Marine-derived pipeline anticancer natural products: a review of their pharmacotherapeutic potential and molecular mechanisms

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Abstract

Background: Cancer is a complex and most widespread disease and its prevalence is increasing worldwide, more in countries that are witnessing urbanization and rapid industrialization changes. Although tremendous progress has been made, the interest in targeting cancer has grown rapidly every year. This review underscores the importance of preventive and therapeutic strategies.

Main text: Natural products (NPs) from various sources including plants have always played a crucial role in cancer treatment. In this growing list, numerous unique secondary metabolites from marine sources have added and gaining attention and became potential players in drug discovery and development for various biomedical applications. Many NPs found in nature that normally contain both pharmacological and biological activity employed in pharmaceutical industry predominantly in anticancer pharmaceuticals because of their enormous range of structure entities with unique functional groups that attract and inspire for the creation of several new drug leads through synthetic chemistry. Although terrestrial medicinal plants have been the focus for the development of NPs, however, in the last three decades, marine origins that include invertebrates, plants, algae, and bacteria have unearthed numerous novel pharmaceutical compounds, generally referred as marine NPs and are evolving continuously as discipline in the molecular targeted drug discovery with the inclusion of advanced screening tools which revolutionized and became the component of antitumor modern research.

Conclusions: This comprehensive review summarizes some important and interesting pipeline marine NPs such as Salinosporamide A, Dolastatin derivatives, Aplidine/plitidepsin (Aplidin®) and Coibamide A, their anticancer properties and describes their mechanisms of action (MoA) with their efficacy and clinical potential as they have attracted interest for potential use in the treatment of various types of cancers.

Keywords: Marine NPs, Anticancer therapy, Dolastatin 10/15, Marizomib, Aplidine/plitidepsin, Coibamide A, Apoptosis

Background

Cancer is a most widespread complex disease and its prevalence is increasing worldwide [1, 2], more in countries that are witnessing urbanization and rapid industrialization changes [3–7]. It is a normal pathologic condition in which dysfunctional mechanisms in cell cycle regulation and insufficient programmed cell death (PCD) [8–10]. Inhibition of PCD or apoptosis plays a prominent role in the origin and progression of cancers [11]. In recent years, technical advancements made an increased attention toward cancer progression both at cellular and molecular level [12–16], this increased attention on multiple human malignancies witnessed huge development which will fight the cancer in multiple
fronts by adopting novel diagnosis and therapeutic options.

Cancer therapy played a key role in the control of tumor progression and help to cure and prolong the life of patients \[17–20\]. The most acceptable preventive and therapeutic approach is to circumvent the exposure to the causative agents of cancer, to enhance the host defence mechanism against cancer, to alter the living style, chemoprevention and treatment using natural products and their derivatives \[21–23\]. This highlights the necessity to explore more novel effective and less toxic chemotherapeutic natural drug components and their sustainable supply for cancer therapy \[24\].

Natural products and their contributions to alleviate human diseases

About 60\% of the chemotherapeutic drugs that are in current use are either natural products (NPs) or small compounds, which are mostly NP based drug leads \[25–28\]. However, the characterization of these NPs and their direct access is still pose a great challenge \[29\]. Though majority of the traditional and the most commonly available medicinal plants have proved to be an excellent source for the bioactive components and are promising as an antitumor agents. In this growing list, a vast diversity on chemical structure with potent biological activity from the marine environment also offers novel structural entities which demonstrates to be an excellent resource for the new and unique source of anticancer drugs \[28, 30–33\]. In addition to the chemical novelty related to those compounds they also possess novel and new mechanism of action \[34, 35\]. However, the intense toxic nature of certain marine bioactive compounds like maitotoxin, brevetoxin B prevents them from being used in therapeutic applications, whereas others such as paltoxin, okadaic acid and fluorescent proteins from marine organisms are used as an indispensable tools for drug development, mostly in clinical or under preclinical tests \[36, 37\].

Early investigations of National Cooperative Drug Discovery Program (NCDDP), an inspired program conducted by the National Cancer Institute (NCI) \[38, 39\] was not translated the jewel of marine entities into well-known drug leads or pharmaceutical components. This may be due to the inadequate connections between the academic researchers and the pharma industries. At present, subsequent to the collaborative interactions between the academics and the major pharmaceutical sectors have encouraged and paved way to the discovery of large number of marine NP materials being tested in modern assays \[40\].

Main text

Marine NPs and the drug leads possess a very distinct structural feature compared to their counterparts on earth \[32, 33\], which is either due to the alterations in the evolutionary origin or the environmental condition which are specific to the marine world \[41\]. When exposed to extreme conditions those marine organisms that live in complex habitats are capable of producing a vast variety of secondary metabolites which is not possible by other organisms \[42\]. Moreover, the production of very potent marine-derived molecules like polyunsaturated fatty acids (PUFAs), sterols, proteins, polysaccharides, antioxidants and pigments have led to inhibit various types of human cancers both in vitro and in vivo murine and human trials. This led to tremendous attention toward other marine sources including cyanobacteria \[43\], which yielded compounds like curacin A and dolastatin 10. As a result, Eribulin (a synthetic derivative based on the structure of halichondrin B), and monomethyl auristatin E (MMAE or vedotin), pipeline warheads of dolastatin 10 derivatives have been approved by FDA for human applications \[44\]. Some of the clinically approved marine drugs for various human cancers \[45\] are listed in Table 1.

There are about 592 marine natural products have exhibited very strong antitumor and cytotoxic activities.

| Compound name | Marine organism | Molecular target | Indication | Approval date |
|---------------|-----------------|------------------|------------|--------------|
| Trabectedin   | Tunicate        | Tunicate DNA (minor groove) | Soft tissue sarcoma and ovarian cancer | October 23, 2015 |
| Brentuximab vedotin | Mollusk/cyanobacteria | CD30, microtubules | Anaplastic large T-cell systemic malignant lymphoma, Hodgkin’s disease | August 19, 2011 |
| Eribulin mesylate | Sponge | Microtubules | Metastatic breast cancer 0 | November 15, 2010 |
| Omega-3-acid ethyl esters | Fish | Triglyceride-producing enzymes | Hypertriglyceridemia | November 10, 2004 |
| Ziconotide | Cone snail | DNA polymerase | Severe and chronic pain | December 28, 2004 |
| Vidarabine | Sponge | Viral DNA polymerase | Herpes simplex virus infection | 1976 current status: Discontinued |
| Cytarabine | Sponge | DNA polymerase | Leukemia | 1969 |
Besides, nearly 666 additional chemicals have demonstrated various pharmacological actions, which include anticoagulant, antimicrobial, antiplatelet with varied mechanisms of actions on multiple systems like cardiovascular, nervous, endocrine and immune were also included in the marine pharmaceutical pipeline worldwide during the period 1998–2008 [37]. Inspite of various successes and setbacks, worldwide focus toward marine compounds as preclinical cum pharmaceutical pipeline drugs still remains very active (Table 2). In this regard, though there are many compounds that have entered the clinical trials for cancer; however, only eight marine drugs have been recognized and approved by FDA and European Agency for the Evaluation of Medicinal Products (EMEA), they are Cephalosporin C, Cytarabine (Ara-C), Yondelis® (ET743), Vidabrine (Ara-A), Ziconotide (Prazil), omega-3-acid ethyl esters (Lovaza), ET-743 (Yondelis), E7389 (Halaven), Brentuximab vedotin (SGN-35) [36, 46].

An undeniable fact is that the constant supply, isolation, and characterization of NPs is a major challenge for the marine as well as other sources as they are one of the major inevitable components in antitumor drug discovery research. However, in recent years, modern approaches are emerging to overcome these obstacles. In the competitive industrial pharmaceutical grounds, the most widely employed methods for antitumor drug discovery is high-throughput in vitro assay, which permits to examine interactions between small molecules and their target proteins. [14, 47–50]. However, these sophisticated high-throughput screening systems typically requires collaborative efforts, enabled by a mutual research between marine combinatorial chemists and molecular and cell biologists [51]. Developments and events in various technologies such as sampling strategies, total chemical synthesis, fermentation, nanoscale nuclear magnetic resonance (NMR) for structure determination, recent biotechnology advancements are imminent for achieving goals to see marine NPs as potential pipeline drug leads. A high degree of novelty and modernization in the area of marine compounds has led to a new arena in the regeneration of new pharmaceuticals in the coming years [29].

Different mechanisms have been proposed for the drugs discovered from marine organisms including cell death like apoptosis, effect on the tubulin-microtubule equilibrium or induction of angiogenesis inhibition. Though these findings has augmented our understanding of these new marine drug leads and their properties and seen as a new option for acquiring enormous potential drug-lead molecules on pharmaceutical discovery [50, 52]. Despite the huge effort made progress of anticancer compounds from marine resources, but in reality this domain of research is stand at the infant stage because only few marine compounds have been identified and isolated till date when compared with other natural sources.

Regardless of the above fact, it is evident that the biological properties of marine NPs potentially interfere with the genesis and progression of many human diseases including cancer [52, 53]. Therefore, to facilitate the importance of jewels of these unique marine world this review summarizes the existing scientific knowledge and highlights few selected potential pipeline marine NPs (such as Salinosporamide A, Dolastatin 10/15 derivative, Aplidine/plitidepsin (Aplidin®) and Coibamide (Figs. 1, 2, 3, 4, 5), which are currently under clinical evaluation as a pipeline anticancer agents to fight against cancer.

**Anticancer potentials of pipeline marine NPs**

### Salinosporamide A in cancer treatment

In the academic drug discovery arena, marine microbes are now emerging as a new sustainable source for novel drug chemical substances [40, 41, 53]. Actinomycetes marine bacteria is one such rich source for novel compounds, which belongs to genus Salinispora [54–56]. One of the most promising drug lead is salinosporamide A, a natural product, which is highly potent proteasome inhibitor discovered by [57]. It is a chlorinated clinically promising anticancer agent, isolated from marine bacterium (Actinomycetes) Salinispora tropica and Salinispora arenicola [54] and is initially assessed in multiple myeloma (MM) xenograft models [58] but later in a series of clinical trials (phase 1) as a single agent against other types of solid tumors and lymphomas [57, 59–62] and under the name NPI-0052/Marizomib (Fig. 1).

Subsequent studies further revealed the mechanism of action of this compound as a proteasome inhibitor [63, 64]. Since proteasome inhibitors play a crucial role in controlling the level of proteins in the control of cancer [65]. Till date, the only clinically approved proteasome inhibitor is bortezomib [66] and others are under clinical trials. Currently, Salinosporamide A is in clinical trials for MM treatment either as a single agent [67–70] or with an aid of the existing treatments [71]. Salinosporamide A covalently binds to the threonine residues in the proteasome active site and inhibits the proteasome 20 s activity. The proteasome inhibition has been applied as an effective strategy in the treatment of MM and some lymphomas [64, 70], as they block nuclear factor-kappa B (NF-kB) activity by interfering with the growth and survival signaling [72–78]. As this drug has moved ahead to phase—1 clinical evaluation, salinosporamide A is at present being manufactured by saline fermentation process [79], to increase the yields and lower the cost of production.
| Indication     | Compounds                | Marine organism source                  | Mechanism of action                                                                 | Current status                                      | References                       |
|---------------|--------------------------|-----------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------|
| Anticancer    | Aplidine (Aplidin®)      | Aplidium, Candida albicans Mediterranean tunicate | Antiproliferative action. Acts by blocking the cell cycle arrest and inducing apoptosis | Multiple myeloma (Phase III of clinical trials) T-cell lymphoma (Phase II of clinical trials) | [147, 150–155]                  |
|               | Plinabulin               | Synthetic analog of a natural product isolated from a marine fungus (Aspergillus spp.) | Inhibition of tubulin polymerization Non-small cell lung cancer (Phase III of clinical trials) | Non-small cell lung cancer (Phase III of clinical trials) | [13]                             |
|               | Salinosporamide A (NPI-0052/ Marizomib) | Marine Actinobacteria Salinispora tropica | Proteasome inhibitor                                                                  | Multiple myeloma (Phase I of clinical trials)       | [54–57, 59–62]                  |
|               | Dolstatin 10             | Sea hare Dolabella auriculata, a cyanobacterial origin | Inhibition of the tubulin polymerization and GTP hydrolysis                           | Phase I and II but it failed in phase II, however, Dolastins are in phase III trials | [117–120, 122, 125, 127, 128, 132, 133] |
|               | Dolstatin 15             | Sea hare Dolabella auriculata            | Antimitotic and capable of disrupting tubulin polymerization                          | Phase II clinical trials                            | [168–172]                       |
| Alzheimer’s disease | Coibamide A             | Leptolyngbya cyanobacterium Ectoprocta species-Bugula Neritina | Induce apoptosis                                                                     | Under preclinical investigation                     | [168–170]                       |
|               | Bryostatin 1, DMXB-A     | Synthetic analog of the toxic alkaloid produced by nemertines worm species, such as Paranemertes peregrine and Amphiporus lactifluenu | Potent modulator of protein kinase C Acts by improving cognition and sensory deficit | Phase II of clinical trials                        | [45]                             |
| Analgesics    | Tetrodotoxin             | Isolated from fish, algae, and bacteria | Blocks voltage-dependent sodium channels                                             | Phase II and III of clinical trials for neuropathic pain in cancer patients and peripheral neuralgia in cancer patients, respectively | [45]                             |
| Antibacterial | Anthracimycin            | Marine Actinobacteria                   | Activity against Bacillus anthracis and MRSA MoA unclear                              | Preliminary stages of drug development              | [45]                             |
Marizomib® (NPI-0052)

Marizomib® (NPI-0052), the second-generation proteasome inhibitor of Salinosporamide A is a more promising pipeline drug and had shown a best clinical activity in bortezomib-resistant cancers. Besides the above, it was effectively developed and found to hold on to various pharmacological properties and broader anticancer activity. Marizomib binds to the active site of the proteasome [69, 77, 80] and has exposed its clinical activity either as a single drug lead or in combination with other antitumor compounds such as dexamethasone. Marizomib shares analogous properties but often is known to exhibit higher efficacy than its parental drug. It also exhibited higher activities in multiple non-clinical tumor models treatment of patients with hematologic and solid tumors [54, 60–62]. MM is a fatal disease with the excessive proliferation of plasma cells. Due to the development of these kinds of novel agents, the survival rate of patients suffering from MM has been improved significantly [81]. Over and above, it also portrayed synergistic effects in the cancer models when combined with immunomodulatory agent lenalidomide, and a range of histone deacetylase inhibitors [82].

Molecular mechanism of Marizomib

Proteasome is an intracellular enzyme complex that is capable of regulating the protein levels in the cell by degrading the ubiquitin-tagged proteins. Proteasome is categorized into its subcomponents based on their Svedbergs sedimentation coefficient. The 20S proteasome is a collection of four stacked disks that forms a hollow complex, each of which includes 7 subunits that are called as α7-β7-β7-α7 structure [83] and three kinds of β-subunits: post-glutamyl peptidyl hydrolytic-like (PGPH, β1), trypsin-like (T-L, β2) and chymotrypsin-like (CT-L, β5) activity area that are capable of performing unique enzyme activities respectively [83, 84]. These β-subunits are distinguished from the other proteases by the presence of an amino terminal (N-terminal) threonine residue in all the three catalytic sites that provide as a nucleophile for proteolysis [74, 85].

Multiple evidences demonstrate that a dysregulation of critical regulatory proteins that relates various signaling pathways lead to cell cycle arrest as apoptosis is been created by the inhibition of proteasome [86, 87] and also exhibited numerous anticancer properties against numerous types of cancer using various xenograft models like prostate [88] pancreatic [89] lymphoma [90], head and neck [91] melanoma [92], lung [93], breast [94], and leukemia [95]. Thus cancer treatments can be accomplished via programmed cell death caused by proteasome inhibitors [96–98]. The nuclear factor of κB (NF-κB) [88, 99], tumor suppressor p53 [100], cyclins [101, 102] etc. are some of the proteasome substrates. While in most cases, the cell death resulting due to proteasome inhibition which requires the activation of caspases [103] and has been linked to increased levels of oxidative radicals [88, 93, 104]. Commonly, both Bortezomib and Marizomib are well to increase caspases 3, 4, 8 and 9 activity [105, 106], yet, NPI-0052 exhibits its potency mostly through caspase-8-dependent pathway [107].

Besides, the evaluation of antitumor efficacy of both bortezomib and Marizomib was carried out by assessing the efficacy of the agent using various preclinical studies [108–113]. In view of the fact that, bortezomib largely interacts with the CT-L and T-L active sites of proteasome and NPI-0052 potently inhibits all the three active sites, it is proposed that using both bortezomib with NPI-0052 would benefit more and seen as a viable approach for wide range of manifestations. In line with this, previous study has established that that the combination strategy of these two agents evident with synergistic anti-MM activity in both in vitro and in vivo models [114]. To support this findings, similar results were obtained with the combination of Marizomib and lenalidomide combination [68, 79, 104, 115]. However, the molecular mechanisms of the synergetic actions, which include the inhibition of proteasome, activation of caspases-8, 9 and 3, and PARP cleavage [79]. Therefore, Marizomib is viewed for their unique exceptional profiles after three verified clinical trials [116].

Dolastatins and their analogs in cancer treatment

In addition to the above, in recent years, microtubules are the prime target and serve as the components of anticancer therapy by using taxanes and vinca alkaloids which are acting as an antimitotic agent that target intracellular...
organelle tubulin [117, 118]. Even though these anti-mitotic drugs are highly successful in the treatment of many types of cancers, the major clinical problem lies are both acquired and intrinsic resistance to these components. Avast array of potential new generation antimitotic drug leads are now under clinical trials. In line with this, Dolastatins and their analogs are emerging as anti-cancer drugs because they function as a vascular disrupting agent (VDA) [119, 120].

Dolastatin 10 (Fig. 2a), a linear pentapeptide has numerous unique amino acid subunits, originally isolated from the sea hare Dolabella auricularia.
[121–125], commonly originate from cyanobacteria, which belongs to the genera *Symploca* and *Lyngbya* upon they feed [126–129]. Elucidating the structure of Dolastatin has taken nearly 15 years for completion due to very little information on this active principle [130, 131]. Preliminary studies have indicated that [129], the binding of the Vinca alkaloids to tubulin and the microtubule assembly is strongly inhibited by Dolastatin 10 [130]. A tripeptide portion of Dolastatin 10 which do not significantly inhibit the binding of vincristine or the exchange of nucleotides however efficiently inhibits the tubulin polymerization and GTP hydrolysis [131]. Besides, another sea hare *D. Auricularia* and cyanobacterial origin is antimitotic Dolastatin 15 (Fig. 2b), results are again strongly implicating that this metabolite is potent pipeline agent as marine cyanobacteria once again proven as a source for the isolation of numerous dolastatin 15–related peptides [122, 125, 132, 133].

**Mechanism of action of Dolastatins**

Dolastatin 10 has demonstrated its potency against various human cancers such as lymphomas, leukemias and solid tumors [129, 134, 135]. At very low concentrations, dolastatin 10 cause microtubules depolymerization and produced multinuclear spindles leading to cell apoptosis [130, 131, 136]. Subsequent research investigation supported that dolastatin 10 binds to the rhizoxin/maytansine binding site [137], which is next to Vinca alkaloid site as well as exchangeable to the guanosine triphosphate site on tubulin, causing cell cycle arrest in metaphase [138]. Currently Dolastatin 10 derivatives are in the clinical trials of both phase I and phase II [1254] as a pipeline compound for treatment of several solid tumors [127, 128]. However, it failed to show any significant clinical activity in Phase II clinical trials due to certain issues such as the productivity based on the multistage chemical synthesis steps and the lack of water solubility, analogues such as TZT-1027 (auristatin PE) (Fig. 2c) [139–141]. Despite the above, these analogs are at phase III clinical trials [142]. This synthetic analog of dolastatin 10, exhibited an enhanced activity in pilot studies using various animal models and showed its synergistic antitumor property in combination with Cisplatin [136] in the human (HCT-116) and murine colon (26 adenocarcinoma) cancer model [143]. It is interesting to note that the outcome of TZT-1027 on tumor blood vessels and HUVEC were considerable when compared to Vincristine. Moreover, TZT-1027 was effective in MX-1 breast carcinoma and LX-1 lung carcinoma [144]—the two human xenograph models.

In line with this, Tasidotin (Fig. 2d) is an analog of Dolastatin with tubulin-interactive activity that inhibits tubulin polymerization very weakly, but suppresses the dynamic instability of microtubules strongly. [129]. At present it is at the Phase III trials [145] and had successfully completed the Phase I trials [134, 135]. Results suggested that both TZT-1027 and Tasidotin with a putative protein kinase-dependent mechanism targeted a quick attack of the vascular system of the advanced cancers and thus blocked the blood flow in the tumor. Henceforth, TZT-1027 has made a tremendous progress and proven as powerful agent for tumor therapy.

Cematodin (LU-103793; Fig. 2e), is a water-soluble and a stabilized analog of dolastatin 15 [146] was synthesized in the year 1995, with a original dolapyrrolidone replaced by benzylamine moiety terminal. It is capable of disrupting tubulin polymerization and inducing
depolymerization of preassembled microtubules through the retention of high cytotoxicity like parent compound [147]. In addition, Synthadotin (Fig. 2f), ILX-651 an orally active 3rd generation dolastatin 15 synthetic analog possessing a terminal tert-butyl moiety when compared to the original dolapyrrolidone is under phase II clinical trials using patients with locally advanced or metastatic non-small cell lung tumors and patients with hormone-refractory prostate cancer previously treated with Docetaxel [148]. A clinical outcome of this phase II trial, in which patients with inoperable advanced or metastatic melanoma treated with ILX-651 for consecutive 5 days on a 3 week period indicated that it was a “safe, well-tolerated treatment for locally advanced and metastatic melanoma patients” [149].

**Plitidepsin (Aplidine) in Cancer treatment**

Plitidepsin (Fig. 3), also known as dehydrodidemnin B, (trade name Aplidin) is a cyclodepsipeptide isolated from Aplidium albicans, which is a Mediterranean tunicate [147, 150]. Plitidepsin is considered as a new generation didemnin that portrays higher anticancer activity and better therapeutic indexes than didemnin B at non-toxic concentrations and now being developed by total synthesis. Plitidepsin is a well-tolerated drug which has exhibited its strong antitumor property both in in vitro and mouse model using numerous human cancer cell lines. To support this, both Phase I and Phase II clinical trials also showed hopeful results of anticancer activity [151–155] and currently undergoing phase III trial as a therapeutic agent for relapsed/refractory MM patients.
Previous studies have demonstrated that plitidepsin is capable of inducing cell cycle arrest either by cell-specific or dose-dependent manner [152, 156, 157]. Besides, a sustained activation of JNK and p38 MAPK is made possible by the combined actions like early oxidative stress induction, activation of Rac1 GTPase and inhibition of protein phosphatases activity [158].

**Mechanism of action of plitidepsin**
The mechanism of action of plitidepsin on tumor cells is well described [152]. In brief, after an interaction with the high affinity binding site in the cell membrane, plitidepsin leads to the rapid activation of Rac1 and the persistent phosphorylation and activation of JNK and p38/MAPK that eventually induce apoptosis [152, 159, 160]. Activation of JNK and p38 MAPK results in the downstream signaling events like cytochrome c release, activation of caspases-9 and -3 and PARP cleavage, thus signifying the mediation/significance of the mitochondrial apoptotic pathway in this process. In addition, several pathways have also involved in Alphidine’s mechanism of action which includes cell cycle arrest and protein synthesis inhibition [161, 162] in leukemic cells with the involvement of translocation of Fas/CD95 in lipid rafts [163–166]. Moreover, the induction of oxidative stress by Plitidepsin incites a stress on the endoplasmic reticulum (ER) also associated to cell death [152]. In this regard, Plitidepsin activates important molecular machinery of the classical ER stress-induced unfolded protein response (UPR) as well as the phosphorylation of eIF2α and JNK. Due to its fast degradation by the ubiquitin/proteasome machinery Plitidepsin also induces the decrease of CHOP protein levels. [167].

**Coibamide A in cancer treatment**
Coibamide A (Fig. 4), is a marine product from Leptolyngbya cyanobacterium, mostly available in Panama [168–170] and identified as a novel and an effective anti-proliferative depsipeptide anticancer drug. The structure represents a methyl-stabilized cyclic depsipeptide with a lariat side chain, and the activity of the structure portrays that there is a direct effect on Coibamide A, if there is a loss in the N-methylation which results in the disjoining of the cyclic and the side chain structures of the molecule or just a drastic linearization of the molecule [171]. Thus it induces the apoptotic activity by activating caspase-3 and caspase-7 and non-apoptotic cell death activity in the apoptosis-resistant human cancer cells which include U87-MG, NCI-SF-295 glioblastoma (GBM) respectively and works in concentration-dependent and cell cycle active [168, 171] manner. The cell death also observed in the wild-type and autophagy-deficient (ATG5-null) and knockout (KO) mouse embryonic fibroblasts (MEFs) indicates its novel mechanism of action [171]. A cytotoxic effect that arrested the G1 phase cell cycle with minor change in G2/M and loss of S phase was portrayed in the flow cytometric analysis. In addition, it also inhibits the glioma cell motility especially invasion and migration [169]. Besides the above, the mutations that occur throughout the GBM, results in the activation and enhancement of receptor tyrosine kinases EGF, PDGF as well as attenuation of the tumor suppressor genes such as p53 and PTEN (phosphatase and tens in homolog [172]. Thus, an increase in the cell signaling is observed due to MAPK (Mitogen Activated Protein Kinase) and PI3K (Phosphatidylinositol 3-kinase) pathways leading to the promotion of the cell survival and henceforth GBM attains resistance to apoptosis. A test for the anticancer activity using 60 cancer cell lines demonstrated that Coibamide A portrayed a high potential of activity in a range that falls between 2.8 and 7.6 nM but mostly selective to 4 different cell lines such as breast (MDAMB-23, melanoma (LOX IMVI), human leukemia (HL-60) and glioblastoma (SNB-75), however exhibited significant histological selectivity for breast, CNS, colon and ovarian cancer cells [168].

Moreover, the effect of this peptide on mTOR protein was studied and concluded that Coibamide A possess mTOR independent cellular response and induces rapid and regular and also sustained autophagic response [171]. Besides, it was portrayed that Coibamide A induced cell death could be accomplished through apoptotic or non-apoptotic pathways not necessarily by autophagy alone. To support the above, evidences show that many cytotoxic marine anticancer NPs trigger apoptosis by targeting multiple cellular proteins by involving both intracellular and extracellular pathways [173]. Those marine NPs that are capable of inducing apoptosis were primarily recognized as cytotoxic agents, however their apoptotic activity was discovered later by various secondary pharmacological evaluations. In fact, Coibamide A has also displayed potent caspases-dependent apoptotic activity in different cancer cells.

**Conclusions**
In summary, the past two decades have witnessed a resurgence and revolution on new drug discovery from marine sources. In this review, we have discussed the role of few important pipeline marine peptides, their mode of action (Fig. 5) and the hitches related to the transfer of marine NPs into various phases of clinical trials. The peptide molecules reviewed are acquired from different marine sources and each of those portrays a different but unique mechanism of action and exhibited their anticancer activities. The peptides from marine sources share a diversified style and class and the presence of more number of cyclic peptides...
or depsipeptide is an important property of the marine organisms. Though several marine peptides display anticancer activities on multiple tumor targets. The available results clearly indicate that these potential pipeline drugs such as Salinosporamide A, Marizomib, Plitidepsin, Coibamide A appears to be very potent and promising pipeline drugs not only biomedical science but also serve as cancer therapeutics. Hence, the diversity of marine peptides both in terms of structure and mode of action provide a valuable source for the drug design and serve as novel new pharmaceuticals for a wide variety of human cancers.

Abbreviations
PCD: Programmed cell death; NPs: Natural products; NCDDP: National Cooperative Drug Discovery Program;PUFAs: Polynsaturated fatty acids; MM: Monomethyl auristatin E; FDA: Food and Drug Administration; EMEA: European Agency for the Evaluation of Medicinal Products; NMR: Nuclear magnetic resonance; MM: Multiple myeloma; NF-κB: Nuclear factor-kappa B; European Agency for the Evaluation of Medicinal Products; NMR: Nuclear magnetic resonance; MM: Multiple myeloma; NF-κB: Nuclear factor-kappa B; TRAIL: TNF-related apoptosis-inducing ligand; GTP: Guanosine-5'-triphosphate; JNK: C-Jun N-terminal kinases; MAPK: Mitogen-activated protein kinase; Rac1: Rac Family Small GTPase 1; ER: Endoplasmic reticulum; eIF2α: Eukaryotic initiation factor-2α; CHOP: CCAAT/ enhancer binding proteins; GBM: Glioblastoma; PSEN: Phosphatase and tens in homolog; EGF: Epidermal growth factor; PDGF: Platelet-derived growth factor; PI3K: Phosphatidylinositol 3-kinase; mTOR: Mammalian target of rapamycin.

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