Biomedicine & Pharmacotherapy 142 (2021) 112038

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Marine peptides in breast cancer: Therapeutic and mechanistic understanding

Salman Ahmed [a], Hamed Mirzaei [b], Michael Aschner [c], Ajmal Khan [d], Ahmed Al-Harrasi [d,*], Haroon Khan [e,*]

[a] Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan
[b] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran
[c] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[d] Natural and Medical Sciences Research Center, University of Nizwa, P.O Box 33, Postal Code, 616, Birkat Al Mauz, Nizwa, Oman
[e] Department of Pharmacy, Abdul Wali Khan University Mardan, 23200, Pakistan

ARTICLE INFO

Keywords:
Marine peptides
Protein hydrolysate
Apoptosis
Metastasis
Cell cycle arrest

ABSTRACT

Breast cancer is the most prevalent invasive form of cancer in females and posing a great challenge for overcoming disease burden. The growth in global cancer deaths mandates the discovery of new efficacious natural anti-tumor treatments. In this regard, aquatic species offer a rich supply of possible drugs. Studies have shown that several marine peptides damage cancer cells by a broad range of pathways, including apoptosis, microtubule balance disturbances, and suppression of angiogenesis. Traditional chemotherapeutic agents are characterized by a plethora of side effects, including immune response suppression. The discovery of novel putative anti-cancer peptides with lesser toxicity is therefore necessary and timely, especially those able to thwart multi drug resistance (MDR). This review addresses marine anti-cancer peptides for the treatment of breast cancer.

1. Introduction

Breast cancer is among the most prevalent cancers in women. Around 0.62 million deaths in 2018 were caused by breast cancer, according to Globocan 2018 figures from the International Organization for Research on Cancer (I.A.R.C.). At the present rate, the number of incidents is forecasted to increase to 3.05 million, and the death toll will approximate 7 million by 2040 [1]. Cancer is conventionally treated with chemotherapy, radiation, and surgery [2]. Conventional cancer chemotherapy has many side effects, and it often targets multiple organs. It is subject to MDR caused by over-expression of membrane transporters, which may expel intracellular anti-cancer drugs, thus decreasing drug accumulation and efficacy [3]. Furthermore, radiation therapy and surgery increase the probability of cancer invasion [2]. Accordingly, developing new efficacious anti-cancer drugs is required [4,5].

Extensive development initiatives have been underway to acquire effective compounds of natural origin [6,7]. Approximately 71% of Earth's atmosphere is aquatic, rendering it an enormous reservoir of novel bioactive substances of rare and special chemical characteristics. Sea species are a treasure trove of anti-cancer drugs. Over the last decade, numerous studies have shown that marine products could act as anti-tumor agents and play a preventive role in tumor management, underlying their promise in the discovery of novel and efficient pharmaceuticals [4].

More than 50% of the FDA-approved medications in the 1980s and

Abbreviations: Akt, Serine / threonine protein-kinase family protein-kinase B; APAF-1, Apoptotic Peptidase-Activating Factor-1; BAD, BCl-2 / Bcl-X associated death-domain protein; BAK, BCl-2 homologous antagonist - killer protein; BAX, BCl-2-associated x protein; Bcl-2, B-Cell lymphoma 2; Bcl-xL, B-Cell lymphoma-extra large; Casp, Caspase; CXCR4, C-X-C chemokine-receptor type-4; Cyt c, cytochrome c; ErbB3, V-erb-b2 Erythroblastic Leukemia Viral Oncogene Homolog 3 (avian); ERK1/2, Extracellular Signal Regulated kinase ½; FoxO3a, Forkhead Box Protein O3; HIF1α, Hypoxia inducible factor 1alpha; MMP, matrix metalloproteinase; Mcl-1, Myeloid Cell Leukemia-1; MDR, Multidrug Resistance; MRP1, Multidrug Resistance-associated Protein 1; PARP, Poly ADP-Ribose Polymerase; P-gp, P-glycoprotein; PI3K, Phosphatidylinositol-3-Kinase; ROS, Reactive Oxygen Species; STAT3, Signal transducer and activator of transcription 3; TNBC, Triple-negative Breast Cancer Cell; VEGF, Vascular Endothelial Growth Factor.

* Corresponding authors.
E-mail addresses: salmanahmed@uok.edu.pk (S. Ahmed), h.mirzaei2002@gmail.com (H. Mirzaei), michael.aschner@einsteinmed.org (M. Aschner), aharrasi@unizwa.edu.om (A. Al-Harrasi), haroonkhan@awkum.edu.pk, hkdr2006@gmail.com (H. Khan).

https://doi.org/10.1016/j.biopha.2021.112038
Received 19 June 2021; Received in revised form 1 August 2021; Accepted 7 August 2021
Available online 16 August 2021
0753-3322/© 2021 Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

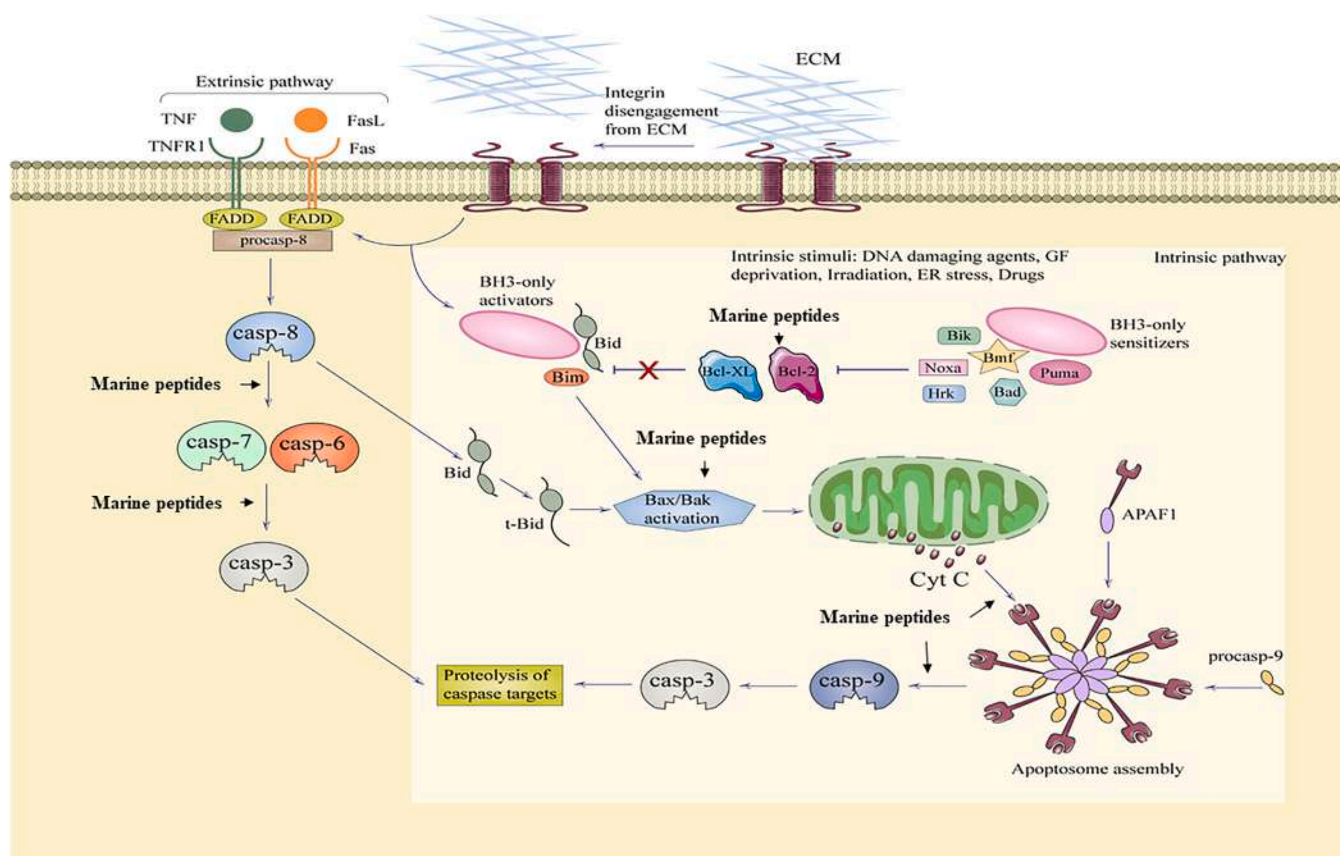

Fig. 1. Scheme of two of the involved pathways in apoptosis.

1990s have aquatic life origin. Indeed, sea-derived medicines are a significant source of anti-cancer drugs [8]. Several marine-derived drugs have been approved as anti-cancer drugs, since the original approval of cytarabine in 1969. The discovery of Didemnin B, obtained from *Trididemnum solidum* in 1981 and dolastatin 10 from *Dolabella auricularia* in 1987, represents a critical point in the synthesis of marine-derived cancer chemotherapy peptides [9]. Bioactive peptides from natural aquatic products, including small marine peptides [10], have shown efficacy as potential drug candidates with distinct modulations of several molecular pathways [11].

There are numerous reasons as to why marine peptides have drawn attention in the search for anti-cancer drugs. They have some significant benefits over proteins or antibodies, such as small size, simple manufacturing, readily modified, cell membrane-crossing capability, low drug-drug interaction, chemical, and biological versatility. An additional value is the fewer number of adverse side effects due to lack of accumulation in the kidneys or liver [12–15]. The current review is predominantly focused on the underlying mechanisms of marine peptides in the treatment of breast cancer coupled with their therapeutic potential.

2. Marine anti-cancer peptides

Marine peptides represent one of the most versatile sources of therapeutically effective drug molecules [16]. Marine anti-cancer peptides have been extracted from cyanobacteria, sponges, mollusks, ascidians, algae, fungi, bacteria (actinomycete and streptomyces), and protein hydrolysates from fish, amphibians, crocodiles, and turtles. Marine peptides can be categorized as linear and cyclic peptides. Linear peptides are formed by a straight amino acid chain connected with amide bonds [17]. Hemiasterlin A-B (tripeptides) [18], Belamide A (tetrapeptides) [19], Symplostatin, Dolastatin 10 and 15 (pentapeptides) [20] are reported from sponges, cyanobacteria and mollusks.

Cyclic penta, hexa, hepta, decapeptides, depsipetides and oligopeptides from marine organisms are reported to possess anti-breast cancer properties [17]. Galaxamide, A1- A5 (cyclic pentapeptides) [21], Mollamide B (cyclic hexapeptides) [22]; Rolloamide A, Stylissatin B (cyclic heptapeptides) [23,24], Stylopeptide 2 (cyclodecapeptides) [25], Laxaphycin B5, B6 and Wewakazole B (cyclic dodecapeptides) [26,27] are obtained from algae, ascidia, sponge and cyanobacteria. Cordyheptapeptide C-E (cyclic heptapeptides) is obtained from marine derived fungus [28]. Cyclic depsipeptides have a more complicated structure, with ester bonds substitutes for amide bonds secondary to the presence of hydroxy acid in the peptide framework [9,17].

Numerous anti-cancer cyclic depsipepides have been recorded from marine organisms. Desmethoxymajusculamide C [29], Cocosamides A-B [30], Hantupeptin A-C [31], Malyngamide 3 [30], Pitiprolamide [32], Pitipeptolide A-F [33], Isomalyngamide A and A-1 [34], Largazole [35]; Cryptophycin [36] Cryptophycin 1 [37], Coibamide A [38,39] are obtained from cyanobacteria. Jaspamide / Jasplakinolide A-P [40], Geodiamolide A-E, H, I [41–43], Pipecolidepsin A-B [44] from sponge; Kahalalide F and Elisidepsin [45,46], Kulokekahilide-2 [47] from mollusk; Dehydrodidemnin B (Aplidin / Plitidepsin) from ascidia *Aplidium albicans* [48] and Ohmyungsamycin A-B from streptomyces [49] are cyclic depsipeptides with antibreast cancer properties.

Cyclic pentadepsipeptide Sansalvamide has been isolated from fungus *Fusarium* sp [50]. Kailuin A-D (cyclic acyldepsipeptides) [51]. Thiocoraline (cyclic thiodepsipeptide) [52] and Marthiapeptide A (polythiazole cyclic peptide) [53] have been isolated from bacteria. Macrocyclic peptide, Diazonamide A has been isolated from ascidia *Diazona angulata* [54]. Cyclic oligopeptides are cyclic peptides consisting of 2–20 amino acids formed by nonribosomal peptide synthesis [17]. Efrapeptin G from fungus *Acremonium* sp. is one such example [55].

Lipopeptides are linear, or cyclic lipid acylated peptides, typically

with the fatty acid side chain [9]. Several anti-cancer Lipopeptides have been isolated from marine sources, including Curacin A-C, Somocystinamide A from cyanobacteria *Lyngbya majuscula*, and *Schizothrix* sp [56,57]. Iturin A from bacteria *Bacillus megaterium* [58]. In triple negative breast cancer, the Cyclo (L-Leucyl-L-Prolyl) a marine peptide has shown propensity to target the EGFR and CD151 signaling pathway [59].

Marine Protein hydrolysates represent a family of nutraceuticals that can prevent cancer [60]. Protein hydrolysates are characterized as oligopeptides and free amino acid complex mixtures with antioxidant, antiproliferative, antihypertensive, and antimicrobial effects [60,61]. Enzymatic hydrolysis is more likely to improve free radical scavenging activity [62]. Protein hydrolysates obtained from fish [60], amphibians [63] and turtles [64] have also been shown to possess anti-breast cancer properties.

Marine anti-cancer peptides modulate/regulate a number of cellular and molecular pathways, like DNA defense, cell-cycle control, apoptosis initiation, angiogenesis suppression, migration, invasion, and metastasis inhibition [4,5,8,65,66]. The current topic emphasizes the importance of large marine peptides as an essential tool for discovering novel anti-breast cancer treatments addressing their mechanistic effects.

3. Mechanistic insights

3.1. Apoptosis

A successful anti-cancer agent should have multidimensional apoptotic targets [67,68]. Intrinsic and extrinsic pathways are linked to caspase-3 (Casp-3) activation and induce DNA damage, nuclear and cytoskeletal protein destruction, protein cross-linking, apoptosis body development, and finally, phagocytic cell uptake (Fig. 1). The intrinsic pathway is controlled by the Bcl-2 protein, releases Cyt c, and reacts with APAF-1 to produce a platform for Casp-3, -7, and -9 activation. Extrinsic pathways do not include mitochondria and are activated by cell-surface death receptors [69–71].

Cyt c discharge from mitochondria plays a pivotal role in apoptosis induction, causing a sequence of biochemical reactions culminating in activation of Casps and subsequent cell death [72,73]. *C*-phycocyanin induces apoptosis in BT-474, HBL 100, MCF7, MDA MB-231, and SKBR-3 cells *in vitro* by Cyt c release and the ensuing activation of Casps -9 [74,75]. Mere15, a linear polypeptide formed by *Meretrix meretrix*, mediates Cyt c discharge and Casp-3,-9 and PARP cleavage [76]. Iturin A, a lipopeptide formed by *Bacillus megaterium* mediates the release of Cyt c, Casp-3,-9 and PARP in MCF7, T47D and MDA-MB-231, -468 [77].

Casps act as core apoptosis executors and are activated upon proteolytic cleavage [78]. For example, symplostatin 1 treatment increases the activity of Casp-3 in MDA-MB-435 and NCI/ADR leading to cell death with IC_{50s} of 0.15 and 2.9 nM, respectively [20],. Jaspamide A-P induces apoptosis by increasing Casp-3 in MCF7 [40]. Activation of Casp-3,-7,-8 and-9 has been detected in response to dolastatin 10 and 15 treatment [54]. Curacin A-C [56], Mere15 [76] Somocystinamide A [57], Dehydrodidemnin B [48] Coibamide A [39], Cryptophycin [79] has shown the same behavior in MCF7, MCF-15, MDA-MB-231 and -435. Galaxamide and Galaxamide analogs A1-A5 have shown cytotoxicity against MCF7 cell-lines by activating Casp-3, -9 and PARP [21]. Similarly, Keyhole limpet hemocyanin (KLH) marine peptides enhances apoptotic activity in MCF7 cells by 250 ng mL^{-1} [48,80].

The combination of Bcl-2 inhibition and Bax induction is a successful means for initiating apoptosis [22]. Jaspamide A-P induces apoptosis in MCF7 by stimulating Casp 3, increasing Bax, decreasing Bcl-2 and PARP protein proteolysis [40]. Symplostatin shows an analogous effect in MDA-MB-435 and NCI/ADR with $IC_{50\,s}$ of 0.15 and 2.9 nM, respectively [20,81]. Similarly, *C*-phycocyanin induced apoptosis in BT-474,HBL 100, MCF7, MDA-MB-231 and SKBR-3 cells [74,75]. Dolastatin 10 and 15 [8,82]; Mere15 leads to the same response in MCF-15, triggered by p53 [76]. BAX upregulation and Bcl-2, Mcl-1, Bcl-xL, downregulation in MDA-MB-231 and MCF7 cells has been noted upon Iturin A [83] and Dehydrodidemnin B treatments [48,84]. Tuna hydrolysate protein (*Thunnus tonggol*) has shown cytotoxicity in MCF7 cells with $IC_{50\,s}$ of 1.39 mg mL^{-1} causing apoptosis by increased Casp-3, -9, PARP, Bcl-2, Bax, and p53 expressions [85].

The PI3K/AKT pathways plays an important role in controlling cell cycle and survival. AKT inhibition reduces the level of phosphorylated Bad, Bax, Bak, triggers Cyt c release, and activates Casp-9 and regulates p53-dependent apoptosis [40]. PI3K/AKT inhibition and decreased ErbB3 have been shown to lead to cell cycle arrest and Bax and Bak activation [86]. Kahalalide F causes PI3K/AKT inhibition and ErbB3 depletion in MCF7, SKBR3 and BT474 cells [45,87,88]. Elisidepsin (PM02734, Irvalec®), a Kahalalide F synthetic derivative, has shown cytotoxic activity in MDA-MB-231, -361, -435 SKBR3 cells through PI3K/AKT inhibition and ErbB3 depletion [46,87,89]. Dolastatins has shown an analogous response [90]. FoxO3a is a tumor suppressor, and has been shown to downregulate Akt transcription factor and induce apoptosis [83]. Iturin A has been shown to downregulate AKT phosphorylation and upregulate FoxO3a in MCF7, MDA-MB-231,-468 and T47D cells [58].

3.2. Antimitotic

Antimitotic drugs act through stabilization, destabilization of microtubule dynamics [91–93]. The microtubule system is essential for mitosis and cell division, making it an effective anti-cancer drugs' target. Microtubules and microtubule-associated proteins are the major constituents of the mitotic spindle having a crucial role in cell division. Alterations in the tubulin-microtubule equilibrium leads to degradation of the mitotic spindle, interrupting the cell cycle during the meta-anaphase transformation, ultimately resulting in cell death [94]. Belamide A [19], Diazonamide A [54,95] and MML from mollusk *Meretrix meretrix* [96] have been shown to exhibit cytotoxicity in MCF7 cells by increasing cell membrane permeability and tubulin depolymerization. Hemiasterlin, Hemiasterlin A, and B interrupt the G2-M phase through disrupting microtubule dynamics in MCF 7 cells with IC50 0.5–7 nM [18]. Hemiasterlin and Hemiasterlin C arrest the G2-M phase secondary to microtubule depolymerization in MDA-MB-435 cells with $IC_{50\,s}$ of 0.0154 and 0.4002 μg mL^{-1}, respectively [97]. Similarly, Microcionamide A, B [98] and Milnamide A - D [42,99] cause microtubules depolymerization in MCF7, SKBR3, and MDA-MB-435 cells. Scleritodermin A, a cyclic peptide, has been shown to be active in SKBR3 cells with $IC_{50\,s}$ 0.67 μM, and inhibited microtubule polymerization and G2-M phase arrest [100]. Symplostatin 1 (dolastatin 10 analog) from cyanobacteria *Symploca* sp. Has shown significant anti-cancer effects in murine mammary 16/C mouse xenograft model (early-stage mammary adenocarcinoma). Increased Casp 3 increment, decreased Bcl-2 decrement and microtubular depolymerization have been suggested as potential anti-cancer mechanisms in mediating these effects [81].

Microtubule stabilizing agents accelerate microtubule polymerization and damage the cytoskeleton and spindle cancer cells framework, thus disrupting mitosis [91,94]. Cryptophycin has shown marked cytotoxicity in MCF7 (IC_{50} of 0.016 nM), MCF-7/ADR (IC_{50} value of 0.017 nM) and MDA-MB-435 (IC_{50} of 50 pM) cells by stabilizing spindle microtubules [36,37,101].

3.3. Antimetastatic

Microfilaments have an essential role in cell migration. Actin polymerization inhibition results in microfilament disruption, reducing cell motility, and mitigates metastatic progression of neoplastic cells [102]. Desmethoxymajusculamide C is potent against MDA-MB-435 (IC_{50} 0.22 μM) cells, via actin microfilament disruption [29]. Geodiamolides A, B, D, E, H, and I have been shown to disrupt the actin filaments in T47D, MCF7, and MDA-MB-435 cells [42,43]. By positively affecting the STAT3 pathway, MMP2 and MMP9 are subjected to upregulation and facilitate cancer invasion. STAT3 inhibition leads to apoptosis and

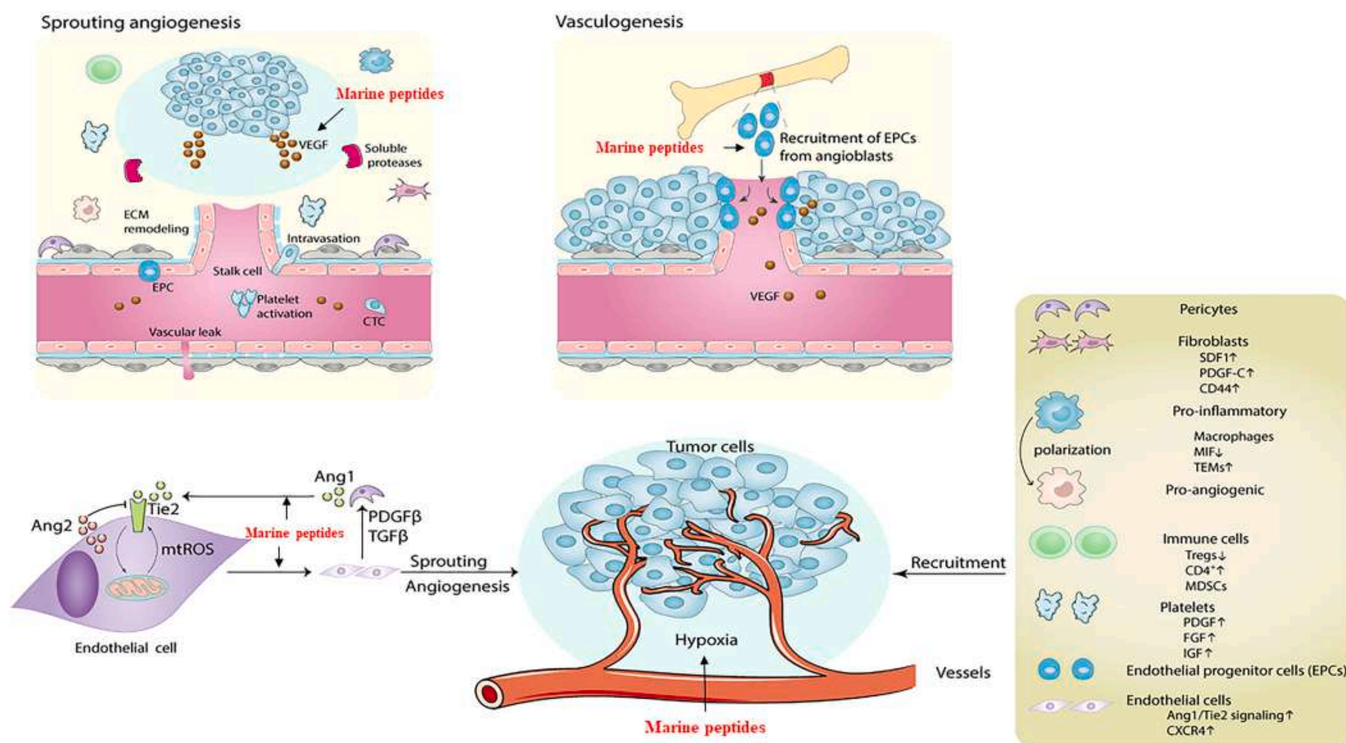

Fig. 2. A schema of angiogenesis and its involved factors.

suppresses metastasis in cancer cells [103]. *C*-phycocyanin inhibits STAT3 in MCF7 and inhibits metastasis [75].

3.4. Antiangiogenic

Angiogenesis plays a central function in carcinogenesis (Fig. 2) [104]. VEGF is abundantly expressed in cancer cells and is the key to angiogenesis activation [105]. The angiogenesis mechanisms include ERK1/2, CXCR4, HIF1α and Akt [106,107]. MMP2 and MMP9 also play an essential role in tumor invasion and metastases [108]. *Petrosaspongia* sponge Mycothiazole blocked HIF1α in T47D (IC_{50} 1 nM) along with repression of the HIF1 reference gene VEGF expression [109]. *C*-phycocyanin [74], Isomalyngamide A and A-1 [34], and Coibamide A [38,39] inhibit MCF7 and MDA-MB-231 cell migration by decreasing VEGFR2 expression and MMP-9.

3.5. Cell cycle arrest

Disruption of the cell cycle is closely linked to apoptosis [110–114]. Activation of the cyclin-dependent kinase (Cyclin D1 and Cyclin E) inhibitors, p21 and p53 suppresses tumor growth and protects against DNA damage by halting the cell cycle and regulates apoptosis [115–117]. Coibamide A has shown G_1 phase arrest in MDA-MB-231 cells at GI_{50} value of 2.8 nM [38,39]. Thiocoraline, a cyclic thiodepsipeptide from *Micromonospora* sp. displayed G1 phase arrest in SKBR3 cells with a GI_{50} value of 2.2 nM [52]. *C*-phycocyanin [74,75] and Dehydrodidemnin B (Aplidin / Plitidepsin) [118] induced G1-G2 phase arrest by decreasing cyclin D1, cyclin E; and CDK2 and increasing p21 in MCF7 and MDA-MB-231 cells, respectively. Hemiasterlin and Hemiasterlin A- C [18,97] and HTI-286 [119] induced G2-M phase arrest in MCF7, MDA-MB-435 and MX-1W cells. Similarly, Mere15 induced p53 upregulation and cell cycle arrest in MCF-15 cells [76]. Peptides from *Porphyra haitanesis* have shown cells cytotoxicity and G0/G1 phase arrest in MCF7 with IC_{50} of 200.97 μg mL^{-1} [120].

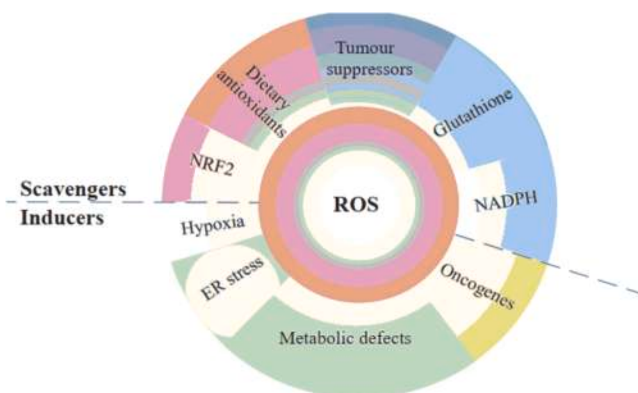

Fig. 3. Various factors that affect ROS generation.

3.6. Oxidative stress

Oxidative stress triggered by mitochondrial disorders is induced by ROS (Reactive Oxygen Species) generation. A variety of factors such as a hypoxia, antioxidants, ER stresses, and NADPH contribute or inhibit ROS generation (Fig. 3) [121]. Aplidin induces apoptosis in MDA-MB-231 cells by promoting increased GSSG/GSH ratio [122]. DNA fragmentation, the most common DNA damage, is directly associated with oxidative stress [123]. Cryptophycin 1 in MDA-MB-435 cells has been shown to induce DNA fragmentation [37]. Iturin A has also been shown to induce DNA fragmentation in MCF7, T47D, MDA-MB-231 and -468 cells [58]. C-phycocyanin scavenges ROS and increases γ-H2AX in MCF7 cells, an indicator of DNA damage [74,124]. Binucleated cells are seen as a consequence of oxidative stress in response to symplostatin [20].

3.7. Destruction of cancer cell membrane

Anti-cancer peptides (ACPs) cause cell membrane depolarization, leading to tumor cells' failure to sustain normal osmotic pressure and a massive leakage of cytoplasmic material [125,126]. Anti-proliferative peptides destroy cancer cells by necrotic mechanisms that trigger cell membrane lysis [60,127,128]. Anti-cancer peptides cause membrane destabilization, cell lyses, and the ensuing death of cancer cells [129, 130]. Anti-proliferative peptides with high ROS reduced activity can prevent cancer incidence [60]. Protein hydrolysate from *Thunnus tonggol* muscle by-product showed an anti-proliferative activity in MCF7 cells with $IC_{50\,s}$ of 8.1 and 8.8 μM, respectively [131]. *Gadus morhua* Atlantic cod, *Pleuronectes platessa* plaice and *Micromesistius poutassou* fish hydrolysates induced anti-proliferative activity of MCF7/6 and MDA-MB-231 cells at 1 g L^{-1} [132]. Loach (*Misgurnus anguillicaudatus*) muscle hydrolysate obtained from the papain enzyme exhibits anti-proliferative activity at 40 mg mL-1 MCF7 cancer cell line [133]. A hydrolysate from *Dosidicus gigas* has shown toxicity in MCF7 cells, with IC_{50} value of 0.13 mg mL^{-1} [134]. Antitumor peptides (RGVKGPR, KLGPKGPR, and SSPGPPVH) from *Cuora trifasciata* turtle have been shown to inhibit MCF7 cancer cells [64].

3.8. Unknown mechanism for anti-cancer activity of marine peptides

Ascidians mollamide B [22] and Spongian Callyptide A [122], Criamide B [11,135], Pipecolidepsin A-B [44], Rolloamide A [23], Stylissatin B [24] and Pembamide [136] induced potent cytotoxicity with unidentified mechanism. Kulokekahilide-2 from mollusks [47] and malyngamide 3 [30] cocosamides A and B [30], wewakazole B [27] from cyanobacteria are other examples. Anti-cancer marine peptides also include Kailuins A–D from bacteria [51,137], Marthiapeptide A from actinomycetes [53], Ohmyungsamycin A and Ohmyungsamycin B from streptomyces [49], Cordyheptapeptide C -E [28], Sansalvamide [50] and Efrapeptin G [138] from the marine sponge-derived fungus. The peptide from saltwater clam *Ruditapes philippinarum* has shown cytotoxicity in MDA-MB-231 cells with IC_{50} of 1.58 mg mL^{-1} [139,140].

4. Marine peptides in MDR cancers

The leading causes of chemotherapy failure are inherent or acquired drug resistance due to overexpression of P-gp [141–143]. MDA-MB-231, -436,-468, BT20, BT-549, SKBR3, and Hs578T are useful for studying molecular aberrations and mechanisms influenced by these aberrations in TNBC [144].

Hemiasterlin and Hemiasterlin C [97], HTI-286 [119,145] and Milnamide A - D [42,99] depolymerize MDA-MB-435 breast cancer microtubules showed their less interaction with MDR P-glycoprotein (P-gp). Preclinical experiments have demonstrated that HTI-286 induces the degradation of the tumor and reduces human MX-1W (MRP1 overexpressed) breast carcinoma xenografts in mice paclitaxel and vincristine were unsuccessful due to P-gp associated resistance [119]. Symplostatin 1 (dolastatin 10 analog) showed Bcl-2 inhibition and microtubule depolymerization in MDR breast cancer MDA-MB-435 (IC_{50} 0.15 nM) and NCI/ADR (IC_{50} 2.9 nM) cells [20]. However, Symplostatin 1 showed marginal antitumor activity against MDR tumors mammary adenocarcinoma 17/Adr and mammary adenocarcinoma 16/C/Adr (adriamycin-resistant murine early stage solid tumors) [81]. Cryptophycin, a cytotoxic macrocyclic depsipeptide isolated from cyanobacteria *Nostoc* sp., is an antimicrotubule agent that tends to be a weaker P-gp substrate than *Vinca* alkaloids.

Breast carcinoma cells are abundantly drug resistant due to increased expression of P-gp and are significantly less cryptophycin resistant than colchicine, vinblastine and taxol. Cryptophycin has shown antimitotic activity in breast cancer MCF7 and MCF7/ADR cells with $IC_{50\,s}$ of 0.016 and 0.017 nM respectively through microtubule stabilization [36]. Cryptophycin (50 pM) also induces mitotic arrest in MDA-MB-435 by developing distorted mitotic spindles without affecting the interphase microtubules [37]. Geodiamolide D-E demonstrated antiproliferative action toward MDA-MB-435, a P-gp upregulating MDR cell line, with actin filament interruption [42]. Kulokekahilide-2 is also active towards MDA-MB-435 cells, with an IC_{50} of 14.6 nM [47]. Stylopeptide 2 had antiproliferative effects on BT-549 and HS 578 T cells at a dosage of 10^{-5} M [25]. Ohmyungsamycin A and Ohmyungsamycin B has been shown to exhibit antiproliferative effects against MDA-MB-231 with IC50s of 0.688 and 12.7 μM, respectively [49]. Interestingly, there was no cytotoxicity (IC50 > 40 μM) in normal epithelial MRC-5 cells [49]. Largazole inhibits MDA-MB-231 with GI_{50} value of 7.7 nM over normal mammary NMuMG cells with IC_{50} of 122 nM [35]. C-phycocyanin affects cancer cell cycle propagation by G0/G1 step arrest in MDA-MB-231, indicating weak P-gp transport substrate [146]. Pipecolidepsin A, Pipecolidepsin B, Pembamide, and Callyptide A inhibit MDA-MB-231 cellular growth with $IC_{50\,s}$ of 0.7, 0.02, 3.35, and 29 μM, respectively [44,122,136]. DZ-2384 has antitumor activity by inhibition of mitotic spindle formation in metastatic TNBC (MDA-MB-231-LM2), lacks neurotoxicity in rats, and significantly increases survival [147]. Frog-derived peptide Hymenochirin-1B [63] and Alyteserin-2a [148] have been shown to be cytotoxic to MDA-MB-231 cells. Microcionamides A and B are cytotoxic to SKBR3 cells [98]. Kahalalide F induced cytotoxicity in SKBR3 via PI3K-AKT inhibition [45,87]. Elisidepsin has shown similar response in MDA-MB-231, -361, -435 and SKBR3 [46,87].

5. Marine peptides in clinical trial status

Up to now, Hemiasterlin (E7974) [149] and Eribulin mesylate (Halaven®) [87] have been approved by FDA for breast cancer. Plitidepsin (Aplidin®) [87], and Keyhole Limpet Hemocyanin (Immucothel®) [149] have been approved by FDA and ATGA for different cancers, but clinical trials for breast cancer are needed.

Dolastatin 10 have not advance to clinical trials due to its insignificant therapeutic index and substantial toxic side effects. Thus, further clinical trials are discontinued, and structural modifications have been established to enhance therapeutic efficacy, especially against TNBC [13,150]. LU 103793 was evaluated in patients for efficacy and tolerability in metastatic breast cancer but experienced neutropenia, asthenia, stomatitis, myalgia, and hypertension resulting in cessation of further assessment [151]. Soblidotin (TZT-1027) was engineered to retain potent antitumor efficacy while reducing the parent drug's toxicity, dolastatin 10. In human MX-1 mammary carcinoma xenografts models, soblidotin showed very efficient outcomes [152]. Soblidotin has reached phase I clinical trials and has demonstrated less neurotoxicity than other tubulin inhibitors with a suggested dosage of 1.8 mg m^2 [12,153].

High toxicity, low solubility, and limited life span resulted in the Didemnin B clinical trials' withdrawal in support of the second generation didemnin, plitidepsin [9,15]. Dehydrodidemnin B, commonly known as (Aplidin or Plitidepsin), is more active than Didemnin preclinical models against breast cancer cell lines and so far has not shown evidence of life-threatening neuromuscular toxicity [15]. Plitidepsin is in phase III clinical research for breast, melanoma, and non-small cell lung cancers [154]. Elisidepsin (PM02734, Irvalec®), one of the most potent analogs of Kahalalide F, was chosen for phase II clinical research owing to its beneficial therapeutic index and non-toxic profile [8].

Taltobulin or SPA-110 (HTI-286) is a synthetic hemiasterlin analog with promising antimitotic action. This compound has progressed to clinical trials for to its potential role in suppressing colchicine-like tubulin polymerization and prevent cell division in MCF7 and MX-1W. The terminations of HTI286 phase I clinical trials due to its toxicity mandate the development of new synthetic formulations with lesser adverse reactions [119,155].

Table 1
Anticancer effects of Marine peptides in the different reported studies.

Peptides	Marine sources (Species name)	Active derivative	*In vitro*		*In vivo*		Anticancer Mechanisms	References
			Human breast cancer cell lines	IC50s	Experimental model	Dose		
Desmethoxymajusculamide C	Cyanobacteria (*Lyngbya majuscula*)	Cyclic depsipeptide	MDA-MB-435	0.22 μM	–	–	Actin microfilament disruption	[29]
Isomalyngamide A and A-1			MDA-MB-231	A, 0.06; A-1: 0.337 μM	–	–	VEGFR2 ↓ and MMP-9 ↓	[34]
Cocosamides A-B			MCF7	A: 30; B: 39 μM	–	–	↓ cell viability	[30]
Hantupeptin A-C				A: 4; B:0.5; C: 1.0 μM	–	–		[31,163]
Malyngamide 3				29 μM	–	–		[30]
Pitiprolamide				33 μM	–	–		[32]
Pitipeptolide A-F				A:13; B: 11; C: 73; D and E: > 100; F: 83 μM	–	–		[33]
Wewakazole B		Cyclic dodecapeptide	MCF7	0.58 μM	–	–		[27]
Curacin A-C		Lipopeptide		A: 0.72; B: 0.82; C: 2.3 μM	–	–	Caspase 3↑; Microtubule depolymerization	[56]
Somocystinamide A	Cyanobacteria (*Lyngbya majuscula* and *Schizothrix* sp.)			210 nM	–	–	Caspase 8 ↑	[57]
Largazole	Cyanobacteria (*Symploca* sp.)	Cyclic depsipeptide	MDA-MB-231	7.7 nM	–	–	↓ cancer cell growth	[35]
Belamide A		Linear tetrapeptide	MCF7	1.6 μM	–	–	Microtubule destabilization	[19]
Symplostatin		Linear Pentapeptide	MDA-MB-435; NCI/ADR	0.15 nM / 2.9 nM	–	–	Caspase 3↑; Bcl2↓; Bax↑; PARP ↑; Microtubules	[20]
			–	–	murine mammary 16/C mouse xenograft model	1.25 mg/kg i.v.	depolymerization	[81]
Cryptophycin	Cyanobacteria (*Nostoc* sp.)	Cyclic depsipeptide	MCF7	0.016 nM	–	–	Microtubule stabilization	[36]
			MCF-7/ADR	0.017 nM	–	–		
Cryptophycin 1			MDA-MB-435	50 pM	–	–	DNA fragmentation; Microtubule stabilization; Caspase 3 ↑	[37]
Laxaphycin B5, B6	Cyanobacteria (*Phormidium* sp.)	Cyclic dodecapeptide	MDA-MB-231	GI_{50} (μM) = B5: 2.2; B6: 0.81	–	–	↓ cell viability	[26]
			MDA-MB-435	GI_{50} (μM) B5: 1.2; B6: 0.58	–	–		
Coibamide A	Cyanobacteria (*Leptolyngbya* sp.)	Cyclic depsipeptide	MDA-MB-231	2.8 nM	–	–	Caspase 3↑, -7 ↑; VEGF↓; G_1 phase arrest	[38,164]
C-phycocyanin	Cyanobacteria (*Limnothrix* sp. NS01 and *Spirulina platensis*)	Peptide	MCF7	15.43 μM	–	–	DNA fragmentation; Caspase-9 ↑; cyt c ↑; Bcl2↓; Bax↑; PARP ↑; Stat3 ↓ G1 - G2 phase arrest (cyclin D1↓, cyclin E↓; p21↑) Antiangiogenic (VEGFR2 ↓ and MMP-9 ↓)	[74,75]
			HBL 100	8.31 μM	–	–	AKT inhibition; γ-H2AX ↑; Production of ROS and singlet oxygen radicals	
			BT-474	8.45 μM	–	–		
			SKBR3	15.73 μM	–	–		
			MDA-MB- 231	5.98 μM	–	–		
Galaxamide, A1- A5	Algae (*Galaxaura filamentosa*)	Cyclic pentapeptide	MCF7	Galaxamide: 14.09; A1: 9.4; A2: 9.64; A3: 7.23; A4: 6.56; A5: 4.18 μg mL^{-1}	–	–	Caspase-9, -3 ↑; PARP ↑	[21]
Callyptide A	Sponge (*Callyspongia* sp.)	Cyclic peptide	MDA-MB-231	GI_{50} = 29 μM			↓ cell viability	[122]
Criamide B	Sponge (*Cymbastela* sp.)	Peptide	MCF7	6.8 μg mL^{-1}	–	–		[11,135]
Jaspamide A-P	Sponge (*Jaspis splendans*)	Cyclic depsipeptide		A: 0.019; B: 3.41; C: 2; D: 0.05; E: 0.02; F: 30; G: 0.6; H: 30; J: 5; K: 0.48; L:	–	–	Caspase-3 ↑; Bcl2↓; Bax↑; PARP ↑	[40]

(*continued on next page*)

Table 1 (*continued*)

Peptides	Marine sources (Species name)	Active derivative	*In vitro*		*In vivo*		Anticancer Mechanisms	References
			Human breast cancer cell lines	IC50s	Experimental model	Dose		
				0.61; M: 0.1; N: 33; O: 0.38; P: 12 μM				
Geodiamolide A-B, H, I	Sponge (*Auletta* sp. and *Geodia corticostylifera*)			A: 17.83; B: 9.82; H: 89.96; I: 65.70 nM	–	–	Actin filament disruption	[43]
			T47D	A: 18.82; B: 113.90; H: 38.36; I: 115.30 nM	–	–		[43]
Geodiamolide H			MDA-MB-231	4.33 × 10^{-7} M	–	–	↓ cancer cell growth	[41]
Geodiamolide H			HS 578 T	2.45 × 10^{-7} M	–	–		
Geodiamolide D-E			MDA-MB-435	D: 0.08; E: 0.25 μg mL^{-1}	–	–	Actin filament disruption	[42]
Pipecolidepsin A-B	Sponge (*Homophymia lamellosa*)		MDA-MB-231	GI_{50} = A: 0.7; B: 0.02 μM	–	–	↓ cell viability	[44]
Rolloamide A	Sponge (*Eurypon laughlini*)	Cyclic heptapeptides	MCF7	0.88 μM	–	–		[23]
			BT549	1.3 μM	–	–		
			MDA-MB-231	2.2 μM	–	–		
			MDA-MB-361	5.8 μM	–	–		
			MDA-MB-435	0.40 μM	–	–		
			MDA-MB-468	0.38 μM	–	–		
Stylissatin B	Sponge (*Stylissa massa*)		MCF7	4.8 μM	–	–		[24]
Stylopeptide 2	Sponge (*Stylotella* sp.)	Cyclic decapeptide	BT-549; HS 578T	10^{-5} M	–	–	Antiproliferative effect	[25]
Scleritodermin A	Sponge (*Scleritoderma nodosum*)	Cyclic peptide	SKBR3	0.67 μM	–	–	Microtubules depolymerization; G2/M phase arrest	[100]
Hemiasterlin and Hemiasterlin A-B	Sponge (*Hemiasterella minor*, *Auletta* sp., *Cymbastela* sp., and *Siphonochalina* sp.)	Linear tripeptide	MCF7	Hemiasterlin: 0.5; A: 2; B: 7 nM	–	–		[18]
Hemiasterlin and Hemiasterlin C			MDA-MB-435	Hemiasterlin: 0.0154; Hemiasterlin C: 0.4002 μg mL^{-1}	–	–		[97]
HTI-286			MCF7	7.3 nM	–	–		[119]
			MX-1W	1.8 nM	–	–		
			–	–	MCF7 mouse xenograft model	1 mg/kg i.v. for 9 days	Antiproliferative effect	[119]
			–	–	MX-1W mouse xenograft model	1.6 mg/kg i.v.		
Pembamide	Sponge (*Cribrochalina* sp.)	*N*-methylated linear peptide	MDA-MB-231	GI_{50} = 3.35 μM	–	–	↓ cell viability	[136]
Microcionamide A-B	Sponge (*Clathria* (*Thalysias*) *abietina*)		MCF7	A: 125; B: 177 nM	–	–	Microtubules depolymerization	[98]
			SKBR3	A: 98; B: 172 nM	–	–		
Milnamide A and D	Sponge (*Auletta* sp. and *Cymbastela* sp.)		MDA-MB-435	A: 6.02; D: 16.9 μM	–	–		[99]
Milnamide B-C				B: 1.48 × 10^{-4}; C: 0.32 ± 0.02 μg mL^{-1}	–	–		[42]
Mycothiazole	Sponge (*Petrosaspongia mycofijiensis*)	Mixed polyketide/ *peptide*-derived compound	T47D	1 nM	–	–	HIF1α inhibition; VEGF ↓	[109]
Dolastatin 10	Mollusk (*Dolabella auricularia*)	Linear Pentapeptide	MCF7	0.06 nM	–	–	Caspase 3 ↑; Bcl2↓; Bax↑; PARP ↑; p53↑; Microtubule depolymerization	[54]
Dolastatin 15				0.9 nM	–	–		
Kahalalide F	Mollusk (*Elysia rufescens*)	Cyclic depsipeptide		0.28 μM	–	–	PI3K-AKT inhibition; ErbB3 depletion	[45]
			SKBR3	0.23 μM	–	–		
			BT474	0.26 μM	–	–		
Elisidepsin			MCF7	8 μM	–	–		[46]
			MDA-MB-231	4.7 μM	–	–		
			MDA-MB-361	1.25 μM	–	–		
			MDA-MB-435	4.4 μM	–	–		
			SKBR3	6 μM	–	–		
			ZR-75–1	0.4 μM	–	–		
Kulokekahilide-2	Mollusk (*Philinopsis speciosa*)		MDA-MB-435	14.6 nM	–	–	↓ cell viability	[47]

(*continued on next page*)

Table 1 (*continued*)

Peptides	Marine sources (Species name)	Active derivative	*In vitro*		*In vivo*		Anticancer Mechanisms	References
			Human breast cancer cell lines	IC50s	Experimental model	Dose		
Mere15	Mollusk (*Meretrix meretrix*)	Polypeptide	MCF-15	57.43 µg mL^{-1}	–	–	G2-M phase arrest; Caspase 3, 9 ↑; cyt c ↑; Bcl2↓; Bax↑; PARP ↑; p53 ↑	[76]
Diazonamide A	Ascidia (*Diazona angulata*)	Macrocyclic peptide	MCF7	1.9 nM	–	–	Microtubule depolymerization	[54]
DZ-2384 (synthetic diazonamide)			BT-549	0.66 nmol	–	–		[147]
			GCRC 1735	7 nmol	–	–		
			GCRC 1915	17 nmol	–	–		
			MDA-MB-231	7.7 nmol	–	–		
			MDA-MB-436	2.8 nmol	–	–		
			–	–	MDA-MB-231-LM2 mouse xenograft model	4.5 mg/m^2 i.v. for 28 days		
Dehydrodidemnin B	Ascidia (*Aplidium albicans*)	Cyclic depsipeptide	MCF7	50 nM	–	–	G1 - G2 phase arrest (cyclin D1↓; cyclin E↓; p21↑), Caspase-9, − 3 ↑; Bcl2↓; Bax↑; PARP ↑	[48]
			MDA-MB-231	5 nM	–	–		[84]
Mollamide B	Ascidia (*Didemnum molle*)	Cyclic hexapeptides	MCF7	100 µM	–	–	↓ cell viability	[22]
Cordyheptapeptide C-E	Fungus (*Acremonium persicinum* SCSIO 115)	Cyclic heptapeptide	MCF7	C: 3; D: 82.7; E: 2.7 µM	–	–		[28]
Efrapeptin G	Fungus (*Acremonium* sp.)	Oligopeptide		0.027 µM	MCF7 mouse xenograft model	0.15 mg/kg i.p. for 28 days	↓ cancer cell growth	[55]
			MDA-MB-231	3.430 µM	MDA-MB-231 mouse xenograft model	0.3 mg/kg i.p. for 28 days		
			T47D	0.057 µM	–	–		
			MDA-MB-453	0.132 µM	–	–		
Sansalvamide	Fungus (*Fusarium* sp.)	Cyclic pentadepsipeptide	MAXF 401	0.02 µg mL^{-1}	–	–	↓ cell viability	[50]
Iturin A	Bacteria (*Bacillus megaterium*)	Lipopeptide	MCF7	12.16 ± 0.24 µM	–	–	DNA fragmentation; AKT inhibition; FoxO3a↑; Bcl2↓; Bax↑; PARP ↑; Bcl-xL ↓; cyt c ↑	[58]
			T47D	26.29 ± 0.78 µM	–	–		
			MDA-MB-231	7.98 ± 0.19 µM	–	–		
			MDA-MB-468	13.30 ± 0.97 µM	–	–		
			–	–	MDA-MB-231 mouse xenograft model	10 mg/kg i.v.	↓ cell viability	[58]
Kailuin A-D	Bacteria (BH-107)	Cyclic acyldepsipeptide	MCF7	GI_{50} (µg mL^{-1}) = A: 3; B: 2; C: 4; D: 3	–	–		[51]
Kailuin D				39 µM	–	–		[137]
Marthiapeptide A	Bacteria *Marinactinospora thermotolerans* SCSIO 00652)	Polythiazole cyclic peptide		0.43 µM	–	–		[53]
Proximicin A-C	Bacteria (*Verrucosispora* sp.)	Polyamide		A: 24.6 µM; B: 12.1 µM; C: 1.8 µM	–	–		[165]
Thiocoraline	Bacteria (*Micromonospora* sp. L-13-ACM2–092)	Cyclic thiodepsipeptide	SKBR3	GI_{50} = 2.2 nM	–	–	G_1 phase arrest	[52]
Ohmyungsamycin A-B	Bacteria (*Streptomyces* strain SNJ042)	Cyclic depsipeptides	MDA-MB-231	A: 0.68 and B: 12.7 µM	–	–	↓ cell viability	[49]

6. Conclusions and future perspectives

The most prevalent and fatal illness in women is breast cancer. The available treatments are effective for cancer treatment but have side effects. There is still an urgent need for novel medications to be effective for the cancer therapy. The discovery of novel clinical chemotherapeutic peptides from diverse aquatic life can be incorporated into breast cancer prevention and care [156]. The lack of ethnomedicinal background, technical difficulties in collecting marine animals, particularly deep-sea organisms; isolation and purification problems are obstacles in anti-cancer peptides research [157]. Thanks to modern technology, it is increasingly possible to extract samples from the sea and different peptides from aquatic materials [158]. 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 have proven to be a valuable and exciting resource for developing anti-cancer drugs and a platform for discovering new cellular targets for therapeutic action [159]. Therefore, it is highly relevant to deepen the study of marine peptides' anti-cancer mechanisms to develop new candidate compounds [160]. 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. The more significant part of the exploration led to marine peptides; anti-cancer power is *in vitro*, making it difficult to give the right determination on its helpfulness.

Of these compounds, only a few progressed to clinical studies, and a relatively small number of peptides have successfully entered the pharmaceutical pipeline and have been used clinically.

Numerous marine peptides are undergoing clinical trials, although there is a widely unexplored area of marine protein hydrolysates [157]. Short half-life, low bioavailability, processing and manufacturing problems, and protease susceptibility are significant drawbacks of therapeutic peptides [12–14,83]. For low cell membrane permeability, cell penetrating peptides are used. Metabolic instability and short half-life in circulation may be overcome by using D-amino acid substitution, peptide cyclization, encapsulation with nanoparticles, pegylation, and XTEN conjugation. D-amino acid substitution reduces immunogenicity [126,161,162]. Protein hydrolysates are an alternative source of anti-cancer, antioxidant, and antiproliferative bioactive compounds. However, further investigation is required on the cell cycle mode or apoptosis of cancer cell lines. *in vivo* and *in silico* studies are also necessary to identify and characterize the mechanism of action and safety of marine peptides and protein hydrolysates to achieve complete anti-cancer drug efficacy [8]. In particular, further analysis of the variability of marine peptides in structural modification and modes of action would provide a rich resource for creating unique and potent new pharmaceuticals (Table 1).

Ethics approval and consent to participate

Not applicable.

Funding

The project was supported by grant from The Oman Research Council (TRC) through the funded project (BFP/RGP/HSS/19/198).

CRediT authorship contribution statement

Salman Ahmed and Ajmal Khan written the initial draft. Hamed Mirzaei drawn the figures. Michael Aschner proof read the article for English and grammatic corrections. Ahmed Al-Harrasi and Haroon Khan designed and supervised the overall review.

Competing interests

The authors of this article have no financial conflict.

Consent for publication

Not applicable.

Availability of data and materials

All datasets on which the conclusions of the manuscript rely are presented in the paper

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.

[2] S. Senapati, A.K. Mahanta, S. Kumar, P. Maiti, Controlled drug delivery vehicles for cancer treatment and their performance, Signal Transduct. Target. Ther. 3 (2018) 7, https://doi.org/10.1038/s41392-017-0004-3.

[3] D. Waghray, Q. Zhang, Inhibit or evade multidrug resistance p-glycoprotein in cancer treatment, J. Med. Chem. 61 (2018) 5108–5121, https://doi.org/10.1021/acs.jmedchem.7b01457.

[4] S. Khalifa, N. Elias, M.A. Farag, L. Chen, A. Saeed, M.F. Hegazy, M.S. Moustafa, A. Abd El-Wahed, S.M. Al-Mousawi, S.G. Musharraf, F.R. Chang, A. Iwasaki, K. Suenaga, M. Alajlani, U. Göransson, H.R. El-Seedi, Marine natural products: a source of novel anticancer drugs, Mar. Drugs 17 (2019) 491, https://doi.org/10.3390/md17090491.

[5] P.C. Jimenez, D.V. Wilke, L.V. Costa-Lotufo, Marine drugs for cancer: surfacing biotechnological innovations from the oceans, Clinics 73 (2018) 482, https://doi.org/10.6061/clinics/2018/e482s.

[6] S. Ahmed, H. Khan, M. Aschner, H. Mirzae, E. Küpeli Akkol, R. Capasso, Anticancer potential of furanocoumarins: mechanistic and therapeutic aspects, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21165622.

[7] S. Ahmed, H. Khan, D. Fratantonio, M.M. Hasan, S. Sharifi, N. Fathi, H. Ullah, L. Rastrelli, Apoptosis induced by luteolin in breast cancer: Mechanistic and therapeutic perspectives, Phytomedicine 59 (2019), 152883, https://doi.org/10.1016/j.phymed.2019.152883.

[8] V. Ruiz-Torres, J.A. Encinar, M. Herranz-López, A. Pérez-Sánchez, V. Galiano, E. Barrajón-Catalán, V. Micol, An updated review on marine anticancer compounds: the use of virtual screening for the discovery of small-molecule cancer drugs, Molecules 22 (2017) 1037, https://doi.org/10.3390/molecules22071037.

[9] M. Barreca, V. Spanò, A. Montalbano, M. Cueto, A.R. Díaz Marrero, I. Deniz, A. Erdoğan, L. Lukić Bilela, C. Moulin, E. Taffin-de-Givenchy, F. Spriano, G. Perale, M. Mehiri, A. Rotter, O. P Thomas, P. Barraja, S.P. Gaudêncio, F. Bertoni, Marine anticancer agents: an overview with a particular focus on their chemical classes, Mar. Drugs 18 (2020) 619, https://doi.org/10.3390/md18120619.

[10] Q.-T. Zhang, Z.D. Liu, Z. Wang, T. Wang, N. Wang, N. Wang, B. Zhang, Y.F. Zhao, Recent advances in small peptides of marine origin in cancer therapy, Mar. Drugs 19 (2021) 115–143.

[11] V. Gogineni, M.T. Hamann, Marine natural product peptides with therapeutic potential: chemistry, biosynthesis, and pharmacology, Biochim. Biophys. Acta (BBA) - Gen. Subj. 1862 (2018) 81–196, https://doi.org/10.1016/j.bbagen.2017.08.014.

[12] Hayashi, M.A., Ducancel, F. & Konno, K. (Hindawi, 2012).

[13] S. Marqus, E. Pirogova, T.J. Piva, Evaluation of the use of therapeutic peptides for cancer treatment, J. Biomed. Sci. 24 (2017) 21.

[14] D.J. Craik, D.P. Fairlie, S. Liras, D. Price, The future of peptide-based drugs, Chem. Biol. Drug Des. 81 (2013) 136–147.

[15] H.K. Kang, M.-C. Choi, C.H. Seo, Y. Park, Therapeutic properties and biological benefits of marine-derived anticancer peptides, Int. J. Mol. Sci. 19 (2018) 919, https://doi.org/10.3390/ijms19030919.

[16] K. Sridhar, B.S. Inbaraj, B.-H. Chen, Recent developments on production, purification and biological activity of marine peptides, Food Res. Int. 147 (2021), 110468.

[17] Y. Lee, C. Phat, S.-C. Hong, Structural diversity of marine cyclic peptides and their molecular mechanisms for anticancer, antibacterial, antifungal, and other clinical applications, Peptides 95 (2017) 94–105, https://doi.org/10.1016/j.peptides.2017.06.002.

[18] H.J. Anderson, J.E. Coleman, R.J. Andersen, M. Roberge, Cytotoxic peptides hemiasterlin, hemiasterlin A and hemiasterlin B induce mitotic arrest and abnormal spindle formation, Cancer Chemother. Pharmacol. 39 (1996) 223–226.

[19] T.L. Simmons, K.L. McPhail, E. Ortega-Barría, S.L. Mooberry, W.H. Gerwick, Belamide A, a new antimitotic tetrapeptide from a Panamanian marine cyanobacterium, Tetrahedron Lett. 47 (2006) 3387–3390, https://doi.org/10.1016/j.tetlet.2006.03.082.

[20] S.L. Mooberry, R.M. Leal, T.L. Tinley, H. Luesch, R.E. Moore, T.H. Corbett, The molecular pharmacology of symplostatin 1: a new antimitotic dolastatin 10 analog, Int. J. Cancer 104 (2003) 512–521.

[21] X. Xiao, X. Liao, S. Qiu, Z. Liu, B. Du, S. Xu, Synthesis, cytotoxicity and apoptosis induction in human tumor cells by galaxamide and its analogues [corrected], Mar. Drugs 12 (2014) 4521–4538, https://doi.org/10.3390/md12084521.

[22] M.S. Donia, B. Wang, D.C. Dunbar, P.V. Desai, A. Patny, M. Avery, M.T. Hamann, Mollamides B and C, cyclic hexapeptides from the Indonesian tunicate Didemnum molle, J. Nat. Prod. 71 (2008) 941–945.

[23] D.E. Williams, K. Yu, H.W. Behrisch, R. Van Soest, R.J. Andersen, Rolloamides A and B, cytotoxic cyclic heptapeptides isolated from the caribbean marine sponge Eurypon laughlini, J. Nat. Prod. 72 (2009) 1253–1257, https://doi.org/10.1021/np900121m.

[24] J. Sun, W. Cheng, N.J. de Voogd, P. Proksch, W. Lin, Stylissatins B–D, cycloheptapeptides from the marine sponge Stylissa massa, Tetrahedron Lett. 57 (2016) 4288–4292, https://doi.org/10.1016/j.tetlet.2016.08.024.

[25] M.R. Brennan, C.E. Costello, S.D. Maleknia, G.R. Pettit, K.L. Erickson, Stylopeptide 2, a proline-rich cyclodecapeptide from the sponge Stylotella sp, J. Nat. Prod. 71 (2008) 453–456, https://doi.org/10.1021/np0704856.

[26] P. Sullivan, A. Krunic, J.E. Burdette, J. Orjala, Laxaphycins B5 and B6 from the cultured cyanobacterium UIC 10484, J. Antibiot. 73 (2020) 526–533, https://doi.org/10.1038/s41429-020-0301-x.

[27] J.A. Lopez, S.S. Al-Lihaibi, W.M. Alarif, A. Abdel-Lateff, Y. Nogata, K. Washio, M. Morikawa, T. Okino, Wewakazole B, a cytotoxic cyanobactin from the cyanobacterium moorea producens collected in the red sea, J. Nat. Prod. 79 (2016) 1213–1218, https://doi.org/10.1021/acs.jnatprod.6b00051.

[28] Z. Chen, Y. Song, Y. Chen, H. Huang, W. Zhang, J. Ju, Cyclic heptapeptides, cordyheptapeptides C–E, from the marine-derived fungus Acremonium persicinum SCSIO 115 and their cytotoxic activities, J. Nat. Prod. 75 (2012) 1215–1219, https://doi.org/10.1021/np300152d.

[29] T.L. Simmons, L.M. Nogle, J. Media, F.A. Valeriote, S.L. Mooberry, W.H. Gerwick, Desmethoxymajusculamide C, a cyanobacterial depsipeptide with potent cytotoxicity in both cyclic and ring-opened forms, J. Nat. Prod. 72 (2009) 1011–1016.

[30] S.P. Gunasekera, C.S. Owle, R. Montaser, H. Luesch, V.J. Paul, Malyngamide 3 and cocosamides A and B from the marine cyanobacterium Lyngbya majuscula from Cocos Lagoon, Guam, J. Nat. Prod. 74 (2011) 871–876, https://doi.org/10.1021/np1008015.

[31] A. Tripathi, J. Puddick, M.R. Prinsep, P.P.F. Lee, L.T. Tan, Hantupeptin A, a cytotoxic cyclic depsipeptide from a singapore collection of Lyngbya majuscula, J. Nat. Prod. 72 (2009) 29–32, https://doi.org/10.1021/np800448t.

[32] R. Montaser, K.A. Abboud, V.J. Paul, H. Luesch, Pitiprolamide, a proline-rich dolastatin 16 analogue from the marine cyanobacterium Lyngbya majuscula from Guam, J. Nat. Prod. 74 (2011) 109–112, https://doi.org/10.1021/np1006839.

[33] R. Montaser, V.J. Paul, H. Luesch, Pitipeptolides C–F, antimycobacterial cyclodepsipeptides from the marine cyanobacterium Lyngbya majuscula from Guam, Phytochemistry 72 (2011) 2068–2074, https://doi.org/10.1016/j.phytochem.2011.07.014.

[34] T.T. Chang, S.V. More, I.H. Lu, J.C. Hsu, T.J. Chen, Y.C. Jen, C.K. Lu, W.S. Li, Isomalyngamide A, A-1 and their analogs suppress cancer cell migration in vitro, Eur. J. Med. Chem. 46 (2011) 3810–3819, https://doi.org/10.1016/j.ejmech.2011.05.049.

[35] K. Taori, V.J. Paul, H. Luesch, Structure and activity of largazole, a potent antiproliferative agent from the floridian marine Cyanobacterium Symploca sp, J. Am. Chem. Soc. 130 (2008) 1806–1807, https://doi.org/10.1021/ja7110064.

[36] C.D. Smith, X. Zhang, S.L. Mooberry, G.M. Patterson, R.E. Moore, Cryptophycin: a new antimicrotubule agent active against drug-resistant cells, Cancer Res. 54 (1994) 3779–3784.

[37] S.L. Mooberry, L. Busquets, G. Tien, Induction of apoptosis by cryptophycin 1, a new antimicrotubule agent, Int. J. Cancer 73 (1997) 440–448.

[38] R.A. Medina, D.E. Goeger, P. Hills, S.L. Mooberry, N. Huang, L.I. Romero, E. Ortega-Barría, W.H. Gerwick, K.L. McPhail, Coibamide A, a potent antiproliferative cyclic depsipeptide from the Panamanian marine cyanobacterium Leptolyngbya sp, J. Am. Chem. Soc. 130 (2008) 6324–6325, https://doi.org/10.1021/ja801383f.

[39] J.D. Serrill, X. Wan, A.M. Hau, H.S. Jang, D.J. Coleman, A.K. Indra, A.W. Alani, K. L. McPhail, J.E. Ishmael, Coibamide A, a natural lariat depsipeptide, inhibits VEGFA/VEGFR2 expression and suppresses tumor growth in glioblastoma xenografts, Investig. N. Drugs 34 (2016) 24–40, https://doi.org/10.1007/s10637-015-0303-x.

[40] F. Gala, M.V. D'Auria, S. De Marino, V. Sepe, F. Zollo, C.D. Smith, S.N. Keller, A. Zampella, Jaspamides M–P: new tryptophan modified jaspamide derivatives from the sponge Jaspis splendans, Tetrahedron 65 (2009) 51–56, https://doi.org/10.1016/j.tet.2008.10.076.

[41] W.F. Tinto, A.J. Lough, S. McLean, W.F. Reynolds, M. Yu, W.R. Chan, Geodiamolides H and I, further cyclodepsipeptides from the marine sponge Geodia sp, Tetrahedron 54 (1998) 4451–4458, https://doi.org/10.1016/S0040-4020(98)00157-4.

[42] R.N. Sonnenschein, J.J. Farias, K. Tenney, S.L. Mooberry, E. Lobkovsky, J. Clardy, P. Crews, A further study of the cytotoxic constituents of a milnamide-producing sponge, Org. Lett. 6 (2004) 779–782.

[43] M. Rangel, M.P. Prado, K. Konno, H. Naoki, J.C. Freitas, G.M. Machado-Santelli, Cytoskeleton alterations induced by Geodia corticostylifera depsipeptides in breast cancer cells, Peptides 27 (2006) 2047–2057, https://doi.org/10.1016/j.peptides.2006.04.021.

[44] L. Coello, F. Reyes, M. a J. s Martín, C. Cuevas, R. Fernández, Isolation and structures of pipecolidepsins A and B, cytotoxic cyclic depsipeptides from the Madagascan sponge Homophymia lamellosa, J. Nat. Prod. 77 (2014) 298–303.

[45] Y. Suárez, L. González, A. Cuadrado, M. Berciano, M. Lafarga, A. Muñoz, Kahalalide F, a new marine-derived compound, induces oncosis in human prostate and breast cancer cells, Mol. Cancer Ther. 2 (2003) 863–872.

[46] M. Serova, A. de Gramont, I. Bieche, M.E. Riveiro, C.M. Galmarini, M. Aracil, J. Jimeno, S. Faivre, E. Raymond, Predictive factors of sensitivity to elisidepsin, a novel Kahalalide F-derived marine compound, Mar. Drugs 11 (2013) 944–959, https://doi.org/10.3390/md11030944.

[47] Y. Nakao, W.Y. Yoshida, Y. Takada, J. Kimura, L. Yang, S.L. Mooberry, P. J. Scheuer, Kulokekahilide-2, a cytotoxic depsipeptide from a cephalaspidean mollusk Philinopsis speciosa, J. Nat. Prod. 67 (2004) 1332–1340.

[48] D.R. Riggs, B. Jackson, L. Vona-Davis, D. McFadden, In vitro anticancer effects of a novel immunostimulant: keyhole limpet hemocyanin, J. Surg. Res. 108 (2002) 279–284.

[49] S. Um, T.J. Choi, H. Kim, B.Y. Kim, S.H. Kim, S.K. Lee, K.B. Oh, J. Shin, D.C. Oh, Ohmyungsamycins a and b: cytotoxic and antimicrobial cyclic peptides produced by Streptomyces sp. from a volcanic Island, J. Org. Chem. 78 (2013) 12321–12329, https://doi.org/10.1021/jo401974g.

[50] G.N. Belofsky, P.R. Jensen, W. Fenical, Sansalvamide: a new cytotoxic cyclic depsipeptide produced by a marine fungus of the genus Fusarium, Tetrahedron Lett. 40 (1999) 2913–2916, https://doi.org/10.1016/S0040-4039(99)00393-7.

[51] G.G. Harrigan, B.L. Harrigan, B.S. Davidson, Kailuins A–D, new cyclic acyldepsipeptides from cultures of a marine-derived bacterium, Tetrahedron 53 (1997) 1577–1582, https://doi.org/10.1016/S0040-4020(96)01136-2.

[52] A. Negri, E. Marco, V. García-Hernández, A. Domingo, A.L. Llamas-Saiz, S. Porto-Sandá, R. Riguera, W. Laine, M.H. David-Cordonnier, C. Bailly, L.F. García-Fernández, J.J. Vaquero, F. Gago, Antitumor activity, X-ray crystal structure, and DNA binding properties of thiocoraline A, a natural bisintercalating thiodepsipeptide, J. Med. Chem. 50 (2007) 3322–3333, https://doi.org/10.1021/jm070381s.

[53] X. Zhou, H. Huang, Y. Chen, J. Tan, Y. Song, J. Zou, X. Tian, Y. Hua, J. Ju, Marthiapeptide A, an anti-infective and cytotoxic polythiazole cyclopeptide from a 60 L scale fermentation of the deep sea-derived Marinactinospora thermotolerans SCSIO 00652, J. Nat. Prod. 75 (2012) 2251–2255, https://doi.org/10.1021/np300554f.

[54] Z. Cruz-Monserrate, H.C. Vervoort, R. Bai, D.J. Newman, S.B. Howell, G. Los, J. T. Mullaney, M.D. Williams, G.R. Pettit, W. Fenical, E. Hamel, Diazonamide A and a synthetic structural analog: disruptive effects on mitosis and cellular microtubules and analysis of their interactions with tubulin, Mol. Pharmacol. 63 (2003) 1273–1280, https://doi.org/10.1124/mol.63.6.1273.

[55] C. Burz, I. Berindan-Neagoe, O. Balacescu, A. Irimie, Apoptosis in cancer: key molecular signaling pathways and therapy targets, Acta Oncol. 48 (2009) 811–821.

[56] P. Verdier-Pinard, J.Y. Lai, H.D. Yoo, J. Yu, B. Marquez, D.G. Nagle, M. Nambu, J. D. White, J.R. Falck, W.H. Gerwick, B.W. Day, E. Hamel, Structure-activity analysis of the interaction of curacin A, the potent colchicine site antimitotic agent, with tubulin and effects of analogs on the growth of MCF-7 breast cancer cells, Mol. Pharmacol. 53 (1998) 62–76.

[57] W. Wrasidlo, A. Mielgo, V.A. Torres, S. Barbero, K. Stoletov, T.L. Suyama, R. L. Klemke, W.H. Gerwick, D.A. Carson, D.G. Stupack, The marine lipopeptide somocystinamide A triggers apoptosis via caspase 8, Proc. Natl. Acad. Sci. USA 105 (2008) 2313–2318.

[58] G. Dey, R. Bharti, G. Dhanarajan, S. Das, K.K. Dey, B.N. Kumar, R. Sen, M. Mandal, Marine lipopeptide Iturin A inhibits Akt mediated GSK3β and FoxO3a signaling and triggers apoptosis in breast cancer, Sci. Rep. 5 (2015) 1–14.

[59] K. Deepak, S. Kumari, G. Shailender, R.R. Malla, Marine natural compound cyclo (L-leucyl-L-prolyl) peptide inhibits migration of triple negative breast cancer cells by disrupting interaction of CD151 and EGFR signaling, Chem.-Biol. Interact. 315 (2020), 108872.

[60] M.I. Shaik, N.M. Sarbon, A review on purification and characterization of anti-proliferative peptides derived from fish protein hydrolysate, Food Rev. Int. (2020) 1–21.

[61] A. Neklyudov, A. Ivankin, A. Berdutina, Properties and uses of protein hydrolysates, Appl. Biochem. Microbiol. 36 (2000) 452–459.

[62] H. Korhonen, A. Pihlanto, Bioactive peptides: production and functionality, Int. Dairy J. 16 (2006) 945–960.

[63] S. Attoub, H. Arafat, M. Mechkarska, J.M. Conlon, Anti-tumor activities of the host-defense peptide hymenochirin-1B, Regul. Pept. 187 (2013) 51–56.

[64] S. He, X. Mao, T. Zhang, X. Guo, Y. Ge, C. Ma, X. Zhang, Separation and nanoencapsulation of antitumor peptides from Chinese three-striped box turtle (Cuora trifasciata), J. Microencapsul. 33 (2016) 344–354.

[65] A.F. Wali, S. Majid, S. Rasool, S.B. Shehada, S.K. Abdulkareem, A. Firdous, S. Beigh, S. Shakeel, S. Mushtaq, I. Akbar, H. Madhkali, M.U. Rehman, Natural products against cancer: review on phytochemicals from marine sources in preventing cancer, Saudi Pharm. J. 27 (2019) 767–777, https://doi.org/10.1016/j.jsps.2019.04.013.

[66] H. Malve, Exploring the ocean for new drug developments: marine pharmacology, J. Pharm. Bioallied Sci. 8 (2016) 83–91, https://doi.org/10.4103/0975-7406.171700.

[67] M. Hassan, H. Watari, A. AbuAlmaaty, Y. Ohba, N. Sakuragi, Apoptosis and molecular targeting therapy in cancer, Biomed. Res. Int. 2014 (2014), 150845, https://doi.org/10.1155/2014/150845.

[68] S. Elmore, Apoptosis: a review of programmed cell death, Toxicol. Pathol. 35 (2007) 495–516.

[69] G. Kroemer, Mitochondrial control of apoptosis: an introduction, Biochem. Biophys. Res. Commun. 304 (2003) 433–435.
[70] L. Oliver, F.M. Vallette, The role of caspases in cell death and differentiation, Drug Resist. Updates 8 (2005) 163–170.
[71] S. Cory, J.M. Adams, The Bcl2 family: regulators of the cellular life-or-death switch, Nat. Rev. Cancer 2 (2002) 647–656.
[72] X. Jiang, X. Wang, Cytochrome C-mediated apoptosis, Annu. Rev. Biochem. 73 (2004) 87–106, https://doi.org/10.1146/annurev.biochem.73.011303.073706.
[73] S. Gupta, G.E. Kass, E. Szegezdi, B. Joseph, The mitochondrial death pathway: a promising therapeutic target in diseases, J. Cell. Mol. Med. 13 (2009) 1004–1033.
[74] Z. Su, Z. Yang, Y. Xu, Y. Chen, Q. Yu, Apoptosis, autophagy, necroptosis, and cancer metastasis, Mol. Cancer 14 (2015) 48.
[75] D. Heras-Sandoval, J.M. Pérez-Rojas, J. Hernández-Damián, J. Pedraza-Chaverri, The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration, Cell. Signal. 26 (2014) 2694–2701.
[76] C. Wang, M. Liu, L. Cheng, J. Wei, N. Wu, L. Zheng, X. Lin, A novel polypeptide from Meretrix meretrix Linnaeus inhibits the growth of human lung adenocarcinoma, Exp. Biol. Med. 237 (2012) 442–450.
[77] G. Dey, R. Bharti, G. Dhanarajan, S. Das, K.K. Dey, B.N. Kumar, R. Sen, M. Mandal, Marine lipopeptide Iturin A inhibits Akt mediated GSK3β and FoxO3a signaling and triggers apoptosis in breast cancer, Sci. Rep. 5 (2015) 10316, https://doi.org/10.1038/srep10316.
[78] Y. Shi, Caspase activation, inhibition, and reactivation: a mechanistic view, Protein Sci. 13 (2004) 1979–1987, https://doi.org/10.1110/ps.04789804.
[79] M. Abotaleb, P. Kubatka, M. Caprnda, E. Varghese, B. Zolakova, P. Zubor, R. Opatrilova, P. Kruzliak, P. Stefanicka, D. Büsselberg, Chemotherapeutic agents for the treatment of metastatic breast cancer: an update, Biomed. Pharmacother. 101 (2018) 458–477, https://doi.org/10.1016/j.biopha.2018.02.108.
[80] D.R. Riggs, B.J. Jackson, L. Vona-Davis, A. Nigam, D.W. McFadden, In vitro effects of keyhole limpet hemocyanin in breast and pancreatic cancer in regards to cell growth, cytokine production, and apoptosis, Am. J. Surg. 189 (2005) 680–684.
[81] H. Luesch, R.E. Moore, V.J. Paul, S.L. Mooberry, T.H. Corbett, Isolation of dolastatin 10 from the marine cyanobacterium symploca species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1, J. Nat. Prod. 64 (2001) 907–910, https://doi.org/10.1021/np010049y.
[82] N.R. Wall, R.M. Mohammad, A.M. Al-Katib, Bax:Bcl-2 ratio modulation by bryostatin 1 and novel antitubulin agents is important for susceptibility to drug induced apoptosis in the human early pre-B acute lymphoblastic leukemia cell line, Reh, Leuk. Res. 23 (1999) 881–888, https://doi.org/10.1016/S0145-2126(99)00108-3.
[83] W. Chiangjong, S. Chutipongtanate, S. Hongeng, Anticancer peptide: physicochemical property, functional aspect and trend in clinical application (Review), Int. J. Oncol. 57 (2020) 678–696, https://doi.org/10.3892/ijo.2020.5099.
[84] A. Cuadrado, L.F. Garcia-Fernandez, L. Gonzalez, Y. Suarez, A. Losada, V. Alcaide, T. Martinez, J.M. Fernandez-Sousa, J.M. Sanchez-Puelles, A. Munoz, AplidinTM induces apoptosis in human cancer cells via glutathione depletion and sustained activation of the epidermal growth factor receptor, Src, JNK, and p38 MAPK*, J. Biol. Chem. 278 (2003) 241–250, https://doi.org/10.1074/jbc.M201010200.
[85] C.-C. Hung, Y.-H. Yang, P.-F. Kuo, K.-C. Hsu, Protein hydrolysates from tuna cooking juice inhibit cell growth and induce apoptosis of human breast cancer cell line MCF-7, J. Funct. Foods 11 (2014) 563–570.
[86] H. Lee, H. Lee, H. Chin, K. Kim, D. Lee, ERBB3 knockdown induces cell cycle arrest and activation of Bak and Bax-dependent apoptosis in colon cancer cells, Oncotarget 5 (2014) 5138–5152, https://doi.org/10.18632/oncotarget.2094.
[87] E. Wang, M.A. Sorolla, P.D.G. Krishnan, A. Sorolla, From seabed to bedside: a review on promising marine anticancer compounds, Biomolecules 10 (2020) 248, https://doi.org/10.3390/biom10020248.
[88] M.L. Janmaat, J.A. Rodriguez, J. Jimeno, F.A.E. Kruyt, G. Giaccone, Kahalalide F induces necrosis-like cell death that involves depletion of ErbB3 and inhibition of akt signaling, Mol. Pharmacol. 68 (2005) 502–510, https://doi.org/10.1124/mol.105.011361.
[89] Y.-H. Ling, M. Aracil, Y. Zou, Z. Yuan, B. Lu, J. Jimeno, A.M. Cuervo, R. Perez-Soler, PM02734 (elisidepsin) induces caspase-independent cell death associated with features of autophagy, inhibition of the Akt/mTOR signaling pathway, and activation of death-associated protein kinase, Clin. Cancer Res. 17 (2011) 5353–5366.
[90] H. Piplani, C. Rana, V. Vaish, K. Vaiphei, S. Sanyal, Dolastatin, along with Celecoxib, stimulates apoptosis by a mechanism involving oxidative stress, membrane potential change and PI3-K/AKT pathway down regulation, Biochim. Biophys. Acta (BBA)-Gen. Subj. 1830 (2013) 5142–5156.
[91] R.A. Stanton, K.M. Gernert, J.H. Nettles, R. Aneja, Drugs that target dynamic microtubules: a new molecular perspective, Med. Res. Rev. 31 (2011) 443–481, https://doi.org/10.1002/med.20242.
[92] J.A. Hadfield, S. Ducki, N. Hirst, A.T. McGown, Tubulin and microtubules as targets for anticancer drugs, Prog. Cell Cycle Res. 5 (2003) 309–326.
[93] E. Mukhtar, V.M. Adhami, H. Mukhtar, Targeting microtubules by natural agents for cancer therapy, Mol. Cancer Ther. 13 (2014) 275–284, https://doi.org/10.1158/1535-7163.mct-13-0791.
[94] D. Fanale, G. Bronte, F. Passiglia, V. Calò, M. Castiglia, F. Di Piazza, N. Barraco, A. Cangemi, M.T. Catarella, L. Insalaco, A. Listì, R. Maragliano, D. Massihnia, A. Perez, F. Toia, G. Cicero, V. Bazan, Stabilizing versus destabilizing the microtubules: a double-edge sword for an effective cancer treatment option? Anal. Cell. Pathol. 2015 (2015), 690916.
[95] M. Lachia, C.J. Moody, The synthetic challenge of diazonamide A, a macrocyclic indole bis-oxazole marine natural product, Nat. Prod. Rep. 25 (2008) 227–253.
[96] X. Ning, J. Zhao, Y. Zhang, S. Cao, M. Liu, P. Ling, X. Lin, A novel anti-tumor protein extracted from Meretrix meretrix Linnaeus induces cell death by increasing cell permeability and inhibiting tubulin polymerization, Int. J. Oncol. 35 (2009) 805–812, https://doi.org/10.3892/ijo_00000393.
[97] W.R. Gamble, N.A. Durso, R.W. Fuller, C.K. Westergaard, T.R. Johnson, D. L. Sackett, E. Hamel, J.H. Cardellina, M.R. Boyd, Cytotoxic and tubulin-interactive hemiasterlins from Auletta sp. and Siphonochalina spp. sponges, Bioorg. Med. Chem. 7 (1999) 1611–1615.
[98] R.A. Davis, G.C. Mangalindan, Z.P. Bojo, R.R. Antemano, N.O. Rodriguez, G. P. Concepcion, S.C. Samson, D. de Guzman, L.J. Cruz, D. Tasdemir, M.K. Harper, X. Feng, G.T. Carter, C.M. Ireland, Microcionamides A and B, bioactive peptides from the Philippine sponge Clathria (Thalysias) abietina, J. Org. Chem. 69 (2004) 4170–4176.
[99] C. Chevallier, A.D. Richardson, M.C. Edler, E. Hamel, M.K. Harper, C.M. Ireland, A new cytotoxic and tubulin-interactive milnamide derivative from a marine sponge Cymbastela sp, Org. Lett. 5 (2003) 3737–3739.
[100] E.W. Schmidt, C. Raventos-Suarez, M. Bifano, A.T. Menendez, C.R. Fairchild, D. J. Faulkner, Scleritodermin A, a cytotoxic cyclic peptide from the lithistid sponge Scleritoderma nodosum, J. Nat. Prod. 67 (2004) 475–478, https://doi.org/10.1021/np034035z.
[101] D. Panda, V. Ananthnarayan, G. Larson, C. Shih, M.A. Jordan, L. Wilson, Interaction of the antitumor compound cryptophycin-52 with tubulin, Biochemistry 39 (2000) 14121–14127.
[102] M. Trendowski, Exploiting the cytoskeletal filaments of neoplastic cells to potentiate a novel therapeutic approach, Biochim. Biophys. Acta (BBA) - Rev. Cancer 1846 (2014) 599–616, https://doi.org/10.1016/j.bbcan.2014.09.007.
[103] H. Lee, A.J. Jeong, S.-K. Ye, Highlighted STAT3 as a potential drug target for cancer therapy, BMB Rep. 52 (2019) 415–423, https://doi.org/10.5483/BMBRep.2019.52.7.152.
[104] D.R. Bielenberg, B.R. Zetter, The contribution of angiogenesis to the process of metastasis, Cancer J. 21 (2015) 267–273.
[105] M. Shibuya, Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies, Genes Cancer 2 (2011) 1097–1105, https://doi.org/10.1177/1947601911423031.
[106] S. Nakamura, Y. Chikaraishi, K. Tsuruma, M. Shimazawa, H. Hara, Ruboxistaurin, a PKCβ inhibitor, inhibits retinal neovascularization via suppression of phosphorylation of ERK1/2 and Akt, Exp. Eye Res. 90 (2010) 137–145.
[107] M. Ushio-Fukai, Redox signaling in angiogenesis: role of NADPH oxidase, Cardiovasc. Res. 71 (2006) 226–235.
[108] A. Winer, S. Adams, P. Mignatti, Matrix metalloproteinase inhibitors in cancer therapy: turning past failures into future successes, Mol. Cancer Ther. 17 (2018) 1147–1155, https://doi.org/10.1158/1535-7163.mct-17-0646.
[109] J.B. Morgan, F. Mahdi, Y. Liu, V. Coothankandaswamy, M.B. Jekabsons, T. A. Johnson, K.V. Sashidhara, P. Crews, D.G. Nagle, Y.D. Zhou, The marine sponge metabolite mycothiazole: a novel prototype mitochondrial complex I inhibitor, Bioorg. Med. Chem. 18 (2010) 5988–5994, https://doi.org/10.1016/j.bmc.2010.06.072.
[110] M. Malumbres, M. Barbacid, Mammalian cyclin-dependent kinases, Trends Biochem. Sci. 30 (2005) 630–641.
[111] R. Suryadinata, M. Sadowski, B. Sarcevic, Control of cell cycle progression by phosphorylation of cyclin-dependent kinase (CDK) substrates, Biosci. Rep. 30 (2010) 243–255.
[112] H.C. Hwang, B.E. Clurman, Cyclin E in normal and neoplastic cell cycles, Oncogene 24 (2005) 2776–2786.
[113] L.J. Hardwick, A. Philpott, Nervous decision-making: to divide or differentiate, Trends Genet. 30 (2014) 254–261.
[114] R. Visconti, R. Della Monica, D. Grieco, Cell cycle checkpoint in cancer: a therapeutically targetable double-edged sword, J. Exp. Clin. Cancer Res. 35 (2016) 153, https://doi.org/10.1186/s13046-016-0433-9.
[115] O. Cazzalini, A.I. Scovassi, M. Savio, L.A. Stivala, E. Prosperi, Multiple roles of the cell cycle inhibitor p21CDKN1A in the DNA damage response, Mutat. Res. /Rev. Mutat. Res. 704 (2010) 12–20.
[116] B. Shamloo, S. Usluer, p21 in cancer research, Cancers 11 (2019) 1178, https://doi.org/10.3390/cancers11081178.
[117] K. Hientz, A. Mohr, D. Bhakta-Guha, T. Efferth, The role of p53 in cancer drug resistance and targeted chemotherapy, Oncotarget 8 (2017) 8921–8946.
[118] M. Pelay-Gimeno, Y. García-Ramos, M. Jesús Martin, J. Spengler, J.M. Molina-Guijarro, S. Munt, A.M. Francesch, C. Cuevas, J. Tulla-Puche, F. Albericio, The first total synthesis of the cyclodepsipeptide pipecolidepsin A, Nat. Commun. 4 (2013) 1–10.
[119] F. Loganzo, C.M. Discafani, T. Annable, C. Beyer, S. Musto, M. Hari, X. Tan, C. Hardy, R. Hernandez, M. Baxter, T. Singanallore, G. Khafizova, M. S. Poruchynsky, T. Fojo, J.A. Nieman, S. Ayral-Kaloustian, A. Zask, R.J. Andersen, L.M. Greenberger, HTI-286, a synthetic analogue of the tripeptide hemiasterlin, is a potent antimicrotubule agent that circumvents P-glycoprotein-mediated resistance in vitro and in vivo, Cancer Res. 63 (2003) 1838–1845.
[120] X. Fan, L. Bai, X. Mao, X. Zhang, Novel peptides with anti-proliferation activity from the Porphyra haitanesis hydrolysate, Process Biochem. 60 (2017) 98–107, https://doi.org/10.1016/j.procbio.2017.05.018.
[121] E.B. Kurutas, The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state, Nutr. J. 15 (2016) 71, https://doi.org/10.1186/s12937-016-0186-5.

[122] L.A. Shaala, D.T. Youssef, S.R. Ibrahim, G.A. Mohamed, Callyptide A, a new cytotoxic peptide from the Red Sea marine sponge Callyspongia species, Nat. Prod. Res. 30 (2016) 2783–2790.
[123] C. Guo, L. Sun, X. Chen, D. Zhang, Oxidative stress, mitochondrial damage and neurodegenerative diseases, Neural Regen. Res. 8 (2013) 2003–2014, https://doi.org/10.3969/j.issn.1673-5374.2013.21.009.
[124] M. Podhorecka, A. Skladanowski, P. Bozko, H2AX phosphorylation: its role in DNA damage response and cancer therapy, J. Nucleic Acids 2010 (2010), 920161, https://doi.org/10.4061/2010/920161.
[125] D. Gaspar, A.S. Veiga, M.A.R.B. Castanho, From antimicrobial to anticancer peptides. A review, Front. Microbiol. 4 (2013) 294, https://doi.org/10.3389/fmicb.2013.00294.
[126] M. Xie, D. Liu, Y. Yang, Anti-cancer peptides: classification, mechanism of action, reconstruction and modification, Open Biol. 10 (2020), 200004.
[127] Y.-b Huang, X.-f Wang, H.-y Wang, Y. Liu, Y. Chen, Studies on mechanism of action of anticancer peptides by modulation of hydrophobicity within a defined structural framework, Mol. Cancer Ther. 10 (2011) 416–426.
[128] E. Teerasak, P. Thongararm, S. Roytrakul, L. Meesuk, P. Chumnanpuen, Prediction of anticancer peptides against MCF-7 breast cancer cells from the peptidomes of Achatina fulica mucus fractions, Comput. Struct. Biotechnol. J. 14 (2016) 49–57.
[129] D. Raucher, J.S. Ryu, Cell-penetrating peptides: strategies for anticancer treatment, Trends Mol. Med. 21 (2015) 560–570.
[130] F. Harris, S.R. Dennison, J. Singh, D.A. Phoenix, On the selectivity and efficacy of defense peptides with respect to cancer cells, Med. Res. Rev. 33 (2013) 190–234.
[131] K.-C. Hsu, E.C. Li-Chan, C.-L. Jao, Antiproliferative activity of peptides prepared from enzymatic hydrolysates of tuna dark muscle on human breast cancer cell line MCF-7, Food Chem. 126 (2011) 617–622.
[132] L. Picot, S. Bordenave, S. Didelot, I. Fruitier-Arnaudin, F. Sannier, G. Thorkelsson, J.P. Bergé, F. Guérard, A. Chabeaud, J.M. Piot, Antiproliferative activity of fish protein hydrolysates on human breast cancer cell lines, Process Biochem. 41 (2006) 1217–1222, https://doi.org/10.1016/j.procbio.2005.11.024.
[133] L. You, M. Zhao, R.H. Liu, J.M. Regenstein, Antioxidant and antiproliferative activities of loach (Misgurnus anguillicaudatus) peptides prepared by papain digestion, J. Agric. Food Chem. 59 (2011) 7948–7953, https://doi.org/10.1021/jf2016368.
[134] A. Alemán, E. Pérez-Santín, S. Bordenave-Juchereau, I. Arnaudin, M.C. Gómez-Guillén, P. Montero, Squid gelatin hydrolysates with antihypertensive, anticancer and antioxidant activity, Food Res. Int. 44 (2011) 1044–1051.
[135] J.E. Coleman, E. Dilip de Silva, F. Kong, R.J. Andersen, T.M. Allen, Cytotoxic peptides from the marine sponge Cymbastela sp, Tetrahedron 51 (1995) 10653–10662, https://doi.org/10.1016/0040-4020(95)00646-P.
[136] C. Urda, M. Pérez, J. Rodríguez, C. Jiménez, C. Cuevas, R. Fernández, Pembamide, a N-methylated linear peptide from a sponge Cribrochalina sp, Tetrahedron Lett. 57 (2016) 3239–3242, https://doi.org/10.1016/j.tetlet.2016.05.054.
[137] C.M. Theodore, N. Lorig-Roach, P.C. Still, T.A. Johnson, M. Drašković, J. A. Schwochert, C.N. Naphen, M.S. Crews, S.A. Barker, F.A. Valeriote, R.S. Lokey, P. Crews, Biosynthetic products from a nearshore-derived gram-negative bacterium enable reassessment of the kailuin depsipeptides, J. Nat. Prod. 78 (2015) 441–452, https://doi.org/10.1021/np500840n.
[138] C.M. Boot, K. Tenney, F.A. Valeriote, P. Crews, Highly N-methylated linear peptides produced by an atypical sponge-derived Acremonium sp, J. Nat. Prod. 69 (2006) 83–92.
[139] E.-K. Kim, Y.S. Kim, J.W. Hwang, J.S. Lee, S.H. Moon, B.T. Jeon, P.J. Park, Purification and characterization of a novel anticancer peptide derived from Ruditapes philippinarum, Process Biochem. 48 (2013) 1086–1090, https://doi.org/10.1016/j.procbio.2013.05.004.
[140] Z.-G. Sun, Z.-N. Li, L.-H. Zhao, J.-M. Zhang, Research progress of anti-breast cancer peptides, Int. J. Innov. Res. Med. Sci. 4 (2019) 504–506, https://doi.org/10.23958/ijirms/vol04-i08/734.
[141] J. Kasaian, F. Mosaffa, J. Behravan, M. Masullo, S. Piacente, M. Ghandadi, M. Iranshahi, Reversal of P-glycoprotein-mediated multidrug resistance in MCF-7/Adr cancer cells by sesquiterpene coumarins, Fitoterapia 103 (2015) 149–154, https://doi.org/10.1016/j.fitote.2015.03.025.
[142] S. Dewanjee, T.K. Dua, N. Bhattacharjee, A. Das, M. Gangopadhyay, R. Khanra, S. Joardar, M. Riaz, V. Feo, M. Zia-Ul-Haq, Natural products as alternative choices for p-glycoprotein (P-gp) inhibition, Molecules 22 (2017), https://doi.org/10.3390/molecules22060871.
[143] J. Jiang, X. Wang, K. Cheng, W. Zhao, Y. Hua, C. Xu, Z. Yang, Psoralen reverses the P-glycoprotein-mediated multidrug resistance in human breast cancer MCF-7/ADR cells, Mol. Med. Rep. 13 (2016) 4745–4750, https://doi.org/10.3892/mmr.2016.5098.
[144] L. Billen, A. Shamas-Din, D. Andrews, Bid: a Bax-like BH3 protein, Oncogene 27 (2008) S93–S104.
[145] A. Yamashita, E.B. Norton, J.A. Kaplan, C. Niu, F. Loganzo, R. Hernandez, C. F. Beyer, T. Annable, S. Musto, C. Discafani, A. Zask, S. Ayral-Kaloustian, Synthesis and activity of novel analogs of hemiasterlin as inhibitors of tubulin polymerization: modification of the A segment, Bioorg. Med. Chem. Lett. 14 (2004) 5317–5322.
[146] L. Jiang, Y. Wang, G. Liu, H. Liu, F. Zhu, H. Ji, B. Li, C-Phycocyanin exerts anti-cancer effects via the MAPK signaling pathway in MDA-MB-231 cells, Cancer Cell Int. 18 (2018) 12, https://doi.org/10.1186/s12935-018-0511-5.
[147] M. Wieczorek, J. Tcherkezian, C. Bernier, A.E. Prota, S. Chaaban, Y. Rolland, C. Godbout, M.A. Hancock, J.C. Arezzo, O. Ocal, C. Rocha, N. Olieric, A. Hall, H. Ding, A. Bramoullé, M.G. Annis, G. Zogopoulos, P.G. Harran, T.M. Wilkie, R. A. Brekken, P.M. Siegel, M.O. Steinmetz, G.C. Shore, G.J. Brouhard, A. Roulston, The synthetic diazonamide DZ-2384 has distinct effects on microtubule curvature and dynamics without neurotoxicity, Sci. Transl. Med. 8 (2016) 365.
[148] J.M. Conlon, M. Mechkarska, M. Prajeep, K. Arafat, M. Zaric, M.L. Lukic, S. Attoub, Transformation of the naturally occurring frog skin peptide, alyteserin-2a into a potent, non-toxic anti-cancer agent, Amino Acids 44 (2013) 715–723.
[149] M.A. Ghareeb, M.A. Tammam, A. El-Demerdash, A.G. Atanasov, Insights about clinically approved and Preclinically investigated marine natural products, Curr. Res. Biotechnol. 2 (2020) 88–102, https://doi.org/10.1016/j.crbiot.2020.09.001.
[150] E.A. Perez, D.W. Hillman, P.A. Fishkin, J.E. Krook, W.W. Tan, P.A. Kuriakose, S. R. Alberts, S.R. Dakhil, Phase II trial of dolastatin-10 in patients with advanced breast cancer, Investig. N. Drugs 23 (2005) 257–261, https://doi.org/10.1007/s10637-005-6735-y.
[151] P. Kerbrat, V. Dieras, N. Pavlidis, A. Ravaud, J. Wanders, P. Fumoleau, O. EORTC Early Clinical Studies Group/New Drug Development, Phase II study of LU 103793 (dolastatin analogue) in patients with metastatic breast cancer, Eur. J. Cancer 39 (2003) 317–320, https://doi.org/10.1016/S0959-8049(02)00531-2.
[152] J. WATANABE, M. MINAMI, M. KOBAYASHI, Antitumor activity of TZT-1027 (Soblidotin), Anticancer Res. 26 (2006) 1973–1981.
[153] A.M. Mayer, K.B. Glaser, C. Cuevas, R.S. Jacobs, W. Kem, R.D. Little, J. M. McIntosh, D.J. Newman, B.C. Potts, D.E. Shuster, The odyssey of marine pharmaceuticals: a current pipeline perspective, Trends Pharmacol. Sci. 31 (2010) 255–265.
[154] M.J. Muñoz-Alonso, L. González-Santiago, N. Zarich, T. Martínez, E. Alvarez, J. M. Rojas, A. Muñoz, Plitidepsin has a dual effect inhibiting cell cycle and inducing apoptosis via Rac1/c-Jun NH2-terminal kinase activation in human melanoma cells, J. Pharmacol. Exp. Ther. 324 (2008) 1093–1101.
[155] A. Zask, J. Kaplan, S. Musto, F. Loganzo, Hybrids of the hemiasterlin analogue taltobulin and the dolastatins are potent antimicrotubule agents, J. Am. Chem. Soc. 127 (2005) 17667–17671.
[156] K. Senthilkumar, V. Jayachandran, K. Se-Kwon, Marine derived bioactive compounds for breast and prostate cancer treatment: a review, Curr. Bioact. Compd. 10 (2014) 62–74, https://doi.org/10.2174/1573407210666140327212945.
[157] G.-M. Suarez-Jimenez, A. Burgos-Hernandez, J.-M. Ezquerra-Brauer, Bioactive peptides and depsipeptides with anticancer potential: sources from marine animals, Mar. Drugs 10 (2012) 963–986, https://doi.org/10.3390/md10050963.
[158] L. Zheng, X. Lin, N. Wu, M. Liu, Y. Zheng, J. Sheng, X. Ji, M. Sun, Targeting cellular apoptotic pathway with peptides from marine organisms, Biochim. Biophys. Acta (BBA)-Rev. Cancer 1836 (2013) 42–48.
[159] R. Beesoo, V. Neergheen-Bhujun, R. Bhagooli, T. Bahorun, Apoptosis inducing lead compounds isolated from marine organisms of potential relevance in cancer treatment, Mutat. Res./Fundam. Mol. Mech. Mutagen. 768 (2014) 84–97, https://doi.org/10.1016/j.mrfmmm.2014.03.005.
[160] L. Zheng, Y. Xu, X. Lin, Z. Yuan, M. Liu, S. Cao, F. Zhang, R.J. Linhardt, Recent progress of marine polypeptides as anticancer agents. Recent patents on anti-cancer drug discovery 13, 445–454, 2018.
[161] A. Sorolla, E. Wang, E. Golden, C. Duffy, S.T. Henriques, A.D. Redfern, P. Blancafort, Precision medicine by designer interference peptides: applications in oncology and molecular therapeutics, Oncogene 39 (2020) 1167–1184, https://doi.org/10.1038/s41388-019-1056-3.
[162] A. Sorolla, M.A. Sorolla, E. Wang, V. Ceña, Peptides, proteins and nanotechnology: a promising synergy for breast cancer targeting and treatment, Expert Opin. Drug Deliv. 17 (2020) 1597–1613, https://doi.org/10.1080/17425247.2020.1814733.
[163] M.T. Hamann, P.J. Scheuer, Kahalalide F: a bioactive depsipeptide from the sacoglossan mollusk Elysia rufescens and the green alga Bryopsis sp, J. Am. Chem. Soc. 115 (1993) 5825–5826.
[164] J.D. Serrill, X. Wan, A.M. Hau, H.S. Jang, D.J. Coleman, A.K. Indra, A.W. Alani, K. L. McPhail, J.E. Ishmael, Coibamide A, a natural lariat depsipeptide, inhibits VEGFA/VEGFR2 expression and suppresses tumor growth in glioblastoma xenografts, Investig. N. Drugs 34 (2016) 24–40.
[165] K. Schneider, S. Keller, F.E. Wolter, L. Röglin, W. Beil, O. Seitz, G. Nicholson, C. Bruntner, J. Riedlinger, H.P. Fiedler, R.D. Süssmuth, Proximicins A, B, and C—antitumor furan analogues of netropsin from the marine actinomycete Verrucosispora induce upregulation of p53 and the cyclin kinase inhibitor p21, Angew. Chem. Int. Ed. 47 (2008) 3258–3261.