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REVIEW

# Therapeutic potential of marine peptides in cervical and ovarian cancers

**Salman Ahmed[1] · Haroon Khan[2] · Sajad Fakhri[3] · Michael Aschner[4] · Wai San Cheang[5]**

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## Abstract

Cervical and ovarian cancers contribute significantly to female morbidity and mortality worldwide. The current standard of treatment, including surgical removal, radiation therapy, and chemotherapy, offers poor outcomes. There are many side effects to traditional chemotherapeutic agents and treatment-resistant types, and often the immune response is depressed. As a result, traditional approaches have evolved to include new alternative remedies, such as natural compounds. Aquatic species provide a rich supply of possible drugs. The potential anti-cancer peptides are less toxic to normal cells and can attenuate multiple drug resistance by providing an efficacious treatment approach. The physiological effects of marine peptides are described in this review focusing on various pathways, such as apoptosis, microtubule balance disturbances, suppression of angiogenesis, cell migration/invasion, and cell viability. The review also highlights the potential role of marine peptides as safe and efficacious therapeutic agent for the treatment of cervical and ovarian cancers.

**Keywords** Marine peptides · Apoptosis · Metastasis · Mitosis · Angiogenesis · Cell cycle arrest

✉ Haroon Khan
haroonkhan@awkum.edu.pk

Salman Ahmed
salmanahmed@uok.edu.pk

Sajad Fakhri
pharmacy.sajad@yahoo.com

Michael Aschner
michael.aschner@einsteinmed.org

Wai San Cheang
annacheang@um.edu.mo

[1] Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan

[2] Department of Pharmacy, Abdul Wali Khan University Mardan, Mardan 23200, Pakistan

[3] Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, 6734667149 Kermanshah, Iran

[4] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA

[5] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Zhuhai, China

## Abbreviations

| | |
|---|---|
| AKT | Protein kinase B |
| BAD | Bcl2/Bcl-X associated death domain protein |
| BAK | Bcl2 homologous antagonist—killer protein |
| BAX | Bcl2-associated X protein |
| Bcl2 | B-cell lymphoma 2 |
| Bcl-xL | B-cell lymphoma-extra large |
| Casps | Caspase |
| CeCa | Cervical cancer |
| CLU | Clusterin |
| CREB | Cyclic AMP response element-binding protein |
| Cyt C | Cytochrome-c |
| ErbB3 | V-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) |
| ERK | Extracellular signal-regulated kinase |
| GI50 | Half-maximal growth inhibitory concentration |
| GSK-3 | Glycogen synthase kinase-3 |
| HE4 | Human epididymis protein 4 |
| IC50 | Half-maximal inhibitory concentration |
| JNK | Jun *N*-terminal kinase |
| MAPK | P38 mitogen-activated protein kinases |
| Mcl-1 | Myeloid cell leukemia-1 |
| MDR | Multidrug resistance |
| MMP | Matrix metalloproteinase |
| OvCa | Ovarian cancer |

| | |
|---|---|
| PACAP | Pituitary adenylate cyclase-activating polypeptide |
| PAR2 | Protease-activated receptors 2 |
| P-gp | P-glycoprotein |
| PI3K | Phosphatidylinositol 3-kinase |
| ROS | Reactive oxygen species |
| VEGF | Vascular endothelial growth factor |
| VGSC | Voltage-gated sodium channels |

## Introduction

Endometrial, cervical, ovarian, vulvar, and vaginal cancers are examples of gynecologic cancers of the female reproductive system. Over 1 million new patients were diagnosed in 2018, and over 580,000 people died as a result of endometrial, cervical, and ovarian malignancies [1]. Cervical cancer (CeCa), which develops from cervical cells, is the most significant cause of death in females. Patients suffering from severe or recurring CeCa have poor prognosis, with just a 10–20% likelihood of survival after one year [2, 3]. Surgery, radiation, and chemotherapy are the most common therapies for CeCa. Cisplatin, paclitaxel, topotecan, ifosfamide, 5-fluorouracil, docetaxel, mitomycin, epirubicin, and carboplatin are the most often used medications to treat CeCa. However, these treatments have commonly adverse effects and complications. Surgery may result in bleeding, organ damage, and the possibility of clots in the deep veins of the legs; radiotherapy may result in menopause, infertility, discomfort, or pain during intercourse. Chemotherapy's adverse effects and drug resistance is another problem [4, 5].

Ovarian cancer (OvCa) is the third most frequent gynecologic cancer, worst gynecological cancer, following breast and cervix cancers. Early detection and diagnosis are difficult as symptoms are often mistaken for other nonmalignant diseases. The disease is linked to a poor diagnosis and may expand to the upper abdomen, lymphatic veins, and brain. As a reason, early detection and efficient treatment are crucial for increasing survival [6, 7]. OvCa's current standard of care is a blend of optimal cytoreductive or debulking surgery, radiation, and platinum-based chemotherapies (typically cisplatin or carboplatin) plus paclitaxel. Despite this treatment, up to 70% of patients relapse, with a 12- to 18-month median progression-free survival. Sensitivity to platinum-based chemotherapies declines with each consecutive relapse as platinum-resistant and refractory illness develops. Furthermore, the side effects of chemotherapy regimens often lead to neurotoxicity, nephrotoxicity, arthralgia, and fatigue, with a detrimental impact on the quality of life. As a result, long-term survival remains poor, with a significant risk of recurrence and side effects [8]. Even though each cancer has its unique treatment guidelines, the most common treatments include surgery, radiation, and chemotherapy. Current therapies, notably anti-cancer medications, frequently result in a plethora of adverse side effects, toxicity, and multidrug resistance (MDR). Natural products have been researched as adjunctive or alternative treatments to enhance clinical outcomes, lessen side effects and toxicity, overcome MDR, and increase survival rates due to the significant toxicity compared with conventional anti-cancer medicines [9, 10].

The marine environment contains a wealth of bioactive compounds that could treat human disorders such as cancer. Hundreds of new sea-based natural products have been extracted from marine micro- and macro-organisms, such as bacteria, fungi, micro-and macro-algae, corals, sponges, tunicates, and mollusks [11–13]. Marine-based medications have begun to impact modern pharmacology, with several anti-cancer therapies derived from marine chemicals receiving clinical approval, including cytarabine, belantamab mafodotin, brentuximab vedotin, enfortumab vedotin, eribulin mesylate, fludarabine phosphate (prodrug of ara-A), lurbinectedin, nelarabine (prodrug of ara-G), trabectedin, polatuzumab vedotin, plitidepsin, and vidarabine [14, 15].

There are numerous reasons why marine peptides have sparked interest in the development of anti-cancer therapies. They have several advantages over proteins or antibodies, including their small size, simple manufacturing, cell membrane-crossing properties, low drug–drug interaction, precise targeting, chemical and biological versatility, and lesser adverse effects due to lack of kidney or liver deposition. Anti-cancer peptides have a short half-life, short-bioavailability, flawed-pharmacokinetics, and protease sensitivity, as drawbacks [16, 17]. Peptides are classified based on apoptosis induction, cell proliferation, migration and angiogenesis inhibition, antioxidative mechanisms, microtubule-destabilization, cytotoxicity, or unidentified pathways in different cancerous cell lines, referring to clinical studies for cancer care assessment [18, 19].

Marine anti-cancer peptides have been isolated from cyanobacteria, sponges, mollusks, ascidians, algae, fungi, bacteria (actinomycete and streptomyces) and protein hydrolysates from fish, clam, and coral. Marine peptides can be categorized as linear and cyclic peptides. Linear peptides are formed by a straight amino acid chain connected with amide bonds [14]. Dolastatins and hemiasterlins (tripeptides) [20–22], symplostatin (pentapeptide) [23], reniochalistatins E (octapeptide) [24] and AGAPGG, AERQ, RDTQ (oligopeptide) [25] have been derived from sponges, cyanobacteria, mollusks, and corals. Cyclic hexa, hepta, dodecapeptides, and depsipeptides from marine organisms have been purported to have anti- CeCa and OvCa effects [26]. Cyclic depsipeptides have a more complicated structure, with ester bond substitutes and amide bonds in the peptide framework [14]. Apratoxin A and E [27], aurilide A [28], cryptophycin [29], grassypeptolide A-E [30, 31], kempopeptins A-B [32],

kohamamide A-C [33], neamphamide B-D [34], palauamide [35], palmyramide A [36], and pitipeptolides A-B [37] have been derived from cyanobacteria. Geodiamolide A and G [38] and homophymine A-E [39] from sponge and majusculamide C [40] from mollusk are cyclic depsipeptides having anti- cancer effects. Furthermore, veraguamide A-G, (cyclic hexadepsipeptide) [41], rolloamide A [42] and trunkamide A (cyclic heptapeptides) [18, 43], laxaphycin B (cyclic dodecapeptide) [44], and urukthapelstatin A (cyclic thiopeptide) [45] have been isolated from ascidia, actinobacteria, cyanobacteria, and sponge. Lipopeptides are linear or cyclic lipid acylated peptides, typically with the fatty acid side chain [14]. Hectochlorin [46] and Hermitamides A and B [47] have been derived from cyanobacteria, and iturins from marine-derived bacteria [48] have been reported as anti-CeCa and anti-OvCa agents. Marine protein hydrolysates represent a category of nutraceuticals that may prevent cancer. Protein hydrolysates have been characterized as oligopeptides and free amino acids' complex mixtures with antioxidant, antiproliferative, antihypertensive, and antimicrobial effects [49, 50]. Protein hydrolysates have been obtained from fish [51], clam [52], and corals [25] possess anti-CeCa properties.

Marine anti-cancer peptides exert their effects by several cellular and molecular pathways, such as DNA defense, cell-cycle control, apoptosis initiation, angiogenesis suppression, migration, invasion, and metastasis inhibition [53–56]. To date, a limited number of studies, based on the biological assessment of marine peptides against CeCa and OvCa, have been carried out. The current topic reveals the importance of marine peptides as an essential asset for discovering novel anti-cancer treatments.

## Mechanistic insights

Several dysregulated pathways are behind the pathogenesis of cancers [57], including CeCa and OvCa. Prevailing reports reveal the critical role of apoptosis, mitosis, metastasis, mitochondria dysfunction, angiogenesis, and miscellaneous mechanisms in the progression of CeCa and OvCa. Apoptosis mediators have shown a potential regulatory effects on mitotic/metastatic pathways [58, 59]. Besides, mitochondrial dysfunction, in turn, orchestrate the apoptotic pathways and aforementioned interconnected ways. Consequently, angiogenesis is located in the downstream of anti-apoptotic mediators and mitochondria-associated dysregulation during CeCa and OvCa [60]. So, highlighting the major signaling pathways and mechanisms will help to introduce pivotal therapeutic targets modulated by marine peptides (Figs. 1, 2).

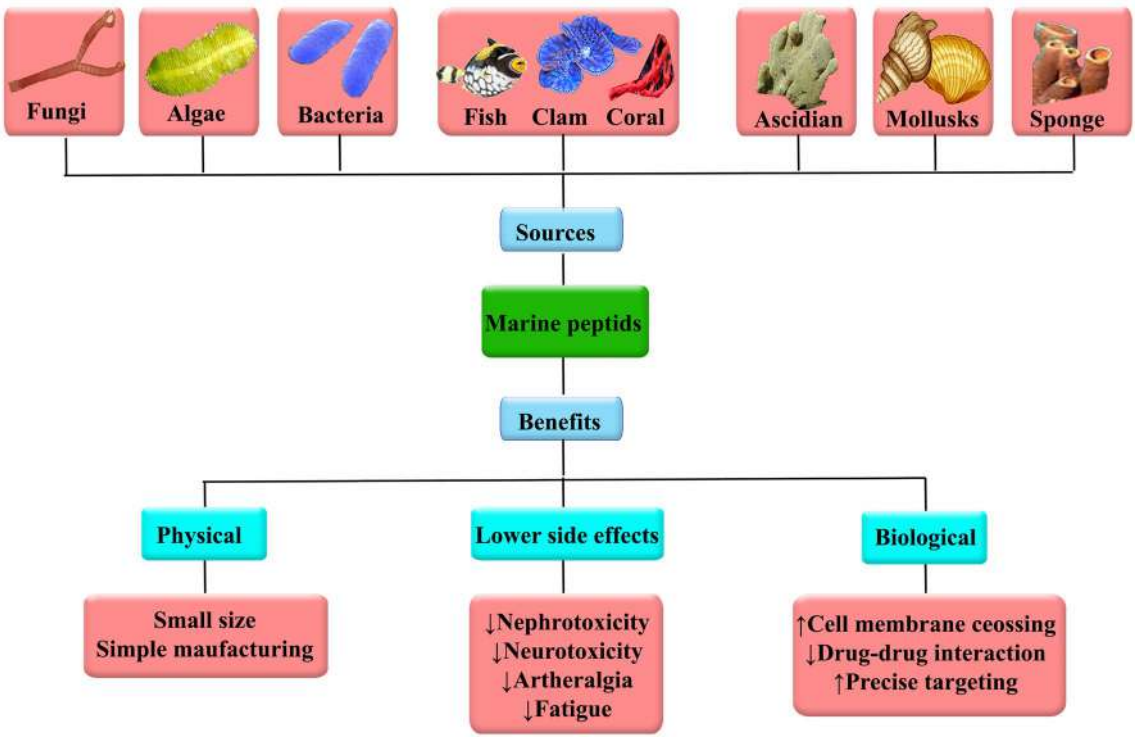


**Fig. 1** Sources, biological activities, and health benefits of marine peptides

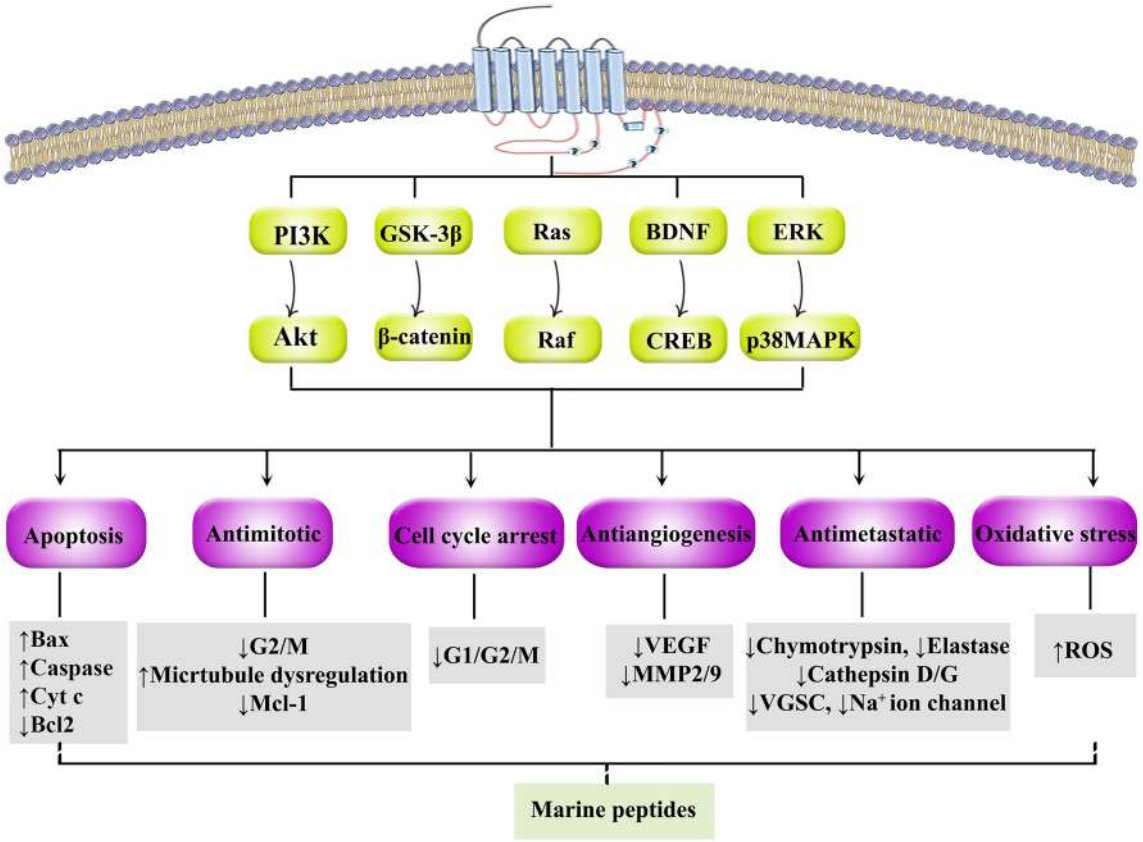


**Fig. 2** The signaling mediators/pathways targeted by marine peptides in combating cervical and ovarian cancer. *Akt* protein kinase B, *Bax* Bcl2-associated X protein, *Bcl2* anti-apoptotic factor, *BDNF* brain-derived neurotrophic factor, *CREB* cAMP-response element-binding protein, *ERK* extracellular signal-regulated kinase, *GSK-3β* glycogen synthase kinase-3β, *MAPK* mitogen-activated protein kinase, *MMP* matrix metalloproteinase, *mTOR* mammalian target of rapamycin, *PI3K* phosphoinositide 3-kinase, *VEGF* vascular endothelial growth factor, *VGSC* voltage-gated sodium channels, *ROS* reactive oxygen species

## Apoptosis

Cytochrome-c (cyt c) discharge is a pivotal stage in apoptosis induction, culminating in caspases (casps) activation and subsequent cell death [61]. Casps are the primary executors of apoptosis and are activated following proteolytic cleavage. Initiator casps, including casps-8, -9, and -10, trigger downstream influencer casps-3, -6, and -7, and activate and mediate a regulated and programmed cell death cascade [62].

Cryptophycin has been shown to induce apoptosis via casps-3 activation in a human ovarian carcinoma SKOV3 cell line [63]. Mere15 has been shown to induce apoptosis by initiating cyt c discharge, enhancing casps-3 and 9 activity in HeLa cells [64]. Similarly, *C*-phycocyanin from *Spirulina platensis* has been shown to trigger cyt c release and increase the activities of casps-2, -3, -4, -6, -8, -9, and -10 in HeLa cells with $IC_{50}$ of 80 µg $mL^{-1}$ [65]. Pardaxin and FW523-3 have shown analogous effects with $IC_{50s}$ of 15 and 0.45 µg $mL^{-1}$ [66–68].

Inhibiting Bcl2 or inducing BAX has been shown a viable method for initiating apoptosis [69]. Symplostatin 1 initiates the Bcl2 phosphorylation and increases casps-3 in OvCa (SKOV3) cells [23]. In cervical HeLa cancer cells treated with Mere15, Bcl2 levels have been shown to decrease, reflecting a rise in the production of BAX, an effect that could be actuated by p53 [64]. BCP-A and FIMGPY are protein hydrolysates from clams and skates capable of inducing apoptosis in HeLa cells by upregulating casps-3 and BAX and reducing Bcl2 [51, 52]. A recent study by Abdullah et al. also showed the potential of MalforminA1, a cyclic pentapeptide derived from marine fungi, to sensitize chemoresistant ovarian cancer cells in cisplatin-induced apoptosis through Bcl2/p53 downregulation [70]. Additionally, gliotoxin, a non-ribosomal peptide secondary metabolite isolated from marine fungus Aspergillus sp, was previously shown to induce apoptosis in HeLa cells, the human CeCa cell line through activation of casps-3, -8 and -9, upregulation of BAX and cyt c release, and downregulation of Bcl2 [71]. More recently, Park et al. reported that gliotoxin

enhances autophagic cell death in paclitaxel-resistant ovarian cancer cells by apoptosis modulation [72]. By inducing apoptotic mediators (e.g., casps and BAX), LvHemB1, a novel cationic antimicrobial peptide derived from hemocyanin of *Litopenaeus vannamei* (whiteleg shrimp), inhibited proliferation of CeCa cells (HeLa) [73].

Mitogen-activated protein kinases (MAPK), such as p38 and Jun N-terminal kinases (JNK), play essential roles in cellular signaling that governs responses to cellular stress. Stimulation of the p38 MAPK and JNK pathway has been to release cyt c and as a result activate casps cascades. Activation of JNK and ERK has been shown to promote mitochondrial-related apoptosis via JNK signaling and S phase arrest secondary to ERK signaling [74]. Aplidine, derived from *Aplidium albicans*, has been shown to promote apoptosis in cervical HeLa cells. Aplidine has been shown to elicit oxidative stress, which in turn activated JNK and p38 MAPK and with ensuing casps-9 and -3 activation and apoptosis [75]. By activating ERK, bisebromoamide from *Lyngbya majuscula* has been shown to cause apoptosis in cervical cancer HeLa S3 and ovarian OVCAR3, OVCAR4, OVCAR5, OVCAR8, and SKOV3 cells [76]. FW523-3, a lipopeptide derived from the *Micromonospora chalcea*, has been shown to cause apoptosis in HeLa human cervix cancer cells by activating casps-3,-7,-9, JNK, p38 MAPK, and ERK [68].

Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) is involved in synchronizing apoptosis in gynecological cancers [77, 78]. Clusterin (CLU), a protein that inhibits apoptosis, is overexpressed in CeCa and promotes tumorigenesis and resistance to cisplatin, doxorubicin, etoposide, and camptothecin, as well as activating AKT. AKT inhibition decreases the levels of phosphorylated BAD, BAX, and BAK, triggers cyt c release, activates casps-9, and regulates p53-dependent apoptosis, and concurrently decreases cyclic AMP response element-binding protein (CREB), glycogen synthase kinase-3 (GSK-3), and Raf for tumor progression inhibition [79, 80]. Pituitary adenylate cyclase-activating polypeptide (PACAP) has been isolated from European green frog (*Rana ridibunda*), salmon (*Oncorhynchus nerka*), cod (*Gadus morhua*), trout (*Oncorhynchus mykiss*), stingray (*Dasyatis akajei*), and bowfin (*Amia calva*) [81]. PACAP has been shown to decrease cervical HeLa and HT-3 cell growth and to induce apoptosis by inhibiting CLU production and secretion, inhibiting CLU's AKT activation activity, and blocking the AKT/Raf/ERK pathway [79].

## Antimitotic

Antimitotic drugs act through stabilization, destabilization of microtubule dynamics, and shifting the equilibrium between tubulin polymerization and depolymerization. The majority of these agents act by preventing the cells from entering the G2/M stage [82].

Microtubules perform vital cellular tasks such as chromosome separation, cell shape stability, transport, motility, and organelle distribution. Microtubules and microtubule-associated proteins are the mitotic spindle's major constituents, having a crucial role in cell division. Microtubule dynamics are required for chromosomal movements during anaphase. A change in tubulin-microtubule balance disrupts the mitotic spindle, interrupting the metaphase–anaphase transition of the cell cycle and leading to cell demise [83, 84]. Microtubule-destabilizing agents also induce apoptosis by inhibiting Bcl2 and myeloid cell leukemia-1 (Mcl-1) [85]. Mcl-1 has been shown to support cell viability by interfering early in a cascade that leads to the cyt c liberation [86]. Hemiasterlin and Hemiasterlin A, tripeptides extracted from *Auletta*, *Cymbastela,* and *Siphonochalina* sp., have been shown to depolymerize microtubules in ovarian OVCAR3 cancer cells [22]. Similarly, Hemiasterlin analogue HTI-286 has demonstrated similar behavior in ovarian 1A9 cell lines with $IC_{50s}$ of 0.6 nM by disrupting microtubule dynamics [87]. Dolastatin 10 ($IC_{50}$ 0.5 nM) and Dolastatin 15 ($IC_{50}$ 3 nM) inhibited microtubule assemblage and tubulin-reliant GTP hydrolysis in Chinese hamster ovary cells (CHO) [20]. The same behavior was shown for Dolastatin 10 and 15 in ovarian OVCAR3 cells with $9.5 \times 10^{-7}$ and $1.5 \times 10^{-4}$ μg $mL^{-1}$, respectively [21]. Scleritodermin A, cyclic peptide, has shown significant cytotoxicity against ovarian A2780 cell with $IC_{50}$ of 0.94 μM and inhibited microtubule polymerization [42]. Symplostatin 1 has been shown to cause microtubule depolymerization in the ovarian SKOV3 cancer cell ($IC_{50}$ 0.09 nM) [23]. Cryptophycin-52 (LY355703), a synthetic member of the cryptophycin, has been sown to block cervical HeLa S3 cell proliferation by depolymerizing spindle microtubules and disrupting chromosome organization [88].

Microtubule-stabilizing agents enhance microtubule polymerization and target the cytoskeleton and spindle apparatus of tumor cells by binding to the microtubules, thereby disrupting mitosis [83]. Aurilide A and cryptophycin have caused microtubule stabilization in cervical HeLa and ovarian SKOV3 and SKVLB1 carcinoma cell lines, respectively [28, 29, 63].

## Antimetastatic

Non-caspase proteases (elastase and trypsin) cause casps activation and apoptosis [89]. Trypsin has been shown to possess tumorigenic activity in CeCa and OvCa mediated through its receptor protease-activated receptors 2 (PAR2), and potentiated by human epididymis protein 4 (HE4). PAR2, a trypsin-activated trans-membrane receptor, has been implied in the etiology of CeCa and OvCa. HE4, a

WAP-family glycoprotein, has been shown to block trypsin breakdown [90, 91]. Similarly, chymotrypsin inhibition has been shown to induce reactivation of p53 and anticancer activity in CeCa cells [92]. Elastase fragmented surface E-cadherin in OvCa cells, causing epithelial mesenchymal transition (EMT), leading to OvCa induction and migration [93]. E-cadherin acts as a tumor suppressor and is frequently found downregulated in OvCa [94]. Symplocamide A, derived from the cyanobacterium *Symploca* sp., has been shown to inhibit chymotrypsin and trypsin with $IC_{50s}$ of 0.38 and 80.2 M, respectively [95]. Kempopeptin A has been shown to inhibit porcine pancreatic elastase (0.32 µM) and bovine pancreatic α-chymotrypsin (2.6 µM), whereas Kempopeptin B only inhibited trypsin activity (8.4 µM) [32]. Bouillomide A-B inhibited porcine pancreatic elastase and chymotrypsin [96]. Molassamide inhibited porcine pancreatic elastase and α-chymotrypsin with $IC_{50s}$ of 0.032 and 0.234 µM, respectively [97]. Largamides are cyclic peptides derived from the algae *Lyngbya confervoides* and *Oscillatoria* sp. Largamides A-C inhibited porcine pancreatic elastase, with $IC_{50}$ values ranging from 0.53 to 1.41 M [98]. Largamides D-G also inhibited chymotrypsin with $IC_{50}$ range from 4 to 25 µM [99]. Pompanopeptin A, a cyclic peptide isolated from *Lyngbya confervoides*, has been shown to inhibit trypsin with an $IC_{50}$ of 2.4 M [100]. Lyngbyastatin 4, cyclic depsipeptide from *Lyngbya* sp., showed inhibitory activity against elastase and chymotrypsin at 0.03 µM [101]. Lyngbyastatin 5–7 inhibited elastase with $IC_{50S}$ 3.2–8.3 nM and chymotrypsin $IC_{50s}$ 2.5–2.8 nM [102]. Lyngbyastatin 8–10 inhibited elastase with $IC_{50S}$ of 120–210 nM [103]. Tiglicamides A-C, cyclodepsipeptides from the same source, inhibited elastase with $IC_{50S}$ 2.14–7.28 µM [104]. Pitipeptolides A and B increased elastase inhibitory activity at 50 µg $mL^{-1}$ [37]. Somamide B from the same source inhibited elastase (9.5 nM) and chymotrypsin (4.2 µM) [102]. Cathepsins D and E are lysosomal proteases have been shown to possess anti-apoptotic properties and to play an important role in CeCa and OvCa [105]. Grassystatins A and B, two linear depsipeptides isolated from *Lyngbya confervoides*, were shown to have a substantial inhibitory effect on cathepsins D ($IC_{50}$ of 26.5 and 7.27 nM, respectively) and E. ($IC_{50}$ of 886 and 354 pM). Grassystatin C, on the other hand, inhibited cathepsins D ($IC_{50}$ 1.62 M) and E ($IC_{50}$ 42.9 nM) [106].

Microfilaments play a critical function in cell migration. Actin is a cytoskeletal microfilament essential for cell movement and cytokinesis and other activities essential for malignant cell stability. Actin polymerization inhibition results in microfilament disruption substantially, reduces cell motility, and mitigates metastatic progression of neoplastic cells [107]. Hectochlorin, a lipopeptide from Cyanobacteria (*Lyngbya majuscula*), showed antiproliferative activity against OvCa cell lines such as OVCAR3,4,5,8, and SKOV3 by actin filament disruption with a $GI_{50}$ of 5.1 µM [46].

Voltage-gated sodium channels (VGSC) are involved in cancer cell invasion and metastasis. Na+ ions are essential second messengers that are finely regulated in normal cells and deregulated in cancer. Apoptosis is characterized by a disorganized volume regulation that causes cell shrinkage under normal osmotic conditions, resulting in an early rise in intracellular sodium concentration [108]. The overexpression of VGSC has a significant impact on cell migration and invasiveness in human CeCa and OvCa and constitutes a proteolytic activity of MMP2 [109–111]. Palmyramide A was shown to have an $IC_{50}$ of 17.2 M for inhibiting ouabain- and veratridine-induced sodium overload by blocking the VGSC [36]. Hermitamides A and B are sodium channel blockers, and both inhibit it by ~ 50 and 80% at 1 M, respectively [47].

## Antiangiogenic

Angiogenesis is crucial in the development of cancer. VEGF, MMP2, and MMP9 all play essential roles in tumor invasion and metastasis [112]. Aplidine from *Aplidium albicans* inhibited cell migration and invasiveness of ovarian 1A9 cells by inhibiting vascular endothelial growth factor-mediated (VEGF) and blocked the production of matrix metalloproteinases (MMP2 and MMP9) [113]. Pardaxin from fish showed a similar effect in HeLa cell lines [66, 67].

## Cell cycle arrest

Several drugs are capable of interfering with the normal cell division, affecting cell viability, which is directly related to apoptosis [114]. For example, both Grassypeptolide A-E and Mere 15 have been shown to induce G1 and G2/M phase arrest in HeLa cells [30, 31, 64].

## Mitochondrial dysfunctions and oxidative damage

A mitochondrial malfunction disrupts the cell's redox state, causing damage to cell components and potentially leading to apoptosis [115]. Aurilide has been shown to induce mitochondrial fragmentation in HeLa cells, followed by mitochondria-induced cell death [116]. ROS accumulation causes oxidative stress induced by mitochondrial abnormalities, and cancerous cells contain high ROS concentrations [117]. DNA fragmentation is another direct result of oxidative stress, with ensuing DNA damage [118]. Cryptophycins 1 in SKOV3 was found to induce DNA fragmentation [63]. Pardaxin induced DNA fragmentation in HeLa and HT-1080 cell lines [66, 67]. C-phycocyanin from *Spirulina platensis* has been also shown to scavenge ROS, specifically peroxyl and hydroxyl radicals [119]. Similarly, BCP-A

protein hydrolysate from blood clam demonstrated strong radical scavenging and lipid peroxidation inhibition properties [52]. Binucleated cells have been localized as a result of oxidative stress in response to the cyanobacterial product symplostatin 1 [23].

### Unknown mechanism for anti-cancer activity

Criamide B, geodiamolide A and G [38], homophymine A-E [39], rolloamide A [120], and yaku'amides A and B [121] have been isolated from sponges; laxaphycin B from cyanobacteria [44]; and urukthapelstatin A from actinobacteria [45]. All have been shown potent cytotoxicity in OvCa cells, but the precise targets have yet to be determined. Majusculamide C [40], kulokekahilide-2 [122], and elisidepsin [123] from mollusks have also been shown to elicit anti-OvCa activity, via as of yet, unknown mechanisms.

Caylobolide A [124], homodolastatin 16 [125], kohamamide A-C [33], palauamide [35], and veraguamide A-G [41] have been isolated from cyanobacteria; neamphamide B-D [34] and reniochalistatins E [24] have been isolated from sponges; polypeptide P2 has been isolated from mollusk [126], styelin D has been isolated from ascidia [127]; epinecidin-1 has been isolated from fish [128]; and iturins have been isolated from marine-derived bacteria [48]. All possess anti-CeCa properties with, as of yet, an unknown mechanism. AGAPGG, AERQ, and RDTQ, isolated from soft coral (*Sarcophyton glaucum*) papain hydrolysate, exhibited significant cytotoxicity in HeLa cells, but modest cytotoxicity on non-cancerous Hek293 cells. The mechanism has yet to be discovered [25].

## MDR cancer

Drug resistance is one of the most common reasons for chemotherapy ineffectiveness in cancer patients. MDR accounts for more than 90% of cancer mortality in patients taking standard chemotherapeutics or novel targeted medicines. One of the primary causes of MDR is increased drug efflux by membrane ATP-binding cassette (ABC) transporters. Targeting ABC transporters to eliminate or reduce drug resistance in cancer treatment is a promising technique. Among these members, P-glycoprotein (P-gp) is the most well-studied efflux pump involved in MDR cancer, responsible for transporting many anti-cancer medications extracellularly [129, 130].

Hapalosin, a novel cyclic depsipeptide from *Hapalosiphon welwitschii* has been shown to reverse P-gp mediated MDR and increases taxol and vinblastine accumulation in SKVLB1 P-gp-overexpressing, vinblastine-resistant cells [131]. Cryptophycin, a cytotoxic macrocyclic depsipeptide isolated from cyanobacteria *Nostoc* sp., is an antimicrotubule compound that appears to be the poorer substrate for P-gp than vinca alkaloids. P-gp overexpression, OvCa cells have been shown to significantly reduce resistance to cryptophycin compared to vinblastine, colchicine, and taxol. This characteristic may afford cryptophycin an advantage in the treatment of drug-resistant malignancies. Ryptophycin showed antimitotic activity in ovarian SKVLB1 via microtubule stabilization [29]. Symplostatin 1, a linear pentapeptide from *Symploca* sp. showed apoptosis in OvCa MDR cells NCI/ADR-RES by casp-3 increment, Bcl2 decrement, and microtubules depolymerization [23]. Hectochlorin showed antiproliferative activity against ovarian MDR cell lines IGROV1 and NCI/ADR-RES by actin filament disruption [46]. Elisidepsin (Kahalalide F synthetic derivative) showed cytotoxicity in another MDR cell line IGROV1 [123].

## Clinical trial status

Several preclinical studies are followed by fewer clinical trials to investigate potential marine peptides against CeCa or OvCa. Dolastatin 10's potency and efficacy in preclinical models led to its inclusion in Phase I and Phase II clinical studies. Dolastatin 10 was well tolerated in Phase II tests in numerous tumor types, although it did not show clinical anti-cancer efficacy for OvCa [132]. The dolastatin derivative TZT–1027 (auristatin PE, soblidotin) was shown to be more efficacious than conventional anticancer medications such as paclitaxel and vincristine in phase II cancer [133, 134]. Aplidine (a second-generation didemin) has successfully completed phase I clinical research for CeCa and OvCa treatments [135]. D'Agostino et al. also reported that in a multi-center phase II clinical trial, LY355703, a synthetic cryptophycin analog, showed only a modest activity in patients with platinum-resistant OvCa; however, the considerable rate of disease stabilization in the absence of serious adverse effects showed promise for further investigation [136]. A Phase II study of a marine cyclic depsipeptide, didemnin-B, was performed in patients with progressive epithelial OvCa; however, no significant effect was expected with epithelial OvCa. Clinical trials with Didemnin B were stopped due to a lack of therapeutic effects [137].

Marine peptide hydrolysates are also evaluated in several other clinical trials in gastrointestinal disorders (NCT03801057) and elderly individuals (NCT03526744) to prevent muscle loss (NCT02890290). Marine-based nutritional supplements are going to be provided against sleep disorder and anxiety (NCT04983355).

Overall, ongoing and future clinical trials will make the way bright and pave the road in treating OvCa and CeCa.

**Table 1** Anti-cancer effects of marine peptides in the different reported studies

| Peptides | Marine sources (Species name) | Active derivative | Cell lines | Cytotoxic concentrations $IC_{50}/(GI_{50})^b$ | Anti-cancer mechanisms | References |
|---|---|---|---|---|---|---|
| Apratoxin A and E | Cyanobacteria (*Lyngbya bouillonii*) | Cyclic depsipeptide | HeLa | A: 10 nM, E: 72 nM | ↓ Cancer cell growth[a] | [27] |
| *E*-Dehydroapratoxin A | | | | 121 nM | | |
| Aurilide A | Cyanobacteria (*Lyngbya majuscula*)<br>Mollusk (*Dolabella auricularia*) | | | A: 0.011 μg $mL^{-1}$ | Microtubule stabilization | [28] |
| Cryptophycin | Cyanobacteria (*Nostoc* sp.) | | SKOV3 and SKVLB1 | 0.007–0.6 nM | | [29] |
| Cryptophycin 1 | | | SKOV3 | 50 nM | DNA fragmentation; Microtubule stabilization; ↑ caspase-3 | [63] |
| Cryptophycin-52 | | | HeLa S3 | 20 nM | Microtubule depolymerization | [88] |
| Grassypeptolide A-C | Cyanobacteria (*Lyngbya majuscula* and *Leptolyngbya* sp.) | | HeLa | A: 1.01 μM, B: 2.93 μM, C: 44.6 μM | G1 and G2/M phase arrest | [30] |
| Grassypeptolide D and E | | | | D: 335 nM, E: 192 nM | | [31] |
| Homodolastatin 16 | Cyanobacteria (*Lyngbya majuscula*) | | ME180 | 8.3 μg $mL^{-1}$ | ↓ Cell viability[a] | [125] |
| Kohamamide A-C | Cyanobacteria (*Okeania* sp.) | | HeLa | A: 29 μM, B: 23 μM, C: 18 μM | | [33] |
| Palauamide | Cyanobacteria (*Lyngbya* sp.) | | | 39 nM | | [35] |
| | | | BGC | 26 nM | | |
| Veraguamide A-G | Cyanobacteria (*Symploca* cf. *hydnoides*) | Cyclic hexadepsipeptide | HeLa | A: 21 μM, B: 17 μM, C: 6.1 μM, D: 0.54 μM, E: 0.83 μM, F: 49 μM, G: 2.3 μM | | [41] |
| Laxaphycin B | Cyanobacteria (*Lyngbya majuscula*) | Cyclic dodecapeptide | PA1 | 0.19 ± 0.03 μM | | [44] |
| Symplostatin 1 | Cyanobacteria (*Symploca* sp.) | Linear Pentapeptide | SKOV3 | 0.09 nM | ↑ Caspase-3; ↓ Bcl2; microtubules depolymerization | [23] |
| | | | NCI/ADR | 2.9 nM | | |
| Hectochlorin | Cyanobacteria (*Lyngbya majuscula*) | Lipopeptide | IGROV1, OVCAR3, OVCAR4, OVCAR5, OVCAR8, SKOV3, NCI/ADR-RES | 5.1 μM | Actin microfilament disruption | [46] |
| Caylobolide A | | Macrolactone peptide | HeLa | 12.2 μM | ↓ Cell viability[a] | [124] |
| Bisebromoamide | | Peptide | HeLa S3 | 0.04 μg $mL^{-1}$ | ↑ ERK (ERK activation) | [76] |
| | | | OVCAR3, OVCAR4, OVCAR5, OVCAR8, SKOV3 | 40 nM | | |

**Table 1** (continued)

| Peptides | Marine sources (Species name) | Active derivative | Cell lines | Cytotoxic concentrations $IC_{50}/(GI_{50})^b$ | Anti-cancer mechanisms | References |
|---|---|---|---|---|---|---|
| Dolastatin 10 | Mollusk (*Dolabella auricularia*) | Linear pentapeptide | CHO | 0.5 nM | Microtubules depolymerization | [20] |
| | | | OVCAR3 | $9.5 \times 10^{-7}$ μg $mL^{-1}$ | | [21] |
| Dolastatin 15 | | | | $1.5 \times 10^{-4}$ μg $mL^{-1}$ | | |
| | | | CHO | 3 nM | | [20] |
| Elisidepsin | Mollusk (*Elysia rufescens*) | Depsipeptide | IGROV1 | 4.2 μM | ↓ Cell viability[a] | [123] |
| | | | OVCAR3 | 7.3 μM | | |
| Kulokekahilide-2 | Mollusk (*Philinopsis speciosa*) | | SKOV3 | 7.5 nM | | [122] |
| Majusculamide C | Mollusk (*Dolabella auricularia*) | Cyclic depsipeptide | OVCAR3 | 0.51 μg $mL^{-1}$ | ↓ Cancer cell growth [a] | [40] |
| Mere15 | Mollusk (*Meretrix meretrix*) | Polypeptide | HeLa | 46 μg $mL^{-1}$ | G2/M phase arrest; ↑ caspase-3, 9, ↑ cyt c release, ↓ Bcl2; ↑ Bax, ↑ P53 | [64] |
| Polypeptide P2 | Mollusk (*Arca subcrenata*) | | | 13 μg $mL^{-1}$ | ↓ Cell viability[a] | [126] |
| Criamide B | Sponge (*Cymbastela* sp.) | Cyclic depsipeptide | HEY | 0.19 μg $mL^{-1}$ | ↓ Cell viability[a] | [38] |
| Geodiamolide A and G | | | | A: 0.043 μg $mL^{-1}$, G: 8.6 μg $mL^{-1}$ | | |
| Homophymine A-E | Sponge (*Homophymia* sp.) | | OV3 | A: 7.5, B: 9.9, C: 3.7, D: 10.6, E: 4.2 nM | | [39] |
| | | | OVCAR8 | A: 5.4, B: 8.0, C: 4.3, D: 8.1, E: 4.6 nM | | |
| Neamphamide B-D | Sponge (*Neamphius huxleyi*) | | HeLa | B: 110 nM, C:170 nM, D: 210 nM | | [34] |
| Rolloamide A | Sponge (*Eurypon laughlini*) | Cyclic heptapeptides | OVCAR3 | 0.17 μM | | [120] |
| | | | SKOV3 | 1.6 μM | | |
| Scleritodermin A | Sponge (*Scleritoderma nodosum*) | Cyclic peptide | A2780 | 0.94 μM | Microtubule depolymerization | [42] |
| Hemiasterlin, A, B and C | Sponge (*Auletta* sp., and *Siphonochalina* sp.) | Tripeptide | OVCAR3 | Hemiasterlin: $1 \times 10^{-6}$ μg $mL^{-1}$, A: 0.0024 μg $mL^{-1}$, C: 0.0066 μg $mL^{-1}$ | | [22] |
| HTI-286 (hemiasterlin analogue) | Sponge (*Hemiasterella minor*, *Auletta* sp., *Cymbastela* sp., and *Siphonochalina* sp.) | | 1A9 | 0.6 nM | | [87] |

**Table 1** (continued)

| Peptides | Marine sources (Species name) | Active derivative | Cell lines | Cytotoxic concentrations $IC_{50}/(GI_{50})^b$ | Anti-cancer mechanisms | References |
|---|---|---|---|---|---|---|
| Reniochalistatins E | Sponge (*Reniochalina stalagmitis*) | Octapeptide | HeLa | 17.3 μM | ↓ Cell viability[a] | [24] |
| Trunkamide A | Ascidia (*Lissoclinum* sp.) | Cyclic heptapeptide | IGROV1 | 7.31 nM | | [18, 43] |
| | | | HeLa | 3.9 nM | | |
| Styelin D | Ascidia (*Styela clava*) | Peptide | ME180 | 50 μg $mL^{-1}$ | | [127] |
| Pardaxin | Fish (*Pardachirus marmoratus*) | | HeLa | 15 μg $mL^{-1}$ | ↑ Caspase-3,7, 8; ↓ MMP2,9, ↑ cyt c release; DNA fragmentation | [66, 67] |
| Epinecidin-1 | Fish (*Epinephelus coioides*) | Linear Peptide | HeLa | 3.5 μg $mL^{-1}$ | ↓ Cancer cell growth[a] | [128] |
| FIMGPY | Fish (*Raja porosa*) | Hexapeptide | | 4.81 mg $mL^{-1}$ | ↑ Caspase-3, ↑ Bax/Bcl2 ratio | [51] |
| AGAPGG | Soft coral (*Sarcophyton glaucum*) | Oligopeptide | | 8.6 mmol $L^{-1}$ | ↓ Cell viability[a] | [25] |
| AERQ | | | | 4.9 mmol $L^{-1}$ | | |
| RDTQ | | | | 5.6 mmol $L^{-1}$ | | |
| BCP-A | Blood clam (*Tegillarca granosa*) | Peptide | | 2.54 mg $mL^{-1}$ | ↑ Caspase-3, ↓ Bcl2; ↑ Bax, ↓ ROS | [52] |
| *C*-phycocyanin | Algae (*Spirulina platensis*) | Peptide | HeLa | 80 μg $mL^{-1}$ | ↑ Caspases-2, 3, 4, 6, 8, 9, and 10; ↑ cyt c release | [65] |
| Urukthapelstatin A | Actinobacteria (*Mechercharimyces asporophorigenens*) | Cyclic thiopeptide | OVCAR3, OVCAR4, OVCAR5, OVCAR8, SKOV3 | 0.828–0.846 nM | ↓ Cell viability[a] | [45] |
| FW523-3 | Bacteria (*Micromonospora chalcea*) | Lipopeptide | HeLa | 0.45 μg $mL^{-1}$ | ↑ Caspase-3,7,9; ERK ↑; p38 MAPK↑ | [68] |
| Iturin $A_8$, $A_9$ | Bacteria (*Bacillus* sp.) | | | A8: 5.6 μM, A9: 4.6 μM | ↓ Cell viability[a] | [48] |
| Iturin $F_1$, $F_2$ | | | | F1: 8.9 μM, F2: 7.8 μM | | |

1A9, A2780, CHO, HEY, NCI/ADR-RES, IGROV1, PA1, OV3, OVCAR3, OVCAR8, SKOV3, SKVLB1 = ovarian cancer cell lines; BGC, HeLa, HeLa S3, ME180 = cervical cancer cell lines

[a]Mechanism is yet to be investigated

[b]If there are parentheses around the value, it means the GI50 value is displayed

## Conclusions and future perspectives

CeCa and OvCa are among the top causes of cancer-related mortality in women around the world. While the number of cases is increasing, present therapy options have adverse effects, and relapses often occur. There is a great need for novel cancer treatments. The discovery of novel clinical chemotherapeutic peptides from diverse aquatic life can be incorporated into cancer prevention and treatment. Despite the fact that CeCa and OvCa affects women all over the world, there is a scarcity of information in the literature regarding the use of marine peptides to inhibit such malignancies [53, 138, 139]. The absence of ethnomedicinal background, technological challenges in gathering marine species, particularly deep-sea critters, and isolation and purification issues are all barriers to anti-cancer peptide research [140]. Thanks to modern technology, it is increasingly possible to extract samples from the sea and isolate different peptides from aquatic materials [141]. Marine peptides have demonstrated possible anti-cancer activities against various forms of cancer, such as cell growth inhibition, antimitotic activity (anti-tubulin effects), apoptosis induction, and migration, invasion, or metastasis inhibition. These marine peptides are rich and exciting resources for generating anti-cancer therapies and a platform for uncovering new therapeutic cellular targets. As a result, it is essential to further investigate the anti-cancer properties of marine peptides. The tolerance of cancer cells to chemotherapy is indeed one of the sources of modern pharmacotherapy's inefficiency. Marine peptides act efficiently as MDR-threatening proteins (Table 1).

Of the isolated compounds to date, only a few have been progressed to clinical studies, and a relatively small number of peptides have successfully entered the pharmaceutical pipeline and have been used clinically. Although individual pharmacologically active marine peptides have been excluded from further drug discoveries due to dangerous toxicity, there remains the need for the synthesis of corresponding analogs to develop new drugs.

Several marine peptides that have been shown to be cytotoxic or anti-cancer in other cell lines should be evaluated for action against CeCa and OvCa. Novel approaches for isolating and identifying marine peptides that could be used as anti-cancer drugs should be developed. The effects of marine peptides in conjunction with conventional chemotherapy, target therapy, or immunotherapy must be studied [18]. Short half-life, low bioavailability, processing and manufacturing problems, and protease susceptibility are significant drawbacks of therapeutic peptides. For low cell membrane permeability, cell-penetrating peptides are used. Metabolic instability and short half-life may be overcome by using D-amino acid substitution, peptide cyclization, encapsulation with nanoparticles, pegylation, and XTEN conjugation. D-amino acid substitution reduces immunogenicity [16, 142–144]. Protein hydrolysates are an excellent source of anti-cancer, antioxidant, and anti-proliferative bioactive chemicals. However, more research on the cell cycle phase or apoptosis of cancer cell lines is needed. In vivo and in silico researches are also required to identify and define the mechanism of action and safety of marine peptides and protein hydrolysates [55]. Further investigation on the variety of marine peptides in modification and modes of action provides a rich resource for developing novel and potent new medicines.

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