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A comprehensive review on chemistry and pharmacology of marine bioactives as antimetastatic agents

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ABSTRACT

Metastasis by and large is responsible for the worldwide deaths associated with various types of cancers. The metastatic variant of cancer cells generated due to the cellular heterogeneity and abnormal activation of various signaling pathways in the tumor population leads to the progressive colonization of cancer cells in various organs. Over the years there has been a constant effort towards developing effective therapeutic strategies for the treatment and prevention of metastasis. The current conventional therapies have lacked efficacy due to the complex nature of metastasis involving multistep processes comprising tumor-tumor and tumor–extracellular matrix adhesion molecules, EMT, proteases, and tumor developing cell pathways. Albeit the exact mechanism of metastasis is somewhat still uncertain, there are a few recognized targets such as EMT markers, MMPs, serine proteases, microtubulin, angiogenic markers, and anoikis resistance, that have been identified as potential therapeutic targets for the inhibition of metastatic progression of cancer cells. Marine biodiversity offers unique chemical compounds due to the exposure to stressful environments for the discovery of novel bioactive compounds that are highly specific to these therapeutic targets. The review discusses various natural and semi-synthetic compounds of marine origin having antimetastatic potential, focusing on the isolation, underlying mechanism of inhibition of multiple signaling pathways, and structural modification of isolated compounds for further development as drug candidates having superior clinical translation potential.

1. Introduction

The metastasis of cancer cells from the site of primary origin to a distal tissue microenvironment, being the most important characteristic of cancer malignancy, accounts for more than 85% of cancer-associated deaths. The initial stage of cancer can effectively be managed by surgery or local irradiation, but the current treatment strategies for metastatic cancers have a meager success rate [1]. The invasion of cancer cells from their original site to the secondary anatomical region involves a multistep process comprising tumor-tumor and tumor–extracellular matrix adhesion molecules, various proteases, epithelial-mesenchymal transition (EMT), and tumor developing cell pathways [2]. The dissemination of tumor cells begins with activation of the metastasis cascade, which is triggered by chromosomal instability [3]. The process of EMT facilitates the seeding of cancer cells with a cluster of other epithelial cells [4], initiating the metastatic cascade, followed by invasion and migration of tumor cells. Although, the EMT is essential for embryonic development where cells transform into mesenchymal phenotype via expression of E-cadherin and vimentin biomarkers [5], in case of cancer metastasis, non-motile cancer (epithelial) cells attached with the adjacent extracellular matrix [6] transform themselves into mesenchymal phenotype via biochemical modifications facilitating the progression and migration of cancer [7–9]. Similarly, to maintain the tissue homeostasis, the normal epithelial cells undergo programmed cell death induced by integrin-mediated loss of attachment between epithelial cells and its suitable extracellular matrix known as anoikis. But the cancer cells develop resistance against the process of anoikis [10,11]. Simultaneously, various signaling pathways participate in the regulation of tumor metastasis starting from invasion, entry into blood circulation, halt either at succeeding capillary bed or in a site-specific manner, extravasation, and ultimately proliferating the secondary site via altering the homeostatic level of various enzymes like; matrix metalloproteases,

Abbreviations: EMT, Epithelial-mesenchymal transition; ATFs, Activating transcription factors; TGF, Transforming growth factor; MAPK, Mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; MMPs, Matrix metalloproteinases; ECM, Extracellular matrix; VEGF, Vascular endothelial growth factor; CLP, Cyclo(l-leucyl-l-prolyl); HUVECs, Human umbilical vein endothelial cells; NHDF, Normal human dermal fibroblast.

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neutrophil elastase, angiogenic markers, growth factors, etc.

The marine compounds over the years have interested the researchers for their structural diversity and eccentric chemical characteristics owing to the exposure to unique environmental conditions. Numerous such compounds from marine sources like algae, bacteria, plants, animals, and fungi have been reported to possess antimetastatic potential targeting the signaling pathways associated with the metastatic progression of cancer. However, the natural compounds from marine sources and their semi-synthetic derivatives have been extensively reported in the past for their antimetastatic, anti-invasion, and anti-migration effect, the mechanistic investigation of their effect has largely been insufficient.

Nevertheless, there are various reported studies where the compounds have been evaluated against the markers associated with metastasis exhibiting promising results and holding the key in developing new therapeutic strategies against the management of metastatic cancers. This review elaborately discusses the isolation, antimetastatic potential, structural modifications, and mechanism of inhibiting the metastatic signaling pathways of reported compounds from marine sources.

2. Regulation of signaling pathways associated with metastasis

The cyclic process of cancer metastasis initiates when tumor cell disperses from the solid tumor mass and invade the neighboring tissue either as a single entity or as a cluster of cells. During metastasis, some molecular pathways like Six1, Cripto, TGF-β, and Wnt/β-catenin along with EMT-activating transcription factors (EMT-ATFs) like SNAIL, TWIST, and ZEB families participate in the execution of epithelial-mesenchymal transition and promotes metastatic progression of tumors [8,9,12,13]. The overexpression of these genes in the tumor microenvironment causes a decrease in the expression of epithelial markers (E-cadherin) and increases the mesenchymal marker (N-cadherin) level. The epithelial cells (primary cancer cells) are connected tightly with each other with the help of E-cadherin, acting as an intercellular junction and an invasion suppressor. The decline in E-cadherin level leads to the dysfunction of cell adhesion and morphological reorganization [14]. Consequently, mesenchymal cells experience reshaping of cytoskeleton along with permanent loss of tight junction leading to enhanced invasive and migrating tendency of cells with an unstable epithelial polarity which facilitates tumor progression and proliferation [15]. In conclusion, the functional loss of E-cadherin decreased the level of cytokeratin, and overexpression of mesenchymal biomarkers such as N-cadherin, fibronectin, and vimentin are the hallmarks of initiation of epithelial-mesenchymal transition. Furthermore, extracellular cytokines like hepatocyte growth factor, fibroblast growth factor, epithelial growth factor, and TGF- β; pathways like MAPK and PI3K; and intracellular oncogenic signals like Ras and NF-κB also regulate the EMT, consequently resulting in enhanced invasion and migration potential of mesenchymal cancer cells.

Moreover, for the progression of metastasis, the cells need to detach from their original site to migrate towards distal organs. But the detached epithelial cells undergo programmed cell death called anoikis induced by integrin-mediated loss of attachment between epithelial cells and its suitable extracellular matrix [16,17]. However, in the tumor cells, defects in death receptor pathways like overexpression of FLIP (caspase-8 inhibitors), anti-apoptotic protein Bcl-2, Mcl-1.

1, and Bcl-xL causes dysregulation of anoikis, rendering the detached cancer cells resistant to cell death after detachment, facilitating colonization to other sites [10,18,19]. Also, anoikis resistance downregulates the expression of E-cadherin and enhances the expression of N-cadherin [11].

Subsequently, the invasive cancer cells produce proteases and enrich the tumor microenvironment with matrix metalloproteinases (MMPs), serine proteases, and cysteine proteases, causing the intravasation of cancer cells. The released proteases cause degradation of various structural components of ECM and facilitate tumor cell migration by disorganizing the cell-cell junctions of the surrounding tissues. These proteases also modulate the expression of growth factor binding protein, tyrosine kinases receptor, cell adhesion molecules, and other types of proteases, which facilitate proliferation, migration, invasion, angiogenesis, and metastasis. Primarily, MMPs initiate tumorigenesis in different ways; promoting the release of the membrane-bound precursor of growth factors such as TGF-α, degradation of peptide growth factors (insulin-like growth factor), affecting ECM composition (modifying growth-promoting signal via integrin). Besides, the growth and metastasis of cancer cells in the vascular phase is encouraged by angiogenesis, where VEGF aids the proliferation of vascular endothelial cells. VEGF plays an essential role in proliferation, migration, invasion, and angiogenesis [20]. Also, the cross-talk between the microtubulin dynamics and actin filament contributes to the migratory characteristics of tumor cells [21]. Fig. 1 illustrates the metastatic progression of the primary tumor to a secondary tumor at the distal anatomical region involving the process of EMT, migration, invasion, and mesenchymal-epithelial transition.

All the aforementioned processes contribute to the metastatic progression of cancer cells and have been reported in the past as potential therapeutic targets for inhibiting metastasis. Over the years, numerous marine compounds have been reported to exhibit anti-metastatic potential. These compounds have elicited promising activity towards inhibiting the signaling cascades involved in EMT, overcoming the anoikis resistance, and targeting proteases, angiogenic markers, and microtubulin dynamics (Fig. 2).

3. Marine compounds as antimetastatic agents

Chemical entities obtained from marine organisms have been identified as potential therapeutic candidates for cancer. A considerable number of naturally occurring marine compounds obtained from plants, animals, algae and fungi are undergoing research showing prominent anti-metastatic activity (Fig. 3). The continued discovery of anti-invasive compounds from marine sources led to the isolation of rakicidin, and its analogue A, B, C, and D from *Streptomyces* and *Micromonospora* genus. All these analogues were evaluated against the 26-L5 murine carcinoma colon cell line. *In vitro* assay showed inhibition of cancer cell invasion by rakicidin D [1] at IC_{50} value of 3.3 μgml^{-1}. While, rakicidin A and B exhibited higher toxicity at IC_{50} values of 0.44 and 0.17 μg/ml, respectively, suggesting that the presence of an alkyl side chain in rakicidin A and B are responsible for higher cytotoxicity [22]. Later the extract containing algal polysaccharide obtained from *M. crassissimum* was investigated for its antimetastatic activity in B16-BL6 (mouse melanoma), JYG-B (mouse mammary carcinoma), and KPL-1 (human mammary carcinoma) cell lines. Its treatment reduces the proliferation, invasive ability and several metastatic foci of B16-BL6 melanoma cells both *in vivo* and *in vitro* [23]. Another study investigated a novel bacterial polysaccharide EPS11 which showed a cytotoxic effect on the growth of Huh7.5 liver carcinoma cell lines. It significantly affects the morphology of proteins associated with cell-cell adhesion and disturbed the formation of filiform structures, subsequently decreasing the rate of cell adhesion of tumor cells. Furthermore, the downregulated expression of transmembrane protein CD99 was observed, suggesting CD99 was responsible for the metastatic ability of Huh7.5 tumor cells [24].

Different bioactive glycosides have been isolated from sea cucumber, having antiproliferative effects against cancer cells. A triterpenoid glycoside, Frondoside A [6] isolated from *Cucumaria frondosa* whose immune-modulatory effect was reported to exhibit an antimetastatic effect against breast cancer. During uncontrolled cancer growth, the level of cyclooxygenase-2 increases, releasing more prostaglandin E2 (PGE2) which results in tumorigenesis and metastasis. Frondoside acts as an antagonist of the prostaglandin E receptor (EP4 and EP2) via suppressing the intracellular cAMP activation associated with EP4 or EP2 and downregulating the ERK signaling pathway. Its exposure to an *in-vivo* model, having mammary gland implanted tumor, blocks the migration of tumor cells to the lung. It suppressed the tumor growth at 0.5 μM and

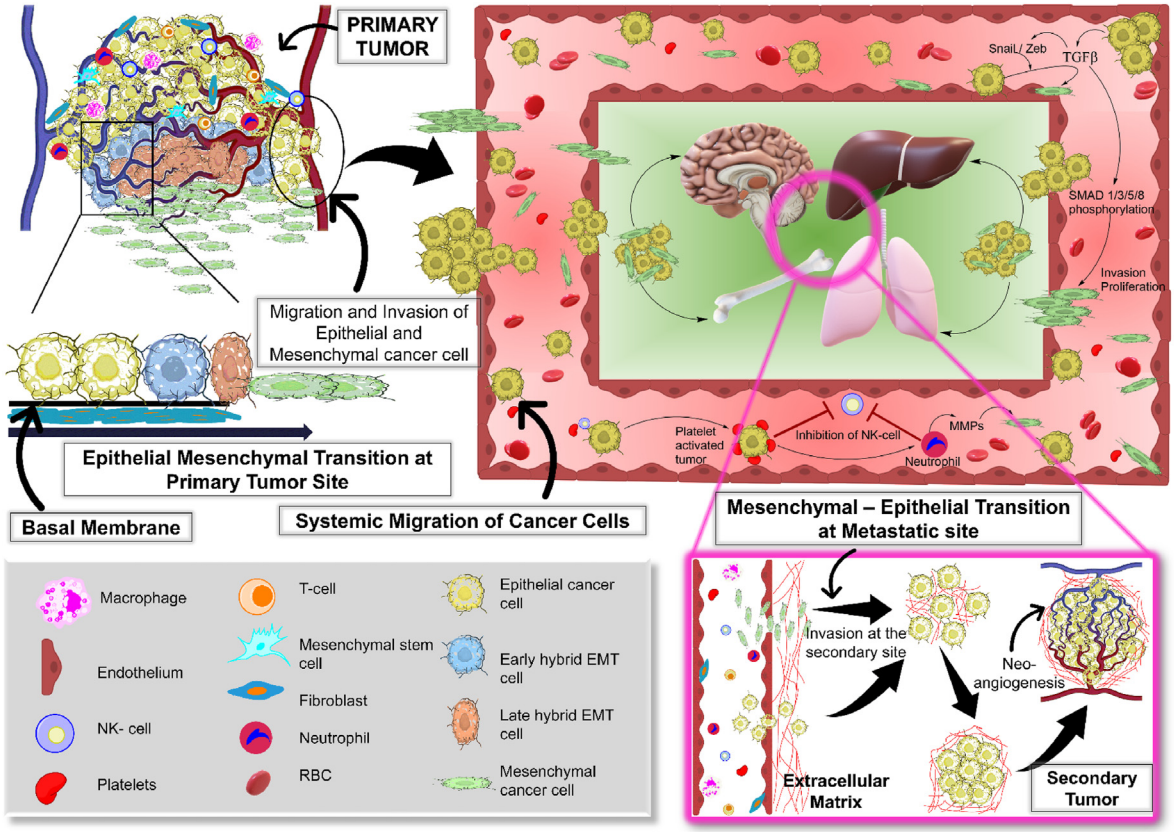


Fig. 1. Schematic illustration of cancer metastasis and progression from primary to secondary site.

inhibited the binding of 3H-PGE2 to recombinant EP4 receptor at IC50 value of 3.7 μM and EP2 receptor at IC50 value of 16.5 μM with a significant decrease in lung tumor colony-formation, dissemination, and angiogenesis of tumor cells [25]. This glycoside was found to be a safe compound and further investigated for its anti-migratory effects, alone or in combination with cisplatin. It induces caspase-dependent cell death in LNM35, A549, NCI–H460-Luc2, MDA-MB-435, MCF-7, and HepG2 cancer cell lines with the IC_{50} values between 1.7 and 2.5 μM. The inhibitory effect of cisplatin, a chemotherapeutic agent on tumor growth, was enhanced remarkably when combined with frondoside. Additionally, anticancer activity was evaluated *in vivo* in a xenografted mice model with LNM35 lung cancer cell line, where the tumor growth and volume of LNM35 xenograft get reduced on exposure to frondoside A, and it showed an anti-angiogenic effect at a concentration of 2 μg/ml. Thus frondoside A can be a novel therapeutic agent for the treatment of metastatic lung cancer [26]. *Rhizophora apiculata,* a halophyte of the family Rhizophoraceae, constitutes antiviral, antifungal, anti-inflammatory, and anti-cancer properties. One of the *in vivo* studies employing a B16F-10 melanoma-induced lung metastasis model of C57BL/6 mice reported antimetastatic action of methanolic extract of *R. apiculata*. The formation of tumor nodules in the lungs was reduced by 41.1%, and the survival rate of animals having metastatic lung cancer increased by 107.3% on treatment with *R. apiculata* extract. Even the biochemical parameters essential for tumor metastasis like uronic acid, serum nitric oxide, lung collagen hydroxyproline, γ-glutamyl transpeptidase and sialic acid, were remarkably decreased [27].

Along with marine microbes and plants, various alkaloids from animals have been reported potentially active against cancer metastasis. A brominated alkaloid, Subereamolline A [5] isolated from *Suberea mollis*, was evaluated for antimetastatic activity against the MDA-MB-231 breast cancer cell line. This alkaloid suppressed the motility and invasive ability of tumor cells at nanomolar concentration, as well as exhibited a cytotoxic effect at 30 μM concentration. The presence of a low molecular size group, like ethyl carbamate moiety, at the terminal end of Subereamolline A enhances its binding capacity with the target receptor and the presence of dibromo group was responsible for its anti-migratory action [28]. Motuporamines [7], another marine compound isolated from barrel sponge *Xestospongia exigua*, was reported to inhibit cancer cell invasion in MDA-231, PC-3, U-87, and U-251 glioma cells. The compound causes a decline in integrin activation, diminishes actin-mediated ruffling and anti-angiogenic effect on cell lines [29]. Different naturally occurring marine compounds having similar anti-metastatic potential have been reported which are summarized in Fig. 3 and the brief discussion of these compounds has been tabulated in Tables S–1 present in the supplementary information [29–43].

3.1. Targeting MMPs and epithelial-mesenchymal markers

MMPs are required in various stages of cancer metastasis as different types of MMPs have different functions like MMP-2, 9, 14, and 19 regulates angiogenesis, MMP-3, 7, 9, and 11 modulates the apoptotic cell death [44,45]. Various bioactive constituents have been extracted from algae, bacteria, sponges, and fungi acting as MMPs Inhibitors which are present in Fig. 4 and Tables S–2. Fucoxanthin [18], a marine carotenoid was reported to have inhibitory activity against tumor cell growth in breast, cervical, colorectal and lung cancer cell lines. Further, its anti-metastatic potential was examined *in vitro* against A549, H1299, and H446 lung cancer cell lines. It was found that fucoxanthin-treated cells showed a significant reduction in migrating and invasive capability of the lung cancer cells. The molecular mechanism involved in attenuating migratory ability was decreased expression of EMT-related proteins like Snail, Twist, MMP-2, fibronectin and N-cadherin. Also, it upregulates the expression of TIMP-2 protein causing reduced cancer cell invasion. Moreover, fucoxanthin inhibited the PI3K/AKT/NF-κB signaling

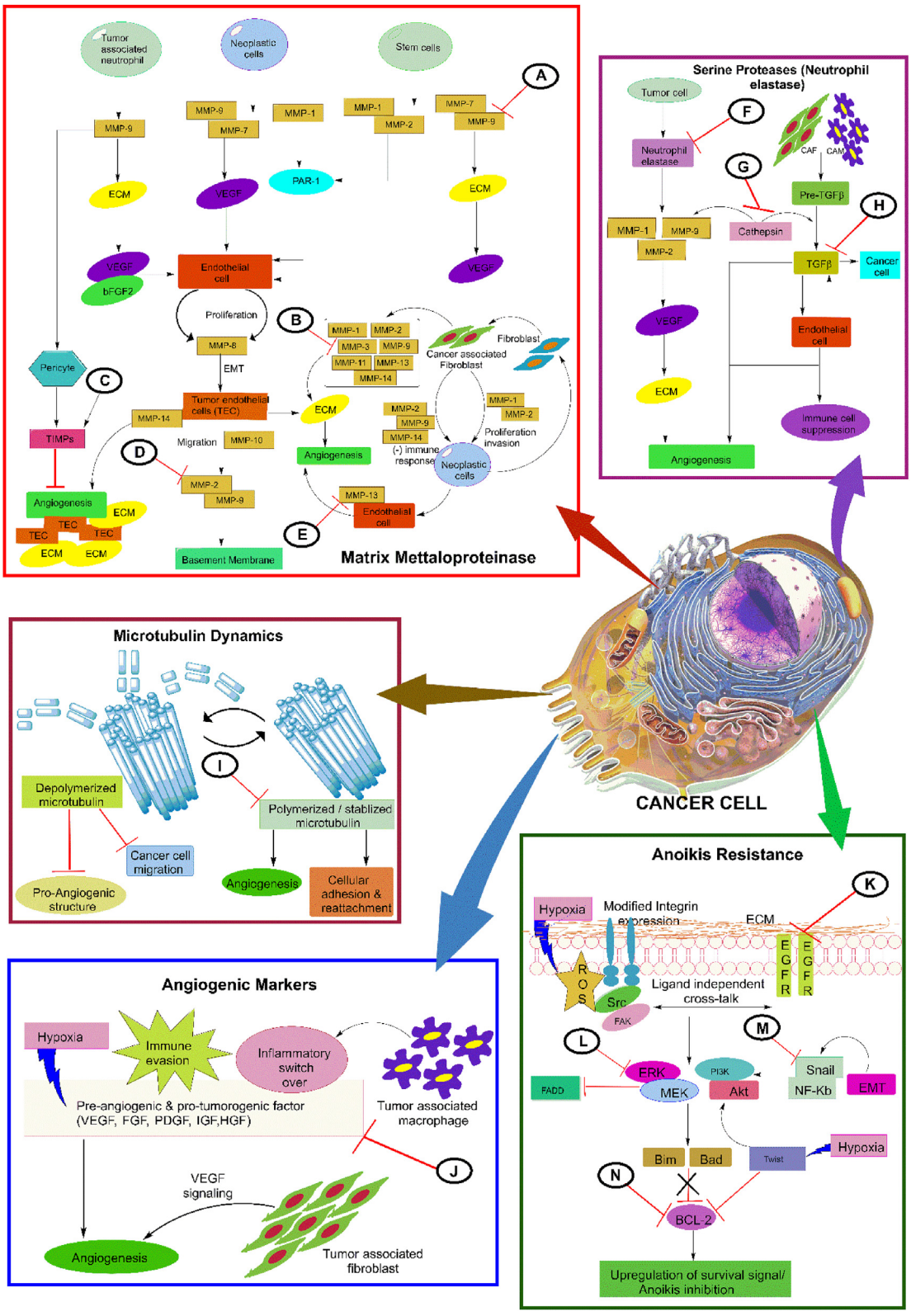


Fig. 2. Pathways involved in cancer metastasis and therapeutic targets of various marine compounds. Examples of marine drugs acting on various targets A) Emodin, B) Selamoellennin, C) Fucoxanthin, D) Halichondramide, E) Diekol, F) Molassamide, G) Grassystatins, H) Fucoidan, I) Viriditoxin, J) Cortistatins, K) CLP-cyclic peptide, L) Frondoside A, M) Jorunnamycin A, N) Penicitrinine.

pathway, which is responsible for lung cancer metastasis via promoting EMT-related gene expressions. Exposure to fucoxanthin decreases the number of metastatic nodules and the density of tumor population in lung tissue *in vivo* also [46]. In another study, fucoxanthin was isolated from *Saccharina japonica* and its antimetastatic activity was investigated in the B16–F10 melanoma cell line. A decreased expression of MMP-9 protein along with the reduced formation of actin fiber, stress fiber, and lamellipodia was observed, which subsequently decreases the

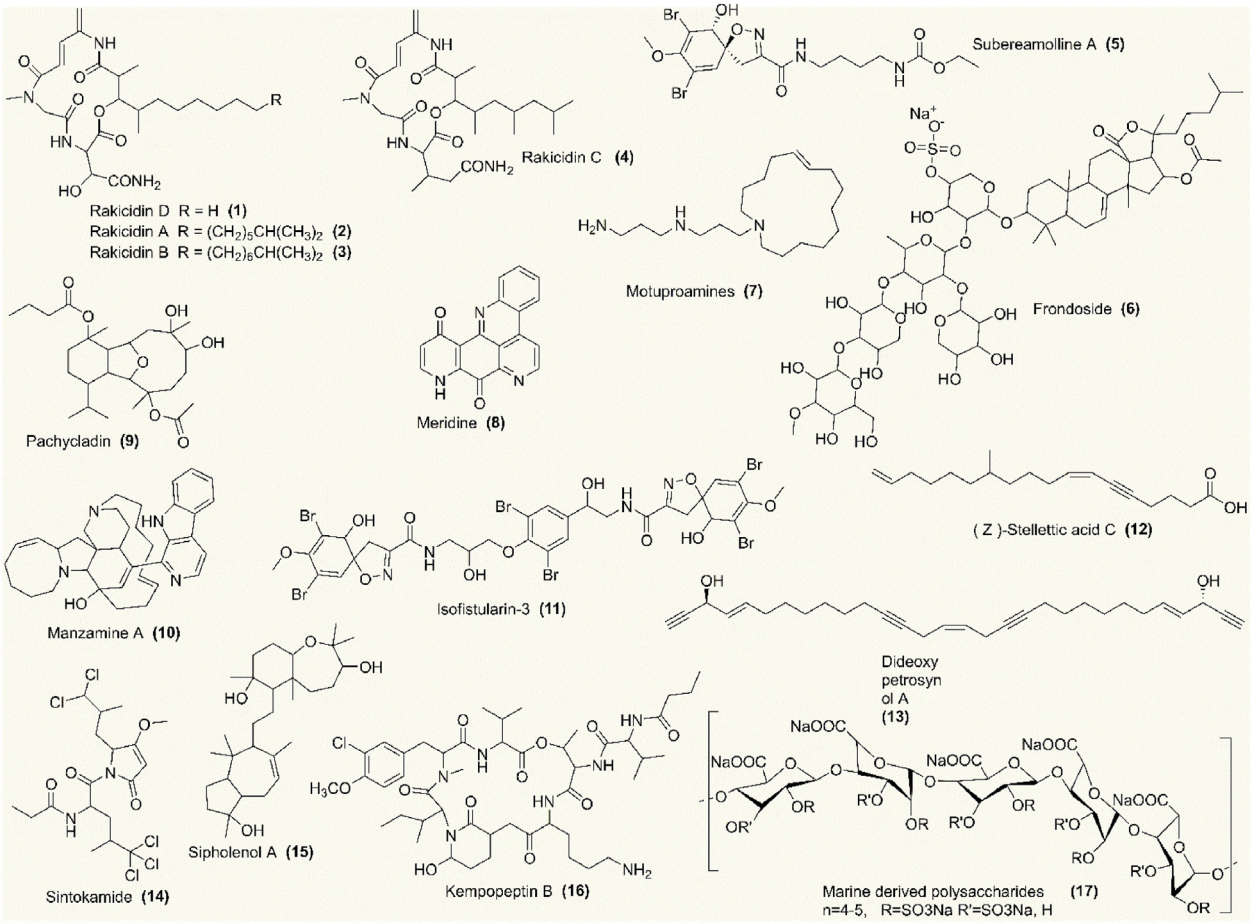


Fig. 3. Marine compounds as anti-metastatic agents.

metastatic cell motility. The expression of CD44 and CXCR-4 cell surface glycoprotein was downregulated, which is a vital element in the adhesion of lung endothelial cells to melanoma cells, binding of melanoma cells to cancer-associated immune cells for extravasation of metastatic cells and cytoskeleton formation [47].

During the later stage of breast cancer, transforming growth factor β1 (TGFβ1) promotes the proliferation and metastasis of tumors by facilitating the separation and migration of epithelial cells from neighboring cells to other regions. This EMT process leads to a decline in E-cadherin and γ-catenin levels while enhancing the mesenchymal marker N-cadherin and vimentin. A sulfated polysaccharide named fucoidan [19] isolated from brown algae was reported to possess antimetastatic activity against 4T1 and MDA-MB-231 breast cancer cell lines via modulation of TGFR/Smad dependent EMT regulation. Fucoidan enhances the expression of EMT-related proteins like E-cadherin, γ-catenin while downregulating the expression of N-cadherin, Vimentin, Snail, Slug and Twist. Further, it stops the tumor cell colony formation in the MDA-MB-231 cell line and decreases the population of metastatic nodules, tumor volumes and expression of phosphorylated Smad in the 4T1 xenograft mice model. Thus, fucoidan was recognized as a novel therapeutic for preventing breast cancer metastasis by modulating the expression of TGFβ receptor [48]. *Jose* et al. isolated an Ethanolic Sulfated Polysaccharides-Column Purified (ESPs-CP) from brown algae, *Padina tetrastromatica,* and examined its anticancer activity on HeLa cell lines. The polysaccharide at 1.2 mg/ml concentration reduces the number of viable tumor cells and downregulated the expression of MMP-2, MMP-9, VEGF, and HIF1A in tumor cells, along with a decline in hemoglobin content insides cells [49].

One of the research groups isolated bioactive anthraquinones-based compounds from marine fungi, *Microsporum* species and the obtained bioactive constituents were chrysophanol, physcion, and emodin, whose cytotoxicity and anti-metastatic activities were examined in HT1080 fibrosarcoma cell lines. All these three compounds affected the migratory and invasive capability of cancer cells while emodin [21] showed higher anti-metastasis activity. These compounds target PI3K and inhibit the phosphorylation of ERK, JNK, and c-jun, which result in downregulation of MMP-2 and MMP-9 and its antimetastatic activity towards fibrosarcoma cells. At 50 μM concentration, a remarkable reduction in migration of cancer cells was observed where its invasive capability was completely blocked [50].

A triterpene glycoside Ds-echinoside A (23, DSEA) was obtained from marine *Pearsonothuria graeffei* and its *in vitro* and *in vivo* assays was performed on Hep G2 (human hepatocellular liver carcinoma) cells, where treatment of DSEA leads to the inhibition of adhesion, migration, invasion, and angiogenesis of tumor cells. At a concentration of 2.65 μM, DSEA completely suppressed the metastasis and proliferation of Hep G2 cells. A decrease in MMP-9 protein, NF-Kb and VEGF expression and increased level of TIMP-1 was observed. During *In vitro* assay, the control cells possessed extensive enclosed tube networks while the treated cells on exposure with DSEA decreased their tube forming capacity leading to incomplete development of tube morphologies and decreased angiogenesis. Also in a modified CAM assay conducted *in vivo* the controlled cells displayed dense vascularization while treated cells showed diminished neovascularization [51].

Rady et al. evaluated the extract of primmorphs and mesohyls obtained from *Negombata magnifica, Hemimycle arabica, Crella spinulata,* and *Stylissa carteri* sponges against HepG2 cancer cell line. The exposure of primmorphs extract induces cell cycle arrest, caspase-mediated apoptotic

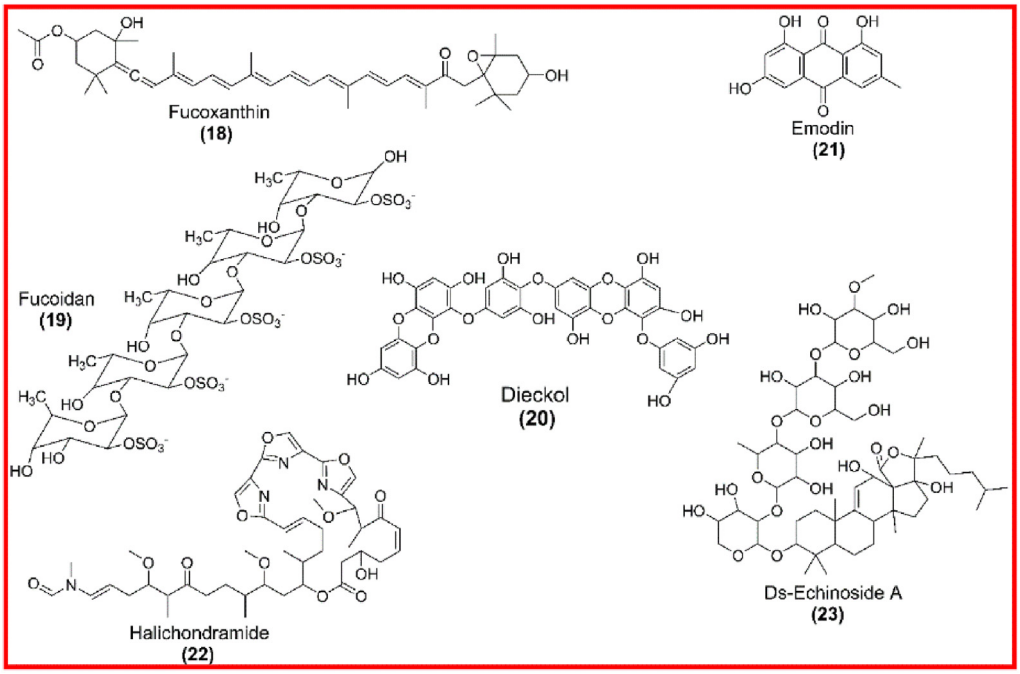


Fig. 4. Marine compounds targeting MMPs and EMT markers.

cell death, inhibits colony formation, angiogenesis, and migration in hepatic cancerous cells. Along with MMP-2, the expression of EMT-related genes like *TGFβ1, FGF4, IGF1*, and cytokines was down-regulated on treatment with primmorphs and mesohyl extract [52].

3.2. Targeting serine protease enzyme

A serine protease, neutrophil elastase plays an important role in breast cancer metastasis. From a marine cyanobacterium, three novel 3-amino-6-hydroxy-2-piperidone containing cyclic depsipeptides popularly known as loggerpeptins (A, B and C) [24–26] (Fig. 5) were found showing antimetastatic activity during breast cancer progression. Similarly, molassamide [30] having 2-amino-butenoic scaffolds were isolated from *Dichothrix utahensis* and evaluated for their action against neutrophil elastase-induced breast cancer metastasis. Both the series of isolated compounds were able to inhibit the cleavage of CD40, an elastase substrate that is highly expressed in various proliferating tumor cells. The molassamide showed dual action on the migration of tumor cells via regulating elastase-induced ICAM-1 gene expression and its proteolytic processing. It showed significant inhibition on the migration of triple-negative breast cancer cells when evaluated *in vitro* in MDA-MB-231 cancer cell lines. The 2-amino-butenoic scaffold present in the compound was found to be an essential functionality for its specificity towards elastase-mediated cancer metastasis. The *in vitro* evaluation also demonstrated that the isolated molassamide reverses the morphological modification instigated by neutrophil elastase in MDA-MB-231 cell lines through downregulating ICAM-1 gene expression. Loggerpeptins A, B, and C inhibited the neutrophil elastase at IC_{50} values of 0.29, 0.89, and 0.62 μM, respectively. In comparison, molassamide was found to be the most potent with an IC_{50} value of 0.11 μM against serine protease neutrophil elastase in breast cancer lines [53].

The normal physiological functioning of the human body requires various protease enzymes, and dysregulation in their action leads to a diseased condition like cancer. The acidic extracellular tumor microenvironment activates lysosomal aspartic proteases like cathepsins. One of the important biomarkers of breast cancer, cathepsin D is highly expressed during tumor progression and metastasis. Some novel peptides were isolated from marine cynobacterium obtained from guam, which was aimed to target aspartic protease, cathepsin D, and cathepsin E. The spectroscopy data suggested that the isolated compound contained a statine moiety, thus, named grassystatins D-F, and acts as dual inhibitors towards cathepsin enzyme. All three isolates were investigated against MDA-MD-231 triple-negative breast cancer cell lines, where grassystatin F [29] was found to be the most active compound against cathepsin D and cathepsin E, possessing IC_{50} values of 50 and 0.5 nM, respectively. Also, grassystatin D [27] and E [28] inhibited both types of cathepsins with low potency, as these compounds could not completely penetrate the cancer cells. Presence of N, N- diMet-Phe moiety at the N-terminal of grassystatin F makes the compound less polar and more permeable to enter the tumor cells. Further, the effect of isolated grassystatins on the substrate of cathepsin, cystatin C and plasminogen activator inhibitor-1 was investigated. Grassystatin F significantly suppressed the cleavage of both the substrates of cathepsin, thus inhibiting the migration of tumor cells through si-RNA knockdown of cathepsin D. it was found that Phe-statin constituting compounds derivatized with N, N-diMet scaffold could be a potential candidate for preventing triple-negative breast cancer metastasis [54].

3.3. Overcoming anoikis resistance to induce apoptotic cell death

Anoikis acts as a crucial shield for the organism that hinders the re-adhesion of detached cells to a new microenvironment in an inaccurate site along with their dysplastic development. The dysregulation in the implementation of anoikis contributes to tumor cells' metastasis, as detached cells survive and start proliferating at ectopic sites. Generally, normal cells experience anoikis in reply to ECM detachment while tumor cells gain resistance against anoikis, leading to malignancy and metastases to other organs. Tumor cells resist anoikis by going through various processes such as epithelial-mesenchymal transition, detachment-induced autophagy, modifying specific integrin switch, and constitutive activation of anti-apoptotic signaling pathways [16,17]. Therefore by counteracting this resistance by suitable drug candidates, metastasis can be completely blocked. Different alkaloids, terpenoids, macrocyclic lactones, and peptides (Fig. 6 and Tables S–2) of marine origin have been found to overcome anoikis resistance. A tetrahydroisoquinolinequinone alkaloid, Renieramycin M [31] was isolated from a Xestospongia (blue

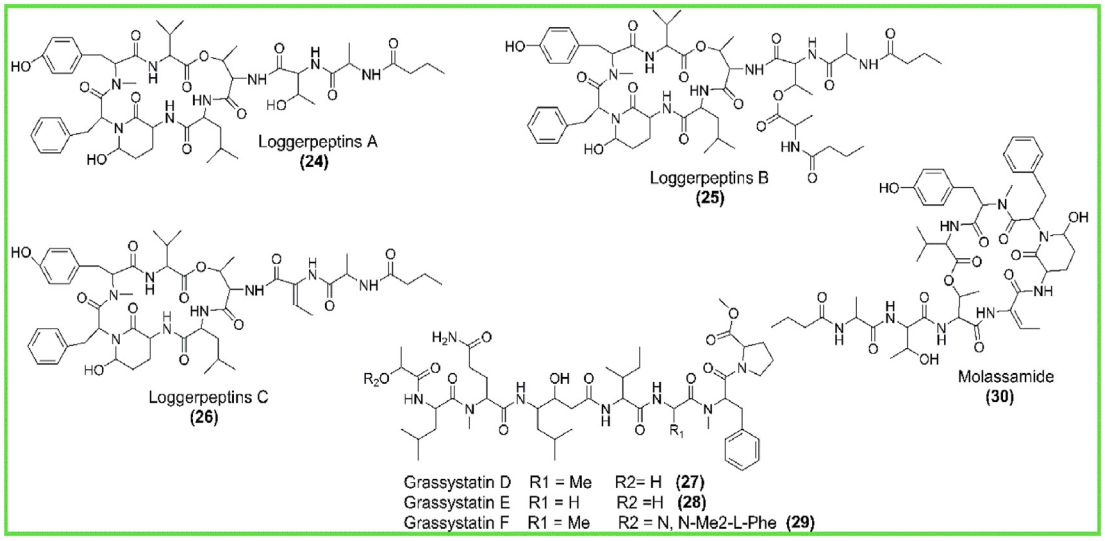


Fig. 5. Marine compounds targeting Serine protease.

sponge) and its antimetastatic action on H460 non-small lung cancer cells was investigated. Exposure to Renieramycin M increased p53 tumor suppressor protein expression subsequently causing apoptotic cell death. The upregulated p53 protein decreased the expression of anti-apoptotic protein BCL-2 and MCL-1, while the increased level of MCL-1 protein inhibited the anoikis. At sub-cytotoxic concentration, this marine compound sensitizes H460 cells to induce anoikis detachment encouraged apoptotic cell death, and prevents metastatic activity along with their cytotoxic action [55]. Similarly, *Xestospongia* species was explored further and a bistetra-hydroisoquinolinequinone compound, jorunnamycin A [32] was isolated and examined for its metastasis inhibition property. Jorunnamycin A inhibits the epithelial-mesenchymal transition by inducing anoikis in H460 lung cancer cells. The detachment-induced apoptosis was observed as the expression of Mcl-1 and Bcl-2 proteins were decreased. In contrast, the expression of pro-apoptotic proteins viz. Bax and p53 were increased when treated with jorunnamycin at 0.05–0.5 μM concentration. The expression of pro-survival proteins *p*-Akt, *p*-Erk, and survival-promoting factor caveolin-1 get reduced, leading to inhibition of Akt and Erk pathways. Also, increased E-cadherin level and reduced N-cadherin, EMT markers such as vimentin, snail, and claudin-1 were reported. Moreover, anchorage-independent growth and colonization of lung cancer cells were suppressed at 0.1–0.5 μM concentration [56]. The architecturally complex spongipyrans family constitutes several marine sponges having macrocyclic lactone, possessing anticancer potentials. One of the most potent members of this family is spongistatin 1 [35], which inhibits the microtubule assembly and thus arrests the mitotic division in cancer cells. *Andrea* et al. conducted *in vivo* study in an orthotopic model of human pancreatic cancer where exposure to a spongistatin-1 causes a significant reduction in cancer cell proliferation due to induced apoptosis. *In vitro* assay was conducted on L3.6 pl human pancreatic cancer cell line suggesting a decrease in metastatic activity due to downregulated matrix-metalloproteinase-9. Also, spongistatin triggers anoikis in metastatic cells and causes phosphorylation of Bcl-2 protein in cancer cells. To explicate the active participation of this marine product in metastasis cascade, the Bcl-2 protein was silenced using siRNA. It was found that a decrease in expression of Bcl-2 sensitizes the pancreatic cancer cell to anoikis and enhances the apoptotic cell death. Approximately forty percent reduction in migration and invasion of L3.6 pl cancer cells was observed during the downregulated expression of Bcl-2 prosurvival protein. The outcome of *in vitro* study showed the establishment of connecting link between apoptotic signaling pathways and metastasis via regulation of Bcl-2 protein [57]. Some marine invertebrates like soft coral contain various terpenoids possessing

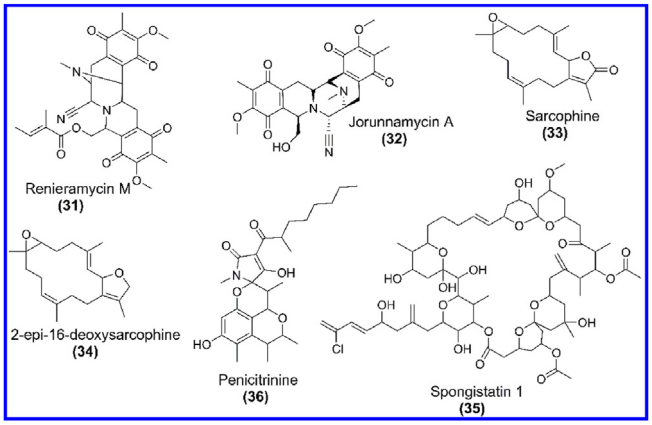


Fig. 6. Marine compounds targeting Aniokis resistance.

anticancer properties. Cembranoids, a terpenoid most abundantly found in red sea soft coral named *Sarcophyton glaucum,* which was reported to be bioactive against various cancer cell lines. Different bioactive cembranoid diterpenes were isolated from this coral reef, of which sarcophytol A and sarcophine [33] possess chemopreventive properties against cancer. To determine the antimetastatic potential of cembranoids, two compounds sarcophine and 2-*epi*-16-deoxysarcophine were reinvestigated on a mouse melanoma cell line (B16B15 b). Both of the diterpenoids revealed dose-dependent enhanced anti-migratory action on the tumor cells [58].

One of the research groups assessed the anticancer activity of a marine metabolite Cyclo (L-Leucyl-L-Prolyl) (CLP) cyclic peptide. Various assays were performed to evaluate its antimetastatic and anti-growth activity against MDA-MB-231 and MDA-MB-468 triple-negative breast cancer cell lines. This peptide showed significant cytotoxicity at concentrations 73.4 μM against MDA-MB-231 and 67.4 μM against MDA-MB-468 cell lines, without any remarkable toxicity against normal epithelial breast cells. Further morphological variation like nuclear condensation, round shape, and shrinkage of tumor cells suggests the pro-apoptotic action of CLP on breast cancer cells. The immunofluorescence staining of γH2AX confirmed the genotoxic effect exerted by CLP, where γH2AX foci were observed in CPL treated cells and no foci were observed in untreated cells. This peptide reduces the invasive capacity of breast cancer cells and inhibited the migration of 45% MDA-MB 231 cells, while

it showed 50% inhibition of the migration of tumor cells in the MDA-MB 468 cell line. It downregulates the expression of the various regulatory proteins of the cell cycle like CyclinD1, CDK4, PAK, Rac1, p27kip1, and arrests the cell cycle in triple-negative breast cancer cell lines. Moreover, CLP also targets EGFR and CD151 signaling pathways to inhibit metastasis of breast cancer cells [59].

3.4. Targeting angiogenic marker

Angiogenesis is the essential element of metastasis, increasing tumor initiation ability by upregulating the expression of various growth factors, like basic fibroblast growth factor (bFGF), vascular endothelial growth factors (VEGF) during EMT. It provides the main route to the cancer cells present at a primary site to enter the circulation and invade. The cancer cells having high vascular density possess higher metastatic potential, consequently contributing to the transition of dormant hyperplasia to the vascularized tumor [60,61]. The various compounds from a marine source have been reported to regulate angiogenesis during cancer metastasis (Fig. 7 and Tables S–2). A macrocyclic brominated tyrosine derivative, bastadin 6 [37], was obtained from sponge *Lanthella basta,* and was examined for its inhibitory action against metastasis in endothelial cells. It emerged as selective inhibitors of proliferating tumor cells in HUVECs (human umbilical vein endothelial cells). This macromolecule inhibited VEGF and bFGF dependent growth of HUVECs at IC_{50} value 0.052 μM. When the HUVEC cells were treated with 1.0 μM of bastadin 6, VEGF-induced cell motility was decreased, and at 0.1 μM concentration, bFGF induced tubular formation was suppressed. Further *in vivo* assay was performed that demonstrated complete inhibition of VEGF and bFGF mediated neovascularization in A431 tumor in mice [62]. Along with bastadine 6, two more bastadins, named bastadine 9 and 16, were isolated and found to be cytostatic and antimetastatic against cancer cell lines [63]. Further cortistatins [41] and their isomers (cortistatins A, B, C, and D) were isolated from *Corticum simplex* and evaluated for their antimetastatic activity against NHDF (Normal human dermal fibroblast), KB3-1 (KB epidermoid carcinoma cells), K562 (Human chronic myelogenous leukemia cells), and Neuro2A (Murine neuroblastoma cells) cell lines. These novel compounds were found to possess highly selective cytostatic antiproliferative action against HUVECs even at 2 nM concentration. Cortistatin A completely blocked the VEGF or bFGF induced tubular formation and migration of tumor cells in HUVECs cell lines. Cortistatin A constitutes 9(10–19)-*abeo*-androstane and isoquinoline skeleton that was essential pharmacophores for its anti-angiogenic activity [64]. Moreover, an isomarabarican-type triterpenoid, Globostellatic acid X methyl ester [38], isolated from marine *Rhabdastrella globostellata* was reported to possess selective anti-metastatic property against HUVECs. Exposure to this compound caused a reduction in migration, proliferation, and bFGF-induced tubular formation in HUVECs [65]. Some SAR studies suggested that the presence of unfunctionalized conjugated penta-ene side-chain, along with 13*E*-stereochemistry in globostellic acid was essential for its selectivity and potency towards tumor cells of HUVECs [66]. A brominated alkaloid, Aeroplysinin-1, which was earlier reported for inhibition of integrin protein, showed apoptotic cell death and decreased migration and invasion capacity of tumor cells in BAE (bovine aortic endothelial) cell lines at an IC_{50} value of 3.0 μM. In CAM assay, it showed dose-dependent anti-angiogenic effects and its treatment causes disarrangement of pre-existing blood vessels, leaky vessels, intra tissue haemorrhage, and decrease in the number of functional vessels [67]. Smenospongine [39]

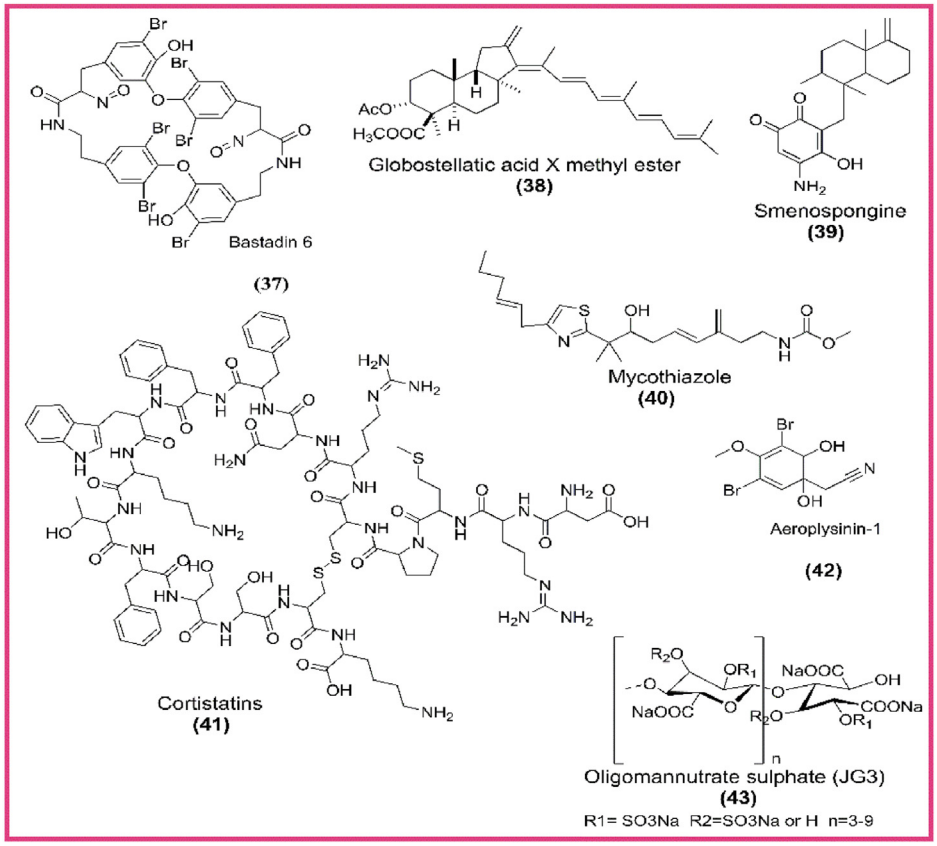


Fig. 7. Marine compounds targeting Angiogenic Markers.

and Mycothiazole [40] are two other compounds obtained from a marine sponge, which inhibited proliferation, migration and tube formation in HUVECs, confirming their antiangiogenic actions [68,69].

3.5. Targeting microtubulin

The microtubules, being the essential elements of the cytoskeleton, maintain the plasticity of moving cells, and the dynamic coordination between microtubules and actin filament contributes to the migratory characteristics of tumor cells [21]. But a collapse in the microtubule system of the cells causes loss of polarization resulting in reduced directed migration [70]. Viriditoxin [44], Latrunculin [45], Azaspiracids [46], Brintonamide A [47] are some of the marine-derived compounds that target microtubulin dynamics (Fig. 8).

Spongistantin 1, a macrocyclic lactone obtained from *Spirastrella spinispirulifera*, activates caspase-dependent cell death by inhibiting overexpression of XIAP (caspase inhibitor) in apoptosis-resistant cancer cells [71]. *Rothmeier* et al. reported spongistatin 1 as a tubulin antagonist, which inhibited angiogenesis in endothelial cells and disintegrated the microtubules by binding to a specific site present on β-tubulin during cancer. It blocks angiogenesis at IC_{50} value less than 50 nM, inhibits tumor cell migration at concentration 1.0 nM, suppress tube formation (1.0 nM), stops chemotaxis (1.0 nM) and inhibits neovascularization (*in vivo* 10 μg/kg) in HUVECs cells [72].

Along with the aforementioned compounds, several marine bioactives have been reported targeting cancer metastasis which is briefly tabulated in *Tables S–2* [73–100].

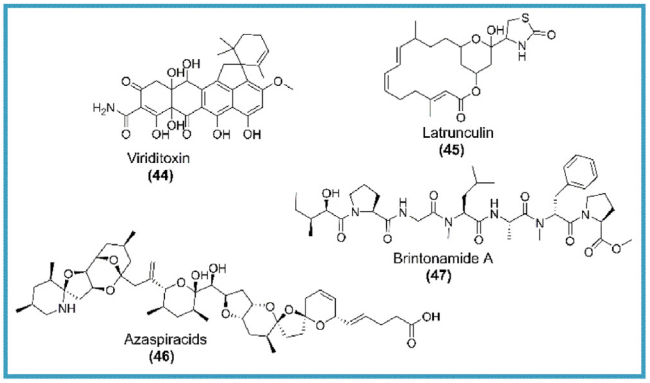


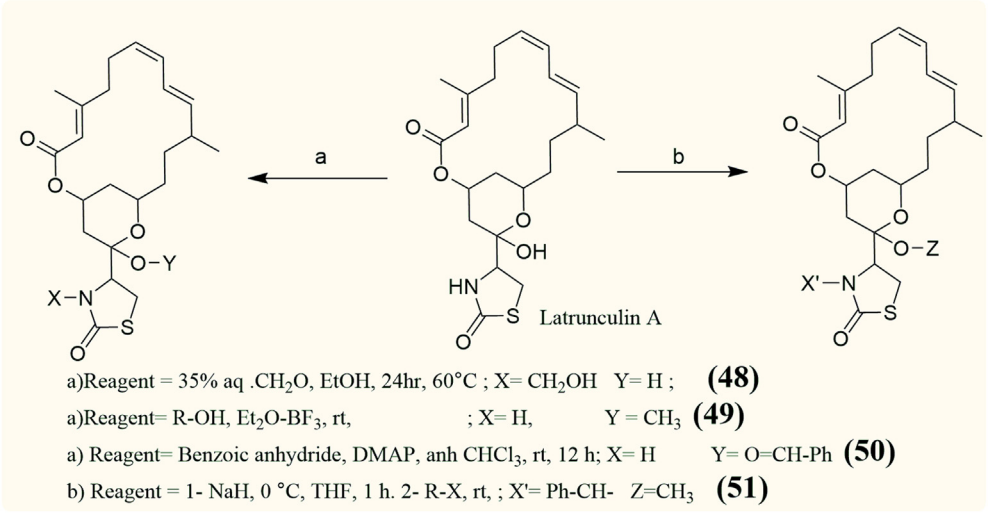
Fig. 8. Marine compounds targeting) microtubulin dynamics.

4. Semisynthetic derivatives of marine origin having anti-metastatic potentials

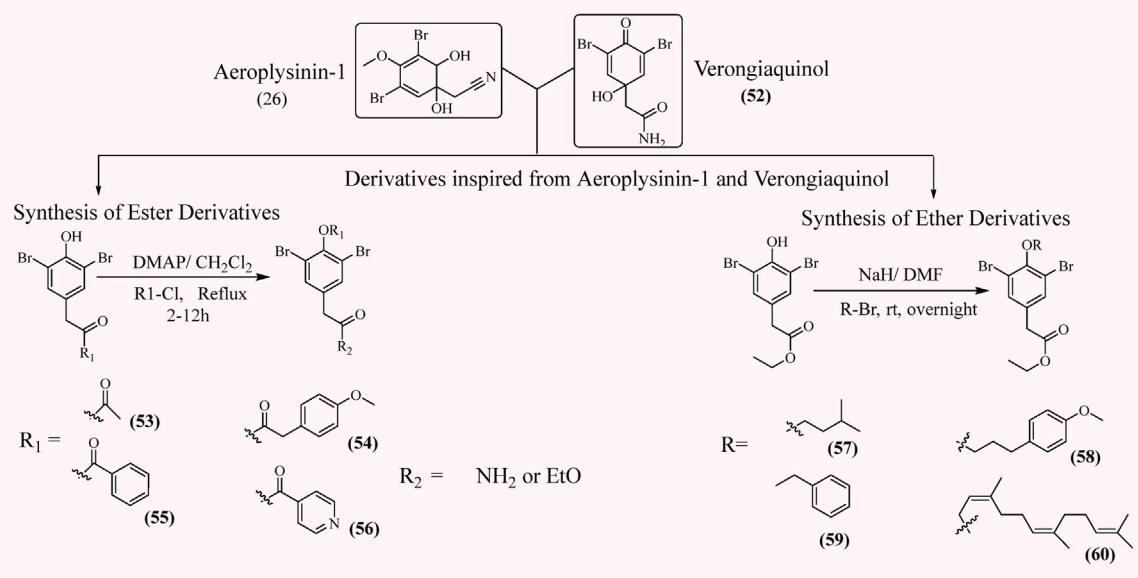
The emergence of resistance to conventional therapies complicates the cancer treatment at the advanced stage. Various bioassay-guided fractionation methods have been employed to find potential pharmacophores from marine sources, which can be further synthesized with required modification. To improve the pharmacokinetic parameters and bioactivity of the drug candidates, numerous changes were made to the basic scaffolds of the marine compounds, which are summarized in *Tables S–3*.

Macrolides latrunculins A and B, obtained from sponge *Negombata magnifica,* were reported to have anti-metastatic action by blocking polymerization of actin monomers that is essential for the proliferation and migration of tumor cells. Latrunculin A reversibly binds and forms a 1:1 complex with G-actin. A series of C-17 lactol hydroxyl or thiazolidinone NH substituted derivatives of latrunculin A were synthesized having aliphatic or aromatic substituents. These semisynthetic derivatives of latrunculin A had required steric, electrostatic, and hydrogen bond donor and acceptor characteristics, to modulate binding affinity toward G-actin. The parent latrunculin undergoes esterification, acetalization, N-alkylation, and demethylation to form different derivatives using various reagents *(*Scheme 1*)*. Further, the analogues were evaluated for their antimetastatic action against MCF7 and MDA-MB-231 cell lines. They showed antiangiogenic, anti-invasive, and anti-migratory action due to interrupted actin polymerization. *N*-Hydroxymethyllatrunculin A was found to be the most potent semi synthesized derivative as it showed improved activity over latrunculin A against cancer cell lines. Substitution of thiazolidinone NH with N-hydroxymethylene group in the basic structure increases the binding affinity through the formation of a strong hydrogen bond. At 1 μM concentration, *N*-Hydroxymethyllatrunculin A showed 90% inhibition of the invasive ability of tumor cells [86].

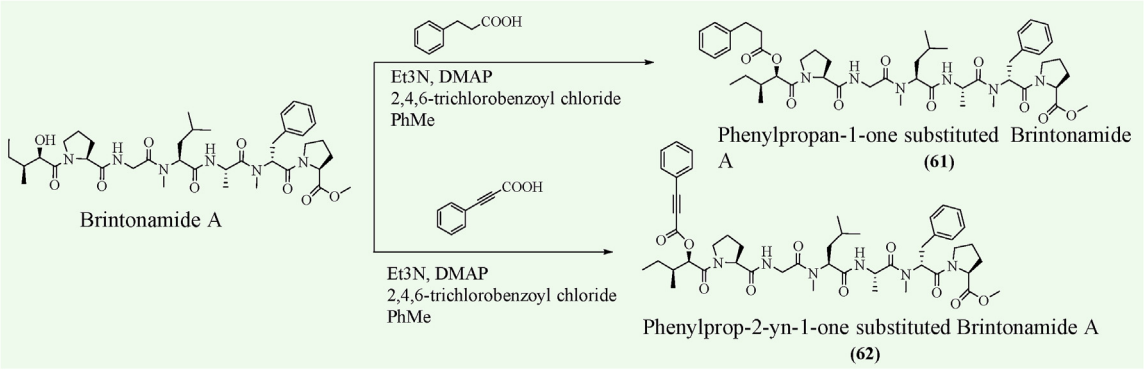
Dibromotyrosine analogues inspired from verongiaquinol and aeroplysinin-1, the marine bioactive secondary metabolites possessing metastasis inhibition properties, were synthesized and evaluated for their anti-metastatic action. The docking experiment was performed at the ATP binding site of VEGFR 2, suggesting the design and synthesis of dibromotyrosine inspired phenolic ester and ether derivatives having a potential anti-angiogenic effect and anti-migratory against prostate cancer. Two reaction schemes were designed guided by in silico study; in one of the schemes, esterification of the phenolic hydroxyl group with alkyl or aryl acid chloride was carried out in the presence of N,N-dimethylaminopyridine (DMAP), and in another, etherification of the phenolic group with alkyl or aryl bromide was carried out in the presence



Scheme 1. Synthesis of Latrunculin A analogues.



Scheme 2. Synthesis of Aeroplysinin-1 and Verongiaquinol inspired analogues.



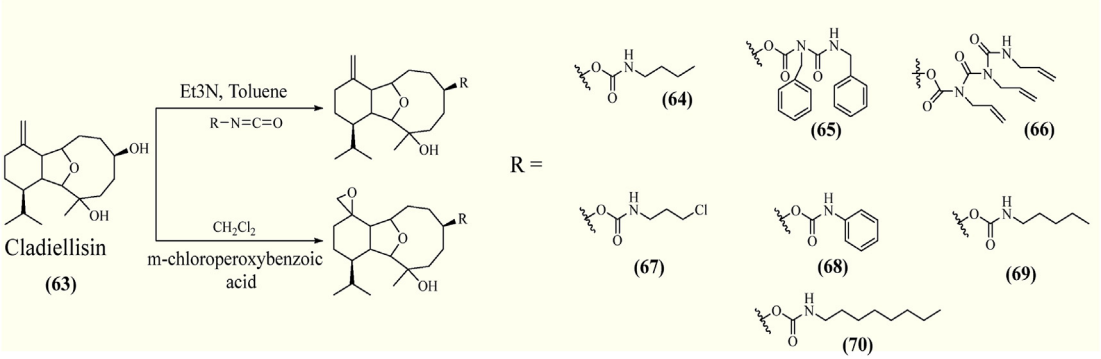
Scheme 3. Synthesis of Brintonamide A analogues.

of NaH (Scheme 2). It was found that ester derivatives possess higher antimetastatic activity, while ether derivatives showed higher antiproliferative activity against PC3 cell lines. The dibrominated scaffold showed a promising anti-angiogenic effect and inhibited migration of prostate cancer cells via targeting VEGFR2 [101].

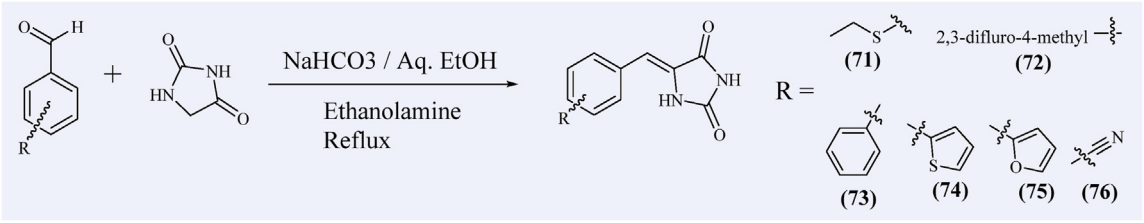
Brintonamides (A-E), novel linear peptides, were isolated from marine cyanobacteria, and their derivatives were synthesized having antimetastatic potential. These peptides modulate GPCR (CCR10, CXCR7, OXTR, SSTR3) mediated migration and proliferation of breast cancer cells. The expression of chemokine at specific sites commands the tumor migration and increases their adhesive and invasive abilities [102,103]. Approximately 40% of the migratory capacity of tumor cells was inhibited when MDA-MB-231 cell lines were treated with brintonamides. Furthermore, brintonamides acts as GPCR antagonists as well as promising protease inhibitors. Two structurally related derivatives were synthesized from esterification of brintonamide A with an acid group via Yamaguchi mixed anhydride conditions, as described in Scheme 3. Brintonamides having a free hydroxyl group were found to be less potent, so regioisomeric analogues were designed constituting cinnamic acid residue at N-terminus. The presence of unsaturation and Michael acceptor in cinnamic acid residue enhances the biological activities against chemokine receptors. Also, Brintonamide and its synthetic analogues exhibited significant inhibitory activity against proteases like chymotrypsin, kallikrein 7, chymase, and cysteine protease [104].

Hossam et al. synthesized semisynthetic derivatives of Eunicellin diterpenoids, isolated from sea coral named *Cladiella pachyclados*, which were found to have significant inhibitory action against migration and invasion of prostate cancer cells. Cladiellisin, one of the constituents of cladiella, was treated as starting material, which undergoes C-6 carbamoylation and epoxidation to produce ten new analogues having potential antimetastatic action against PC-3 cells. The C-6 secondary alcohol and C-11,17 exomethylene position were explored. The carbamate analogue was more potent than cladiellisin (IC_{50} = 88 μM) due to the rigid system at C-16/C-17, which subsequently increased their anti-invasive action. While the incorporation of the aromatic group at an optimal distance from C-6 oxygen enhances anti-migratory activity. The general chemistry involved in the synthesis was carbomylation of cladiellisin with various aliphatic and olefinic aromatic isocyanates, which produced corresponding C-6 carbamate derivatives (Scheme 4). This carbamate functionality provided hydrogen bond acceptor carbonyl group along with hydrogen bond donor group in synthesized analogues, making them potential inhibitors of prostate cancer metastasis [105].

The natural phenylmethylene hydantoin (PMH), obtained from marine sponge *Laxosubrites* species, served as a novel lead for the synthesis of various hydantoin derivatives having control over metastatic prostate cancer. PMH and its derivatives demonstrated remarkable anti-invasive action in xenograft and transgenic mice models. At 50 μM concentration, PMH inhibited the disruption of cell-cell adhesion, while at 15.5



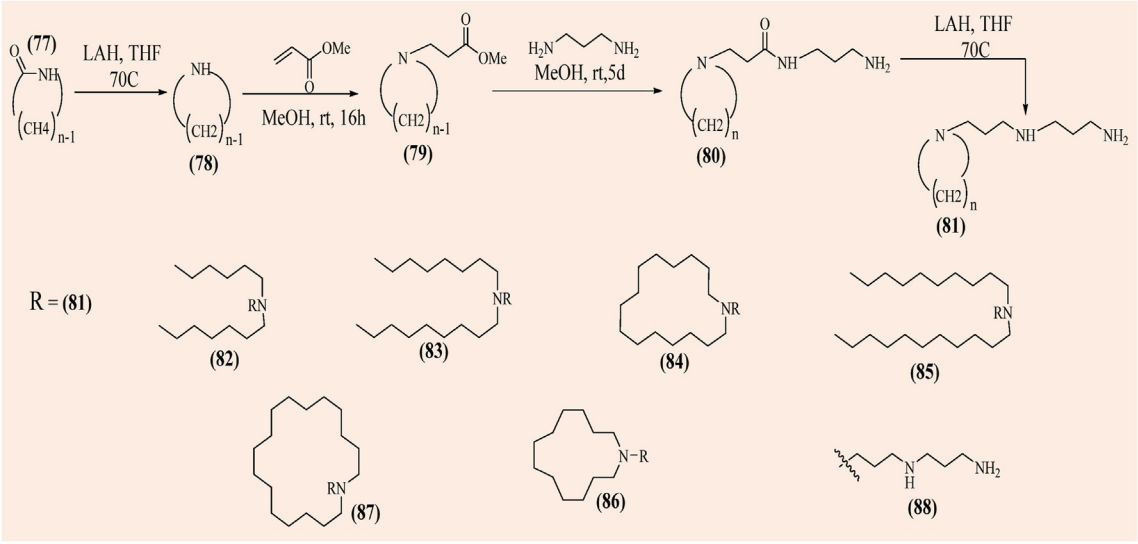
Scheme 4. Synthesis of Cladiellisin analogues.



Scheme 5. Synthesis of phenylmethylene hydantoin (PMH) analogues.

μM, the most potent derivative of hydantoin reduces the formation of tumor metastases at the distant organ. The synthetic derivatives were prepared through a base-catalyzed condensation reaction of PMH with substituted benzaldehyde in the presence of ethanolamine (Scheme 5). These hydantoin-derived compounds were introduced with different electronic, lipophobic, and lipophilic factors. They suppressed the development and growth of tumor micrometastases in distant organs and destabilized the junctional complex, a vital step in the transformation of localized to the metastatic tumor [106].

Bioassay-guided fractionation of extract of *Xetospongia* species led to the recognition of motuaporamine (A-C) as anti-metastatic compounds. Further, the extract was explored, which afforded motuporamine D, E, and a mixture of G, H, I, showing anti-invasive activity. The saturated 15-membered cyclic amine fused to natural motuporamine diamine side-chain emerges as a potent compound having inhibitory action against tumor invasion. A series of synthetic derivatives were prepared using motuporamine (A-C), and evaluated for anti-invasion activity against MDA-231 and HUMEC breast cells. The X-ray, SAR data, along with conformational analyses, predicted the functionality and shape of the designed compound for better anti-invasion action. The synthetic analogue was prepared to evaluate the effect of varying macrocyclic amine scaffold, through modification in ring size, substituting ring with two linear saturated alkyl chains, substituting macrocyclic amine with polycyclic or partially aromatic amines. Also, diamino side chain was modified by altering the space between amines and the number of amines. The general chemistry involved in the synthesis of motuporamine analogues is described in Scheme 6. Replacing cyclic amine with dihexylamine, dioctylamine, and didecylamine resulted in the formation of the most potent acyclic motuporamine derivatives of the series. At a concentration less than 15 μM, these derivatives showed inhibitory



Scheme 6. Synthesis of Motuporamine analogues.

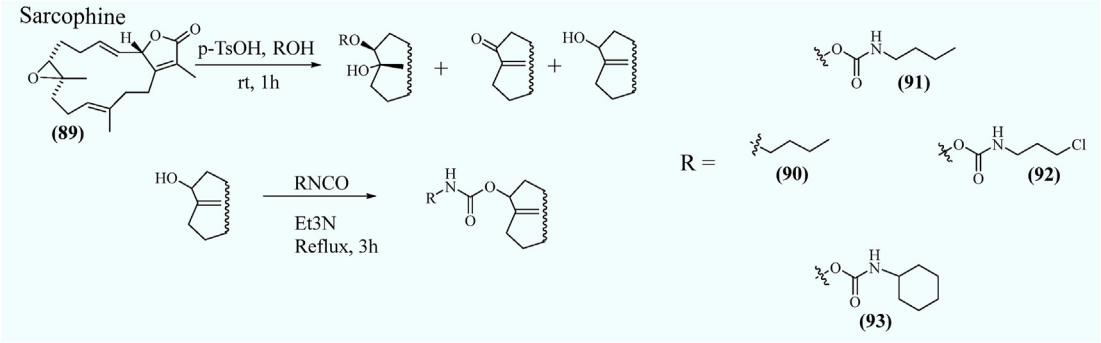
action against the invasion of MDA-231 and HUMEC cancer cells [107].

Sarcophyton glaucum contains a cembranoid diterpene, Sarcophine having metastasis inhibition property. Sarcophine analogues were synthesized and evaluated for antimetastatic action against breast (MDA-MB-231) and prostate cancer (PC-3) cell lines. The semisynthetic derivatives were prepared by modifying the C-7 of sarcophine via etherification and carbamoylation (Scheme 7). Remarkable improvement in anti-migratory action was observed when epoxide moiety was converted to secondary alcohol or ketone with an exomethylene group at C-7 that contributed to the increased binding ability to the targets. It was found that carbamates and saturated ethers revealed better action than olefinic or aromatic carbamates, while the incorporation of halogen decreased the anti-metastatic action. The synthesized cembranoids were found effective at a concentration lower than 20 μM, as they showed antiproliferative, anti-migratory, anti-invasive, and cytotoxic activity against MDA-MB-231 and PC-3 cancer cell lines [108].

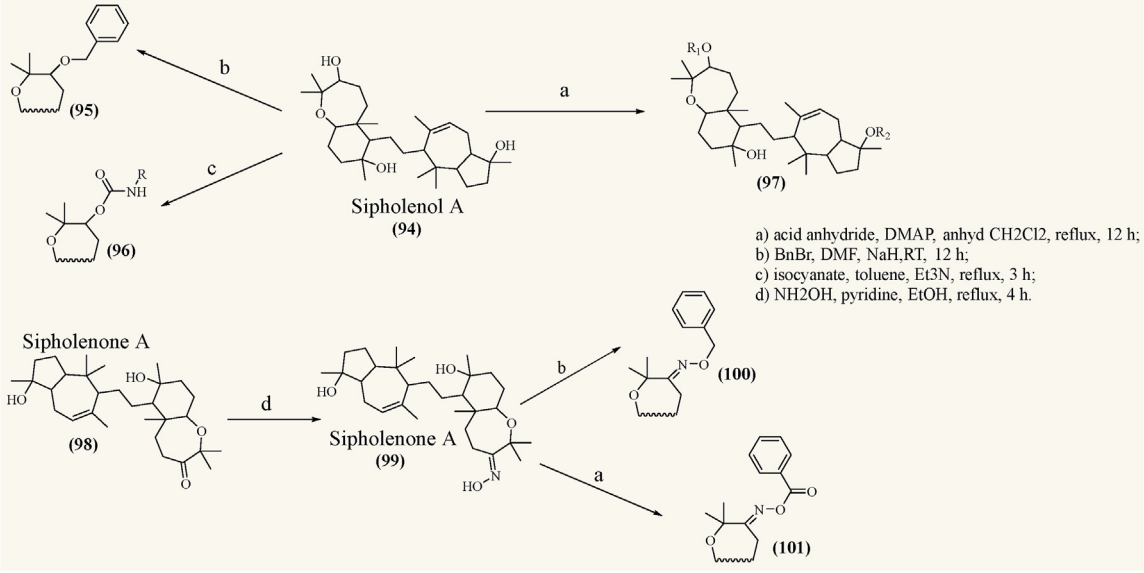
The sipholanes triterpenoids, obtained from *Callyspongia siphonella*, were reported to have anti-metastatic activity [42,109]. Sipholenol A and Sipholenone A were found to be highly antimetastatic against human breast cancer cell lines. Both of these compounds were semisynthetically optimized, and their oxime, ester, ether, and carbamate analogues were prepared to increase their anti-invasive and anti-migratory activities. The ester derivatives possess better anti-migratory action as compared to other analogues. The most potent compound of the series was 4β-4-chlorobenzoate, and 19, 20-anhydrosipholenol A esters, with an IC_{50} value of 5.3 μM and 5.9 μM, respectively, against MDA-MB-231 cell lines with no cytotoxicity in normal epithelial breast cells. These compounds were able to reverse the multidrug resistance of tumor cells overexpressing P-glycoprotein. Furthermore, they showed significant suppression of PTK6 phosphorylation, which is responsible for the growth and migration of breast cancer cells. The sipholane triterpenoids undergo various reactions like acid-catalyzed, elimination, esterification, etherification, carbamoylation, and oxime formation to produce several semisynthetic derivatives which are described in Scheme 8 [110].

5. Clinical status of marine-derived anti-metastatic compounds

The marine habitat has proven to be a highly rich source of bioactive compounds with potential anti-proliferative, anti-migratory, cytotoxic, and anti-invasive properties exhibiting clinical translational potential. A significant number of molecules have been semisynthetically obtained from marine sources, which have reached clinical trials for the treatment of metastatic cancers. With some natural marine compounds like Dolastatin 10 and semisynthetic compounds like Eribulin mesylate and edotecarin already being approved for clinical use in the past, the marine origin compounds have shown translational value along with safety and efficacy. Considering the natural abundance, distinct chemical structure, and yet largely being untapped, marine sources still exhibit the immense potential to develop novel therapeutic candidates for antimetastatic activity. Some of the semisynthetic derivatives of marine compounds established as a clinical candidate have been sum up in Table S-4 [111, 112].



Scheme 7. Synthesis of Sarcophine analogues.



Scheme 8. Synthesis of Sipholenol A and Sipholenone A analogues.

6. Conclusion

Metastasis, being the most significant characteristic of cancer, determines its clinical stages and prognosis. The tumor cell goes through complex modification and achieves an invasive phenotype to become metastatic. The published data illustrates that the marine ecosystem provides cancer metastasis modulating entities as well as serves as a tool to discover new molecular targets for therapeutic interventions. The polysaccharides, alkaloids, terpenoids, carotenoids, peptides, and glycosides obtained from marine microbes, plants, and animals are a favorable source of unexploited drugs having structural variability and diverse antimetastatic activities targeting various molecular targets of metastasis. The sui generis structures of compounds from the marine sources make them distinct and highly specific towards different molecular targets of metastatic signaling like; MMPs, integrins, apoptotic proteins, microtubulin protein, and angiogenic markers. These compounds have shown prominent metastatic inhibition properties in different cancer cell lines and many of them have exhibited synergistic effects with traditional anticancer drugs with decreased toxicity and improved therapeutic index. Besides, to improve pharmacokinetic parameters, numerous modifications in the parent molecule have also been reported, which subsequently exhibited enhanced inhibitory action against several metastatic cancers.

The compounds discussed here signify the importance of the marine ecosystem as a promising source of drug candidates for antimetastatic activity, optimization of the structure of marine entities for enhanced specificity, selectivity, and stronger efficacy against metastatic molecular targets, and provides a broader perspective on the role of these compounds in regulating the signaling pathways associated with cancer metastasis. However, the marine resources are restricted due to sourcing issues that need to be solved by the integration of microbiological and biotechnological methods that has significantly advanced in the past few decades to develop methods for large-scale production of naturally available compounds. Furthermore, advancement in chemical synthesis to achieve structural modifications in marine-derived compounds is also an important aspect to be focussed on in the future. Therefore, considering the ever so growing market of marine biology, plethora of naturally occurring compounds exhibiting anti-metastatic activity, and fast-growing technologies worldwide marine diversity holds immense potential to provide numerous clinically relevant anti-metastatic compounds for cancer therapy in the near future.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

SKJ and NB were involved in conceptualization. NB, BG, NT, and BS did data curation. NB and NT worked on visualization. NB, BG and NT did review and editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmcr.2021.100023.

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