



Therapeutic Potential of Marine Peptides in Prostate Cancer: Mechanistic Insights

Salman Ahmed, Waqas Alam, Philippe Jeandet, Michael Aschner, Khalaf Alsharif, Luciano Saso, Haroon Khan

► To cite this version:

Salman Ahmed, Waqas Alam, Philippe Jeandet, Michael Aschner, Khalaf Alsharif, et al.. Therapeutic Potential of Marine Peptides in Prostate Cancer: Mechanistic Insights. *Marine drugs*, 2022, 20 (8), pp.466. 10.3390/md20080466 . hal-03756327

HAL Id: hal-03756327

<https://hal.univ-reims.fr/hal-03756327>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.







L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Review

Therapeutic Potential of Marine Peptides in Prostate Cancer: Mechanistic Insights

Salman Ahmed ¹, Waqas Alam ², Philippe Jeandet ³, Michael Aschner ⁴, Khalaf F. Alsharif ⁵, Luciano Saso ⁶ and Haroon Khan ^{2,*}

¹ Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan; salmanahmed@uok.edu.pk

² Department of Pharmacy, Abdul Wali Khan University, Mardan 23200, Pakistan; waqasalamyousafzai@gmail.com

³ Research Unit “Induced Resistance and Plant Bioprotection”, Department of Biology and Biochemistry, Faculty of Sciences, University of Reims, EA 4707-USC INRAE 1488, SFR Condorcet FR CNRS 3417, P.O. Box 1039, CEDEX 02, 51687 Reims, France; philippe.jeandet@univ-reims.fr

⁴ Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA; michael.aschner@einsteinmed.org

⁵ Department of Clinical Laboratory, College of Applied Medical Science, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia; alsharif@tu.edu.sa

⁶ Department of Physiology and Pharmacology, “Vittorio Erspamer” Sapienza University, 00185 Rome, Italy; luciano.saso@uniroma1.it

* Correspondence: haroonkhan@awkum.edu.pk

Abstract: Prostate cancer (PCa) is the leading cause of cancer death in men, and its treatment is commonly associated with severe adverse effects. Thus, new treatment modalities are required. In this context, natural compounds have been widely explored for their anti-PCa properties. Aquatic organisms contain numerous potential medications. Anticancer peptides are less toxic to normal cells and provide an efficacious treatment approach via multiple mechanisms, including altered cell viability, apoptosis, cell migration/invasion, suppression of angiogenesis and microtubule balance disturbances. This review sheds light on marine peptides as efficacious and safe therapeutic agents for PCa.

Keywords: marine peptides; apoptosis; antimetastatic; antimitotic; antiangiogenic; cell cycle arrest



Citation: Ahmed, S.; Alam, W.; Jeandet, P.; Aschner, M.; Alsharif, K.F.; Saso, L.; Khan, H. Therapeutic Potential of Marine Peptides in Prostate Cancer: Mechanistic Insights. *Mar. Drugs* **2022**, *20*, 466. <https://doi.org/10.3390/md20080466>

Academic Editor: Marc Diederich

Received: 21 June 2022

Accepted: 18 July 2022

Published: 22 July 2022

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Prostate cancer (PCa) is one of the most often diagnosed cancers worldwide. It is the second leading source of cancer-related mortality in males, trailing behind only lung cancer, based on GLOBOCAN 2020 estimates [1]. Radiation and surgical procedures are used to treat this disease when it first appears and is localized. Despite a considerable increase in disease-free life following first surgical or radiation therapy, the illness recurs in more than 30% of patients. Androgen deprivation treatment (ADT) is the most often alternative for PCa treatment, because of the tumor’s requirement for male hormones for progression. This treatment is focused on pharmacological castration achieved via GnRH agonists alone or in conjunction with anti-androgens. However, despite an excellent initial response, most patients relapse within 2–3 years, and the tumor advances. Chemotherapeutic drugs, such as docetaxel, cabazitaxel, doxorubicin, abiraterone and enzalutamide, provide a few months of progression-free survival with highly toxic effects. Therefore, the development and refinement of unique anticancer drugs with minimal adverse side effects are required [2,3].

Natural products provide benefits over synthetic compounds because of their broader variety of targets, larger structural diversity and low toxicity against PCa [4,5]. Many bioactive substances found in the marine ecosystem have potential applications in the treatment of human diseases including cancer. A large number of novel sea-based biological

compounds have been derived from corals, sponges, tunicates, bacteria, fungi, micro- and macroalgae, and other marine micro- and macro-organisms. Treatments have been impacted by marine-based medicines, with anticancer treatments made available with several marine chemical compounds. Indeed, clinical approval has been granted for several such treatments, including belantamab mafodotin, cytarabine, enfortumab vedotin, brentuximab vedotin, eribulin mesylate, lurbinectedin, fludarabine phosphate (prodrug of ara-A), nelarabine (prodrug of ara-G), polatuzumab vedotin, trabectedin, vidarabine, and plitidepsin [6–9]. Improvement in the physiological state of cancer patients depends on the introduction of natural strategies for clinical treatment. Due to their small size, ease of synthesis, capacity to cross cell membranes, low drug–drug interactions, precision targeting, and reduced side responses, marine peptides have also spurred attention in the development of anticancer medicines. The downsides of anticancer peptides include their short half-life, low bioavailability, poor pharmacokinetics, and protease sensitivity [10–12]. A schematic representation of the pathophysiology of prostate cancer is shown in Figure 1.

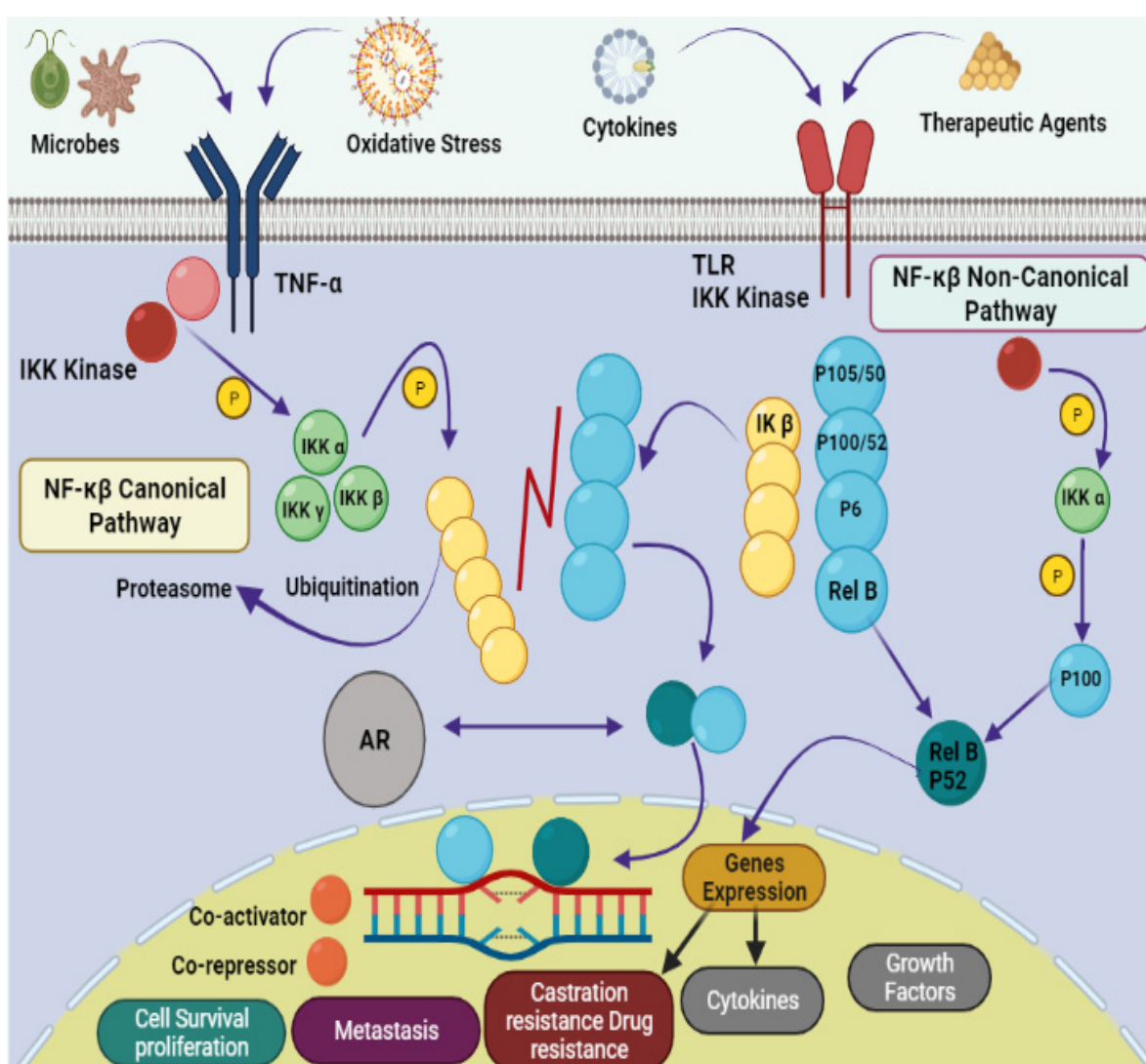


Figure 1. Pathophysiology of prostate cancer via NF-κB canonical and non-canonical pathways. The leading dimers of NF-κB are P50-P65, which activate the transcription process in canonical pathways. Different subunits like Toll-like receptor (TLR); tumor necrosis factor receptor (TNF-R); Inhibitor of NF-κB (IκB); IκB kinase; NF-κB-inducing kinase (NIK); mitogen-activated protein kinase (MAP); androgen receptor (AR); bone marrow-derived cell (BMDC) and major histocompatibility complex (MHC) are also involved in the pathology of prostate cancer.

Presently, more than 60% of clinically accessible anticancer medications have been derived from natural sources. Peptides are categorized depending on their ability to induce antioxidative mechanisms, cytotoxicity, apoptosis, inhibit cell proliferation, migration, and angiogenesis, microtubule-destabilization, or undiscovered mechanisms in diverse malignant cell lines, relating to clinical research for cancer treatment evaluation [12,13]. Anticancer peptides from algae, ascidians, bacteria, fungi, cyanobacteria, mollusks, sponges, and protein hydrolysates from clam, coral and fish, have been isolated. Linear and cyclic peptides are the two types of marine peptides. A straight-chain of amino acids linked together by amide bonds forms a linear peptide (Figure 2) [7]. HTI-286 [14], SHP [15], SIO [16] (tripeptides); Microsporin A [17], SCH-P9 and SCH-P10 [18] (tetrapeptides); dolastatin 10 [19], ILYMP [20] (pentapeptides); AAP-H (oligopeptide) [21] are reported from mollusk, sponges, fish, clam, sea anemone and marine derived fungus. Cyclic tetra, penta, hepta, octa, dodecapeptides and depsipeptides are claimed to have anti-PCa effects. Cyclic depsipeptides have more complex structures, where successive ester linkages replace more amide bonds due to the presence of hydroxy acids in the peptide structure [7]. Aurilide B [22], lagunamide C [23], cryptophycin-52 [24] and coibamide A [25] are obtained from cyanobacteria. Geodiamolides D–F [26], homophymines A–E [27], jaspamide [28,29] and neamphamides B–D [30] from sponges are cyclic depsipeptides with anti-cancer effects. Kahalalide F from (mollusk) [31]; tamandarins A,B (ascidia) [32,33] sansalvamide A (fungus) [34] are other reported anticancer cyclic depsipeptides. Furthermore, microsporin A (cyclic tetrapeptide) [17], zygosporamide (cyclic pentadepsipeptide) [35] rolloamide A [36] and trunkamide A (a cyclic heptapeptide) [12,37], patellamides B and F (cyclic octapeptides) [38] and laxaphycin B (a cyclic dodecapeptide) [39] have been isolated from ascidia, cyanobacteria, sponge and marine derived fungus. Protein hydrolysates, the complex mixtures of oligopeptides and free amino acids have antioxidant, antiproliferative, antihypertensive, and antibacterial properties [40–42]. Protein hydrolysates obtain from mollusk [43], fish [15,16,44,45] and clam [18,20] have anti-PCa properties.

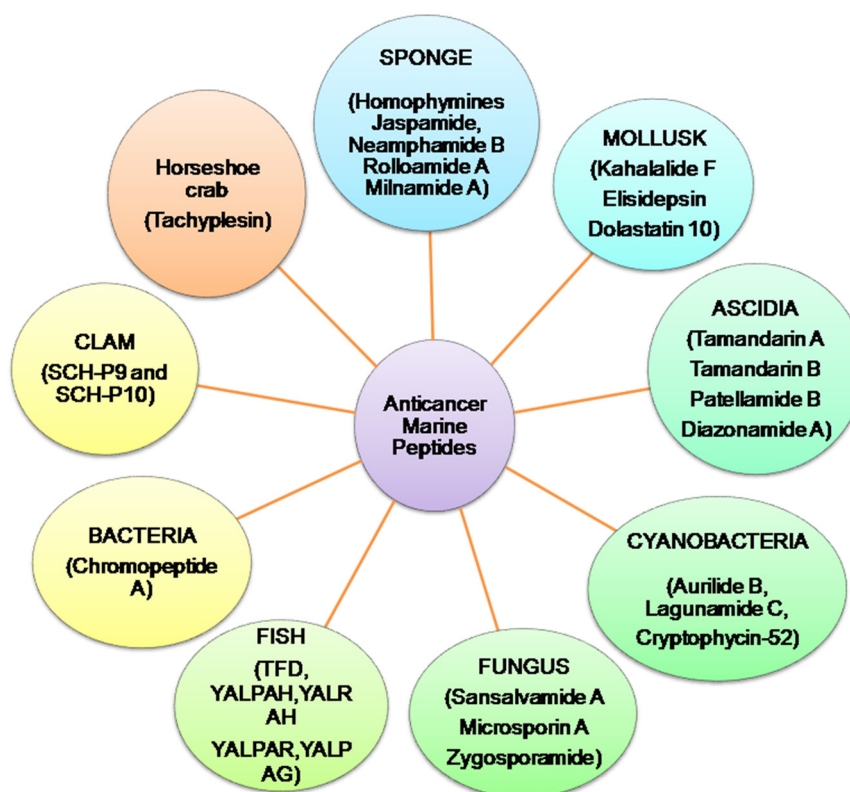


Figure 2. Summary of anticancer marine peptides isolated from different marine sources.

Several physiological and molecular mechanisms are used by marine anticancer peptides, including DNA repair, apoptosis induction, cell-cycle regulation, angiogenesis inhibition, migration, invasion, and metastasis suppression (Table 1) [8,46]. This review emphasizes marine anti-PCa peptides and their significance in the development of novel anticancer therapeutics.

2. Mechanistic Insights

2.1. Apoptosis

One of the most critical mechanisms of cell death is apoptosis, and its failure is a severe barrier to cancer therapy. Cytochrome-c (cyt c) release leads to caspases activation and ensuing apoptosis [47]. C-phycocyanin from cyanobacteria [48] and AAP-H from sea anemone [21] have shown apoptotic efficacy by initiating cyt c release in DU145 and LNCaP cells. Caspases are the main executors of apoptosis, which are activated after proteolytic cleavage. Initiator caspases that include caspase-8, -9 and -10 initiate a regulated and programmed cell death cascade to trigger downstream caspases-3, -6, and -7 expression [49]. Tachyplesin, a cyclic peptide from horseshoe crab, triggers cyt c release, increasing caspases-3, -6, -7, -8, and -9 expression in TSU cells with IC_{50} of $75 \mu\text{g mL}^{-1}$ [50]. AAP-H from sea anemone has shown apoptotic efficacy by initiating cyt c release, enhancing caspases-3 and -9 activity in DU145 cells [21]. Cryptophycin-52 increases caspases-3 and -7 activities in DU145 and LNCaP cells [24]. The chromopeptide A from *Chromobacterium* sp. also increases caspase-3 activities and PARP cleavage in PC-3, DU145 and LNCaP cells [51]. Similarly, protein hydrolysates from clam, such as ILYMP, SCH-P9 and SCH-P10 [18,20] and MCH from mollusk have shown efficacy in DU145 and PC-3 [43]. SHP and SIO from fish increase caspase-3 activity in PC-3 and DU145 with IC_{50} s of 15 and 1 mg mL^{-1} , respectively [15,44,45].

Bcl-2 inhibition and BAX induction represents another method for initiating apoptosis [52]. C-phycocyanin induces apoptosis via caspases-3 and -9 activation, increasing BAX and decreasing Bcl2 and Bcl-xL in human prostate carcinoma DU145 and LNCaP cell lines with the IC_{50} s in the range of 1–10 pM [48]. When DU145 cancer cells are treated with AAP-H oligopeptide, Bcl-2 is reduced, an effect related to the increased production of BAX, with IC_{50} of 2.298 mM [21]. Similarly, Sepia ink peptides SHP and SIO have been shown to induce apoptosis in PC-3 and DU145 by upregulating BAX and reducing Bcl-2 [15,44,45]. ILYMP initiates the phosphorylation of Bcl-2 and increases BAX in DU145 cells with IC_{50} of 11.25 mM [20]. Similarly, SCH-P9 and SCH-P10 from clam [18] and MCH from mollusk have shown the same behavior in DU145 and PC-3 [43].

PI3K/AKT pathways play a significant role in regulating cell cycle and survival. AKT inhibitors attenuate the degree of BAK, BAX, and BAD phosphorylation, cause cyt c release, and activate casp-9 [53]. Decreased PI3K/AKT and ErbB3 levels are involved in cell cycle arrest as well as BAX and BAK activation [54]. PI3K/AKT and ErbB3 deficiency in PC-3 and DU145 have been noted upon treatment with Kahalalide F [31,55]. Elisidepsin or Irvalec (a Kahalalide F synthetic derivative) have been shown to inhibit PI3K/AKT and deplete ErbB3 in PC-3 and DU145 cells [56,57]. Furthermore, elisidepsin causes cellular swelling, plasma membrane rupture, and loss of intracellular contents, as well as necrotic cell death in PC-3 and 22RV1 at IC_{50} s of 0.6M and 0.3M, respectively [58]. p38 mitogen-activated protein kinases (MAPKs) and Jun N-terminal kinases (JNKs) are activated by microtubule inhibitors, suggesting this may represent a general stress response to microtubule dysfunction. Cyt c release is induced by JNK and p38 MAPK activation, which, in turn, triggers caspase cascades. Activation of JNK and ERK induces mitochondrial-related apoptosis via JNK signaling and S phase cell cycle arrest via ERK signaling [59,60]. Cryptophycin-52 induces apoptosis in DU145 and LNCaP cells via caspases-3, -7; JNK, p38 MAPK and ERK activation, increasing BAX and decreasing Bcl2 and Bcl-xL expression (Figure 3) [24].

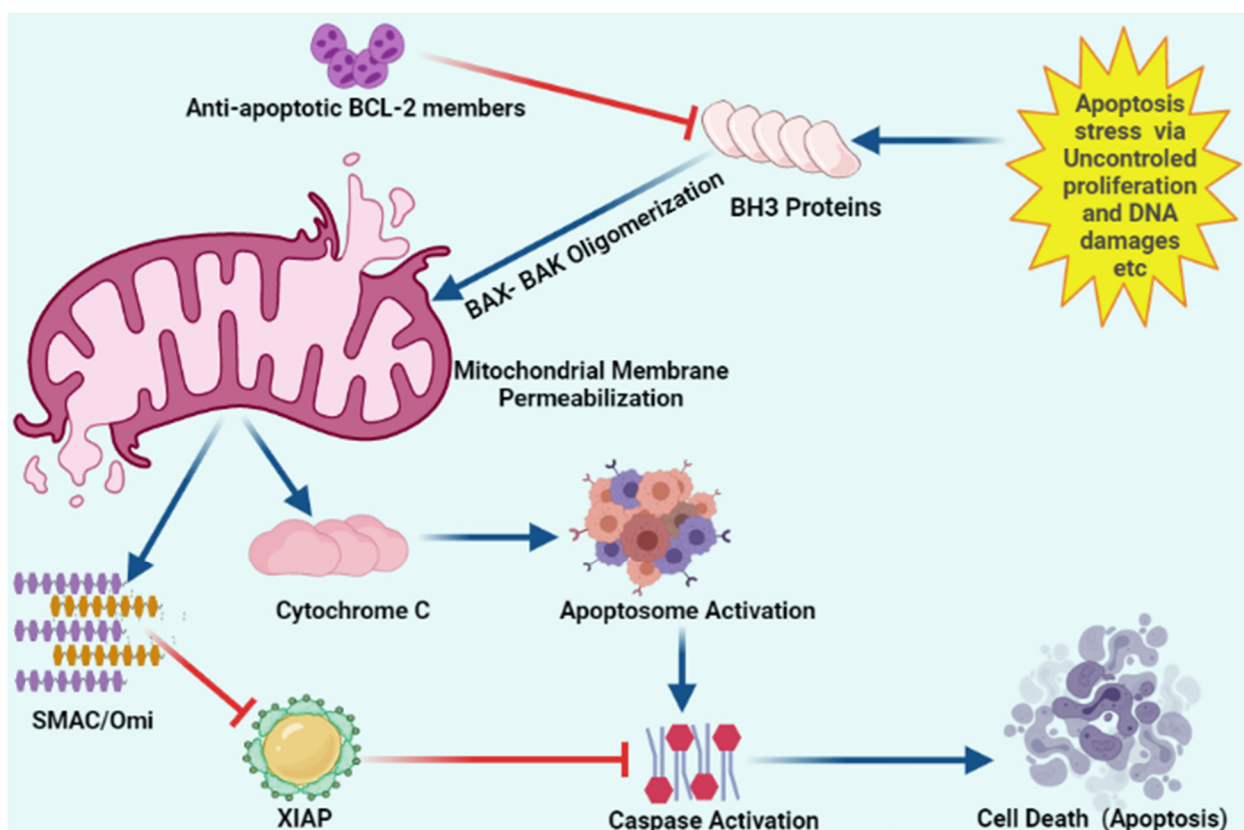


Figure 3. Schematic representation of intracellular apoptosis pathway.

Apoptosis stress involves mitochondrial outer membrane permeabilization via uncontrolled BH3 only proteins. BH-3 only proteins lead to oligomerization of BAK/BAX multimers. These BAK/BAX multimers within the outer membrane of the mitochondria form pores that allow cytochrome C release. Released cytochrome C interacts with Apaf-1 and pro-caspase-9 to form the apoptosome. Upon release, mitochondria-derived activator of caspase (SMAC) Cytochrome C and Omi activate apoptosome from procaspase-9 and cytochrome C. Caspases upon activation results in the cleavage of cellular proteins that leads to apoptosis. “Activation” is represented by blue arrows, whereas red T-bars show “inhibition”.

2.2. Antimitotic Effect

Antimitotic drugs function by stabilizing and destabilizing microtubule dynamics, as well as shifting the balance between tubulin polymerization and depolymerization. The majority of these drugs act via G2/M phase arrest [61]. Microtubules provide a variety of critical cellular activities, including chromosomal segregation, cell shape preservation, transport, motility, and organelle distribution. Microtubules, the key components of the mitotic spindle, play an important role in cell division. Microtubular dynamic disruption arrests the cell cycle at the metaphase–anaphase transition leading to cell death [62]. Hemiasterlin and its analogue HTI-286 depolymerize microtubules by disrupting microtubular dynamics in LNCaP, C4-2, PC-3, PC-3dR cell lines with IC_{50} s in the range of 0.65–4.6 nM. The same effect has been noted in PC3-MM2, PC-3 and PC-3dR xenografts at 1–1.5 mg/kg i.v. [26,63]. Dolastatin 10 (IC_{50} :0.5 nM) inhibits microtubule assembly in DU145 cells [19]. Analogous behavior has been observed for Diazonamide A in PC-3 cells with IC_{50} of 2.3 nM [64]. Cryptophycin-52 (LY355703), a synthetic cryptophycin, inhibits DU145 and LNCaP cell growth during mitosis by depolymerizing spindle microtubules and alters chromosomal organization [24]. By attaching to the microtubules, microtubule-stabilizing drugs promote microtubule polymerization and target the cytoskeleton and spindle apparatus of tumor

cells, leading to mitotic interruption [62]. Aurilide B has been shown to cause microtubular destabilization in PC-3 and DU145 carcinoma cell lines with GI₅₀ < 10 nM [22].

2.3. Antimetastatic Activity

Non-caspase proteases (elastase, trypsin and chymotrypsin) are critical regulators of PCa progression. The PCa metastatic cascade is characterized by a defined chain of steps, beginning with neoangiogenesis or lymphangiogenesis, culminating in the loss of tumor cell adhesion, local invasion of host stroma, and tumor cell escape into the vasculature or lymphatics, and eventually dissemination, extravasation, and colonization of specific metastatic sites. Proteases secrete angiogenic factors, cell adhesion molecules, breakdown basement membranes, induce epithelial–mesenchymal transition, participate in extravasation, and are necessary for metastatic site colonization. Several proteases are increased in tumor cells, and have specific roles in facilitating various phases of this cascade [65,66]. Trypsin plays a tumorigenic role in PCa and suppressing trypsin/mesotrypsin activity may provide a new PCa therapeutic strategy. PC-3 cells originating from a grade IV prostate cancer bone metastases exhibit an extremely significant overexpression of PRSS3/mesotrypsin [67]. LNCaP human prostate cells have shown upregulation of chymotrypsin-like proteasomal activity, suggesting the involvement of chymotrypsin in PCa [68]. Elastase increases PCa proliferation, migration, invasion and has been used as a therapeutic target [69]. Symplocamide A blocks chymotrypsin and trypsin with IC₅₀s of 0.38 and 80.2 µM, respectively [70]. Kempopeptin A inhibits porcine pancreatic elastase (0.32 µM) and bovine pancreatic α-chymotrypsin (2.6 µM), whereas, Kempopeptin B only inhibits trypsin activity (8.4 µM) [71]. Bouillomides A and B inhibit elastase and chymotrypsin from porcine pancreas [72]. Molassamide, a depsipeptide from the cyanobacteria *Dichothrixutahensis*, inhibits porcine pancreatic elastase (IC₅₀:0.032 µM) and α-chymotrypsin (IC₅₀: 0.234 µM) from bovine pancreas [73]. Largamides are cyclic peptides isolated from *Lyngbyaconfervoides* and *Oscillatoria* sp. Largamides A–C inhibit elastase with IC₅₀ ranges from 0.53 to 1.41 µM [74]. Chymotrypsin is also inhibited by argamides D through G, with IC₅₀ values between 4 and 25 M [75]. Pompanopeptin A inhibits trypsin with IC₅₀ of 2.4 µM [76]. Elastase and chymotrypsin were inhibited by Lyngbyastatin 4, a cyclic depsipeptide from *Lyngbya* sp., at 0.03 M [77]. With IC₅₀s of 3.2–8.3 nM for elastase and 2.5–2.8 nM for chymotrypsin, ligbystatin 5–7 inhibit both enzymes [78]. Lyngbyastatin 8–10 inhibit elastase with IC₅₀s of 120–210 nM [79]. Tiglicamides A–C and cyclodepsipeptides from the same source have IC₅₀s that range from 2.14 to 7.28 M for inhibiting elastase [80]. The pitipeptolides A and B inhibit elastase activity at 50 µg mL^{−1} [81]. Somamide B from the same source inhibits elastase (9.5 nM) and chymotrypsin (4.2 µM) [78]. Cathepsins D and E are lysosomal proteases having anti-apoptotic functions and which play an important role in PCa [82,83]. Grassystatins A and B depsipeptides strongly inhibit cathepsins D (IC₅₀:26.5 and 7.27 nM, respectively) and E (IC₅₀:886 and 354 pM), whereas grassystatin C inhibits cathepsins D (IC₅₀:1.62 µM) and E (IC₅₀:42.9 nM) [84].

The cytoskeletal microfilament, actin, is required for cytokinesis, cell migration, and a host of other processes crucial for the stability of cancerous cells. Inhibiting actin polymerization slows the growth of metastatic neoplastic cells by causing the breakdown of microfilaments, which, in turn, reduces cell motility [85]. Jaspamide, a cyclicdepsipeptide from sponge (*Jaspis johnstoni*), has shown antiproliferative activity against DU145, LNCaP, and PC-3 with IC₅₀s of 0.8, 0.07 and 0.3µM by actin filament disruption. The same peptide has shown anticancer activity in a DU-145 xenograft [85].

Voltage-gated sodium channels (VGSC) are considered to have a role in cancer cell invasion and metastasis. In PCa, VGSC overexpression is crucial for cell movement and invasiveness [86–88]. Palmyramide A, a cyclic depsipeptide with an IC₅₀ of 17.2 µM, and hermitamides A and B (lipopeptides) with IC₅₀s of 1 µM have been shown to block sodium channels via VGSC inhibition [89,90].

2.4. Antiangiogenic Effect

Angiogenesis is crucial in the development of cancer [90]. VEGF is produced in cancer cells and is required for angiogenesis. During low oxygen (hypoxia) periods, Mucin 1 (MUC1) increases HIF-1 α to stimulate tumor development and angiogenesis. Its overexpression restricts apoptosis via upregulating Bcl-xL and inactivating BAD protein. A decline in VEGF expression level is associated with MUC1 silencing, establishing that MUC1 downregulation has an anti-angiogenic impact [91–93]. TFD and SIO peptides from fish inhibit PC-3 and DU145 cell migration by decreasing *VEGFR1* and *MUC1* protein expression [44,45,94].

2.5. Cell Cycle Arrest

Cell cycle arrest limits cell viability and is related to apoptosis [95]. The two main regulators of G2/M transition/progression are *cdc2* and cell division cycle-25C (*cdc25C*). Multiple signaling pathways influence their regulation in the cell cycle, and are linked to carcinogenesis and tumor formation. *cdc2* and *cdc25C* have been shown to enhance mitotic cell G2/M transition by dephosphorylating cyclin-dependent kinase-1 (CDK1) and activating the cyclin B1/CDK1 complex. Their downregulation causes G2/M cell cycle arrest via p53-mediated signal transduction [96]. *cdc2* and *cdc25C* are highly expressed in PCa [97]. Chromopeptide A promotes G2/M phase arrest in PCa cells by suppressing *cdc2* and *cdc25C* phosphorylation [51]. Similarly, cryptophycin-52 induces G2/M phase arrest in DU145 and LNCaP cells [24].

2.6. p53 Upregulation

The functional tumor protein p53 (*p53*) protein takes part in apoptosis initiation via BAK, BAX increment and Bcl2, Bcl-xL decrement. Cells also arrest in the G1 and G2/M stages when p53 is activated. Low p53 level has been detected in PCa [98–100]. Cryptophycin-52 [24], chromopeptide A [51] and sepia ink peptides [15,44,45] induce p53 upregulation in PC-3, DU145 and LNCaP cells and hence regulate p53-dependent apoptosis and cell cycle arrest.

2.7. Stimulation of Histone Hyperacetylation

Histone deacetylases (HDACs) are widely produced and over-activated in PCa. Stimulation of histone hyperacetylation in tumor through cellular HDAC inhibition results in G2/M phase arrest, apoptosis, activates p53, DNA-damage response and inhibition of metastasis and angiogenesis [101]. The chromopeptide A from marine-derived *Chromobacterium* sp. stimulates histone hyperacetylation by HDAC inhibition in PC-3, DU145, LNCaP cell lines and human PC-3 xenograft mouse model [51].

2.8. Mitochondrial Dysfunctions and Oxidative Damage

Reactive oxygen species (ROS) accumulation induces oxidative stress caused by mitochondrial abnormalities, and malignant cells require high ROS concentrations [102]. The most frequent type of DNA damage is DNA fragmentation, a direct consequence of oxidative stress [103]. Dolastatin 10 induces DNA damage in DU145 [19]. Similarly, Cryptophycin 52 and C-phycocyanin induce DNA damage in DU145 and LNCaP [24,48]. A schematic representation of the anticancer mechanisms of marine peptides is depicted in Figure 4 as under:

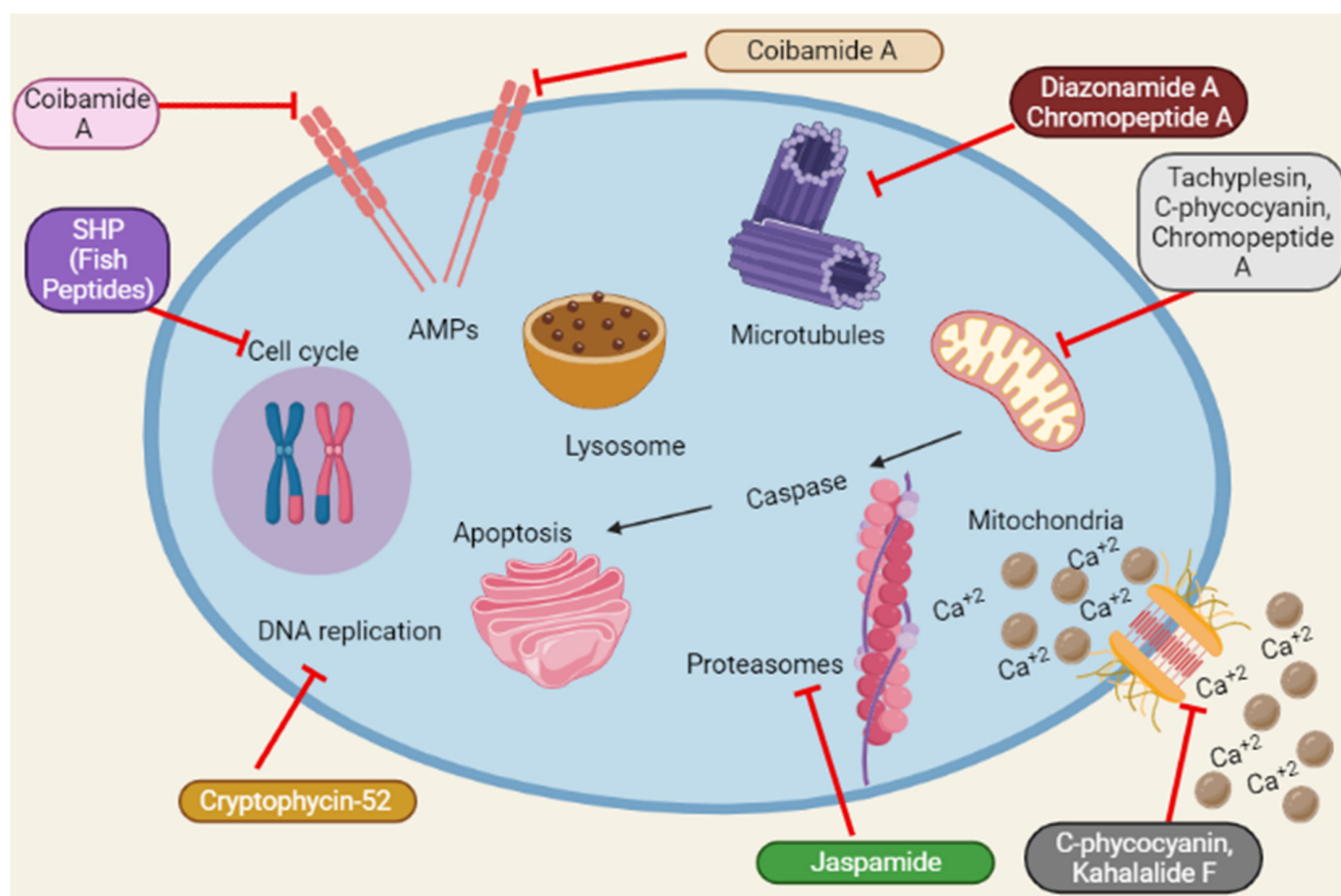


Figure 4. Summary of the schematic representation of the anticancer mechanisms of marine peptides at different cellular pathways. Marine peptides inhibit different pathways such as inhibition of cell cycle, Amps, caspase, Ca^{+2} influx, DNA replication, protein synthesis and lysosomal pathways.

2.9. Unidentified Mechanisms for Anticancer Activity

Geodiamolides D–F [26], homophymines A–E [27], milnamides A–G [26], neamphamides B–D [30], rolloamide A [36], yaku'amides A and B [104] from sponges; lagunamide C [23], coibamide A [25], laxaphycin B [39] from cyanobacteria exhibit strong cytotoxicity in several PCa cells, although the specific targets are yet unknown. Patellamides B and F, ulithiacyclamide [38], trunkamide A [12,37], tamandarins A–B [32,33] from ascidia also elicit anti-PCa activity via unrevealed process. Microsporin A [17], sansalvamide A [34] and zygosporamide [35] from marine derived fungus; YALPAH from fish [105] possess anti-PCa properties via an unknown mechanism. Some of the anticancer effects of marine peptides are summarized in Table 1:

Table 1. Summary of the sources, active peptides and anticancer mechanisms of action of Marine peptides.

Peptides	Marine Sources (Species Name)	Active Derivative	Anticancer Mechanisms	References
Aurilide B	Cyanobacteria (<i>Lyngbya majuscula</i>)	Cyclic depsipeptide	Microtubule stabilization	[22]
Lagunamide C			↓ cell viability	[23]

Table 1. Cont.

Peptides	Marine Sources (Species Name)	Active Derivative	Anticancer Mechanisms	References
Cryptophycin-52 (LY355703)	Cyanobacteria (<i>Nostoc</i> sp.)	Cyclic dodecapeptide	DNA fragmentation; Bcl2 ↓; Bax ↑; Bcl-xL ↓; caspase 3, 7 ↑; PARP ↑; p53 ↑; G2/M phase arrest; Microtubule depolymerization	[24]
Coibamide A	Cyanobacteria (<i>Leptolyngbya</i> sp.)		↓ cell viability	[25]
Laxaphycin B	Cyanobacteria (<i>Lyngbya majuscula</i>)		[39]	
C-phycocyanin	Cyanobacteria (<i>Limnothrix</i> sp.)	Peptide	Caspases 3, 9 ↑; cyt c release ↑; DNA fragmentation	[48]
Bisebromoamide	Cyanobacteria (<i>Lyngbya</i> sp.)	Cyclic depsipeptide	↓ cancer cell growth	[106]
Jaspamide	Sponge (<i>Jaspis johnstoni</i>)		Actin filament disruption	[28] [29]
Homophymines A–E	Sponge (<i>Homophymia</i> sp.)			[27]
Neamphamides B–D	Sponge (<i>Neamphius huxleyi</i>)			[30]
Geodiamolides D–F	Sponge (<i>Pipestela candelabra</i>)		N-methylated linear peptide	↓ cell viability
Milnamides A–G				
Rolloamide A	Sponge (<i>Eurypon laughlini</i>)	Cyclic heptapeptide		[36]
HTI-286	Sponge (<i>Hemiassterella minor</i>)	Tripeptide	Microtubule depolymerization	[14] [107]
Kahalalide F	Mollusk (<i>Elysia rufescens</i>)	Cyclic depsipeptide	PI3K-AKT inhibition; ErbB3 depletion	[31]
Elisidepsin			↓ cancer cell growth	[108]
Dolastatin 10	Mollusk (<i>Dolabella auricularia</i>)	Pentapeptide	Microtubule depolymerization	[19]
MCH	Mollusk (<i>Mytilus coruscus</i>)	Peptide	Bcl2 ↓; Bax ↑; caspase 3, 9 ↑	[43]
KLH	Mollusk (<i>Megathura crenulata</i>)		↓ cancer cell growth	[109]
Tamandarin A	Ascidia (<i>Trididemnum solidum</i>)	Cyclic depsipeptide		[32]
Tamandarin B				[33]
Patellamide B	Ascidia (<i>Lissoclinum patella</i>)	Cyclic octapeptide	↓ cell viability	[38]
Patellamide F				
Ulithiacyclamide		Cyclic peptide		
Trunkamide A	Ascidia (<i>Lissoclinum</i> sp.)	Cyclic heptapeptide		[12,37]
Diazonamide A	Ascidia (<i>Diazona angulata</i>)	Macrocyclic peptide	Microtubule depolymerization	[64]

Table 1. Cont.

Peptides	Marine Sources (Species Name)	Active Derivative	Anticancer Mechanisms	References
Chromopeptide A	Bacteria (<i>Chromobacterium</i> sp. HS-13-94)	Depsipeptide	caspase 3 ↑; PARP cleavage; HDAC inhibition; G ₂ /M phase arrest; p53 ↑	[51]
Sansalvamide A	Fungus (<i>Fusarium</i> sp.)	Cyclic depsipeptide	↓ cell viability	[34]
Microsporin A	Fungus (<i>Microsporum</i> cf. <i>gypseum</i>)	Cyclic tetrapeptide		[17]
Zygosporamide	Fungus (<i>Zygosporium masonii</i>)	Cyclic pentadepsipeptide	↓ cancer cell growth	[35]
SHP	Fish (<i>Sepia esculenta</i>)	Tripeptide	Bcl2 ↓; Bax ↑; caspase 3 ↑; p53 ↑	[15]
SIO			Bcl2 ↓; Bax ↑; caspase 3 ↑; p53 ↑; VEGF ↓	[44,45]
			S and G ₂ /M phase cell cycle arrest	[16]
TFD	Fish (<i>Gadus</i> sp.)		VEGFR1 ↓; MUC1 ↓	[94]
YALPAH	Fish (<i>Setipinna taty</i>)	Peptide	↓ cancer cell growth	[105]
YALRAH				
YALPAR				
YALPAG				
ILYMP	Clam (<i>Cyclina sinensis</i>)	Pentapeptide		[20]
SCH-P9 and SCH-P10	Clam (<i>Sinonovacula constricta</i>)	Tetrapeptide	Bcl2 ↓; Bax ↑; caspase 3, 9 ↑; cyt c release ↑	[18]
AAP-H	Sea anemone (<i>Anthopleura anjunae</i>)	Oligopeptide		[21]
Tachyplesin	Horseshoe crab (<i>Tachypleus tridentatus</i>)	Cyclic peptide	caspase 3, 6, 7, 8, 9 ↑; cyt c release ↑	[50]

3. Clinical Trial Status

Several marine peptides with potential PCa efficacy are presently undergoing clinical trials. Soblidotin (TZT-1027) has shown efficacy in DU145 cell lines and has entered a phase I clinical trial (Table 2). It was designed to maintain significant anticancer activity while lowering the toxicity of the parent medication, dolastatin 10 [110–112]. Tasi-dotin/synthadotin (ILX651), a dolastatin 15 derivative is in Phase II clinical trial for hormone refractory PCa [113].

Didemnin B displays anti-PCa activity, and has progressed into phase II studies. Due to its high toxicity, low solubility, and short life span, clinical studies were halted favouring second generation dehydrodidemnine B, (aplidin or plitidepsin). Dehydrodidemnine B is in phase III clinical trials [10,32,114].

In phase I study, Kahalalide F was effective against PCa, with a favorable safety profile [115]. It was withdrawn from phase II due to lack of efficacy, short half-life, restricted range of activity, and poor patient response. However, given this compound's potent cytotoxicity, it has facilitated the development of synthetic analogues to overcome its limitations by increasing its potency and half-life [63,116]. Elisidepsin (Irvalec®), one of PharmaMar's most powerful Kahalalide F analogues, has progressed to phase II clinical trial due to its superior efficacy and nontoxic profile [117]. The preclinical studies (in vivo, in vitro) are separated according to xenograft's approach and listed in Table 3.

Table 2. Marine peptides as anticancer agents in clinical trials.

Cell lines/ (Peptides)	Phase	Clinical Trials.Gov Identifier	References
DU145 (Soblidotin)	Phase I	NCT00072228	[22,110,111]
Dolastatin 10	Phase II	NCT00003626	[23,110]
Tasidotin/synthadotin (ILX651)	Phase II	NCT00082134	[24,113]
Dehydrodidemnine B	Phase III	NCT00780975	[10,25,32]
Kahalalide F	Phase I	NCT00106418	[39,115]
Elisidepsin (Irvalec®)	Phase II	NCT00884845	[48,117]

Table 3. Marine peptides as anticancer agents in pre-clinical trials.

In Vitro		In Vivo		References
Human Prostate Cancer Cell Lines	IC ₅₀	Experimental Model	Dose	
DU145 and PC-3 Aurilide B	<10 nM	—	—	[22]
PC-3 Lagunamide C	2.6 nM	—	—	[23]
DU145 and LNCaP Cryptophycin-52	1–10 pM	—	—	[24]
DU145 and PC-3 Coibamide A	300 ng mL ^{−1}	—	—	[10,25,32]
PC-3 Laxaphycin B	0.58 µM	—	—	[39]
LNCaP C-phycocyanin	500 µg mL ^{−1}	—	—	[48]
DU145 and PC-3 Bisbromoamide	GI50:40 nM	—	—	[106]
DU145 Jaspamide	0.8 µM	DU-145 xenograft	10 mg/kg s.c.	[28]
LNCaP Jaspamide	0.07 µM	—	—	
PC-3 Jaspamide	0.3 µM	—	—	
TSU-Pr1 Jaspamide	170 nM	—	—	[29]
PC-3 Homophymines A–E	A:4.2, B:6.2, C:3.0, D:6.3, E:3.9 nM	—	—	[27]
LNCaP Neamphamides B–D	B:230, C:190, D:110 nM	—	—	[30]
PC-3 Geodiamolides D–F	B: 170, C:110, D:130 nM	—	—	
	D:33.1, E:118, F:155 nM	—	—	[26]
DU145 Rolloamide A	0.85 µM	—	—	[36]
LNCaP Rolloamide A	0.8 µM	—	—	
PC-3 Rolloamide A	1.4 µM	—	—	
PC3MM2 Rolloamide A	4.7 µM	—	—	

Table 3. Cont.

In Vitro		In Vivo		References
Human Prostate Cancer Cell Lines	IC ₅₀	Experimental Model	Dose	
LNCaP, C4-2, PC-3, PC-3dR, HTI-286	0.65–4.6 nM	PC-3 and PC-3dR xenografts	1.5 mg/kg i.v.	[14]
—	—	PC3-MM2 xenograft	1.0 mg/kg i.v.	[107]
PC-3 Kahalalide F	0.07 µM	—	—	[31]
DU145 and LNCaP	0.28 µM	—	—	
—	—	PC-3 and DU145 xenografts	123 µg/kg i.v.	[108]
PC-3 Elisidepsin	1.80 µM	—	—	[56]
DU145	1.26 µM	—	—	
DU145 Dolastatin 10	0.5 nM	DU145 xenograft	5 µg q4d i.p.	[19]
PC-3 MCH	LC50: 0.94 mg mL ^{−1}	—	—	[43]
DU145 Tamandarin A	GI ₅₀ : 12.5 µg	—	—	[109]
	1.36 ng mL ^{−1}	—	—	[32]
PC-3 Tamandarin B	1.4 µM	—	—	[33]
DU145 and PC-3 Patellamide B Patellamide F	LC ₅₀ : 48 µM	—	—	[38]
	LC ₅₀ : 13 µM	—	—	
	LC50: 3 µM	—	—	
DU145 Trunkamide A	7.08 nM	—	—	[12,37]
PC-3	2.3 nM	—	—	[64]
Diazonamide A	2.43 nmol L ^{−1}	PC-3 xenograft	1.6 mg/kg i.v.	
DU145 Chromopeptide A	2.08 nmol L ^{−1}	—	—	[51]
LNCaP Chromopeptide A	1.75 nmol L ^{−1}	—	—	
PC-3 Sansalvamide A	27.4 µg mL ^{−1}	—	—	[34]
DU145 and PC-3 Microsporin A	2.7 µM	—	—	[17]
Zygosporamide	GI ₅₀ : 9.1 µM	—	—	[35]
PC-3 SHP	15 mg mL ^{−1}	—	—	[15]
DU145	1 mg mL ^{−1}	—	—	[44,45]
DU145 and PC-3 SIO	15 mg mL ^{−1}	—	—	[16]

Table 3. Cont.

In Vitro		In Vivo		References
Human Prostate Cancer Cell Lines	IC ₅₀	Experimental Model	Dose	
PC-3 TFD, YALRAH, YALPAH, YALPAG, YALPAR	3.5 nM	—	—	[94]
	GI50:16.9 μ M	—	—	[105]
	GI50:11.1 μ M	—	—	
	GI50:19.0 μ M	—	—	
	GI50:71.2 μ M	—	—	
DU145, ILYMP, SCH-P9 and SCH-P10	11.25 mM	—	—	[20]
	SCH-P9:1.21, SCH-P10: 1.41 mg mL ^{−1}	—	—	[18]
PC-3	SCH-P9:1.09, SCH-P10: 0.91 mg mL ^{−1}	—	—	
DU145, AAP-H	2.298 mM	—	—	[21]
TSU, Tachyplesin	75 μ g mL ^{−1}	—	—	[50]

4. Conclusions and Future Perspectives

Worldwide, PCa is a major cause of cancer-related mortality in men. While its frequency has increased, present therapy options are limited and have adverse effects, with relapses often occurring, highlighting the need for novel cancer treatments.

Information is scant on the use of marine peptides to treat this malignancy [5,6,118]. Marine peptides have been shown to have multiple anticancer effects. To date, most of the research has focused on the effects of marine peptides in vitro, making it difficult to extrapolate their in vivo efficacy. Only a few of these drugs have advanced to clinical trials. Although individual pharmacologically active marine peptides have been excluded from further drug discovery due to toxicity, there is a push to assess corresponding analogues for their efficacy. Substitution with D-amino acids, cyclization, pegylation, nanoparticles encapsulation, and XTEN conjugation can be used to overcome short half-life and metabolic instability. Namely, immunogenicity has been reduced by D-amino acid substitution [11,119–121]. Protein hydrolysates represent a rich source of antiproliferative, anticancer, and antioxidant compounds. Additional studies on the cell cycle phase arrest and increased apoptotic rates by these analogues are required to determine the pharmacological efficacies of protein hydrolysates.

The marine world offers a diversity of potential novel anticancer medications. However, there are several serious drawbacks to marine peptides, such as their stability in vivo. They are extremely vulnerable to cleavage by serum proteases in vivo, have a brief half-life, do have poor bioavailability, and provide manufacturing and production issues. The development of marine pharmaceuticals would benefit by interdisciplinary collaborations to overcome existing constraints. These innovative findings must be quickly translated into treatments for prostate cancers. Additionally, whether employed alone or in combination with a number of other chemotherapy agents, marine medicines and comparable generic compounds may provide insights into prospective clinical anticancer therapeutics. Additionally, to find out new concepts in the discovery of marine natural products in the future, analytical methods should be combined to the use of computational genetics, gene mining, experimental therapies, and other ground-breaking techniques.

Finally, further research into marine peptides and their mechanisms of action will be needed, resulting in an invaluable source of novel and potent new medications for the treatment of prostate cancer, and a better understanding of their mechanisms of action and

their putative target sites. Taking into account the already available clinical trials' data, the upcoming studies might utilize them for further clinical trials.

Author Contributions: S.A., W.A. and K.F.A. have written the initial draft of the article. P.J. and M.A. revised and added valuable inputs. L.S. and H.K. designed and supervised the overall study. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)] [[PubMed](#)]
2. Rebello, R.J.; Oing, C.; Knudsen, K.E.; Loeb, S.; Johnson, D.C.; Reiter, R.E.; Gillissen, S.; Van der Kwast, T.; Bristow, R.G. Prostate cancer. *Nat. Rev. Dis. Primers* **2021**, *7*, 9. [[CrossRef](#)] [[PubMed](#)]
3. Rawla, P. Epidemiology of Prostate Cancer. *World J. Oncol.* **2019**, *10*, 63–89. [[CrossRef](#)] [[PubMed](#)]
4. Mokbel, K.; Wazir, U.; Mokbel, K. Chemoprevention of Prostate Cancer by Natural Agents: Evidence from Molecular and Epidemiological Studies. *Anticancer. Res.* **2019**, *39*, 5231. [[CrossRef](#)]
5. Fontana, F.; Raimondi, M.; Marzagalli, M.; Di Domizio, A.; Limonta, P. Natural Compounds in Prostate Cancer Prevention and Treatment: Mechanisms of Action and Molecular Targets. *Cells* **2020**, *9*, 460. [[CrossRef](#)]
6. Alves, C.; Diederich, M. Marine Natural Products as Anticancer Agents. *Mar. Drugs* **2021**, *19*, 447. [[CrossRef](#)]
7. Barreca, M.; Spanò, V.; Montalbano, A.; Cueto, M.; Marrero, A.R.D.; Deniz, I.; Erdoğan, A.; Bilela, L.L.; Moulin, C.; Taffin-De-Givenchy, E.; et al. Marine Anticancer Agents: An Overview with a Particular Focus on Their Chemical Classes. *Mar. Drugs* **2020**, *18*, 619. [[CrossRef](#)]
8. Ahmed, S.; Mirzaei, H.; Aschner, M.; Khan, A.; Al-Harrasi, A.; Khan, H. Marine peptides in breast cancer: Therapeutic and mechanistic understanding. *Biomed. Pharmacother.* **2021**, *142*, 112038. [[CrossRef](#)]
9. Ahmed, S.; Hasan, M.M.; Aschner, M.; Mirzaei, H.; Alam, W.; Shah, S.M.M.; Khan, H. Therapeutic potential of marine peptides in glioblastoma: Mechanistic insights. *Cell. Signal.* **2021**, *87*, 110142. [[CrossRef](#)]
10. Kang, H.K.; Choi, M.-C.; Seo, C.H.; Park, Y. Therapeutic Properties and Biological Benefits of Marine-Derived Anticancer Peptides. *Int. J. Mol. Sci.* **2018**, *19*, 919. [[CrossRef](#)]
11. Chiangjong, W.; Chutipongtanate, S.; Hongeng, S. Anticancer peptide: Physicochemical property, functional aspect and trend in clinical application (Review). *Int. J. Oncol.* **2020**, *57*, 678–696. [[CrossRef](#)] [[PubMed](#)]
12. Zhang, Q.-T.; Liu, Z.-D.; Wang, Z.; Wang, T.; Wang, N.; Wang, N.; Zhang, B.; Zhao, Y.-F. Recent Advances in Small Peptides of Marine Origin in Cancer Therapy. *Mar. Drugs* **2021**, *19*, 115. [[CrossRef](#)] [[PubMed](#)]
13. Ucak, I.; Afreen, M.; Montesano, D.; Carrillo, C.; Tomasevic, I.; Simal-Gandara, J.; Barba, F. Functional and Bioactive Properties of Peptides Derived from Marine Side Streams. *Mar. Drugs* **2021**, *19*, 71. [[CrossRef](#)]
14. Hadaschik, B.; Ettinger, S.; Sowery, R.D.; Zoubeydi, A.; Andersen, R.J.; Roberge, M.; Gleave, M.E. Targeting prostate cancer with HTI-286, a synthetic analog of the marine sponge product hemiasterlin. *Int. J. Cancer* **2008**, *122*, 2368–2376. [[CrossRef](#)]
15. Huang, F.; Jing, Y.; Ding, G.; Yang, Z. Isolation and purification of novel peptides derived from Sepia ink: Effects on apoptosis of prostate cancer cell PC-3. *Mol. Med. Rep.* **2017**, *16*, 4222–4228. [[CrossRef](#)] [[PubMed](#)]
16. Huang, F.; Yang, Z.; Yu, D.; Wang, J.; Li, R.; Ding, G. Sepia ink oligopeptide induces apoptosis in prostate cancer cell lines via caspase-3 activation and elevation of Bax/Bcl-2 ratio. *Mar. Drugs* **2012**, *10*, 2153–2165. [[CrossRef](#)] [[PubMed](#)]
17. Gu, W.; Cueto, M.; Jensen, P.R.; Fenical, W.; Silverman, R.B. Microsporins A and B: New histone deacetylase inhibitors from the marine-derived fungus *Microsporium cf. gypseum* and the solid-phase synthesis of microsporin A. *Tetrahedron* **2007**, *63*, 6535–6541. [[CrossRef](#)]
18. Huang, F.; Ding, G.; Yang, Z.; Yu, F. Two novel peptides derived from *Sinonovacula constricta* inhibit the proliferation and induce apoptosis of human prostate cancer cells. *Mol. Med. Rep.* **2017**, *16*, 6697–6707. [[CrossRef](#)]
19. Turner, T.; Jackson, W.H.; Pettit, G.R.; Wells, A.; Kraft, A.S. Treatment of human prostate cancer cells with dolastatin 10, a peptide isolated from a marine shell-less mollusc. *Prostate* **1998**, *34*, 175–181. [[CrossRef](#)]
20. Yu, F.; Zhang, Y.; Ye, L.; Tang, Y.; Ding, G.; Zhang, X.; Yang, Z. A novel anti-proliferative pentapeptide (ILYMP) isolated from *Cyclina sinensis* protein hydrolysate induces apoptosis of DU-145 prostate cancer cells. *Mol. Med. Rep.* **2018**, *18*, 771–778.
21. Wu, Z.-Z.; Ding, G.F.; Huang, F.F.; Yang, Z.S.; Yu, F.M.; Tang, Y.P.; Jia, Y.L.; Zheng, Y.Y.; Chen, R. Anticancer Activity of *Anthopleura anjunae* Oligopeptides in Prostate Cancer DU-145 Cells. *Mar. Drugs* **2018**, *16*, 125. [[CrossRef](#)] [[PubMed](#)]
22. Han, B.; Gross, H.; Goeger, D.E.; Mooberry, S.L.; Gerwick, W.H. Aurilides B and C, Cancer Cell Toxins from a Papua New Guinea Collection of the Marine Cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2006**, *69*, 572–575. [[CrossRef](#)] [[PubMed](#)]
23. Tripathi, A.; Puddick, J.; Prinsep, M.R.; Rottmann, M.; Chan, K.P.; Chen, D.Y.K.; Tan, L.T. Lagunamide C, a cytotoxic cyclodepsipeptide from the marine cyanobacterium *Lyngbya majuscula*. *Phytochemistry* **2011**, *72*, 2369–2375. [[CrossRef](#)]
24. Drew, L.; Fine, R.L.; Do, T.N.; Douglas, G.P.; Petrylak, D.P. The Novel Antimicrotubule Agent Cryptophycin 52 (LY355703) Induces Apoptosis via Multiple Pathways in Human Prostate Cancer Cells. *Clin. Cancer Res.* **2002**, *8*, 3922. [[PubMed](#)]

25. Medina, R.A.; Goeger, D.E.; Hills, P.; Mooberry, S.L.; Huang, N.; Romero, L.I.; Ortega-Barría, E.; Gerwick, W.H.; McPhail, K.L. Coibamide A, a potent antiproliferative cyclic depsipeptide from the Panamanian marine cyanobacterium *Leptolyngbya* sp. *J. Am. Chem. Soc.* **2008**, *130*, 6324–6325. [[CrossRef](#)] [[PubMed](#)]
26. Tran, T.D.; Pham, N.B.; Fechner, G.A.; Hooper, J.N.A.; Quinn, R.J. Potent cytotoxic peptides from the Australian marine sponge *Pipestela candelabra*. *Mar. Drugs* **2014**, *12*, 3399–3415. [[CrossRef](#)] [[PubMed](#)]
27. Zampella, A.; Sepe, V.; Bellotta, F.; Luciano, P.; D’Auria, M.V.; Cresteil, T.; Debitus, C.; Petek, S.; Poupat, C.; Ahond, A. Homophymines B–E and A1–E1, a family of bioactive cyclodepsipeptides from the sponge *Homophymia* sp. *Org. Biomol. Chem.* **2009**, *7*, 4037–4044. [[CrossRef](#)]
28. Takeuchi, H.; Ara, G.; Sausville, E.A.; Teicher, B. Jaspilakinolide: Interaction with radiation and hyperthermia in human prostate carcinoma and Lewis lung carcinoma. *Cancer Chemother. Pharmacol.* **1998**, *42*, 491–496. [[CrossRef](#)]
29. Senderowicz, A.M.J.; Pham, N.B.; Fechner, G.; Zencak, D.; Vu, H.T.; Hooper, J.N.; Quinn, R.J. Jaspilakinolide’s Inhibition of the Growth of Prostate Carcinoma Cells In Vitro with Disruption of the Actin Cytoskeleton. *J. Natl. Cancer Inst.* **1995**, *87*, 46–51. [[CrossRef](#)]
30. Tran, T.D.; Pham, N.B.; Fechner, G.; Zencak, D.; Vu, H.T.; Hooper, J.N.; Quinn, R.J. Cytotoxic Cyclic Depsipeptides from the Australian Marine Sponge *Neamphius huxleyi*. *J. Nat. Prod.* **2012**, *75*, 2200–2208. [[CrossRef](#)]
31. Suárez, Y.; González, L.; Cuadrado, A.; Berciano, M.; Lafarga, M.; Muñoz, A. Kahalalide F, a new marine-derived compound, induces oncosis in human prostate and breast cancer cells. *Mol. Cancer Ther.* **2003**, *2*, 863. [[PubMed](#)]
32. Vervoort, H.; Fenical, W.; Epifanio, R.D.A. Tamandarins A and B: New Cytotoxic Depsipeptides from a Brazilian Ascidian of the Family Didemnidae. *J. Org. Chem.* **2000**, *65*, 782–792. [[CrossRef](#)] [[PubMed](#)]
33. Liang, B.; Richard, D.J.; Portonovo, P.S.; Joullie, M.M. Total Syntheses and Biological Investigations of Tamandarins A and B and Tamandin A Analogs. *J. Am. Chem. Soc.* **2001**, *123*, 4469–4474. [[CrossRef](#)] [[PubMed](#)]
34. Liu, S.; Gu, W.; Lo, D.; Ding, X.-Z.; Ujiki, M.; Adrian, T.E.; Soff, G.A.; Silverman, R.B. N-Methylsalsalvamide A Peptide Analogues. Potent New Antitumor Agents. *J. Med. Chem.* **2005**, *48*, 3630–3638. [[CrossRef](#)]
35. Oh, D.-C.; Jensen, P.R.; Fenical, W. Zygosporamide, a cytotoxic cyclic depsipeptide from the marine-derived fungus *Zygosporium masonii*. *Tetrahedron Lett.* **2006**, *47*, 8625–8628. [[CrossRef](#)]
36. Williams, D.E.; Yu, K.; Behrisch, H.W.; Van Soest, R.; Andersen, R.J. Rolloamides A and B, Cytotoxic Cyclic Heptapeptides Isolated from the Caribbean Marine Sponge *Eurypon laughlini*. *J. Nat. Prod.* **2009**, *72*, 1253–1257. [[CrossRef](#)]
37. McKeever, B.; Pattenden, G. Total synthesis of trunkamide A, a novel thiazoline-based prenylated cyclopeptide metabolite from *Lissoclinum* sp. *Tetrahedron* **2003**, *59*, 2713–2727. [[CrossRef](#)]
38. Rashid, M.A.; Gustafson, K.R.; Li, J.H.C.; Boyd, M.R. Patellamide F, a New Cytotoxic Cyclic Peptide from the Colonial Ascidian *Lissoclinum patella*. *J. Nat. Prod.* **1995**, *58*, 594–597. [[CrossRef](#)]
39. Bonnard, I.; Rolland, M.; Salmon, J.-M.; Debiton, E.; Barthomeuf, C.; Banaigs, B. Total Structure and Inhibition of Tumor Cell Proliferation of Laxaphycins. *J. Med. Chem.* **2007**, *50*, 1266–1279. [[CrossRef](#)]
40. Rabiei, S.; Rezaei, M.; Asgharzade, S.; Nikoo, M.; Rafieia-Kopai, M. Antioxidant and cytotoxic properties of protein hydrolysates obtained from enzymatic hydrolysis of Klunzinger’s mullet (*Liza klunzingeri*) muscle. *Braz. J. Pharm. Sci.* **2019**, *55*, e18304. [[CrossRef](#)]
41. Da Rocha, M.; Alemán, A.; Bacca, G.C.; López-Caballero, M.E.; Gómez-Guillén, C.; Montero, P.; Prentice, C. Anti-Inflammatory, Antioxidant, and Antimicrobial Effects of Underutilized Fish Protein Hydrolysate. *J. Aquat. Food Prod. Technol.* **2018**, *27*, 592–608. [[CrossRef](#)]
42. Shaik, M.I.; Sarbon, N.M. A review on purification and characterization of anti-proliferative peptides derived from fish protein hydrolysate. *Food Rev. Int.* **2020**, *38*, 1389–1409. [[CrossRef](#)]
43. Eun-Kyung, K.; Joung, H.J.; Kim, Y.S.; Hwang, J.W.; Ahn, C.B.; Jeon, Y.J.; Moon, S.H.; Park, P.J. Purification of a Novel Anticancer Peptide from Enzymatic Hydrolysate of *Mytilus coruscus*. *J. Microbiol. Biotechnol.* **2012**, *22*, 1381–1387.
44. Ding, G.-F.; Huang, F.F.; Yang, Z.-S.; Yu, D.; Yang, Y.F. Anticancer Activity of an Oligopeptide Isolated from Hydrolysates of Sepia Ink. *Chin. J. Nat. Med.* **2011**, *9*, 151–155.
45. Jing, Y.; Yang, Z.; Huang, F. Mechanism of Sepia ink polypeptide-induced apoptosis in DU-145 prostate cancer cells. *Mod. Food Sci. Technol.* **2014**, *30*, 1–6.
46. Khalifa, S.A.M.; Elias, N.; Farag, M.A.; Chen, L.; Saeed, A.; Hegazy, M.-E.F.; Moustafa, M.S.; El-Wahed, A.A.; Al-Mousawi, S.M.; Musharraf, S.G.; et al. Marine natural products: A source of novel anticancer drugs. *Mar. Drugs* **2019**, *17*, 491. [[CrossRef](#)]
47. Pfeffer, C.M.; Singh, A.T. Apoptosis: A target for anticancer therapy. *Int. J. Mol. Sci.* **2018**, *19*, 448. [[CrossRef](#)]
48. Gantar, M.; Dhandayuthapani, S.; Rathinavelu, A. Phycocyanin Induces Apoptosis and Enhances the Effect of Topotecan on Prostate Cell Line LNCaP. *J. Med. Food* **2012**, *15*, 1091–1095. [[CrossRef](#)]
49. Parrish, A.B.; Freil, C.D.; Kornbluth, S. Cellular mechanisms controlling caspase activation and function. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a008672. [[CrossRef](#)]
50. Chen, Y.; Xu, X.; Hong, S.; Chen, J.; Liu, N.; Underhill, C.B.; Creswell, K.; Zhang, L. RGD-Tachyplesin Inhibits Tumor Growth. *Cancer Res.* **2001**, *61*, 2434.
51. Sun, J.-Y.; Wang, J.-D.; Wang, X.; Liu, H.-C.; Zhang, M.-M.; Liu, Y.-C.; Zhang, C.-H.; Su, Y.; Shen, Y.-Y.; Guo, Y.-W.; et al. Marine-derived chromopeptide A, a novel class I HDAC inhibitor, suppresses human prostate cancer cell proliferation and migration. *Acta Pharmacol. Sin.* **2017**, *38*, 551–560. [[CrossRef](#)] [[PubMed](#)]
52. Campbell, K.J.; Tait, S.W. Targeting BCL-2 regulated apoptosis in cancer. *Open Biol.* **2018**, *8*, 180002. [[CrossRef](#)] [[PubMed](#)]
53. Jeong, S.-J.; Dasgupta, A.; Jung, K.-J.; Um, J.-H.; Burke, A.; Park, H.U.; Brady, J.N. PI3K/AKT inhibition induces caspase-dependent apoptosis in HTLV-1-transformed cells. *Virology* **2008**, *370*, 264–272. [[CrossRef](#)] [[PubMed](#)]

54. Lee, H.; Chin, H.; Kim, K.; Lee, D. ERBB3 knockdown induces cell cycle arrest and activation of Bak and Bax-dependent apoptosis in colon cancer cells. *Oncotarget* **2014**, *5*, 5138–5152. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Janmaat, M.L.; Rodriguez, J.A.; Jimeno, J.; Kruyt, F.A.E.; Giaccone, G. Kahalalide F Induces Necrosis-Like Cell Death that Involves Depletion of ErbB3 and Inhibition of Akt Signaling. *Mol. Pharmacol.* **2005**, *68*, 502. [\[CrossRef\]](#)
56. Serova, M.; de Gramont, A.; Bieche, I.; Riveiro, M.E.; Galmarini, C.M.; Aracil, M.; Jimeno, J.; Faivre, S.; Raymond, E. Predictive factors of sensitivity to elisidepsin, a novel Kahalalide F-derived marine compound. *Mar. Drugs* **2013**, *11*, 944–959. [\[CrossRef\]](#)
57. Wang, E.; Sorolla, M.A.; Krishnan, P.D.G.; Sorolla, A. From Seabed to Bedside: A Review on Promising Marine Anticancer Compounds. *Biomolecules* **2020**, *10*, 248. [\[CrossRef\]](#)
58. Molina-Guijarro, J.M.; Macías, Á.; García, C.; Muñoz, E.; García-Fernandez, L.F.; David, M.; Núñez, L.; Martínez-Leal, J.F.; Moneo, V.; Cuevas, C.; et al. Irvalec inserts into the plasma membrane causing rapid loss of integrity and necrotic cell death in tumor cells. *PLoS ONE* **2011**, *6*, e19042. [\[CrossRef\]](#)
59. Yue, J.; López, J.M. Understanding MAPK Signaling Pathways in Apoptosis. *Int. J. Mol. Sci.* **2020**, *21*, 2346. [\[CrossRef\]](#)
60. Canovas, B.; Nebreda, A.R. Diversity and versatility of p38 kinase signalling in health and disease. *Nat. Rev. Mol. Cell Biol.* **2021**, *22*, 346–366. [\[CrossRef\]](#)
61. van Vuuren, R.J.; Visagie, M.H.; Theron, A.E.; Joubert, A.M. Antimitotic drugs in the treatment of cancer. *Cancer Chemother. Pharmacol.* **2015**, *76*, 1101–1112. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Fanale, D.; Bronte, G.; Passiglia, F.; Calò, V.; Castiglia, C.; Di Piazza, F.; Barraco, N.; Cangemi, A.; Catarella, M.T.; Insalaco, L.; et al. Stabilizing versus destabilizing the microtubules: A double-edge sword for an effective cancer treatment option? *Anal. Cell. Pathol.* **2015**, *2015*, 690916. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Alves, C.; Silva, J.; Pinteus, S.; Gaspar, H.; Alpoim, M.C.; Botana, L.M.; Pedrosa, R. From Marine Origin to Therapeutics: The Antitumor Potential of Marine Algae-Derived Compounds. *Front. Pharmacol.* **2018**, *9*, 777. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Cruz-Monserrate, Z.; Vervoort, H.C.; Bai, R.; Newman, D.J.; Howell, S.B.; Los, G.; Mullaney, J.T.; Williams, M.D.; Pettit, G.R.; Fenical, W.; et al. Diazonamide A and a Synthetic Structural Analog: Disruptive Effects on Mitosis and Cellular Microtubules and Analysis of Their Interactions with Tubulin. *Mol. Pharmacol.* **2003**, *63*, 1273. [\[CrossRef\]](#)
65. Welch, D.R.; Hurst, D.R. Defining the Hallmarks of Metastasis. *Cancer Res.* **2019**, *79*, 3011. [\[CrossRef\]](#)
66. Lambert, A.W.; Pattabiraman, D.R.; Weinberg, R.A. Emerging Biological Principles of Metastasis. *Cell* **2017**, *168*, 670–691. [\[CrossRef\]](#)
67. Hockla, A.; Miller, E.; Salameh, M.D.A.; Copland, J.A.; Radisky, D.C.; Radisky, E.S. PRSS3/mesotrypsin is a therapeutic target for metastatic prostate cancer. *Mol. Cancer Res.* **2012**, *10*, 1555–1566. [\[CrossRef\]](#)
68. Wei, X.; Zeng, W.; Xie, K.; Diao, P.; Tang, P. Potential use of chymotrypsin-like proteasomal activity as a biomarker for prostate cancer. *Oncol. Lett.* **2018**, *15*, 5149–5154. [\[CrossRef\]](#)
69. Lerman, I. *Neutrophil Elastase and SERPINB1 Are Critical Regulators of Prostate Cancer Progression*; University of Rochester: Ann Arbor, MI, USA, 2018; p. 159.
70. Linington, R.G.; Edwards, D.J.; Shuman, C.F.; McPhail, K.L.; Matainaho, T.; Gerwick, W.H. Symplocamide A, a potent cytotoxin and chymotrypsin inhibitor from the marine Cyanobacterium *Symploca* sp. *J. Nat. Prod.* **2008**, *71*, 22–27. [\[CrossRef\]](#)
71. Taori, K.; Paul, V.J.; Luesch, H. Kempopeptins A and B, Serine Protease Inhibitors with Different Selectivity Profiles from a Marine Cyanobacterium, *Lyngbya* sp. *J. Nat. Prod.* **2008**, *71*, 1625–1629. [\[CrossRef\]](#)
72. Rubio, B.K.; Parrish, S.M.; Yoshida, W.; Schupp, P.J.; Schils, T.; Williams, P.G. Depsipeptides from a Guamanian marine cyanobacterium, *Lyngbyabouillonii*, with selective inhibition of serine proteases. *Tetrahedron Lett.* **2010**, *51*, 6718–6721. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Gunasekera, S.P.; Miller, M.W.; Kwan, J.C.; Luesch, H.; Paul, V.J. Molassamide, a Depsipeptide Serine Protease Inhibitor from the Marine Cyanobacterium *Dichothrixutahensis*. *J. Nat. Prod.* **2010**, *73*, 459–462. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Matthew, S.; Paul, V.J.; Luesch, H. Largamides A–C, tiglic acid-containing cyclodepsipeptides with elastase-inhibitory activity from the marine cyanobacterium *Lyngbya confervoides*. *Planta Med.* **2009**, *75*, 528–533. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Plaza, A.; Bewley, C.A. Largamides A–H, Unusual Cyclic Peptides from the Marine Cyanobacterium *Oscillatoria* sp. *J. Org. Chem.* **2006**, *71*, 6898–6907. [\[CrossRef\]](#)
76. Matthew, S.; Ross, C.; Rocca, J.R.; Paul, V.J.; Luesch, H. Pompanopeptins A and B, new cyclic peptides from the marine cyanobacterium *Lyngbyaconfervoides*. *Tetrahedron* **2008**, *64*, 4081–4089. [\[CrossRef\]](#)
77. Matthew, S.; Ross, C.; Rocca, J.R.; Paul, V.J.; Luesch, H. Lyngbyastatin 4, a Dolastatin 13 Analogue with Elastase and Chymotrypsin Inhibitory Activity from the Marine Cyanobacterium *Lyngbyaconfervoides*. *J. Nat. Prod.* **2007**, *70*, 124–127. [\[CrossRef\]](#)
78. Taori, K.; Matthew, S.; Rocca, J.R.; Paul, V.J.; Luesch, H. Lyngbyastatins 5–7, Potent Elastase Inhibitors from Floridian Marine Cyanobacteria, *Lyngbya* sp. *J. Nat. Prod.* **2007**, *70*, 1593–1600. [\[CrossRef\]](#)
79. Kwan, J.C.; Taori, K.; Paul, V.J.; Luesch, H. Lyngbyastatins 8–10, elastase inhibitors with cyclic depsipeptide scaffolds isolated from the marine cyanobacterium *Lyngbyasemiplena*. *Mar. Drugs* **2009**, *7*, 528–538. [\[CrossRef\]](#)
80. Matthew, S.; Paul, V.J.; Luesch, H. Tiglicamides A–C, cyclodepsipeptides from the marine cyanobacterium *Lyngbyaconfervoides*. *Phytochemistry* **2009**, *70*, 2058–2063. [\[CrossRef\]](#)
81. Luesch, H.; Pangilinan, R.; Yoshida, W.Y.; Moore, R.E.; Paul, V.J. Pitipeptolides A and B, New Cyclodepsipeptides from the Marine Cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2001**, *64*, 304–307. [\[CrossRef\]](#)
82. Pruitt, F.L.; He, Y.; Franco, O.E.; Jiang, M.; Cates, J.; Hayward, S.W. Cathepsin D acts as an essential mediator to promote malignancy of benign prostatic epithelium. *Prostate* **2013**, *73*, 476–488. [\[CrossRef\]](#)

83. Eatemadi, A.; Aiyelabegan, H.T.; Negahdari, B.; Mazlomi, M.A.; Daraee, H.; Daraee, N.; Eatemadi, R.; Sadroddiny, E. Role of protease and protease inhibitors in cancer pathogenesis and treatment. *Biomed. Pharmacother.* **2017**, *86*, 221–231. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Kwan, J.C.; Eksioglu, E.A.; Liu, C.; Paul, V.J.; Luesch, H. Grassystatins A–C from Marine Cyanobacteria, Potent Cathepsin E Inhibitors That Reduce Antigen Presentation. *J. Med. Chem.* **2009**, *52*, 5732–5747. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Jiang, X.; Qin, Y.; Kun, L.; Zhou, Y. The Significant Role of the Microfilament System in Tumors. *Front. Oncol.* **2021**, *11*, 620390. [\[CrossRef\]](#)
86. Yildirim, S.; Altun, S.; Gumushan, H.; Patel, A.; Djamgoz, M.B. Voltage-gated sodium channel activity promotes prostate cancer metastasis in vivo. *Cancer Lett.* **2012**, *323*, 58–61. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Angus, M.; Ruben, P. Voltage gated sodium channels in cancer and their potential mechanisms of action. *Channels* **2019**, *13*, 400–409. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Mao, W.; Zhang, J.; Körner, H.; Jiang, Y.; Ying, S. The Emerging Role of Voltage-Gated Sodium Channels in Tumor Biology. *Front. Oncol.* **2019**, *9*, 124. [\[CrossRef\]](#) [\[PubMed\]](#)
89. De Oliveira, E.O.; Graf, K.M.; Patel, M.K.; Baheti, A.; Kong, H.-S.; MacArthur, L.H.; Dakshanamurthy, S.; Wang, K.; Brown, M.L.; Paige, M. Synthesis and evaluation of hermitamides A and B as human voltage-gated sodium channel blockers. *Bioorganic Med. Chem.* **2011**, *19*, 4322–4329. [\[CrossRef\]](#)
90. Taniguchi, M.; Nunnery, J.K.; Engene, N.; Esquenazi, E.; Byrum, T.; Dorrestein, P.C.; Gerwick, W.H. Palmyramide A, a Cyclic Depsipeptide from a Palmyra Atoll Collection of the Marine Cyanobacterium *Lyngbya majuscula*. *J. Nat. Prod.* **2010**, *73*, 393–398. [\[CrossRef\]](#)
91. Shibuya, M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes Cancer* **2011**, *2*, 1097–1105. [\[CrossRef\]](#)
92. Ceci, C.; Atzori, M.G.; Lacal, P.M.; Graziani, G. Role of VEGFs/VEGFR-1 Signaling and its Inhibition in Modulating Tumor Invasion: Experimental Evidence in Different Metastatic Cancer Models. *Int. J. Mol. Sci.* **2020**, *21*, 1388. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Khodabakhsh, F.; Merikhian, P.; Eisavand, M.R.; Farahmand, L. Crosstalk between MUC1 and VEGF in angiogenesis and metastasis: A review highlighting roles of the MUC1 with an emphasis on metastatic and angiogenic signaling. *Cancer Cell Int.* **2021**, *21*, 200. [\[CrossRef\]](#)
94. Guha, P.; Kaptan, E.; Bandyopadhyaya, G.; Kaczanowska, S.; Davila, E.; Thompson, K.; Martin, S.S.; Kalvakolanu, D.V.; Vasta, G.R.; Ahmed, H. Cod glycopeptide with picomolar affinity to galectin-3 suppresses T-cell apoptosis and prostate cancer metastasis. *Proc. Natl. Acad. Sci.* **2013**, *110*, 5052–5057. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Visconti, R.; Della Monica, R.; Grieco, D. Cell cycle checkpoint in cancer: A therapeutically targetable double-edged sword. *J. Exp. Clin. Cancer Res.* **2016**, *35*, 153. [\[CrossRef\]](#)
96. Liu, K.; Zheng, M.; Lu, R.; Du, J.; Zhao, Q.; Li, Z.; Li, Y.; Zhang, S. The role of CDC25C in cell cycle regulation and clinical cancer therapy: A systematic review. *Cancer Cell Int.* **2020**, *20*, 213. [\[CrossRef\]](#) [\[PubMed\]](#)
97. Ozen, M.; Ittmann, M. Increased Expression and Activity of CDC25C Phosphatase and an Alternatively Spliced Variant in Prostate Cancer. *Clin. Cancer Res.* **2005**, *11*, 4701. [\[CrossRef\]](#)
98. Wan, J.; Zhang, J.; Zhang, J. Expression of p53 and its mechanism in prostate cancer. *Oncol. Lett.* **2018**, *16*, 378–382. [\[CrossRef\]](#)
99. Pietsch, E.C.; Sykes, S.M.; McMahon, S.B.; Murphy, M.E. The p53 family and programmed cell death. *Oncogene* **2008**, *27*, 6507–6521. [\[CrossRef\]](#)
100. Chen, J. The Cell-Cycle Arrest and Apoptotic Functions of p53 in Tumor Initiation and Progression. *Cold Spring Harb. Perspect. Med.* **2016**, *6*, a026104. [\[CrossRef\]](#)
101. Li, G.; Tian, Y.; Zhu, W.-G. The Roles of Histone Deacetylases and Their Inhibitors in Cancer Therapy. *Front. Cell Dev. Biol.* **2020**, *8*, 576946. [\[CrossRef\]](#)
102. Aggarwal, V.; Tuli, H.S.; Varol, A.; Thakral, F.; Yerer, M.B.; Sak, K.; Varol, M.; Jain, A.; Khan, M.A.; Sethi, G. Role of Reactive Oxygen Species in Cancer Progression: Molecular Mechanisms and Recent Advancements. *Biomolecules* **2019**, *9*, 735. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Poetsch, A.R. The genomics of oxidative DNA damage, repair, and resulting mutagenesis. *Comput. Struct. Biotechnol. J.* **2020**, *18*, 207–219. [\[CrossRef\]](#)
104. Ueoka, R.; Ise, Y.; Ohtsuka, S.; Okada, S.; Yamori, T.; Matsunaga, S. Yaku'amides A and B, Cytotoxic Linear Peptides Rich in Dehydroamino Acids from the Marine Sponge Ceratopsions. *J. Am. Chem. Soc.* **2010**, *132*, 17692–17694. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Song, R.; Wei, R.B.; Luo, H.Y.; Yang, Z.S. Isolation and identification of an antiproliferative peptide derived from heated products of peptic hydrolysates of half-fin anchovy (*Setipinnataty*). *J. Funct. Foods* **2014**, *10*, 104–111. [\[CrossRef\]](#)
106. Teruya, T.; Sasaki, H.; Fukazawa, H.; Suenaga, K. Bisebromoamide, a Potent Cytotoxic Peptide from the Marine Cyanobacterium *Lyngbya* sp.: Isolation, Stereostructure, and Biological Activity. *Org. Lett.* **2009**, *11*, 5062–5065. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Loganzo, F.; Discafani, C.M.; Annable, T.; Beyer, C.; Musto, S.; Hari, M.; Tan, X.; Hardy, C.; Hernandez, R.; Baxter, M.; et al. 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.* **2003**, *63*, 1838–1845.
108. Faircloth, G.; Marchante, M.d.C.C. Kahalalide F and ES285: Potent anticancer agents from marine molluscs. In *Molluscs*; Springer: Berlin/Heidelberg, Germany, 2006; pp. 363–379.
109. Riggs, D.R.; Jackson, B.; Vona-Davis, L.; McFadden, D. In vitro anticancer effects of a novel immunostimulant: Keyhole limpet hemocyanin. *J. Surg. Res.* **2002**, *108*, 279–284. [\[CrossRef\]](#)
110. Vaishampayan, U.; Glode, M.; Du, W.; Kraft, A.; Hudes, G.; Wright, J.; Hussain, M. Phase II study of dolastatin-10 in patients with hormone-refractory metastatic prostate adenocarcinoma. *Clin. Cancer Res.* **2000**, *6*, 4205–4208.

111. Kobayashi, M.; Natsume, T.; Watanabe, J.-I.; Fujio, N.; Mikami, T.; Miyasaka, K.; Tsukagoshi, S. Activity of a novel antitumor agent, TZT-1027. *Nihon yakurigakuzasshi. Folia Pharmacol. Jpn.* **1999**, *114*, 230–235. [[CrossRef](#)]
112. Greystoke, A.; Blagden, S.; Thomas, A.L.; Scott, E.; Attard, G.; Molife, R.; Vidal, L.; Pacey, S.C.; Sarkar, D.; Jenner, A.; et al. A phase I study of intravenous TZT-1027 administered on day 1 and day 8 of a three-weekly cycle in combination with carboplatin given on day 1 alone in patients with advanced solid tumours. *Ann. Oncol.* **2006**, *17*, 1313–1319. [[CrossRef](#)]
113. Gogineni, V.; Hamann, M.T. Marine natural product peptides with therapeutic potential: Chemistry, biosynthesis, and pharmacology. *Biochim. Biophys. Acta Gen. Subj.* **2018**, *1862*, 81–196. [[CrossRef](#)] [[PubMed](#)]
114. Lee, J.; Currano, J.N.; Carroll, P.J.; Joullie, M.M. Didemnins, tamandarins and related natural products. *Nat. Prod. Rep.* **2012**, *29*, 404–424. [[CrossRef](#)] [[PubMed](#)]
115. Rademaker-Lakhai, J.M.; Horenblas, S.; Meinhardt, W.; Stokvis, E.; de Reijke, T.M.; Jimeno, J.M.; Lopez-Lazaro, L.; Martin, J.A.L.; Beijnen, J.H.; Schellens, J.H. Phase I clinical and pharmacokinetic study of kahalalide F in patients with advanced androgen refractory prostate cancer. *Clin. Cancer Res.* **2005**, *11*, 1854–1862. [[CrossRef](#)] [[PubMed](#)]
116. Ghareeb, M.A.; Tammam, M.A.; El-Demerdash, A.; Atanasov, A.G. Insights about clinically approved and Preclinically investigated marine natural products. *Curr. Res. Biotechnol.* **2020**, *2*, 88–102. [[CrossRef](#)]
117. Ruiz-Torres, V.; Encinar, J.A.; Herranz-López, M.; Pérez-Sánchez, A.; Galiano, V.; Barraón-Catalán, E.; Micol, V. An Updated Review on Marine Anticancer Compounds: The Use of Virtual Screening for the Discovery of Small-Molecule Cancer Drugs. *Molecules* **2017**, *22*, 1037. [[CrossRef](#)]
118. Kalimuthu, S.; Venkatesan, J.; Kim, S.-K. Marine derived bioactive compounds for breast and prostate cancer treatment: A review. *Curr. Bioact. Compd.* **2014**, *10*, 62–74. [[CrossRef](#)]
119. Craik, D.J.; Kan, M.-W. How can we improve peptide drug discovery? Learning from the past. *Expert Opin. Drug Discov.* **2021**, *16*, 1399–1402. [[CrossRef](#)]
120. Muttenthaler, M.; King, G.F.; Adams, D.J.; Alewood, P.F. Trends in peptide drug discovery. *Nat. Rev. Drug Discov.* **2021**, *20*, 309–325. [[CrossRef](#)]
121. Lee, A.C.-L.; Harris, J.L.; Khanna, K.K.; Hong, J.-H. A Comprehensive Review on Current Advances in Peptide Drug Development and Design. *Int. J. Mol. Sci.* **2019**, *20*, 2383. [[CrossRef](#)]