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Marine-Derived Bioactive Proteins and Peptides: A Review of Current Knowledge on Anticancer Potentials, Clinical Trials, and Future Prospects

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Abstract

The rise in cancer cases has prompted searching for novel and alternative sources of natural bioactive compounds with antitumor potential. Nearly three-quarters of our planet is covered by the ocean, the habitat of numerous prokaryotic and eukaryotic organisms and sustainable alternative nutrient sources. The marine ecosystem is a rich reservoir of proteins and novel bioactive peptides with diverse biochemical and therapeutic potentials, including antioxidant, anti-inflammatory, and antiproliferative activities. Marine peptides are valuable due to their high stability, bioactivity, and low immunogenicity. This review focused on tracking the recent progress in studying marine-derived peptides for potential cancer treatment. We have highlighted that some of these peptides have progressed to clinical trials in the last 2 decades, while many candidates were discontinued due to failure to exhibit therapeutic-relevant activities. Due to the results from old clinical trials, interest in marine sources for antitumor peptides has dwindled in recent years. We presented other possible limitations in this field and proposed attractive future research prospects. In conclusion, we emphasize the need for increased scientific attention to explore marine organisms' untapped nutraceutical and bioactive natural products, particularly in uncovering their potential anticancer properties.

Keywords

bioactive peptide, cancer, antiproliferative activity, marine protein, nutraceuticals, clinical trials

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Introduction

Oceans cover over 70% of the earth's surface, hosting many chemicals and biological and ecological biodiversity. The interest in marine organisms as alternative and novel natural product sources has recently increased.[1] Several compounds with distinctive physical properties have been identified in the marine ecosystem, such as phlorotannin, ziconotide, arenastatin A, and others.[2-4] The biological and chemical diversity of the marine environment is abundant. Compounds derived from marine organisms have been employed as fine chemicals, molecular probes, cosmeceuticals, medicines, agrochemicals, and nutraceuticals. The macro and microorganisms in the marine ecosystem house many secondary metabolites, such as steroids, terpenes, polyketides, alkaloids, polysaccharides, proteins, porphyrins, and peptides, with promising therapeutic potentials.[5-7] They are also rich sources of enzymes with potential applications in agro-pharmaceutical industries.[8,9]

Numerous marine organisms have been equipped with the necessary mechanisms by evolutionary processes to survive in a harsh environment that includes attacks from viral and bacterial pathogens, pressure shifts, high temperatures, and salinity variations. These harsh chemical and physical environmental factors of the sea have also aided the production of a wide range of novel biological molecules in marine organisms that

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are distinct in terms of structural features, diversity, and functional properties compared to substances isolated from terrestrial plants and serve as a reservoir of new bioactive substances with significant pharmaceutical potential. Marine organisms such as fish, seaweed, shellfish, microalgae, crustaceans, cephalopods, and mollusks are rich sources of proteins and bioactive peptides, which have gained significant attention due to their promising anticancer therapeutic effects.[6] About 16 of the 20 marine anticancer drugs currently being clinically tested are from microbial origins, and many more are anticipated to join the drug discovery pipeline.[10]

Nevertheless, little is still known about the marine ecosystem. Despite more than 1.2 million species already being cataloged in a central database and 250 years of taxonomic classification, it is predicted that 91% of marine species still need to be described. As a result, there is a growing interest in studying and evaluating the marine environment, particularly regarding marine proteins and peptides, to uncover novel chemical constituents as sources for new lead compounds for anticancer therapy.

Cancer is a common cause of death globally and a significant global public health issue, leading to over 8.2 million deaths.[11] The reported incidence of the disease and mortality has not decreased over the past 30 years despite real advancements in cancer therapy. A critical cancer prevention and treatment component is understanding the molecular changes that lead to cancer growth and progression.[12] Targeting particular cancer cells can prevent tumor growth, progression, and spread without adverse side effects. A combination of chemotherapy, radiation, and surgery is currently the most widely used treatment for eliminating cancerous cells, preventing cancer recurrence, and managing cancer by suppressing cell growth and lessening symptoms.[13]

Numerous drugs have been developed to increase the effectiveness of treatment for particular forms of cancer as scientific study advances. High-energy radiation is used in radiotherapy to destroy cancer cells and reduce tumor size. Because they are comparatively radiosensitive, normal tissues are frequently preserved during therapy. Chemotherapies are applied to treat cancer and can kill or stop cancer cells from proliferating. However, this treatment method could lead to the death or damage of healthy cells. Similarly, many anticancer drugs come with numerous side effects and observable anticancer drug resistance.[14] As a result, finding alternative natural anticancer agents with high efficacy and low toxicity have received significant attention in recent times.[15]

Proteins are essential macronutrients since they provide vital energy and amino acids for average body function growth, development, and maintenance.[16] Bioactive peptides are thought to be responsible for several functional and physiological properties of proteins.[17] The prominence of bioactive peptides derived from food proteins has increased as more people become aware of their positive effects on health. Bioactive peptides, which include between 2 and 20 amino acid residues, can be released by enzymatic hydrolysis during food preparation or digestion in the body.[18] These peptides are inactive within the sequence of their parent proteins.[19] Depending on their constituent, structure, and amino acid sequence, bioactive peptides can act as possible physiological modulators in the metabolism during intestinal digestion.[20] Among various health-derived benefits, some bioactive peptides from diverse plants, animals, or microbial origin have been reported to have anticancer properties and the potential to manage/prevent its onset.[21-26]

Consequently, this review presents an overview of the cancer pathogenesis and treatment protocols, their limitations, and the source, isolation, and unique properties of marine-derived proteins and peptides. Furthermore, we extensively presented and elucidated the mechanisms of actions and structure–activity relationships of proteins and peptides of marine origin. The future prospects of exploiting marine-derived proteins and peptide emphasizing their anticancer potentials were comprehensively discussed.

Critical Properties Conferring Marine-Derived Proteins and Peptides With Promising Potential

Marine-derived proteins and peptides have several unique properties that make them of interest for various industrial and biomedical applications (Figure 1). Some of these properties are:

High Bioactivity

Marine-derived proteins and peptides have been found to exhibit high bioactivity due to their unique amino acid composition, which differs from terrestrial proteins. The high bioactivity of marine-derived proteins and peptides is due to several factors, including their unique amino acid composition, 3-dimensional structure, and molecular size.[27,28] This is due to the unique environment in which marine organisms live, which affects the types and amounts of amino acids available for protein synthesis.[29,30] A distinctive feature of marine-derived proteins and peptides is their high content of nonpolar amino acids, such as leucine, isoleucine, and valine. These amino acids are essential for stabilizing the protein structure and are often found in hydrophobic regions of the protein. Marine organisms also have a high content of sulfur-containing amino acids, such as cysteine and methionine, which are essential for protein folding and stability. Also, marine-derived proteins and peptides often have a higher content of essential amino acids, such as lysine and threonine, which are not synthesized by the human body and must be obtained through the diet.[31,32] The presence of disulfide bonds in the 3-dimensional structure of some marine-derived peptides can result in increased stability and bioactivity. Marine-derived proteins and peptides are known for their high bioactivity, making them valuable for various food, pharmaceuticals, and biotechnology applications.[33] An example of a highly bioactive marine-derived protein is collagen, found in the connective tissues of marine organisms such as fish, cephalopods, and jellyfish. Collagen is

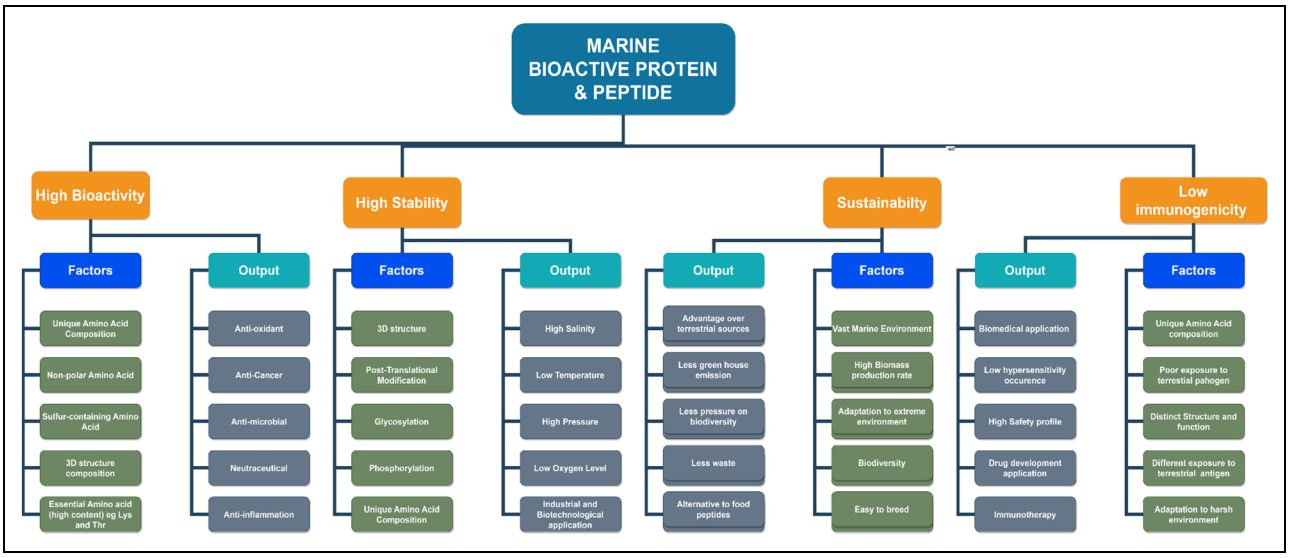

Figure 1. Keyword representation of characteristics of marine protein and peptide which confers its promising potentials for. Some of the prot.

known for improving skin health and has been used in various cosmetic and nutraceutical products.[34] Other highly bioactive marine-derived peptides include antimicrobial peptides, which can kill or inhibit the growth of harmful bacteria, and anticancer peptides, which have cytotoxic effects on cancer cells.[30]

Relative Stability Profile

Marine-derived proteins and peptides are often more stable than their terrestrial counterparts due to the extreme conditions of the marine environment, such as high salinity, low temperature, and high pressure. The high stability of marine-derived proteins and peptides is due to several factors, including their unique amino acid composition, 3-dimensional structure, and posttranslational modifications, such as glycosylation and phosphorylation, which can increase their stability and functionality. Many marine organisms have evolved unique proteins and peptides to survive in harsh environments, such as extreme temperatures, high pressures, and low oxygen levels.[29,32] These unique proteins and peptides often have specialized functions that require high stability, such as enzymatic activity or structural support. Collagen is known for its high stability and resistance to degradation, making it valuable for various applications, including wound healing and tissue engineering. The stability of marine-derived peptides can make them effective therapeutic agents, as they are less likely to degrade *in vivo* and can remain active for extended periods. Additionally, the stability of marine-derived proteins and peptides can make them valuable for use in food and beverage applications, where they can provide functional benefits such as improved texture and stability.[34,35]

Low Immunogenicity

Marine-derived proteins and peptides are less immunogenic than those derived from terrestrial organisms. Marine-derived proteins and peptides are known for their low immunogenicity due to several factors, including their unique amino acid composition and lack of exposure to terrestrial pathogens.[29,33] Marine organisms have evolved in an environment with unique biological and physical characteristics, which has led to the development of proteins and peptides with distinct structural and functional properties. These unique properties can make marine-derived proteins and peptides less likely to trigger an immune response in the body. Additionally, marine-derived proteins and peptides are less likely to be contaminated with terrestrial pathogens, such as bacteria and viruses, which can also contribute to their low immunogenicity.[36,37] This makes them attractive candidates for biomedical and pharmaceutical applications where low immunogenicity is desirable, such as in drug development, tissue engineering, and immunotherapy.

Sustainable Source

The oceans are a vast and largely untapped resource for producing proteins and peptides. Marine organisms are often more abundant and easier to breed than terrestrial ones, making them a sustainable protein and peptide production source.[30] Marine organisms are a promising sustainable source for obtaining proteins and peptides, offering several advantages over traditional terrestrial sources. Marine organisms have a high biomass production rate; many are considered renewable resources. This means they can be harvested or farmed sustainably without depleting their populations or damaging their habitats. Marine organisms have evolved unique proteins and peptides with specialized functions, such as defense against predators or adaptation to extreme environments. Obtaining proteins and peptides from marine sources can have a lower environmental impact than traditional terrestrial sources since they require less land and water than livestock or crops and

produce less greenhouse gas emissions and waste.[38] However, it is essential to note that the sustainable use of marine resources requires careful management and monitoring to prevent overexploitation and damage to marine ecosystems. This includes the implementation of sustainable harvesting and farming practices, as well as the development of regulations and policies to protect marine biodiversity and habitats. Also, the diversity of marine organisms offers a broad range of bioactive compounds that can be used for various industrial and biomedical applications.[38,39]

Sources of Marine Bioactive Protein/Peptides

Despite the diversity of the marine ecosystem, studies on their bioactive protein and peptides have only been on a few organisms, such as some fishes, algae, shellfish, and marine microbes. In general, we shall present an overview of these marine lives and the nature of their peptides.

Fishes are sources of high-quality proteins primarily containing essential amino acids for human metabolism. Fish protein includes collagen, myoglobin, actins, and others abundant in their tissue, such as skin, bones, scales, and internal organs.[40] Other interesting fish sources of marine-derived peptides and proteins from fish include fish fillets, fish wastes, and byproducts.[41,42] The fish peptides are produced by the digestion of fish protein, majorly by enzymatic hydrolysis. These peptides have been implicated with several bioactivities, hence categorized as angiotensin-converting enzyme (ACE)-inhibitory, antioxidant, antimicrobial, anticancer, and anti-inflammatory peptides.[43] Recent studies have vastly obtained these bioactive peptides from tuna, salmon, herring, and cod.[44]

Various bioactive peptide groups found in fish contribute to various physiological benefits. Among these are ACE inhibitory peptides, known for their ability to lower blood pressure by impeding the activity of ACE—an enzyme responsible for blood vessel constriction.[45] Angiotensin-converting enzyme-inhibition and antihypertensive activities have been popular with fish peptides and hydrolysate.[46,47] Examples of ACE inhibitory peptides from fish are tuna hydrolysate, Val-Leu-Pro from salmon muscle, and Ile-Asn-Pro identified in tilapia muscle. Additionally, antioxidant peptides in fish play a crucial role in safeguarding the body against oxidative stress, a significant contributor to numerous chronic diseases.[48] Furthermore, fish-derived opioid peptides exhibit pain-relieving effects, suggesting their potential as natural painkillers.[49] Other well-known peptide groups from fish are the immunomodulatory peptides that can help regulate the immune system, improving its ability to fight infections and diseases, and the antimicrobial peptides that can kill or inhibit the growth of bacteria, fungi, and viruses.[50] Some antimicrobial peptides include piscidins (piscidins-1) from Tilapia hydrolysate and Rainbow trout, gaduscidin-1 from Cod, and hepcidin from catfish.

Shellfish comprises shrimp, crab, and lobster and is good sources of proteins and peptides.[51,52] Bioactive peptides in shellfish include opioid peptides standard in mussels and clams; antimicrobial peptides in blue mussels, oysters, scallops, and shrimp; ACE-inhibitory peptides in shrimp and crab, which can help lower blood pressure; immunomodulatory peptides found in mussels and scallops and antioxidant peptides in scallops.[53,54] Opioid peptides in shellfish include dynorphins in blue mussels (*Mytilus edulis*), methionine-enkephalins in oysters and clams, and β-endorphins in shrimp. These peptides have been shown to have analgesic properties and can act as natural painkillers.[51,55]

Several types of ACE-inhibitory peptides have been identified in shellfish, which can help to lower blood pressure by blocking the activity of ACE, including: Valyl-tyrosine (VY) peptide from protein hydrolysate of shrimp (*Litopenaeus vannamei*), isoleucyl-prolyl-proline peptide in oysters (*Crassostrea gigas*), isoleucyl-leucine-proline peptide identified in the protein hydrolysate of crab (*Portunus trituberculatus*), and leucine-aspartic acid peptide in the protein hydrolysate of clams (*Meretrix meretrix*).[56,57] The immunomodulatory proteins and peptides in shellfish have been shown to have various immunomodulatory effects, such as enhancing phagocytosis and stimulating the production of cytokines; they include hemocyanins in mollusks and crustin found in crustaceans, such as crabs and shrimps.[37]

Other interesting sources of these bioactive peptides are marine algae and microbes. Algae is a rich source of proteins, including phycobiliproteins and lectins, which are potent sources of peptides with diverse bioactivities such as antioxidant peptides, anti-inflammatory peptides, antimicrobial peptides, and others.[5,58-60] The antioxidant proteins and peptides in algae include Fucoidan peptides standard in brown algae and C-phycocyanin in *Spirulina platensis*.[61] Some bioactive peptides in algae have been shown to have anti-inflammatory effects, such as reducing the production of pro-inflammatory cytokines and inhibiting the activation of NF-κB, a key transcription factor involved in inflammation such as C-phycocyanin and ulvan peptides of green algae.[62,63] However, marine microorganisms, such as bacteria and fungi, are also sources of proteins and peptides with potential applications in the pharmaceutical and biomedical industries. Some examples of marine-derived peptide microorganisms produce include lantibiotics and cyanobactins.[64] Going forward, our focus shall be on marine bioactive proteins or peptides which potential anticancer properties.

An Overview of Cancer Pathogenesis and Challenges of Modern Cancer Therapy

Cancer, characterized by uncontrolled cell growth and division, presents complex challenges rooted in disrupting normal cellular processes. The hallmark characteristics of cancer involve anomalies in the cell cycle, resulting in the unbridled proliferation of malignant cells. This unregulated growth is compounded by the loss of apoptosis, contact inhibition, and impaired cellular communication.[65]

A crucial aspect of cancer progression is the ability of cancer cells to invade nearby tissues and metastasize. Cancer cells release proteases, such as collagenase, which facilitate the breakdown of the extracellular matrix, enabling penetration into adjacent normal tissues. Additionally, promoting angiogenesis—new blood vessel formation—is essential for sustaining tumor growth beyond a certain size.[66] Growth factors secreted by cancer cells stimulate the development of new blood vessels, supplying the expanding tumor with oxygen and nutrients. This angiogenic process also plays a pivotal role in metastasis, allowing cancer cells to circulate through blood and lymphatic vessels and disseminate to distant areas.[67]

The primary cause of cancer lies in DNA mutations, which can either be hereditary or acquired due to exposure to various environmental factors, including carcinogens such as toxic chemicals, contaminated food and water, radiation, and biological agents such as bacteria, viruses, and parasites (Figure 2). The intricate process by which healthy cells transform into cancerous cells is carcinogenesis or oncogenesis. The widely accepted 3-stage carcinogenesis theory includes initiation, promotion, and progression, each stage contributing to the transformation and aggressive behavior of cancer cells.[67]

Cancer treatment strategies encompass a range of modalities, each with its own set of challenges. Surgery, a traditional approach, involves the removal of localized solid tumors. However, the trauma induced by surgery may inadvertently promote tumor recurrence by shedding cancer cells into the bloodstream and lymphatic circulation. Surgery also triggers immune escape mechanisms, downregulating the adaptive immune response.[68,69]

Chemotherapy, another common treatment, suffers from issues such as lack of selectivity, short half-lives, poor solubility, cytotoxicity, and the development of multidrug resistance. The nonspecific nature of chemotherapy affects both cancer and healthy cells, leading to debilitating side effects.[70] Radiation therapy, utilizing high-energy waves to destroy cancer cells' DNA, faces limitations due to potential collateral damage to adjacent healthy tissues.[71,72]

Gene therapy involves inserting a normal copy of a defective gene into the genome to address DNA disorders, with ongoing clinical trials focusing on cancer.[71] However, challenges such as selecting optimal conditions and delivery methods, genome integration, limited efficacy, and potential immune system neutralization pose hurdles to widespread adoption.[72]

Immunotherapy, a rapidly advancing field, harnesses the body's immune system to eliminate cancer cells. Adoptive T cell treatment and CAR-T cell therapy are promising immunotherapeutic approaches.[73] Despite their practical outcomes, challenges such as cytotoxicity, poor *in vivo* persistence, cytokine release syndrome, and potential fatal side effects hinder their broader application.[74,75]

In conclusion, the intricate complexities of cancer necessitate a profound comprehension of its underlying mechanisms and the pursuit of innovative treatment approaches. Although several treatment and options have been developed, each encounters unique challenges that constrain their efficacy. It is imperative to underscore the significance of persistent research

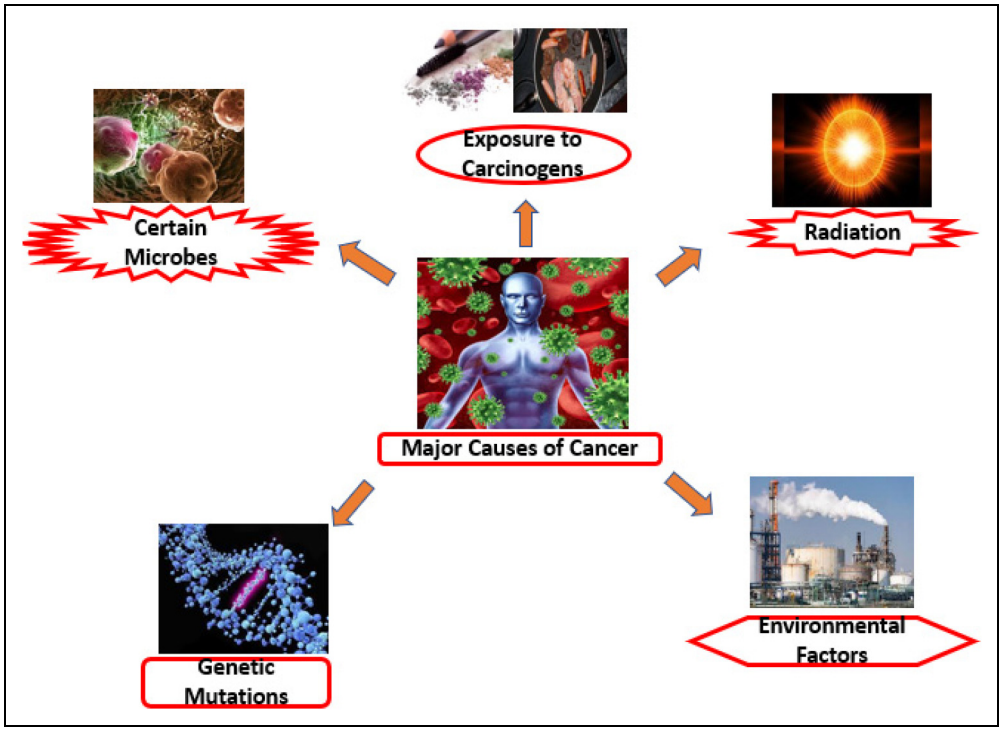

Figure 2. Major causes of cancer.

and development efforts in surmounting these obstacles and advancing the landscape of cancer treatment. Notably, recent studies have provided compelling evidence that natural products, including marine bioactive peptides, hold promising potential in the management and treatment of cancer.[76-79] This underscores the importance of exploring and harnessing the therapeutic benefits offered by these marine-derived compounds to further enhance the armamentarium against this formidable disease.

Marine-Derived Bioactive Peptides and Their Antiproliferative Properties—Potential for Cancer Management

In the last 2 decades, natural products of marine origin have generated serious scientific attention for cancer prevention and treatment due to their inhibitory effects on several cancer cells.[40,80-84] Among the natural products with interesting anticancer potentials, proteins, and novel peptides from marine origin have been shown to be potential candidates for cancer management, as documented in many recent studies.[85,86] Protein hydrolysates and peptides from marine organisms such as mollusks, microalgae, and different varieties of fishes, including crabs, shellfish, catfish, and others have been shown to possess anticancer properties whose protein hydrolysates and peptides have been reported.[87] Notably, cyclic peptides of aquatic origin have been shown to inhibit the proliferation of several cancer cells in a concentration-related fashion by activating apoptosis pathways such as cytochrome C, c-Jun N-terminal kinase (JNK), and Mitogen-Activated Protein Kinase (MAPK) and caspases and inhibiting survival mechanisms such as microtubule assembly, Bcl2 expression, and "Phosphoinositide 3-Kinase/Protein Kinase B" (PI3 K/Akt) signaling pathways.[88] The peptides appear to induce the production of reactive oxygen species (ROS) in the cancer cells, considering that the activation of JNK/MAPK signaling pathways mostly depends on ROS.[89] In another study, Sea cucumber peptides were also shown to abrogate multiplication and metastasis of A549 cells *in vitro* and inhibited tumor growth in tumor-bearing mouse model by upregulating the expression of tumor suppressor gene TUSC2.[90]

A pentapeptide, ILYMP from *Cyclina sinensis*-induced apoptosis in prostate cancer cells (DU-145) via a 5-fold increase in Bax/Bcl-2 ratio to inhibit cell survival while promoting cell death via activation of caspases 3 and 9-mediated apoptosis.[91] Similarly, LKEENRRRRD from *Sepia esculenta* exhibited moderate antiproliferative effects against prostate cancer cell line (PC-3) by activating p53 and caspase-3-mediated apoptosis by 57% and 64%, respectively, at 15 mg/mL.[92] Proline-rich tripeptide, WPP, which was isolated from *Tegillarca granosa* protein hydrolysate exhibited appreciable antiproliferative activities via induction of apoptosis against several cancer cell-lines including PC-3, DU-145, H-1299, and HeLa cell with IC_{50} values of 1.99, 2.80, 3.3 and 2.54 mg/mL, respectively.[93] Other peptides, including AGAPGG, AERQ, and RDTQ from *Sarcophyton glaucum,*[94] FIMGPY from *Raja porosa,*[95] YVPGP from *Anthopleura anjunae*, LPGP and DYVP from *Sinonovacula constricta,*[96] LANAK from *Saccostrea cucullate*[97] and QPK from *Sepia esculenta*[92] and other unidentified peptides in protein hydrolysates,[98] respectively, induced apoptosis in human cervical cancer (HeLa), DU-145, colon carcinoma (HT-29), and lung cancer (A549 and H1299) cells. Interestingly, all the above peptides possess hydrophobic amino acids at the terminal position, suggesting that terminal hydrophobic amino acids may have partially contributed to their anticancer activities. Hydrophobic amino acids have been suggested to interact with calcium channels on the outer leaflets of cancer cell membrane bilayers to increase calcium influx-mediated cell death.[93]

In addition to inducing apoptosis, marine-derived anticancer peptides also induce cancer cell cycle arrest at different checkpoints. For example, VECYGPNRPQF from *Chlorella vulgaris* was shown to inhibit the proliferation of gastric cancer (AGS) cells (IC_{50} value of 70.7 μg/mL) via induction of cell cycle arrest at post-G1 phase, leading to the death of the cells.[99] A tripeptide from *S. esculenta*, SIO was also reported to induce the arrest of the PC-3 cell cycle at the G0/G1 phase,[98] while DWPH from *Ruditapes philippinarum* arrested DU-145 cells proliferation at the G2/M phase by reducing the number of cells in the S-phase which resulted in apoptosis of the cells.[100] Other possible mechanisms by which specific marine-derived peptides can benefit against cancer differentiation and proliferation include the inhibition of angiogenesis and DNA synthesis and suppression of pathways through which cancer cells survive and spread, such as cyclooxygenase-2 and vascular endothelial growth factor receptor type-2 expression.[76] These should be established in future studies. Figure 3 summarizes the molecular mechanisms of action of marine-derived proteins and peptides against different cancer cells, while Table Y summarizes marine-derived peptides with anticancer properties.

While marine-derived proteins and peptides have displayed anticancer properties ranging from weak to moderate, as evidenced by their lower activities compared to conventional anticancer drugs (summarized in Table 1), it is crucial to note that the majority of studies were conducted *in vitro* on cell lines. This *in vitro* approach is typically the initial step in drug discovery. It is necessary to confirm these anticancer properties using an animal cancer model. Some of the studies reported anticancer effects of long-chain oligopeptides such as FIHHIIGGL FSAGKAIHRLIRRRRR from *Tilapia piscidin,*[101] KPEGMD PPLSEPEDRRDGAAGPK and KLPPLLLAKLLMSGKLL AEPCTGR from Tuna oil,[102] and YGFVMPRSGLWFR from *Spirulina platensis*[103]; bioavailability of peptides are highly dependent on the chain length with the shorter chain being more bioavailable.[104,105] It is necessary that transepithelial transport assays should be added as part of the study designs in future studies to validate the oral bioavailability of the peptides reported to be active *in vitro*.

Nevertheless, the action of intestinal brush border proteases and serum peptidases may convert the long-chain peptides to more active short-chain peptides, as shown in the bioactivities

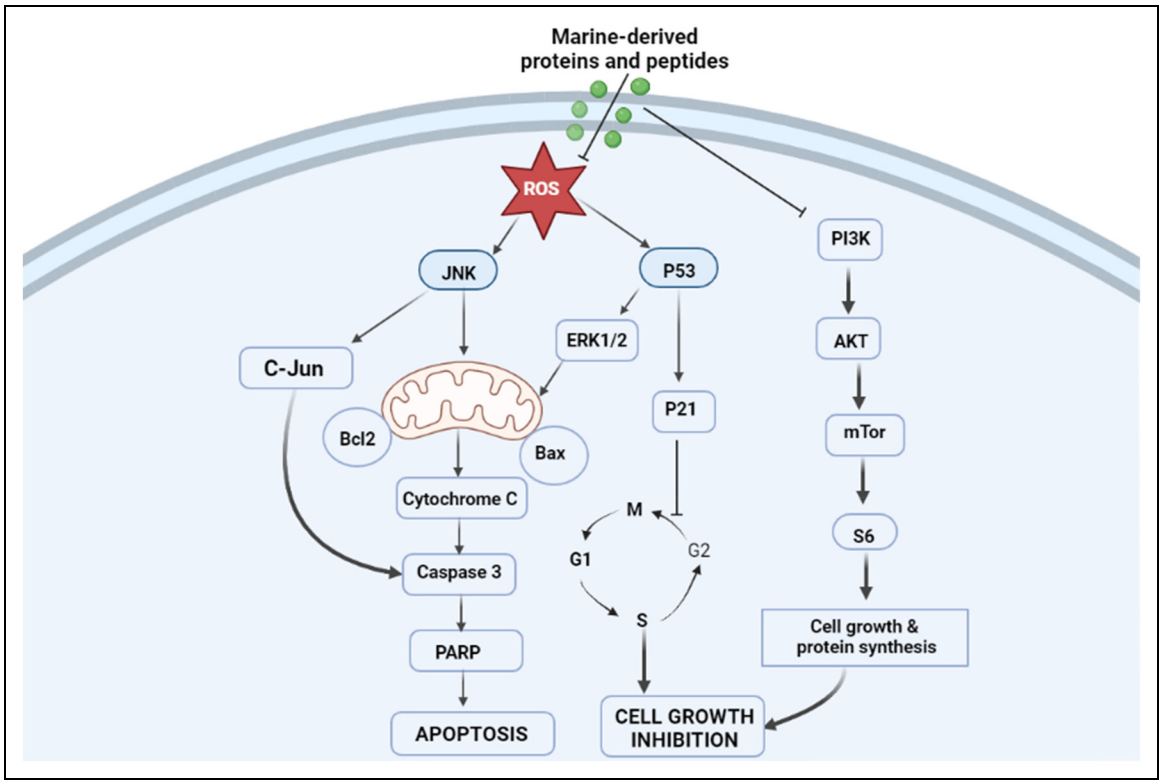

Figure 3. Summary of mechanisms of anticancer activities of marine-derived proteins and peptides.

of lupin-sourced peptides, which increased after transepithelial transport.[116-118] To conclude this section, marine-derived peptides still hold good promise as potential candidates for cancer management as they are selectively cytotoxic to cancer cells while sparing host cells. This is unlike many synthetic anticancer drugs that effectively halt replication and DNA synthesis in cancer cells while inducing apoptosis of cancer cells but elicit severe toxicity due to a lack of selectivity.[83]

Clinical Trials of Marine Peptides With Anticancer Potentials

Clinical trials are interestingly critical hurdles for natural products, which are necessarily overcome to transit novel natural products with seemingly attractive bioactive potentials from bench to market.[119] Several marine peptides have been identified up-to-date, and only a few have been through clinical trials. Although with little or no success, it is worth highlighting interesting clinical trial findings of some of these marine peptides with anticancer potentials.[120] Peptides such as dolastatin-10, plitidepsin, kahalalide F, didemnin B (DB), hemiasterlin analog (HTI-286), and elisidepsin of different marine sources have been investigated for their potential against several forms of cancer via clinical trials (Figure 4).[121]

In the last 4 decades, DB, an interesting marine peptide from *Tridemnin cyanophorum*, was popular due to its potent activities against cancer cells owing to results from several *in vitro* and *in vivo* studies.[122] Didemnin B progressed to clinical trials 1 and 2 and was not approved for clinical trial 3 because of the severe toxicities such as muscular necrosis as well as other neurological and gastrointestinal abnormalities recorded from the first 2 trials. Moreover, the therapeutic activities against several advanced cancers were negligible, and individuals in the trials were not better off.[123]

Plitidepsin (Alplidine) is a well-studied marine peptide isolated from the Mediterranean tunicate *Applidium albicans*. The novel Alplidine is a derivative of DB; in principle, it is dehydrodidemnin B.[124] Studies have shown that this cyclic depsipeptide likely binds to the transcription factor eEF1A2 and alters several pathways, thereby fostering cell-cycle arrest, growth inhibition, and reduction of apoptosis.[125] Plitidepsin based on its *in vitro* activities has undergone the clinical trial phases I to III. It was reported from the phase 1 study that Alplidine showed optimal therapeutic activities in patients with solid tumors treated at a dosage of 1200 $\mu g/m^2$ daily for 5 days, every 3 weeks, and the adverse toxicity was well tolerated.[126] In another clinical study, a dosage of 7 and 5 mg/m^2 with and without carnitine was recommended for patients with advanced malignancy. However, muscle toxicity was observed at a higher dosage. The peptide was recommended for the Phase II trials to investigate the pharmacokinetics and the active role of coadministration with carnitine.[127] In the phase II trials, Plitidepsin was reportedly actively distributed by red

Table 1. Selected Marine-Derived Proteins and Peptides With Anticancer Properties, Highlighting Their Mode of Actions and Mechanisms.

Peptide	Source	Model	Mechanisms	Mode of actions and bioactivities	Ref.
WPP	*Tegillarca granosa* (blood clam)	Human multiple cancer cell lines (PC-3, DU-145, H-1299, and HeLa cells)	Antiproliferation	WPP inhibited tumor cell proliferation (PC-3, DU-145, H-1299, and HeLa cell lines) at 5 and 15 mg/mL for 24 h, with increased interaction between hydrophobic amino acids (Trp and Pro) and the tumor cell membrane bilayers containing high phospholipid composition. Additionally, it induced apoptosis in PC-3 cells.	93
ILYMP	*Cyclina sinensis*	Prostate cancer cells (DU-145)	Antiproliferation and pro-apoptosis	Inducing antiproliferative effects with an IC50 value of 11.25 mM at 72 h, the compound promotes apoptosis by upregulating protein expression levels of Bax/Bcl-2 (5-folds) and caspases-3 and -9, attributed to the hydrophobic nature of the amino acids A and L.	91
VECYGPNRPQF	*Chlorella vulgaris*	Gastric cancer (AGS) cells	Antiproliferative Cell cycle arrest	VECYGPNRPQF exhibited antiproliferative activity, it exhibited an IC50 value of 70.7 μg/mL by inducing post G1 cell cycle arrest in AGS cells, eventually causing cell death.	99
KPEGMDPPLSEPEDRRDGAAGPK and KLPPLLLAKLLMSGKLLAEPCTGR	Tuna cooking juice	Human breast cancer cell line (MCF-7)	Antiproliferation Cell cycle arrest	The peptides showed antiproliferative properties with an IC50 value of 1.39 mg/mL, it induced cell cycle arrest in the S phase through an increase in p21 and p27 and a decrease in cyclin A expression. Additionally, the hydrolysate caused apoptosis in MCF-7 cells by downregulating the expression of Bcl-2, PARP, and caspase 9, while upregulating the expression of p53, Bax, and cleaved caspase 3.	102
LANAK, PSLVGRPPVGKLTL and VKVLLEHPVL	*Saccostrea cucullata* (Oyster)	Human colon carcinoma (HT-29) cell lines	Cytotoxicity	LANAK demonstrated anticancer activity by inhibiting cell growth by 70% at 70 μg/mL, reaching maximum inhibition at 100 μg/mL. Furthermore, LANAK exhibited cytotoxic activity with IC50 values of 90.31, 70.87, and 60.21 μg/mL, inducing increased apoptosis to 62%, 70%, and 76% after 24, 48, and 72 h of administration, respectively, by enhancing DNA damage.	97
LPGP and DYVP	*Sinonovacula constricta*	Human prostate cancer cells	Pro-apoptosis	LPGP and DYVP inhibited the cell growth of DU-145, with IC50 values of 1.21 and 1.41 mg/mL after 24 h. This was achieved by reducing the number of cells in G0/G1 phase, thereby increasing the number in sub-G1 phase and inducing apoptosis. Similarly, LPGP and	96

(Continued)

Table 1. Continued

Peptide	Source	Model	Mechanisms	Mode of actions and bioactivities	Ref.
				DYVP dose-dependently inhibited the cell growth of PC-3 cells, with IC50 values of 1.09 and 0.91 mg/mL after 24 h. Notably, LPGP reduced the number of PC-3 cells in sub-G1 phase, inducing apoptosis.	
YVPGP	*Anthopleura anjunae*	Prostate cancer DU-145 cells	Cytotoxicity	YVPGP exhibited cytotoxic activities, with IC50 values of 9.61, 7.91, and 2.30 mM at 24, 48, and 72 h, respectively, resulted in an increase in apoptosis. This was accompanied by an upregulation in the expression of Bax, cytochrome C, caspases 3 and 9, and a decrease in the expression of Bcl-2, indicating activation of the mitochondria-mediated apoptotic pathway.	106
FIMGPY	*Raja porosa* (Skate)	HeLa cells	Antiproliferation and pro-apoptosis	Exhibited antiproliferative activities in HeLa cells, it achieved IC50 values of 4.81 mg/mL by initiating apoptosis. The activation of Bax/Bcl-2 and caspase-3 increased by 2.63 and 1.83 folds compared to the control. Additionally, it heightened apoptotic activities in HeLa cells by 8.64%, 11.72%, and 19.25.	95
QPK	*Sepia esculenta* (Sepia ink)	Human lung cancer cells (A549 and H1299)	Antiproliferation	Exhibited time-dependent antiproliferative activities, it achieved reductions of 54% and 70% at 48 and 72 h, respectively. QPK induced apoptosis by upregulating the expression of P53 and caspase-3 by 1.5 and 3.5 folds, while concurrently reducing the expression of Bcl-2 by 0.5-fold.	107
AGAPGG, AERQ and RDTQ	*Sarcophyton glaucum* (soft coral)	Human cervical cancer (HeLa) cell line	Cytotoxicity	Exhibiting cytotoxic activities on HeLa cell lines, it displayed EC50 values of 8.6, 4.9, and 5.6 mmol/l, respectively. Notably, these values were 3.3-, 5.8-, and 5.1-fold stronger than 5-fluorouracil. In contrast, AGAPGG, AERQ, and RDTQ demonstrated 16%, 25%, and 11% cytotoxic activities in noncancerous Hek293 cells, respectively.	94
LKEENRRRRD	*Sepia esculenta* (Sepia ink)	Prostate cancer cell (PC-3)	Antiproliferation Pro-apoptosis	Demonstrating antiproliferative activities in a time- and dose-dependent manner, it exhibited a 0.5- to 3-fold increase between 5 and 20 mg/mL after 72 h compared to its % proliferation inhibition at 24 h. Additionally, LKEENRRRRD increased early-stage apoptosis from 8.85% to 29% at	92

(Continued)

Table 1. Continued

Peptide	Source	Model	Mechanisms	Mode of actions and bioactivities	Ref.
				5-15 mg/mL for 24 h. This was accompanied by the activation of p53 (57%) and caspase-3 (64%), as well as an increase in Bax and a decrease in Bcl-2 gene expression at 15 mg/mL.	
Loach protein hdrolysates (LPH)-(I-IV)	*Misgurnus anguillicaudatus*	Human liver (HepG2), breast (MCF-7), and colon (Caco-2) cell lines	Antiproliferation	LPH-IV exhibited the highest antiproliferative activities in HepG2 and MCF-2 by 7% and 4% at 40 mg/mL, respectively, but displayed the lowest activity in Caco-2 colon cancer cell lines. Interestingly, LPH-I and LPH-II inhibited Caco-2 by 12.8- and 8.7-fold higher than LPH-IV.	108
Gelatin hydrolysates	*Lates calcarifer*	Human colon cancer (HepG2) and liver cancer (Caco-2) cell lines	Antiproliferation	Antiproliferative activity in Caco-2 cells by 20% at 25 mg/mL and a 39% inhibition in HepG2 cells at same dose compared to untreated cells. This difference could be due to difference in membrane composition, fluidity, and surface area.	109
LPHVLTPEAGAT and PTAEGGVYMVT	Tuna dark muscle byproduct	Human breast cancer cell line (MCF-7)	Antiproliferation	Exhibit dose-dependent antiproliferative activity, the compound demonstrated IC50 values of 8.1 and 8.8 μM in MCF-7 cells.	110
Pituitary adenylate cyclase-activating peptide (PACAP)	*Clarias gariepinus* (North African catfish)	Human non-small cell lung cancer cell line (H460)	Cytotoxicity	Demonstrated dose-dependent cytotoxic activity in H460 cells, it yielded IC50 values of 13.17 μM. At concentrations ≥18.75 μM, it achieved a 72.9% inhibition, in comparison to the chemotherapeutic drugs cisplatin and paclitaxel, which resulted in 81.6% and 87.2% inhibition, respectively.	111
FIHHIIGGLFSAGKAIHRLIRRRRR (Tilapia piscidin (TP) 4)	Nile tilapia	Non-small cell lung cancer (NSCLC) cells; A549, NCI-H661, NCI-H209, NCI-H1975, BEAS-2B, and MRC-5	Cytotoxicity	TP4 demonstrated cytotoxic activities with IC50 values ranging from 1.922 to 27.62 μM in A549 cells, 3.769 to 14.17 μM in NCI-H661 cells, 1.241 to 5.472 μM in NCI-H1975 cells, and 10.61 to 18.52 μM in HCC827 cells. These activities lead to cell death via necrosis, as evidenced by the induction of lactate dehydrogenase production in cells.	101
HVLSRAPR (TR1) Hydrolysate faction 2 (TR2)	*Spirulina platensis*	HT-29 cancer cells MCF-7, HepG-2, and SGC-7901 cancer cells	Antiproliferation	HVLSRAPR exhibited antiproliferative activities in HT-29 cancer cells with an IC50 value of 99.88 μg/mL. It displayed a weak inhibitory effect on normal liver cells (L-02) with only 5.37% inhibition at 500 μg/mL, indicating cell type specificity. Additionally, HVLSRAPR demonstrated	112

(Continued)

Table 1. Continued

Peptide	Source	Model	Mechanisms	Mode of actions and bioactivities	Ref.
				antiproliferative activities in MCF-7, HepG-2, and SGC-7901 cancer cells with IC50 values of <31.25, 36.42, and 48.25 μg/mL, respectively. These values were comparable to the anticancer drug 5-Fluorouracil.	
YALPAH	*Setipinna taty* (half-fin anchovy)	Prostate cancer cells (PC-3)	Antiproliferation	Exhibited antiproliferative activity with an IC50 value of 4.47 μM, it resulted in a significant increase in apoptosis (35.91%) compared to the control (8.41%). This effect was attributed to the interaction of hydrophobic amino acids with cellular components.	112
Fish protein hydrolysates (FPH)- L and C	*Dicentrarchus labrax, Linnaeus* (European seabass) (L) *Sparus aurata, Linnaeus* (gilthead seabream) (C)	Human colon adenocarcinoma cell line (HT-29) Canine kidney cell culture (MDCK1) cell lines	Chemopreventive Antiproliferation	FPH-L demonstrated a chemopreventive effect with a 40%-60% suppression of HT-29 cell viability observed between concentrations of 0.25-0.5 mg/mL. The antiproliferative activities of FPH-L and FPH-C in MDCK1 cells are 147% and 134%, respectively, at a concentration of 1 mg/mL.	113
Gombamide A	*Clathria gombawuiensis*	*invitro*	Cytotoxicity	The peptide exhibited cytotoxic activities in A549 and K562 cell lines and demonstrated inhibitory activity against Na+/K+ATPase.	114
YGFVMPRSGLWFR (papain-digested hydrolysates) Trypsin and alcalase-derived hydrolysates	*Spirulina (Arthrospira) platensis*	Human hepatoblastoma cells (HepG-2), breast cancer cells (MCF-7), gastric cancer cells (SGC-7901), lung cancer cells (A549), colon cancer cells (HT-29), and immortalized liver cells (L-o2)	Antiproliferation Antiproliferation	The peptide displayed antiproliferative activity in A549 cancer cells, achieving an IC50 value of 104.05 μg/mL. Fifteen polypeptides exhibited antiproliferation activities on HepG-2, MCF-7, SGC-7901, A549, and HT-29 cells, with IC50 values ranging from <31.25 to 336.57 μg/mL.	103
Alcalase-derived hydrolysates fraction 2 (F_2)	*Styela clava*	Stomach cancer (AGS), Colon cancer (DLD-1), and Cervical cancer (HeLa) cells.	Anti proliferation	F_2 exhibited higher anticancer activity, with IC50 values of 577.1, 1163.3, and 887.2 μg/mL against AGS, DLD-1, and HeLa cells, respectively. However, these values were lower than paclitaxel (IC50 values, 2.2-24.6 μg/mL) and 5-Fluorouracil (IC50 values, 3.4-34.5 μg/mL).	115

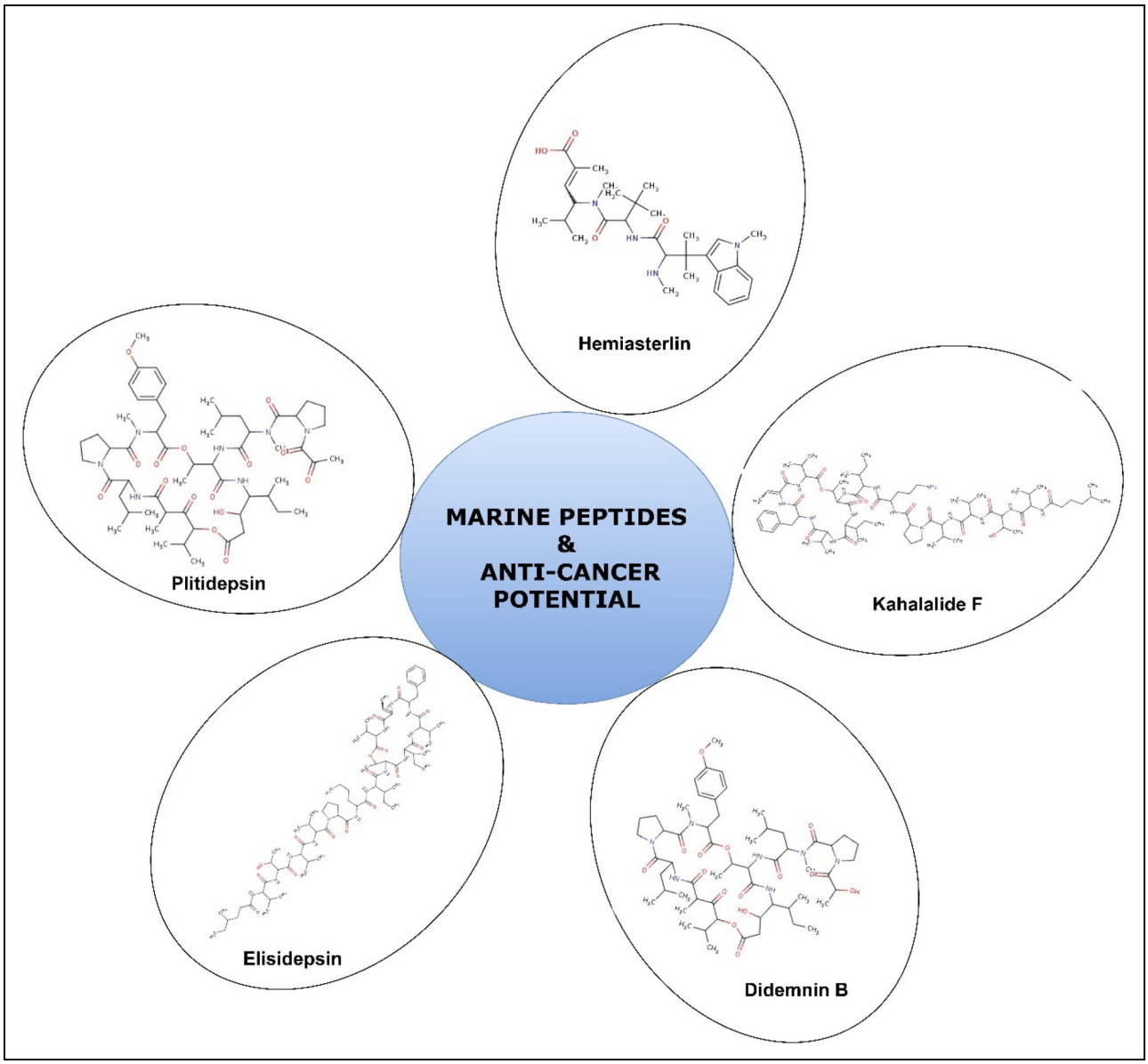

Figure 4. Chemical structure (2D) of some marine peptides that have undergone clinical trials.

blood cells and excreted from the bile. The concentration in whole blood was 3.7 times higher compared to the plasma. This peptide showed a broad distribution but relatively low clearance.[124] In the phase III trials, Plitidepsin combined with dexamethasone (5 mg/m^2 and 40 mg, respectively) improved the median progression-free survival (PFS) and the overall PFS without disease progression when compared with the arm administered with only dexamethasone. Moreover, the safety profile of this peptide was confirmed, and the adverse effects were grade 3, such as fatigue, myalgia, and nausea.[125]

A few other marine peptides entered into clinical trials but stopped at phase I or phase II due to their inability to show convincing therapeutic effects or possibly severe adverse effects (Table 2). Peptides such as Dolastatin 10 went through both Phase I and II but not Phase III because of their nonsignificant effect on different forms of cancer. Similarly, Cematodin (TZT-1027) and tasidotin, a derivative of Dolastatin 15, failed at phase II trials due to poor therapeutic effects against malignant melanoma.[128,129] Finally, kahalalide F was terminated after the second clinical trial; there were no quantifiable therapeutic responses.[130] Despite the tremendous growth of biopeptide research over the last decade, and more new bioactive peptides from marine organisms are being reported, no active clinical trials are testing these novel peptides. There is a need for more clinical testing on some of these novel therapeutic peptides for more applicability in cancer treatment.

Table 2. Summary of Major Clinical Trials on Marine Peptides With Anticancer Potentials.

Peptide name	Marine organism sources	Peptide type/sequences	Clinical trial phase	Cancer type	Recommendation/inferences	Ref.
Didemnin B	Marine tunicate *Trididemnin cyanophorum*	Depsipeptide	Phase 1	Advanced cancer	Severe toxicity, such as the spiking of hepatic enzymes, anaphylactic shock, nausea, and vomiting, was observed in patience administered with 0.03 to 2.00 mg/m^2/d. Although tolerable, the recommended dosage for phase II was 1.6 mg/m^2/d for 5 days.	122,131-133
			Phase I/II	Small cell lung cancer	There was no significant antitumor activity at the recommended dosage of 6.3 mg/m^2 for 30 min every 28 days, and studies did not proceed to clinical trial 3. Moreover, dose-limiting neuromuscular toxicity was reported.	123,134
Aplidine	*Aplidium albicans*	Cyclic depsipeptide	Phase 1	- Non-small cell lung and colorectal cancer	- A dosage of 1200 μg/m^2 i.v. Infusion daily for 5 days, every 3 weeks was recommended, with tolerable toxicity	126
			Phase 1	-Medullary thyroid carcinoma	5 and 7 mg/m^2 without and with carnitine, respectively, recommended for 2 h IV infusion every 2 weeks	127
			Phase III	Advanced cancer	It was shown that the RBC was the central distribution compartment, while the bile was the excretory route.	124
			Phase II	Advanced medullary thyroid carcinoma	At recommended doses, clinical benefit was observed in patients with MTC and manageable toxicity.	135
			Phase II	Advanced renal cell carcinoma	At the recommended doses, 7 mg/m^2 incorporation of L-carnitine did not cause a significant enhancement of treatment, neither did it prevent the muscular toxicity associated with plitidepsin	136
Plitidepsin (Aplidine) and dexamethasone			Phase II	Refractory multiple myeloma	At 5 mg/m^2 doses as a 3-h i.v. Infusion every 2 weeks and incorporation of dexamethasone (0 mg/d on days 1-4) showed interesting activities suggested for a phase 3 trial.	137
Kahalalide F	Green algae *Bryopsis* sp and mollusk, *Elysia rufescens*	Dehydroaminobutyric acid–containing cyclic depsipeptide.	Phase 1	Androgen refractory prostate cancer	The recommended dosage for KF was 560 μg per m^2 per day at a 1 h i.v infusion for 3 weeks.	130
			Phase 1	Advanced solid tumors	The drug peptide was recommended for phase 2 at 650 μg/m^2 at a 1 h i.v infusion.	138
Dolastatin 10 (DOLA-10)	Mollusc Dolabella auricularia	Pentapeptide	Phase 1	Advanced solid tumors	Maximal tolerated doses were 300-400 μg/m^2, and Granulocytopenia was the form of dependent toxicity.	139,140
			Phase II	Metastatic melanoma pancreaticobiliary cancers	The study was halted after the trial of Dola-10 at μg/m^2, prolonged elimination or systemic clearance, and the presence of grade 2 and 3 toxicities.	141
			Phase II	Pancreaticobiliary cancers	Dola-10 did not show activities against hepatobiliary and pancreatic carcinomas. Grade 3 and 4 toxicities were experienced.	142

Limitations, Research Prospects, and Conclusions

Like other biological entities, marine organisms are exciting sources of diverse bioactive peptides, including numerous linear amide chain peptides, cyclic peptides, and peptide derivatives.[59,120] In the review, we have presented an overview of the nature, sustainable sources, and unique properties of bioactive peptides of marine origin. However, we focused on providing an updated review of new marine peptides with antiproliferative or cancer activities and their progression to clinical trials.

Optimizing the extraction, isolation, and identification process from marine peptides can be one direction for future studies.[143] Developing new extraction methods and efficient hydrolytic techniques fosters the isolation of novel bioactive peptides for further research on their bioactive potencies, especially against cancerous cells. Furthermore, other new studies can delve into examining the activities of the peptide more in a mechanistic approach. Many novel marine peptides with seeming bioactivities are only tested through *in vitro* experiments, and their effects *in vivo* are yet to be determined.[94] From the previous section, we can assert that only a few marine peptides progress to clinical trial stages, making it practically impossible to move transit from bench to market. Future studies may focus on more detailed pharmacokinetics of the drugs and the peptides' bioactivities. Moreover, possibilities of improved anticancer activities can be investigated by coadministering the novel peptide with popular chemo or immunotherapy against cancer.[139,144]

Although many studies have highlighted that bioactive peptides from other sources are commonly implicated with several challenges, including short half-life, protease susceptibility, peptide instability, possible toxicities, and other processing issues.[77,104,145] Achieving a marine peptide or developing some conjugates or derivatives with better advantages to overcome those limitations is also a plus. Tweaking the marine peptides through nano-conjugation or encapsulation can improve their targeted delivery. Moreover, D-amino acid enrichment, pegylation, cyclization, or XTEN conjugation possibly enhance their shelf life as well as their safety profile.[120]

In conclusion, marine-derived peptide research fields are still underexplored and need more attention from natural product scientists to harness their hidden potential, especially in cancer treatments.

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