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Review Article
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Marine Pharmaceuticals: A New Wave of Anti-angiogenic Drugs

Sweta Agrawal, Sachin Chaugule and Madhavi Indap*

Central Research Laboratory, D. G. Ruparel College, Mahim, Mumbai- 400 016, India

Abstract

The biodiversity of the marine environment and its associated chemical diversity constitute a practically unlimited resource of new active substances. Marine natural products (MNP) have exhibited a wide spectrum of pharmacological properties because of their bioactive secondary metabolites. At present, MNPs are progressively being used as anti-angiogenic drugs as summed up in several research reports. Although there are several anti-angiogenic marine natural products currently in different phases of clinical trials, challenges like large scale production of these drugs and further exploration of the marine sources still remain. This review summarizes the current knowledge on importance of marine bioactives as potential anti-angiogenic drugs. The report also highlights various MNPs altering angiogenic targets like endothelial cells, kinases, angiogenic growth factors and matrix metalloproteinases (MMPs).

Keywords: Marine natural products (MNP); Anti-angiogenic compounds; Endothelial cells; Angiogenic factors; Anti-cancer agents

Introduction

Oceans cover three fourth of the earth's surface and contains approximately 80% of the biological diversity. Multiple factors including complex sea-water habitats and adaptation to extreme conditions have led to the evolution of secondary (biologically active) metabolites in marine organisms. These secondary metabolites are now known as bioactive compounds or marine natural products (MNPs) owing to their significance as medicinal substances [1]. Due to its enormous biodiversity, the marine environment offers equally infinite chemical diversity and scope for finding several bioactive compounds which includes alkaloids, sterols, poly-unsaturated fatty acids (PUFAs), proteins, polysaccharides, pigments, amongst others [2].

Marine bioactives are mostly derived from animals like molluscs, bryozoans, sponges, tunicates, soft corals, fishes, algae and many microorganisms. The search for new bioactives from marine organisms has resulted in the extraction of more than 25,700 metabolites till date [3]. Most of these compounds possess pharmacological properties including anti-tumour, anti-angiogenic, anti-proliferative, cytotoxic, photo protective, anti-inflammatory, anti-oxidant as well as antibiotic and antifouling [4].

In this review, we have compiled the most relevant data regarding the marine-derived compounds, specifically targeting tumour angiogenesis and the factors involved in it. With the latest increase in natural product research, the purpose of this review is to facilitate discussion on marine bioactives since these are one of the most recent approaches in development of cancer therapeutics.

Angiogenesis in Cancer Therapeutics

Angiogenesis is a physiological process of growth of nascent blood vessels from the existing vasculature. It is a complex multistep process that involves the activation, migration, invasion, and proliferation of vascular endothelial cells, followed by formation of sprout, tube-like structures, and finally capillary network formation [5]. It is a well-known fact that angiogenesis plays a prime role in the development of primary tumour into metastasis or malignancies. Physiological angiogenesis varies significantly from tumour angiogenesis. These differences are mainly in the form of altered endothelial-cell–pericyte interactions, unusual vasculature morphology, higher blood vessel permeability, irregular blood flow and delayed maturation. Such abnormal features of the tumour vasculature lead to tissue hypoxia which in turn upsurges the expression of angiogenic promoters or pro-angiogenic factors [6].

The most commonly found pro-angiogenic factors are VEGF (Vascular endothelial growth factor), bFGF (basal fibroblast growth factor) and PDGF (platelet derived growth factor). As these factors come in contact with the host endothelial cells (ECs), they bind to the tyrosine kinase receptors on the EC surface. This binding causes dimerization of the receptors as well as activation of auto-phosphorylation of tyrosinases on the receptor surface, thereby instigating a signalling cascade [7]. This process initiates up-regulation of many other pro-angiogenic factors like angiopoietins, matrix metalloproteinases (MMPs), Transforming growth factor (TGF-b), Interleukin-8 (IL-8) and many more [8]. However, just the increased expression of angiogenic factors is not sufficient in itself for a tumour to convert to angiogenic phenotype. For this, down-regulation of certain endogenous anti-angiogenic factors like angiostatin, endostatin, tissue inhibitor of metalloproteinases (TIMPs) and other proteolytic fragments may be required [9]. The net outcome is the promotion of endothelial cell migration and proliferation. The tumour vasculature, not only delivers oxygen and nutrients to proliferating tumour cells but also allows the tumour cells to enter the blood stream, thus facilitating tumour growth and metastases [10].

Overall, the excess production of pro-angiogenic molecules and diminished expression of anti-angiogenic factors produces abnormal tumour blood vessels and microenvironments. This consecutively causes insufficient drug delivery and therapeutic inefficacy [11]. Therefore, targeted anti-angiogenic therapies are required to normalize these tumour blood vessels.

Overview of Marine Derived Anti-Angiogenic Agents

The concept of using marine bioactives in the field of anti-angiogenesis has gained momentum in the last three decades after the landmark study by Dr Judah Folkman [12]. Marine organisms including

***Corresponding author:** Madhavi Indap, Central Research Laboratory, D. G. Ruparel College, Senapati Bapat Marg, Mahim, Mumbai-400 016, India, Tel: +91-9820400675; Fax: +9122 2430 3042; E-mail: madhavi.indap@ruparel.edu

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sponges, sponge-associated bacteria, gorgonia, molluscs, soft coral and actinomycetes, have been extensively explored for potential anti-angiogenic agents. According to a recent review, currently more than 43 marine derived compounds are known to possess anti-angiogenic properties, out of which 10 have entered the different phases of clinical trials for cancer therapy [13]. These compounds show great structural and chemical diversity which includes saccharides, macrocycles, terpenes, peptides, saponins, pyrones, alkaloids and xanthones. Due to their unique structures and diversity, these compounds show specific mechanism of their anti-angiogenic activity by altering distinct targets.

Anti-angiogenic agents act either on the endothelial cells or on the signalling- pathways involved in the angiogenic cascade (Figure 1). The agents targeting endothelial cells inhibit their growth either by cell cycle arrest during mitosis or by inducing DNA damage leading to apoptosis. Another major target is the family of tyrosine kinases which is responsible for angiogenic factor-receptor binding in cellular signalling. Tyrosine kinases are a large group of families out of which two are almost entirely endothelial cell specific: the vascular endothelial growth factor (VEGF) receptors and the Tie receptors. Dis-regulated expression of tyrosine kinases is responsible for tumor development, proliferation, angiogenesis, invasion and chemo-resistance. There has been intriguing interest in discovering novel marine derived multi targeted tyrosine kinases inhibitors [14]. Pro-Angiogenic factors are yet another key target as they are required in every step of the angiogenic process. Lastly, the tumour extracellular membrane (ECM) is an emerging target because cleavage of ECM molecules by Matrix metalloproteinases (MMPs) aid in cancer cell invasion, migration and metastasis.

Marine-Derived Agents Targeting Endothelial Cells

Endothelial cells are the key players in the process of angiogenesis. During tumour angiogenesis, the increase in pro-angiogenic factors cause the migration and proliferation of endothelial cells, leading to tip cell and stalk cell differentiation. Tip cells navigate towards angiogenic signal and stalk cells proliferate behind to create vessel lumen [15]. Thus, the migration, proliferation and differentiation of the endothelial cells are responsible for the formation of neo-vasculature. Targeting this ability of endothelial cells to migrate, proliferate and differentiate regulates angiogenesis.

In eukaryotic cells, microtubules play several key roles that are important in cell proliferation, trafficking, signalling, and migration. For this reason, several microtubule binding agents have been developed with different aims, including their use as anti-cancer agents. Over the course of time, it has been discovered that both proliferation and migration of endothelial cells appear to be extremely sensitive to microtubule-targeted drugs [16]. Apart from its role in formation of spindle fibres during mitosis, Microtubule (MT) also plays important role in endothelial cell migration and signal transduction. Therefore, it has been suggested that microtubule-targeted drugs can be very beneficial as anti-angiogenic agents [17]. Until today, nature has proven to be the best source of new microtubule-stabilizing compounds by far, with most of the microtubule targeting agents (MTAs) originating from marine organisms. Although several MTAs have been isolated or derived from marine biota, marine sponges remain as the chief source of MTAs [18] (Figure 2).

Dolastatins

The dolastatins, potent antimitotic and cytostatic agents, are a class of small oligo-peptides with four unique amino acids isolated from the shell-less mollusc, *Dolabella auricularia* [19]. Dolastatin 10 and 15 are small linear peptides which inhibit microtubule assembly and tubulin-dependent GTP binding, arresting the cells in metaphase [20]. Several structural modifications of Dolastatin 10 and 15 have been attempted and the analogues were found to have better activities. Dolastatin 10 reached up to phase II of clinical trials as a single agent in cancer therapy, whereas Dolastatin 15 analogue, Tasidotin has shown promising results in the pre-clinical trials on mice [21]. Recently, a synthetic derivative of Dolastatin 10, Soblidotin (TZT-1027) was tested in phase 1 clinical trial for advanced solid tumours and it gave encouraging results with comparatively lesser side-effects [22].

Peloruside A

Peloruside A is a polyketide isolated from New Zealand marine sponge *Mycale hentscheli* [23]. Previous studies have shown that Peloruside A causes hyper-stabilization of microtubules by binding to a site on β-tubulin in a manner similar to that of Paclitaxel. It is reported to have potent cytotoxic activity against murine leukemia cells P388 and also inhibits endothelial cell migration [24,25]. Although there is ample evidence of *in vitro* anti-mitotic effect of Peloruside A, there is scarcity of scientific data in support of its *in vivo* and clinical studies.

Hemiasterlin

Hemiasterlins are small cytotoxic tri-peptides found as secondary metabolites in several sponges and were first isolated from the sponge *Hemiasterella minor*. The potent cytotoxicity of hemiasterlins is

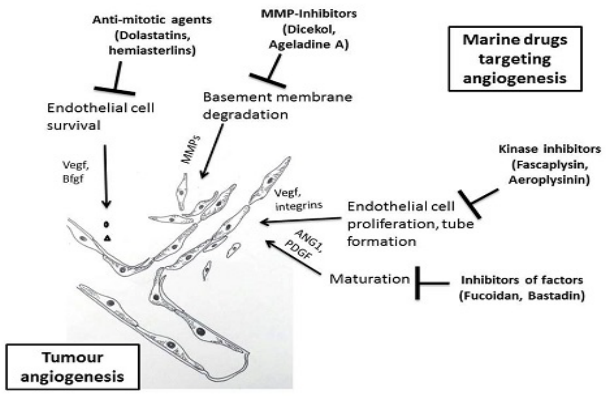

Figure 1: Diagrammatic representation of different classes of marine derived drugs targeting tumour angiogenesis.

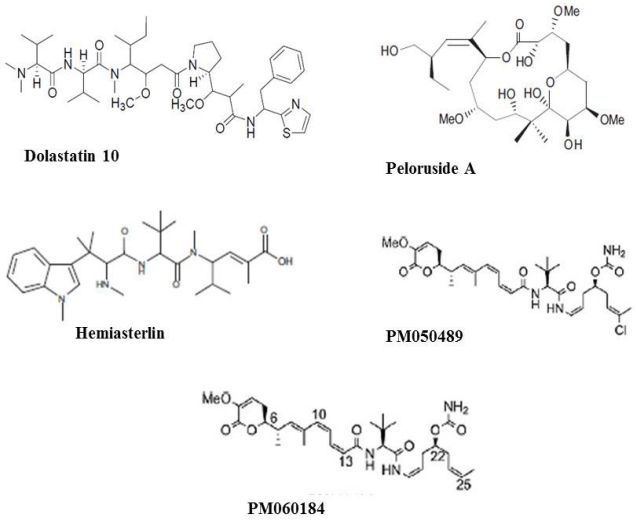

Figure 2: Chemical structures of marine agents such as Dolastatin 10, Peroruside A, Hemiasterlin, PM050489, and PM060148 which are involved in targeting endothelial cells.

because of their interference with mitotic spindle formation at low concentrations and tubulin de-polymerization at higher concentrations [26]. In addition, hemiasterlin was found to be more potent *in vitro* cytotoxic and antimitotic agent than both taxol as well as vincristine, which are anticancer drugs. Quite a few derivatives and synthetic analogues have been prepared from this compound, the most potent one being HTI-286. Studies have shown that HTI-286 exerts stronger activity and is more accessible than Hemiasterlins [27]. It had reached the phase II clinical trials but was discontinued due to lack of objective responses along with observance of toxicities in patients [28]. In 2009, another synthetic hemiasterlins analogue E7974 was found which showed strong *in vivo* anti-tumour efficacy in many human xenograft cancer models along with decreased drug resistance in cancer cells [29]. It has cleared the phase I clinical trial for the treatment of advanced solid tumours in colorectal, pancreatic and liposarcoma cancer patients and is currently undergoing human clinical trial [30].

PM050489 and PM060184

PM050489 and PM060184 are a new class of marine polyketides, initially isolated from the sponge *Lithoplocamia lithistoides* and first synthesized by Martin et al. [31]. These polyketides have shown *in vitro* anti-mitotic activity against multiple types of human tumours, at sub-nanomolar concentrations. They potently disrupt cellular microtubules and mitosis by binding to αβ-tubulin dimers and distinctly modulating tubulin association reactions [32]. Observing its distinct mechanism of action and good safety profile, PM060184 has entered phase I clinical trials in several countries including the United States of America [33,34].

Besides these, there are several other compounds derived from marine invertebrates, vertebrates and other organisms that target endothelial cells with the anti-mitotic or other mechanisms. The best example, Squalamine, an aminosterol derived from the shark, *Squalus acnathicus* shows anti-angiogenic activity by inhibiting endothelial cells. It affects the hydrogen-ion efflux system in the endothelial cells and subsequently causes reduction in cell proliferation [35]. The phase I clinical trial of squalamine displayed promising results in its efficacy and safety profile.

Marine Derived Kinase Inhibitors

Kinases are enzymes that carry out phosphorylation of proteins by catalysing the transfer of the terminal phosphate of ATP to substrates containing serine, threonine or tyrosine residue. This group includes an array of substrate specific kinases like Protein Kinase C (PKC), Cyclin-dependent kinases (CDK-1, CDK-4), tyrosine protein kinase (TPK), Epidermal growth factor receptor (EGFR), Mitogen-activated protein kinase (MAPK), glycogen synthase kinase 3 (GSK-3) among others. They play varied and important role in angiogenic signal transmission pathways by controlling cell differentiation, cell proliferation, DNA damage repair, cell migration and apoptosis [36]. Currently known kinase inhibitors are mostly competitive inhibitors which act by mimicking the adenine region of ATP which is the binding region of kinase and ATP [37].

In the recent years, a large number of kinase inhibitor molecules have been derived from marine organisms. Many of the anti-angiogenic MNPs exert their effect through inhibition of phosphorylation of membrane receptors as well as hindering cell signalling cascades. Currently, cytarabine and trabectedin are FDA-approved marine-derived small-molecule drugs which function as kinase modulators (Figure 3) [38].

Fascaplysin

Fascaplysin is a pigment, first isolated from marine sponge *Fascaplysinopsis Bergquist* sp in 1988 and identified as an anti-microbial agent [39]. It was later found to exert anti-proliferative activity against HeLa (ovarian cancer) cell line though apoptosis. Fascaplysin showed *in vitro* anti-angiogenic activity via vascular endothelial growth factor (VEGF) blockage, cell cycle arrest and apoptosis on human umbilical vein endothelial cells (HUVEC) [40]. It also showed selective inhibition of Cyclin-dependent kinase 4 (CDK4) and correspondingly arrested the cell cycle in the growth of multiple cancer cell types at the G0/1 phase. CDK-4 is a catalytic subunit whose presence is crucial for the succession of the cell cycle through the G1 phase [41]. Studies have also shown that fascaplysin does not inhibit any other tyrosine kinases and is a poor inhibitor of other types of CDK [42].

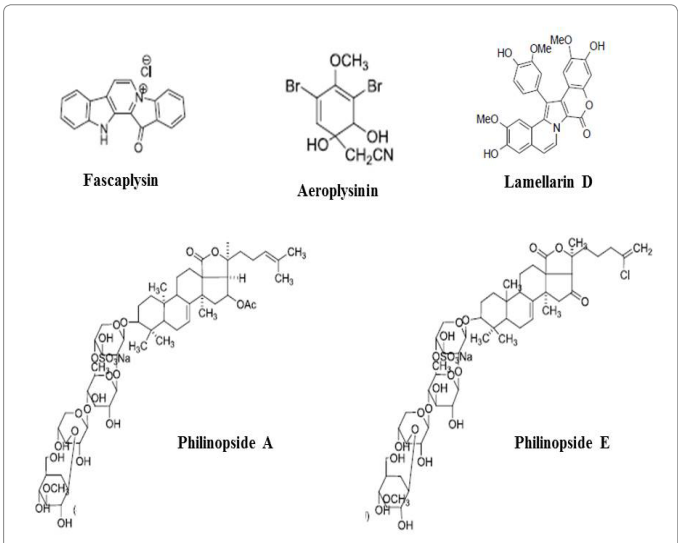

Figure 3: Chemical structures of marine derived kinase inhibitors; fascaplysin, Aeroplysinin, Lamellarin D, Philinopside A and Philinopside E.

Philinopside A and Philinopside E

Philinopsides A, B, E and F are triterpene glycosides isolated from the sea cucumber *Pentacta quadrangularis*, exhibiting significant cytotoxicity against various cancer cell lines. Philinopside A and E have shown potent anti-angiogenic activity in chick chorio-allantoic membrane model, rat aortic ring assay and murine models as well as in Human Umbilical Vein Endothelial Cells (HUVEC) [43]. Studies on Philinopside A have confirmed its inhibitory property of angiogenesis-related receptor tyrosine kinases (RTK) including FGFR1 (fibroblast growth factor receptor 1), PDGFR-β (platelet derived growth factor receptor-β), VEGFR (vascular endothelial growth factor receptor) and EGFR (epidermal growth factor receptor). Philinopside E is known to reduce the levels of phosphorylated angiogenic receptors like VEGFR and their related signalling transduction [44].

Aeroplysinin

Aeroplysinin-1 is a brominated metabolite isolated from the sponge *Verongia aerophoba*, possessing antibacterial, anti-parasitic, anticancer and anti-angiogenic activities. Aeroplysinin inhibits the key steps of angiogenesis by affecting endothelial cell proliferation, migration, invasion and tube formation. It is also known to induce apoptosis in endothelial cells via caspase pathway, BAD dephosphorylation and reduction of EGFR and VEGFR2 [45].

Lamellarin D

Lamellarin D is a pyrole alkaloid, isolated from a marine mollusc *Lamellaria* sp. It exerts potent cytotoxicity by apoptosis against multiple cancer cell lines [46]. Lamellarin D interferes with the activity of multiple kinases involved in cancer including CDKs and Glycogen Synthase Kinase-3 (GSK-3) [47]. CDKs play important role in endothelial cell cycle and migration, therefore they directly affect angiogenesis. However, there is no report of the direct anti-angiogenic effect of Lamellarin D and therefore, future studies in this direction are expected to give promising results.

Some other well-known kinase inhibitors are cortistatins, Ageladin A and Xanthones derived from sponges, neovostat from shark cartilage and several saccharides from marine algae. All of them show strong anti-angiogenic activity through modulation of different types of kinases and are likely to proceed for clinical trials.

Agents Inhibiting Pro-Angiogenic Factors

An array of pro-angiogenic factors are involved in the process of angiogenesis. Some of the important factors are VEGF, PDGF, EGF, HIF (hypoxia inducible factor), etc. These factors involved in every step of the angiogenic process and therefore they play key roles in regulation of tumour related angiogenesis. Out of these, VEGF is considered as the driving force of angiogenesis since it triggers the endothelial cells to form the sprout and directs it to form new blood vessels [48]. Therefore, most of the anti-angiogenic drugs are designed to target VEGF so as to break the pathological angiogenesis cascade. Many sponge derived and algae-derived compounds are reported to inhibit one or more of these angiogenic factors. Some of the more famous ones are described as follows (Figure 4).

Fucoidan

Fucoidan is a sulphated polysaccharide that is found in many brown macroalgae. It displays several pharmacological properties including anti-inflammatory, anti-viral, anti-malarial, anti-angiogenic, anti-carcinogenic and oxidative stress reducer [49]. It induces anti-tumour

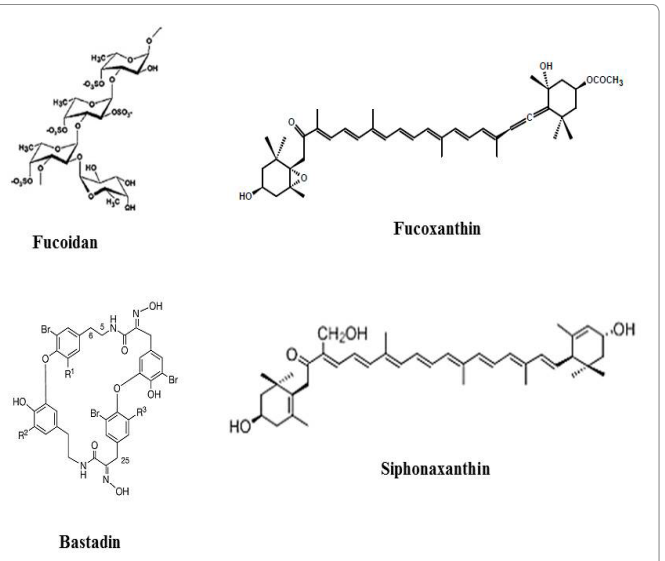

Figure 4: Chemical structures of marine agents such as Fucoidan, Fucoxanthin, Bastadin and Siphonoxanthin which are involved in targeting pro-angiogenic factors.

activity by causing apoptosis in cancer cells. Fucoidan exerts anti-angiogenic effect by inhibiting endothelial cell migration, proliferation and tube formation *in vitro*. It also has the ability to reduce VEGF and bFGF (basal fibroblast growth factor) in HUVEC. Apart from this, Fucoidan has shown promising chemo-preventive effects *in vivo* as well [50]. It demonstrated exceptionally good results against lung cancer cells both *in vivo* and *in vitro*. It has shown anti-metastatic effect on A549 (lung) cancer cells via inhibition of MMP-2 and similar effect in transplanted lung carcinoma *in vivo* by affecting several cell surface protein including integrin, VEGF 1, p-selectin, etc. [51]. The excellent results given by Fucoidan in several anti-cancer studies point out the fact that it is now ready for the next step towards its therapeutic use, clinical trials.

Bastadin

Bastadins are brominated tyrosine derivative initially isolated from the marine sponge *Ianthella basta*. Around 30 different Bastadins have been reported till date, out of which Bastadin-6, 9 and 16 are some of the more potent forms [52]. Bastadins generally exhibit anti-angiogenic as well as cytotoxic activity. They have displayed cytotoxicity and cytostatic activity against many human and mouse cell lines apart from their anti-angiogenic, anti-migratory effects in the HUVEC. Bastadin 6 has inhibited angiogenesis in HUVEC by reducing levels of VEGF and bFGF at very low concentration (IC 50- 0.052 μM). Furthermore, it completely blocked the VEGF and bFGF induced neo-angiogenesis *in vivo* and also suppressed A431 solid tumour transplanted in nude mice [53]. Although, its preclinical results are encouraging, it has yet to reach any type of clinical study.

Fucoxanthin and Siphonaxanthin

Fucoxanthin and Siphonaxanthin are both carotenoids isolated from algae. Fucoxanthin is found in several microalgae and brown seaweeds whereas siphonoxanthin is present in some of the edible green algae. Fucoxanthin exerts pleiotropic anti-cancer effect by targeting cell death, cell cycle and angiogenesis all at once. It exerts anti-proliferative effect and cell cycle arrest in a range of different cancer cell lines. The anti-angiogenic activity exercised by this compound is associated with

its ability to inhibit endothelial cell proliferation, migration and tube formation via reduction in VEGF. Besides, it also illustrates synergistic effects with established cytotoxic drugs [54].

Siphonaxanthin is known to possess apoptotic, anti-angiogenic and anti-inflammatory properties. As compared to Fucoxanthin, Siphonaxanthin shows more potent apoptosis at lower concentration through suppression of Bcl-2 (B cell lymphoma-2) and activation of caspase-3. It exerted anti-angiogenic effect *in vitro* in HUVECs and *in vivo* in rat aortic ring model. The anti-angiogenic activity of Siphonaxanthin was accompanied by reduction in angiogenic factors like VEGF, FGF-2 and their receptors FGFR-1, EGR-1 and VEGFR-2 [55]. These findings suggest that Fucoxanthin and Siphonaxanthin have great potential to be used as anti-angiogenic drugs in future.

Marine Compounds Targeting MMPs

Matrix metalloproteinases (MMPs) are zinc dependent enzymes responsible for the degradation of ECM in physiology and pathology. MMPs play a crucial role in apoptosis, signal transduction, cancer cell migration, metastasis, tumour invasion and angiogenesis, thereby making them valuable targets in cancer therapy [56]. Around 26 different MMPs are known till now and they basically function to degrade the basement membrane and extracellular matrix, thus facilitating the invasion of malignant cells through connective tissues and blood vessel walls and resulting in metastasis and tumour growth [57]. In a normal body, the activity of MMPs is regulated by pro-enzyme activation after its secretion and inhibited by endogenous natural inhibitors called as Tissue inhibitor of matrix metalloproteinases (TIMP). TIMP directly inhibit MMPs and therefore are considered to affect cancer invasion and metastasis [58]. At present, MMPs are one of the major targets in anti-cancer therapy and research is focussed on finding MMP inhibitors from natural sources [59]. The major sources of MMP inhibitors (MMPIs) from marine environment are algae and sponges. However, compounds with MMP inhibitory activity have been isolated from fishes, cephalopods, crustaceans and micro-organisms as well. Few of the widely known MMP inhibitors are explained below (Figure 5).

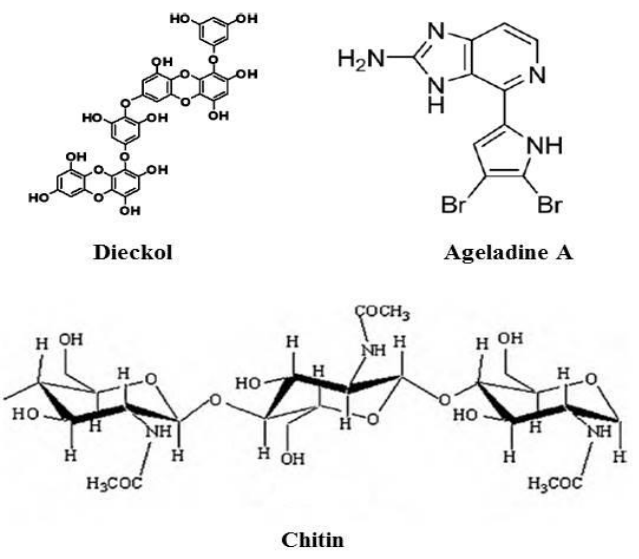

Figure 5: Chemical structure of Dieckol, Ageladine A and Chitin derived from marine sources which are involved in targeting MMPs.

Neovastat

Neovastat (or AE-941) is actually an extract, which is a mixture of several water-soluble components derived from shark cartilage [60]. The anti-angiogenic and anti-tumour benefits of Neovastat are quite well known. It is a multi-targeting agent that induces apoptosis in endothelial cells, interferes with VEGF-VEGFR2 binding and reduces expression of Hypoxia inducible factor (HIF-2α). Besides these, it also inhibits several MMPs primarily MMP-2. Studies have found the presence of TIMP-like (tissue inhibitors of matrix metalloproteinases) proteins in neovastat that might be causing MMP inhibitory effects. It has also showed promising anti-angiogenic and anti-tumour effects in the *in vivo* mouse glioma model. Neovastat cleared the phase II clinical trials but failed the phase III because of it being an extract and not a purified compound [61].

Dieckol

Dieckol is a type of phlorotannin (polyphenol derivative) isolated from the marine alga *Ecklonia cava*. It is known to produce anti-oxidant, anti-enzymatic, bactericidal, anti-HIV, anti-cancer and anti-allergic effects [62]. Its anti-cancer activity is due to its ability to induce apoptosis in various cancer cell lines. It is also a potent anti-proliferative and anti-angiogenic agent. It has demonstrated significant MMP-2 and MMP-9 inhibitory potential at very low doses [63]. Consequently, Dieckol has great potential to be used as an anti-cancer drug in near future.

Ageladine A

Ageladine A is a fluorescent alkaloid present in the marine sponge *Agelas nakamurai*. Ageladine A exerts anti-angiogenic activity *in vivo* as well as *in vitro*. It has shown the ability to inhibit not only MMP-2 but also MMP- 1, 8, 9, 12 and 13; although its mechanism of inhibiting MMPs is yet to be understood [64].

Chitin

Chitin is a muco-polysaccharide occurring in several crustacean shells including that of shrimps and crabs. It is widely known as nutraceutical product because of its versatile biological activities and edible sources [65]. Several derivatives and synthetic analogues of chitin are currently available that illustrate varied biological activities. One such derivative carboxymethyl-chitin exhibited anti-tumour activity by suppression of MMP-2 and MMP-9 as well as down-regulation of NF-κβ (Nuclear factor- κ β) [66]. It is also reported to be a strong anti-oxidant.

Sulphated ink polysaccharide

Sulphated ink polysaccharide (SIP) has been isolated from marine cuttlefish *Sepiella maindroni* and has shown anti-angiogenic and anti-tumour properties. Its anti-tumour properties are associated with its ability to induce anti-invasion and anti-migration effects. It has been reported to exert significant inhibition of MMP-2 in the human ovarian carcinoma cells SKOV3 [67]. Accordingly, SIP has great potential to be developed into a potent anti-angiogenic drug in future.

As synthetic MMP inhibitors pose quite a few drawbacks and side-effects, most of them have been put out of clinical trials. On the other hand, MMP inhibitors from marine animals, algae and cyanobacteria have given more encouraging results. However, compared to the vast marine biodiversity, these compounds are just a handful, accordingly more extensive exploration of marine flora and fauna is required in order to obtain better candidates as MMPIs.

Anti-angiogenic Marine Natural Products (MNP) in Clinical Trials

The increasing attention gained by MNPs have resulted in discovery of more and more marine derived anti-angiogenic compounds that can compete even with the best of synthetic drugs. Currently, two out of the four FDA approved marine drugs are anti-cancer agents and many more are in different phases of clinical trials. Some of the important anti-angiogenic drugs in clinical trials are debriefed here (Figure 6).

Eribulin mesylate (E7389)

Eribulin mesylate is an analogue of Halichondrin B, which is isolated from the marine sponge *Halichondria okadai*. Eribulin exerts anti-tumour effects by inducing apoptosis and acting as anti-microtubule agent. A phase III trial has approved Eribulin in U.S for treatment of metastatic breast cancer in combination with chemotherapy. Another phase III trial is still undergoing in order to check the safety and efficacy of this drug [68].

Plitidepsin

Plitidepsin (Aplidin®) is a cyclic depsipeptide which was originally isolated from the Mediterranean tunicate *Aplidium albicans* and currently produced synthetically. It exerts anti-angiogenic effect in tumours by reducing the expression of VEGF and VEGFR. It is currently in phase II/III clinical trials for the treatment of multiple types of cancer [69].

Bryostatin I

Bryostatin-I is a MNP isolated from the organism *Bugula neritina*. It exerts anti-angiogenic activity in multiple cancer types through activation of protein kinase C. At present, it is participating in clinical phase I/II against several malignancies. Although, its monotherapy has failed the clinical trials, it can still produce significant results in combination with chemotherapy. However, the toxicity and efficacy of the drug are questionable [13].

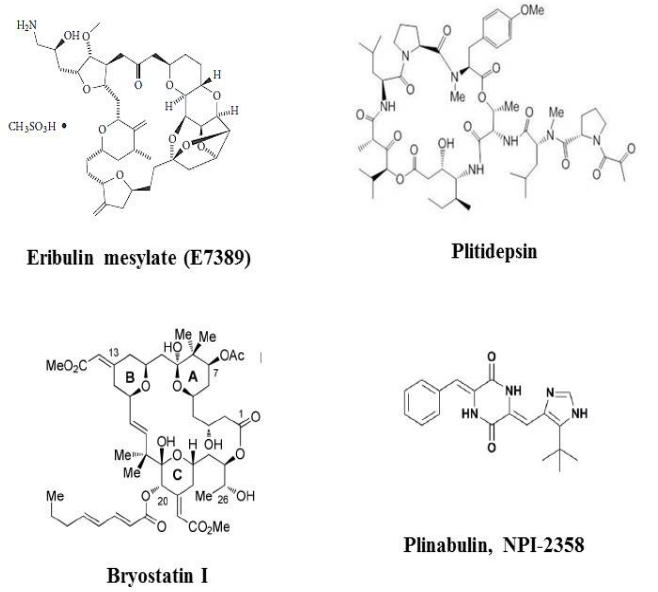

Figure 6: Chemical structures of Eribulin mesylate (E7389), Plintidepsin, Bryostatin 1, and Plinabulin- NPI- 235; anti-angiogenic marine drugs currently in clinical trials.

ABT-414

This is an antibody-drug conjugate (ADC) linking the anti-EGFR antibody ABT-806 to Monomethyl Auristatin F (MMAF) instead of Monomethyl Auristatin E (MMAE), another analogue of Dolastatin 10. As explained by the type of antibody, it suppresses the expression of EGFR, thereby reducing tumour blood supply. Currently in the initial phase of clinical trial for treatment of solid tumours that are heavily dependent on EGFR [70].

Plinabulin, NPI-2358, KPU-2

Plinabulin is a synthetic drug originally developed from halimide by modification at the phenyl ring. Halimide is a diketopiperazine metabolite, isolated from the marine fungus *Aspergillus ustus* [71], which is found to inhibit the growth of colon carcinoma and ovarian carcinoma *in vitro* and increased the survival rate of leukemic mice. It is a micro-tubule depolymerizing agent that shows potent anti-tumour activity against A549 lung carcinoma cells. Apart from this, it also disrupts the vasculature by depolymerizing tubulin in Human umbilical vein endothelial cells and is more potent than colchicine or vincristine [72]. It has been tested at Phase I and II randomized trials comparing docetaxel to plinabulin plus docetaxel in patients with advanced Non-small cell lung cancer (NSCLC) who have failed an initial therapy, and the combination has demonstrated marked anti-tumour activity along with an acceptable safety profile [73].

Some other drugs

Marizomib is a type of proteasome inhibitor, derived from marine actinomycete *Salinispora tropica*; currently undergoing Phase-I clinical trial. Besides these, some other recently discontinued anticancer drugs from MNPs are Squalamine (shark), Kahalide F (sea slug), HTI-286 (sponge), Discodermolide (sponge), Tasidoxin (sea hare), spisulosine (marine clam), etc. [13,69].

Future Prospects

To summarize, MNPs have proved their efficacy against a wide range of angiogenic targets and are increasingly becoming sources of novel and potentially life-saving drugs. MNPs are chemically more diverse than terrestrial compounds therefore, many of them possess novel mechanisms of action and others show higher potency. As specified earlier, two out of the four FDA approved marine drugs are anti-cancer drugs. However, regardless of such developments in cancer therapy, there is still an ever-growing need for new drugs in oncology. A recent review has stated that "until recently, roughly 60% of drugs used in haematology and oncology were originally derived from natural sources, and one third of the top-selling agents are either natural agents or derivatives" [74]. Despite of such achievements, production of anti-cancer drugs by use of marine natural products is still in its infancy. The major challenges in the way of large scale production of marine-derived drugs are supply and the need for deeper exploration. But then these challenges might be overcome, by the increasing development in the field of aquaculture and biomedical science. With the ever-growing number of MNPs in the literature, there are many other marine organisms just "waiting in the wings" for their chance of glory; it is our task as marine biotechnologists to find them and, ultimately, to develop them as either drugs or their sources.

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