidin-1 is a cationic antimicrobial peptide (AMP) that occurs naturally and is obtained from the mast cells of hybrid striped bass (*Morone saxatilis* × *M. chrysops*) [35]. By cleaving caspase 3, piscidin-1 triggers apoptosis through both internal and extrinsic mechanisms. Piscidin-1 reduced mitochondrial function, mitochondrial membrane potential ($\Delta\Psi m$), and the OXPHOS complex protein levels. It also increases intracellular Ca^{2+} levels and induces endoplasmic reticulum stress in Oral squamous cell carcinoma (OSCC) cells. Furthermore, Piscidin-1 inhibits angiogenesis in human umbilical vein endothelial cells (HUVECs) [36]. The microwave-extracted clam polysaccharide (MCP) derived from *Ruditapes philippinarum* demonstrated inhibitory effects on the growth of HT-29 cells while exhibiting minimal toxicity in RAW 264.7 cells. MCP induces apoptosis in HT-29 cells by lowering intrinsic mitochondrial membrane potential, facilitating the release of cytochrome C, activating caspase-3, and suppressing *Bcl-2* gene expression. MCP has the potential to reverse the polarization of M2-type tumor-associated macrophages (TAMs) to M1-type within the tumor microenvironment (TME) and to promote the differentiation of original macrophages into M1-type cells, thus increasing their anticancer effects. MCP also decreases the level of reactive oxygen species in tumor cells [37].

This manuscript presents a comprehensive narrative review that aims to analyze the anticancer potential of marine-derived bioactive compounds. It examines a wide range of bioactive molecules, including alkaloids, peptides, polysaccharides, and terpenoids, derived from various marine organisms such as algae, invertebrates, and fungi. By synthesizing relevant and impactful literature, this review highlights recent advancements in the discovery, clinical evaluation, and FDA approvals of these compounds. It addresses the molecular pathways behind their anticancer mechanisms while identifying and addressing gaps in current research. By emphasizing their unique chemical structures, mechanisms of action, and clinical relevance, this work contributes to ongoing efforts to develop more effective, safer, and sustainable cancer treatments derived from marine sources, catering to researchers, clinicians, and professionals in drug discovery and marine pharmacology. This review is tailored for researchers, clinicians, and professionals in drug discovery, marine pharmacology, and oncology, providing insights to support both scientific exploration and clinical application.

2. Characteristics of Marine-Derived Bioactives

Marine-derived bioactive products exhibit distinctive molecular signatures such as their distinctive amino acid composition, three-dimensional structure, molecular size, etc. [3,38,39]. The characteristics encompass a high percentage of proline and branched amino acid residues [40–43], the existence of both D and L amino acids [40,42,44,45], and the presence of uncommon amino acid residues, such as bromotryptophan [40,44,46,47].

In the unique marine environment characterized by high salt, high pressure, low temperature, and low oxygen, marine polysaccharides (MPs) exhibit unique structural features and remarkable pharmacological stability when in comparison with terrestrial polysaccharides (TPs) [48–50]. The combination of flexible monosaccharides and modified sidechains results in MPs displaying a complex structural skeleton [51]. Marine-

derived terpenoids offer a wide variety of molecular structures. The marine bacteria primarily generate meroterpenoids, whereas the fungi are recognized for their production of isoprenoids. Marine-derived microbial terpenoids exhibit intriguing structural features, including halogenation, which is catalyzed by specific enzymes that possess unique substrate specificity [52].

Marine-derived bioactives are thought to have increased bioactivity and bioavailability, offering significant potential for the development of novel anticancer agents [53–55]. The significant bioactivity, bioavailability, and reduced immunogenicity of these marine-derived products can be attributed to the distinctive molecular signatures that distinguish them in contrast to terrestrial proteins [3]. The relative stability allows them to serve as effective therapeutic agents since they are less prone to degradation in vivo and can maintain their activity for prolonged durations [3]. Collagen, a highly bioactive protein obtained from marine sources, is present in the connective tissues of marine creatures, including *fish*, *cephalopods*, and *jellyfish* [3,56]. The molecular weight (Mw), monosaccharide composition, branching structures, functional groups, and chain conformation of MPs are intricately linked to their bioactivity [50,57,58].

Because of their wide range of chemical structures, organic frameworks, broad-spectrum biological activity, and high target specificity, marine-derived bioactives have become a valuable source for new anticancer medications [59]. Their alignment with human body receptors increases their possibilities for future medical applications [59].

3. Marine Sources of Bioactives

Microalgae are single-celled, photosynthetic organisms found in both freshwater and marine environments. These organisms are known for their rich production of bioactive compounds, including flavonoids, carotenoids, phenolics, and polysaccharides, all exhibiting significant therapeutic potential [60]. Microalgae like *Chlorella vulgaris*, *Scenedesmus* sp., and *Phaeodactylum tricornutum* are prominent producers of such bioactives [61]. These microalgae thrive in aquatic ecosystems, playing a crucial role in the carbon cycle while serving as the base of the food chain. Their ability to rapidly reproduce and adapt to varying environmental stresses enables them to yield high amounts of bioactive compounds [62]. The ease of cultivating microalgae, coupled with their high yield of bioactives, makes them an attractive source for industrial-scale bioactive production [63].

Macroalgae, commonly known as seaweeds, are multicellular algae found in marine environments and are classified into brown, red, and green algae [64]. Brown algae, such as *Fucus vesiculosus*, *Laminaria japonica*, and *Macrocystis pyrifera*; red algae, such as *Kappaphycus alvarezii* and *Gracilaria* sp.; and green algae, such as *Ulva lactuca* and *Codium isthmocladum*, are key sources of bioactives [12]. These algae grow in shallow coastal waters where they absorb nutrients and produce secondary metabolites to protect themselves from environmental stresses like UV radiation, salinity, and herbivory [13].

Refs. [10,65] Echinoderms, including sea cucumbers, sea urchins, and starfish, are marine animals that produce a variety of bioactive compounds [66]. Sea cucumbers such as *Holothuria scabra* and *Cucumaria frondosa*, sea urchins like *Diadema savignyi*, and starfish-like *Astropecten polyacanthus* are prominent echinoderms known for their bioactive potential [24]. These organisms inhabit ocean floors, where they filter feed and extract nutrients from the sediment [4]. Their slow-moving lifestyles have led to the evolution of unique bioactive compounds, which serve as defense mechanisms against predators and microbial infections [5].

Marine fungi are an emerging source of bioactive compounds with significant potential in cancer treatment [67]. These fungi thrive in diverse marine environments, such as seawater, sediments, marine plants, and invertebrates, and produce secondary metabolites that show anticancer, antioxidant, and antimicrobial activities [68]. Marine fungi are primarily found in the phyla Ascomycota and Basidiomycota, and their unique ability to adapt to the harsh conditions of the ocean, such as high salinity, low temperature, and pressure, leads to the production of structurally diverse bioactive compounds not found in terrestrial fungi [17]. Some well-known species of marine fungi that have shown potential to produce

anticancer compounds include *Aspergillus fumigatus*, *Penicillium citrinum*, *Aspergillus terreus*, and *Gliocladium* sp., among others [17,69].

Marine sponges are one of the most prolific sources of bioactive compounds, particularly for cancer treatment [70]. These sessile organisms, which belong to the phylum *Porifera*, have evolved to produce a wide range of secondary metabolites to defend against predation and microbial infections [71]. Marine sponges inhabit diverse environments, from shallow coastal regions to the deep sea, and their slow-moving, porous nature makes them susceptible to environmental challenges [72]. As a result, they have developed unique biochemical pathways to synthesize complex compounds, many of which exhibit potent biological activities, including anticancer properties [73].

Mollusks and tunicates, two classes of marine invertebrates, are valuable sources of bioactive compounds with significant potential in cancer treatment [74–77]. Both groups have evolved in marine environments where they are exposed to various stressors, prompting them to produce secondary metabolites as defense mechanisms [78]. These metabolites have been found to possess strong cytotoxic, antimicrobial, and anticancer properties, making them essential in drug discovery and development, particularly for cancer therapies [3]. Mollusks, especially *sea hares*, *gastropods*, and *cone snails*, produce a range of bioactive compounds [68,72,79–81]. Tunicates, or sea squirts, are another rich source of anticancer compounds [23]. These sessile organisms are particularly abundant in marine ecosystems and have developed unique bioactive metabolites, many of which have advanced to clinical use [1,2,22,24].

4. Marine Bioactives Towards Cancer Therapy

Marine-derived bioactive compounds can be grouped based on their chemical nature and biological activity, highlighting their broad application in therapeutic areas. In the following section, we will address some of these marine-derived bioactives that are used for cancer treatment.

4.1. Alkaloids

Alkaloids from marine sources have shown substantial anticancer potential. Trabectedin ($C_{39}H_{43}N_3O_{11}S$), derived from the sea squirt *Ecteinascidia turbunata*, is widely used to treat soft tissue sarcomas [15,77,82].

Another notable alkaloid, Variolin B ($C_{14}H_{11}N_7O$), isolated from the sponge *Kirkpatrickia variolosa*, demonstrates cytotoxicity against prostate cancer cells [26,83]. Manzamine A ($C_{36}H_{44}N_4O_4$), sourced from the sponge *Acanthostrongylophora* sp., exhibits intense activity against prostate and breast cancer cells by inhibiting critical cancer signaling pathways [27,84,85]. Debromohymenialdisine ($C_9H_8BrN_3O$), derived from marine sponges, effectively treats melanoma and prostate cancers by inhibiting cell proliferation and migration [27]. Fascaplysin ($C_{18}H_{11}N_2O^+$), from the sponge *Fascaplysinopsis reticulata*, induces cell-cycle arrest in breast cancer cells [86–88]. Lamellarin D ($C_{28}H_{21}NO_8$), from the mollusk *Lamellaria* sp., triggers apoptosis in multidrug-resistant leukemia cells [29], and Pyridoacridine ($C_{19}H_{12}N_3O_2$), from *Cystodytes* sp., inhibits tumor growth in breast cancer models [29].

4.2. Flavonoids

Marine-derived flavonoids demonstrate anticancer solid and antioxidant properties. Apigenin ($C_{15}H_{10}O_5$), derived from *Chlorella vulgaris*, induces apoptosis in breast cancer cells by regulating cell-cycle proteins [28,89]. Kaempferol ($C_{15}H_{10}O_6$), from *Scenedesmus* sp., inhibits cancer cell migration, particularly in breast cancer models [29]. Quercetin ($C_{15}H_{10}O_7$), isolated from *Synechocystis* sp., inhibits tumor growth by inducing apoptosis in breast and colorectal cancer cells [90,91]. Similarly, Luteolin ($C_{15}H_{10}O_6$), found in *Spirulina* and *Anabaena doliolum*, reduces cell proliferation and induces apoptosis in colon cancer cells [30]. Other flavonoids like Naringenin ($C_{15}H_{12}O_5$) from *Leptolyngbya* sp., Epigallocatechin gallate (EGCG, $C_{22}H_{18}O_{11}$) from *Spirulina platensis*, Hesperidin ($C_{28}H_{34}O_{15}$)

from *Spirulina maxima*, and Baicalein ($C_{15}H_{10}O_5$) from *Chlorella pyrenoidosa* have shown efficacy against various cancer types by targeting key signaling pathways and promoting apoptosis [92–94].

4.3. Polysaccharides

Polysaccharides derived from marine sources exhibit significant anticancer and immunomodulatory effects. Fucoidan ($C_8H_{16}O_7S$), extracted from brown algae like *Fucus vesiculosus* and *Laminaria japonica*, induces apoptosis and inhibits angiogenesis in breast and colon cancer cells [95,96]. Carrageenan ($C_{24}H_{34}O_{31}S_4$), extracted from red algae such as *Kappaphycus alvarezii*, induces cell-cycle arrest and apoptosis in colorectal and gastric cancer cells [32,97,98]. Laminarin ($C_6H_{10}O_5$)n, found in brown algae like *Laminaria Digitata*, enhances immune response and induces apoptosis in colon cancer cells [3] sulfated galactan (-4-ted galact→3-β-d-Galp-1→) from green algae like *Codium isthmocladum* inhibits cancer cell proliferation and prevents metastasis [31]. Other polysaccharides like Alginate ($C_6H_{10}O_7$) from *Macrocystis pyrifera*, Chitosan ($C_{56}H_{103}N_9O_{39}$) from crustacean waste, and Porphyran ($C_{26}H_{44}O_{27}S_2^{2-}$) from *Porphyra yezoensis* exhibit strong anticancer effects through immune microenvironment modulation and apoptosis induction [7].

4.4. Terpenoids

Terpenoids from marine organisms demonstrate potent anticancer properties. Farnesene ($C_{15}H_{24}$), found in *Synechocystis* sp., shows cytotoxicity against leukemia and breast cancer cells by disrupting cell membranes [5], while Geranylgeraniol ($C_{20}H_{34}O$), derived from *Synechococcus elongatus*, induces apoptosis in lung and liver cancer cells [66]. Limonene ($C_{10}H_{16}$), present in *Lyngbya majuscula*, reduces tumor growth in lung cancer models [69], and Squalene ($C_{30}H_{50}$), extracted from *Oscillatoria* sp., enhances immune response and induces apoptosis in melanoma and liver cancer cells [99]. Astaxanthin, from *Haematococcus pluvialis*, inhibits the growth of breast, prostate, and colon cancers by inducing apoptosis [100] Similarly, Fucoxanthin ($C_{42}H_{58}O_6$), found in brown algae like *Undaria pinnatifida*, reduces tumor growth in leukemia and breast cancer cells [101]. Other notable terpenoids include β-Carotene ($C_{40}H_{56}$) from *Dunaliella salina*, both of which promote cell death in various cancer cells [102,103].

4.5. Steroids and Glycosides

Steroids and glycosides extracted from marine sources display promising anticancer and antimicrobial activities. Astero saponins ($C_{57}H_{92}O_{26}$), isolated from starfish, induce apoptosis in breast cancer cells [103], while Echinosides ($C_{35}H_{46}O_{20}$), derived from *Holothuria scabra*, inhibit fungal pathogens and show efficacy against cancer cells [104]. Bryostatin-1 ($C_{47}H_{68}O_{17}$), a glycoside from bryozoans, modulates protein kinase C in leukemia and breast cancer cells [17]. Fucosterol ($C_{29}H_{48}O$), found in brown algae and sea urchins, exhibits cytotoxic effects against breast and colon cancer cells [17]. Other steroidal compounds, such as Asteropectenols ($C_{21}H_{34}O_3$) from starfish and 20-Hydroxyecdysone ($C_{27}H_{44}O_7$) from sea cucumbers, demonstrate anti-inflammatory and anticancer properties, particularly through the inhibition of cancer cell growth [105].

4.6. Peptides

Peptides from marine sources are another major class of bioactives with potent anticancer properties. Kahalalide F ($C_{75}H_{124}N_{14}O_{16}$), isolated from the marine mollusk *Elysia rufescens* and marine algae *Bryopsis* sp., exhibits cytotoxicity against prostate and lung cancer cells through membrane disruption and necrosis induction [18].

Episulosine (ES285, $C_{18}H_{39}NO$), derived from the bivalve *Mactromeris polynyma*, induces apoptosis by disrupting the cytoskeleton in cancer cells [106]. Didemnins ($C_{57}H_{89}N_7O_{15}$), cyclic peptides from the tunicate *Tridemnum solidum*, have antiviral and anticancer properties, inducing apoptosis by inhibiting protein synthesis [107]. Other peptides like Chaetoglobosin A ($C_{32}H_{36}N_2O_5$) from *Chaetomium globosum*, Halichondrin B ($C_{60}H_{86}O_{19}$), and its synthetic

analog, Eribulin mesylate (Halaven), have been used for the treatment of metastatic breast cancer and liposarcoma [108], and Cryptophycin ($C_{35}H_{43}ClN_2O$) exhibit cytotoxic effects by targeting cancer cell membranes and inhibiting key cellular processes, including protein synthesis and microtubule polymerization [19,109–111].

Overall, marine-derived bioactive compounds, including alkaloids, flavonoids, polysaccharides, terpenoids, steroids, and peptides, offer immense potential in cancer treatment due to their diverse mechanisms of action. These compounds exhibit strong cytotoxic, antiproliferative, and immunomodulatory properties, highlighting the ocean as a vast and promising source of novel therapeutic agents.

5. Molecular Mechanisms of Marine-Derived Bioactives Towards Cancer Treatment

Marine-derived bioactives mediate its anticancer effects through a varied range of mechanisms. NF-κB, mTOR, and PI3K/Akt are among the signaling pathways frequently targeted by bioactives derived from marine sources in cancer treatment. NF-κB serves as an inducible factor and functions as a proinflammatory transcription factor [112]. The NF-κB family includes five members: *NF-κB1 (p50)*, *NF-κB2 (p52)*, *RelA (p65)*, *c-Rel*, and *RelB*. These members can form both homo- and heterodimeric protein complexes [113]. The NF-κB signaling pathway consists of three distinct categories such as the canonical pathway, the noncanonical pathway, and the atypical pathway. Lipopolysaccharide (LPS), tumor necrosis factor α (TNFα), and interleukin-1 (IL-1) have been shown to activate Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR), and IL-1 receptor (IL-1R) in the canonical NF-κB signaling pathway, respectively [114]. In response to certain external stimuli, active IκB kinase (IKK) phosphorylates the NF-κB inhibitor (IκB). IκB is recognized and degraded by the 26S proteasome following ubiquitination, leading to the rapid translocation of the NF-κB dimer from the cytoplasm to the nucleus, where it interacts with target gene promoters to induce their expression [115]. In the noncanonical signaling pathway, the activation of B cell activating factor receptor (BAFFR), CD40, or lymphotoxin beta (LTβ) results in the phosphorylation of IKKα via NF-κB-inducible kinase (NIK) [114]. NIK phosphorylates IKKα, subsequently phosphorylating and degrading NF-κB p100, leading to the formation of the NF-κB p52/RelB heterodimer, which translocates to the nucleus and modulates the transcription of target genes. In the atypical pathway, genotoxic stress leads to the migration of NEMO into the nucleus, where it undergoes sumoylation followed by ubiquitination [115]. The process is facilitated by the ataxic telangiectasia mutation (ATM) checkpoint kinase [114]. Upon their return to the cytoplasm, NEMO and ATM trigger IKKβ expression [114]. The disruption of the NF-κB signaling pathway by marine compounds plays a crucial role in cancer treatment. The bioactives derived from marine sources primarily target the canonical NF-κB pathway, the noncanonical NF-κB pathway, and the atypical NF-κB pathways, leading to cancer prevention [116].

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt or PKB) signaling pathway is an essential cell signal transduction pathway, with its activation identified as a critical determinant for cell survival [117,118]. PI3K and Akt represent the two most essential proteins within the PI3K/Akt signaling pathway. PI3K is an intracellular phosphatidylinositol kinase characterized by serine/threonine kinase activity, comprising a regulatory subunit, p85, and a catalytic subunit, p110. PI3K is triggered by stimulation from various growth factors, leading to the conversion of PIP2 to PIP3 through the action of activated PI3K [119]. Akt, a serine/threonine kinase, is induced by phosphorylated PIP3 through the action of phosphoinositide-dependent kinase 1 (PDK1) and serves as a downstream effector of PI3K [120]. Upon activation, Akt can induce various biological effects associated with cellular physiological activities, including cell proliferation and apoptosis, through the activation of downstream effector molecules [121]. Aberrant activation of this pathway, especially the overexpression or overactivation of Akt, frequently results in abnormal signal transduction associated with cancer. Various marine-derived compounds hinder tumor growth or metastasis by lowering the overexpression or over-phosphorylation of PI3K and Akt proteins, subsequently regulating the activity of their downstream pro-

teins. This leads to biological inhibitory effects such as antiproliferation, cell-cycle arrest, and apoptosis [122].

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays a crucial role in cellular growth and survival [123]. In mammalian cells, mTOR is found in two evolutionarily conserved complexes: mTORC1, which controls protein synthesis by phosphorylating p70S6K1 and 4E-BP1, and mTORC2, which influences the survival and proliferation of cells via the phosphorylation of AKT/PKB [124,125]. The deregulation of mTORC1 and mTORC2, both upstream and downstream, is associated with several types of cancer, including breast, ovarian, prostate, and lung cancer [126]. Various marine-derived bioactives serve as potent mTOR inhibitors, functioning as effective anticancer agents.

Mitochondrial dysfunction is implicated in the onset of apoptosis and is suggested to play a central role in the apoptotic pathway [127]. The intrinsic signaling pathways that trigger apoptosis are mitochondrial-initiated processes that entail a wide range of non-receptor-mediated stimuli that generate intracellular signals that directly affect targets inside the cell [128]. The stimuli induce alterations in the inner mitochondrial membrane, leading to the opening of the mitochondrial permeability transition (MPT) pore, a loss of the mitochondrial transmembrane potential, and the release of two primary categories of typically sequestered pro-apoptotic proteins from the intermembrane space into the cytosol [129]. One of them includes cytochrome c, Smac/DIABLO, together with the serine protease HtrA2/Omi [128,130–133]. The proteins trigger the caspase-dependent mitochondrial pathway. Cytochrome c interacts with and activates Apaf-1 and procaspase-9, resulting in the formation of an "apoptosome" [134,135]. The clustering of procaspase-9 results in an induction of caspase-9. Furthermore, Smac/DIABLO and HtrA2/Omi have been shown to induce apoptosis through the inhibition of IAP (inhibitors of apoptosis proteins) activity [128,131,136]. Another category includes AIF, endonuclease G, and CAD, which are released from the mitochondria during apoptosis. During the process, AIF translocates to the nucleus, resulting in DNA fragmentation [137]. This initial phase of nuclear condensation is designated as "stage I" condensation [138]. Following this, endonuclease G translocates into the nucleus and cleaves nuclear chromatin to produce oligonucleosomal DNA fragments [139]. The actions of endonuclease G and AIF are independent of caspase. Following its release from the mitochondria, CAD moves to the nucleus, where it is cleaved by caspase-3, causing oligonucleosomal DNA breakage and enhanced chromatin condensation known as "stage II" condensation [138,140]. The members of the Bcl-2 protein family play a pivotal role in the regulation and control of these apoptotic mitochondrial processes [141]. The tumor suppressor protein p53 plays a crucial role in regulating the Bcl-2 family of proteins; however, the precise mechanisms remain incompletely understood [142]. The Bcl-2 protein family regulates mitochondrial membrane permeability and can function as either pro-apoptotic or anti-apoptotic agents. The primary mechanism of action of the Bcl-2 family of proteins is believed to involve regulating the amount of cytochrome c release from the mitochondria through alterations in mitochondrial membrane permeability [128]. Marine-derived bioactives can influence apoptotic pathways in cancer cells, therefore inducing cell death through numerous mechanisms.

In the following section, we will illustrate some potential molecular mechanisms behind their proposed anticancer effects from various marine sources.

5.1. Algae

An enormous and potential natural source of anticancer chemicals is derived from marine algae (Table 1).

Table 1. Representative examples of marine-derived products from Algae used in cancer treatment.

Macroalgae			
Marine-Derived Product	**Source**	**Mechanism**	**References**
Fucoidan extracted with water	*Turbinaria conoides* (Brown Algae)	Fucoidan significantly inhibited the proliferation of Mia PaCa-2 and PANC-1 human pancreatic cancer cell lines. Induced apoptotic cell death in both cell lines [143,144]. Demonstrated substantial anti-angiogenic properties (30).	[143,144]
Fucoidan-derived fractions	*Turbinaria conoides* (Brown algae)	Fractions showed anticancer activity towards PANC-1, MiaPaCa-2, Panc-3.27, and BxPC-3 human pancreatic cancer cell lines. The effect is initiated through the triggering of apoptosis, leading to the cleavage of poly-ADP ribose polymerase, a DNA repair enzyme, along with the activation of caspases 3, 8, and 9. This leads to apoptotic cell death.	[143,145]
Dioxinodehydroeckol 31, a derivative of phloroglucinol	*Ecklonia cava* (Brown algae)	The compound exhibited significant anticancer activity against MCF-7 and MDA-MB-231 breast cancer cell lines. This may be attributed to the induction of apoptosis driven by the NF-κB dependent pathway.	[146]
Dieckol	*Ecklonia cava* (Brown algae)	The compound inhibited cellular migration and invasion of A549 lung cancer cells. Additionally, it also induces apoptosis. The bioactives induce apoptosis through their blocking of the mTOR signaling pathway (34).	[143,147,148]
Fucoidan	*Sargassum crassifolium* (Brown algae)	Induces apoptosis in A549 lung cancer cells. The compound mediates activity through the reduction in mitochondrial membrane potential (Δψm), accompanied by a rise in cytochrome c release along with a rise in caspase 9 and 3 levels. There is also a reduction in *Bcl-2* expression.	[143,149]
Phlorofucofuroeckol A	*Eisenia bicyclis* (brown algae)	Phlorofucofuroeckol A causes apoptosis and lowers cell viability in HCT116, SW480, LoVo, and HT-29 human colorectal cancer cells through a pathway involving ATF3.	[143,150,151]
Kahalalide F	*Bryopsis* sp. (Green algae)	The effect is mediated through alterations in the permeability of the plasma membrane leading to oncosis together with the changes in lysosomal morphology together with the inhibition of ErbB3 signaling pathways. The primary function of KF involves disrupting lysosome organization. This effect may arise from its hydrophobic characteristics, leading to its incorporation into lysosome membranes as an ionophore. This ultimately influences the exchange of protons for sodium, causing passive water influx into the cisternae, which in turn produces a swelling effect and the formation of large vacuoles. The development of these vacuoles seems to result from alterations in lysosomal membranes.	[152–154]
Serine-containing polysaccharide–protein complexes (Se-PPCs)	*U. fasciata* (Green algae)	Se-PPC drastically reduced the synthesis of cyclin D1 and cyclin-dependent kinase (CDK) 4, therefore impeding the transition of cells from the G1 phase to the S phase, thus leading to the proliferation of apoptotic sub-G1 phase cells. It also promotes the activation of the caspase-3 protein along with the upregulation of p53 protein. It induces a breakdown of the mitochondrial membrane potential (Δψm), leading to the release of cytochrome C into the cytoplasm of A549 cells. Additionally, it also inhibits caspase-9 activation by modulating the synthesis of pro-apoptotic proteins Bax and Bid, as well as anti-apoptotic proteins Bcl-2 and Bcl-XL protein.	[152,155]

Table 1. *Cont.*

Macroalgae			
Marine-Derived Product	**Source**	**Mechanism**	**References**
Glycoprotein (Cf-GP)	*Capsosiphon fulvescens* (Green algae)	Inhibits the proliferation and metastasis of AGS human gastric cancer cells by reducing the expression of matrix metalloproteinase (MMPs) and tight junction proteins (TJPs).	[156]
Nigricanosides 10/11, ether-linked glycoglycerolipids	*Avrainvillea nigrans* (Green algae)	Promotes tubulin polymerization therefore inhibiting the growth of both MCF-7 and HCT-116 cell lines.	[152,157]
Polysaccharides	*Gracilariopsis lemaneiformis* (Red algae)	Demonstrate antitumor efficacy in human A549 lung, MKN28 gastric cancer together B16, mouse melanoma cell line by regulating cell shape and viability together with the Fas/Fas ligand pathway associated with apoptosis across all cell types.	[143,158]
Polyphenols and Flavonoids	*Gelidiella acerosa* (Red algae)	Inhibited cellular proliferation, migration, and colonization of A549 lung cancer cells. Additionally, it triggers apoptosis by increasing the production of *Bcl-2* and *Bcl-XL* and activating caspase 3 and Bax protein. Furthermore, Glycogen synthase kinase-3 beta (GSK3b) was activated, accompanied by the downregulation of PI3K/Akt alongside decreased matrix metalloproteinase-2 (MMP2) expression in vitro, resulting in reduced tumor proliferation and enhanced anti-metastatic activity.	[143,159]
Diterpene laurenditerpenol	*L. intricata* (Red algae)	The compound exhibited significant inhibitory effects on the hypoxia-induced angiogenic factor (VEGF) and hypoxia-activated HIF-1 in human breast ductal cancer cells (T47D).	[152,160]
Halogenated monoterpene	*Pterocladiella capillacea* (Red algae)	Halogenated monoterpene causes cell-cycle arrest along with the production of apoptosis-linked proteins. It inhibits the proliferation of the HT-29 cell line by modulating the expression of ERK-1/-2, AKT, and NF-κB pathways.	[152,161]
Microalgae			
Astaxanthin	*Haematococcus pluvialis and Chlorella zofingiensis* (Green microalgae)	Astaxanthin can inhibit NF-κB and Wnt signaling pathways while promoting apoptosis through the downregulation of key regulatory enzymes IKKβ and GSK-3β, thus mediating its anticancer effects.	[64,162]
β-sitosterol, a phytosterol derivative	*Diacronema lutheri (syn. Pavlova lutheri), Tetraselmis* sp., and *Nannochloropsis sp*	ß-sitosterol exerts its anticancer effects in leukemia cells by enhancing the *Bax/Bcl-2* ratio and activating caspase-3. Treatment of human breast cancer cells with β-sitosterol can increase the *Bax/Bcl-2* ratio as well as cause depolarization of mitochondrial membrane potential (Δψm).	[64,163]

5.1.1. Brown Algae

Two sesquiterpene hydroquinones, yahazunol 13 and cyclozonarone 14, were derived from the brown algae *Dictyopteris undulata*, demonstrating anticancer effects towards HM02, HepG2, and MCF-7 cell lines. The treatment of MCF-7 cells with yahazunol 13 induces apoptosis and arrests the cells in the mitotic phase (G2/M-phase) [152,164]. A spatan diterpinoid, 5(R), 19-diacetoxy-15,18(R and S), dihydro spata-13, 16(E)-diene (DDSD), derived from *Stoechospermum marginatum*, exhibited significant cytotoxicity against several types of cancer, including histiocytic lymphoma (U937), acute monocytic leukemia (THP-1), colon adenocarcinoma (Colo205), promyelocytic leukemia (HL-60), and mouse melanocarcinoma (B16F10) [165]. Treatment of B6F10 cells with DDSD leads to apoptosis through a caspase-dependent mitochondrial pathway mediated by reactive oxygen species (ROS). Furthermore, it exhibits an inhibitory impact on tumor formation in C57BL/6 mice bearing B16F10 tumors in vivo [165].

A separate investigation examined the impact of a purified acetonic extract of *Fucus vesiculosus*, a Baltic brown seaweed, on PANC-1: PancTu1, Panc89, and Colo357 human pancreatic cancer cell lines [143,166]. The treatment resulted in decreased viability, as demonstrated by the inhibition of the cell cycle in proliferating cells [166]. Conversely, *F. vesiculosus* extract demonstrated minimal cytotoxic effects towards terminally differentiated cells, such as erythrocytes and non-malignant resting T cells, indicating that proliferation is necessary for the efficacy provided by the macroalgae extract [166].

Several human cancer cell lines, such as A549, human gastric carcinoma adenocarcinoma cell line (BGC-823), MCF-7, human HCC cell line (Bel7402), human colorectal adenocarcinoma cell line (HCT-8), etc., demonstrated cytotoxicity when exposed to novel dibenzyl bromophenols isolated from the brown algae *Leathesia nana*. Its inhibitory function is demonstrated in protein tyrosine kinase overexpressing c-kit [143,152,167,168]. c-kit is a well-known proto-oncogene that encodes a receptor tyrosine kinase (RTK), which interacts with stem cell factor (SCF) [169]. Dysregulated c-KIT activity, resulting from overexpression or mutations in c-kit, facilitates tumor development and progression in multiple human cancers [169]. According to the study's findings, dibenzyl bromophenol can be employed as a powerful antitumor drug against overexpressed c-kit and is being explored as a potential novel cancer therapy approach [167]. This may subsequently diminish the downstream signaling cascades mediated by c-kit that are responsible for cancer development.

Fucoidan extracted from brown algae such as *Fucus vesiculosus* mainly exhibits its anticancer effect through the induction of apoptosis. Fucoidan causes HT-29 and HCT116 human colon cancer cells to undergo apoptosis in a dose-dependent manner through both the mitochondrial and death receptor-mediated apoptotic mechanisms.

In HT-29 cells, fucoidan elevated the expression levels of cleaved caspases-8, -9, -7, and -3, as well as cleaved poly (ADP-ribose) polymerase (PARP). Furthermore, fucoidan-treated cells showed reduced levels of survivin and the X-linked inhibitor of apoptosis protein. The findings indicate that fucoidan enhances mitochondrial membrane permeability alongside facilitating the release of cytochrome c and Smac/Diablo from the mitochondria. The levels of Bak and truncated Bid proteins are increased, while Mcl-1 levels are decreased. Fucoidan also enhanced the levels of death receptor 5 proteins, Fas, and the apoptosis-inducing ligand associated with tumor necrosis factor [170]. In addition, fucoidan exerts its anticancer effects through numerous different mechanisms. Fucoidan inhibits VEGF formation, thus inhibiting angiogenesis [171]. Tse-Hung's lab demonstrated that treatment of mice implanted with Lewis lung cancer cells using fucoidan significantly decreased the expression levels of VEGF in serum and lung tissue compared to those not receiving fucoidan [172]. Fucoidan also hinders neovascularization caused by human prostate cancer cells (DU-145) in mice, and its antitumor activity is linked to its anti-angiogenic effect [173]. Fucoidan can activate the immune response by enhancing the cytotoxic capabilities of natural killer cells and T cells against tumor cells [174]. Researchers administered fucoidan to mice transplanted with acute promyelocytic leukemia cells NB4. Results from that study have shown that fucoidan significantly enhances the cytotoxic activity of NK cells [174].

A study investigated the effects of fucoidan, extracted with water from *Turbinaria conoides*, on Mia PaCa-2 and PANC-1 human pancreatic cancer cell lines [144]. Fucoidan significantly impeded the proliferation of cells as well as induced apoptotic death in both cell lines [143,144]. Furthermore, the extract demonstrated substantial anti-angiogenic properties [144]. The same group recently investigated the mechanisms underlying the anticancer effects of the active fractions derived from the fucoidan extract from *Turbinaria conoides* [145]. Five fractions (F1–F5) of fucoidan were evaluated for their effects on the PANC-1, MiaPaCa-2, Panc-3.27, and BxPC-3 human pancreatic cancer cell lines. All fractions exhibited a dose-dependent together with time-dependent regulation of cell survival [143,145]. Furthermore, fucoidan triggered apoptosis, leading to the cleavage of poly-ADP ribose polymerase, a DNA repair enzyme, in addition to the activation of caspases 3, 8, and 9, all of which are essential in facilitating apoptotic cell death [145]. The fraction F5 impeded the NF-κB pathway, which is linked to the gene expression involved in tumorigenesis and progression in Mia PaCa-2

and PANC-1 cells [145]. Additionally, fucoidan suppressed both constitutive and tumor necrosis factor-α (TNF-α) driven NF-κB DNA-binding activity in PC cells [145], making cells more susceptible to chemotherapy treatments [175,176].

Dioxinodehydroeckol, a derivative of phloroglucinol derived from the brown algae *Ecklonia cava*, exhibited significant inhibition against the MCF-7 and MDA-MB-231 cell lines. This may be attributed to the induction of apoptosis driven by the NF-κB dependent pathway [146]. Another study examined the effects of Dieckol obtained from *Ecklonia cava* on human A549 lung cancer cells [143,147]. This compound effectively inhibited cellular migration and invasion while inducing apoptosis [143,148].

Wu's lab investigated the impact of a native fucoidan and three degraded variants from *Sargassum crassifolium* on A549 cells [143,149]. The fucoidans exhibited variations in their chemical compositions; however, they shared structural similarities [149]. Results indicate that A549 cells undergo apoptosis in response to every type of fucoidan. There is a reduction in mitochondrial membrane potential ($\Delta\psi m$), accompanied by the concomitant rise in cytochrome c release together with the rise in caspase 9 and 3 levels, in addition to a reduction in Bcl-2 expression [149].

Wang et al. investigated the impact of alginic acid in vitro on A549 and H1155 lung cancer cells, as well as in vivo, using an A549-xenograft mouse cancer model [143,177]. The data obtained highlighted the anti-angiogenic potential of alginic acid partly because of its effect in downregulating VEGF-A (angiogenesis promoter) expression [177].

A separate report highlighted the capability of the carotenoid fucoxanthin, derived from *Undaria pinnatifida*, towards human lymphatic endothelial cells (LEC) and MDA-MB-231 breast cancer cells [143,178]. Fucoxanthin hindered the migration, proliferation, and buildup of tube-like structures by human LEC, resulting in cytotoxicity [178]. Eo Lab investigated the molecular mechanisms of phlorofucofuroeckol A, a phlorotannin derived from *Eisenia bicyclis*, towards colorectal cancer [178]. Phlorofucofuroeckol A causes apoptosis and lowers cell viability in four types of human colorectal cancer cells (HCT116, SW480, LoVo, and HT-29) through a pathway involving ATF3. ATF3 serves as a crucial regulator of metabolic homeostasis and has a significant effect on cancer proliferation [143,150,151].

In a compelling study, researchers examined the impact of phlorethols derived from *Costaria costata*, a brown macroalga, on HT-29 and HCT 116 cells [37]. These compounds demonstrated cytotoxic potential and increased cancer cell sensitivity to relatively low doses of X-ray irradiation [143,179]. Additionally, the combined use of phlorethols alongside radiation resulted in a synergistic effect. The treatment with X-rays (2 Gy) and phlorethols at concentrations of 5, 10, and 20 mg/mL significantly inhibited the colony-forming potential of HT-29 and HTC-116 cells in comparison to cells that were irradiated alone [179].

5.1.2. Green Algae

A depsipeptide, Kahalalide F (KF), derived from the green algae *Bryopsis* sp., and from the mollusk *Elysia rufescens* exhibits cytotoxicity towards solid tumor cell lines and even multidrug-resistant cell lines [152,180,181]. It also demonstrates anticancer efficacy against tumors transplanted in mice in vivo and has progressed to Phase I clinical trials [152,182,183]. The anticancer mechanism of KF is mediated through alterations in the permeability of the plasma membrane leading to oncosis together with the changes in lysosomal morphology along with the inhibition of ErbB3 signaling pathways [153]. The primary function of KF involves disrupting lysosome organization. This effect may arise from its hydrophobic characteristics, leading to its incorporation into lysosome membranes as an ionophore. This could influence the exchange of protons for sodium, causing passive water influx into the cisternae, which in turn produces a swelling effect and the formation of large vacuoles. The development of these vacuoles seems to result from alterations in lysosomal membranes. Therefore, lysosomes serve as a target for the action of Kahalalide F [152,154].

Zhao et al. (2020) investigated ULP 6, a type of polysaccharide (SP), which demonstrates the ability to inhibit tumor cell growth and exhibits significant anticancer activity through the inhibition of the PI3K/AKT/mTOR pathway while also showing poten-

tial in ameliorating tumor-induced cellular heterogeneity and immune system impairment [152,184]. *U. fasciata* is an abundant source of serine (SE)-containing polysaccharide–protein complexes (Se-PPCs) [152,155]. Reports from Sun's lab suggest that Se-PPC-induced apoptosis in A549 cells through cell-cycle inhibition [152,155]. Se-PPC drastically reduced the synthesis of cyclin D1 and cyclin-dependent kinase (CDK) 4, therefore impeding the transition of cells from the G1 phase to the S phase, thus leading to the proliferation of apoptotic sub-G1 phase cells. Moreover, Se-PPC promotes the activation of the caspase-3 protein along with the upregulation of the p53 protein. Both of these events are associated with apoptosis. Further investigations demonstrated that Se-PPC induces a breakdown of the mitochondrial membrane potential ($\Delta\psi m$), leading to the release of cytochrome C into the cytoplasm of A549 lung cancer cells. It also suppresses caspase-9 activation by modulating the synthesis of pro-apoptotic proteins Bax and Bid, as well as anti-apoptotic proteins Bcl-2 and Bcl-XL proteins [152,155].

Polysaccharides (CFPs) derived from *C. fragile* elicited a strong immune response against cancer in murine models. This is achieved by activating macrophages and dendritic cell subsets in the mediastinal lymph nodes. This, in turn, stimulates an induction of cytotoxic immune cells [185]. IFN-γ secretion, granzyme-B, and perforin release, together with NKp30 and FasL production, are all triggered by sulfated polysaccharides (SP-F_2), which are mostly present in red algae but may also be found in green algae. The events resulted in a substantial rise in NK cell proliferation, subsequently enhancing their cytotoxicity toward HeLa cells. Sulfates and proteins play a crucial role in the communication that exists between NK cells and SP-F_2 [152,186]. In TRAIL-resistant colorectal cancer cells, *C. fragile* F2 fraction, when coupled with TRAIL, can inhibit the production of FLICE-inhibitory protein, therefore inducing apoptosis [152,187].

The glycoprotein (Cf-GP) extracted from *Capsosiphon fulvescens* exhibits anticancer effects in numerous cancer cell lines. It significantly inhibits the proliferation and metastasis of AGS human gastric cancer cells [152,156]. Furthermore, the compound effectively inhibits the proliferation and metastasis of AGS human gastric cancer cells by reducing the expression of matrix metalloproteinase (MMPs) and tight junction proteins (TJPs) [156]. Caulerpin, an algal pigment derived from *Caulerpa* sp., has been shown to reduce hypoxia-induced induction of hypoxia-inducible factor-1 (HIF-1), making it a promising candidate for anticancer drug development [152,188,189]. Natural lycopene derived from green algae *Chlorella marina* exhibited a substantial antiproliferative and apoptotic effect in human prostate cancer cell lines, as demonstrated by G0/G1 phase cell accumulation [188,190].

The green algae *Avrainvillea nigrans* synthesized nigricanosides 10 and 11: Nigricanoside dimethyl ester, classified within a novel group of ether-linked glycoglycerolipids, has been identified as a potent antimitotic agent. The mechanism of action involves the promotion of tubulin polymerization therefore inhibiting the growth of both MCF-7 and HCT-116 cell lines [152,157]. Two novel unsaturated fatty acids, 3(″)-hydroxy-octadeca-4(E),6(Z),15(Z)-trienoic acid 15 and 3(″)-hydroxy-hexadeca-4(E),6(Z)-dienoic acid 16, in addition to the previously identified 3(″)-hydroxyoctadeca-4(E),6(Z)-dienoic acid isolated from *Tydemania expeditionsis*, demonstrated significant antineoplastic efficacy against numerous tumor cell lines [191,192].

5.1.3. Red Algae

Kang's lab isolated polysaccharides consisting of 3,6-anhydro-L-galactose and D-galactose, forming a linear structure characterized by repeating disaccharide agarobiose units from *Gracilariopsis lemaneiformis* and assessed their efficacy against human A549 lung and MKN28 gastric cancer cell lines, together with the mouse melanoma cell line B16 [143,158]. The polysaccharides demonstrated antitumor efficacy by regulating cell shape and viability together with the Fas/Fas ligand pathway associated with apoptosis across all cell types [158].

A similar investigation evaluated an extract utilizing solvents of varying polarity, abundant in polyphenols and flavonoids, derived from the red algae *Gelidiella acerosa*

against A549 cells in both in vitro and in vivo conditions [143,159]. *Gelidiella acerosa* extract inhibited cell proliferation, migration, and colonization. Additionally, it triggers apoptosis by increasing the production of Bcl-2 and Bcl-XL together with the activation of caspase 3 and Bax protein [143,159]. Furthermore, Glycogen synthase kinase-3β (GSK3β) was activated, accompanied by the downregulation of PI3K/Akt alongside decreased matrix metalloproteinase (MMP2) expression in vitro, resulting in reduced tumor proliferation and enhanced anti-metastatic activity [143,159].

Brominated diterpenes prevezols 1 and 3, along with neorogioldiol 4 (prevezol 2), derived from *Laurencia obtusa*, demonstrate varying levels of cytotoxicity towards human tumor cell lines [152,180,193]. A newly discovered laurene sesquiterpene 16 isolated from *L. obtusa* exhibits significant anticancer properties in vitro in Ehrlich ascites carcinoma [152,194,195]. Diterpene laurenditerpenol 5, derived from *L. intricata*, displayed significant inhibitory effects on the hypoxia-induced angiogenic factor (VEGF) and hypoxia-activated HIF-1 in human breast ductal cancer cells (T47D) [152,160]. Breast cancer cells that are both estrogen-dependent and independent undergo apoptosis when exposed to the marine polyether triterpenoid dehydrothyrsiferol that was isolated from *L. pinnatifida* [180,196]. Similar research by the Zaleta Pinet lab assessed seven sesquiterpenoids from *L. pacifica*; enhanced cytotoxicity was demonstrated by isoaplysin and debromoaplysinol against cancer cell lines, including HT-29, human glioma cells (U87), MCF-7, A2780, and NCL-H460. The presence of the hydroxyl group in debromoaplysinol boosted its cytotoxicity [197]. A study assessed the efficacy of sesquiterpene laurinterol, isolated from red algae, demonstrating potential anticancer effects against B16F1 melanoma cells. It triggers cell death and elevates the percentage of cells in the G1 phase in B16F1 through the activation of the p53 transcription factor, which exerts an anticancer effect [152,198]. Halogenated monoterpene, which leads to cell-cycle arrest along with the production of apoptosis-linked proteins, is derived from *Pterocladiella capillacea*. It inhibits the proliferation of the HT-29 cell line by modulating the expression of ERK-1/-2 and AKT together with NF-κB pathways [152,161]. Sulfated galactans extracted from the red algae *Gracilaria fisheri*, exhibiting a structure comparable to heparan sulfate proteoglycan, impede the advancement of cholangiocarcinoma cells (CCA). The effect is mediated via the suppression of the MAPK/ERK signal transduction pathway [199].

Phenylethanol and phenylethanol sulfate bromophenols, derived from *Rhodomela confervoides*, displayed cellular cytotoxicity against several human cancer cell lines [200,201]. Research indicates that the amount and configuration of bromine atoms, together with the degree of hydroxyl groups and aliphatic side chains, influenced their overall activity [152,202]. Reports from Wu's lab indicate that marine bromophenol bis-(2,3-dibromo-4,5-dihydroxy-phenyl)-methane inhibits the proliferation, migration, and invasive properties of HCC cells (BEL-7402). It functions by reducing cellular adherence to collagen IV and fibronectin alongside inhibiting the production of MMPs, β1-integrin, and focal adhesion kinase (FAK). Moreover, it has the potential to disrupt certain angiogenesis mechanisms [203].

Two sulfur-containing polybromoindoles, derived from *L. brongniartii*, exhibited selective activity towards P-388 and HT-29 cells [152,204]. The human melanoma cell line A375-S2 exhibited cytotoxicity when exposed to several cyclopropyl derivatives such as ceramides gracilamides and cerebroside gracilarioside derived from *G. asiatica* [152,200].

5.1.4. Microalgae

Diacronema lutheri (syn. *Pavlova lutheri*), *Tetraselmis* sp., and *Nannochloropsis* sp. constitute the leading producers of phytosterol. β-sitosterol, a phytosterol derivative, exerts its anticancer effects in leukemia cells by enhancing the Bax/Bcl-2 ratio alongside activating caspase-3 [64,205]. During the G0/G1 phase of the cell cycle, phytosterol has been shown to promote apoptosis in MDA-MB-231 cells. According to the study, treating human breast cancer cells to β-sitosterol can increase the Bax/Bcl-2 ratio and cause depolarization of mitochondrial membrane potential (Δψm) [64,163].

The primary natural sources of astaxanthin, a carotenoid pigment, are the green microalgae *Haematococcus pluvialis* and *Chlorella zofingiensis*. The high intracellular astaxanthin concentration of *H. pluvialis* made it a promising astaxanthin producer. Findings from the hamster buccal pouch (HBP) carcinogenesis model indicate that astaxanthin can inhibit NF-κB and Wnt signaling pathways while promoting apoptosis through the downregulation of key regulatory enzymes IKKβ and GSK-3β, thus mediating its anticancer effects. The findings provide conclusive evidence that astaxanthin, derived from *Haematococcus pluvialis*, exhibits antiproliferative effects through the inhibition of transcription factors [64,162].

Fucoxanthin-containing diatoms are a significant class of marine microalgae that provide 20–25% of global net primary output and 40% of marine primary productivity. Fucoxanthin has been reported to be the primary carotenoid produced by several microalgae. In comparison to other microalgae, *P. tricornutum* exhibits a strong potential for synthesizing greater amounts of fucoxanthin [64,206]. Peng's lab reported that fucoxanthin exhibited antiproliferative effects on the human promyelocytic leukemia HL-60 cell line and could also cause apoptosis in HL-60 cells [207,208]. Fucoxanthin induced apoptosis promoted the permeabilization of the mitochondrial membrane as well as the induction of caspase-9 and caspase-3 [209]. Additionally, fucoxanthin greatly reduced the migration of endothelial cells by blocking the phosphorylation of fibroblast growth factor 2 (FGF-2), which is mediated by extracellular signal-regulated kinases (ERK1/2) and protein kinase B (Akt) as well as intracellular signaling proteins. Fucoxanthin isolated from *Codium fragile* and *Undaria pinnatifida* likewise suppresses its receptor (FGFR-1) and EGR-1, the trans-activation factor [210–213].

One of the main forms of provitamin A, β-carotene, is well recognized for its capacity to scavenge harmful nitrogen and oxygen radicals. The highest concentration of β-carotene accumulation—more than 10–12% of their dry weight—is seen in *Dunaliella salina*, *Dunaliella bardawil*, and *Dunaliella parva* [64,214]. According to HPLC analysis, 9-cis-beta-carotene, which is produced by *Dunaliella*, is tenfold more efficient than regular carotene in preventing cancer. High levels of β-carotene produced by the *D. salina* strain have been shown to have anticancer properties against the PC-3 human prostate adenocarcinoma cell line [214]. *Dunaliella* sp. had the greatest carotenoids concentration out of the three microalgae species compared: *Chlorella* sp., *Dunaliella* sp., and *Isochrysis* sp. β-carotene significantly damages MCF-7 cancer cells, lowering their viability and preventing them from triggering an inflammatory response [64,215]. This process reduces the synthesis of iNOS and COX-2, leading to the deactivation of reactive oxygen species (ROS) and the promotion of gastric healing [215].

The macula lutea of the retina in humans contains two essential pigments: lutein and zeaxanthin. Lutein, whether administered alone or in conjunction with chemotherapy treatments, improves the antiproliferative and apoptotic effects of anticancer drugs and inhibits the advancement of the cell cycle in prostate cancer cell lines [216]. Additionally, lutein suppresses the expression of biomarker genes that are linked to the development and prognosis of prostate cancer. The antiproliferative effect on breast cancer cell lines is achieved by elevating intracellular ROS levels and facilitating apoptotic cell death caused by the downregulation of Bcl2 genes and the upregulation of pro-apoptotic genes, in addition to enhancing the p53 signaling pathway [64,217]. This is corroborated by Chang's lab, which demonstrated that lutein has anticancer properties via activating the NrF2/ARE pathway and inhibiting the NF-κB signaling pathway. In addition, Bcl-2 and poly-ADP ribose polymerase expression were downregulated, causing apoptosis in a breast cancer line [218]. In another investigation, phlorotannin eckol has been shown to reduce stemness and carcinogenesis in glioma stem-like cells [64,219].

5.2. Fungi

Fungi represent a substantial category of microorganisms that produce secondary metabolites exhibiting various anticancer properties [220]. Numerous fungal species, such as *Aspergillus* spp. and *Penicillium* spp., have garnered significant attention in recent

years due to their capacity to produce various secondary metabolites with anticancer properties [68]. These metabolites exhibit efficacy against a range of cancers, including caucasian colon adenocarcinoma, breast cancer, hepatocellular carcinoma, colorectal cancer, and prostate cancer [68] (Table 2).

Table 2. Representative examples of marine-derived products from Fungi, Tunicates, and Mollusks used in cancer treatment.

Fungi			
Plinabulin, a derivative of the diketopiperazine alkaloid halimide.	*Aspergillus* sp.	It binds to the alpha-tubulin's colchicine-binding site, therefore impairing microtubule dynamics. This, in turn, leads to the disruption of tumor vasculature, which facilitates the dissemination of neoplasms, leading to the reduction in tumor growth.	[74,221,222]
Gliotoxin	*Aspergillus* spp.	Gliotoxin exhibits antitumor efficacy against human cervical cancer (HeLa) and chondrosarcoma cells through DNA fragmentation along with the activation of caspases (caspase-3, 8, and 9). It also downregulates Bcl-2 and upregulates Bax expression.	[68,223]
Physcion	*Microsporum* sp.	Physcion causes reactive oxygen species to develop, downregulated Bcl-2 expression, and upregulated Bax expression, leading to the death of HeLa cells.	[68,224].
L-asparaginase (ASNase)	*Fusarium oxysporum*, *Fusarium fujikuroi*, *Pyrenophora triticirepentis*, and *Aspergillus niger*	ASNase degrades L-asparagine, therefore inhibiting the development of cancer cells.	[68]
Tunicates and Mollusks			
Didemnin B	*Tridemnum solidum (Tunicate)*	Didemnin B hinders the proliferation of human prostate cancer cells by interfering with the synthesis of DNA, RNA, and proteins.	[225].
Aplidine (Plitidepsin), a cyclic depsipeptide	*Aplidium albicans* (Tunicate)	Aplidine interacts with the transcription factor eEF1A2, modifying various pathways and consequently promoting cell-cycle arrest, inhibiting growth, and decreasing apoptosis. Also inhibits ornithine decarboxylase, an essential enzyme in tumor growth and development. Also inhibits the expression of genes that encode endothelial vascular growth factors and demonstrates anti-inflammatory properties.	[3,226,227]
Trabectedin	*Ecteinascidia turbinate (Tunicate)*	Trabectedin shows potential for treating tumors characterized by high TC-NER activity or, more broadly, those with functional DNA repair mechanisms. Trabectedin leads to persistent single-strand breaks (SSBs) in a TC-NER-dependent manner in cells exhibiting hypersensitivity to the drug. Furthermore, trabectedin-DNA adducts inhibit the incision activity of XPG endonuclease, leading to sustained XPF-mediated breaks. Furthermore, during TC-NER of trabectedin, the 3′ incision by XPG is inhibited, therefore hindering one of the two sequential NER incisions.	[82]
Kahalalide F	*Elysia rufescens* (Mollusk)	Kahalalide F impairs the activity of lysosomes and triggers cell death through intracellular acidification in prostate cancer cells.	[228]

Earlier model studies that looked at the potential use of fungal metabolites in cancer therapy included Chinese medicine's use of edible mushrooms [220,229,230]. One primary mechanism by which anticancer fungal metabolites exert their effects is through the inhibition of the transcription factor NF-κB [220,231]. NF-κB plays a crucial role in inflammation, cancer development, and progression. Additionally, NF-κB promotes cell proliferation and inhibits apoptosis, promoting tumor angiogenesis and metastasis [220,232]. Fucoidan, a novel therapeutic bioactive isolated from the fungus *Fucus vesiculosus*, has tremendous promise in combating ovarian cancer [74]. Another investigation identified Plinabulin, a derivative of the diketopiperazine alkaloid halimide, as an inhibitor of tubulin polymerization. It was isolated from the marine fungus *Aspergillus* sp. It binds to the alpha-tubulin's colchicine-binding site, therefore impairing microtubule dynamics. This leads to the disruption of tumor vasculature, which facilitates the dissemination of neoplasms, leading to the reduction in tumor growth [74,221,222]. Plinabulin could act as an immunomodulator and reduce chemotherapy side effects by reducing the destruction of white blood cells caused by the drug [74,233–235].

Alterporriol L, derived from *Alternaria* sp., demonstrated substantial anticancer effects on breast cancer cells. It impacts cellular morphology alongside inducing apoptosis or necrosis in breast cancer cell lines [68,236]. Additionally, human erythroleukemia, human gastric cancer cells, and hepatocellular carcinoma cells are susceptible to the cytotoxic effects of phthalide racemates isolated from *Alternaria* sp. [68,237]. Gliotoxin isolated from *Aspergillus sp.*, when tested on human cervical cancer (HeLa) and chondrosarcoma cells, showed anticancer activity and DNA fragmentation along with the activation of caspases (caspase-3, 8, and 9). It also downregulates Bcl-2 and upregulates Bax expression [68,223]. The butenolide derivatives, Asperlides A–C, Butenolides (+)-3′,3′-di-(dimethylallyl)-butyrolactone II and Versicolactone B derived from *A. terreus* demonstrated significant anticancer efficacy against hepatocellular carcinoma and pancreatic duct cancer [68,238]. In HeLa cells, physcion from *Microsporum* sp. caused reactive oxygen species to develop, downregulated Bcl-2 expression, and upregulated Bax expression, all of which led to cell death [68,224].

A quinolinone derivative from *Aspergillus versicolor* Y31-2 exhibits cytotoxicity against MCF-7 and SMMC-7721 cell lines [67,239]. A study identified Penicitrinine A, a novel alkaloid obtained from the marine fungus *Penicillium citrinum*. The alkaloid displayed toxicity against A-375, SPC-A1, and HGC-27 cancer cell lines [67,240]. By reducing Bcl-2 expression and upregulating Bax expression, Penicitrinine A may dramatically cause A-375 cellular apoptosis and produce anticancer effects. Furthermore, Penicitrinine A markedly inhibited the metastatic activity of A-375 cells through the modulation of MMP-9 expression and its specific inhibitor TIMP-1 [67,240].

Trichodermamide B, DC1149B, and nafuredin A, secondary metabolites derived from *Trichoderma lixii*, demonstrate significant antiproliferative activity against three cancer cell lines: human myeloma KMS-11, colorectal HT-29, and pancreas PANC-1. Under glucose-limiting conditions, DC1149B showed intriguing anti-austerity efficacy against PANC-1 cancer cells [241]. The marine-derived fungus *Penicillium citrinum* VM6 yielded eight metabolites (1–8), including one citrinin dimer, dicitrinone F (1). While compound 5 showed specific cytotoxicity against the MCF7 cell lines, compounds 1 and 8 demonstrated cytotoxicity against all examined cell lines, including A549, MCF7, MDA-MB-231, HeLa, and AGS [242]. The marine-derived fungus *Emericellopsis maritima* BC17 has been identified as a producer of novel eremophilane-type sesquiterpenoids. Among them PR toxin 3-deacetyl demonstrated cytotoxic effects towards HepG2, MCF-7, A549, A2058, and Mia PaCa-2 human cancer cell lines [243]. Ten novel ergone derivatives (1–10) and five previously identified analogs (11–15) have been extracted from the deep-sea-derived fungus *Aspergillus terreus* YPGA10. Compounds **1** and **11** exhibited cytotoxic activity on human colon cancer SW620 cells by inducing apoptosis while showing minimal cytotoxicity towards the human normal lung epithelial cell line BEAS-2B. Conversely, compound **1** exhibited cytotoxic activity against five human leukemia cell lines [244].

L-asparaginase (ASNase) is a type of hydrolase enzyme that catalyzes the hydrolysis of L-asparagine into ammonia and L-aspartic acid [68]. While cancer cells rely solely on extracellular L-asparagine, normal cells can manufacture L-asparagine. Consequently, the enzyme functions by degrading L-asparagine, therefore inhibiting the development of cancer cells [68]. In 1962, researchers published the initial investigation into the efficacy of L-asparaginase against cancer cells, focusing on acute lymphoblastic leukemia. Researchers have documented the production of ASNase by a variety of fungal species, including *Fusarium oxysporum*, *Fusarium fujikuroi*, *Pyrenophora triticirepentis*, and *Aspergillus niger* [68]. Basker's lab incorporated L-Asparaginase into nanobiocomposites composed of cyclodextrin and chitosan. They subsequently tested it against lymphoma and prostate cancer cells. The findings indicated significant activity against lymphoma cancer cells (U937) [68,245].

Modified dipeptides known as trichodermamides have been identified in a broad range of fungi, including *Trichoderma virens*. According to several earlier investigations, Trichodermamide B induced cytotoxicity in HCT-116 colorectal cancer cells. In a similar study, trichodermamide B demonstrated significant anticancer effects against the HeLa cell line [67,246]. Aspergiolide A, a new anthraquionone derivative derived from *Aspergillus glaucus*, functions similarly to adriamycin by inhibiting Topoisomerase II. Additional studies using BEL-7402 cells demonstrated that the compound inhibited the development of cancer through a caspase-dependent mechanism [67,247].

5.3. Tunicates (Ascidians) and Mollusks

Ascidians have been shown to be rich in bioactive peptides with distinct structures that have robust anticancer properties [73] (Table 2). After being first isolated from the Caribbean tunicate *Tridemnum solidum*, didemnin was later discovered in additional species of the same genus [248,249]. Didemnin B is recognized for its significant antitumor activity and its capacity to hinder the proliferation of human prostate cancer cells by interfering with the synthesis of DNA, RNA, and proteins [225]. The results from preclinical studies, which demonstrated dose-dependent effects and tolerance to toxicity, led to the initiation of Phase I clinical trials for Didemnin B [250]. However, Phase II trials indicated that Didemnin B, at the recommended doses, demonstrated ineffectiveness in treating cancer [251–253]. Tamandarin A and B, cyclic depsipeptides extracted from sea ascidians of the Didemnidae family, were extensively investigated for their effects on various human cancer cells [254]. Mollamide, a cyclic depsipeptide obtained from the ascidian *Didemnum molle*, demonstrates significant cytotoxic activity against various cancer cell lines, including murine leukemia P388, human lung cancer A549, and colon cancer HT29 [255]. Aplidine (Plitidepsin), a cyclic depsipeptide derived from the tunicate *Aplidium albicans*, demonstrates significant anticancer efficacy against various human cancer cell lines [256]. Research indicates that this cyclic depsipeptide likely interacts with the transcription factor eEF1A2, modifying various pathways and consequently promoting cell-cycle arrest, inhibiting growth, and decreasing apoptosis [3,226,227]. Aplidine's selectivity and uniqueness stem from its distinct cytotoxic mechanism, which inhibits ornithine decarboxylase, an essential enzyme in tumor growth and development [227]. Aplidine also inhibits the expression of genes that encode endothelial vascular growth factors and demonstrates anti-inflammatory properties [257]. Trabectedin, derived from the sea squirt *Ecteinascidia turbunata*, used to treat soft tissue sarcomas, primarily inhibits the transcription-coupled nucleotide excision repair (TC-NER), leading to apoptosis in cancer cells, therefore causing cancer cell death [77,80]. Trabectedin exhibits increased toxicity in cells characterized by elevated repair capacity. This drug shows potential for treating tumors characterized by high TC-NER activity or, more broadly, those with functional DNA repair mechanisms. Trabectedin leads to persistent single-strand breaks (SSBs) in a TC-NER-dependent manner in cells exhibiting hypersensitivity to the drug. The findings indicate that trabectedin-DNA adducts inhibit the incision activity of Xeroderma pigmentosum group G (XPG) endonuclease, leading to sustained XPF-mediated breaks. Furthermore, during TC-NER of trabectedin, the 5′ incision by XPF occurs as expected, whereas the 3′ incision by XPG is inhibited, therefore hindering one of

the two sequential NER incisions. Trabectedin-induced single-strand breaks predominantly arise in the transcribed strands of active genes, with a peak occurrence near transcription start sites [82].

Mollusks represent a diverse array of species that possess considerable pharmacological capacity [258]. Among them, the sea hare generates bioactive compounds that can be used in the treatment of cancer [73,259]. Cone snails from the genus Conus are recognized as a significant source of active peptides referred to as Conotoxins [260]. Numerous studies suggest that Conotoxins may hold promise for cancer treatment. Furthermore, dolastatin, a group of cytotoxic peptides derived from the mollusk *Dollabella auricularia*, has shown significant antiproliferative activity [261].

A cytotoxic cyclic hexapeptide called Keenamide A was extracted from the mollusk *Pleurobranchus forskahii*. It has strong anticancer properties against several tumor cell lines, including A549, MEL20, P388, and HT29. However, its precise mode of action is yet unknown [262]. A significant group of peptides obtained from mollusks is the Kahalalids, which have been isolated from the mollusk *Elysia rufescens* [263]. Kahalalide F contains dihydro-amino-butyric acid and exhibits significant antitumor activity, especially against prostate cancer tumors. A mollusk-derived antitumor chemical called jorumycin also has strong antibacterial properties. In 1990, the compound was first isolated from the mucus and mantle of the Pacific nudibranch species called *Jorunna funebris* [60,228,264]. This substance belongs to the tetrahydroisoquinoline alkaloid family, which has structural characteristics with ecteinascidin, renieramycins, and saframycins [60,265]. Jorumycin demonstrates substantial effectiveness against NIH 3T3 fibroblast cells, fully inhibiting their growth at a concentration of 50 ng/mL. Additionally, it exhibits significant activity against the P388, A549, HT29, and SK-MEL-28 lung tumor cell lines [60,264].

5.4. Sponges

Sponges are regarded as a significant source for identifying bioactive natural products [71,266,267] (Table 3).

Table 3. Representative examples of marine-derived products from Sponges and Echinodermata used in cancer treatment.

Marine-Derived Product	Source	Mechanism	Reference
		Sponges	
Renieramycin T	*Xestospongia* sp.	Renieramycin T exhibits its cytotoxicity by triggering apoptosis in non-small cell lung cancer (NSCLC). It also induces the activation of *p53* and caspases 9 and 3 while facilitating the degradation of Mcl-1, a pro-apoptotic protein within the *Bcl-2* family, in the proteasome.	[75,268]
Acetylenic compounds such as (3S)-icos-4E-en-1-yn-3-ol and (3S)-14-methyldocos-4E-en-1-yn-3-ol	*Cribrochalina vasculum*	The compound exhibits antitumor efficacy against NSCLC cell line U-1810 along with the SCLC cell lines U-1285, H69, and H82. The primary mechanism of cytotoxicity is the cleavage of PARP, caspase-9, and caspase-3, which triggers apoptosis. Additionally, there are some conformational changes in Bak and Bax, resulting in the loss of mitochondrial potential together with the release of cytochrome C. The compounds initiate a decline in the phosphorylation of Akt, mTOR, and ERK while increasing the phosphorylation of JNK.	[269]
Sesterterpene BA6 (heteronemin)	*Hyrtios erecta*	BA6 primarily causes mitochondrial dysfunction by upregulating the generation of mitochondrial reactive oxygen species (mtROS). Additionally, BA6 stimulated cytochrome C release, triggered caspase-9 and -3 expression, and downregulated the anti-apoptotic protein Bcl-2, along with the elevation of the pro-apoptotic protein Bax. This leads to the induction of apoptosis in A549 lung cancer cells.	[270]

Table 3. *Cont.*

Marine-Derived Product	Source	Mechanism	Reference
		Sponges	
Motuporamines	*Xestospongia exigua*	Motuporamine C causes cytoskeletal alterations in cancer cells, therefore preventing ß1-integrin from activating, which is essential for cancer cell adhesion and invasion. This eventually suppresses angiogenesis and cell migration in PC-3 prostate cancer cells and MDA-231 breast carcinoma cells.	[81,271]
Stelletin B	*Jaspis stellifera*	It mediates its effects through targeting the PI3K/Akt/mTOR pathway. In addition to inducing apoptosis linked to an increase in ROS production and PARP cleavage, the drug was shown to cause G1 arrest, ascribed to a decrease in cyclin D1 and an increase in p27 expression.	[75,272]
		Echinodermata	
A novel steroid known as (cholest-8(14)-ene-3β,5a,6β,7a-tetraol)	*Diadema savignyi*	The steroid induces apoptosis followed by changes in the expression of proteins linked to apoptosis, such as reduced c-Myc expression along with the inactivation of extracellular signal-regulated kinase (ERK)1/2 mitogen-activated protein kinase (MAPK) signaling cascade.	[273,274]
Triterpenoid glycoside Echinoside A and Ds-echinoside A	*Pearsonothuria graeffei*	The glycosides induce a cell cycle halt in hepatocellular carcinoma cells. Ds-echinoside A inhibits the expression of the mouse double minute 2 homolog (MDM2) and C-X-C chemokine receptor type 4 (CXCR4), therefore increasing apoptosis through p53 modulation as well as decreases cell growth and proliferation by means of protein tyrosine kinase 2 regulation. Furthermore, Ds-echinoside A has been demonstrated to impede the growth of human hepatocellular carcinoma cells together with the repression of angiogenesis, migration, adhesion, and invasion of cells by modulating the expression of TIMP-1, VEGF, and MMP9.	[275,276]
The two sulfated triterpene glycosides, holothurin A (HA) and dehydroechinoside A (DHEA)	*Pearsonothuria graeffe*	The glycosides affect metastasis by notably inhibiting MMP-9 and consequently elevating TIMP-1. HA and DHEA reduce the levels of NF-κB and VEGF, therefore restricting cell invasion and migration in HepG2 cells.	[277]
Anthraquinone derivatives such as rhodoptilometrin (SE16) and deoxyrhodoptilometrin (SE11)	*Comanthus* sp.,	The compound demonstrates cytotoxicity against C6 glioma and HCT116 colon carcinoma cell lines by promoting both apoptotic and necrotic cell death. Both compounds hinder the expression of various protein kinases, including EGFR kinase, IGF1-receptor kinase, and focal adhesion kinase, which are linked to cell survival and the subsequent advancement of cancer cells. By reducing ERK phosphorylation, SE11 reduces the activity of EGF receptor kinase.	[225,278]
Cucumarioside A_0-1 (Cuc A_0-1) and djakonovioside A (Dj A)	*Cucumaria djakonovi*	The compound induces cell-cycle arrest, enhances reactive oxygen species (ROS) production, and reduces mitochondrial membrane potential (Δψm) in MDA-MB-231 cells. The depolarization of the mitochondrial membrane resulted in elevated levels of APAF-1 and cytochrome C. This results in the induction of caspase-9 and caspase-3, along with an increase in the levels of their cleaved forms. They also influenced the levels of Bax and Bcl-2 proteins, which are linked to mitochondria-mediated apoptosis in MDA-MB-231 cells.	[279]

The first known marine-derived anticancer agent, cytarabine (Ara-C), was approved in 1969 and continues to be utilized in treating acute myelocytic leukemia and non-Hodgkin's lymphoma. It was obtained from the Caribbean sponge *Tethya crypta*. Eribulin, a different anticancer agent that was created from the polyether metabolite halichondrin B and marketed as Halaven [71,280], was isolated from the sponge *Halichondria okadai* in 2010 [71,281]. Renieramycin T, isolated from the Thai blue sponge *Xestospongia* sp., appeared to have greater toxicity to NSCLC cells than to the BEAS-2B non-tumor cell line. The cytotoxic effect was mediated by the triggering of apoptosis [75,268]. Reinieramycin T induced the induction of p53 and caspases 9 and 3 while facilitating the degradation of Mcl-1, a pro-apoptotic protein within the Bcl-2 family, in the proteasome [75,268]. Nguyen and colleagues were

able to separate three sterols from the sea sponge *Xestospongia testudinaria*. Langcosterol A and 24-hydroperoxy-24-vinyl cholesterol, among the isolated sterols, demonstrated cytotoxic effects towards the A549 cell line, with IC50 values of 63 μM and 29 μM, respectively [75,282]. Zovko's lab assessed the anticancer properties of two different acetylenic compounds: (3S)-icos-4E-en-1-yn-3-ol and (3S)-14-methyldocos-4E-en-1-yn-3-ol derived from *Cribrochalina vasculum*. The compound exhibits notable tumor-specific toxicity in the NSCLC cell line U-1810 along with the SCLC cell lines U-1285, H69, and H82 [269]. The primary mechanism of cytotoxicity is the cleavage of PARP, caspase-9, and caspase-3, which triggers apoptosis. Further studies revealed conformational changes in Bak and Bax, resulting in the loss of mitochondrial potential together with the release of cytochrome C. Furthermore, the compounds initiate a decline in the phosphorylation of Akt, mTOR, and ERK while increasing the phosphorylation of JNK [269].

Stylissamide A and Stylissoside A, derived from the marine sponge *Stylissa carteri* found in the Red Sea, demonstrate cytotoxic effects against MCF7 and HepG2 cell lines [71,283]. Another investigation indicated that 5-bromotrisindoline and 6-bromotrisindoline, obtained from *Callyspongia siphonella*, exhibited efficacy against HT29 (colon carcinoma), OVCAR3 (ovarian carcinoma), and MM.1S (multiple myeloma) [71,284]. The marine sponge *Geodia macandrewii* yielded a new chemical called Geodiataurine, which showed modest cytotoxicity towards the melanoma cancer cell line (A2058) [71,285].

Cheng's lab assessed the cytotoxic effects of the sesterterpene BA6 (heteronemin) derived from the marine sponge *Hyrtios erecta* on A549 cells [270]. BA6 primarily causes mitochondrial dysfunction by increasing the generation of mitochondrial reactive oxygen species (mtROS) [1–3]. Additionally, BA6 stimulated cytochrome C release, triggered caspase-9 and -3 expression, and downregulated the anti-apoptotic protein Bcl-2, along with the elevation of the pro-apoptotic protein Bax. This leads to the induction of apoptosis in lung cancer cells [81,270]. The sea sponge *Xestospongia exigua* (Kirkpatrick) yielded the cytotoxic alkaloids, motuporamines A–C, which showed anti-angiogenic and anti-invasive characteristics. Motuporamines inhibited the invasion of numerous types of tumor cells, such as PC-3 prostate cancer cells and MDA-231 breast carcinoma cells, through basement membranes in vitro [72,271]. Of these compounds, motuporamine C is the most potent alkaloid. It causes cytoskeletal alterations in cancer cells, therefore preventing β1-integrin from activating, which is essential for cancer cell adhesion and invasion. This eventually suppresses angiogenesis and cell migration [72,271]. Two novel meroterpenoids, hyrtamide A and hyrfarnediol A, were identified alongside two known compounds, 3-farnesyl-4-hydroxybenzoic acid methyl ester and dictyoceratin C, in the South China Sea sponge *Hyrtios* sp. The anti-invasive actions of 3-farnesyl-4-hydroxybenzoic acid methyl ester and dictyoceratin C on HCT116 cells are mainly initiated through blocking VEGFR-1 expression and preventing Epithelial to Mesenchymal transition (EMT) [286].

Irciniastatin A is a psymberin that was extracted from the marine sponges *Psammocinia* and *Ircinia ramose*. It mainly acts as a translation inhibitor that activates the JNK, p38 MAP kinase, and ERK pathways This activation resulted in the shedding of the ectodomain of TNF receptor 1 in A549 cells [287].

Ptilomycaline A, a novel guanidine alkaloid, has been isolated from *Hemimycale.* sp. demonstrated cytotoxic effects on the leukemia P-388 cell line [70,288]. The cytotoxicity of Stelletin B derived from the marine sponge *Jaspis stellifera* was evaluated on A549 cells. The antitumor effect was mediated through the targeting of the PI3K/Akt/mTOR pathway [75,272]. In addition to inducing apoptosis linked to an increase in ROS production and PARP cleavage, the drug was shown to cause G1 arrest, which was ascribed to a decrease in cyclin D1 and an increase in p27 expression [272].

5.5. Bacteria and Actinomycetes

Several marine-derived bioactives from marine bacteria have been used to treat cancer (Table 4).

Table 4. Representative examples of marine products derived from bacteria and actinomycetes used in cancer treatment.

Marine-Derived Product	Source	Mechanism	References
Streptodepsipeptides P11A and P11B	*Streptomyces* sp.	Inhibit the proliferation of glioma cell lines by inducing apoptosis and cell-cycle arrest at the G0/G1 phase. P11A reduces the expression of critical tumor metabolic enzymes: hexokinase 2 (HK2) (a key regulator of glycolysis), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) (a regulator of the glycolytic flux), pyruvate kinase M2 (PKM2) (linked to aerobic glycolysis in cancer cells), lactate dehydrogenase (LLS), and fatty acid synthase (FASN) (involved in lipid biosynthesis essential for tumor cell survival).	[72,289]
Streptochlorin, an indole	*Streptomyces*, specifically 04DH110.	Demonstrates potent anticancer effects by inducing apoptosis in U937 (human leukemia) and Hep3B (hepatocarcinoma) cells. Mechanisms involve a significant reduction in mitochondrial membrane potential ($\Delta\psi m$), activation of executioner caspase-3, and downregulation of anti-apoptotic Bcl-2. Pro-apoptotic proteins such as Bax and FasL are upregulated, leading to apoptosis. In U937 cells, degradation of poly (ADP-ribose) polymerase (PARP) and phospholipase C-γ1 disrupts DNA repair and cell survival signaling. Anti-angiogenic effects are achieved through inhibition of VEGF-induced endothelial cell migration and tube formation, mediated via NF-κB pathway suppression.	[216,224,231,238]
Violacein, a violet pigment similar to indole	*Chromobacterium violaceum*	Induces apoptosis through mechanisms involving DNA fragmentation, chromatin condensation, and caspase activation. Violacein directly targets protein kinases involved in signal transduction, disrupting critical pathways for cancer cell proliferation. Studies in U937 (human leukemia) and HL 60 (human promyelocytic leukemia) cells indicate that violacein modulates signaling processes necessary for cell survival and tumor progression, particularly those involved in apoptosis and the cell cycle.	[290,291]

Preclinical studies have utilized thiocoraline, a depsipeptide produced by the marine bacterium *Micromonospora* sp., to treat cancer. The peptide primarily inhibits DNA polymerase-α [72,292]. Cycloprodigiosin and prodigiosins, which are part of the prodiginin family, have been extracted from *Pseudoalteromonas rubra* found in Mediterranean coastal waters and the Pacific Coast of Japan [293–295]. Williamson's lab reported that the compounds exhibited anticancer and immunosuppressive properties. The cytotoxicity of prodigiosin and its analogs, 2-methyl-3-butyl-prodiginine, 2-methyl-3-pentyl-prodiginine, 2-methyl-3-hexyl-prodiginine, and 2-methyl-3-heptyl-prodigi-nine, has recently been assessed in U937 leukemia cells. Among the compounds, 2-methyl-3-butyl-prodiginine exhibited the most promising effect. The proposed molecular mechanism underlying this

anticancer effect involves the activation of caspase-3 and subsequent DNA fragmentation, suggesting an ability to induce apoptosis in leukemia cells [293,296]. Violacein, a violet pigment similar to indole, has been derived from *Chromobacterium violaceum* [290,291]. This compound showed significant cytotoxic effects on U937 and HL-60 cells, with IC50 values between 0.5 and 1 μM [297]. This bioactive pigment triggers several apoptosis-related processes, including DNA fragmentation, chromatin condensation, and caspase activation. Additionally, it targets protein kinases, which have a role in cancer and signal transduction [296,297]. Furthermore, it has been determined that *Zooshikella rubidus* S1-1 is a significant source of prodigiosin and cycloprodigiosin, which have anticancer and immunosuppressive properties by regulating the NF-κB pathway [298].

Actinomycetes derived from natural sources are known to generate secondary metabolites, including various antimicrobials such as streptomycin, erythromycin, and tetracycline, characterized by unique structures and significant biological activities [299,300]. Several investigations have examined the potential of marine-derived actinomycetes as sources of anticancer agents. The marine actinomycete *Nocardiopsis lucentensis* (strain CNR-712) yielded the bioactive compounds lucentamycins A and B [296,301]. The peptides provide notable cytotoxic effects on HCT-116 cells (human colon carcinoma) [296,301]. The *Streptomyces strain* CNR-698 also produces ammosamides, which are pyrrole-based structures (pyrrolaminoquinones). Ammosamides A and B exhibit a significant level of cytotoxicity against HCT-116 cells. These substances have been proven to be selectively cytotoxic to a range of cancer cell types. The compound selectively targets the myosin protein family member [296,302]. Research has revealed 18 metabolites generated by the marine-derived *Streptomyces* sp. ZZ735. Streptonaphthothiazines A, B, and streptomycinoic acids A, B exhibit antiproliferative activity against human glioma U87MG or U251 cells [303].

Additionally, clinical studies on salinosporamide are being conducted for the management of multiple myeloma, solid tumors, and lymphomas using salinosporamide A, isolated from cultures of the marine actinobacterium *Salinispora tropica* [72,304–306]. Further studies elucidated the mechanism that governs the effects of this compound as a proteasome inhibitor [307–309]. Proteasome inhibitors are essential in regulating protein levels, which is significant for the prevention of cancer [309,310]. Salinosporamide A covalent bond forms with the threonine residues in the proteasome active site, leading to the inhibition of the proteasome 20S activity. Proteasome inhibition has emerged as a potent approach in the management of multiple myeloma and certain lymphomas, as it disrupts nuclear factor-kappa B (NF-κB) activity by intervening with growth and survival signaling [311–313].

In a separate investigation, the bacterium *Streptomyces* sp. *P11-238* produces two cyclodepsipeptides identified as streptodepsipeptides P11A and P11B. Research has shown that these compounds can inhibit the proliferation of different glioma cell lines.

Reports from the lab have shown that streptodepsipeptide P11A, in particular, has been reported to cause apoptosis, halting the cells in the G0/G1 phase of the cell cycle, alongside lowering the expression of certain tumor metabolic enzymes (HK2, PFKFB3, PKM2, LLS, and FASN) [72,289]. A separate study highlighted that the *Streptomyces* strain *CNQ-583* generates pyrrolizidine alkaloids such as bohemamine and deoxybohemamine. Both of them effectively inhibited the adhesion of human promyelocytic leukemia (HL-60 cells) to Chinese hamster ovary (CHO) cells that were transfected with human ICAM-1 [296,314]. The interplay between LFA-1 and ICAM-1 stimulates angiogenesis and is linked to autoimmune disorders, cancer metastasis, and chronic inflammation [296,315,316]

A compound related to indole, streptochlorin, exhibiting anticancer activity, was isolated from a marine actinomycete strain of *Streptomyces*, specifically *04DH110*. Streptochlorin exhibits strong cytotoxic effects in K-562 cells. Furthermore, the compound induces apoptosis in U937 (human leukemia) and Hep3B (hepatocarcinoma) cells, showing a reduction in mitochondrial membrane potential ($\Delta\psi m$), activation of caspase-3, and downregulation of the anti-apoptotic Bcl-2 protein [296,317,318]. The observed effects are linked to the generation of reactive oxygen species (ROS) in Hep3B cells. In contrast, U937 cells exhibited an increase in pro-apoptotic factors such as Bax and FasL, together with the

degradation of poly-(ADP-ribose) polymerase (PARP) and phospholipase C-.1 [296,317]. Furthermore, streptochlorin exhibits significant anti-angiogenic properties by inhibiting VEGF-stimulated endothelial cell migration and tube formation, potentially through the reduction of NF-κB activation [296,301].

Five isoquinoline quinones, including four new derivatives named Mansouramycin A-D, along with the known compound 3-methyl-7-(methylamino)-5,8-isoquinolinedione, have been identified from the ethyl acetate extract of the marine-derived Mei37 isolate of *Streptomyces* sp. These compounds exhibited substantial cytotoxicity with a high degree of selectivity towards non-small cell lung cancer, breast cancer, melanoma, and prostate cancer cells [300,319].

5.6. Echinodermata

Echinoderms represent the second largest category of deuterostomes, encompassing approximately 7000 living species, and are recognized as a novel source of various bioactives [225]. Various bioactive molecules, including peptides, sterols, and saponins, have been isolated from echinoderms, demonstrating significant cytotoxic effects on multiple cancer cell lines [225,320] (Table 3). According to reports, sea cucumber extracts have antiproliferative and anticancer properties because they are rich in flavonoids and phenols, which function as antioxidants to prevent oxidative imbalances that might cause cancer [225,321].

A study identified the molecule leucospilotaside B, derived from the sea cucumber *Holothuria leucospilota*, displaying cytotoxic effects against leukemia, hepatocellular carcinoma, and human lung adenocarcinoma epithelial cell lines [273,322,323]. Thao's lab showed the promotion of cell death via apoptosis by a novel steroid (cholest-8(14)-ene-3ß,5a,6ß,7a-tetraol) isolated from the sea urchin *Diadema savignyi* [273,274]. The induction of apoptosis was followed by changes in the expression of proteins linked to apoptosis, such as reduced c-Myc expression along with the inactivation of extracellular signal-regulated kinase (ERK)1/2 mitogen-activated protein kinase (MAPK) signaling cascade [273,274]. *Pseudoconus californica*, *Holothuria impatiens*, and *Pharia pyramidata* demonstrate cytostatic effects and cytotoxicity against HT-29 and A549 cell lines [324]. Benzo[g]chromen-4-one and benzo[h]Chromen-4-one pigments obtained from *Comantheria rotula* govern HIF-1 expression that promotes tumor cell survival under oxidative stress [225,325].

A separate report indicated that novel triterpene glycosides derived from *Pentamera calcigera*, *Staurocucumis liouvillei*, *Hemoiedema spectabilis*, and *Mensamaria intercedens* demonstrate antineoplastic efficacy against various cancer cell lines [326]. Stychorenosides A–D and Stychhoposide A–B, two of the triterpene diglycosides that were isolated from *Stychhopus horrens*, exhibit cytotoxicity towards LNCaP, MCF-7, Caco-2, and HepG2 cell lines [327]. Echinoside A and Ds-echinoside A are triterpenoid glycosides derived from *Pearsonothuria graeffei*, which induce a cell cycle halt in hepatocellular carcinoma cells [275,328]. It has been demonstrated that Ds-echinoside A inhibits the expression of the *mouse double minute 2 homolog* (*MDM2*) and *CXC chemokine receptor type 4* (*CXCR4*), ultimately increasing apoptosis through p53 modulation as well as decreases cell growth and proliferation by means of protein tyrosine kinase 2 regulation [275,276]. Furthermore, Ds-echinoside A has been demonstrated to impede the growth of human hepatocellular carcinoma cells together with the repression of angiogenesis, migration, adhesion, and invasion of cells by modulating the expression of TIMP-1, VEGF, and MMP9 [275,329].

Frondoside A, cucumarioside A2-5, koreoside A, and okhotosides B1-3, obtained from *Cucumaria okhotensis* and *Cucumaria frondosa*, demonstrate profound cytotoxic effects against THP-1, PC-3, LNCaP, HeLa, and urothelial carcinoma cell lines. This is achieved by triggering caspase-dependent intrinsic apoptosis, which is accompanied by immune modulation, inhibiting cytoprotective autophagy, and triggering cell-cycle arrest [225,330–332]. Frondoside A activates caspases 3, 8, and 9 to cause apoptosis. Furthermore, apoptosis is aided by the regulation of *PARP*, *Bcl-2*, and *Bax*. Additionally, the regulation of *P21* and DNA fragmentation facilitates the initiation of apoptosis [332].

The two sulfated triterpene glycosides that were isolated from *Pearsonothuria graeffe*, holothurin A (HA) and dehydroechinoside A (DHEA), are said to affect metastasis by notably inhibiting MMP-9 and consequently elevating TIMP-1 [225,333]. HA and DHEA reduce the levels of NF-κB and VEGF, therefore restricting cell invasion and migration in HepG2 cells [277].

A separate study indicates that anthraquinone derivatives, rhodoptilometrin (SE16) and deoxyrhodoptilometrin (SE11), isolated from *Comanthus* sp., exhibit cytotoxicity against C6 glioma and HCT116 colon carcinoma cell lines by promoting both apoptotic and necrotic cell death [278]. SE16 and SE11 hinder the expression of various protein kinases, including EGFR kinase, IGF1-receptor kinase, and focal adhesion kinase, which are linked to cell survival and the subsequent advancement of cancer cells. By reducing ERK phosphorylation, SE11 reduces the activity of EGF receptor kinase [225,278].

Sea star-derived polyhydroxysterols and saponins have been shown to have strong anticancer effects on human solid tumor cell lines [225,334]. A study revealed that Astropectenols isolated from the chloroform fraction of *Astropecten polyacanthus* demonstrate significant cytotoxicity against HL-60 through the induction of apoptosis, chromatin condensation, and sub-G1 phase cell-cycle arrest. Astropectenols induce apoptosis through a caspase-dependent mechanism and modulate the expression of Bcl-2, Bax, and PARP in HL-60 cells [225,274].

The steroidal compounds extracted from the sea urchin *Diadema savignyi* Michelin displayed lethal effects against numerous human cancer cell lines, including human promyelocytic leukemia, prostate cancer, and embryonic lung cells [274,275]. The steroidal components suppressed cellular proliferation and survival, inducing apoptosis through the regulation of apoptosis-related protein production, inactivation of the MAPK pathway, and reduction of c-Myc expression [274]. Conversely, Ovothiols derived from the eggs of the sea urchin *Paracentrotus lividus*, have demonstrated a significant function in cellular defense through the control of redox balance and the recycling of oxidized glutathione [335].

Plancitoxin I, extracted from the venom of *Acanthaster planci*, has demonstrated potent cytotoxicity against human malignant melanoma cells. Plancitoxin I reduced cell viability by producing reactive oxygen species nitric oxide generation alongside decreasing mitochondrial membrane potential ($\Delta\psi m$), therefore triggering apoptosis [275,336]. It has been shown by another investigation that pancitoxin I caused mitochondrial dysfunction and decreased antioxidant enzymes, including catalase and SOD [337]. Philinopside A, extracted from the sea cucumber *Pentacta quadrangularis*, has proved to be effective in reducing cellular proliferation, migration, and tube formation in human microvascular endothelial cells and animal models. Philinopside A decreased tumor volume via inducing apoptosis along with the inhibition of angiogenesis-related receptor tyrosine kinases [275,338]. Research has demonstrated that philinopside E interacts with the extracellular domain of the kinase domain-containing receptor KDR. This interaction blocks KDR's ability to bind to VEGF, hence impeding other downstream signaling pathways [275,339].

In the latest study, it was revealed that cucumarioside A_0-1 (Cuc A_0-1) and djakonovioside A (Dj A), derived from the sea cucumber *Cucumaria djakonovi*, induced cell-cycle arrest, enhanced reactive oxygen species (ROS) production, and reduced mitochondrial membrane potential ($\Delta\psi m$) in MDA-MB-231 cells. The depolarization of the mitochondrial membrane induced by cucumarioside A_0-1 and djakonovioside A resulted in elevated levels of APAF-1 and cytochrome C [279]. This led to the induction of caspase-9 and caspase-3, along with an increase in the levels of their cleaved forms. Glycosides influenced the levels of Bax and Bcl-2 proteins, which are linked to mitochondria-mediated apoptosis in MDA-MB-231 cells [279]. The findings demonstrate that cucumarioside A_0-1 and djakonovioside A trigger the intrinsic apoptotic pathway in triple-negative breast cancer cells. Furthermore, treatment with Cuc A_0-1 demonstrated in vivo inhibition of tumor growth and metastasis in murine solid Ehrlich adenocarcinoma [279].

6. Recent Clinical Trials and FDA Approvals on Some Marine-Derived Bioactives

To date, several marine peptides have been identified, with only a limited number having undergone clinical trials [3]. Didemnin B advanced to clinical trials 1 and 2 but was not authorized for clinical trial 3 due to severe toxicities, including muscular necrosis and other neurological and gastrointestinal abnormalities observed in the first two trials. Furthermore, the therapeutic effects on various advanced cancers were minimal, and participants in the trials did not experience any significant improvement [3,340]. Aplidine, due to its in vitro activities, has progressed through clinical trial phases I to III. The Phase I study indicated that Alplidine demonstrated optimal therapeutic effects in patients with solid tumors [341]. A clinical study recommended dosages of 7 and 5 mg/m^2, both with and without carnitine, for patients who had advanced malignancy. Nonetheless, muscle toxicity was noted as a side effect at an elevated dosage [342]. During the Phase II trials, it was reported that Aplidine was actively distributed by red blood cells and excreted through the bile. Although it was widely distributed, this peptide had a poor clearance rate. In the Phase III trials, Aplidine in combination with dexamethasone (5 mg/m^2 and 40 mg, respectively) demonstrated an enhancement in the median progression-free survival (PFS) and the overall PFS with no disease progression when compared to dexamethasone alone. Additionally, the safety profile of this peptide was validated, with adverse effects classified as grade 3, including fatigue, myalgia, and nausea [226].

Trabectedin has demonstrated efficacy in the treatment of soft tissue sarcomas in early clinical trials. A clinical trial analyzed a combination therapy of gemcitabine and trabectedin for L-sarcomas (NCT01426633) [275,343]. This Phase I study assessed the antitumor efficacy of combination therapy and yielded negative outcomes for the management of advanced and/or metastatic leiomyosarcoma or liposarcoma. According to the data, the combination treatment has anticancer properties and is safe and well tolerated. Additionally, a Phase II clinical trial has been finished (TRAVELL Study) to verify the therapeutic benefit of trabectedin for well-differentiated/dedifferentiated liposarcoma and retroperitoneal leiomyosarcoma. Although the main goal of the study was not achieved, we observed a subgroup of patients exhibiting a significantly different treatment: time to progression with trabectedin compared to their prior treatment [344]. A Phase III clinical trial, designed to assess the effectiveness of trabectedin towards advanced relapsed ovarian cancer, has been completed (NCT00113607) [275,345]. This Phase III study evaluated the impact of the combination of trabectedin and pegylated liposomal doxorubicin. The findings demonstrated that the combined treatment resulted in controllable and non-cumulative toxicity together with fewer side effects, a notable increase in progression-free survival, and an overall response rate, with little to no decline in patient-reported functional status and symptoms [275,345]. It has received approval (NDA 021790) in the European Union to be used for the treatment of advanced soft tissue sarcoma and recurrent platinum-sensitive ovarian cancer.

Marizomib (salinosporamide A; NPI-0052), an irreversible proteasome inhibitor, is currently undergoing Phase III clinical trials for the treatment of multiple cancers [346,347]. Marizomib (NPI-0052) is being studied in Phase I in patients with advanced cancers. A total of 42 patients underwent treatment on a weekly basis (Schedule A), whereas the remaining 44 patients received treatment twice a week (Schedule B). The most frequent adverse effects from this treatment include infusion site discomfort, nausea, diarrhea, and exhaustion. In Schedule A, one patient with transformed marginal zone lymphoma responded completely. The overall response (OR) rate for Schedule B was 11%, with all responses noted in 27 patients with relapsed and/or refractory multiple myeloma (RRMM) [347]. A further Phase I trial (NPI-0052-107) assessed marizomib (0.3–0.5 mg/m^2), pomalidomide (3–4 mg), and low-dose dexamethasone (0.5 mg/m^2) involving 38 patients with relapsed/refractory multiple myeloma (RRMM). The treatment commonly resulted in side effects such as pneumonia, anemia, neutropenia, and thrombocytopenia. The overall response rate in this trial was 53% (19 out of 36), while the clinical benefit rate was 64% (23 out of 36) [348]. Plocabulin, derived from the sponge *Lithoplocamia lithistoides*, is being evaluated in clinical trials

(NCT03042793) for its ability to disrupt tubulin polymerization, a crucial pathway in cancer cell proliferation [21]. A Phase I clinical trial evaluated the safety and pharmacokinetics of Episulosine in patients with advanced solid tumors (NCT00231448) [23]. Limonene is going through clinical trials for head and neck squamous cell cancer (NCT04392622) [98]. Fucoidan is under a clinical trial (NCT06295588) for evaluating its impact on inflammation and fatigue in cancer survivors. [96].

Peptides like Dolastatin 10 have completed both Phase I and II trials but did not progress to Phase III due to their barely significant impact on various types of cancer. In the same manner, Cematodin (TZT-1027) and tasidotin, a derivative of Dolastatin 15, did not succeed in Phase II trials because of inadequate therapeutic effects on malignant melanoma [3,349,350]. Variolin B has not progressed to clinical trials or received FDA approval, primarily due to challenges in sourcing and synthesizing the compound [83]. Despite Manzamine A showing promising preclinical results, it has not yet received FDA approval for clinical use [84]. Apigenin has not received FDA approval for cancer treatment. Clinical trials investigating its efficacy are limited. One such study (NCT00609310) aimed to evaluate apigenin's effect on tumor recurrence in colorectal cancer patients, but this trial was suspended [89]. Quercetin lacks FDA approval for cancer treatment but is under investigation in a Phase II trial (NCT04063124) assessing its combination with dasatinib to reduce senescence and frailty in childhood cancer survivors [92]. Kahalalide F has undergone Phase I clinical trials to assess its safety and efficacy in patients with advanced solid tumors (NCT00003858) [77], while it was ultimately discontinued following the second clinical trial due to the absence of measurable therapeutic effects [183]. Further clinical testing of these novel therapeutic bioactives is necessary to enhance their applicability in cancer treatment.

7. Discussion and Future Perspectives

Marine-derived bioactive compounds hold significant promise for advancing cancer therapy, primarily due to their unique chemical structures and diverse biological activities [2,6]. These compounds, including alkaloids, peptides, polysaccharides, and terpenoids, have demonstrated a wide range of anticancer properties, such as inducing apoptosis, inhibiting angiogenesis, and reducing metastasis [10,65] (Figure 1).

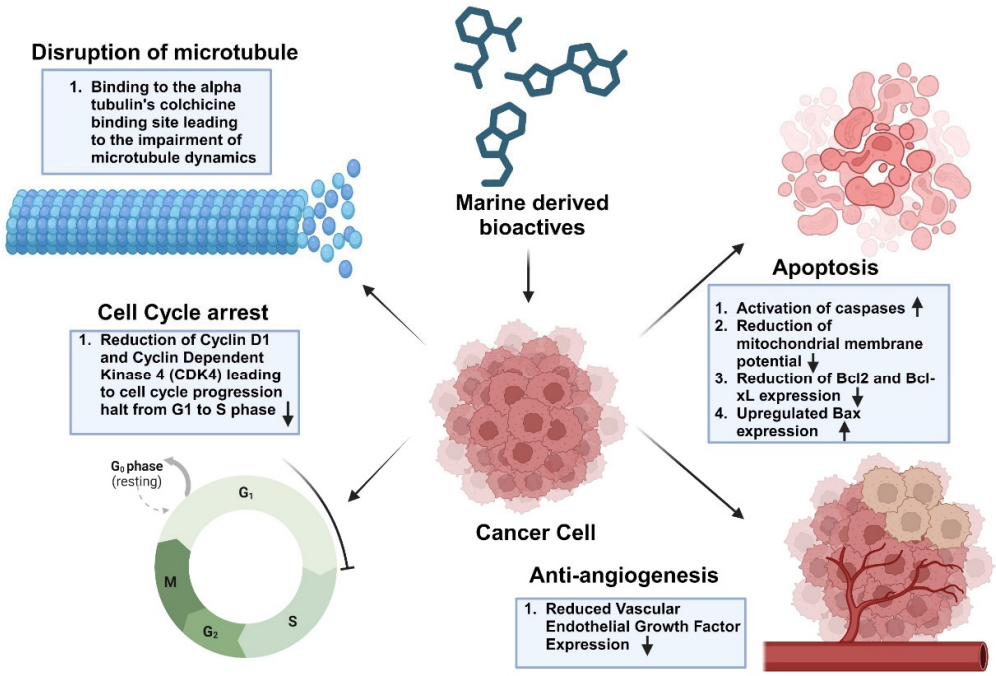

Figure 1. Mechanisms of marine-derived bioactives towards targeted cancer therapy.

Despite the promising outcomes of some compounds, such as trabectedin and fucoidan, which have moved into clinical use or trials, a large majority of marine bioactives remain underexplored [26,27,86]. This presents a major opportunity for researchers to delve deeper into the vast marine biodiversity for new drug candidates [28].

One of the challenges in utilizing marine bioactives is the sustainable sourcing of these compounds, as excessive harvesting of marine organisms may have detrimental ecological consequences [95]. Thus, advancements in biotechnology, such as marine bioprospecting, synthetic biology, and microbial fermentation, could provide solutions by enabling the production of these bioactives in laboratories, reducing the environmental impact [16,31]. Additionally, improving the bioavailability and pharmacokinetics of marine bioactives through novel drug delivery systems, such as nanoparticles or liposomal formulations, could enhance their therapeutic efficacy and minimize side effects [17,104].

Another promising avenue for future research is the use of omics technologies, including genomics, proteomics, and metabolomics, to better understand the molecular mechanisms of action of these compounds [19,109]. This knowledge could facilitate the design of targeted therapies, allowing for more personalized treatment approaches for cancer patients [60]. Furthermore, investigating synergistic effects between marine bioactives and conventional cancer treatments, such as chemotherapy and immunotherapy, could lead to the development of combination therapies that enhance treatment outcomes [296,300].

Collaborative efforts between marine biologists, chemists, pharmacologists, and oncologists will be essential to unlocking the full potential of marine bioactives [67,68]. Partnerships with the pharmaceutical industry are also crucial to translating these discoveries from the lab to clinical application [71]. Moreover, policies that support the sustainable use of marine resources and promote marine conservation will be critical for ensuring that this promising field of research continues to grow without harming the environment [72].

8. Conclusions

Marine-derived bioactive compounds offer significant potential for advancing cancer therapy, with unique mechanisms such as apoptosis induction, inhibition of angiogenesis, and metastasis suppression. However, challenges remain in sustainable sourcing, enhancing bioavailability, and large-scale production. Future advancements in biotechnological methods, such as microbial fermentation and synthetic biology, will help reduce ecological impacts while improving drug delivery systems, including nanotechnology, to optimize therapeutic outcomes. Understanding the molecular mechanisms of these compounds and exploring synergistic effects with conventional therapies will further enhance their clinical application. Overall, marine bioactives hold great promise for developing novel, targeted cancer therapies with improved efficacy and reduced side effects. Continued research and sustainable practices are key to unlocking their full potential in oncology.

Author Contributions: Conceptualization: S.D., Data curation: N.N.T. and M.M.R., Writing—original draft: S.D., Writing—review and editing: All authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors appreciate the reviewers for dedicating their time and effort to evaluate the manuscript. We are grateful for all the insightful comments and suggestions that have contributed to enhancing the quality of the manuscript. Figure 1 was created using Biorender.com.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Malekhayati, H.; Bargahi, A.; Khorami, S.; Khataminejad, M.; Fouladvand, M. Anti-Trichomonas Vaginalis Activity of Marine Ascidians (Tunicates; Ascidiacea) from the Bushehr Province, Iran. *Turk. Parazitoloji Derg.* **2024**, *48*, 21–26. [CrossRef] [PubMed]
2. Ahmadi, P.; Setiawan, A.; Tanaka, J. Coral Reef Organisms as a Potential Source of Anticancer Agents. In Proceedings of the 4th International Conference on Applied Sciences, Mathematics, and Informatics: Icasmi2022, Bandar Lampung, Indonesia, 8–9 September 2022; Volume 2970, p. 060011. Available online: https://pubs.aip.org/aip/acp/article-abstract/2970/1/060011/3311478/Coral-reef-organisms-as-a-potential-source-of?redirectedFrom=fulltext (accessed on 4 December 2024).
3. Okeke, E.S.; Okagu, I.U.; Chukwudozie, K.; Ezike, T.C.; Ezeorba, T.P.C. Marine-Derived Bioactive Proteins and Peptides: A Review of Current Knowledge on Anticancer Potentials, Clinical Trials, and Future Prospects. *Nat. Prod. Commun.* **2024**, *19*, 3. [CrossRef]
4. Nagy, N.S.; Essawy, A.E.; Al-Sherif, S.S.; Ali, M.M.; Alsawy, E.S.; Helal, M. Characterization and Biological Applications of Gonadal Extract of Paracentrotus Lividus Collected along the Mediterranean Coast of Alexandria, Egypt. *PLoS ONE* **2024**, *19*, e0296312. [CrossRef] [PubMed]
5. Nagarajan, P.; Sivakumar, A.S.; Govindasamy, C.; El Newehy, A.S.; Rajathy Port Louis, L.; Sivanandham, M.; Rangarajalu, K.; Sangeetha, C.C.; Ghidan, A.Y.; Yousef Ghidan, A. Molecular Perspective on Starfish Tissue Extracts: Targeting Human Carcinoma KB Cells for Anticancer Therapy. *J. King Saud Univ. Sci.* **2024**, *36*, 103035. [CrossRef]
6. Cai, C.; Yang, D.; Cao, Y.; Peng, Z.; Wang, Y.; Xi, J.; Yan, C.; Li, X. Anticancer Potential of Active Alkaloids and Synthetic Analogs Derived from Marine Invertebrates. *Eur. J. Med. Chem.* **2024**, *279*, 116850. [CrossRef]
7. Li, L.; Yu, Y.; Wu, W.; Wang, P. Extraction, Characterization and Osteogenic Activity of a Type I Collagen from Starfish (*Asterias Amurensis*). *Mar. Drugs* **2023**, *21*, 274. [CrossRef]
8. Kaliaperumal, K.; Salendra, L.; Liu, Y.; Ju, Z.; Sahu, S.K.; Elumalai, S.; Subramanian, K.; Alotaibi, N.M.; Alshammari, N.; Saeed, M.; et al. Isolation of Anticancer Bioactive Secondary Metabolites from the Sponge-Derived Endophytic Fungi *Penicillium* sp. and in-Silico Computational Docking Approach. *Front. Microbiol.* **2023**, *14*, 1216928. [CrossRef] [PubMed]
9. Hassan, M.G.; Elmezain, W.A.; Baraka, D.M.; AboElmaaty, S.A.; Elhassanein, A.; Ibrahim, R.M.; Hamed, A.A. Anti-Cancer and Anti-Oxidant Bioactive Metabolites from Aspergillus Fumigatus WA7S6 Isolated from Marine Sources: In Vitro and In Silico Studies. *Microorganisms* **2024**, *12*, 127. [CrossRef]
10. Kalyani, B.S.; Krishna, P.S.; Laxminarayana, E.; Sreenivasulu, K. Novel Bioactive Compounds from *Streptomyces* sp. NLKPB45 Isolated from Marine Soil Sediment. *Pharm. Chem. J.* **2023**, *57*, 834–841. [CrossRef]
11. Esim, N.; Dawar, P.; Arslan, N.P.; Orak, T.; Doymus, M.; Azad, F.; Ortucu, S.; Albayrak, S.; Taskin, M. Natural Metabolites with Antioxidant Activity from Micro-and Macro-Algae. *Food Biosci.* **2024**, *62*, 105089. [CrossRef]
12. Leong, Y.K.; Chang, J.S. Proteins and Bioactive Peptides from Algae: Insights into Antioxidant, Anti-Hypertensive, Anti-Diabetic and Anti-Cancer Activities. *Trends Food Sci. Technol.* **2024**, *145*, 104352. [CrossRef]
13. Visuddho, V.; Halim, P.; Helen, H.; Muhar, A.M.; Iqhrammullah, M.; Mayulu, N.; Surya, R.; Tjandrawinata, R.R.; Ribeiro, R.I.M.A.; Tallei, T.E.; et al. Modulation of Apoptotic, Cell Cycle, DNA Repair, and Senescence Pathways by Marine Algae Peptides in Cancer Therapy. *Mar. Drugs* **2024**, *22*, 338. [CrossRef] [PubMed]
14. El-Sheekh, M.M.; Alkafaas, S.S.; Rady, H.A.; Abdelmoaty, B.E.; Bedair, H.M.; Ahmed, A.A.; El-Saadony, M.T.; Abuqamar, S.F.; El-Tarabily, K.A. How Synthesis of Algal Nanoparticles Affects Cancer Therapy?—A Complete Review of the Literature. *Int. J. Nanomed.* **2023**, *18*, 6601–6638. [CrossRef]
15. FDA Approves Trabectedin for Sarcoma—NCI. Available online: https://www.cancer.gov/news-events/cancer-currents-blog/2015/fda-trabectedin-sarcoma (accessed on 21 November 2024).
16. Eribulin | FDA. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/eribulin (accessed on 21 November 2024).
17. Haggag, Y.A.; Abd Elrahman, A.A.; Ulber, R.; Zayed, A. Fucoidan in Pharmaceutical Formulations: A Comprehensive Review for Smart Drug Delivery Systems. *Mar. Drugs* **2023**, *21*, 112. [CrossRef] [PubMed]
18. Fenical, W.; Jensen, P.R.; Palladino, M.A.; Lam, K.S.; Lloyd, G.K.; Potts, B.C. Discovery and Development of the Anticancer Agent Salinosporamide A (NPI-0052). *Bioorg. Med. Chem.* **2008**, *17*, 2175. [CrossRef]
19. Jeong, G.J.; Khan, S.; Tabassum, N.; Khan, F.; Kim, Y.M. Marine-Bioinspired Nanoparticles as Potential Drugs for Multiple Biological Roles. *Mar. Drugs* **2022**, *20*, 527. [CrossRef]
20. Thompson, R.E.; Tuchman, A.J.; Alkon, D.L. Bryostatin Placebo-Controlled Trials Indicate Cognitive Restoration Above Baseline for Advanced Alzheimer's Disease in the Absence of Memantine1. *J. Alzheimers Dis.* **2022**, *86*, 1221–1229. [CrossRef]
21. Jørgensen, N.G.; Klausen, U.; Grauslund, J.H.; Helleberg, C.; Aagaard, T.G.; Do, T.H.; Ahmad, S.M.; Olsen, L.R.; Klausen, T.W.; Breinholt, M.F.; et al. Peptide Vaccination Against PD-L1 With IO103 a Novel Immune Modulatory Vaccine in Multiple Myeloma: A Phase I First-in-Human Trial. *Front. Immunol.* **2020**, *11*, 595035. [CrossRef] [PubMed]
22. Thaman, J.; Saxena Pal, R.; Chaitanya, M.V.N.L.; Yanadaiah, P.; Thangavelu, P.; Sharma, S.; Amoateng, P.; Arora, S.; Sivasankaran, P.; Pandey, P.; et al. Reconciling the Gap between Medications and Their Potential Leads: The Role of Marine Metabolites in the Discovery of New Anticancer Drugs: A Comprehensive Review. *Curr. Pharm. Des.* **2023**, *29*, 3137–3153. [CrossRef]
23. Cooreman, K.; De Spiegeleer, B.; Van Poucke, C.; Vanavermaete, D.; Delbare, D.; Wynendaele, E.; De Witte, B. Emerging Pharmaceutical Therapies of Ascidian-Derived Natural Products and Derivatives. *Environ. Toxicol. Pharmacol.* **2023**, *102*, 104254. [CrossRef]

24. Popov, A.; Kozlovskaya, E.; Rutckova, T.; Styshova, O.; Vakhrushev, A.; Kupera, E.; Tekutyeva, L. Antitumor Properties of Matrikines of Different Origins: Prospects and Problems of Their Application. *Int. J. Mol. Sci.* **2023**, *24*, 9502. [CrossRef] [PubMed]
25. Kumari, A.; Garima; Bharadvaja, N. A Comprehensive Review on Algal Nutraceuticals as Prospective Therapeutic Agent for Different Diseases. *3 Biotech* **2023**, *13*, 44. [CrossRef] [PubMed]
26. Zeng, M.; Tao, J.; Xu, S.; Bai, X.; Zhang, H. Marine Organisms as a Prolific Source of Bioactive Depsipeptides. *Mar. Drugs* **2023**, *21*, 120. [CrossRef] [PubMed]
27. Wong, Y.H.; Wong, S.R.; Lee, S.H. The Therapeutic Anticancer Potential of Marine-Derived Bioactive Peptides: A Highlight on Pardaxin. *Int. J. Pept. Res. Ther.* **2023**, *29*, 90. [CrossRef]
28. Qiu, Y.; Chen, S.; Yu, M.; Shi, J.; Liu, J.; Li, X.; Chen, J.; Sun, X.; Huang, G.; Zheng, C. Natural Products from Marine-Derived Fungi with Anti-Inflammatory Activity. *Mar. Drugs* **2024**, *22*, 433. [CrossRef]
29. Rachman, F.; Wibowo, J.T. Exploring Marine Rare Actinomycetes: Untapped Resources of Bioactive Compounds in Clinical Development. *BIO Web Conf.* **2024**, *92*, 02012. [CrossRef]
30. Rudayni, H.A.; Rabie, A.M.; Aladwani, M.; Alneghery, L.M.; Abu-Taweel, G.M.; Al Zoubi, W.; Allam, A.A.; Abukhadra, M.R.; Bellucci, S. Biological Activities of Sargassum Algae Mediated ZnO and Co Doped ZnO Nanoparticles as Enhanced Antioxidant and Anti-Diabetic Agents. *Molecules* **2023**, *28*, 3692. [CrossRef]
31. Liu, G.; Zhang, S.; Lin, R.; Cao, X.; Yuan, L. Anti-Tumor Target Screening of Sea Cucumber Saponin Frondoside A: A Bioinformatics and Molecular Docking Analysis. *Front. Oncol.* **2023**, *13*, 1307838. [CrossRef]
32. Venkatachalam, J.; Jeyadoss, V.S.; Bose, K.S.C.; Subramanian, R. Marine Seaweed Endophytic Fungi-Derived Active Metabolites Promote Reactive Oxygen Species-Induced Cell Cycle Arrest and Apoptosis in Human Breast Cancer Cells. *Mol. Biol. Rep.* **2024**, *51*, 611. [CrossRef]
33. Lin, X.; Dong, L.; Miao, Q.; Huang, Z.; Wang, F. Cycloheptylprodigiosin from Marine Bacterium Spartinivicinus Ruber MCCC 1K03745T Induces a Novel Form of Cell Death Characterized by Golgi Disruption and Enhanced Secretion of Cathepsin D in Non-Small Cell Lung Cancer Cell Lines. *Eur. J. Pharmacol.* **2024**, *974*, 176608. [CrossRef]
34. Xu, S.; Li, Z.; Xin, X.; An, F. Curdepsidone A Induces Intrinsic Apoptosis and Inhibits Protective Autophagy via the ROS/PI3K/AKT Signaling Pathway in HeLa Cells. *Mar. Drugs* **2024**, *22*, 227. [CrossRef] [PubMed]
35. Lin, H.-J.; Huang, T.-C.; Muthusamy, S.; Lee, J.-F.; Duann, Y.-F.; Lin, C.-H. Piscidin-1, an Antimicrobial Peptide from Fish (Hybrid Striped Bass *Morone saxatilis* x *M. chrysops*), Induces Apoptotic and Necrotic Activity in HT1080 Cells. *Zool. Sci.* **2012**, *29*, 327–332. [CrossRef]
36. Chiu, F.-C.; Kuo, H.-M.; Yu, C.-L.; Selvam, P.; Su, I.-L.; Tseng, C.-C.; Yuan, C.-H.; Wen, Z.-H. Marine-Derived Antimicrobial Peptide Piscidin-1 Triggers Extrinsic and Intrinsic Apoptosis in Oral Squamous Cell Carcinoma through Reactive Oxygen Species Production and Inhibits Angiogenesis. *Free Radic. Biol. Med.* **2024**, *220*, 28–42. [CrossRef]
37. Liu, M.; Li, F.; Feng, S.; Guo, J.; Yu, J.; Zou, S.; Gao, X.; Wei, Y. Evaluation of Anticancer and Immunomodulatory Effects of Microwave-Extracted Polysaccharide from Ruditapes Philippinarum. *Foods* **2024**, *13*, 3552. [CrossRef] [PubMed]
38. Cai, W.-W.; Hu, X.-M.; Wang, Y.-M.; Chi, C.-F.; Wang, B. Bioactive Peptides from Skipjack Tuna Cardiac Arterial Bulbs: Preparation, Identification, Antioxidant Activity, and Stability against Thermal, PH, and Simulated Gastrointestinal Digestion Treatments. *Mar. Drugs* **2022**, *20*, 626. [CrossRef] [PubMed]
39. Suo, S.-K.; Zhao, Y.-Q.; Wang, Y.-M.; Pan, X.-Y.; Chi, C.-F.; Wang, B. Seventeen Novel Angiotensin Converting Enzyme (ACE) Inhibitory Peptides from the Protein Hydrolysate of *Mytilus edulis*: Isolation, Identification, Molecular Docking Study, and Protective Function on HUVECs. *Food Funct.* **2022**, *13*, 7831–7846. [CrossRef] [PubMed]
40. Pavlicevic, M.; Maestri, E.; Marmiroli, M. Marine Bioactive Peptides—An Overview of Generation, Structure and Application with a Focus on Food Sources. *Mar. Drugs* **2020**, *18*, 424. [CrossRef]
41. Shinnar, A.E.; Butler, K.L.; Park, H.J. Cathelicidin Family of Antimicrobial Peptides: Proteolytic Processing and Protease Resistance. *Bioorg. Chem.* **2003**, *31*, 425–436. [CrossRef]
42. Phyo, Y.Z.; Ribeiro, J.; Fernandes, C.; Kijjoa, A.; Pinto, M.M.M. Marine Natural Peptides: Determination of Absolute Configuration Using Liquid Chromatography Methods and Evaluation of Bioactivities. *Molecules* **2018**, *23*, 306. [CrossRef]
43. Arai, M.; Yamano, Y.; Fujita, M.; Setiawan, A.; Kobayashi, M. Stylissamide X, a New Proline-Rich Cyclic Octapeptide as an Inhibitor of Cell Migration, from an Indonesian Marine Sponge of *Stylissa* sp. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1818–1821. [CrossRef]
44. Sable, R.; Parajuli, P.; Jois, S. Peptides, Peptidomimetics, and Polypeptides from Marine Sources: A Wealth of Natural Sources for Pharmaceutical Applications. *Mar. Drugs* **2017**, *15*, 124. [CrossRef] [PubMed]
45. Zagon, J.; Dehne, L.-I.; Bögl, K.-W. D-Amino Acids in Organisms and Food. *Nutr. Res.* **1994**, *14*, 445–463. [CrossRef]
46. Jimenez, E.C. Bromotryptophan and Its Analogs in Peptides from Marine Animals. *Protein Pept. Lett.* **2019**, *26*, 251–260. [CrossRef] [PubMed]
47. Nguyen, B.; Caer, J.-P.; Mourier, G.; Thai, R.; Lamthanh, H.; Servent, D.; Benoit, E.; Molgó, J. Characterization of a Novel Conus Bandanus Conopeptide Belonging to the M-Superfamily Containing Bromotryptophan. *Mar. Drugs* **2014**, *12*, 3449–3465. [CrossRef]
48. Wang, Z.; Xu, Z.; Yang, X.; Li, M.; Yip, R.C.S.; Li, Y.; Chen, H. Current Application and Modification Strategy of Marine Polysaccharides in Tissue Regeneration: A Review. *Biomater. Adv.* **2023**, *154*, 213580. [CrossRef]

49. Ren, X.; Xie, X.; Chen, B.; Liu, L.; Jiang, C.; Qian, Q. Marine Natural Products: A Potential Source of Anti-Hepatocellular Carcinoma Drugs. *J. Med. Chem.* **2021**, *64*, 7879–7899. [CrossRef]
50. Wang, Y.; Guo, X.; Huang, C.; Shi, C.; Xiang, X. Biomedical Potency and Mechanisms of Marine Polysaccharides and Oligosaccharides: A Review. *Int. J. Biol. Macromol.* **2024**, *265*, 131007. [CrossRef] [PubMed]
51. Li, J.; He, Z.; Liang, Y.; Peng, T.; Hu, Z. Insights into Algal Polysaccharides: A Review of Their Structure, Depolymerases, and Metabolic Pathways. *J. Agric. Food Chem.* **2022**, *70*, 1749–1765. [CrossRef]
52. Gozari, M.; Alborz, M.; El-Seedi, H.R.; Jassbi, A.R. Chemistry, Biosynthesis and Biological Activity of Terpenoids and Meroterpenoids in Bacteria and Fungi Isolated from Different Marine Habitats. *Eur. J. Med. Chem.* **2021**, *210*, 112957. [CrossRef]
53. Liu, Y.; Lu, T.; Li, R.; Xu, R.; Baranenko, D.; Yang, L.; Xiao, D. Discovery of Jaspamycin from Marine-Derived Natural Product Based on MTA3 to Inhibit Hepatocellular Carcinoma Progression. *Sci. Rep.* **2024**, *14*, 25294. [CrossRef]
54. Saini, N.; Sirohi, R.; A., A.; Saini, N.; Wadhwa, P.; Kaur, P.; Sharma, V.; Singh, G.; Singh, I.; Sahu, S.K. Marine-Derived Natural Products as Anticancer Agents. *Med. Chem.* **2023**, *19*, 538–555. [CrossRef]
55. Khalifa, S.A.M.; Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.-E.F.; Moustafa, M.S.; Abd El-Wahed, A.; Al-Mousawi, S.M.; Musharraf, S.G.; et al. Marine Natural Products: A Source of Novel Anticancer Drugs. *Mar. Drugs* **2019**, *17*, 491. [CrossRef]
56. Macedo, M.W.F.S.; da Cunha, N.B.; Carneiro, J.A.; Costa, R.A.d.; Alencar, S.A.d.; Cardoso, M.H.; Franco, O.L.; Dias, S.C. Marine Organisms as a Rich Source of Biologically Active Peptides. *Front. Mar. Sci.* **2021**, *8*, 667764. [CrossRef]
57. Tang, L.; Xiao, M.; Cai, S.; Mou, H.; Li, D. Potential Application of Marine Fucosyl-Polysaccharides in Regulating Blood Glucose and Hyperglycemic Complications. *Foods* **2023**, *12*, 2600. [CrossRef] [PubMed]
58. Xia, S.; Zhai, Y.; Wang, X.; Fan, Q.; Dong, X.; Chen, M.; Han, T. Phosphorylation of Polysaccharides: A Review on the Synthesis and Bioactivities. *Int. J. Biol. Macromol.* **2021**, *184*, 946–954. [CrossRef] [PubMed]
59. Banday, A.H.; Azha, N.u.; Farooq, R.; Sheikh, S.A.; Ganie, M.A.; Parray, M.N.; Mushtaq, H.; Hameed, I.; Lone, M.A. Exploring the Potential of Marine Natural Products in Drug Development: A Comprehensive Review. *Phytochem. Lett.* **2024**, *59*, 124–135. [CrossRef]
60. Dalisay, D.S.; Tenebro, C.P.; Sabido, E.M.; Suarez, A.F.L.; Paderog, M.J.V.; Reyes-Salarda, R.; Saludes, J.P. Marine-Derived Anticancer Agents Targeting Apoptotic Pathways: Exploring the Depths for Novel Cancer Therapies. *Mar. Drugs* **2024**, *22*, 114. [CrossRef] [PubMed]
61. Chinnathambi, A.; Salmen, S.H.; Al-Garadi, M.A.; Wainwright, M.; Ali Alharbi, S. Marine Actinomycetes: An Endless Source of Potentially Therapeutic Novel Secondary Metabolites and Other Bioactive Compounds. *J. King Saud Univ. Sci.* **2023**, *35*, 102931. [CrossRef]
62. Ghareeb, A.; Fouda, A.; Kishk, R.M.; El Kazzaz, W.M. Unlocking the Therapeutic Potential of Bioactive Exopolysaccharide Produced by Marine Actinobacterium Streptomyces Vinaceusdrappus AMG31: A Novel Approach to Drug Development. *Int. J. Biol. Macromol.* **2024**, *276*, 133861. [CrossRef]
63. Agena, R.; de Jesús Cortés-Sánchez, A.; Hernández-Sánchez, H.; Jaramillo-Flores, M.E. Pro-Apoptotic Activity of Bioactive Compounds from Seaweeds: Promising Sources for Developing Novel Anticancer Drugs. *Mar. Drugs* **2023**, *21*, 182. [CrossRef]
64. Basha, A.N.; Akhir, F.N.M.; Othman, N.; Hara, H. Anticancer Potential of Bioactive Compounds from Microalgae. A Review. *J. Adv. Res. Micro Nano Eng.* **2024**, *20*, 1–9. [CrossRef]
65. Fu, Y.; Jiao, H.; Sun, J.; Okoye, C.O.; Zhang, H.; Li, Y.; Lu, X.; Wang, Q.; Liu, J. Structure-Activity Relationships of Bioactive Polysaccharides Extracted from Macroalgae towards Biomedical Application: A Review. *Carbohydr. Polym.* **2024**, *324*, 121533. [CrossRef] [PubMed]
66. Khursheed, M.; Ghelani, H.; Jan, R.K.; Adrian, T.E. Anti-Inflammatory Effects of Bioactive Compounds from Seaweeds, Bryozoans, Jellyfish, Shellfish and Peanut Worms. *Mar. Drugs* **2023**, *21*, 524. [CrossRef] [PubMed]
67. Deshmukh, S.K.; Prakash, V.; Ranjan, N. Marine Fungi: A Source of Potential Anticancer Compounds. *Front. Microbiol.* **2018**, *8*, 2536. [CrossRef]
68. Noman, E.; Al-Shaibani, M.M.; Bakhrebah, M.A.; Almoheer, R.; Al-Sahari, M.; Al-Gheethi, A.; Radin Mohamed, R.M.S.; Almulaiky, Y.Q.; Abdulaal, W.H. Potential of Anti-Cancer Activity of Secondary Metabolic Products from Marine Fungi. *J. Fungi* **2021**, *7*, 436. [CrossRef]
69. Dembitsky, V.M. Bioactive Diepoxy Metabolites and Highly Oxygenated Triterpenoids from Marine and Plant-Derived Bacteria and Fungi. *Microbiol. Res.* **2023**, *15*, 66–90. [CrossRef]
70. Elgoud Said, A.A.; Mahmoud, B.K.; Attia, E.Z.; Abdelmohsen, U.R.; Fouad, M.A. Bioactive Natural Products from Marine Sponges Belonging to Family Hymedesmiidae. *RSC Adv.* **2021**, *11*, 16179–16191. [CrossRef]
71. Esposito, R.; Federico, S.; Glaviano, F.; Somma, E.; Zupo, V.; Costantini, M. Bioactive Compounds from Marine Sponges and Algae: Effects on Cancer Cell Metabolome and Chemical Structures. *Int. J. Mol. Sci.* **2022**, *23*, 10680. [CrossRef]
72. Barzkar, N.; Sukhikh, S.; Babich, O. Study of Marine Microorganism Metabolites: New Resources for Bioactive Natural Products. *Front. Microbiol.* **2024**, *14*, 1285902. [CrossRef]
73. Rafieezadeh, D. Marine Bioactive Peptides with Anticancer Potential, a Narrative Review. *Int. J. Biochem. Mol. Biol.* **2024**, *15*, 118–126. [CrossRef]
74. Rai, T.; Kaushik, N.; Malviya, R.; Sharma, P.K. A Review on Marine Source as Anticancer Agents. *J. Asian Nat. Prod. Res.* **2024**, *26*, 415–451. [CrossRef] [PubMed]
75. Ortigosa-Palomo, A.; Quiñonero, F.; Ortiz, R.; Sarabia, F.; Prados, J.; Melguizo, C. Natural Products Derived from Marine Sponges with Antitumor Potential against Lung Cancer: A Systematic Review. *Mar. Drugs* **2024**, *22*, 101. [CrossRef] [PubMed]

76. Elissawy, A.M.; Soleiman Dehkordi, E.; Mehdinezhad, N.; Ashour, M.L.; Pour, P.M. Biomolecules Cytotoxic Alkaloids Derived from Marine Sponges: A Comprehensive Review. *Biomolecules* **2021**, *11*, 258. [CrossRef] [PubMed]
77. Sasikumar, P.; Aparna, V.; Sebastian, A.T.; Muneer, A.; Prabha, B.; Vipin, C.L.; Ijinu, T.P. Clinically Tested Marine Mollusk-Derived Anticancer Agents: Chemico-Pharmacological Aspects. *Stud. Nat. Prod. Chem.* **2024**, *83*, 95–131. [CrossRef]
78. Romano, G.; Almeida, M.; Coelho, A.V.; Cutignano, A.; Gonçalves, L.G.; Hansen, E.; Khnykin, D.; Mass, T.; Ramšak, A.; Rocha, M.S.; et al. Biomaterials and Bioactive Natural Products from Marine Invertebrates: From Basic Research to Innovative Applications. *Mar. Drugs* **2022**, *20*, 219. [CrossRef]
79. Avhad, A.B.; Bhangale, C.J. Marine Natural Products and Derivatives. *RPS Pharm. Pharmacol. Rep.* **2023**, *2*, rqad008. [CrossRef]
80. Wang, E.; Sorolla, M.A.; Krishnan, P.D.G.; Sorolla, A. From Seabed to Bedside: A Review on Promising Marine Anticancer Compounds. *Biomolecules* **2020**, *10*, 248. [CrossRef]
81. Barzkar, N.; Sukhikh, S.; Babich, O. A Comprehensive Review of Marine Sponge Metabolites, with Emphasis on *Neopetrosia* sp. *Int. J. Biol. Macromol.* **2024**, *280*, 135823. [CrossRef]
82. Son, K.; Takhaveev, V.; Mor, V.; Yu, H.; Dillier, E.; Zilio, N.; Püllen, N.J.L.; Ivanov, D.; Ulrich, H.D.; Sturla, S.J.; et al. Trabectedin Derails Transcription-Coupled Nucleotide Excision Repair to Induce DNA Breaks in Highly Transcribed Genes. *Nat. Commun.* **2024**, *15*, 1388. [CrossRef]
83. Alsalmi, O.; Mashraqi, M.M.; Alshamrani, S.; Almasoudi, H.H.; Alharthi, A.A.; Gharib, A.F. Variolin B from Sea Sponge against Lung Cancer: A Multitargeted Molecular Docking with Fingerprinting and Molecular Dynamics Simulation Study. *J. Biomol. Struct. Dyn.* **2024**, *42*, 3507–3519. [CrossRef]
84. Zayed, A.O.H.; Altarabeen, M.; AlShamaileh, E.; Zain, S.M. The Potential of Some Functional Group Compounds Substituted 8-Manzamine A as RSK1 Inhibitors: Molecular Docking and Molecular Dynamics Simulations. *J. Biomol. Struct. Dyn.* **2024**, 1–10. [CrossRef] [PubMed]
85. Rahman, N.I.A.; Ramzi, M.M.; Rawi, N.N.; Siong, J.Y.F.; Bakar, K.; Bhubalan, K.; Ariffin, F.; Saidin, J.; Azemi, A.K.; Ismail, N. Characterization of Antibiofilm Compound from Marine Sponge Stylissa Carteri. *Environ. Sci. Pollut. Res.* **2024**, *31*, 37552–37563. [CrossRef] [PubMed]
86. Wibowo, J.T.; Bayu, A.; Aryati, W.D.; Fernandes, C.; Yanuar, A.; Kijjoa, A.; Putra, M.Y. Secondary Metabolites from Marine-Derived Bacteria with Antibiotic and Antibiofilm Activities against Drug-Resistant Pathogens. *Mar. Drugs* **2023**, *21*, 50. [CrossRef] [PubMed]
87. Sivaganesan, P.; VL, S.; Sahoo, A.; Elanchezhian, C.; Nataraj, G.; Chaudhuri, S. A Comprehensive Review of Synthetic Approaches Toward Lamellarin D and Its Analogous. *ChemistrySelect* **2024**, *9*, e202403112. [CrossRef]
88. Ghosh, S.; Das, D.; Mandal, R.D.; Das, A.R. Harnessing the Benzyne Insertion Consequence to Enable π-Extended Pyrido-Acridine and Quinazolino-Phenanthridine. *Org. Biomol. Chem.* **2024**, *22*, 5591–5602. [CrossRef]
89. Singh, A.; Singh, J.; Parween, G.; Khator, R.; Monga, V. A Comprehensive Review of Apigenin a Dietary Flavonoid: Biological Sources, Nutraceutical Prospects, Chemistry and Pharmacological Insights and Health Benefits. *Crit. Rev. Food Sci. Nutr.* **2024**, 1–37. [CrossRef]
90. Chen, M.; Xiao, J.; El-Seedi, H.R.; Woźniak, K.S.; Daglia, M.; Little, P.J.; Weng, J.; Xu, S. Kaempferol and Atherosclerosis: From Mechanism to Medicine. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 2157–2175. [CrossRef]
91. Rivera-Pérez, C.; Ponce González, X.P.; Hernández-Savedra, N.Y. Antimicrobial and Anticarcinogenic Activity of Bioactive Peptides Derived from Abalone Viscera (*Haliotis fulgens* and *Haliotis corrugata*). *Sci. Rep.* **2023**, *13*, 15185. [CrossRef]
92. Zhu, X.; Ding, G.; Ren, S.; Xi, J.; Liu, K. The Bioavailability, Absorption, Metabolism, and Regulation of Glucolipid Metabolism Disorders by Quercetin and Its Important Glycosides: A Review. *Food Chem.* **2024**, *458*, 140262. [CrossRef]
93. Yin, Q.; Qin, W.; Liu, T.; Song, W.; Yang, Y.; Shan, W.; Kuang, J.; Chen, J.; Lu, W. MaMYB4 Is Involved in the Accumulation of Naringenin Chalcone, Phloretin and Dihydrokaempferol in the Peels of Banana Fruit under Chilling Injury. *Postharvest Biol. Technol.* **2024**, *212*, 112844. [CrossRef]
94. Mod Razif, M.R.F.; Chan, S.Y.; Chew, Y.-L.; Hassan, M.; Ahmad Hisham, S.; Abdul Rahman, S.; Mai, C.-W.; Teo, M.Y.M.; Kee, P.E.; Khoo, K.S.; et al. Recent Developments in Luteolin-Loaded Nanoformulations for Enhanced Anti-Carcinogenic Activities: Insights from In Vitro and In Vivo Studies. *Sci* **2024**, *6*, 68. [CrossRef]
95. Trivedi, M.; Vasani, P.; Sonowal, A.; Mukherjee, R.; Chatterjee, A.; Banerjee, D. Marine Biotherapeutics: Delving Into The Vast Untapped Resource Of Therapeutic Molecules Showing Better Outcomes Against Diseases. *Educ. Adm. Theory Pract.* **2024**, *30*, 01–07. [CrossRef]
96. Yu, H.; Zhang, Q.; Farooqi, A.A.; Wang, J.; Yue, Y.; Geng, L.; Wu, N. Opportunities and Challenges of Fucoidan for Tumors Therapy. *Carbohydr. Polym.* **2024**, *324*, 121555. [CrossRef] [PubMed]
97. Unger-Manhart, N.; Morokutti-Kurz, M.; Zieglmayer, P.; Lemell, P.; Savli, M.; Zieglmayer, R.; Prieschl-Grassauer, E. Carrageenan-Containing Nasal Spray Alleviates Allergic Symptoms in Participants with Grass Pollen Allergy: A Randomized, Controlled, Crossover Clinical Trial. *Int. J. Gen. Med.* **2024**, *17*, 419–428. [CrossRef] [PubMed]
98. Vasconcelos, A.D.; Donado-Pestana, C.M.; More, T.H.; Duarte, G.B.S.; Duarte, S.G.; Dias, C.G.; Rodrigues, L.; Hernandez, G.N.; Fock, R.; Hiller, K.; et al. D-Limonene Supplementation Does Not Alter Postprandial Metabolism of Postmenopausal Women Challenged with a Mixed Macronutrient Tolerance Test: A Pilot Study. *Food Prod. Process. Nutr.* **2024**, *6*, 26. [CrossRef]

99. Nagarajan, P.; Louis, L.R.P.; Patil, S.J.; Adam, J.K.; Krishna, S.B.N. Therapeutic Potential of Biologically Active Peptides from Marine Organisms for Biomedical Applications. In *Studies in Natural Products Chemistry*; Elsevier B.V.: Amsterdam, The Netherlands, 2024; Volume 81, pp. 467–500.
100. Malyarenko, T.V.; Kicha, A.A.; Kuzmich, A.S.; Malyarenko, O.S.; Kalinovsky, A.I.; Popov, R.S.; Dmitrenok, P.S.; Ivanchina, N.V.; Stonik, V.A. New Rare Triterpene Glycosides from Pacific Sun Star, Solaster Pacificus, and Their Anticancer Activity. *Mar. Drugs* **2024**, *22*, 19. [CrossRef] [PubMed]
101. Menchinskaya, E.S.; Dyshlovoy, S.A.; Venz, S.; Jacobsen, C.; Hauschild, J.; Rohlfing, T.; Silchenko, A.S.; Avilov, S.A.; Balabanov, S.; Bokemeyer, C.; et al. Anticancer Activity of the Marine Triterpene Glycoside Cucumarioside A2-2 in Human Prostate Cancer Cells. *Mar. Drugs* **2024**, *22*, 20. [CrossRef]
102. Niu, F.; Xie, W.; Zhang, W.; Kawuki, J.; Yu, X. Vitamin C, Vitamin E, β-Carotene and Risk of Parkinson's Disease: A Systematic Review and Dose–Response Meta-Analysis of Observational Studies. *Nutr. Neurosci.* **2024**, *27*, 329–341. [CrossRef] [PubMed]
103. Ngamcharungchit, C.; Chaimusik, N.; Panbangred, W.; Euanorasetr, J.; Intra, B. Bioactive Metabolites from Terrestrial and Marine Actinomycetes. *Molecules* **2023**, *28*, 5915. [CrossRef]
104. Ramu, A.K.; Rajendran, R.; Sivalingam, A.M.; Seshadri, V.D.; Bakrudeen Ali Ahmed, A. Anticancer Potentiated Bioactive Compounds from Marine Flora. In *Marine Antioxidants: Preparations, Syntheses, and Applications*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 421–432, ISBN 9780323950862.
105. Goutzourelas, N.; Kevrekidis, D.P.; Barda, S.; Malea, P.; Trachana, V.; Savvidi, S.; Kevrekidou, A.; Assimopoulou, A.N.; Goutas, A.; Liu, M.; et al. Antioxidant Activity and Inhibition of Liver Cancer Cells' Growth of Extracts from 14 Marine Macroalgae Species of the Mediterranean Sea. *Foods* **2023**, *12*, 1310. [CrossRef]
106. Hsiao, H.H.; Wu, T.C.; Tsai, Y.H.; Kuo, C.H.; Huang, R.H.; Hong, Y.H.; Huang, C.Y. Effect of Oversulfation on the Composition, Structure, and In Vitro Anti-Lung Cancer Activity of Fucoidans Extracted from Sargassum Aquifolium. *Mar. Drugs* **2021**, *19*, 215. [CrossRef]
107. Hussain, A.; Bourguet-Kondracki, M.L.; Majeed, M.; Ibrahim, M.; Imran, M.; Yang, X.W.; Ahmed, I.; Altaf, A.A.; Khalil, A.A.; Rauf, A.; et al. Marine Life as a Source for Breast Cancer Treatment: A Comprehensive Review. *Biomed. Pharmacother.* **2023**, *159*, 114165. [CrossRef]
108. Dissanayake, D.S.; Nagahawatta, D.P.; Lee, J.-S.; Jeon, Y.-J. Immunomodulatory Effects of Halichondrin Isolated from Marine Sponges and Its Synthetic Analogs in Oncological Applications. *Mar. Drugs* **2024**, *22*, 426. [CrossRef]
109. Ibrahim, W.M.; Olama, Z.A.; Abou-elela, G.M.; Ramadan, H.S.; Hegazy, G.E.; El Badan, D.E.S. Exploring the Antimicrobial, Antiviral, Antioxidant, and Antitumor Potentials of Marine Streptomyces Tunisiensis W4MT573222 Pigment Isolated from Abu-Qir Sediments, Egypt. *Microb. Cell Fact.* **2023**, *22*, 94. [CrossRef] [PubMed]
110. Flores-Contreras, E.A.; Araújo, R.G.; Rodríguez-Aguayo, A.A.; Guzmán-Román, M.; García-Venegas, J.C.; Nájera-Martínez, E.F.; Sosa-Hernández, J.E.; Iqbal, H.M.N.; Melchor-Martínez, E.M.; Parra-Saldivar, R. Polysaccharides from the Sargassum and Brown Algae Genus: Extraction, Purification, and Their Potential Therapeutic Applications. *Plants* **2023**, *12*, 2445. [CrossRef] [PubMed]
111. Elshiekh, R.M.; Elissawy, A.M.; Nasser, A.; Singab, B. Unearthing the Potential Fungal Bioactive Secondary Metabolites from the Red Sea: A Comprehensive Review. *Arch. Pharm. Sci. Ain Shams Univ.* **2023**, *7*, 254–273. [CrossRef]
112. Dolcet, X.; Llobet, D.; Pallares, J.; Matias-Guiu, X. NF-KB in Development and Progression of Human Cancer. *Virchows Arch.* **2005**, *446*, 475–482. [CrossRef] [PubMed]
113. Orlikova, B.; Tasdemir, D.; Golais, F.; Dicato, M.; Diederich, M. The Aromatic Ketone 4′-Hydroxychalcone Inhibits TNFα-Induced NF-KB Activation via Proteasome Inhibition. *Biochem. Pharmacol.* **2011**, *82*, 620–631. [CrossRef]
114. Hoesel, B.; Schmid, J.A. The Complexity of NF-KB Signaling in Inflammation and Cancer. *Mol. Cancer* **2013**, *12*, 86. [CrossRef]
115. Giridharan, S.; Srinivasan, M. Mechanisms of NF-κB P65 and Strategies for Therapeutic Manipulation. *J. Inflamm. Res.* **2018**, *11*, 407–419. [CrossRef]
116. Wei, J.; Liu, Y.; Teng, F.; Li, L.; Zhong, S.; Luo, H.; Huang, Z. Anticancer Effects of Marine Compounds Blocking the Nuclear Factor Kappa B Signaling Pathway. *Mol. Biol. Rep.* **2022**, *49*, 9975–9995. [CrossRef] [PubMed]
117. Kandel, E.S.; Hay, N. The Regulation and Activities of the Multifunctional Serine/Threonine Kinase Akt/PKB. *Exp. Cell Res.* **1999**, *253*, 210–229. [CrossRef]
118. Luo, J.; Manning, B.D.; Cantley, L.C. Targeting the PI3K-Akt Pathway in Human Cancer. *Cancer Cell* **2003**, *4*, 257–262. [CrossRef]
119. Fruman, D.A.; Chiu, H.; Hopkins, B.D.; Bagrodia, S.; Cantley, L.C.; Abraham, R.T. The PI3K Pathway in Human Disease. *Cell* **2017**, *170*, 605–635. [CrossRef] [PubMed]
120. Hay, N. The Akt-MTOR Tango and Its Relevance to Cancer. *Cancer Cell* **2005**, *8*, 179–183. [CrossRef] [PubMed]
121. Vivanco, I.; Sawyers, C.L. The Phosphatidylinositol 3-Kinase–AKT Pathway in Human Cancer. *Nat. Rev. Cancer* **2002**, *2*, 489–501. [CrossRef]
122. Wei, J.; Gou, Z.; Wen, Y.; Luo, Q.; Huang, Z. Marine Compounds Targeting the PI3K/Akt Signaling Pathway in Cancer Therapy. *Biomed. Pharmacother.* **2020**, *129*, 110484. [CrossRef]
123. Parate, S.; Kumar, V.; Lee, G.; Rampogu, S.; Hong, J.C.; Lee, K.W. Marine-Derived Natural Products as ATP-Competitive MTOR Kinase Inhibitors for Cancer Therapeutics. *Pharmaceuticals* **2021**, *14*, 282. [CrossRef]
124. Sabatini, D.M. MTOR and Cancer: Insights into a Complex Relationship. *Nat. Rev. Cancer* **2006**, *6*, 729–734. [CrossRef] [PubMed]
125. Abraham, R.T.; Gibbons, J.J. The Mammalian Target of Rapamycin Signaling Pathway: Twists and Turns in the Road to Cancer Therapy. *Clin. Cancer Res.* **2007**, *13*, 3109–3114. [CrossRef]

126. Kim, L.C.; Cook, R.S.; Chen, J. MTORC1 and MTORC2 in Cancer and the Tumor Microenvironment. *Oncogene* **2017**, *36*, 2191–2201. [CrossRef] [PubMed]
127. Ly, J.D.; Grubb, D.R.; Lawen, A. The Mitochondrial Membrane Potential (Δψm) in Apoptosis; an Update. *Apoptosis* **2003**, *8*, 115–128. [CrossRef] [PubMed]
128. Elmore, S. Apoptosis: A Review of Programmed Cell Death. *Toxicol. Pathol.* **2007**, *35*, 495–516. [CrossRef] [PubMed]
129. Saelens, X.; Festjens, N.; Walle, L.V.; Gurp, M.v.; Van Loo, G.; Vandenabeele, P. Toxic Proteins Released from Mitochondria in Cell Death. *Oncogene* **2004**, *23*, 2861–2874. [CrossRef]
130. Du, C.; Fang, M.; Li, Y.; Li, L.; Wang, X. Smac, a Mitochondrial Protein That Promotes Cytochrome c–Dependent Caspase Activation by Eliminating IAP Inhibition. *Cell* **2000**, *102*, 33–42. [CrossRef]
131. van Loo, G.; van Gurp, M.; Depuydt, B.; Srinivasula, S.M.; Rodriguez, I.; Alnemri, E.S.; Gevaert, K.; Vandekerckhove, J.; Declercq, W.; Vandenabeele, P. The Serine Protease Omi/HtrA2 Is Released from Mitochondria during Apoptosis. Omi Interacts with Caspase-Inhibitor XIAP and Induces Enhanced Caspase Activity. *Cell Death Differ.* **2002**, *9*, 20–26. [CrossRef]
132. Cai, J.; Yang, J.; Jones, D.P. Mitochondrial Control of Apoptosis: The Role of Cytochrome c. *Biochim. Biophys. Acta (BBA)-Bioenerg.* **1998**, *1366*, 139–149. [CrossRef]
133. Garrido, C.; Galluzzi, L.; Brunet, M.; Puig, P.E.; Didelot, C.; Kroemer, G. Mechanisms of Cytochrome c Release from Mitochondria. *Cell Death Differ* **2006**, *13*, 1423–1433. [CrossRef]
134. Chinnaiyan, A.M. The Apoptosome: Heart and Soul of the Cell Death Machine. *Neoplasia* **1999**, *1*, 5–15. [CrossRef]
135. Hill, M.M.; Adrain, C.; Duriez, P.J.; Creagh, E.M.; Martin, S.J. Analysis of the Composition, Assembly Kinetics and Activity of Native Apaf-1 Apoptosomes. *EMBO J.* **2004**, *23*, 2134–2145. [CrossRef]
136. Schimmer, A.D. Inhibitor of Apoptosis Proteins: Translating Basic Knowledge into Clinical Practice. *Cancer Res.* **2004**, *64*, 7183–7190. [CrossRef]
137. Joza, N.; Susin, S.A.; Daugas, E.; Stanford, W.L.; Cho, S.K.; Li, C.Y.J.; Sasaki, T.; Elia, A.J.; Cheng, H.-Y.M.; Ravagnan, L.; et al. Essential Role of the Mitochondrial Apoptosis-Inducing Factor in Programmed Cell Death. *Nature* **2001**, *410*, 549–554. [CrossRef]
138. Susin, S.A.; Daugas, E.; Ravagnan, L.; Samejima, K.; Zamzami, N.; Loeffler, M.; Costantini, P.; Ferri, K.F.; Irinopoulou, T.; Prévost, M.-C.; et al. Two Distinct Pathways Leading to Nuclear Apoptosis. *J. Exp. Med.* **2000**, *192*, 571–580. [CrossRef] [PubMed]
139. Li, L.Y.; Luo, X.; Wang, X. Endonuclease G Is an Apoptotic DNase When Released from Mitochondria. *Nature* **2001**, *412*, 95–99. [CrossRef] [PubMed]
140. Enari, M.; Sakahira, H.; Yokoyama, H.; Okawa, K.; Iwamatsu, A.; Nagata, S. A Caspase-Activated DNase That Degrades DNA during Apoptosis, and Its Inhibitor ICAD. *Nature* **1998**, *391*, 43–50. [CrossRef] [PubMed]
141. Cory, S.; Adams, J.M. The Bcl2 Family: Regulators of the Cellular Life-or-Death Switch. *Nat. Rev. Cancer* **2002**, *2*, 647–656. [CrossRef]
142. Schuler, M.; Green, D.R. Mechanisms of P53-Dependent Apoptosis. *Biochem. Soc. Trans.* **2001**, *29*, 684. [CrossRef]
143. Nova, P.; Gomes, A.M.; Costa-Pinto, A.R. It Comes from the Sea: Macroalgae-Derived Bioactive Compounds with Anti-Cancer Potential. *Crit. Rev. Biotechnol.* **2024**, *44*, 462–476. [CrossRef]
144. Delma, C.R.; Somasundaram, S.T.; Srinivasan, G.P.; Khursheed, M.; Bashyam, M.D.; Aravindan, N. Fucoidan from Turbinaria Conoides: A Multifaceted 'Deliverable' to Combat Pancreatic Cancer Progression. *Int. J. Biol. Macromol.* **2015**, *74*, 447–457. [CrossRef]
145. Delma, C.R.; Thirugnanasambandan, S.; Srinivasan, G.P.; Raviprakash, N.; Manna, S.K.; Natarajan, M.; Aravindan, N. Fucoidan from Marine Brown Algae Attenuates Pancreatic Cancer Progression by Regulating P53–NFκB Crosstalk. *Phytochemistry* **2019**, *167*, 112078. [CrossRef] [PubMed]
146. Kong, C.-S.; Kim, J.-A.; Yoon, N.-Y.; Kim, S.-K. Induction of Apoptosis by Phloroglucinol Derivative from Ecklonia Cava in MCF-7 Human Breast Cancer Cells. *Food Chem. Toxicol.* **2009**, *47*, 1653–1658. [CrossRef]
147. Wang, C.; Li, X.; Jin, L.; Zhao, Y.; Zhu, G.; Shen, W. Dieckol Inhibits Non-small–Cell Lung Cancer Cell Proliferation and Migration by Regulating the PI3K/AKT Signaling Pathway. *J. Biochem. Mol. Toxicol.* **2019**, *33*, e22346. [CrossRef]
148. Xu, J.W.; Yan, Y.; Wang, L.; Wu, D.; Ye, N.K.; Chen, S.H.; Li, F. Marine Bioactive Compound Dieckol Induces Apoptosis and Inhibits the Growth of Human Pancreatic Cancer Cells PANC-1. *J. Biochem. Mol. Toxicol.* **2021**, *35*, e22648. [CrossRef]
149. Wu, T.-C.; Hong, Y.-H.; Tsai, Y.-H.; Hsieh, S.-L.; Huang, R.-H.; Kuo, C.-H.; Huang, C.-Y. Degradation of Sargassum Crassifolium Fucoidan by Ascorbic Acid and Hydrogen Peroxide, and Compositional, Structural, and In Vitro Anti-Lung Cancer Analyses of the Degradation Products. *Mar. Drugs* **2020**, *18*, 334. [CrossRef]
150. Eo, H.J.; Kwon, T.-H.; Park, G.H.; Song, H.M.; Lee, S.-J.; Park, N.-H.; Jeong, J.B. In Vitro Anticancer Activity of Phlorofucofuroeckol A via Upregulation of Activating Transcription Factor 3 against Human Colorectal Cancer Cells. *Mar. Drugs* **2016**, *14*, 69. [CrossRef]
151. Ku, H.-C.; Cheng, C.-F. Master Regulator Activating Transcription Factor 3 (ATF3) in Metabolic Homeostasis and Cancer. *Front. Endocrinol.* **2020**, *11*, 556. [CrossRef]
152. Liao, W.; Chen, Y.; Shan, S.; Chen, Z.; Wen, Y.; Chen, W.; Zhao, C. Marine Algae-derived Characterized Bioactive Compounds as Therapy for Cancer: A Review on Their Classification, Mechanism of Action, and Future Perspectives. *Phytother. Res.* **2024**, *38*, 4053–4080. [CrossRef] [PubMed]
153. Cruz, L.J.; Luque-Ortega, J.R.; Rivas, L.; Albericio, F. Kahalalide F, an Antitumor Depsipeptide in Clinical Trials, and Its Analogues as Effective Antileishmanial Agents. *Mol. Pharm.* **2009**, *6*, 813–824. [CrossRef] [PubMed]

154. García-Rocha, M.; Bonay, P.; Avila, J. The Antitumoral Compound Kahalalide F Acts on Cell Lysosomes. *Cancer Lett.* **1996**, *99*, 43–50. [CrossRef]
155. Sun, X.; Zhong, Y.; Luo, H.; Yang, Y. Selenium-Containing Polysaccharide-Protein Complex in Se-Enriched Ulva Fasciata Induces Mitochondria-Mediated Apoptosis in A549 Human Lung Cancer Cells. *Mar. Drugs* **2017**, *15*, 215. [CrossRef] [PubMed]
156. Kim, Y.-M.; Kim, I.-H.; Nam, T.-J. Inhibition of AGS Human Gastric Cancer Cell Invasion and Proliferation by Capsosiphon Fulvescens Glycoprotein. *Mol. Med. Rep.* **2013**, *8*, 11–16. [CrossRef]
157. Blunt, J.W.; Copp, B.R.; Hu, W.-P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2009**, *26*, 170. [CrossRef]
158. Kang, Y.; Wang, Z.-J.; Xie, D.; Sun, X.; Yang, W.; Zhao, X.; Xu, N. Characterization and Potential Antitumor Activity of Polysaccharide from Gracilariopsis Lemaneiformis. *Mar. Drugs* **2017**, *15*, 100. [CrossRef] [PubMed]
159. S.M., F.M.B.; Chitra, K.; Joseph, B.; Sundararajan, R.; S., H. Gelidiella Acerosa Inhibits Lung Cancer Proliferation. *BMC Complement. Altern. Med.* **2018**, *18*, 104. [CrossRef]
160. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2006**, *23*, 26. [CrossRef] [PubMed]
161. Tarhouni-Jabberi, S.; Zakraoui, O.; Ioannou, E.; Riahi-Chebbi, I.; Haoues, M.; Roussis, V.; Kharrat, R.; Essafi-Benkhadir, K. Mertensene, a Halogenated Monoterpene, Induces G2/M Cell Cycle Arrest and Caspase Dependent Apoptosis of Human Colon Adenocarcinoma HT29 Cell Line through the Modulation of ERK-1/-2, AKT and NF-KB Signaling. *Mar. Drugs* **2017**, *15*, 221. [CrossRef]
162. Palozza, P.; Torelli, C.; Boninsegna, A.; Simone, R.; Catalano, A.; Mele, M.C.; Picci, N. Growth-Inhibitory Effects of the Astaxanthin-Rich Alga Haematococcus Pluvialis in Human Colon Cancer Cells. *Cancer Lett.* **2009**, *283*, 108–117. [CrossRef] [PubMed]
163. Vundru, S.S.; Kale, R.K.; Singh, R.P. β-Sitosterol Induces G1 Arrest and Causes Depolarization of Mitochondrial Membrane Potential in Breast Carcinoma MDA-MB-231 Cells. *BMC Complement. Altern. Med.* **2013**, *13*, 280. [CrossRef] [PubMed]
164. Laube, T.; Beil, W.; Seifert, K. Total Synthesis of Two 12-Nordrimanes and the Pharmacological Active Sesquiterpene Hydroquinone Yahazunol. *Tetrahedron* **2005**, *61*, 1141–1148. [CrossRef]
165. Velatooru, L.R.; Baggu, C.B.; Janapala, V.R. Spatane Diterpinoid from the Brown Algae, *Stoechospermum Marginatum* Induces Apoptosis via ROS Induced Mitochondrial Mediated Caspase Dependent Pathway in Murine B16F10 Melanoma Cells. *Mol. Carcinog.* **2016**, *55*, 2222–2235. [CrossRef]
166. Geisen, U.; Zenthoefer, M.; Peipp, M.; Kerber, J.; Plenge, J.; Managò, A.; Fuhrmann, M.; Geyer, R.; Hennig, S.; Adam, D.; et al. Molecular Mechanisms by Which a Fucus Vesiculosus Extract Mediates Cell Cycle Inhibition and Cell Death in Pancreatic Cancer Cells. *Mar. Drugs* **2015**, *13*, 4470–4491. [CrossRef]
167. Shi, D.; Li, J.; Guo, S.; Su, H.; Fan, X. The Antitumor Effect of Bromophenol Derivatives in Vitro and Leathesia Nana Extract in Vivo. *Chin. J. Oceanol. Limnol.* **2009**, *27*, 277–282. [CrossRef]
168. Xu, X.; Song, F.; Wang, S.; Li, S.; Xiao, F.; Zhao, J.; Yang, Y.; Shang, S.; Yang, L.; Shi, J. Dibenzyl Bromophenols with Diverse Dimerization Patterns from the Brown Alga *Leathesia nana*. *J. Nat. Prod.* **2004**, *67*, 1661–1666. [CrossRef]
169. Sheikh, E.; Tran, T.; Vranic, S.; Levy, A.; Bonfil, R.D. Role and Significance of C-KIT Receptor Tyrosine Kinase in Cancer: A Review. *Bosn. J. Basic Med. Sci.* **2022**, *22*, 683–698. [CrossRef] [PubMed]
170. Kim, E.J.; Park, S.Y.; Lee, J.-Y.; Park, J.H.Y. Fucoidan Present in Brown Algae Induces Apoptosis of Human Colon Cancer Cells. *BMC Gastroenterol.* **2010**, *10*, 96. [CrossRef] [PubMed]
171. Lin, Y.; Qi, X.; Liu, H.; Xue, K.; Xu, S.; Tian, Z. The Anti-Cancer Effects of Fucoidan: A Review of Both in Vivo and in Vitro Investigations. *Cancer Cell Int.* **2020**, *20*, 154. [CrossRef] [PubMed]
172. Huang, T.-H.; Chiu, Y.-H.; Chan, Y.-L.; Chiu, Y.-H.; Wang, H.; Huang, K.-C.; Li, T.-L.; Hsu, K.-H.; Wu, C.-J. Prophylactic Administration of Fucoidan Represses Cancer Metastasis by Inhibiting Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMPs) in Lewis Tumor-Bearing Mice. *Mar. Drugs* **2015**, *13*, 1882–1900. [CrossRef] [PubMed]
173. Rui, X.; Pan, H.-F.; Shao, S.-L.; Xu, X.-M. Anti-Tumor and Anti-Angiogenic Effects of Fucoidan on Prostate Cancer: Possible JAK-STAT3 Pathway. *BMC Complement. Altern. Med.* **2017**, *17*, 378. [CrossRef]
174. Atashrazm, F.; Lowenthal, R.M.; Woods, G.M.; Holloway, A.F.; Karpiniec, S.S.; Dickinson, J.L. Fucoidan Suppresses the Growth of Human Acute Promyelocytic Leukemia Cells In Vitro and In Vivo. *J. Cell. Physiol.* **2016**, *231*, 688–697. [CrossRef]
175. Albensi, B.C. What Is Nuclear Factor Kappa B (NF-KB) Doing in and to the Mitochondrion? *Front. Cell Dev. Biol.* **2019**, *7*, 154. [CrossRef]
176. Silke, J.; O'Reilly, L.A. NF-KB and Pancreatic Cancer; Chapter and Verse. *Cancers* **2021**, *13*, 4510. [CrossRef] [PubMed]
177. Wang, K.; Wang, B.; Wang, Z.; Yang, R. Alginic Acid Inhibits Non-Small Cell Lung Cancer-Induced Angiogenesis via Activating MiR-506 Expression. *J. Nat. Med.* **2021**, *75*, 553–564. [CrossRef] [PubMed]
178. Wang, J.; Ma, Y.; Yang, J.; Jin, L.; Gao, Z.; Xue, L.; Hou, L.; Sui, L.; Liu, J.; Zou, X. Fucoxanthin Inhibits Tumour-related Lymphangiogenesis and Growth of Breast Cancer. *J. Cell. Mol. Med.* **2019**, *23*, 2219–2229. [CrossRef] [PubMed]
179. Malyarenko, O.S.; Imbs, T.I.; Ermakova, S.P. In Vitro Anticancer and Radiosensitizing Activities of Phlorethols from the Brown Alga Costaria Costata. *Molecules* **2020**, *25*, 3208. [CrossRef] [PubMed]
180. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2005**, *22*, 15. [CrossRef]

181. López-Macià, À.; Jiménez, J.C.; Royo, M.; Giralt, E.; Albericio, F. Synthesis and Structure Determination of Kahalalide F [1,2]. *J. Am. Chem. Soc.* **2001**, *123*, 11398–11401. [CrossRef]
182. Pardo, B.; Paz-Ares, L.; Tabernero, J.; Ciruelos, E.; García, M.; Salazar, R.; López, A.; Blanco, M.; Nieto, A.; Jimeno, J.; et al. Phase I Clinical and Pharmacokinetic Study of Kahalalide F Administered Weekly as a 1-Hour Infusion to Patients with Advanced Solid Tumors. *Clin. Cancer Res.* **2008**, *14*, 1116–1123. [CrossRef]
183. Rademaker-Lakhai, J.M.; Horenblas, S.; Meinhardt, W.; Stokvis, E.; de Reijke, T.M.; Jimeno, J.M.; Lopez-Lazaro, L.; Lopez Martin, J.A.; Beijnen, J.H.; Schellens, J.H.M. Phase I Clinical and Pharmacokinetic Study of Kahalalide F in Patients with Advanced Androgen Refractory Prostate Cancer. *Clin. Cancer Res.* **2005**, *11*, 1854–1862. [CrossRef]
184. Zhao, C.; Lin, G.; Wu, D.; Liu, D.; You, L.; Högger, P.; Simal-Gandara, J.; Wang, M.; da Costa, J.G.M.; Marunaka, Y.; et al. The Algal Polysaccharide Ulvan Suppresses Growth of Hepatoma Cells. *Food Front.* **2020**, *1*, 83–101. [CrossRef]
185. Wang, Y.; An, E.-K.; Kim, S.-J.; You, S.; Jin, J.-O. Intranasal Administration of Codium Fragile Polysaccharide Elicits Anti-Cancer Immunity against Lewis Lung Carcinoma. *Int. J. Mol. Sci.* **2021**, *22*, 10608. [CrossRef]
186. Surayot, U.; You, S. Structural Effects of Sulfated Polysaccharides from Codium Fragile on NK Cell Activation and Cytotoxicity. *Int. J. Biol. Macromol.* **2017**, *98*, 117–124. [CrossRef] [PubMed]
187. Park, S.H.; Kim, J.L.; Jeong, S.; Kim, B.R.; Na, Y.J.; Jo, M.J.; Yun, H.K.; Jeong, Y.A.; Kim, D.Y.; Kim, B.G.; et al. Codium Fragile F2 Sensitize Colorectal Cancer Cells to TRAIL-Induced Apoptosis via c-FLIP Ubiquitination. *Biochem. Biophys. Res. Commun.* **2019**, *508*, 1–8. [CrossRef] [PubMed]
188. Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.G.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2016**, *33*, 382–431. [CrossRef] [PubMed]
189. Liu, Y.; Morgan, J.B.; Coothankandaswamy, V.; Liu, R.; Jekabsons, M.B.; Mahdi, F.; Nagle, D.G.; Zhou, Y.-D. The *Caulerpa* Pigment Caulerpin Inhibits HIF-1 Activation and Mitochondrial Respiration. *J. Nat. Prod.* **2009**, *72*, 2104–2109. [CrossRef] [PubMed]
190. Renju, G.L.; Muraleedhara Kurup, G.; Bandugula, V.R. Effect of Lycopene Isolated from Chlorella Marina on Proliferation and Apoptosis in Human Prostate Cancer Cell Line PC-3. *Tumor Biol.* **2014**, *35*, 10747–10758. [CrossRef]
191. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2010**, *27*, 165. [CrossRef]
192. Jiang, R.-W.; Hay, M.E.; Fairchild, C.R.; Prudhomme, J.; Roch, K.L.; Aalbersberg, W.; Kubanek, J. Antineoplastic Unsaturated Fatty Acids from Fijian Macroalgae. *Phytochemistry* **2008**, *69*, 2495–2500. [CrossRef]
193. Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. Novel Cytotoxic Brominated Diterpenes from the Red Alga *Laurencia o Btusa*. *J. Org. Chem.* **2003**, *68*, 7667–7674. [CrossRef]
194. Alarif, W.M.; Al-Lihaibi, S.S.; Ayyad, S.-E.N.; Abdel-Rhman, M.H.; Badria, F.A. Laurene-Type Sesquiterpenes from the Red Sea Red Alga Laurencia Obtusa as Potential Antitumor–Antimicrobial Agents. *Eur. J. Med. Chem.* **2012**, *55*, 462–466. [CrossRef]
195. Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.G.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2014**, *31*, 160. [CrossRef]
196. Pec, M.K.; Aguirre, A.; Moser-Thier, K.; Fernández, J.J.; Souto, M.L.; Dorta, J.; Diáz-González, F.; Villar, J. Induction of Apoptosis in Estrogen Dependent and Independent Breast Cancer Cells by the Marine Terpenoid Dehydrothyrsiferol. *Biochem. Pharmacol.* **2003**, *65*, 1451–1461. [CrossRef]
197. Zaleta-Pinet, D.A.; Holland, I.P.; Muñoz-Ochoa, M.; Murillo-Alvarez, J.I.; Sakoff, J.A.; van Altena, I.A.; McCluskey, A. Cytotoxic Compounds from Laurencia Pacifica. *Org. Med. Chem. Lett.* **2014**, *4*, 8. [CrossRef] [PubMed]
198. Kim, M.-M.; Mendis, E.; Kim, S.-K. *Laurencia Okamurai* Extract Containing Laurinterol Induces Apoptosis in Melanoma Cells. *J. Med. Food* **2008**, *11*, 260–266. [CrossRef] [PubMed]
199. Sae-lao, T.; Luplertlop, N.; Janvilisri, T.; Tohtong, R.; Bates, D.O.; Wongprasert, K. Sulfated Galactans from the Red Seaweed Gracilaria Fisheri Exerts Anti-Migration Effect on Cholangiocarcinoma Cells. *Phytomedicine* **2017**, *36*, 59–67. [CrossRef] [PubMed]
200. Blunt, J.W.; Copp, B.R.; Hu, W.-P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2008**, *25*, 35. [CrossRef]
201. Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. Bromophenols Coupled with Methyl γ-Ureidobutyrate and Bromophenol Sulfates from the Red Alga *Rhodomela confervoides*. *J. Nat. Prod.* **2006**, *69*, 206–210. [CrossRef]
202. Shoeib, N.A.; Bibby, M.C.; Blunden, G.; Linley, P.A.; Swaine, D.J.; Wheelhouse, R.T.; Wright, C.W. In-Vitro Cytotoxic Activities of the Major Bromophenols of the Red Alga *Polysiphonia lanosa* and Some Novel Synthetic Isomers. *J. Nat. Prod.* **2004**, *67*, 1445–1449. [CrossRef]
203. Wu, N.; Luo, J.; Jiang, B.; Wang, L.; Wang, S.; Wang, C.; Fu, C.; Li, J.; Shi, D. Marine Bromophenol Bis (2,3-Dibromo-4,5-Dihydroxy-Phenyl)-Methane Inhibits the Proliferation, Migration, and Invasion of Hepatocellular Carcinoma Cells via Modulating B1-Integrin/FAK Signaling. *Mar. Drugs* **2015**, *13*, 1010–1025. [CrossRef] [PubMed]
204. Blunt, J.W.; Copp, B.R.; Hu, W.-P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2007**, *24*, 31. [CrossRef]
205. Park, C.; Moon, D.-O.; Rhu, C.-H.; Choi, B.T.; Lee, W.H.; Kim, G.-Y.; Choi, Y.H. β-Sitosterol Induces Anti-Proliferation and Apoptosis in Human Leukemic U937 Cells through Activation of Caspase-3 and Induction of Bax/Bcl-2 Ratio. *Biol. Pharm. Bull.* **2007**, *30*, 1317–1323. [CrossRef]
206. Kim, S.M.; Kang, S.-W.; Kwon, O.-N.; Chung, D.; Pan, C.-H. Fucoxanthin as a Major Carotenoid in Isochrysis Aff. Galbana: Characterization of Extraction for Commercial Application. *J. Korean Soc. Appl. Biol. Chem.* **2012**, *55*, 477–483. [CrossRef]

207. Peng, J.; Yuan, J.-P.; Wu, C.-F.; Wang, J.-H. Fucoxanthin, a Marine Carotenoid Present in Brown Seaweeds and Diatoms: Metabolism and Bioactivities Relevant to Human Health. *Mar. Drugs* **2011**, *9*, 1806–1828. [CrossRef] [PubMed]
208. Miyashita, K.; Nishikawa, S.; Beppu, F.; Tsukui, T.; Abe, M.; Hosokawa, M. The Allenic Carotenoid Fucoxanthin, a Novel Marine Nutraceutical from Brown Seaweeds. *J. Sci. Food Agric.* **2011**, *91*, 1166–1174. [CrossRef] [PubMed]
209. Kim, K.-N.; Ahn, G.; Heo, S.-J.; Kang, S.-M.; Kang, M.-C.; Yang, H.-M.; Kim, D.; Roh, S.W.; Kim, S.-K.; Jeon, B.-T.; et al. Inhibition of Tumor Growth in Vitro and in Vivo by Fucoxanthin against Melanoma B16F10 Cells. *Environ. Toxicol. Pharmacol.* **2013**, *35*, 39–46. [CrossRef] [PubMed]
210. Méresse, S.; Fodil, M.; Fleury, F.; Chénais, B. Fucoxanthin, a Marine-Derived Carotenoid from Brown Seaweeds and Microalgae: A Promising Bioactive Compound for Cancer Therapy. *Int. J. Mol. Sci.* **2020**, *21*, 9273. [CrossRef] [PubMed]
211. Zorofchian Moghadamtousi, S.; Karimian, H.; Khanabdali, R.; Razavi, M.; Firoozinia, M.; Zandi, K.; Abdul Kadir, H. Anticancer and Antitumor Potential of Fucoidan and Fucoxanthin, Two Main Metabolites Isolated from Brown Algae. *Sci. World J.* **2014**, *2014*, 768323. [CrossRef]
212. Martin, L. Fucoxanthin and Its Metabolite Fucoxanthinol in Cancer Prevention and Treatment. *Mar. Drugs* **2015**, *13*, 4784–4798. [CrossRef]
213. Ganesan, P.; Matsubara, K.; Sugawara, T.; Hirata, T. Marine Algal Carotenoids Inhibit Angiogenesis by Down-Regulating FGF-2-Mediated Intracellular Signals in Vascular Endothelial Cells. *Mol. Cell. Biochem.* **2013**, *380*, 1–9. [CrossRef]
214. Jayappriyan, K.R.; Rajkumar, R.; Venkatakrishnan, V.; Nagaraj, S.; Rengasamy, R. In Vitro Anticancer Activity of Natural β-Carotene from Dunaliella Salina EU5891199 in PC-3 Cells. *Biomed. Prev. Nutr.* **2013**, *3*, 99–105. [CrossRef]
215. Shamsuddin Ahmad, A.; Julius Siong, Y.F.; Fitrya Syamsumir, D.; Atikah Mohamed Zin, N.; Aisha Mohd Radzi, S.; Nur Islamiah Kassim, M.; Ariff Muzamel, M.; Ridzuan Yusof, M.; Chandra Segaran, T. The potential of carotenoids from marine tropical microalgae in the healing process of gastritis. *J. Sustain. Sci. Manag.* **2015**, *10*, 92–106.
216. Rafi, M.M.; Kanakasabai, S.; Gokarn, S.V.; Krueger, E.G.; Bright, J.J. Dietary Lutein Modulates Growth and Survival Genes in Prostate Cancer Cells. *J. Med. Food* **2015**, *18*, 173–181. [CrossRef]
217. Gong, X.; Smith, J.; Swanson, H.; Rubin, L. Carotenoid Lutein Selectively Inhibits Breast Cancer Cell Growth and Potentiates the Effect of Chemotherapeutic Agents through ROS-Mediated Mechanisms. *Molecules* **2018**, *23*, 905. [CrossRef] [PubMed]
218. Kavalappa, Y.P.; Gopal, S.S.; Ponesakki, G. Lutein Inhibits Breast Cancer Cell Growth by Suppressing Antioxidant and Cell Survival Signals and Induces Apoptosis. *J. Cell. Physiol.* **2021**, *236*, 1798–1809. [CrossRef] [PubMed]
219. Venkatesan, J.; Keekan, K.K.; Anil, S.; Bhatnagar, I.; Kim, S.-K. Phlorotannins. In *Encyclopedia of Food Chemistry*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 515–527.
220. Rybczyńska-Tkaczyk, K.; Grenda, A.; Jakubczyk, A.; Krawczyk, P. Natural Bacterial and Fungal Peptides as a Promising Treatment to Defeat Lung Cancer Cells. *Molecules* **2023**, *28*, 4381. [CrossRef]
221. Kim, S.; Duncan, P.W.; Groban, L.; Segal, H.; Abbott, R.M.; Williamson, J.D. Patient-Reported Outcome Measures (PROM) as A Preoperative Assessment Tool. *J. Anesth. Perioper. Med.* **2017**, *4*, 274–281. [CrossRef]
222. Kanoh, K.; Kohno, S.; Katada, J.; Takahashi, J.; Uno, I.; Hayashi, Y. Synthesis and Biological Activities of Phenylahistin Derivatives. *Bioorg. Med. Chem.* **1999**, *7*, 1451–1457. [CrossRef]
223. Ashok, A.; Doriya, K.; Rao, J.V.; Qureshi, A.; Tiwari, A.K.; Kumar, D.S. Microbes Producing L-Asparaginase Free of Glutaminase and Urease Isolated from Extreme Locations of Antarctic Soil and Moss. *Sci. Rep.* **2019**, *9*, 1423. [CrossRef] [PubMed]
224. Malhão, F.; Ramos, A.A.; Buttachon, S.; Dethoup, T.; Kijjoa, A.; Rocha, E. Cytotoxic and Antiproliferative Effects of Preussin, a Hydroxypyrrolidine Derivative from the Marine Sponge-Associated Fungus Aspergillus Candidus KUFA 0062, in a Panel of Breast Cancer Cell Lines and Using 2D and 3D Cultures. *Mar. Drugs* **2019**, *17*, 448. [CrossRef]
225. Patra, S.; Praharaj, P.P.; Panigrahi, D.P.; Panda, B.; Bhol, C.S.; Mahapatra, K.K.; Mishra, S.R.; Behera, B.P.; Jena, M.; Sethi, G.; et al. Bioactive Compounds from Marine Invertebrates as Potent Anticancer Drugs: The Possible Pharmacophores Modulating Cell Death Pathways. *Mol. Biol. Rep.* **2020**, *47*, 7209–7228. [CrossRef]
226. Spicka, I.; Ocio, E.M.; Oakervee, H.E.; Greil, R.; Banh, R.H.; Huang, S.-Y.; D'Rozario, J.M.; Dimopoulos, M.A.; Martínez, S.; Extremera, S.; et al. Randomized Phase III Study (ADMYRE) of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma. *Ann. Hematol.* **2019**, *98*, 2139–2150. [CrossRef]
227. Erba, E.; Bassano, L.; Di Liberti, G.; Muradore, I.; Chiorino, G.; Ubezio, P.; Vignati, S.; Codegoni, A.; Desiderio, M.A.; Faircloth, G.; et al. Cell Cycle Phase Perturbations and Apoptosis in Tumour Cells Induced by Aplidine. *Br. J. Cancer* **2002**, *86*, 1510–1517. [CrossRef]
228. Avendaño, C.; Menéndez, J.C. Other Approaches to Targeted Therapy. In *Medicinal Chemistry of Anticancer Drugs*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 307–349.
229. Song, F.-Q.; Liu, Y.; Kong, X.-S.; Chang, W.; Song, G. Progress on Understanding the Anticancer Mechanisms of Medicinal Mushroom: Inonotus Obliquus. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 1571–1578. [CrossRef] [PubMed]
230. Szychowski, K.A.; Rybczyńska-Tkaczyk, K.; Tobiasz, J.; Yelnytska-Stawasz, V.; Pomianek, T.; Gmiński, J. Biological and Anticancer Properties of Inonotus Obliquus Extracts. *Process Biochem.* **2018**, *73*, 180–187. [CrossRef]
231. Evidente, A.; Kornienko, A.; Cimmino, A.; Andolfi, A.; Lefranc, F.; Mathieu, V.; Kiss, R. Fungal Metabolites with Anticancer Activity. *Nat. Prod. Rep.* **2014**, *31*, 617–627. [CrossRef] [PubMed]
232. Kaltschmidt, B.; Greiner, J.F.W.; Kadhim, H.M.; Kaltschmidt, C. Subunit-Specific Role of NF-KB in Cancer. *Biomedicines* **2018**, *6*, 44. [CrossRef]

233. Kashyap, A.S.; Fernandez-Rodriguez, L.; Zhao, Y.; Monaco, G.; Trefny, M.P.; Yoshida, N.; Martin, K.; Sharma, A.; Olieric, N.; Shah, P.; et al. GEF-H1 Signaling upon Microtubule Destabilization Is Required for Dendritic Cell Activation and Specific Anti-Tumor Responses. *Cell Rep.* **2019**, *28*, 3367–3380.e8. [CrossRef]
234. Matikas, A.; Georgoulias, V.; Kotsakis, A. Emerging Agents for the Prevention of Treatment Induced Neutropenia in Adult Cancer Patients. *Expert Opin. Emerg. Drugs* **2016**, *21*, 157–166. [CrossRef]
235. Tonra, J.R.; Lloyd, G.K.; Mohanlal, R.; Huang, L. Plinabulin Ameliorates Neutropenia Induced by Multiple Chemotherapies through a Mechanism Distinct from G-CSF Therapies. *Cancer Chemother. Pharmacol.* **2020**, *85*, 461–468. [CrossRef]
236. Gederaas, O.A.; Søgaard, C.D.; Viset, T.; Bachke, S.; Bruheim, P.; Arum, C.-J.; Otterlei, M. Increased Anticancer Efficacy of Intravesical Mitomycin C Therapy When Combined with a PCNA Targeting Peptide. *Transl. Oncol.* **2014**, *7*, 812–823. [CrossRef]
237. Dasari, S.; Bernard Tchounwou, P. Cisplatin in Cancer Therapy: Molecular Mechanisms of Action. *Eur. J. Pharmacol.* **2014**, *740*, 364–378. [CrossRef]
238. Elshafei, A.; El-Ghonemy, D. Screening and Media Optimization for Enhancing L-Asparaginase Production, an Anticancer Agent, from Different Filamentous Fungi in Solid State Fermentation. *Br. Biotechnol. J.* **2015**, *9*, 1–15. [CrossRef]
239. Li, P.; Fan, Y.; Chen, H.; Chao, Y.; Du, N.; Chen, J. Phenylquinolinones with Antitumor Activity from the Indian Ocean-Derived Fungus Aspergillus Versicolor Y31-2. *Chin. J. Oceanol. Limnol.* **2016**, *34*, 1072–1075. [CrossRef]
240. Liu, Q.-Y.; Zhou, T.; Zhao, Y.-Y.; Chen, L.; Gong, M.-W.; Xia, Q.-W.; Ying, M.-G.; Zheng, Q.-H.; Zhang, Q.-Q. Antitumor Effects and Related Mechanisms of Penicitrinine A, a Novel Alkaloid with a Unique Spiro Skeleton from the Marine Fungus Penicillium Citrinum. *Mar. Drugs* **2015**, *13*, 4733–4753. [CrossRef] [PubMed]
241. Sirimangkalakitti, N.; Lin, J.; Harada, K.; Setiawan, A.; Arisawa, M.; Arai, M. Chemical Constituents and Anticancer Activities of Marine-Derived Fungus Trichoderma Lixii. *Molecules* **2024**, *29*, 2048. [CrossRef] [PubMed]
242. Anh, N.M.; Huyen, V.T.T.; Quyen, V.T.; Dao, P.T.; Quynh, D.T.; Huong, D.T.M.; Van Cuong, P.; Dat, T.T.H.; Minh, L.T.H. Antimicrobial and Cytotoxic Secondary Metabolites from a Marine-Derived Fungus Penicillium Citrinum VM6. *Curr. Microbiol.* **2024**, *81*, 32. [CrossRef] [PubMed]
243. Virués-Segovia, J.R.; Pinedo, C.; Zorrilla, D.; Sánchez-Márquez, J.; Sánchez, P.; Ramos, M.C.; de la Cruz, M.; Aleu, J.; Durán-Patrón, R. Discovery of New Eremophilanes from the Marine-Derived Fungus Emericellopsis Maritima BC17 by Culture Conditions Changes: Evaluation of Cytotoxic and Antimicrobial Activities. *Front. Mar. Sci.* **2024**, *11*, 1386175. [CrossRef]
244. Zhang, Z.; Li, Y.; Wang, H.; Xu, W.; Wang, C.; Ma, H.; Zhong, F.; Ou, J.; Luo, Z.; Luo, H.-B.; et al. Ergone Derivatives from the Deep-Sea-Derived Fungus *Aspergillus Terreus* YPGA10 and 25,28-Dihydroxyergone-Induced Apoptosis in Human Colon Cancer SW620 Cells. *J. Nat. Prod.* **2024**, *87*, 1563–1573. [CrossRef] [PubMed]
245. Paul, V.; Tiwary, B.N. An Investigation on the Acrylamide Mitigation Potential of L-Asparaginase from BV-C Strain. *Biocatal. Agric. Biotechnol.* **2020**, *27*, 101677. [CrossRef]
246. Jans, P.E.; Mfuh, A.M.; Arman, H.D.; Shaffer, C.V.; Larionov, O.V.; Mooberry, S.L. Cytotoxicity and Mechanism of Action of the Marine-Derived Fungal Metabolite Trichodermamide B and Synthetic Analogues. *J. Nat. Prod.* **2017**, *80*, 676–683. [CrossRef]
247. Li, J.; Wang, Y.; Qi, X.; Li, D.; Zhu, T.; Mo, X. Anticancer Efficacy and Absorption, Distribution, Metabolism, and Toxicity Studies of Aspergiolide A in Early Drug Development. *Drug Des. Dev. Ther.* **2014**, *8*, 1965–1977. [CrossRef]
248. Ankisetty, S.; Khan, S.; Avula, B.; Gochfeld, D.; Khan, I.; Slattery, M. Chlorinated Didemnins from the Tunicate Tridemnum Solidum. *Mar. Drugs* **2013**, *11*, 4478–4486. [CrossRef] [PubMed]
249. Youssef, D.T.A.; Almagthali, H.; Shaala, L.A.; Schmidt, E.W. Secondary Metabolites of the Genus Didemnum: A Comprehensive Review of Chemical Diversity and Pharmacological Properties. *Mar. Drugs* **2020**, *18*, 307. [CrossRef]
250. Maroun, J.A.; Stewart, D.; Verma, S.; Eisenhauer, E. Phase I Clinical Study of Didemnin B. *Investig. New Drugs* **1998**, *16*, 51–56. [CrossRef] [PubMed]
251. Kucuk, O.; Young, M.L.; Habermann, T.M.; Wolf, B.C.; Jimeno, J.; Cassileth, P.A. Phase II Trial of Didemnin B in Previously Treated Non-Hodgkin's Lymphoma. *Am. J. Clin. Oncol. Cancer Clin. Trial* **2000**, *23*, 273–277. [CrossRef]
252. Benvenuto, J.A.; Newman, R.A.; Bignami, G.S.; Raybould, T.J.G.; Raber, M.N.; Esparza, L.; Walters, R.S. Phase II Clinical and Pharmacological Study of Didemnin B in Patients with Metastatic Breast Cancer. *Investig. New Drugs* **1992**, *10*, 113–117. [CrossRef]
253. Weiss, G.R.; Liu, P.Y.; O'Sullivan, J.; Alberts, D.S.; Brown, T.D.; Neefe, J.R.; Hutchins, L.F. A Randomized Phase II Trial of Trimetrexate or Didemnin B for the Treatment of Metastatic or Recurrent Squamous Carcinoma of the Uterine Cervix: A Southwest Oncology Group Trial. *Gynecol. Oncol.* **1992**, *45*, 303–306. [CrossRef]
254. Vervoort, H.; Fenical, W.; Epifanio, R.d.A. Tamandarins A and B: New Cytotoxic Depsipeptides from a Brazilian Ascidian of the Family Didemnidae. *J. Org. Chem.* **2000**, *65*, 782–792. [CrossRef] [PubMed]
255. Arumugam, V.; Venkatesan, M.; Ramachandran, S.; Sundaresan, U. Bioactive Peptides from Marine Ascidians and Future Drug Development—A Review. *Int. J. Pept. Res. Ther.* **2018**, *24*, 13–18. [CrossRef]
256. van Andel, L.; Fudio, S.; Rosing, H.; Munt, S.; Miguel-Lillo, B.; González, I.; Tibben, M.M.; de Vries, N.; de Vries Schultink, A.H.M.; Schellens, J.H.M.; et al. Pharmacokinetics and Excretion of 14C–Plitidepsin in Patients with Advanced Cancer. *Investig. New Drugs* **2017**, *35*, 589–598. [CrossRef]
257. Broggini, M.; Marchini, S.V.; Galliera, E.; Borsotti, P.; Taraboletti, G.; Erba, E.; Sironi, M.; Jimeno, J.; Faircloth, G.T.; Giavazzi, R.; et al. Aplidine, a New Anticancer Agent of Marine Origin, Inhibits Vascular Endothelial Growth Factor (VEGF) Secretion and Blocks VEGF-VEGFR-1 (Flt-1) Autocrine Loop in Human Leukemia Cells MOLT-4. *Leukemia* **2003**, *17*, 52–59. [CrossRef]

258. Ngandjui, Y.A.T.; Kereeditse, T.T.; Kamika, I.; Madikizela, L.M.; Msagati, T.A.M. Nutraceutical and Medicinal Importance of Marine Molluscs. *Mar. Drugs* **2024**, *22*, 201. [CrossRef] [PubMed]
259. Kigoshi, H.; Kita, M. Antitumor Effects of Sea Hare-Derived Compounds in Cancer. In *Handbook of Anticancer Drugs from Marine Origin*; Springer International Publishing: Cham, Switzerland, 2015; pp. 701–739.
260. Mir, R.; Karim, S.; Amjad Kamal, M.; Wilson, C.M.; Mirza, Z. Conotoxins: Structure, Therapeutic Potential and Pharmacological Applications. *Curr. Pharm. Des.* **2016**, *22*, 582–589. [CrossRef]
261. Gao, G.; Wang, Y.; Hua, H.; Li, D.; Tang, C. Marine Antitumor Peptide Dolastatin 10: Biological Activity, Structural Modification and Synthetic Chemistry. *Mar. Drugs* **2021**, *19*, 363. [CrossRef] [PubMed]
262. Wesson, K.J.; Hamann, M.T. Keenamide A, a Bioactive Cyclic Peptide from the Marine Mollusk *Pleurobranchus Forskalii*. *J. Nat. Prod.* **1996**, *59*, 629–631. [CrossRef] [PubMed]
263. Saeed, A.F.U.H.; Su, J.; Ouyang, S. Marine-Derived Drugs: Recent Advances in Cancer Therapy and Immune Signaling. *Biomed. Pharmacother.* **2021**, *134*, 111091. [CrossRef]
264. Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C.G.; Cimino, G. A New Antitumor Isoquinoline Alkaloid from the Marine Nudibranch Jorunna Funebris. *Tetrahedron* **2000**, *56*, 7305–7308. [CrossRef]
265. Lane, J.W.; Chen, Y.; Williams, R.M. Asymmetric Total Syntheses of (−)-Jorumycin, (−)-Renieramycin G, 3-*epi*-Jorumycin, and 3-*epi*-Renieramycin G. *J. Am. Chem. Soc.* **2005**, *127*, 12684–12690. [CrossRef]
266. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine Natural Products. *Nat. Prod. Rep.* **2011**, *28*, 196–268. [CrossRef]
267. Romano, G.; Costantini, M.; Sansone, C.; Lauritano, C.; Ruocco, N.; Ianora, A. Marine Microorganisms as a Promising and Sustainable Source of Bioactive Molecules. *Mar. Environ. Res.* **2017**, *128*, 58–69. [CrossRef]
268. Petsri, K.; Chamni, S.; Suwanborirux, K.; Saito, N.; Chanvorachote, P. Renieramycin T Induces Lung Cancer Cell Apoptosis by Targeting Mcl-1 Degradation: A New Insight in the Mechanism of Action. *Mar. Drugs* **2019**, *17*, 301. [CrossRef]
269. Zovko, A.; Viktorsson, K.; Hååg, P.; Kovalerchick, D.; Färnegårdh, K.; Alimonti, A.; Ilan, M.; Carmeli, S.; Lewensohn, R. Marine Sponge *Cribrochalina Vasculum* Compounds Activate Intrinsic Apoptotic Signaling and Inhibit Growth Factor Signaling Cascades in Non–Small Cell Lung Carcinoma. *Mol. Cancer Ther.* **2014**, *13*, 2941–2954. [CrossRef]
270. Cheng, M.-H.; Huang, H.-L.; Lin, Y.-Y.; Tsui, K.-H.; Chen, P.-C.; Cheng, S.-Y.; Chong, I.-W.; Sung, P.-J.; Tai, M.-H.; Wen, Z.-H.; et al. BA6 Induces Apoptosis via Stimulation of Reactive Oxygen Species and Inhibition of Oxidative Phosphorylation in Human Lung Cancer Cells. *Oxidative Med. Cell Longev.* **2019**, *2019*, 6342104. [CrossRef]
271. Roskelley, C.D.; Williams, D.E.; McHardy, L.M.; Leong, K.G.; Troussard, A.; Karsan, A.; Andersen, R.J.; Dedhar, S.; Roberge, M. Inhibition of Tumor Cell Invasion and Angiogenesis by Motuporamines. *Cancer Res.* **2001**, *61*, 6788–6794.
272. Wang, R.; Zhang, Q.; Peng, X.; Zhou, C.; Zhong, Y.; Chen, X.; Qiu, Y.; Jin, M.; Gong, M.; Kong, D. Stellettin B Induces G1 Arrest, Apoptosis and Autophagy in Human Non-Small Cell Lung Cancer A549 Cells via Blocking PI3K/Akt/MTOR Pathway. *Sci. Rep.* **2016**, *6*, 27071. [CrossRef]
273. Gomes, A.R.; Freitas, A.C.; Duarte, A.C.; Rocha-Santos, T.A.P. Echinoderms: A Review of Bioactive Compounds with Potential Health Effects. In *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, The Netherlands, 2016; Volume 49, pp. 1–54.
274. Thao, N.P.; Luyen, B.T.T.; Kim, E.J.; Kang, J.I.; Kang, H.K.; Cuong, N.X.; Nam, N.H.; Kiem, P.V.; Van Minh, C.; Kim, Y.H. Steroidal Constituents from the Edible Sea Urchin *Diadema savignyi* Michelin Induce Apoptosis in Human Cancer Cells. *J. Med. Food* **2015**, *18*, 45–53. [CrossRef]
275. Yun, C.W.; Kim, H.J.; Lee, S.H. Therapeutic Application of Diverse Marine-Derived Natural Products in Cancer Therapy. *Anticancer Res.* **2019**, *39*, 5261–5284. [CrossRef]
276. Wargasetia, T.; Permana, S.; Widodo, N. Potential Use of Compounds from Sea Cucumbers as MDM2 and CXCR4 Inhibitors to Control Cancer Cell Growth. *Exp. Ther. Med.* **2018**, *6*, 2985–2991. [CrossRef]
277. Bordbar, S.; Anwar, F.; Saari, N. High-Value Components and Bioactives from Sea Cucumbers for Functional Foods—A Review. *Mar. Drugs* **2011**, *9*, 1761–1805. [CrossRef] [PubMed]
278. Wätjen, W.; Ebada, S.S.; Bergermann, A.; Chovolou, Y.; Totzke, F.; Kubbutat, M.H.G.; Lin, W.; Proksch, P. Cytotoxic Effects of the Anthraquinone Derivatives 1′-Deoxyrhodoptilometrin and (S)-(−)-Rhodoptilometrin Isolated from the Marine Echinoderm *Comanthus* sp. *Arch. Toxicol.* **2017**, *91*, 1485–1495. [CrossRef] [PubMed]
279. Menchinskaya, E.S.; Chingizova, E.A.; Pislyagin, E.A.; Yurchenko, E.A.; Klimovich, A.A.; Zelepuga, E.A.; Aminin, D.L.; Avilov, S.A.; Silchenko, A.S. Mechanisms of Action of Sea Cucumber Triterpene Glycosides Cucumarioside A0-1 and Djakonovioside A Against Human Triple-Negative Breast Cancer. *Mar. Drugs* **2024**, *22*, 474. [CrossRef] [PubMed]
280. Menis, J.; Twelves, C. Eribulin (Halaven): A New, Effective Treatment for Women with Heavily Pretreated Metastatic Breast Cancer. *Breast Cancer Targets Ther.* **2011**, *3*, 101–111. [CrossRef] [PubMed]
281. Hirata, Y.; Uemura, D. Halichondrins-Antitumor Polyether Macrolides from a Marine Sponge. *Pure Appl. Chem.* **1986**, *58*, 701–710. [CrossRef]
282. Nguyen, H.M.; Ito, T.; Win, N.N.; Vo, H.Q.; Nguyen, H.T.; Morita, H. A New Sterol from the Vietnamese Marine Sponge *Xestospongia Testudinaria* and Its Biological Activities. *Nat. Prod. Res.* **2019**, *33*, 1175–1181. [CrossRef]
283. Abdelhameed, R.F.A.; Habib, E.S.; Eltahawy, N.A.; Hassanean, H.A.; Ibrahim, A.K.; Mohammed, A.F.; Fayez, S.; Hayallah, A.M.; Yamada, K.; Behery, F.A.; et al. New Cytotoxic Natural Products from the Red Sea Sponge Stylissa Carteri. *Mar. Drugs* **2020**, *18*, 241. [CrossRef] [PubMed]

284. El-Hawary, S.S.; Sayed, A.M.; Mohammed, R.; Hassan, H.M.; Rateb, M.E.; Amin, E.; Mohammed, T.A.; El-Mesery, M.; Bin Muhsinah, A.; Alsayari, A.; et al. Bioactive Brominated Oxindole Alkaloids from the Red Sea Sponge Callyspongia Siphonella. *Mar. Drugs* **2019**, *17*, 465. [CrossRef]
285. Olsen, E.K.; Søderholm, K.L.; Isaksson, J.; Andersen, J.H.; Hansen, E. Metabolomic Profiling Reveals the *N* -Acyl-Taurine Geodiataurine in Extracts from the Marine Sponge *Geodia macandrewii* (Bowerbank). *J. Nat. Prod.* **2016**, *79*, 1285–1291. [CrossRef] [PubMed]
286. Wang, J.; Yan, Y.-L.; Yu, X.-Y.; Pan, J.-Y.; Liu, X.-L.; Hong, L.-L.; Wang, B. Meroterpenoids from Marine Sponge *Hyrtios* sp. and Their Anticancer Activity against Human Colorectal Cancer Cells. *Mar. Drugs* **2024**, *22*, 183. [CrossRef] [PubMed]
287. Quach, H.T.; Hirano, S.; Fukuhara, S.; Watanabe, T.; Kanoh, N.; Iwabuchi, Y.; Usui, T.; Kataoka, T. Irciniastatin A Induces Potent and Sustained Activation of Extracellular Signal-Regulated Kinase and Thereby Promotes Ectodomain Shedding of Tumor Necrosis Factor Receptor 1 in Human Lung Carcinoma A549 Cells. *Biol. Pharm. Bull.* **2015**, *38*, 941–946. [CrossRef]
288. Kashman, Y.; Hirsh, S.; McConnell, O.J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. Ptilomycalin A: A Novel Polycyclic Guanidine Alkaloid of Marine Origin. *J. Am. Chem. Soc.* **1989**, *111*, 8925–8926. [CrossRef]
289. Ye, X.; Anjum, K.; Song, T.; Wang, W.; Liang, Y.; Chen, M.; Huang, H.; Lian, X.-Y.; Zhang, Z. Antiproliferative Cyclodepsipeptides from the Marine Actinomycete *Streptomyces* sp. P11-23B Downregulating the Tumor Metabolic Enzymes of Glycolysis, Glutaminolysis, and Lipogenesis. *Phytochemistry* **2017**, *135*, 151–159. [CrossRef]
290. Rettori, D.; Durán, N. Production, Extraction and Purificationof Violacein: An Antibiotic Pigment Producedby Chromobacterium Violaceum. *World J. Microbiol. Biotechnol.* **1998**, *14*, 685–688. [CrossRef]
291. Sánchez, C.; Braña, A.F.; Méndez, C.; Salas, J.A. Reevaluation of the Violacein Biosynthetic Pathway and Its Relationship to Indolocarbazole Biosynthesis. *ChemBioChem* **2006**, *7*, 1231–1240. [CrossRef]
292. Ameen, F.; AlNadhari, S.; Al-Homaidan, A.A. Marine Microorganisms as an Untapped Source of Bioactive Compounds. *Saudi J. Biol. Sci.* **2021**, *28*, 224–231. [CrossRef] [PubMed]
293. Wang, Y.; Nakajima, A.; Hosokawa, K.; Soliev, A.B.; Osaka, I.; Arakawa, R.; Enomoto, K. Cytotoxic Prodigiosin Family Pigments from *Pseudoalteromonas* sp. 1020R Isolated from the Pacific Coast of Japan. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 1229–1232. [CrossRef]
294. Gerber, N.N.; Gauthier, M.J. New Prodigiosin-like Pigment from Alteromonas Rubra. *Appl. Environ. Microbiol.* **1979**, *37*, 1176–1179. [CrossRef] [PubMed]
295. Fehér, D.; Barlow, R.S.; Lorenzo, P.S.; Hemscheidt, T.K. A 2-Substituted Prodiginine, 2-(*p*-Hydroxybenzyl)Prodigiosin, from *Pseudoalteromonas rubra*. *J. Nat. Prod.* **2008**, *71*, 1970–1972. [CrossRef] [PubMed]
296. Riera-Romo, M.; Wilson-Savón, L.; Hernandez-Balmaseda, I. Metabolites from Marine Microorganisms in Cancer, Immunity, and Inflammation: A Critical Review. *J. Pharm. Pharmacogn. Res.* **2020**, *8*, 368–391. [CrossRef]
297. Choi, S.Y.; Yoon, K.; Lee, J.I.; Mitchell, R.J. Violacein: Properties and Production of a Versatile Bacterial Pigment. *Biomed. Res. Int.* **2015**, *2015*, 465056. [CrossRef]
298. Lee, J.S.; Kim, Y.-S.; Park, S.; Kim, J.; Kang, S.-J.; Lee, M.-H.; Ryu, S.; Choi, J.M.; Oh, T.-K.; Yoon, J.-H. Exceptional Production of Both Prodigiosin and Cycloprodigiosin as Major Metabolic Constituents by a Novel Marine Bacterium, Zooshikella Rubidus S1-1. *Appl. Environ. Microbiol* **2011**, *77*, 4967–4973. [CrossRef]
299. Takahashi, Y.; Omura, S. Isolation of New Actinomycete Strains for the Screening of New Bioactive Compounds. *J. Gen. Appl. Microbiol.* **2003**, *49*, 141–154. [CrossRef]
300. Bhatnagar, I.; Kim, S.-K. Immense Essence of Excellence: Marine Microbial Bioactive Compounds. *Mar. Drugs* **2010**, *8*, 2673–2701. [CrossRef]
301. Choi, I.-K.; Shin, H.J.; Lee, H.-S.; Kwon, H.J. Streptochlorin, a Marine Natural Product, Inhibits NF-KappaB Activation and Suppresses Angiogenesis in Vitro. *J. Microbiol. Biotechnol.* **2007**, *17*, 1338–1343.
302. Hughes, C.C.; MacMillan, J.B.; Gaudêncio, S.P.; Jensen, P.R.; Fenical, W. The Ammosamides: Structures of Cell Cycle Modulators from a Marine-Derived *Streptomyces* Species. *Angew. Chem. Int. Ed.* **2009**, *48*, 725–727. [CrossRef] [PubMed]
303. Dai, Q.; Ma, M.; Wang, N.; Zhou, Y.; Zhang, Z. Antiproliferative Metabolites against Glioma Cells from the Marine-Associated Actinomycete *Streptomyces* sp. ZZ735. *Fitoterapia* **2024**, *178*, 106176. [CrossRef] [PubMed]
304. Sun, W.; Wu, W.; Liu, X.; Zaleta-Pinet, D.A.; Clark, B.R. Bioactive Compounds Isolated from Marine-Derived Microbes in China: 2009–2018. *Mar. Drugs* **2019**, *17*, 339. [CrossRef] [PubMed]
305. Chung, D.; Nguyen, H.T.; Yu, N.H.; Yu, W.-J.; Kwon, Y.M.; Bae, S.S.; Choi, G.; Kim, J.-C. In Vitro and in Vivo Antimicrobial Activity of the Fungal Metabolite Toluquinol against Phytopathogenic Bacteria. *Front. Microbiol.* **2023**, *14*, 1221865. [CrossRef]
306. Nugraha, A.S.; Firli, L.N.; Rani, D.M.; Hidayatiningsih, A.; Lestari, N.D.; Wongso, H.; Tarman, K.; Rahaweman, A.C.; Manurung, J.; Ariantari, N.P.; et al. Indonesian Marine and Its Medicinal Contribution. *Nat. Prod. Bioprospect.* **2023**, *13*, 38. [CrossRef]
307. Dou, Q.; Zonder, J. Overview of Proteasome Inhibitor-Based Anti-Cancer Therapies: Perspective on Bortezomib and Second Generation Proteasome Inhibitors versus Future Generation Inhibitors of Ubiquitin-Proteasome System. *Curr. Cancer Drug Targets* **2014**, *14*, 517–536. [CrossRef] [PubMed]
308. Voorhees, P.M.; Orlowski, R.Z. The proteasome and proteasome inhibitors in cancer therapy. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 189–213. [CrossRef]
309. Seyed, M.A.; Ayesha, S. Marine-Derived Pipeline Anticancer Natural Products: A Review of Their Pharmacotherapeutic Potential and Molecular Mechanisms. *Futur. J. Pharm. Sci.* **2021**, *7*, 203. [CrossRef]

310. Twombly, R. First Proteasome Inhibitor Approved for Multiple Myeloma. *JNCI J. Natl. Cancer Inst.* **2003**, *95*, 845. [CrossRef] [PubMed]
311. Russo, S.M.; Tepper, J.E.; Baldwin, A.S.; Liu, R.; Adams, J.; Elliott, P.; Cusack, J.C. Enhancement of Radiosensitivity by Proteasome Inhibition: Implications for a Role of NF-KB. *Int. J. Radiat. Oncol. Biol. Phys.* **2001**, *50*, 183–193. [CrossRef] [PubMed]
312. Hideshima, T.; Chauhan, D.; Richardson, P.; Mitsiades, C.; Mitsiades, N.; Hayashi, T.; Munshi, N.; Dang, L.; Castro, A.; Palombella, V.; et al. NF-KB as a Therapeutic Target in Multiple Myeloma. *J. Biol. Chem.* **2002**, *277*, 16639–16647. [CrossRef] [PubMed]
313. Fuchs, O. Targeting of NF-KappaB Signaling Pathway, Other Signaling Pathways and Epigenetics in Therapy of Multiple Myeloma. *Cardiovasc. Hematol. Disord.-Drug Targets* **2013**, *13*, 16–34. [CrossRef]
314. Zhang, Q.; Schrader, K.K.; Elsohly, H.N.; Takamatsu, S. New Cell-Cell Adhesion Inhibitors from *Streptomyces* sp. UMA-044. *J. Antibiot.* **2003**, *56*, 673–681. [CrossRef]
315. Zimmerman, T.; Blanco, F. Inhibitors Targeting the LFA-1/ICAM-1 Cell-Adhesion Interaction: Design and Mechanism of Action. *Curr. Pharm. Des.* **2008**, *14*, 2128–2139. [CrossRef]
316. Cossío, F.P.; Mendoza, M.L.; Zubia, A.; Valcárcel, M.; Vara, Y.I.; Solaun, M.S.; López, J.J.; San Sebastian, E. Novel Inhibitors of the Lfa-1/Icam-1 Interaction and Uses Thereof. WIPO Patent WO/2007, 2007. p. 54128.
317. Park, C.; Shin, H.J.; Kim, G.-Y.; Kwon, T.K.; Nam, T.-J.; Kim, S.-K.; Cheong, J.; Choi, I.-W.; Choi, Y.H. Induction of Apoptosis by Streptochlorin Isolated from *Streptomyces* sp. in Human Leukemic U937 Cells. *Toxicol. In Vitro* **2008**, *22*, 1573–1581. [CrossRef]
318. Shin, D.Y.; Shin, H.J.; Kim, G.-Y.; Cheong, J.; Choi, I.-W.; Kim, S.-K.; Moon, S.-K.; Kang, H.S.; Choi, Y.H. Streptochlorin Isolated from *Streptomyces* sp. Induces Apoptosis in Human Hepatocarcinoma Cells through a Reactive Oxygen Species-Mediated Mitochondrial Pathway. *J. Microbiol. Biotechnol.* **2008**, *18*, 1862–1868. [CrossRef]
319. Hawas, U.W.; Shaaban, M.; Shaaban, K.A.; Speitling, M.; Maier, A.; Kelter, G.; Fiebig, H.H.; Meiners, M.; Helmke, E.; Laatsch, H. Mansouramycins A−D, Cytotoxic Isoquinolinequinones from a Marine Streptomycete. *J. Nat. Prod.* **2009**, *72*, 2120–2124. [CrossRef]
320. Nalini, S.; Sandy Richard, D.; Mohammed Riyaz, S.U.; Kavitha, G.; Inbakandan, D. Antibacterial Macro Molecules from Marine Organisms. *Int. J. Biol. Macromol.* **2018**, *115*, 696–710. [CrossRef]
321. Kareh, M.; El Nahas, R.; Al-Aaraj, L.; Al-Ghadban, S.; Naser Al Deen, N.; Saliba, N.; El-Sabban, M.; Talhouk, R. Anti-Proliferative and Anti-Inflammatory Activities of the Sea Cucumber *Holothuria polii* Aqueous Extract. *SAGE Open Med.* **2018**, *6*. [CrossRef]
322. Han, H.; Yi, Y.-H.; Li, L.; Liu, B.-S.; Pan, M.-X.; Yan, B.; Wang, X.-H. Triterpene Glycosides from Sea Cucumber *Holothuria leucospilota*. *Chin. J. Nat. Med.* **2010**, *7*, 346–350. [CrossRef]
323. Han, H.; Zhang, W.; Yi, Y.; Liu, B.; Pan, M.; Wang, X. A Novel Sulfated Holostane Glycoside from Sea Cucumber *Holothuria leucospilota*. *Chem. Biodivers.* **2010**, *7*, 1764–1769. [CrossRef] [PubMed]
324. Carballo, J.L.; Hernández-Inda, Z.L.; Pérez, P.; García-Grávalos, M.D. A Comparison between Two Brine Shrimp Assays to Detect in Vitrocytotoxicity in Marine Natural Products. *BMC Biotechnol.* **2002**, *2*, 17. [CrossRef] [PubMed]
325. Dai, J.; Liu, Y.; Jia, H.; Zhou, Y.-D.; Nagle, D.G. Benzochromenones from the Marine Crinoid Comantheria Rotula Inhibit Hypoxia-Inducible Factor-1 (HIF-1) in Cell-Based Reporter Assays and Differentially Suppress the Growth of Certain Tumor Cell Lines. *J. Nat. Prod.* **2007**, *70*, 1462–1466. [CrossRef] [PubMed]
326. Janakiram, N.; Mohammed, A.; Rao, C. Sea Cucumbers Metabolites as Potent Anti-Cancer Agents. *Mar. Drugs* **2015**, *13*, 2909–2923. [CrossRef] [PubMed]
327. Cuong, N.X.; Vien, L.T.; Hoang, L.; Hanh, T.T.H.; Thao, D.T.; Van Thanh, N.; Nam, N.H.; Thung, D.C.; Kiem, P.V.; Minh, C. Van Cytotoxic Triterpene Diglycosides from the Sea Cucumber Stichopus Horrens. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2939–2942. [CrossRef]
328. Zhao, Q.; Xue, Y.; Wang, J.; Li, H.; Long, T.; Li, Z.; Wang, Y.; Dong, P.; Xue, C. *In Vitro* and *in Vivo* Anti-tumour Activities of Echinoside A and *Ds* -echinoside A from *Pearsonothuria graeffei*. *J. Sci. Food Agric.* **2012**, *92*, 965–974. [CrossRef] [PubMed]
329. Zhao, Q.; Liu, Z.; Xue, Y.; Wang, J.; Li, H.; Tang, Q.; Wang, Y.; Dong, P.; Xue, C. Ds-Echinoside A, a New Triterpene Glycoside Derived from Sea Cucumber, Exhibits Antimetastatic Activity via the Inhibition of NF-KB-Dependent MMP-9 and VEGF Expressions. *J. Zhejiang Univ. Sci. B* **2011**, *12*, 534–544. [CrossRef]
330. Silchenko, A.S.; Avilov, S.A.; Kalinin, V.I.; Kalinovsky, A.I.; Dmitrenok, P.S.; Fedorov, S.N.; Stepanov, V.G.; Dong, Z.; Stonik, V.A. Constituents of the Sea Cucumber *Cucumaria okhotensis*. Structures of Okhotosides B_1–B_3 and Cytotoxic Activities of Some Glycosides from This Species. *J. Nat. Prod.* **2008**, *71*, 351–356. [CrossRef] [PubMed]
331. Li, X.; Roginsky, A.B.; Ding, X.-Z.; Woodward, C.; Collin, P.; Newman, R.A.; Bell, J.R.H.; Adrian, T.E. Review of the Apoptosis Pathways in Pancreatic Cancer and the Anti-apoptotic Effects of the Novel Sea Cucumber Compound, Frondoside A. *Ann. New York Acad. Sci.* **2008**, *1138*, 181–198. [CrossRef] [PubMed]
332. Dyshlovoy, S.A.; Madanchi, R.; Hauschild, J.; Otte, K.; Alsdorf, W.H.; Schumacher, U.; Kalinin, V.I.; Silchenko, A.S.; Avilov, S.A.; Honecker, F.; et al. The Marine Triterpene Glycoside Frondoside A Induces P53-Independent Apoptosis and Inhibits Autophagy in Urothelial Carcinoma Cells. *BMC Cancer* **2017**, *17*, 93. [CrossRef]
333. Zhao, Q.; Xue, Y.; Liu, Z.; Li, H.; Wang, J.; Li, Z.; Wang, Y.; Dong, P.; Xue, C. Differential Effects of Sulfated Triterpene Glycosides, Holothurin A_1, and 24-Dehydroechinoside A, on Antimetastasic Activity via Regulation of the MMP-9 Signal Pathway. *J. Food Sci.* **2010**, *75*, H285–H288. [CrossRef]
334. Wang, W.; Hong, J.; Lee, C.-O.; Im, K.S.; Choi, J.S.; Jung, J.H. Cytotoxic Sterols and Saponins from the Starfish *Certonardoa semiregularis*. *J. Nat. Prod.* **2004**, *67*, 584–591. [CrossRef] [PubMed]

335. Russo, G.; Russo, M.; Castellano, I.; Napolitano, A.; Palumbo, A. Ovothiol Isolated from Sea Urchin Oocytes Induces Autophagy in the Hep-G2 Cell Line. *Mar. Drugs* **2014**, *12*, 4069–4085. [CrossRef] [PubMed]
336. Lee, C.; Hsieh, H.J.; Hwang, D. Cytotoxic and Apoptotic Activities of the Plancitoxin I from the Venom of Crown-of-thorns Starfish (*Acanthaster planci*) on A375.S2 Cells. *J. Appl. Toxicol.* **2015**, *35*, 407–417. [CrossRef] [PubMed]
337. Lee, C.-C.; Hsieh, H.J.; Hsieh, C.-H.; Hwang, D.-F. Plancitoxin I from the Venom of Crown-of-Thorns Starfish (*Acanthaster planci*) Induces Oxidative and Endoplasmic Reticulum Stress Associated Cytotoxicity in A375.S2 Cells. *Exp. Mol. Pathol.* **2015**, *99*, 7–15. [CrossRef]
338. Tong, Y.; Zhang, X.; Tian, F.; Yi, Y.; Xu, Q.; Li, L.; Tong, L.; Lin, L.; Ding, J. Philinopside a, a Novel Marine-derived Compound Possessing Dual Anti-angiogenic and Anti-tumor Effects. *Int. J. Cancer* **2005**, *114*, 843–853. [CrossRef]
339. Tian, F.; Zhu, C.; Zhang, X.; Xie, X.; Xin, X.; Yi, Y.; Lin, L.; Geng, M.; Ding, J. Philinopside E, a New Sulfated Saponin from Sea Cucumber, Blocks the Interaction between Kinase Insert Domain-Containing Receptor (KDR) and Alphavbeta3 Integrin via Binding to the Extracellular Domain of KDR. *Mol. Pharmacol* **2007**, *72*, 545–552. [CrossRef]
340. Shin, D.M.; Holoye, P.Y.; Forman, A.; Winn, R.; Perez-Soler, R.; Dakhil, S.; Rosenthal, J.; Raber, M.N.; Hong, W.K. Phase II Clinical Trial of Didemnin B in Previously Treated Small Cell Lung Cancer. *Investig. New Drugs* **1994**, *12*, 243–249. [CrossRef]
341. Maroun, J.A.; Belanger, K.; Seymour, L.; Matthews, S.; Roach, J.; Dionne, J.; Soulieres, D.; Stewart, D.; Goel, R.; Charpentier, D.; et al. Phase I Study of Aplidine in a Daily×5 One-Hour Infusion Every 3 Weeks in Patients with Solid Tumors Refractory to Standard Therapy. A National Cancer Institute of Canada Clinical Trials Group Study: NCIC CTG IND 115. *Ann. Oncol.* **2006**, *17*, 1371–1378. [CrossRef]
342. Faivre, S.; Chièze, S.; Delbaldo, C.; Ady-vago, N.; Guzman, C.; Lopez-Lazaro, L.; Lozahic, S.; Jimeno, J.; Pico, F.; Armand, J.P.; et al. Phase I and Pharmacokinetic Study of Aplidine, a New Marine Cyclodepsipeptide in Patients With Advanced Malignancies. *J. Clin. Oncol.* **2005**, *23*, 7871–7880. [CrossRef]
343. Kasper, B.; Reichardt, P.; Pink, D.; Sommer, M.; Mathew, M.; Rauch, G.; Hohenberger, P. Combination of Trabectedin and Gemcitabine for Advanced Soft Tissue Sarcomas: Results of a Phase I Dose Escalating Trial of the German Interdisciplinary Sarcoma Group (GISG). *Mar. Drugs* **2015**, *13*, 379–388. [CrossRef]
344. Fabbroni, C.; Grignani, G.; Vincenzi, B.; Fumagalli, E.; De Pas, T.M.; Mazzocca, A.; Pantaleo, M.A.; Brunello, A.; Baldi, G.G.; Boglione, A.; et al. TRAbectedin in AdVanced REtroperitoneal Well Differentiated/Dedifferentiated Liposarcoma and Leiomyosarcoma (TRAVELL): Results of a Phase II Study from the Italian Sarcoma Group. *ESMO Open* **2024**, *9*, 103667. [CrossRef] [PubMed]
345. Krasner, C.N.; Poveda, A.; Herzog, T.J.; Vermorken, J.B.; Kaye, S.B.; Nieto, A.; Claret, P.L.; Park, Y.C.; Parekh, T.; Monk, B.J. Patient-Reported Outcomes in Relapsed Ovarian Cancer: Results from a Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) versus PLD Alone. *Gynecol. Oncol.* **2012**, *127*, 161–167. [CrossRef] [PubMed]
346. Zuo, W.; Kwok, H.F. Development of Marine-Derived Compounds for Cancer Therapy. *Mar. Drugs* **2021**, *19*, 342. [CrossRef] [PubMed]
347. Harrison, S.J.; Mainwaring, P.; Price, T.; Millward, M.J.; Padrik, P.; Underhill, C.R.; Cannell, P.K.; Reich, S.D.; Trikha, M.; Spencer, A. Phase I Clinical Trial of Marizomib (NPI-0052) in Patients with Advanced Malignancies Including Multiple Myeloma: Study NPI-0052-102 Final Results. *Clin. Cancer Res.* **2016**, *22*, 4559–4566. [CrossRef] [PubMed]
348. Spencer, A.; Harrison, S.; Zonder, J.; Badros, A.; Laubach, J.; Bergin, K.; Khot, A.; Zimmerman, T.; Chauhan, D.; Levin, N.; et al. A Phase 1 Clinical Trial Evaluating Marizomib, Pomalidomide and Low-dose Dexamethasone in Relapsed and Refractory Multiple Myeloma NPI-0052-107): Final Study Results. *Br. J. Haematol.* **2018**, *180*, 41–51. [CrossRef]
349. Ebbinghaus, S.; Rubin, E.; Hersh, E.; Cranmer, L.D.; Bonate, P.L.; Fram, R.J.; Jekunen, A.; Weitman, S.; Hammond, L.A. A Phase I Study of the Dolastatin-15 Analogue Tasidotin (ILX651) Administered Intravenously Daily for 5 Consecutive Days Every 3 Weeks in Patients with Advanced Solid Tumors. *Clin. Cancer Res.* **2005**, *11*, 7807–7816. [CrossRef]
350. Tamura, K.; Nakagawa, K.; Kurata, T.; Satoh, T.; Nogami, T.; Takeda, K.; Mitsuoka, S.; Yoshimura, N.; Kudoh, S.; Negoro, S.; et al. Phase I Study of TZT-1027, a Novel Synthetic Dolastatin 10 Derivative and Inhibitor of Tubulin Polymerization, Which Was Administered to Patients with Advanced Solid Tumors on Days 1 and 8 in 3-Week Courses. *Cancer Chemother. Pharmacol.* **2007**, *60*, 285–293. [CrossRef] [PubMed]