International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 3, Issue4 (July-August 2015), PP. 211-219

DRUGS FROM THE SEA: A REVIEW OF MARINE DRUGS IN THE PIPELINE AND THE CHALLENGES FACED BY RESEARCHERS IN MARINE DRUG DEVELOPMENT.

S G Paradkar1*, S R Sinha, D K Dhodi, A S Beldar, S B Patel, S B Bhagat
Department of Pharmacology,
Grant Government Medical College And Sir JJ Group Of Hospitals,
Byculla, Mumbai

Abstract— **The past decade has seen a dramatic increase in the number of marine derived products in the market. The sea houses a wide variety of flora and fauna whose extracts have proved to have therapeutic potential in various disorders like cancer, macular degeneration etc. This has prompted researchers to shift their focus from synthetic compounds to these natural products. However, drug development and research is a tedious process. Researchers have to face challenges at every step beginning from procurement to obtaining successful trial results. Moreover, the sea as a source is getting rapidly depleted due to global warming and human activities like tourism and deforestation. In this article we have briefly reviewed some promising marine compounds. Also we have presented a few compounds which are under study and could prove to be a therapeutic boon. This review also outlines the obstacles that need to be overcome for increasing the success rate of marine drugs..**

Index Terms— **Marine, therapeutic, challenges**

Abbreviations-

b-FGF- basic fibroblast growth factor

COX - Cyclooxygenase

F-actin- Filamentous actin

HCT- Human colon tumor

5-LOX- 5-Lipooxygenase

MCF- Michigan cancer foundation

NHE- Na+ - H+ exchanger

PLA2- Phospholipase A2

TAR- Trans activation response

Tat- Trans activator of transcription

VE- Cadherin- Vascular endothelial cadherin

VEGF- Vascular endothelial growth factor

I. INTRODUCTION

The use of nature for medicine procurement has always interested mankind. Natural products are believed to have the advantage of having enormous structural and chemical diversity, increased protein binding characteristics (due to complex structure) and specific biological activity. Also these serve as good lead compounds suitable for further modification [1].

Oceans cover 70% of earth's surface. Oceans contain more than 300,000 species of invertebrates and algae [2]. Precious marine ecosystems like coral reefs, the largest living structures on the planet, are among the greatest storehouses of biodiversity on Earth. Spanning over an area of 284,300 sq.km these ocean rainforests host about 2 million plants and animals and a quarter of all marine fish [3]. A growing proportion of today's promising pharmaceutical research focuses on the sea, where marine organisms have evolved secondary metabolites to attack their prey or to defend their habitat [4]. These metabolites possess antitumor, antiinfective, antiangiogenetic and nutritional properties [5], [6]. Hence, it is necessary to exploit the therapeutic potential of these extracts to our advantage. A wide array of marine drugs has been approved for various therapeutic indications. Prialt (Ziconotide) isolated from the venom of cone snail conus magus is prescribed for pain associated with cancer, AIDS and other neuropathies. Lovaza (Ethyl esters of omega-3 fatty acids) obtained from fish oils is used in the treatment of hypertriglyceridemia [7]. A significant number of drugs/extracts showing promising potential are under clinical trials and studies. Aplidine is under phase III trial for the treatment of multiple myeloma [8].

However, drug procurement is an arduous task requiring technology as well as expertise. Obtaining pure extracts in sufficient quantities is vital for studying a potential drug. Adequate funding too is an important prerequisite for research. Some of the drugs may be dropped midway from trials due to

inadequate efficacy or toxicity. This may lead to huge economic losses [7]. Hence researchers have to face challenges at every step beginning from extract sampling to drug approval.

This review presents a brief discussion of a few promising marine drugs. In addition it contains in tabulated form a handful of drugs which are being studied for their therapeutic potential. It highlights the roadblocks faced in the pursuit of marine drug research and the possible solutions for overcoming them. It also stresses on the importance of conservation of this valuable resource.

II. DRUGS CURRENTLY UNDER TRIAL-

A. Aplidine-

Source-Also known as dihydrodemnin B, it is a second generation didemnin obtained from Mediterranean tunicate aplidium albicans [9].

Mechanism of action (MOA)- It activates epidermal growth factor receptor, the nonreceptor protein tyrosine kinase Src, serine threonine kinases c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase. It alters glutathione homeostasis. All these events lead to induction of apoptosis [10]. It induces G1 arrest and G2 blockage. [11]. It restricts tumor growth by inhibiting ornithine descarboxylase enzyme. It exerts antiangiogenic effect by inhibiting the expression of the vascular endothelial growth factor gene[9]. The sensitivity to Aplidine correlates inversely with the levels of expression of the cyclin-dependent kinase inhibitor p27kip1(p27) by specific short hairpin RNA[12].

Trials-It is under phase III trial for the treatment of multiple myeloma[8]. It is currently under phase 2 trial for treatment of primary myelofibrosis, post polycythemia vera myelofibrosis[13] and solid tumors[9]. It has been awarded orphan drug status for the treatment of acute lymphoblastic leukemia and multiple myeloma[12].

Adverse drug reactions (ADR) -Apart from hypersensitivity, nausea, transient transaminitis etc toxicity includes muscular atrophy and loss of thick myosin filaments. This may however be ameliorated with use of L-carnitine [9].

B. Bryostatin-1

Source-Bryostatin-1 is a macrocyclic lactone isolated from the marine invertebrate Bugula neritine [9].

MOA-Bryostatin-1 is a potent activator of protein kinase C (PKC), antagonises tumor-promoting phorbol esters, induces the differentiation of myeloid and lymphoid cell lines, platelet aggregation and promotes hematopoiesis, inhibits the production of components of the matrix metalloproteinases family, down-regulates multidrug-resistance 1 (MDR1) gene expression, modulates bcl-2 and p53 gene expression and induces apoptosis. It also has immunomodulatory functions [9].

Trials- It is currently under phase II trial for treatment of Non-Hodgkin's Lymphoma, Chronic lymphocytic leukemia. Its mechanism of action is thought to be up-regulation in the coexpression of CD11c/CD22 on CD20+ B cells [14]. It is under phase I study in patients with metastatic renal carcinoma and soft tissue sarcoma, to be used with temsirolimus [15].

ADR-The dose-limiting toxicity (DLT) of bryostatin-1 has consistently been severe myalgias, which were dose-related, cumulative and independent of the schedule of administration. Patients treated at doses over the maximum tolerated dose had significant decrement in platelets, leukocytes and, particularly, hemoglobin in the immediate post-treatment period. However, there was no effect on bone marrow progenitors. Hence it was thought to be due to peripheral blood cells pooling. These elevations typically recovered to baseline shortly after treatment, with the exception of haemoglobin, a decrement which persisted 1–2 weeks after dosing [9].

New studies- It is currently under study for the treatment of Alzheimers. Its mechanism of action is activation of PKC, reduction in protein Aβ and recovery of lost synapses[16]. It can also be potential treatment of HIV as it activates PKC, downregulates CD4/CXCR4 expression and causes purging of latent virus from cellular reservoirs like brain and lymphoid organs [17].

C. Kahalalide F-

Source- It is obtained from Indopacific mollusc Elysia rufescens [18].

MOA-It causes loss of mitochondrial membrane potential and lysosomal integrity, severe cytoplasmic swelling and vacuolization, irregular clumping of chromatin within the cell nucleus, and finally, cell death [19]. Elisidepsin is a synthetic marine derived cyclic peptide of Kahalalide F family. It is more active in cells harboring epithelial phenotype with high E-cadherin and low vimentin expression[20].

Trials- It is undergoing phase II trial for the treatment of non small cell lung cancer[21]. Elisidepsin is currently under phase Ib/II trial for the treatment of locally advanced or metastatic esophageal and gastric cancer [22].

ADR- Side effects are non-cumulative increase of transaminases (ALT/AST) and gamma-glutamyltransferase (GGT) [23].

Studies-It has shown antileishmanial activity. It alters plasma membrane of parasite, reduces intracellular ATP and has the advantage of being less prone to resistance development[24]. Its analogues are under studies for the treatment of psoriasis, pancreatic carcinoma, hepatocellular carcinoma, melanoma, breast cancer and prostatic carcinoma [25].

D. Plinabulin-

Source - Plinabulin is a synthetic analog of the diketopiperazine phenylahistin (halimide) discovered from marine and terrestrial Aspergillus sp

MOA- Plinabulin causes disruption of tumor vascular endothelial cells by inhibiting cell migration and endothelial cell tubule formation. This leads to tumor necrosis. In tumor cells, Plinabulin-induced apoptosis is mediated through

activation of caspase-3, caspase-8, caspase-9, and poly (ADP-ribose) polymerase cleavage. Moreover, plinabulin triggers phosphorylation of stress response protein JNK, as a primary target. Plinabulin blocks cells in metaphase with irregular chromosome alignment. It disrupts the formation of microtubules and microfilaments, causing mitotic arrest in proliferating tumor cells.

Trials-A phase 1 study of plinabulin as a single agent in patients with advanced malignancies (lung, prostrate, and colon cancers) showed a favorable pharmacokinetic, pharmacodynamics, and safety profile; phase 2 study combining plinabulin with docetaxel in patients with non–small cell lung cancer showed encouraging safety, pharmacokinetic, and efficacy data.

Studies- It induced cell death in patient multiple myeloma cells without affecting viability of normal mononuclear cells[26].

Adverse drug reactions- It causes transient increase in blood pressure. Serious adverse events included infusion reaction (bradycardia with syncope), myocardial infarction, vomiting, confusion, and pain. Infusion reaction is attributed to the transient increases in blood pressure or emesis induced by plinabulin as opposed to an allergic reaction. Significant emesis although observed, it is manageable with antiemetics. Tumor pain is proposed to result from structural and pain mediator effects on surrounding tissues from the tumor necrosis elicited by plinabulin and is managed well with analgesics and/or improves with continued treatment. Myocardial infarction is a rare yet alarming adverse effect. However, intensive cardiac monitoring did not show that plinabulin affects cardiac function, other than the transient changes in blood pressure and heart rate described above [27].

E. Cytarabine-

Source-it is obtained from the marine sponge cryptotethia crypta [7]

MOA- it blocks transition of cells from G-phase to S-phase [28].

Trials- it is under various phases of clinical trial for treatment of acute myeloid leukemia. It is undergoing phase II trial for the treatment of CNS lymphoma. It has completed phase II trial for acute lymphocytic leukemia and neoplastic meningitis as a complication of breast cancer. It is currently under phase III trial for the treatment of chronic myeloid leukemia [29].

ADR- The principal toxicity of cytarabine is myelotoxicity. Intermittent high-dose cytarabine is extremely myelosuppressive. The other important dose limiting adverse effect of standard-dose cytarabine is gastrointestinal toxicity, especially oral mucositis, diarrhoea, intestinal ulceration, ileus and subsequent Gram-negative septicaemia. The maximum tolerable cumulated dose of cytarabine is significantly lower when the agent is administered as a continuous infusion, due to myelosuppression and gastrointestinal toxicity. Idiosyncratic reactions like exanthema, fever and elevation of hepatic enzymes are relatively frequent. Severe, and sometimes irreversible, cerebellar/cerebral toxicity in 5 to 15% of courses of treatment limits the peak dose of cytarabine. Continuous infusion may be less neurotoxic. These major toxicities are age-related and prohibitive to the use of high-dose cytarabine therapy in patients older than 55 to 60 years. Subacute noncardiogenic pulmonary oedema occurs in some patients, with an incidence of about 20%, and seems to have an intriguing coincidence with precedent streptococcal septicaemia; high-dose systemic steroids may be beneficial. Corneal toxicity is very frequent in high-dose cytarabine therapy but is always reversible. It is largely preventable with prophylactic steroid or 2-deoxycytidine eyedrops [30].

Intrathecal liposomal cytarabine when given in children and adolescents for the treatment of recurrent brain tumors showed side effects like chemical arachnoiditis and neurological progression in few patients. Rarely, lethargy, slurring of speech and ataxia is also observed. Hence dexamethasone prophylaxis should be given to prevent these effects [31].

F. Dolastatins:

Source-Dolastatins(10,15) are peptides initially thought to be isolated from Dolabella auricularia, a mollusc from the Indian Ocean. (Amador ML et al., 2003). However, their analogues are found to be obtained from cyanobacteria symploca hydnoides (symplostatin 1, 2)[32], [33] and lyngbya majuscule (Pitiprolamide) [34].

MOA- The dolastatins inhibit cell proliferation and induce apoptosis, alter microtubule function. Cell cycle arrest in G2-M phase occurs due to accumulation of checkpoint proteins BubR1 and MAD2 at the kinetochoric region[35].

Trials- Tasidotin is undergoing Phase I/IIa trials for the treatment of Non-Hodgkins lymphoma [36].

ADR-Side effects are myelosuppression and phlebitis. LU103793 has the advantage of being water soluble and devoid of peripheral neuropathy (cumulative effects not studied). However, it exhibits side effects like hypertension or acute myocardial infarction in the pre treatment period on weekly administration and myelosuppression, particularly neutropenia on 24 hr administration [9].

New studies- Pitiprolamide showed weak cytotoxic activity against HCT116 colon and MCF7 breast cancer cell lines, as well as weak antibacterial activities against Mycobacterium tuberculosis and Bacillus cereus[34]. Dolabella auricularia extracts show activity against pathogens like Pseudomonas, Staphylococcus Aureus, Salmonella Paratyphi And Vibrio Cholerae [37].

G. Ectenaisdin 743 (ET-743)/Trabectedine/Yondelis:

Source-Ectenaisdins (Ets) are tetrahydroisoquinolone alkaloids isolated from Ectenaiscidia turbinata, a tunicate that grows on mangrove roots throughout the Caribbean sea[9].

MOA- ET-743 alters the interaction of DNA with transcription factors and other proteins, produces a delay in cell progression from G1 to G2 phase, inhibition of DNA synthesis

and cell cycle arrest in G2 phase, that eventually results in p53-independent apoptosis. ET-743 inhibits translational activation of the MDR1 gene[9].

Trials- It is currently under phase III trials for the treatment of ovarian, peritoneal and fallopian tube neoplasms[38], soft tissue sarcoma[39] and translocation related sarcoma. It is under phase II trial for the treatment of pleural mesothelioma, liposarcoma, leiomyosarcoma, prostate cancer, Ca pancreas and Ca breast[40].

ADR- It shows side effects like neutropenia and transaminase elevation [41].

H. Squalamine-

Source- It is an aminosterol obtained from liver of dogfish shark, Squalus acanthias[42].

MOA- It is known to interrupt and reverse the process of angiogenesis. It causes disorganization of F-actin stress fibers and reduction of surface molecular endothelial cadherin i.e VE-cadherin [43].

Trials- It is under phase III trial for the treatment of Subfoveal Choroidal Neovascularization associated with Age-Related Macular Degeneration[44].

ADR- It shows side effects like hepatotoxicity and neurosensory changes [45].

New studies- Aminosterols have shown invitro activity against dermatophytes[46]. Squalamine shows potent bactericidal activity against both Gram-negative and Gram-positive bacteria. While its action on gram negative organisms is thought to be interaction with phosphate groups it kills gram positive bacteria mainly by depolarisation[47]. Squalamine lactate, is in the process of being tested as a treatment of fibrodysplasia ossificans progressive.

Aminosterol 1436 obtained from dogfish shark is structurally related to squalamine. It has shown antiviral activity in HIV tissue cultures. It causes inhibition of a lymphocyte-specific NHE, which leads to suppression of cytokine responsiveness and subsequent depression of the capacity of the lymphocyte to support HIV replication. It causes potent appetite suppression and promotion of dose-dependent weight loss [42].

Inhaled squalamine tested in rat model with pseudomonas aeruginosa pneumonia has shown significant reduction in count and lesions because it causes destabilisation of external membrane [48].

I. Pseudopterosins and Seco - pseudopterosins-

Source-These are compounds isolated from the octocoral Pseudopterogorgia elisabethae of San Andrés and Providencia islands.

MOA- They have anti-inflammatory properties. They prevent eicosanoid biosynthesis by inhibition of PLA2, 5-LOX and COX, degranulation of leukocytes and the consequent liberation of lysosomal enzymes. They possess antimicrobial properties especially against gram positive bacteria

Trials- Methopterosin is a simple derivative of Pseudopterosin A and has completed Phase I and II clinical trials as a wound healing agent..

Studies-It has shown effect on Staphylococcus aureus, Enterococcus faecalis and Streptococcus pyogenes strains [49].

J. Eribulin mesylate-

Source- This synthetic analogue of halichondrin B is obtained from rare Japanese marine sponge halichondria okadai [50].

MOA- It inhibits microtubule dynamics. It causes irreversible arrest at G2-M phase and ultimately apoptosis after prolonged mitotic blockade [51].

Trials- It is approved for the treatment of metastatic Ca breast under the trade name Halaven [51]. It is currently under phase Ib/II for treatment of Non small cell lung cancer [52]. It is under phase III trials for treatment of soft tissue sarcoma [53].

ADR- It shows side effects like sensory neuropathy and myelosuppression [54].

K. Cortistatin-

Source- These steroidal alkaloids are obtained from the marine sponge Corticium simplex.

MOA- It inhibits VEGF-induced migration of human umbilical vein endothelial cells and bFGF-induced tubular formation [55].

Studies- Didehydro cortistatin A inhibits Tat mediated transactivation of the integrated provirus in HIV by binding specifically to TAR binding domain of Tat. Hence, it abrogates spontaneous viral particle release from $CD4^+$ T cells from virally suppressed subjects on highly active antiretroviral therapy (HAART) [56]. Also cortistatin A analogues are under study for the treatment of ocular wet macular degeneration [57].

L. Thiocoraline

Source- It is a thiodepsipeptide antitumor compound produced by two actinomycetes Micromonospora sp. ACM2-092 and Micromonospora sp. ML1, isolated from two marine invertebrates, a soft coral and a mollusc found of the Indian Ocean coast of Mozambique [58] and marine bacterium Verrucosispora sp [59].

MOA- It inhibits DNA elongation by DNA polymerase α. It causes an arrest in G1 phase of the cell cycle and a decrease in the rate of S phase progression towards G2/M phases[60].

Studies- It has shown an inhibitory effect on medullary thyroid cancer cell lines [59].

13. Clavulone II-

Source- It is obtained from soft corals cladiella australis, klyxum simplex and clavularia viridis [61].

MOA- It causes downregulation of cyclin D1 expression, G1 phase arrest and apoptosis induction [62].

Studies- It has shown inhibitory effect on oral squamous cell carcinoma[61] and acute promyelocytic leukemia cell lines [62]. It has shown antiviral activity in mouse fibroblasts. [63]. Bromovulone III a marine prostanoid obtained from clavularia viridis shows activity in hepatocellular carcinoma cells [64]

III. MARINE SPONGES AS SOURCE OF UPCOMING COMPOUNDS-

Marine sponges (Phylum porifera) produce a plethora of secondary metabolites to repel and deter predators and to compete for space with other sessile marine organisms. Sponges are acknowledged as the most versatile source of marine natural products with biomedical applications.

Cytotoxic activity is regarded as the first indicator in identifying anticancer drugs. apoptosis is a natural cell death mechanism. Apoptosis induction is widely accepted as an effective strategy for the identification of potential anticancer drugs [65]. Table I (at the end of the review) contains a few potential drugs obtained from marine sponges which have apoptosis as their primary mechanism of action.

A. Roadblocks – The sea is a vast resource making inaccessibility the major hindrance in drug procurement. Hence, use of submersibles and remotely operated vehicles is needed. Also we lack the taxonomic experience required to classify the organisms and plants obtained. Some organisms eg. sponges require specific environment for metabolite generation. Sometimes microorganisms may be the real drug producers. Moreover, large quantities of drug are needed even for testing. Hemisynthesis (extraction of intermediates) is a process by which can get large quantities of drug as well as its analogues. Another method is combinatorial biosynthesis, in which genes responsible for individual metabolic reactions from different organisms are combined to divert metabolic pathways towards novel products that were previously inaccessible or difficult to obtain.

High Throughput Screening is most common method of screening assay used to identify hit molecules in natural products. High quality libraries are needed for this purpose. Pre-fractionated libraries eliminate compounds too hydrophilic or hydrophobic, less drug-like, and compounds found in each fraction can be tested in detectable concentrations. Also, the reduced complexity can reduce the number of cycles of bioassay-guided fractionation needed to isolate and identify the active components [7].

B. Resource depletion and conservation- Coral reefs are extremely sensitive to changes in light, temperature (bleaching), overfishing, damaging fishing practices, pollution, and excess sediment from development and erosion. The destruction of mangrove forests that naturally absorb sediment and nutrients suffocates coral reefs with silt and algae blooms. Harmful fishing practices like cyanide fishing, hitting reefs with crowbars stuns and injures valuable fish. Many reefs once teeming with life are now wastelands that even the most vigorous conservation efforts can't begin to restore. Coral bleaching occurs when the single-celled algae vital for coral reef survival and known as symbiotic zooxanthellae are rejected from the coral, soft corals, some sponges and even Tridacna clams. The pigment containing organisms are lost as temperature or stress level due to increased light reaches intolerable levels. As temperatures return to normal, some reefs can recover within several weeks or months. However, equilibrium may not be restored due to global warming and the bleaching effect exposes corals to white and black band diseases.

Conservation efforts include roping off Marine Protected Areas (MPAs) , research and implementation of electrolysis as stimulant for growth, moving reefs to new places and cutting back on harmful fishing practices. MPAs will have to overcome challenges that include finding participants, streamlining viewpoints about how effective certain ideas will be and raising enough money to implement change. The Marine Aquarium Council or MAC is an international and non-profit organization which helps in making aquarium fish trade more responsible and limits harmful fishing practices. It works via avoiding stock depletion, adding more governmental regulation of reefs, managing reefs better and creating a reliable data record. Coral can be grown using a process known as mineral accretion where limestone is stimulated to collect on metal by a safe low voltage current, providing a nice place for baby coral to latch on and grow. The voltage itself can be provided using solar panels or energy from wave action. Scientists active in the Global Coral Reef Alliance (GCRA) grow coral reefs and will even show others the technique [66].

C. Discussion-

This review gives an overview of the marine drugs which have curative potential and are in various phases of clinical trials. Also it tries to highlight few compounds which can be developed further to obtain fruitful results. However, procuring and developing marine drugs is ridden with challenges. The cost factor too has to be taken into account. Moreover this resource is getting rapidly depleted due to human destruction. This review makes an attempt at understanding the roadblocks in this pursuit and tries to offer vital solutions which could aid in this fast growing area of research.

REFERENCES-

[1] Mouhssen Lahlou (2013). The Success Of Natural Products In Drug Discovery Pharmacology & Pharmacy 4:17-31

[2] Pomponi S, The oceans and human health: New drugs from the sea (2003), http://www.biologyeducation.net/news-and-articles/the-oceans-and-human-health/.

[3] Spalding MD, Green EP, Ravilious C, The most detailed assessment ever of the status and distribution of the world's coral reefs. In: World Atlas of Coral Reefs. (University of California Press Berkeley, USA, 2001)

[4] Simmons TL, Andrianasolo E, McPhail K, Flatt P, Gerwick WH (2005). Marine natural products as anticancer agents Mol Cancer Ther 4:333-342

[5] Bhatnagar I, Se-Kwon Kim (2010). Marine antitumor drugs: status, shortfalls and strategies Mar Drugs 8(10):2702–2720

[6] Pietras RJ, Weinberg OK (2005). Antiangiogenic Steroids In Human Cancer Therapy Evid Based Complement Alternat Med 2(1): 49–57

[7] Martins A, Vieira H, Gaspar H, Santos S (2014). Marketed Marine Natural Products in the Pharmaceutical and Cosmeceutical Industries: Tips for Success Mar Drugs12(2): 1066–1101

[8] Aplidin-dexamethasone in relapsed/refractory myeloma (2014), clinical trials.gov/show/NCT01102426.

[9] Amador M. L., Jimeno J., Paz-Ares L., Cortes-Funes H. and Hidalgo M (2003). Progress in the development and acquisition of anticancer agents from marine sources Annals Of Oncology 14:1607-1615

[10] Cuadrado A, Garcia-Fernandez LF, Gonzalez L, Suarez Y, Losada A, Alcaide V, Martinez T, Fernandez-Sousa JM, Sanchez-Puelles JM, Munoz A(2003). Aplidin Induces Apoptosis In Human Cancer Cells Via Glutathione Depletion And Sustained Activation Of The Epidermal Growth Factor Receptor, Src, JNK and p38 MAPK J Biol Chem 278(1): 241-50.

[11] Erba E, Bassano L, Di Liberti G, Muradore I, Chiorino G, Ubezio P, Vignati S, Codegoni A, Desiderio MA, Faircloth G, Jimeno J, D'Incalci M(2002). Cell Cycle Phase Perturbations And Apoptosis In Tumor Cells Induced By Aplidine British Journal Of Cancer 86(9): 1510-1517

[12] Moneo V, Serelde BG, Leal JFM, Blanco-Aparicio C, Diaz-Uriarte R, Aracil M, Tercero JC, Jimeno J, Carnero A (2007). Levels Of p27kip1 Determine Aplidin Sensitivity Molecular Cancer Therapeutics 6(4):1310-1316

[13] Clinical trial of aplidin in patients with primary myelofibrosis (2011), clinical trials.gov/show/NCT01149681.

[14] Varterasian M.L, Mohammad R.M, Shurafa M.S, Hulburd K, Pemberton P.A, Rodriguez D.H (2000). Phase II Trial of Bryostatin 1 in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia Clin Cancer Res 6:825-828

[15] Plimack ER, Tan T, Wong Y, Von Mehren MM, Malizzia L, Roethke SK, Litwin S, Li T, Hudes GR, Haas NB (2014). A Phase I Study Of Temsirolimus And Bryostatin-1 In Patients With Metastatic Renal Cell Carcinoma And Soft Tissue Sarcoma The Oncologist 19(4):354-355

[16] Schrott LM, Ping Yi, Johnson GS, Basting T, Castor TP, Alexander JS (2012). Acute Oral Bryostatin-1 Treatment Improves Morris Water Maze Acquisition In A Transgenic Mouse Model Of Alzheimer's Disease The FASEB Journal 26:Ib516

[17] Mehla R, Bivalkar-Mehla S, Zhang R, Handy I, Albrecht H, Giri S, Nagarkatti P, Nagarkatti M, Chauhan A (2010). Bryostatin Modulates Latent HIV-1 Infection Via PKC and AMPK Signalling But Inhibits Acute Infection In A Receptor Independent Manner PLoS One 5(6):e11160

[18] Faircloth G, Cuevas C (2006). Kahalalide F and ES285: potent anticancer agents from marine molluscs Prog Mol Subcell Biol 43:363-379

[19] Pardo B, Paz-Ares L, Tabernero J, Ciruelos E, García M,Salazar R, López A, Blanco M, Nieto A, Jimeno J, Izquierdo MA, Trigo JM(2008). Phase I Clinical and Pharmacokinetic Study of Kahalalide F Administered Weekly as a 1-Hour Infusion to Patients with Advanced Solid Tumors Clin Cancer Res 14:1116

[20] Serova M, de Gramont A, Bieche I, Riveiro ME, Galmarini CM, Aracil M, Jimeno J, Faivre S, Raymond E(2013). Predictive Factors of Sensitivity to Elisidepsin, a Novel Kahalalide F-Derived Marine Compound Mar Drugs 11:944-959

[21] EudraCT Database (European Medicines Agency, London), Clinical Trials for kahalalide f, https://www.clinicaltrialsregister.eu/ctr-search/search?query=kahalalide+f.

[22] EudraCT Database (European Medicines Agency, London), Clinical trials for elisidepsin. https://www.clinicaltrialsregister.eu/ctr-search/search?query=elisidepsin.

[23] Martín-Algarra S, Espinosa E, Rubió J, Juan José López López JJ, Manzano JL, Carrión LA, Plazaola A Tanovic A, Paz-Ares L (2009). Phase II study of weekly Kahalalide F in patients with advanced malignant melanoma Eur J Cancer 45(5):732-735

[24] Cruz LJ, Luque-Ortega JR, Rivas L, Albericio F(2009). Kahalalide F, an antitumor depsipeptide in clinical trials, and its analogues as effective antileishmanial agents Mol Pharm 6(3):813-824

[25] GT Faircloth, M del Carmen, C Marchante, US patent 7507708

[26] Singh AV, Bandi M, Raje N, Richardson P, Palladino MA, Chauhan D, Anderson KC (2011). A novel vascular disrupting agent plinabulin triggers JNK-mediated apoptosis and inhibits angiogenesis in multiple myeloma cells Blood 117(21):5692-5700

[27] Mita MM, Spear MA, Yee LK, Mita AC, Heath EI, Papadopoulos KP, Federico KC, Reich SD, Romero O, Malburg L , Pilat MJ, Lloyd GK, Neuteboom STC, Cropp G, Ashton E, LoRusso PM(2010). Phase 1 First-in-Human Trial of the Vascular Disrupting Agent Plinabulin (NPI-2358) in Patients with Solid Tumors or Lymphomas Clin Cancer Res16:5892

[28] PubChem Compound database (National Center for Biotechnology Information), Cytarabine. http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6253

[29] EudraCT Database (European Medicines Agency, London), Clinical trials for cytarabine. https://www.clinicaltrialsregister.eu/ctr-search/search?query=cytarabine.

[30] Stentoft J(1990). Toxicity Of Cytarabine Drug Saf 5(1):7-27

[31] Benesch M, Siegler N, Hoff K, Lassay L, Kropshofer G, Müller H, Sommer C, Rutkowski S, Fleischhack G, Urban C (2009). Safety and toxicity of intrathecal liposomal cytarabine (Depocyte) in children and adolescents with recurrent or refractory brain tumors: a multi-institutional retrospective study Anticancer Drugs20(9):794-799

[32] Harrigan GG, Luesch H, Yoshida WY, Moore RE, Nagle DG, Paul VJ (1999). Symplostatin 2 : a dolastatin 13 analogue from the marine cyanobacterium symploca hydnoides J Nat Prod 62(4):655-8

[33] Harrigan GG, Luesch H, Yoshida WY, Moore RE, Nagle DG, Paul VJ, Mooberry SL, Corbett TH, valeriote FA (1998). Symplostatin 1:a dolastatin 10 analogue from the marine cyanobacterium symploca hydnoides Journal Of Natural Products 61(9):1075-1077

[34] Montaser R, Abboud KA, Paul VJ, Luesch H (2011). Pitiprolamide, a Proline rich Dolastatin 16 analogue from the marine cyanobacterium Lyngbya Majuscula from Guam J Nat Prod74(1):109-112

[35] Gajula PK, Asthana J, Panda D, Chakraborty TK (2013). A synthetic dolastatin 10 analogue suppresses microtubule dynamics, inhibits cell proliferation, and induces apoptotic cell death J Med Chem 56(6):2235-2245

[36] EudraCT Database (European Medicines Agency, London), An Open-Label, Multi-Center Phase I/IIa Dose Escalation Study to Investigate the Safety and Tolerability of Multiple Doses of Oral Tasidotin HCL in Patients with Relapsed/Refractory Aggressive Non-Hodgkin's Lymphomas. https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-000124-15/DE.

[37] Abirami P, Arumugam M, Ajithkumar TT, Balasuramanian T (2011). Isolation and characterisation of 37kDA heparinase from the purple fluid of Dolabella auricularia Indian Journal Of Geo-Marine Sciences 40(1):112-116

[38] A Study Comparing the Combination of Trabectedin (YONDELIS) and DOXIL/CAELYX With DOXIL/CAELYX for the Treatment of Advanced-Relapsed Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer. http://clinicaltrials.gov/show/NCT01846611.

[39] A Study to Provide Access to Trabectedin in Patients With Non L-type Soft Tissue Sarcoma Who Have Persistent or Recurrent Disease and Who Are Not Expected to Benefit From Currently Available Standard of Care Treatment. http://clinicaltrials.gov/show/NCT00210665.

[40] EudraCT Database (European Medicines Agency, London), Clinical trials for trabectedin,https://www.clinicaltrialsregister.eu/ctr-search/search?query=Trabectedin.

[41] Schmitt T, Keller E, Dietrich S, Wuchter P, Ho AD, Egerer G (2010). Trabectedin for metastatic soft tissue sarcoma: a retrospective single center analysis Mar Drugs 8(10):2647-58

[42] M Zasloff, U.S. Patent 8623416

[43] Williams JI, Weitman S, Gonzalez CM, Jundt CH, Marty J, Stringer SD, Holroyd KJ, Mclane MP, Chen Q, Zasloff M, Von Hoff DD (2001). Squalamine treatment of human tumors in nu/nu mice enhances platinum-based chemotherapies Clin Cancer Res7(3):724-733

[44] EudraCT Database (European Medicines Agency, London), Clinical trials for squalamine. https://www.clinicaltrialsregister.eu/ctr-search/search?query=squalamine.

[45] Hao D, Hammond LA, Eckhardt SG, Patnaik A, Takimoto CH, Schwartz GH, Goetz AD, Tolcher AW, McCreery HA, Mamun K, Williams JI, Holroyd KJ, Rowinsky EK(2003). A Phase I and pharmacokinetic study of squalamine, an aminosterol angiogenesis inhibitor Clin Cancer Res 9(7):2465-2471

[46] Coulibaly O, Alhanout K, L'Ollivier C, Brunel JM, Thera MA, Djimdé AA, Doumbo OK, Piarroux R, Ranque S (2013). In vitro activity of aminosterols against dermatophytes Med Mycol 51(3):309-312

[47] Alhanout K, Malesinki S, Vidal N, Peyrot V, Rolain JM, Brunel JM(2010). New insights into the antibacterial mechanism of action of squalamine J Antimicrob Chemother 65(8):1688-1693

[48] Hraiech S, Brégeon F, Brunel JM, Rolain JM, Lepidi H, Andrieu V, Raoult D, Papazian L, Roch A (2012). Antibacterial efficacy of inhaled squalamine in a rat model of chronic Pseudomonas aeruginosa pneumonia J Antimicrob Chemother 67(10):2452-2458

[49] Correa H, Aristizabal F, Duque C, and Kerr R (2011). Cytotoxic and Antimicrobial Activity of Pseudopterosins andseco-Pseudopterosins Isolated from the Octocoral Pseudopterogorgia elisabethae of San Andrés and Providencia Islands (Southwest Caribbean Sea) Mar Drugs 9(3): 334–343

[50] McBride A, Butler SK (2012). A Novel Halichondrin B Analogue for the Treatment of Metastatic Breast Cancer Am J Health Syst Pharm 69(9):745-755

[51] Jain S, Cigler T (2012). Eribulin Mesylate in the treatment of metastatic breast cancer Biologics 6:21-29

[52] EudraCT Database (European Medicines Agency, London), https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-016047-19/CZ/.

[53] Phase 3 Study to Compare the Efficacy and Safety of Eribulin With Dacarbazine in Subjects With Soft Tissue Sarcoma, http://clinicaltrials.gov/show/NCT01327885

[54] Gitlitz BJ, Tsao-Wei DD, Groshen S, Davies A, Koczywas M, Belani CP, Argiris A, Ramalingam S, Vokes EE, Edelman M, Hoffman P, Ballas MS, Liu SV, Gandara DR (2012). A phase II study of halichondrin B analogue eribulin mesylate (E7389) in patients with advanced non-small cell lung cancer previously treated with a taxane: a California Cancer Consortium Trial J Thorac Oncol7(3):574-578

[55] Aoki S, Watanabe Y, Tanabe D, Arai M, Suna H, Miyamoto K, Tsujibo H, Tsujikawa K, Yamamoto H, Kob M (2007). Structure-activity relationship and biological property of cortistatins, anti-angiogenic spongean steroidal alkaloids Bioorg Med Chem 15(21):6758-6762

[56] Mousseau G, Clementz MA, Bakeman WN, Nagarsheth N, Cameron M, Shi J, Baran P, Fromentin R, Chomont N, Valente ST(2012). An analog of the natural steroidal alkaloid cortistatin A potently suppresses Tat-dependent HIV transcription Cell Host Microbe12(1):97-108

[57] Czako B, Kurti L, Mammoto A, Ingber DE, Corey EJ (2009). Discovery of potent and practical antiangiogenic agents inspired by cortistatin A J Am Chem Soc 131(25):9014-9019

[58] Lombó F, Velasco A, Castro A, de la Calle F, Braña AF, Sánchez-Puelles JM, Méndez C, Salas JA (2006). Deciphering the biosynthesis pathway of the antitumor thiocoraline from a marine actinomycete and its expression in two streptomyces species Chembiochem 7(2):366-376

[59] Tesfazghi S, Eide J, Dammalapati A, Korlesky C, Wyche TP, Bugni TS, Chen H, Jaskula-Sztul R(2013). Thiocoraline alters neuroendocrine phenotype and activates the Notch pathway in MTC-TT cell line Cancer Medicine 2(5):734-743

[60] Erba E, Bergamaschi D, Ronzoni S, Faretta M, Taverna S, Bonfanti M, Catapano CV, Faircloth G, Jimeno J, D'Incalci M(1999). Mode of action of thiocoraline, a natural marine compound with anti-tumour activity Br J Cancer 80(7):971-980

[61] Liang C, Wang G, Liaw C, Lee M, Wang S, Cheng D, Chou T(2008). Extracts from Cladiella australis, Clavularia viridis and Klyxum simplex (Soft Corals) are Capable of Inhibiting the Growth of Human Oral Squamous Cell Carcinoma Cells Mar Drugs 6(4):595-606

[62] Huang YC, Guh JH, Shen YC, Teng CM(2005). Investigation of anticancer mechanism of clavulone II, a coral cyclopentenone prostaglandin analog, in human acute promyelocytic leukemia J Biomed Sci 12(2):335-45

[63] Bader T, Yamada Y, Ankel H(1991). Antiviral activity of the prostanoid clavulone II against vesicular stomatitis virus Antiviral Res 16(4):341-355

[64] Chiang PC, Chien CL, Pan SL, ChenWP, Teng CM, Shen YC, Guh JH(2005). Induction of endoplasmic reticulum stress and apoptosis by a marine prostanoid in human hepatocellular carcinoma Journal of Hepatology 43(4):679-686

[65] Essack M, Bajic VB, Archer JAC(2011). Recently Confirmed Apoptosis-Inducing Lead Compounds Isolated from Marine Sponge of Potential Relevance in Cancer Treatment Mar Drugs 9(9):1580–1606

[66] Coral Reefs - MarineBio.org (MarineBio conservation society, US, 2014), http://marinebio.org/oceans/coral-reefs/.

[67] Table I- Upcoming anticancer agents procured from marine sponges. Apoptosis is the main modality of cytotoxicity of these drugs.

Name	**Source**	**Mechanism of action**	**Cell lines**
Renieramycin M	Xestospongia	Apoptosis via P53 dependent pathway	NSCLC
Psammaplysene A	Psammaplysilla sp.(indian ocean sponge)	Inhibitor of FOXO1 nuclear export	Endometrial cancer
Monanchocidin	Monanchora pulchra	Externalisation of phosphatidylserine	Human monocytic leukemia, human cervical cancer, mouse epidermal cells
Kuanoniamines	Oceanapia sagittaria	DNA synthesis inhibitor	Estrogen dependant and independent breast adenocarcinoma, NSCLC, diploid embryonic lung fibroblast, glioblastoma, melanoma cells
Rhabdastrellic Acid-A	Rhabdastrella globostellata	Condensation of nuclear chromatin and DNA fragmentation, caspase-independent autophagy associated cell death	Hepatocellular carcinoma, human promyelocytic leukemia
Smenospongine	Smenospongia sp., Indonesian marine sponge Dactylospongia elegans	cell-cycle arrest in the G1 phase and increased expression of p21, DNA fragmentation, cytotoxic and antimicrobial activity, antiproliferative and antiangiogenic activities such as endothelial migration and tube formation of human umbilical vein endothelial cells (HUVECs)	human leukemic monocyte lymphoma
Pachastrissamine	Pachatrissa sp.	Externalization of phosphatidylserine, release of cytochrome c, PARP cleavage and activation of caspase-3 and -9. It inhibits the activity of sphingomyelin synthase (SMS), an enzyme that converts ceramide into the membrane lipid sphingomyelin	mouse lymphocytic leukemia (P388), A-549, human colon adenocarcinoma (HT-29) and human melanoma (SK-Mel-28) cells