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Exploring the Diversity of the Marine Environment for New Anti-cancer Compounds

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Marine ecosystems contain over 80% of the world's biodiversity, and many of these organisms have evolved unique adaptations enabling survival in diverse and challenging environments. The biodiversity within the world's oceans is a virtually untapped resource for the isolation and development of novel compounds, treatments, and solutions to combat human disease. In particular, while over half of our anti-cancer drugs are derived from natural sources, almost all of these are from terrestrial ecosystems. Yet, even from the limited analyses to date, a number of marine-derived anti-cancer compounds have been approved for clinical use, and several others are currently in clinical trials. Here, we review the current suite of marine-derived anti-cancer drugs, with a focus on how these compounds act upon the hallmarks of cancer. We highlight potential marine environments and species that could yield compounds with unique mechanisms. Continued exploration of marine environments, along with the characterization and screening of their inhabitants for unique bioactive chemicals, could prove fruitful in the hunt for novel anti-cancer therapies.

Keywords: cancer hallmarks, natural products, marine biodiversity, cancer therapy, marine medicine

INTRODUCTION

Cancer is a disease found in nearly all multicellular organisms (Aktipis et al., 2015). For most organisms, cancer is strongly associated with aging (Aunan et al., 2017). As individuals age, mutations accumulate within somatic cells of the body, giving rise to dysfunctional cells that forego their roles as members of a multicellular organism and activate functions, such as unregulated growth and invasion, which work against the health of the organism. In addition to uncontrolled growth, cancer displays several known "hallmarks" – phenotypic characteristics that are nearly universal across cancers. These hallmarks, described in two landmark papers by Hanahan and Weinberg, are genomic instability and mutation, sustained proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, inducing angiogenesis, reprogramming of energy metabolism, tumor-promoting inflammation, avoiding immune destruction, and activating invasion and metastasis (Hanahan and Weinberg, 2000, 2011).

Decades-long research efforts into the fundamentals of cancer and its hallmarks have led to substantial improvements in clinical outcomes for patients with several cancer types through the development of new diagnostics and therapeutics. However, many of these new technologies also come at a tremendous cost. For example, in the U.S., the national expenditure on cancer totaled more than $147.3 billion in 2017, with some patients spending as much as $10,000 a month on their cancer treatments. Moreover, for many patients, even the best and most costly therapies extend survival by only a few months. Continued efforts are urgently needed to identify promising new therapies to treat cancer.

Cancer therapies can be broadly segregated into two general classes: (1) naturally derived compounds and (2) synthetic compounds. Within each of these classes are two subcategories: small molecules and biologics. Small molecules are low molecular weight compounds that can readily enter cells to elicit a biological effect. Biologics, on the other hand, are larger biomolecules, such as monoclonal antibodies or small RNAs, which often cannot penetrate cells and/or require a delivery system to enter the cell membrane and exert their effects (Mocsai et al., 2014). Over three-fourths of all anti-cancer compounds are derived from natural sources (Newman and Cragg, 2020). For example, paclitaxel and docetaxel, two of the primary chemotherapy agents used to treat breast, prostate, and other cancers, were discovered and purified from naturally occurring plant taxanes (Verweij et al., 1994). Further chemical diversification of these natural plant taxanes has led to potent derivatives with unique properties, such as cabazitaxel.

Interestingly, while the majority of approved therapeutics are derived from natural sources, almost all of these are from terrestrial ecosystems. Hundreds of thousands of natural compounds have been discovered for a variety of uses, with over 100,000 from plants alone. In contrast, in the past three decades, over 2,000 marine-derived compounds have shown a wide range of application (Hu et al., 2015).

Despite the lower number of compounds identified from the marine environment, the enormous volume of the ocean comprises 99% of the total living space on earth and is home to 80% of the world's species (Malve, 2016). In addition to its species richness, the ocean is also comprised of extraordinary environmental diversity, with temperatures that span from −2°C to over 400°C (Mullineaux et al., 2018), pressures from 1 to over 1000 atm (Trenberth et al., 1987), salinities from 0 to over 36 ppt (Srokosz and Banks, 2019), from anoxic to normoxic, bright light to no light, and chemicals including H_2S, CH_4 (Lyman and Fleming, 1940), heavy metals, allelopathic defenses, and anthropogenic pollutants. Based on this environmental diversity, the earth's marine-dwelling inhabitants contain a potential treasure trove of anti-cancer therapeutics.

Although extraordinary potential still lies unexplored within the oceans, many marine-derived compounds that have been discovered have been discovered possess extremely potent anti-cancer properties (Montaser and Luesch, 2011). These compounds are derived from diverse organisms, act through multiple molecular mechanisms, and collectively target numerous cancer hallmarks. In this review, we discuss natural products or compounds directly derived from those natural products from marine macroorganisms with known activity against the hallmarks of cancer. While a number of reviews have exhaustively cataloged the suite of marine natural products with anti-cancer activity, we focus here on the cancer hallmarks as a framework to understand the spectrum of anti-cancer activity from marine-derived sources. We highlight key features of these potential therapies and their sources, and pinpoint strategies to maximize future efforts to identify novel compounds from the marine environment.

MARINE-DERIVED CANCER THERAPIES SHOW ACTIVITY SPANNING THE HALLMARKS OF CANCER

Over 40 years of active research in marine natural products has identified a host of bioactive compounds. We focused on literature that makes explicit reference to one or more of the cancer hallmarks. Analysis of these marine-derived anti-cancer compounds across the cancer hallmarks reveals that most marine-derived therapies act on the specific hallmark of resisting cell death. Out of the 42 compounds reviewed here, including those that act against more than one hallmark, 31 act on the resisting cell death hallmark (**Figure 1A**). The majority of drugs we categorized under this hallmark affect microtubule dynamics and induce apoptosis through cell cycle arrest. The next largest category of 11 compounds represents drugs that inhibit angiogenesis (**Figure 1A**). Most of these drugs act by suppressing vascular endothelial growth factor (VEGF) signaling. Interestingly, nine compounds target multiple hallmarks (**Figures 1B,C**). All other hallmarks are targeted by at least one marine-derived compound, with the exception of the genomic instability and mutation hallmark.

This variation in coverage across the cancer hallmarks is likely due to several factors. For one, bias in the methods used to evaluate anti-cancer properties is very likely, with the vast majority of research directed toward rapid assays for biological activity, such as proliferation, apoptosis, and cytotoxicity. Studies designed to interrogate hallmarks related to immune function, metabolism, and invasion/metastasis often require more complex, costly, and time-consuming experiments. Integrating existing statistical frameworks to predict mechanism of action (Huang et al., 2006) with a panel of simple assays to test newly isolated compounds for activity across the spectrum of cancer hallmarks would aid in identifying compounds with unique activities. In addition to the potential bias in assays used, it is also likely that many marine-derived compounds evolved to be toxins (Haefner, 2003), which may explain the increased representation of agents that target cell death pathways.

Among the compounds reviewed in this paper (see **Figure 2**), 19 have been tested in clinical trials, with six United States Food and Drug Administration (US FDA) approvals (eribulin, trabectedin, brentuximab vedotin, polatuzumab vedotin, cytarabine, and aplidin) and one approval in Australia (aplidin). All of these tested compounds target the resisting cell death cancer hallmark. Below we summarize specific marine-derived

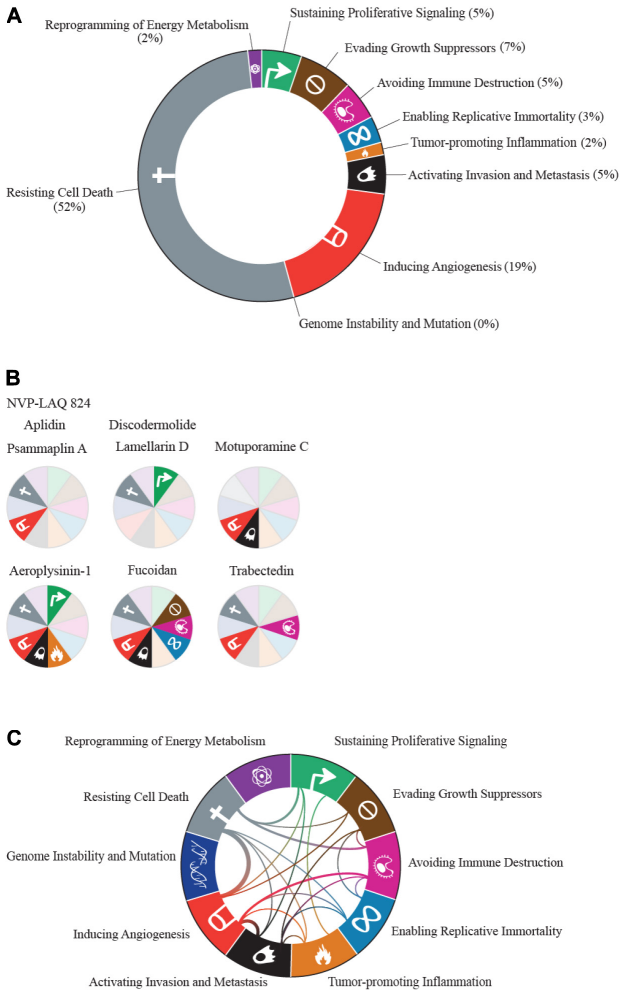

FIGURE 1 | The hallmarks of cancer, adapted from Hanahan and Weinberg (2011), visualized according to marine drug representation. **(A)** All proportions were calculated based on the number of drugs classified under each hallmark. Drugs that were categorized under more than one hallmark were counted multiple times. **(B)** Representation of compounds that are classified under multiple hallmarks. Hallmarks that the compound acted on are represented in brighter colors with hallmark symbols. Compounds that have the same classifications are represented with the same wheel. **(C)** Connections between hallmarks that share at least one compound. Thicker lines represent more compounds shared between the hallmarks.

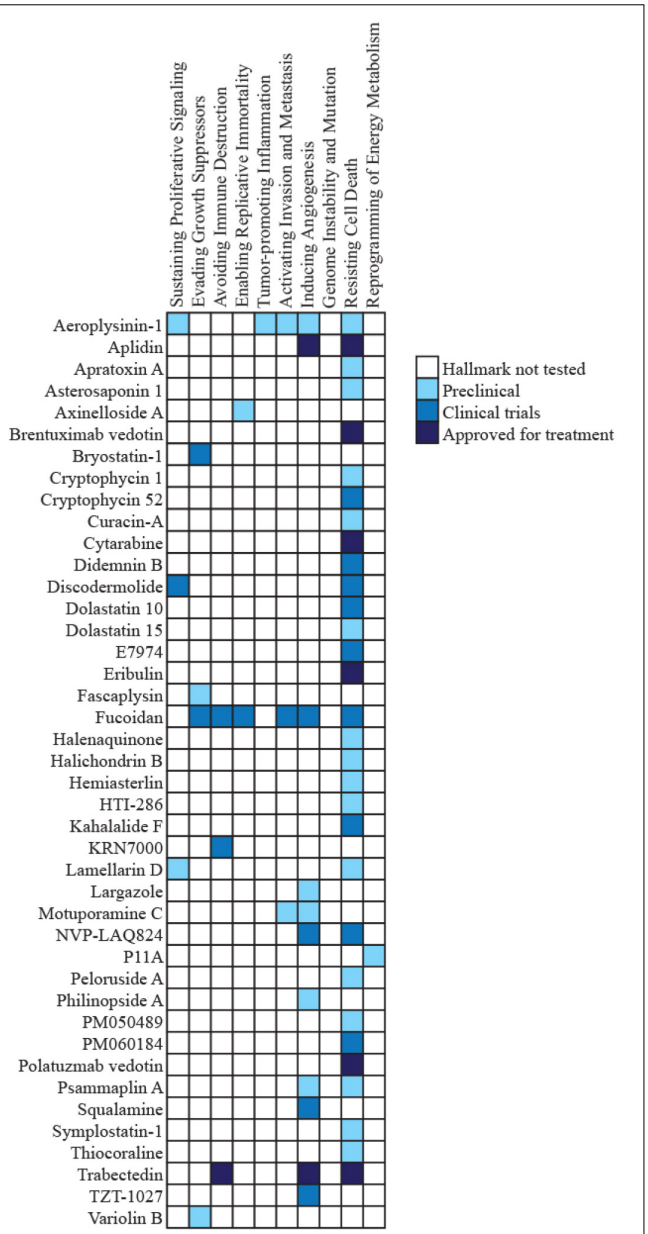

FIGURE 2 | Clinical trial status of marine-derived compounds. The heat map depicts the clinical trial status of each of the compounds discussed in this review, categorized by hallmark. Compounds that were categorized under more than one hallmark have the same color for clinical trial status across those hallmarks. Hallmarks that were not tested for the compound are colored white.

compounds and their known mechanisms of action across the cancer hallmarks.

Sustaining Proliferative Signaling

Healthy tissues carefully regulate cell division by controlling the release of growth-promoting signals that help determine precise timings in cycles of cell division (Jones and Kazlauskas, 2001). Cell cycle regulators only allow cell growth and division when all cellular requirements are met (Schafer, 1998). Unlike healthy cells, cancer cells co-opt growth signals to generate autocrine signals to divide or have dysfunctional receptors that are hypersensitive to growth signals (Hanahan and Weinberg, 2011). Imbued with these dysfunctional growth signaling properties, the cancer cells ultimately grow and divide more frequently than their neighboring normal cells, overtaking the space and resources available.

Inhibiting Epidermal Growth Factor Receptor (EGFR)

Some marine-derived drugs combat unchecked proliferation by preventing cell division through targeting of receptor-mediated growth signaling. For example, aeroplysinin-1 is a brominated

tyrosine metabolite first isolated from the marine sponge *Verongia aerophoba* originally collected from Capo Caccia (Fattorusso et al., 1972; Ciminiello et al., 1997). Aeroplysinin-1 is a cytostatic agent, which inhibits the growth of cells without killing them (Kreuter et al., 1989, 1990). Aeroplysinin-1 leads to growth arrest by inhibiting epidermal growth factor receptor (EGFR) phosphorylation and preventing downstream EGFR-mediated signaling (Kreuter et al., 1990).

Inducing Senescence

A group of growth-arresting marine compounds is the lamellarin family of alkaloids first isolated from the mollusk *Lamellaria* sp. found in Koror, Palau (Andersen et al., 1985). Lamellarins induce cancer cell growth arrest and subsequent cell death. The most notable of the lamellarins is lamellarin D, which has antiproliferative activity in cancer cells through a variety of mechanisms, including induction of senescence (Bailly, 2015). Ballot et al. (2014) reported that lamellarin D induces senescence in P388 mouse leukemia and HBL cutaneous melanoma cells by arresting them in the G2 phase of the cell cycle. Like lamellarin D, another compound that induces cell cycle arrest in G2 is discodermolide. Discodermolide is a polyketide first isolated from the sponge *Discodermia dissoluta* found at Lucaya, Grand Bahama Island (Gunasekera et al., 1990). Discodermolide stabilizes microtubules, which leads to cell cycle arrest and the induction of senescence (ter Haar et al., 1996; Klein et al., 2005).

Evading Growth Suppressors

In addition to growth promoting signals, normal cells use cell cycle checkpoints to limit cell division. One class of cell cycle checkpoint molecules is the cyclin-dependent kinases (CDKs). CDKs act as gatekeepers at key points in the cell cycle. In healthy cells, CDKs regulate whether a cell can progress to the next stage based on environmental and intracellular conditions (Canavese et al., 2012). A number of CDK inhibitors are currently approved for treatment of breast cancer (Schettini et al., 2018), and clinical trials of CDK inhibitors are completed or ongoing for liposarcoma (Dickson et al., 2013, 2016), non-small cell lung cancer (Gopalan et al., 2014), gastric and esophageal cancer (Karasic et al., 2020), ovarian cancer (Konecny et al., 2016), and prostate cancer[1] (NCT02905318).

Inhibiting Cyclins and Cyclin-Dependent Kinases

One marine-derived compound with known anti-CDK activity is fucoidan. Fucoidan is a sulfated polysaccharide that is a cell wall constituent first isolated in many types of brown seaweed, including *Laminaria* spp. (Bird and Haas, 1931). Fucoidan causes G1 arrest in 5637 and T-24 human bladder cancer cells as well as MCF-7 human breast cancer cells, which is mediated by downregulation of CDK2 and CDK4 (Banafa et al., 2013; Cho et al., 2014). Like fucoidan, fascaplysin also directly affects CDKs. It is a bis-indole alkaloid first isolated from the sponge *Fascaplysinopsis* Bergquist sp. in Ndravuni, Fiji (Roll et al., 1988; Hamilton, 2014). Fascaplysin inhibits CDK4 and induces G1 arrest. Fascaplysin also induces the build-up of reactive oxygen species and induces apoptosis (Soni et al., 2000; Hamilton, 2014). Another marine-derived CDK inhibitor, variolin B, is a pyridopyrrolopyrimidine alkaloid first extracted from the sponge *Kirkpatrickia varialosa* found in Cape Armitage in McMurdo Sound, Antarctica (Perry et al., 1994). Variolin B inhibits the activity of CDK1-cyclin B, CDK2-cyclin A, and CDK2/cyclin E complexes, causing HCT-116 human colon adenocarcinoma and A2780 human ovarian carcinoma cells to arrest in G2 and undergo apoptosis (Simone et al., 2005). One compound that inhibits cyclins is bryostatin-1, a PKC agonist. It is a macrocyclic lactone first isolated from *Bugula neritina* in the Gulf of Mexico (Pettit et al., 1982). Bryostatin-1 activates GSK3β, which induces the degradation of cyclin D1. This results in the induction of cell cycle arrest in the G2 phase (Wang et al., 2019). Bryostatin-1 has been tested in phase II clinical trials, but did not progress due to minimal activity (Raghuvanshi and Bharate, 2020). However, it is an effective anti-cancer agent when administered in combination with other drugs (Raghuvanshi and Bharate, 2020), such as dolastatin 10 or paclitaxel (Kortmansky and Schwartz, 2003; Kollar et al., 2014).

Resisting Cell Death

Apoptosis is a type of programmed cell death that is tightly regulated by multiple signaling cascades. The process can be initiated by either extrinsic or intrinsic pathways. In the extrinsic pathway, an extracellular ligand activates a death receptor that induces a signaling cascade to trigger cell death (Galluzzi et al., 2018). In the intrinsic pathway, mitochondrial instability induces mitochondrial outer membrane permeabilization through the B-cell lymphoma 2 (BCL2) apoptosis regulatory protein family (Galluzzi et al., 2018). Apoptosis occurs naturally within populations of normal cells to regulate cell number and control tissue and organ patterning, such as during embryonic development (Elmore, 2007). Tumor cells evade apoptosis in multiple ways, including loss of function in tumor suppressor genes and increased expression of anti-apoptotic regulators (Fernald and Kurokawa, 2013). By preventing apoptosis, cancer cells are able to survive for longer periods of time, which could lead to the acquisition of additional genetic and epigenetic lesions that contribute to the development of therapy resistance and metastasis.

Inducing Apoptosis Through Cell Cycle Arrest

Apoptosis is intimately linked to cell cycle regulation. Many genes involved in cell cycle progression are also involved in initiating apoptosis, and disrupting the cell cycle can trigger apoptosis (Evan et al., 1995). Drugs developed from marine sources combat the anti-apoptotic effects of cancer cells by inducing cell death in a variety of ways. Several of these compounds act by targeting cell cycle arrest, which subsequently induces apoptosis. One example of a class of compounds that inhibits cell cycle function is dolastatins. Dolastatins were first extracted from the sea hare, *Dolabella auricularia*, collected from the eastern coast of Mauritius (Pettit et al., 1993). Fifteen structurally unique dolastatins were identified (Pettit et al., 1989, 1993), of which the most active were dolastatins 10 and 15. Although dolastatin 10 is a pentapeptide and dolastatin 15 is a depsipeptide, both are

[1] clinicaltrials.gov

thought to bind to the vinca domain of tubulin and interfere with tubulin polymerization, disrupting mitotic cell division (Bai et al., 1990, 1992). Interfering with the formation and function of microtubules triggers the intrinsic mitochondrial apoptosis pathway (Bai et al., 1992; Bhalla, 2003). Like dolastatin 10, a variety of other marine-derived compounds exhibit similar ability to induce apoptosis (**Table 1**). Dolastatin 10 reached Phase II clinical trials in multiple cancers (Vaishampayan et al., 2000; Margolin et al., 2001; Saad et al., 2002; Hoffman et al., 2003; Kindler et al., 2005; Perez et al., 2005), but despite its favorable toxicity profile, it failed to show efficacy in any of these solid tumors.

Subsequent studies have developed antibody-drug conjugates using dolastatin 10 derivatives. In brentuximab vedotin, the dolastatin 10 analog monomethyl auristatin E (MMAE) is covalently bound to an antibody against CD30, an activator of B and T cells (Muta and Podack, 2013), to make an antibody-drug conjugate (Younes et al., 2010). While antibodies against CD30 were not significantly effective against lymphomas by themselves, the addition of MMAE greatly increased its efficacy (Younes et al., 2010). In March 2018, brentuximab vedotin was approved by the FDA for the treatment of Hodgkin's lymphoma[2]. Another similar antibody-drug conjugate is polatuzumab vedotin. This conjugate is comprised of MMAE covalently bound to an antibody against CD79b, a component of B cell receptors (Deeks, 2019). The antibody helps guide the drug to its target cells, where the drug is internalized and induces apoptosis (Deeks, 2019). This form of targeting and drug delivery greatly reduces the toxicity to normal cells, so long as the antibody target is highly specific to a target on tumor cells. Polatuzumab vedotin was approved for treatment of relapsed/refractory diffuse large B-cell lymphoma in June 2019 (Deeks, 2019).

Other marine-derived compounds induce cell-cycle arrest and apoptosis through mechanisms that are independent of the disruption of microtubule dynamics. For example, the disulfide bromotyrosine derivative, psammaplin A, first isolated from the sponge *Psammaplin aplysilla* in the Kingdom of Tonga (Quinoa and Crews, 1987), is a histone deacetylase inhibitor. In Ishikawa endometrial cancer cells, psammaplin A induces cell cycle arrest and apoptosis through the downregulation of cyclins and CDKs in a p53-independent manner (Ahn et al., 2008). The cinnamic hydroxamic acid NVP-LAQ824 is a synthetic derivative of psammaplin A and is also a histone deacetylase inhibitor (Atadja et al., 2004). It activates the p21 promoter, selectively causes cell cycle arrest at the G2/M phase, and induces apoptosis in H1299, HCT116, A549, DU145, PC3, and MDA435 cancer cells (Atadja et al., 2004). NVP-LAQ824 successfully passed Phase I clinical trials for advanced solid tumors (de Bono et al., 2008). Aplidin, which was first isolated from ascidian *Aplidium albicans* in the Mediterranean Sea (Erba et al., 2002), is a cyclic depsipeptide that causes cell cycle arrest in G1/G2 through an unknown mechanism (Erba et al., 2002). In addition, the cyclodepsipeptide apratoxin A first extracted from the cyanobacterium *Lyngbya majuscula* found in Finger's Reef, Guam induces apoptosis through cell cycle arrest (Luesch et al., 2001, 2006). Paatero et al. (2016) showed that apratoxin A specifically prevents protein translocation by inhibiting Sec61α, and thus blocks biogenesis.

[2]https://www.fda.gov/

TABLE 1 | Compounds classified under the resisting cell death hallmark that have a mechanism involving microtubules and cell cycle arrest to induce apoptosis.

Compound	Class	Species	Location	References
Asterosaponin 1	Sulfated steroidal glycoside	*Culcita novaeguineae*	Sanya Bay, South China Sea	Cheng et al., 2006; Tang et al., 2006
Cryptophycin 1	Cyclic depsipeptide	*Nostoc* sp. GSV 224	Of aquatic origin but grown in labs	Golakoti et al., 1995; Kerksiek et al., 1995
Curacin-A	Thiazole lipid	*Lyngbya majuscula*	Curaçao	Gerwick et al., 1994; Chang et al., 2004
Discodermolide	Polyhydroxylated lactone	*Discodermia dissoluta*	Lucaya, Grand Bahama Island	Gunasekera et al., 1990; Balachandran et al., 1998
E7974	Tripeptide	Synthetic analog of Hemiasterlin	–	Kuznetsov et al., 2009
Eribulin	Macrocyclic ketone	Synthetic derivative of Halichondrin B	–	Kuznetsov et al., 2004; Huyck et al., 2011
Halichondrin B	Polyether macrolide	*Halichondria okadai* Kadota	Aburatsubo, Japan	Hirata and Uemura, 1986; Bai et al., 1991
Hemiasterlin	Peptide	*Hemiasterella minor*	Sodwana Bay, South Africa	Talpir et al., 1994; Bai et al., 1999
HTI-286	Linear peptide	Synthetic analog of Hemiasterlin	–	Loganzo et al., 2003
Peloruside A	Polyketide	*Mycale hentscheli* (Carmia)	Pelorus Sound, New Zealand	West et al., 2000; Hood et al., 2002; Huzil et al., 2008; Chan et al., 2017
PM050489	Polyketide	*Lithoplocamia lithistoides*	Madagascar	Martin et al., 2013
PM060184	Polyketide	*Lithoplocamia lithistoides*	Madagascar	Martin et al., 2013
Symplostatin-1	Pentapeptide	*Symploca hydnoides*	Guam	Harrigan et al., 1998a; Khalifa et al., 2019; Mooberry et al., 2003
Thiocoraline	Depsipeptide	*Micromonospora*	Mozambique	Romero et al., 1997; Erba et al., 1999

Among these compounds, discodermolide (Mita et al., 2004) and E7974 (Rocha-Lima et al., 2012) reached Phase I clinical trials. PM060184 is in Phase II (see footnote 1, NCT03427268). Eribulin is FDA-approved for the treatment of metastatic breast cancer and liposarcoma, and aplidin is FDA-approved to treat multiple myeloma.

Inducing Apoptosis Through Replication, Translation, or Signaling Inhibition

While some marine-derived compounds act by inducing apoptosis through cell cycle arrest, other compounds induce apoptosis by targeting molecules that either activate apoptosis directly or are essential for cell survival. For example, didemnins are a class of depsipeptides that were first extracted from the Caribbean tunicate, *Tridemnum solidum* (Rinehart et al., 1981a). Among these peptides, didemnin B was the most potent (Rinehart et al., 1981a). Didemnin B inhibits protein synthesis by preventing eukaryotic elongation factor 2 (EEF2)-dependent translation elongation (Li et al., 1984; SirDeshpande and Toogood, 1995). Didemnin B reached Phase II clinical trials for the treatment of small cell lung cancer, but failed to show efficacy (Shin et al., 1994).

Another mechanism of inducing apoptosis is by disrupting pro-survival signaling cascades. The pentacyclic polyketide halenaquinone was first extracted from the sponge *Xestospongia exigua* found in Palau (Roll et al., 1983). Halenaquinone inhibits phosphoinositide 3-kinase (PI3K) and induces apoptosis in PC12 adrenal phaeochromocytoma cells (Fujiwara et al., 2001). Aeroplysinin-1, in addition to its effects on multiple hallmarks (**Figure 1B**), induces cytotoxic effects by inhibiting β-catenin signaling (Park et al., 2016).

Other compounds induce apoptosis by interacting with DNA in unique ways, such as trabectedin and cytarabine. Trabectedin is a tetrahydroisoquinoline alkaloid first isolated from the Caribbean tunicate *Ecteinascidia turbinata* (Rinehart et al., 1981b, 1991; D'Incalci and Galmarini, 2010). By binding to the minor groove of DNA, it causes DNA to bend at the major groove. The binding of trabectedin interferes with other factors that interact with DNA, such as transcription factors and DNA repair machinery, and ultimately results in induction of apoptosis (D'Incalci and Galmarini, 2010). Moreover, trabectedin can cause DNA strands to break by interacting with transcription-coupled nucleotide excision repair machinery (Takebayashi et al., 2001). Cytarabine, a synthetic analog of naturally occurring spongothymidine, also interferes with DNA replication (Bergmann and Feeney, 1951; Jimenez et al., 2018). This compound inserts into newly replicating DNA in place of nucleotides, which prevents elongation of the new daughter strand, and induces apoptosis (Iacobini et al., 2001; Jimenez et al., 2018). Cytarabine is FDA-approved for the treatment of leukemia and lymphoma.

Inducing Apoptosis Through Mitochondrial Interactions

In healthy cells, apoptosis can be initiated through mitochondrial instability. Outer mitochondrial membrane permeabilization releases cytochrome c into the cytoplasm where it activates apoptosis-inducing caspases (Lopez and Tait, 2015). Lamellarin D induces mitochondrial permeability by opening pores in the inner mitochondrial membrane, which leads to caspase activation and subsequent apoptosis (Kluza et al., 2006). Aplidin also disturbs mitochondrial permeability in addition to its ability to induce cell cycle arrest. It activates the Fas/CD95 pathway, which leads to mitochondria-mediated apoptosis in AML HL-60, T-lymphoid Jurkat, and HEL cells (Gajate et al., 2003).

Cancer cells overcome apoptotic signaling by upregulating anti-apoptotic proteins, such as BCL-2, to inhibit mitochondrial permeabilization (Lopez and Tait, 2015), or by inhibiting caspase-mediated downstream targets (Lopez and Tait, 2015). Compounds directed toward overcoming these resistance mechanisms by targeting multiple pathways or apoptosis mechanisms could represent promising candidates to treat apoptosis-resistant cancers. For example, some cryptophycins, first extracted from cyanobacteria *Nostoc* sp. GSV 224 (Golakoti et al., 1995), have anti-cancer properties. Treatment of human H460 non-small cell lung carcinoma cells with the depsipeptide cryptophycin 52 induces phosphorylation of BCL-2 and causes apoptosis in lung carcinoma cells (Lu et al., 2001). Cryptophycin 52 reached Phase II clinical trials. Similarly, fucoidan, in addition to targeting other hallmarks (**Figure 1B**), induces apoptosis by targeting parallel apoptotic-inducing pathways, including release of cytochrome c from mitochondria (Xue et al., 2012), and activation of caspases 3, 7, 8, and 9 (Kim et al., 2010; Xue et al., 2017).

Inducing Cell Death by Necrosis

While apoptosis is a well-studied mechanism of cell death, numerous mechanisms and pathways of cell death exist (Galluzzi et al., 2018). One of these mechanisms, necrosis, involves vacuolization and autolysis of cells in response to extreme stress. Necrosis can occur either as a result of ATP depletion or through specific signaling pathways (Edinger and Thompson, 2004). One drug that can induce cancer cell necrosis is kahalalide F, a peptide first isolated from the sea slug, *Elysia rufescens,* in Black Point, O'ahu, Hawaii (Hamann et al., 1996; Becerro et al., 2001). Experiments with HeLa cells suggested that kahalalide F targets lysosomes, which results in extreme vacuolization and swelling (Garcia-Rocha et al., 1996). Moreover, PC3, DU1445, LNCaP, SKBR-3, BT474, MCF7, MDA-MB-231, and LoVo cells treated with kahalalide F die from a combination of swelling, karyolysis, and necrosis (Suarez et al., 2003; Molinski et al., 2009). Kahalalide F reached Phase II clinical trials for melanoma, but showed no clinical benefit (Martin-Algarra et al., 2009).

Enabling Replicative Immortality

Normal cells have a limited number of cell divisions before they either die or enter senescence (Hayflick, 1992). This limit is driven by telomere shortening at each cell division (Allsopp et al., 1995), ultimately leading to crisis and death (Muraki et al., 2012). Cancer cells, however, enable replicative immortality, often through alterations in telomere maintenance, such as re-activation of telomerase or the alternative lengthening of telomeres pathway (Muraki et al., 2012).

Drugs That Inhibit Telomerase

Axinelloside A, a sulfated lipopolysaccharide first isolated from the sponge *Axinella infundibula* near Shikine-jima Island (Warabi et al., 2005), inhibits telomerase activity with an IC_{50} of 400 nM (Warabi et al., 2005). Given the potency of axinelloside A and its mechanism of telomerase inhibition, subsequent efforts have established a scalable system to develop compounds similar to the structure of axinelloside A (Guang et al., 2017). Like axinelloside A, fucoidan, in addition to its other mechanisms of cancer cell inhibition (**Figure 1B**), also inhibits telomerase activity by reducing human telomerase reverse transcriptase (hTERT) expression (Han et al., 2017).

Inducing Angiogenesis

Tissues require sufficient blood supply to transport oxygen, nutrients, and waste products (Potente et al., 2011). Under normal circumstances, the growth of new blood vessels, known as angiogenesis, only occurs in certain conditions, such as wound healing, menstruation, and embryonic development (Tonini et al., 2003). Cancer cells induce angiogenesis, which provides nutrient supplies to sustain tumor growth. One of the main activators of angiogenesis is VEGF (Carmeliet, 2005; Goel and Mercurio, 2013). VEGF signals to its receptor, VEGFR, which induces signaling and gene expression pathways related to cell survival, actin reorganization, cytoskeletal rearrangement, migration, and vascular cell permeability.

Inhibiting Vascular Endothelial Growth Factor (VEGF)

A number of compounds affect tumor vasculature through VEGF inhibition. The cyclodepsipeptide TZT-1027, a synthetic derivative of dolastatin 10, causes necrosis by damaging tumor vasculature (Otani et al., 2000). TZT-1027 enhances vascular permeability, resulting in the accumulation of red blood cells and damage to tumor vasculature (Watanabe et al., 2007). Damage to the vasculature causes the depletion of oxygen and nutrients to the tumor, resulting in necrosis-mediated cell death (Natsume et al., 2003). However, a Phase II clinical trial of TZT-1027 in non-small cell lung cancer was inconclusive (Riely et al., 2007). Similarly, largazole, first extracted from cyanobacteria of *Symploca* sp. in Key Largo, Florida Keys (Taori et al., 2008), is a cyclodepsipeptide that inhibits VEGF signaling. Largazole rapidly metabolizes into a thiol in the cell and inhibits histone deacetylases (Ying et al., 2008). It also inhibits VEGF and its receptor, thus inhibiting angiogenesis and inducing apoptosis (Liu et al., 2013). Like largazole, Motuparamine C also affects VEGF signaling (Roskelley et al., 2001). It is an alkaloid first extracted from the sponge *Xestospongia exigua* in Motupore Island, Papua New Guinea (Williams et al., 1998).

Interestingly, several compounds that affect VEGF signaling also affect the hallmark of resisting cell death, including aplidin, trabectedin, NVP-LAQ824, and fucoidan. A schematic representation of all drugs that inhibit multiple hallmarks is provided in **Figure 1B**. Aplidin prevents angiogenesis by inhibiting VEGF signaling. It also blocks VEGF secretion and inhibits the formation of capillary-like structures (Broggini et al., 2003; Taraboletti et al., 2004). Trabectedin inhibits VEGF mRNA expression, inhibits the activity of cytokines, and induces the activity of anti-angiogenic cytokines, such as tissue inhibitor metalloproteinase 1 (TIMP-1) and Serpin E1 (Atmaca and Uzunoglu, 2014). NVP-LAQ824 downregulates the expression of VEGF *in vivo* in mouse models (Qian et al., 2004). In a similar manner, philinopside A affects VEGF signaling through the VEGF receptor. Philinopside A is a sulfated triterpene glycoside first extracted from the sea cucumber, *Pentacta quadrangulari*, found in the South China Sea (Tong et al., 2005; Aminin et al., 2015). Fucoidan, which acts across multiple hallmarks (**Figure 1B**), including resisting cell death, evading growth suppressors, and enabling replicative immortality, also prevents angiogenesis by inhibiting VEGF and suppressing neovascularization (Xue et al., 2012; Senthilkumar et al., 2013).

Inhibiting Angiogenesis Through Other Mechanisms

In addition to direct inhibition or downregulation of VEGF signaling/expression, a number of compounds suppress angiogenesis through alternative mechanisms. For example, squalamine is an aminosterol first isolated in a dogfish shark, *Squalus acanthias*, from off the New England Coast (Moore et al., 1993). Squalamine was originally identified as an antibiotic and fungicide, but was later found to inhibit neovascularization by suppressing mitogen-induced proliferation of endothelial cells that form blood vessels (Sills et al., 1998). It was successful in a Phase I/II trial for non-small cell lung cancer (Herbst et al., 2003). By contrast, psammaplin A, in addition to its role in suppressing cell death resistance, also inhibits aminopeptidase N, a galectin 3 binding partner that induces endothelial cell migration (Yang et al., 2007).

While squalamine and psammaplin A have defined mechanisms of action, other compounds, such as aeroplysinin-1, have unknown mechanisms of anti-angiogenic activity. Aeroplysinin-1 caused severe disorganization in existing blood vessels and inhibition of new blood vessel growth in the areas where the drug was applied (Rodriguez-Nieto et al., 2002). Moreover, blood vessels outside the area of application grew around the site (Rodriguez-Nieto et al., 2002). Aeroplysinin-1 also affects the sustaining proliferative signaling and resisting cell death hallmarks (**Figure 1B**).

Activating Invasion and Metastasis

The cause of death for nearly all patients with solid tumors is by metastatic spread of their cancer to a new site in the body. Metastasis is often a multi-step process involving detachment from neighboring tumor cells, invasion, intravasation, dissemination, extravasation, seeding, and colonization. Drugs that target one or more steps in this process have potential to prolong the lives of patients with advanced, metastatic disease.

One marine-derived compound with potential anti-metastatic capability is motuparamine C. Motuparamine C inhibits the migratory ability of cancer cells (Roskelley et al., 2001) by inducing actin filament disassembly, ultimately resulting in a decrease in cancer cell invasion (Roskelley et al., 2001). Aeroplysinin-1 downregulates integrin β1, preventing cell

migration and adhesion (Bechmann et al., 2018). Another potential anti-metastatic agent is fucoidan, which targets multiple cancer hallmarks (**Figure 1B**). Fucoidan inhibits cancer cell invasion and metastasis through numerous mechanisms, including preventing interactions between tumor cells and fibronectin within the extracellular matrix, interfering with tumor cell-platelet interactions, and inhibiting invasion through suppression of matrix metallopeptidase 2 (MMP-2) (Liu et al., 2005; Cumashi et al., 2007; Lee et al., 2012; Atashrazm et al., 2015). Fucoidan also prevents epithelial-mesenchymal transition (Senthilkumar et al., 2013), a key process in metastasis of many solid tumors in which epithelial-like cancer cells undergo a reversible phenotypic transition to a more invasive, mesenchymal-like state (Jolly et al., 2017, 2019). Fucoidan is currently in Phase II clinical trials for metastatic colorectal cancer (see footnote 1, NCT04066660).

Genome Instability and Mutation

For normal cells to become cancerous, they must acquire mutations that enable the traits of the cancer hallmarks. These new mutations can lead to tumor formation if they favor long-term proliferation and allow cells to dominate their environment (Hanahan and Weinberg, 2011). Mutations in DNA repair machinery or telomeres are particularly harmful to healthy cells and can increase the rate of mutations, and thus the likelihood of developing cancer (Kinzler and Vogelstein, 1997). Unfortunately, no marine-derived compounds have been identified to date that can target cells with dysfunctional DNA repair machinery.

Reprogramming of Energy Metabolism

Metabolic reprogramming by cancer cells has been recognized as a key hallmark for almost a century, with landmark discoveries by Otto Warburg in the 1920s showing that cancer cells can utilize aerobic glycolysis to produce ATP even in oxygen-rich conditions (Warburg et al., 1927; Liberti and Locasale, 2016). Renewed focus on this cancer hallmark has also revealed numerous other metabolic alterations and has pinpointed how these alterations affect both gene expression and interactions between cancer cells and the tumor microenvironment (Pavlova and Thompson, 2016).

The compound P11A is a streptodepsipeptide that was first isolated from the actinobacterium, *Streptomyces* S11-23B in the East China Sea (Ye et al., 2017). It counteracts alterations in metabolism by downregulating genes involved in glycolysis and glutaminolysis in glioma cells, including HK2, PFKFB3, PKM2, GLS, and FASN (Ye et al., 2017).

Tumor-Promoting Inflammation

The relationship between inflammation and cancer is complex. The inflammatory response can be either a cancer-protective or cancer-enabling feature. For example, inflammation at the sites of solid tumors has been shown to promote tumorigenesis and aid cancer cells in the process of gaining the characteristics of other hallmarks (Qian and Pollard, 2010). Moreover, factors secreted by immune cells can increase mutation rates in cancer cells, thus enabling cancer cells to take on characteristics of other hallmarks (Grivennikov et al., 2010). Aeroplysinin-1 has the potential to inhibit inflammation by decreasing the levels of total reactive oxygen species (Garcia-Vilas et al., 2018), which may make this compound a promising agent to reduce the tumor-promoting effects of inflammation.

Evading Immune Destruction

The immune system is critically important for surveilling and eliminating precancerous and cancerous cells. Cancer cells evade immune surveillance by (1) escaping immune recognition and (2) inducing immune suppression through the secretion of immunosuppressive ligands (Gonzalez et al., 2018). The burgeoning area of immuno-oncology seeks to activate a patient's immune system by targeting tumor-immune interactions to eradicate cancer cells. Interestingly, several marine-derived compounds act on the immune system to inhibit cancer, making these compounds promising agents for use as single agents or in combination with existing immunotherapies.

For example, KRN7000 is a synthetic analog of agelasphin-9b, which was extracted from the sponge *Agelas mauritianus* (Haefner, 2003). KRN7000 is a potent immunostimulant that induces lymphocyte proliferation (Morita et al., 1995), enhances invariant natural killer cell activity (Tashiro, 2012), and inhibits both tumor growth (Morita et al., 1995) and metastasis in mouse models (Yamaguchi et al., 1996). Natural killer cell activity is stimulated by interaction of KRN7000 with the CD1d receptor (Nicol et al., 2000). In a Phase I-II study of KRN7000-pulsed peripheral blood mononuclear cells in non-small cell lung cancer, KRN7000 stimulation was associated with increased production of interferon gamma and prolonged median survival times in a subset of patients (Motohashi et al., 2009). Since the discovery of KRN7000, a number of analogs and modifications have been reported that have increased immunostimulatory effects (Shiozaki et al., 2013; Tashiro et al., 2013).

Like KRN7000, fucoidan also improves the activity of the immune system against cancer cells. As mentioned above, fucoidan has demonstrated activity across multiple cancer hallmarks (**Figure 1B**). In addition to its roles across these hallmarks, fucoidan also works broadly as an immune stimulant across multiple immune subsets, including decreasing neutrophil apoptosis, activation of splenic dendritic and T-cells (Zhang et al., 2015), and activation of natural killer cells (Ale et al., 2011).

Trabectedin, which is approved for the treatment of soft tissue sarcoma, has been shown to have anti-tumor efficacy by inducing cell death of monocytes. The selective induction of apoptosis in monocytes is due to the differential expression of signaling tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors on monocytes and decoy receptor expression in other immune subsets, such as neutrophils and lymphocytes (Germano et al., 2013). Trabectedin increased the number of infiltrating T-lymphocytes in a spontaneous model of osteosarcoma metastasis, many of which expressed programmed cell death-1 (PD-1) (Ratti et al., 2017). Combination with an anti-PD-1 therapeutic antibody led to significantly increased control of osteosarcoma growth (Ratti et al., 2017), highlighting the importance of testing biologically informed immunotherapy combinations with these marine-derived agents.

Compound Classification by Common Mechanisms

The compounds discussed in this review were broadly classified by mechanism of action in **Figure 3**. Of these, the largest group of compounds with a common mechanism inhibits the activity of microtubules (**Figure 3A**). These compounds predominantly belong to the peptide and polyketide classes. There were a similar number of compounds that inhibit the growth of blood vessels and interfere with the cell cycle (**Figures 3B,C**). Compounds that inhibit new blood vessel growth are more diverse in their structures (**Figure 3B**) while those that interfere with the cell cycle are mostly alkaloids and peptides (**Figure 3C**).

BIOGEOGRAPHY OF MARINE SPECIES THAT ARE SOURCES OF ANTI-CANCER COMPOUNDS

The marine organisms that harbor anti-cancer chemicals span many phyla, but share some phenotypic characteristics. Many of these organisms lack significant structural defenses and have evolved the ability to create or harness secondary metabolites to reduce predation by being unpalatable or toxic. Many are benthic and either sessile, like sponges (phylum Porifera), bryozoans (phylum Bryozoa), and tunicates (phylum Chordata) or slow moving, like sea hares and sea slugs (phylum Mollusca) and sea cucumbers (phylum Echinodermata) (see **Table 2** for examples). Sponges and cnidarians have long been used as sources of marine chemicals and are the two most common marine macrofaunal taxa from which bioactive compounds have been isolated (Mehbub et al., 2014). Indeed, soft, sessile, and slow marine species of any taxa are good candidates for the presence of novel metabolites to test, since they often lack other means of avoiding predation or foraging. The annual reviews of these compounds by Carroll et al. (2019, 2020) provide a comprehensive overview of compounds, their origins, and biological activities.

Not all novel compounds are necessarily created by the macrofauna from which they were isolated. Many come from symbiotic bacteria, like *Candidatus Endobugula sertula*, the symbiont in *Bugula neritina* that produces bryostatin-1 (Davidson et al., 2001). Others come from the microorganisms an animal consumes. For example, Luesch et al. (2001) proposed

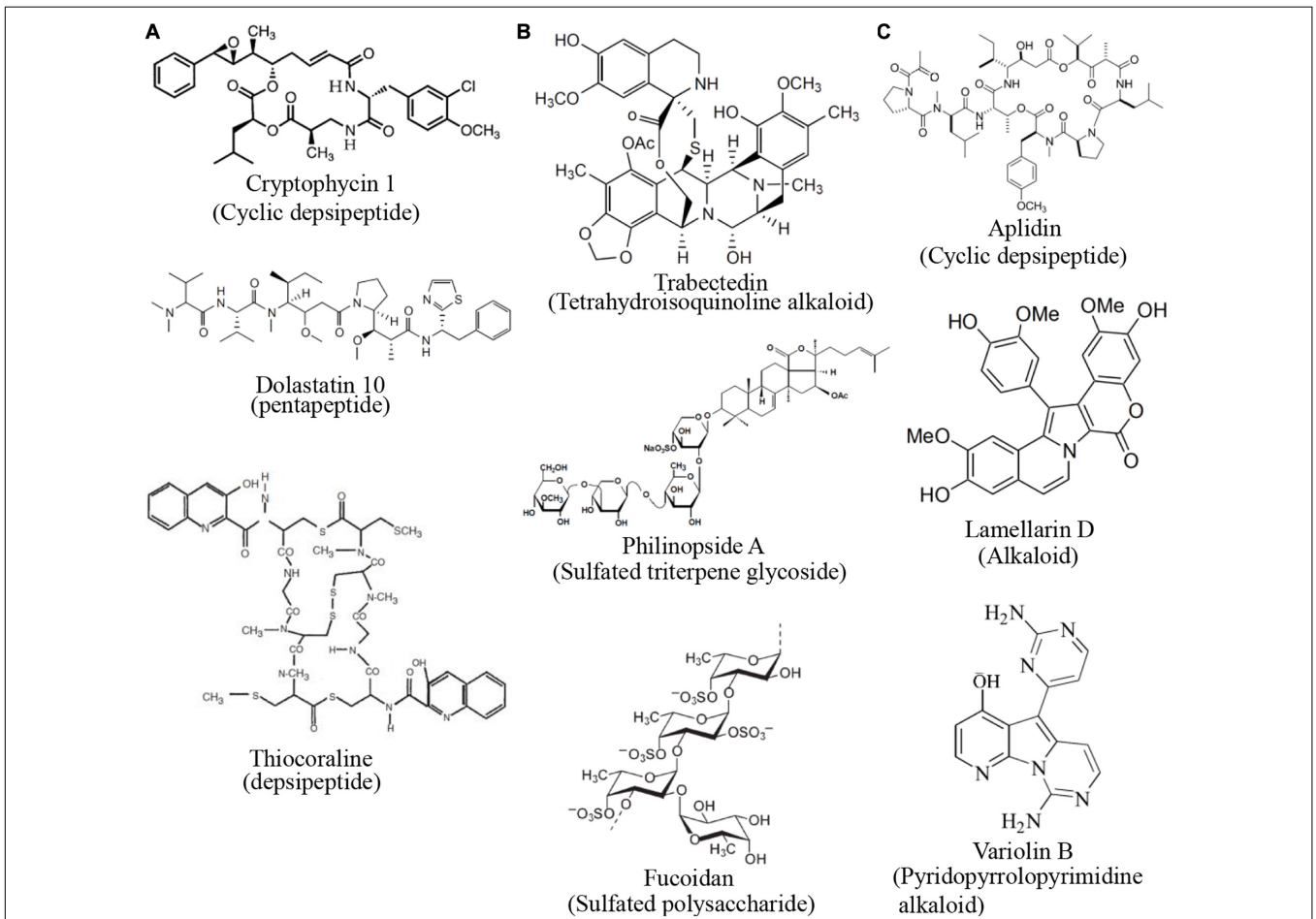

FIGURE 3 | Structures of compounds with common mechanisms. **(A)** Some compounds that inhibit the activity of microtubules **(B)** Some compounds that inhibit blood vessel growth **(C)** Some compounds that interfere with the cell cycle. Structure images were taken from cited journals.

TABLE 2 | Compound use in marine species.

Compound	Species	Compound use	Symbionts	References
Aeroplysinin-1	*Verongia aerophoba* (sponge)	Chemical defense	–	Garcia-Vilas et al., 2015
Apratoxin A	*Lyngbya majuscula* (cyanobacteria)	Secondary metabolite formed during photosynthesis	–	Paerl et al., 2016
Asterosaponin 1	*Culcita novaeguineae* (starfish)	Chemical defense	–	Tang et al., 2006
Bryostatin-1	*Bugula neritina*	Antipredator chemical defense role	Similar to metabolites produced by bacterial symbiont *Candidatus Endobugula sertula*	Davidson et al., 2001
Dolastatin 10	*Dolabella auricularia* (sea hare /shell-less mollusk)	Dietary origin	Also found in Paulauan Cyanobacteria	Luesch et al., 2001
Dolastatin 15	*Dolabella auricularia* (sea hare/shell-less mollusk)	–	Found in *Lyngbya majuscula/Schizothrix calcicola* (cyanobacteria)	Harrigan et al., 1998b
Halichondrin B	*Halichondria okadai Kadota* (sponge)	Collect micro-organism by filteration of sea-water	Produced by symbiont bacteria	Hirata and Uemura, 1986; Lichota and Gwozdzinski, 2018
Kahalalide F	*Elysia rufescens* (sea slug)	Chemical defense	Possible bacterial origin	Davis et al., 2013
Lamellarin D	*Lamellaria* sp. (prosobranch mollusc)	Used by host as a predatory mechanism	–	Bailly, 2015
Peloruside A	*Mycale hentscheli (Carmia)* (sponge)	Seasonal and spatial variation in metabolite production	Multiproducer consortium	Page et al., 2005; Rust et al., 2020; Storey et al., 2020
Psammaplin A	*Psammaplin aplysilla* (sponge)	–	Also found in marine microalgae, cyanobacteria, and symbiotic, heterotrophic bacteria	Lichota and Gwozdzinski, 2018
Trabectedin	*Ecteinascidia turbinata* (tunicate)	–	Produced by bacterial symbiont, *Candidatus Endoecteinascidia frumentensis*.	Le et al., 2015; Lichota and Gwozdzinski, 2018
Variolin B	*Kirkpatrickia varialosa* (sponge)	Aposematic coloration against predation	–	Perry et al., 1994

that dolastatin 10 may not be produced by the sea hare *Dolabella auricularia*, but rather by the cyanobacteria that it consumes. Likewise, the sea slug *Elysia rufescens* accumulates high concentrations of the anti-cancer compound Kahalalide F by consuming algae and their associated bacteria (Zan et al., 2019).

However, the interaction between the sea hare and the cyanobacterium is important, since the sea hare is responsible for accumulating the compound at higher concentrations in its tissues, facilitating identification and isolation. Thus, marine bacteria, fungi, algae, and the species that host them or eat them represent worthwhile candidates for further investigation.

Like the diversity of organisms that contain anti-cancer compounds, the habitats from which marine anti-cancer chemicals have been isolated are also diverse. These habitats span the globe, with the majority located near coastal areas or small islands in the tropical Pacific Ocean (**Figure 4A**). This, like most historical marine research, is likely due to ease of access to species at those locations. Estuarine and coastal environments are often home to vibrant communities of the taxa outlined above. Tropical coral reefs and shallow fouling communities are amongst the most studied and can have high abundance, biodiversity, and species richness with plentiful predators. These biological factors likely contribute to evolution of defensive chemicals in soft bodied organisms (Bakus, 1981).

Very few chemical isolations have been reported from the open ocean or in extreme environments, which is likely the result of substantial barriers associated with exploring these environments. While the barriers to exploration are often substantial, extreme environments can provide the biological, chemical, and/or physical challenges that might lead to the evolution of compounds with anti-cancer properties, and may be prime locations in which to search. One such extreme environment is Antarctica with extremes in day length and ocean temperatures normally below 0°C and a variety of known physiological adaptations. In addition, Antarctica is also home to abundant benthic communities composed of soft-bodied species likely because of a lack of large crustacean predators (Aronson and Blake, 2001). Interesting examples of compounds isolated from the cold waters of Antarctica include Variolin B, which was isolated from the sponge *Kirkpatrickia variolosa*, and displays pro-apoptotic activity and inhibits CDK activity (Simone et al., 2005), and Palmerlolide A and other macrolides isolated from the tunicate *Synoicum adareanum*, with cytotoxicity against melanoma cells by inhibiting vacuolar ATPase (Diyabalanage et al., 2006; Noguez et al., 2011).

Another extreme environment that is a promising location in which to search for anti-cancer compounds is the deep sea. The deep sea is the largest environment on Earth. With its

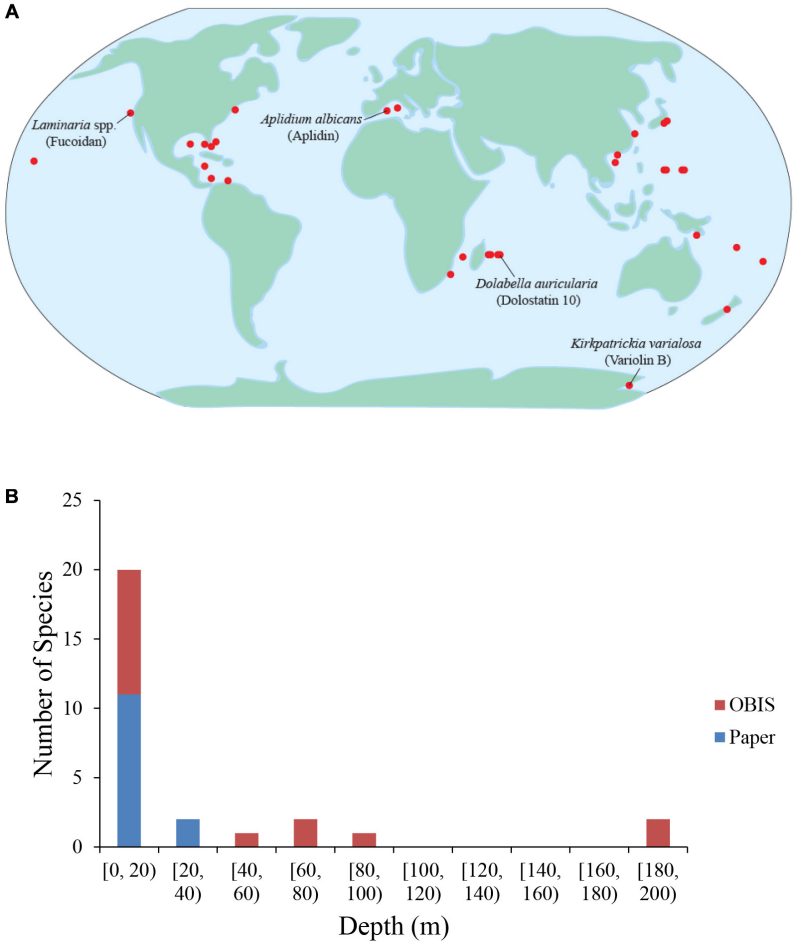

FIGURE 4 | Geographic and depth distribution of known marine drug sources. **(A)** Each dot represents one marine source for one drug. No synthetic compounds were included. Some species and their compounds are labeled. **(B)** Depths of the marine drug source species at times of collection. The red color depicts species whose depth was determined by data from the Ocean Biogeographic Information System (OBIS), while the blue color depicts species whose depth was reported in the original papers describing the characterization/extraction/etc. of the compound (indicated as "Paper").

decreasing sunlight and available organic carbon and increasing hydrostatic pressure with depth, the deep sea pelagic and benthic realms are full of novel biological adaptations. An analysis of the sampling depths across identified species and compounds reviewed herein reveals that nearly all reported isolations thus far have taken place between the surface and approximately 200 m (**Figure 4B**). The lack of isolations at depths deeper than 200 m is likely due to the difficulties associated with sampling at greater depths and/or the inability to recollect promising organisms. The deep-sea floor is commonly home to sea cucumbers, and rocky outcrops are often the sites of deep-sea coral reefs, many of them made of soft corals. In the deep-sea, other even more extreme environments exist that add toxic chemicals to the physical challenges. Deep-sea hydrothermal vents and cold seeps host abundant endemic communities dependent on organic carbon from hydrogen sulfide- or methane-based chemosynthesis (Van Dover, 2000). These environments are so toxic that often only endemic species can survive. Often, these species either utilize the abundant sulfide available or employ detoxification strategies to remove it from their systems (Zierenberg et al., 2000). Some species from these deep-sea environments that are particularly promising with respect to anti-cancer compounds are those that produce chemical deterrents to render them unpalatable as food (Kicklighter et al., 2004). Interestingly, all the species in the study that employed chemical defenses contained chemoautotrophic bacteria, which emphasizes the importance of symbiotic relationships with bacteria and the role their hosts play in accumulating these chemicals.

The sea also contains many hypoxic areas that support organisms with adaptations to low-oxygen conditions, which may promote the adaptation of compounds with unique properties. Hypoxic zones are home to microbes, invertebrates, and fish with adaptations for survival under chronic hypoxic stress (Childress and Seibel, 1998). Adaptations to these oxygen-poor zones include smaller and thinner bodies, more efficient respiratory surface area, and symbiosis with

sulfide-oxidizing organisms (Levin, 2003). Deep bodies of water, like the Black Sea and many high-latitude fjords, with limited deep circulation often become hypoxic or anoxic at depth. The hypoxic marine ecosystems that are easiest to access are muddy, coastal benthic areas. The interstitial water within the sediments is decreasingly oxygenated with depth, yet can be full of organisms across the spectrum of taxa. Bivalved molluscs (e.g., clams and mussels) often close their valves for hours at a time and transition to anaerobic metabolism for the duration (McMahon, 1988). The adaptations observed throughout marine hypoxic environments are often unique to these locations, which increases the probability that species living in such environments utilize unique compounds.

CONCLUSION

With their diverse and highly complex habitats and lifestyles, marine species represent a vast, largely unexplored source of potential anti-cancer agents. Despite the current successes and enormous potential of exploring the marine chemical landscape, several barriers must be overcome before additional, substantial progress can be made. First, improvements in synthesis, isolation chemistry, and production of synthetic derivatives are needed to address the high complexity of many of these compounds, which often have multiple chiral centers. Indeed, with thousands of these bioactive compounds having been isolated and tested over the years, the few compounds that have entered clinical trials were among the rare minority that were abundant enough or simple enough to isolate for testing. Second, there is an urgent need to conserve and preserve marine natural habitats, both for its inherent and anthropocentric value: Innovations in synthesis and isolation must be combined with sustainable efforts to increase sampling across more diverse and extreme marine environments. Third, the development of a platform to analyze newly isolated compounds for activity across the hallmarks of cancer would provide a robust and rapid system to identify new anti-cancer therapies with enhanced specificity to target multiple hallmarks and hallmarks of advanced disease, such as metastasis and immune evasion. Encouragingly, among the compounds already discovered, they collectively target nearly all of the hallmarks of cancer, mirroring the substantial diversity inherent within the marine ecosystem. With many marine species yet to be discovered, countless novel compounds may exist with the potential to enhance and complement the existing arsenal of anti-cancer therapeutics.

AUTHOR CONTRIBUTIONS

DD, JS, SK, ES, and CR conceived and designed the study. DD, BT, SK, and ES performed the literature review. DD, BT, JO, SK, ES, MD-D, TS, DR, WE, CR, and JS wrote the manuscript. All the authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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