Marine Bioactive Peptides in cancer treatment

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Abstract. Marine bioactive peptides (MBPs) are secondary metabolites, which are natural compounds isolated from several species such as sponges, tunicates, mollusks, fungi, algae, and cyanobacteria. MBPs represent a novel source in the field of cancer drug discovery since they contain important pharmaceutical properties and an impressive structural diversity. Their anticancer mechanisms are mediated through multiple mechanisms, including induction of apoptosis and cell cycle arrest, inhibition of angiogenesis, metastatic suppression by modulation of different oncogenic proteins, disruption of cytoskeletal organizations, and interference activity to some signaling pathways. Notable examples include Dola statin 10, Didemnin B, Plitidepsin, Kahalalide F, Jaspa ide, Homothymine, and Larrazolo, which have progressed to clinical trials. The antibody–drug conjugate technology enabled derivatives such as Adcetris® to be feasible for the clinical research. However, the major challenges, like oral bioavailability, enzymatic stability, and toxicity, still exist. Current research is focusing on structural modification, targeted delivery systems, and nanotechnology-based formulations to address these limitations. Collectively, MBPs hold enormous promise for being lead compounds in designing new generations of anticancer therapeutics that define the maritime environment as a crucial frontier in oncology drug discovery.

Keywords: Marine bioactive peptides, Cancer, Cancer treatment.

1. Introduction

The global economy is expanding, and with it, the burden of cancer continues to rise [1]. Recent studies show that cancer mortality has steadily increased in recent years. By 2040, cancer cases worldwide are expected to be 47% higher than in 2020 [2]. Science has achieved remarkable progress, and therapies continue to improve. However, conventional cancer treatments still face built-in limits. Chemotherapy drugs, for example, attack fast-dividing tumor cells. But they also harm normal cells that divide quickly. Normal tissues can even develop resistance to treatment at an early stage, sometimes right at the beginning. As a result, many patients fail to achieve effective clinical outcomes [3].

Exploration of marine biodiversity is bringing to light MBPs as a potentially important pharmaceutical modality; in fact, it is one of the most crucial areas in medicinal chemistry with great possibilities for clinical translation. Marine ecosystems are structurally prolific reservoirs of compounds with biological activities. High salinity, very extreme thermal conditions, and hydrostatic pressure have led marine creatures to develop specific biochemical defense mechanisms that resist pathogenic genetic mutations as well as microbial and viral attacks. Among the marine microorganisms (bacteria/fungi), antimicrobial peptides and polyketides can be exemplified [4]. The sponges offer macrocyclic lactones and alkaloids; the former mostly act as precursors for antitumor agents. Seaweed contains mainly sulfated polysaccharides and carotenoids; the former has strong antioxidant activity. Fish and shellfish mainly contain omega-3 fatty acids and anticoagulant peptides. MBPs are low-molecular-weight, structurally diverse functional protein fragments with experimentally validated target-specific bioactivities. They can be classified by either chemical structure—such as α-helical peptides, β-sheet or cyclic peptides, thioether-containing cyclic peptides, linear enriched peptides, and lipopeptides—or by their biological function, including cardiovascular-regulating, anticancer, antimicrobial, antioxidant, and bone-regenerative peptides [5].

The pursuit of new anticancer candidates remains the main research priority in oncology drug discovery. Recent studies highlight MBPs' peculiar scientific and clinical validation as new anticancer

candidates. MBPs may individually exert their pharmacological actions through different mechanistic pathways, providing multi-target modulation to overcome the limitations associated with conventional therapeutics. For instance, mollusk-derived peptide MML activates apoptosis by the Caspase-8/3 signaling pathway and overcomes resistance against chemotherapy. Most tumors rely heavily on vascular endothelial growth factors (VEGF) and its receptors to sustain angiogenesis; in this context, polysaccharides derived from the sea cucumber Cucumaria strongly inhibit neovascularization, thereby preventing tumor growth and metastasis. Furthermore, peptides like Dola statin 10 found in sea mollusks stick to the peptide-sharing spot on β-tubulin, stopping tubulin from joining. They are disrupting the assembly of microtubules and thereby halting cell division, ultimately triggering apoptosis. Importantly, some MBPs also exhibit synergistic effects, further enhancing their anticancer efficacy. This review aims to systematically collate the most recent advances in MBP research, indicating their broad bioactivities, mechanistic diversity, and potential as lead compounds in the development of next-generation anticancer therapeutics.

2. Sources and Characteristics of Marine Bioactive Peptides

Marine organisms are a tremendous source of bioactive peptides representing different structural and organic diversity. Marine fungi, sponges, tunicates, mollusks, cyanobacteria, and algae produce their peptides through both ribosomal and non-ribosomal pathways. These peptides are typically found in linear, cyclic, and depsipeptide forms [6–7]. Table 1 provides an overview of the biosynthetic origins, structural diversity, stability, and bioavailability of peptides from various marine sources.

Table 1. Sources and Characteristics of Marine Bioactive Peptides

Producers	Biosynthetic pathways	Structural diversity	Stability	Bioavailability
Marine Sponges	Nonribosomal (NRPS) [6]	·Cyclic depsipeptides · D-amino acids/Br-tryptophan modifications ·Linear peptides with disulfide bonds	·High enzymatic resistance	·Poor oral absorption ·Requires parenteral administration.
tunicates	Nonribosomal (NRPS) dominant [7]	·Cyclic depsipeptides ·Linear anticancer peptides with fatty acid chains [7]	·High enzymatic resistance ·High oxidation sensitivity [6, 7]	
mollusks	Hybrid: Ribosomal and NRPS [6]	· Linear antimicrobial peptides ·Cyclic depsipeptides · Brominated residues	·Low protease resistance (Degradation by gastrointestinal protease) [6]	·Low ·Intravenous delivery only
cyanobacteria	Nonribosomal (NRPS/PKS hybrid)6]	·Linear/cyclic depsipeptides ·Thiazole rings/polyketide chains [6, 7]	·High enzymatic resistance ·Extreme photosensitivity [6, 7]	
algae	Ribosomal (enzymatic hydrolysis/fermentation) [6]	·Linear antioxidant/ACE-inhibitory peptides ·Sulfated/glycosylated modifications [6]	·Susceptible to digestive proteases ·Requires stabilization [6]	·Oral administration ·Low bioavailability
marine fungi	Nonribosomal (NRPS) [6]	·Depsipeptides ·Cyclic peptides with D-amino acids/polyene chains [6]	·High enzymatic resistance ·Thermolabile [6]	

In general, peptides derived from marine sources are stable against enzymatic and thermal degradation, although they possess unfavorable physicochemical properties. When administered

orally, most often, peptides face challenges that include exposure to gastric acid as well as degradation by enzymes of the gastrointestinal tract. Therefore, further approaches to preserving their integrity are also required. Nanocapsules, nanoemulsions, and nanotubes are proposed to be used as future innovative pharmaceutical forms to ensure that bioactive peptides reach the place of exertion in an intact form and exert their effects where needed.

3. Mechanisms of Anticancer Action of Marine Peptides

3.1. Induction of Apoptosis

Pectenotoxin-2 (PTX-2) has been identified as the main compound responsible for the observed toxicity, demonstrating potent cytotoxic activity against selected human cancer cell lines. PTX-2 exerts differential effects on multiple signaling pathways in cancer cells. In some cancer cells, PTX-2 induces apoptosis by down-regulating anti-apoptotic Bcl-2 family members and inhibitor of apoptosis (IAP) proteins, or by up-regulating the pro-apoptotic Bax protein along with TRAIL receptors DR4 and DR5, which are involved in apoptotic signaling pathways. Similarly, Dolastatin 10 (Dol-10) has been extensively investigated as a marine-derived peptide with strong anticancer potential. A recent study led by Gang Gao and his colleagues proved that Dol-10 also mediates cell proliferation and apoptosis by modulating the expression of oncoproteins [8]. More particularly, Dol-10 suppresses the expression of anti-apoptotic protein Bcl-2, hence facilitating overexpression of either c-myc or p53 as initial signals to reactivate the apoptotic pathway; it further causes tumor cell apoptosis.

3.2. Cell Cycle Arrest

A study led by Gi-Young Kim et al. also observed the fact that PTX-2 could inhibit cancer cell growth by imposing cell cycle arrest at different stages of the cell cycle [9]. For example, PTX-2 facilitates the phosphorylation of Cdc25C while simultaneously reducing the protein levels of Cdc2 and cyclin B1, which disrupts the G2/M phase transition; however, it also enhances cell proliferation. In addition, PTX-2 induced the expression of p21Waf1/Cip1/Sdi1, a cyclin-dependent kinase inhibitor involved in both senescence and damage-induced growth arrest, as indicated by research.

3.3. Anti-proliferative and Anti-metastatic Effects

Vanessa M. Freitas et al. investigated geodiamolide H, a depsipeptide isolated from the Brazilian sponge Geodia corticostylifera, and found that it induced cytoskeletal alterations and reversal of the malignant phenotype in Hs578T cells, thereby reducing cancer cell migration and invasion in vitro [10]. Cryptophycin-52 inhibited cancer cell proliferation by altering microtubule conformation and regulating microtubule dynamics.

3.4. Anti-angiogenic Activity

Guha, P., et al. investigated a glycopeptide from cod known as Thomsen-Friedenreich disaccharide (TFD100) and demonstrated that it at nanomolar concentrations could block GAL3-mediated angiogenesis in mice; hence, it has a prospective pathway consideration for therapeutic intervention in different types of cancer, particularly prostate cancer [11]. Aplidine is an isolated cyclic depsipeptide derived from Aplidium albicans and was found by Broggini, M., et al. [12] to inhibit VEGFR-1 expression while reducing the production of VEGF.

4. Notable Marine Peptides with Anticancer Properties

4.1. Dolastatins

Dolastatin 10 has been the best-studied and is considered one of the most potent antiproliferative components within the Dolastatins family. Its anticancer activity involves the regulation of cell

proliferation and cell death by modulating the expression of oncogenic proteins, as well as interacting with β-tubulin or through chromosomal aberrations to further induce apoptosis. Research has shown that proper clinical application of Dol-10 should be administered through an intravenous infusion, not a bolus injection. As noted in clinical trials, Dol-10 used alone in Phase II studies is largely ineffective and has caused neuropathy as a side effect. Therefore, some studies used antibody–drug conjugate (ADC) technology to attach Dol-10 derivatives (MMAE or MMAF) to monoclonal antibodies so that the specificity of antibodies could be applied for direct delivery of the drug to target tissues, consequently reducing systemic toxicity. Currently, Adcetris® has already made it through the clinical gate, standing as the solution to all barriers concerning the Dol-10 application while opening up novel directions regarding its further development [9].

4.2. Didemnin B

Didemnin B came from the Caribbean tunicate Tridemnin solidum and has shown that it can stop the growth of human cancer cells mainly by blocking the creation of RNA, DNA, and proteins, which leads to inhibiting the growth of the tumor cells. Structural studies found that Didemnin B has a new type of cyclic setup, which adds to its better molecular strength. However, a Phase II clinical trial of Didemnin B reported grade 3–4 toxicities in all participants, underscoring the compound's high toxicity and resulting in discontinuation of the study [13].

4.3. Aplidine

Plitidepsin (Aplidin) was derived from the Mediterranean tunicate Aplidium albicans and exhibits potent activity across a broad range of tumor models even at low concentrations. It enables the induction of cell cycle arrest and apoptosis, while it also carries anti-angiogenic characteristics. Compared with Didemnin B, it presents a better safety profile with relatively lower toxicity [12]. At present, Aplidin is being evaluated in a Phase III clinical trial for the treatment of multiple myeloma.

4.4. Kahalalide F

Kahalalide F is a peptide from the marine mollusk Elysia rufescens. Janmaat et al. reported that it can induce necrotic cell death through lysosomal membrane function alteration [14]. Researchers further discovered that Kahalalide F induced the apoptosis pathway in a p53-independent manner. This peptide was involved in several phase II clinical trials for solid tumors, including hepatocellular carcinoma, non-small cell lung cancer (NSCLC), and melanoma, up to 2006. More recently, clinical evaluation has continued in the context of severe psoriasis.

4.5. Cyclodepsipeptides

Jaspamide is recognized as a cyclodepsipeptide and was extracted from the sea sponges Jaspis and Hemiastrella. Its structure has a substantial ring of 15 carbon atoms plus three residues of amino acids. It regulates the expression of Bcl-2 family proteins in opposite directions, hence increasing the proapoptotic protein Bax and reducing the anti-apoptotic protein Bcl-2, thereby inducing apoptosis. Homophymines represent a novel category of cyclic depsipeptides that have been reported from the sponge Hamophymia [5]. They were reported to show moderate cytotoxic as well as anti-HIV activity.

4.6. Cyanobacterial peptides

Largazole is a cyanobacterial peptide derived from the species Symploca. Yongcheng Ying et al. discovered that it can selectively inhibit histone deacetylases (HDACs), through which it exerts potent antiproliferative effect [15]. Structure–activity relationship (SAR) analyses have established that the thiol group serves as the essential pharmacophore, with biological activity contingent upon its existence. Largazole has demonstrated the ability to trigger cell cycle arrest and apoptosis in various cancer cell lines [16]. The derivative, OKI-179, is presently in Phase II clinical trials to assess its anticancer efficacy.

5. Conclusion

Marine peptides represent a pharmacologically active plethora of structurally diverse molecules, with an attractive source for the development of anticancer agents due to their useful peculiar modes of action. They can bring about the induction of apoptosis, cell cycle arrest, and angiogenesis inhibition in addition to modulation of oncogenic pathways. Toxicity and poor bioavailability notwithstanding, because structural modification and delivery approaches have recently been developed, including antibody-drug conjugates, marine peptides can be considered clinically translatable. Continued investment in the laboratory-based scientific discovery process is required to obtain nanotechnology tools for medicinal chemistry intervention aimed at maximizing clinical applications of MBPs while keeping their potential as a promising source for future anticancer therapies.

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