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MARINE PHARMACOGNOSY: TURNING THE TIDE IN DRUG DISCOVERY

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ABSTRACT: A significant share of the drugs that are used in current therapeutics are sourced from natural sources. More often than once, these sources tend to be from terrestrial plants or animals; this is where the prospect of drug development from a novel alternative source comes into play. The marine environment is a vast and yet scarcely explored field for obtaining a new source of bioactive compounds. Starting from 1969, since the approval of the first marine-derived drug cytarabine, technology has advanced by great strides over the past 46 years making the process of drug discovery and development relatively feasible. This review follows the timeline of the FDA approved marine-derived drugs by discussing their pharmacology and clinical trial updates and simultaneously addresses the challenges faced today in drug development from marine sources.

Key words: Marine pharmacology, Ziconotide, Brentuximab, Trabectedin, Eribulin

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INTRODUCTION

Novelty of the marine environment

The marine environment comprising oceans and seas makes up for more than 95% of the biosphere and 70% of Earth's surface. The most accepted claim that life originated in the oceans gives more credit to the notion that this vast yet unexplored territory holds a tremendous resource in terms of likely natural compounds that can be developed as potential therapeutic agents.

Most of the present day natural product-derived drugs are sourced from terrestrial sources but the vast and unexplored marine environment offers a new arena for drug discovery. Kong *et al*. established the superiority of marine products over terrestrial products as novel chemical compounds (Kong DX et al, 2010).

Owing to the harsh environments present in the ocean depths like salinity, extremes of pressure and temperature the organisms have evolved to adapt to the surroundings by either physical or chemical mechanisms which are used both in defence by the prey and in hunting by predators (Jimeno J et al, 2004). Chemical compounds produced by these organisms as an adaptation will be highly potent despite the dilution effect of seawater (Newman DJ, Cragg GM 2004).

Sample collection

As opposed to sample collection from terrestrial sources, the process of sample collection from marine sources is more sophisticated due to the difficulty in accessibility of marine environment. Traditional methods of sample collection like beachcombing and wading are still followed along with the introduction of automated equipments like submersibles for deep sea sample collection. The advancement in technology has led to the emergence of efficient techniques of sample collection which in turn benefits the prospects of drug discovery from marine sources.

i) Beachcombing

It refers to the task of manually searching the seashores and shallow waters for materials of interest. As it involves individual people searching a vast area, the process becomes a laborious one.

ii) Wading/Swimming

As the term implies wading requires the person to swim in shallow waters for raw material. The swimmer can only spent limited time for collection and that too without venturing into greater depths or farther away from the shore.

iii) Snorkeling

It involves swimming at surface of water using a snorkel tube and diving mask. By helping to move with minimum effort and also to breathe while swimming face down in the water, snorkeling offers the swimmer the added benefit of spending more time for sample collection.

iv)Dredging

An excavation procedure carried out in shallow seas or freshwater sources by which bottom sediments are obtained,dredging is an invasive procedure that destroys the local habitat and also has the demerits of compromising sample integrity and does not allow for multiple sampling from same site (Newman DJ, Cragg GM, 2004).

v) SCUBA Diving

Self Contained Underwater Breathing Apparatus (SCUBA) enables divers to swim to greater depths but unfortunately can offer only limited time for the diver to spend underwater.

vi) Submersibles

Submersibles are small vehicles designed to operate underwater with the support of a surface vessel and other operating staff. While having the unique advantage of being operated remotely, using submersibles requires trained personnel and is also very expensive.

Screening for bioactive compounds

The marine organisms considered to be potential sources for bioactive compounds includes sponges, tunicates and other invertebrates that use chemicals as a method of defence or for killing its prey. These chemicals or secondary metabolites offer an additional survival advantage for the organism rather than being utilised for constitutive cellular functions. Secondary metabolites are also often identified as the target compound for extraction and isolation. The most common compounds extracted from marine sources include volatile phenolic compounds, carotenoids, sterols, fatty acids (Grosso C et al, 2015).

Presently, due to the overwhelming number of sources for potential bioactive compounds in the marine environment, screening tools for the rapid detection of the compound of interest assumes paramount importance. The design of such screening methods depends on multiple factors like solubility, molecular weight and heat resistance of the compound of interest. The different extracts obtained under varying parameters are then tested for the confirmation of its proposed biological activity by performing functional activity assays like antimicrobial, anti-inflammatory and anticancer assays. This is followed by the chemical characterization of the active component present in the extract which is useful for correlating to its observed biological activity (Ibañez E, 2012). (Fig.1)

Extraction

Solvents of varying polarity like methanol, chloroform, ethanol, acetonitrile are used to extract the compound of interest. The compound selected is usually one with ‘medium polarity’ as such compounds are considered to be a better candidate for drug development. Polar compounds like sugars, peptides, salts and non-polar compounds like lipids are left behind as they are not considered to be ‘drug-like’ owing to their difficulties in transport across biological membranes. Freeze drying/lyophilization of the raw extract can be done to remove excess water and limit the quantity of polar compounds obtained in chromatography.

Chromatographic Purification

The primary extract is run in solvents of varying polarity to obtain multiple fractions of compounds present. The fractions thus obtained are repeatedly subjected to same chromatographic purification till the fraction contains a single pure compound.

Dereplication

Using LC-MS (Liquid chromatography mass spectrometry) or NMR (Nuclear mass spectrometry) techniques the newly isolated compound is compared with the database of previously reported compounds to avoid rediscovering the same compound

Structure Elucidation

Structure elucidation studies are carried out to confirm the nature of the isolated compound by identifying the molecular structure of the pure compound and it helps in performing structure-activity relationship studies. Various techniques such as high resolution mass spectrometry, nuclear mass spectrometry and X-ray crystallography are used for elucidating compound structure.

Bioassay testing

The bioactivity of the compound is then assessed using multiple bioassays like anticancer, anti-inflammatory, antimicrobial and antiviral assays. Toxicity assays are carried out to ascertain the efficacy of the compound.

FDA approved drugs

The potential of marine compounds in pharmacotherapeutics was given a head start by the approval of cytarabine in 1969 by USFDA. Following the approval of vidarabine in 1976, new drug approvals from marine sources went into a hiatus for the next 28 years, till the approval of ziconotide in 2004.In the past decade, the number of drug approvals has risen steadily owing to technological advances in sample collection, high throughput screening methods and synthetic processes for mass production of drugs.

CYTARABINE (Cytosine arabinoside; Ara-C)

In 1969, cytarabine or cytosine arabinoside; Ara-C, was the first FDA approved drug obtained from a marine source.The compound was isolated from the Caribbean sponge species *Tectitethya crypta* (Montaser R, Luesch H, 2011).The chemical structure of cytarabine resembles that of cytidine; the difference being that cytosine combines with arabinose sugar rather than a deoxyribose sugar.

Mechanism of action

Cytarabine enters the cell through a transporter hENT1, which is highly expressed in ALL and t (4;11) MLL tumour cells. Inside the cell, it undergoes repeated phosphorylation by kinases to form arabinose cytidine triphosphate (ara-CTP) which competes with the normal cellular counterpart deoxyribosecytidine triphosphate (d-CTP) to disrupt the DNA synthesis and cell cycle.

Deaminase enzymes metabolise the intracellular cytarabine and cytarabine monophosphate into arabinosyluridine and uridine monophosphate respectively which are inactive metabolites; the high activity of deaminases in cells of gastrointestinal system makes cytarabine ineffective per orally. The up regulation of deaminases causes rapid conversion of cytarabine to inactive metabolites which is one of the mechanisms of drug resistance to cytarabine.The other resistance mechanisms being the down regulation of kinase enzymes especially deoxycytidine kinase which leads to reduced production of ara-CTP. Genetic polymorphisms leading to reduced expression of hENT1 transporter is yet another albeit rare resistance mechanism (Chabner BA et al, 2011).

Pharmacokinetics

Owing to the higher activity of deaminases in gastrointestinal system, cytarabine is ineffective orally with only 20% bioavailabilty, so it is given as intravenous infusion.It has a short elimination half-life of 10 minutes.90% of drug is excreted in urine as ara-U and 10% is excreted unchanged.

Dosage and administration

Due to short elimination half-life, cytarabine is given as continuous i.v. infusion of 100mg/m^2/day for 5-7 days or as a rapid i.v. infusion of 100mg/m^2 every 12 hours. Higher CSF concentrations are achieved on continuous i.v. infusion rather than on rapid i.v. infusion. For meningeal and lymphomatous leukemia, intrathecal dose of 30mg/m^2 is administered once every 4 days. Intrathecal depot liposomal formulations of cytarabine are available; a 50 mg strength dose can maintain the cytotoxicity levels in CSF for 12 days leading to less frequent lumbar punctures which can prove beneficial to the patient by increasing the patient compliance and also reduce the frequency of lumbar puncture associated adverse events.

Indications

For inducing remission in AML, cytarabine is the most efficacious chemotherapeutic agent. It is also used in blast phase of ALL and CML. Other therapeutic indications include acute promyelocyticleukemia and high grade lymphomas.

Adverse drug reactions

Cytarabine being an antimetabolite chemotherapeutic drug inhibits rapidly dividing cells thus causing myelosuppression encompassing anemia, thrombocytopenia and granulocytopenia. Gastrointestinal tract disturbances like nausea and vomiting are frequently ascribed to cytarabine. Stomatitis, dermatitis and conjunctivitis are other adverse drug reactions noted.

VIDARABINE (Adenosine arabinoside;ara-A)

Similar to cytarabine, vidarabine is also obtained from the marine sponge *Tectitethya crypta*. It was approved by FDA in 1976. Initially used as an ophthalmic ointment for treatment of Herpes simplex virus keratitis, the drug is now discontinued due to its adverse effect profile and also because of the development of acyclovir class of drugs which are more efficacious and have a better side effect profile.

Mechanism of action

Similar to the action of cytarabine, vidarabine enters cell where it is sequentially phosphorylated to vidarabine triphosphate which competes with dNTP to inhibit viral DNA synthesis. Adenosine deaminase enzyme metabolises vidarabine to arabinosyl hypoxanthine (ara-HX) which has less potent action than vidarabine.

Dosage and administration

Vidarabine was used as ophthalmic ointment and solution for treatment of Herpes simplex viral keratitis.It was indicated to apply 5 times a day in both eyes and tapered to 3 times a day on healing of the corneal ulcer.

Indications

Herpes simplex virus keratitis/kerato conjunctivitis and also in superficial herpetic keratitis refractory to treatment with Idoxurudine or in patients having hypersensitivity to idoxurudine.

Adverse drug reactions

Including drug hypersensitivity, majority of the adverse drug reactions are associated with its topical use in ophthalmic conditions where it has the propensity to cause foreign body sensation in the eye, increased light sensitivity and lacrimal punctal occlusion.

ZICONOTIDE

In 2004, Ziconotide was the first of its kind marine derived peptide drug and the first marine derived analgesic to get FDA approval. Ziconotide is the synthetic congener of ω-conotoxin found in the venom of fish eating marine snail, *Conus magus.*

Mechanism of action

Throughout the CNS, N-type calcium channels are present in the presynaptic nerve endings. By allowing calcium influx, these channels are involved in the neurotransmitter release from these nerve endings. In the dorsal horn of spinal cord, N-type calcium channels are localized in Aδ and C fibres, along with substance P mediating the pain signalling pathway. Ziconotide blocks α1 subunit of N-type calcium channel which prevents calcium influx and thus inhibits the neurotransmitter release leading to analgesic action. (McGivern JG. Ziconotide, 2007).

Indications

Ziconotide is administered as an intrathecal infusion to treat pain that is refractory to treatment with conventional analgesics like opioids.

Adverse drug reactions

Being administered as an intrathecal infusion by lumbar puncture technique, the risk of meningitis is high. Altered level of consciousness and elevated levels of serum creatine kinase has been associated with ziconotide use. Of particular concern is the occurrence of cognitive and neuropsychiatric disturbances with ziconotide use especially suicidal ideation.

Efficacy studies

In a randomized controlled trial in 2004; patients who were administered ziconotideintrathecally, reported 53% improvement on an objective pain assessment scale compared to 18% in placebo administered patients. The data obtained from the study was clinically and statistically significant to conclude that intrathecalziconotide administration offered better pain relief in patients suffering from chronic illness like AIDS or cancer who were refractory to treatment with conventional analgesics (Staats PS et al, 2004). In a case series report in 2015, intrathecal infusion of ziconotide exhibited superior analgesic action in patients with neuropathic and cancer pain who were refractory to treatment with high doses of intrathecal morphine and fentanyl (Wallace MS, 2010).

OMEGA 3 FATTY ACID ESTERS

The drug was approved by FDA in 2004 for treatment of hypertriglyceridemia. A 1g capsule contains 900mg of ethyl esters of omega-3 fatty acids sourced from fish oils which has approximately 465mg eicosapentaenoic acid (EPA) and 375mg docosahexaenoic acid (DHA).

Mechanism of action
Although the exact mechanism of action of omega 3 fatty acids has not been elucidated, several potential mechanisms of action has been put forward.

Dosage and contraindications
It is administered at a dose of 4g per day. The capsules are swallowed whole. It is contraindicated in patients with known allergy to shellfish/fish products.

Indications
Omega 3 fatty acids are given as adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia (>500 mg/dL). Patients are advised to be on appropriate lipid-lowering diet both pre and post drug administration period. (*Lovaza* package insert)

Efficacy studies
In a population-based cohort study to assess the association of omega 3 fatty acid intake and cardiovascular death it was determined that higher dietary intake of marine and non-marine sources of omega 3 fatty acids offered significant protection (hazard ratio=0.67) against the lowest obtained value of dietary intake of omega 3 fatty acids (hazard ratio=1) (Koh AS et al, 2015). The data from the PREDIMED study demonstrated that although reduction in overall mortality was influenced by intake of both plant and marine sources of omega 3 fatty acids, only marine omega 3 fatty acids offered protection in cardiovascular mortality (Sala-Vila A et al, 2016).

ERIBULIN
Eribulin is a synthetic analogue of the cytotoxic compound Halichondrin B. In 1986, it was isolated for the first time from the sponge *Halichondria okadai*. In November 2010, FDA approved eribulin for patients with metastatic breast cancer who had prior treatment with a minimum of two chemotherapeutic regimens. The initial regimen should have been a combination of an anthracycline and a taxane (Kaufman PA et al, 2015).

Mechanism of action
Eribulin is an inhibitor of microtubule polymerization. By binding predominantly to a small number of high-affinity sites on the growing plus ends of microtubules; it sequesters tubulin dimers into non-productive aggregates and causes a block in the G2-M phase of cell cycle. It is less sensitive to multidrug resistance mediated P-glycoprotein efflux pump and hence is active in drug-resistant tumours that overexpress P-glycoprotein. Eribulin causes irreversible mitotic blockade and so intermittent administration of the drug can cause long-term inhibition of cell growth.

Dosage and administration
Eribulin is administered in a dose of 1.4 mg/m^2 intravenously over 5 minutes on Days 1 and 8 of a 21 -day cycle. It is excreted unchanged mainly in faeces. The elimination half-life is 40 hours (*Halaven* package insert).

Adverse reactions
Suppression of bone marrow activity leads to significant neutropenia. Peripheral neuropathy and QT prolongation have also been reported with use of eribulin. Eribulin has demonstrated teratogenic potential in animal toxicity studies.

Efficacy studies
In a phase III, open label randomized study to compare the efficacy of eribulin monotherapy with conventional chemotherapeutic agents in treatment of metastatic breast cancer it was determined that eribulin monotherapy offered an additional 2.5 months in overall survival (13.1 months vs 10.6 months) (Lin NU et al, 2011). But another phase III open-label randomized study that compared the efficacy of eribulin with capecitabine in metastatic breast cancer patients who were previously treated with an anthracycline and taxane failed to demonstrate any superiority in efficacy of eribulin over capecitabine in terms of both overall survival or progression-free survival (Cortes J et al, 2015).

BRENTUXIMAB VEDOTIN
Brentuximab vedotin was approved by FDA in August 2011. It belongs to a class of drugs known as antibody-drug conjugate (ADC). 3 to 5 units of the cytotoxic agent, i.e. monomethylauristatin E (MMAE) and monoclonal antibody (MAB) brentuximabare connected via a spacer paraaminobenzoic acid, a cathepsin-cleavable linker and an attachment group consisting of caproic acid and maleimide. Brentuximab is targeted against CD30 (Francisco JA et al, 2003). MMAE is the more potent synthetic derivative of Dolastatin 10. Dolastatins are produced by cyanobacteria that are consumed by the Sea Hare, *Dolabella auricularia*.

Indications
Brentuximab is indicated in classical Hodgkin lymphoma (HL) with failed autologous hematopoietic stem cell transplantation (auto-HSCT) or after at least two failed combination-chemotherapy regimens in patients who are not auto-HSCT candidates. Brentuximab is also indicated in systemic anaplastic large cell lymphoma (sALCL) after at least one failed multi-agent chemotherapy regimen (Gopal AK et al, 2015).

Mechanism of action

Brentuximabvedotin binds to the CD30 receptor expressed on the tumour cell. The compound is then internalized and transported into the lysosome where the linker is cleaved and MMAE is released. The free MMAE is cytotoxic and disrupts microtubules leading to apoptosis.

Dosage and Pharmacokinetics

Brentuximab is given as 1.8 mg/kg as i.v. infusion over 30 minutes every 3 weeks. It undergoes CYP3A4/5 metabolism. (*Adcetris* package insert)

Adverse drug reactions

A serious adverse reaction associated with brentuximabvedotin is the occurrence of Progressive Multifocal Leukoencephalopathy (PML) that led the FDA to issue it as a black box warning. Bone marrow suppression leads to pancytopenia. Peripheral neuropathy, dermatalogical manifestations like Steven-Johnson syndrome and Toxic Epidermal Necrolysis have been reported with brentuximabvedotin. ARDS, interstitial lung disease and hepatotoxicity are other adverse drug reactions.

Efficacy studies

The results of a phase II study demonstrated improved overall survival and progression-free survival benefit for patients receiving brentuximabvedotin in relapsed or refractory Hodgkin's lymphoma [(17)]. In a retrospective study to assess the impact on progression-free survival after brentuximabvedotin consolidation therapy in relapsed or refractory CD30+ Hodgkin's lymphoma; patients treated with brentuxima bvedotin demonstrated significantly higher progression-free survival periods (median of 18.8 months) opposed to 6.8 months of progression-free survival in non brentuximab treated patients (Perrot A et al, 2015).

TRABECTEDIN

Chemically known as Eicteinascidin 743 or ET743, Trabectedin is an alkaloid obtained from the marine tunicate *Ecteinascidia turbinata*. In 2009, European Medicines Agency (EMA) approved trabectedin for platinum sensitive ovarian cancer in combination with pegylated liposomal doxorubicin. In October 2015, FDA approved it as an add-on therapy for unresectable or metastatic liposarcoma or leiomyosarcoma in anthracycline treated patients.

Mechanism of action

Trabectedin belongs to class of alkylating drugs. By promoting binding of guanidine residues in the DNA minor groove, trabectedin causes adduct formation and bending of DNA helix to the major groove. The adduct formation leads to a cascade of events that inhibits transcription factors and DNA repair mechanisms, that eventually leads to cell death by pro-apoptotic mechanisms. (FDA, 2015).

Pharmacokinetics, dosage and administration

Trabectedin has elimination half-life of 175 hours. It undergoes CYP3A metabolism and is excreted mainly in faeces. It is administered at a dose of 1.5 mg/m^2 body surface area as a 24-hour intravenous infusion, once in every 3 weeks through a central venous line.

Adverse drug reactions

The most common adverse drug reactions include gastrointestinal disturbances, fatigue and peripheral edema. Serious adverse reactions include rhabdomyolysis which warrants monitoring of CPK levels, hepatotoxicity and severe neutropenia that sometimes requires withholding of drug on the event of neutropenic sepsis. As it causes cardiomyopathy, it is contraindicated in patients with LV dysfunction. Animal toxicity studies have demonstrated theteratogenic potential for trabectedin. (*Yondelis* package insert).

Efficacy studies

In a retrospective analytical study to demonstrate the efficacy of trabectedin in fibrous sarcoma patients the data obtained pointed to the additional survival benefit offered by trabectedin both in terms of overall survival and progression-free survival (Khalifa J, et al 2015). In another retrospective study, trabectedin was established to be effective in prolonging the progression-free survival (7.3 months versus 0.9 months) in patients with failed standard chemotherapeutic regimens in translocation-related sarcoma (Araki N et al, 2016).

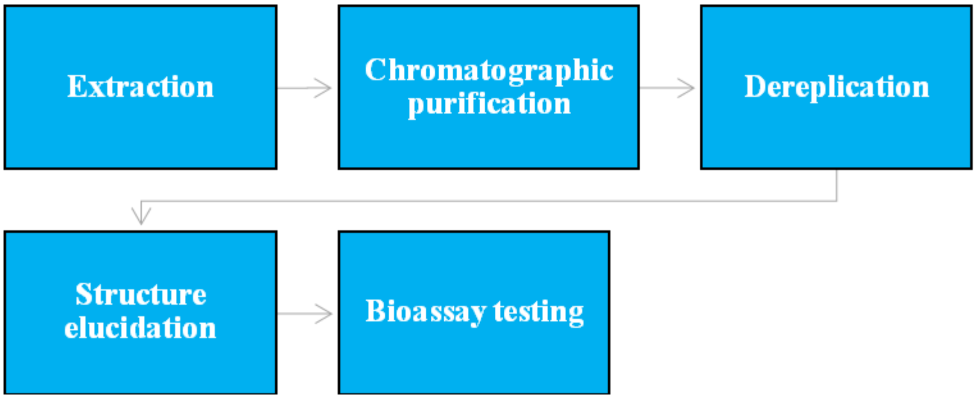

Figure 1. The steps involved in isolation and testing of the chemical compounds present in marine sources

Table 1: FDA approved drugs obtained from marine sources with year of approval

Drug	Year of approval by US FDA
Cytarabine	1969
Vidarabine	1976
Ziconotide	2004
Omega 3 fatty acid esters	2004
Eribulin	2010
Brentuximabvedotin	2011
Trabectedin	2015

Table 2: Proposed mechanisms of action of omega 3 fatty acid esters

Potential mechanisms of action of Omega 3 fatty acid esters
Inhibition of acyl-CoA
Increased mitochondrial and peroxisomalβ- oxidation in liver
Decreased lipogenesis in liver
Increased plasma lipoprotein lipase activity
Reduce triglyceride synthesis in liver
Inhibit esterification of other fatty acids

DRUG PIPELINE

Apart from the FDA approved drugs in the market now, an exhaustive list of marine compounds are undergoing various stages of clinical trials in several nations especially in the US, Europe and China. A major share of the compounds show promising results in therapeutics of cancer along with a few compounds showing potential in treatment of pain and also in neuropsychiatric disorders:

Future challenges

The main challenge faced in the development of a drug from a marine source is the supply problem. The compound of interest is present in the organism in minute quantities which makes the process of obtaining the compound more sophisticated and expensive. For example, the yield of ET-743/trabectedin from the tunicate *Ecteinascidia turbinata* is 2g per ton. This would require several tonnes of the tunicate to obtain trabectedin in sufficient quantities for drug manufacturing. Due to improvement in technology, the process of drug development has changed considerably. The industrial production of marine drugs involves:

I. Total chemical synthesis

The development of a chemical synthesis process for an active compound has can be beneficial in meeting the demands for large scale production and moreover provides source material for future research based on structure activity relationship (SAR) studies and optimizing the lead molecule.

Halichondrin B, a naturally occurring compound exists as a complex with 32 stereocenters (Hirata Y, Uemura D, 1986). Halichondrin acts by inhibiting the microtubule assembly, which was established by cytotoxicity studies on tumour cell lines (Bai RL et al, 1991). In 1992, Kishi *et al.* were successful in the total chemical synthesis of this compound (Aicher TD et al, 1992). Eribulin with 19 stereocenters is the structurally simpler analogue of Halichondrin B, synthesized based on structure activity relationship studies.

II. Fermentation

The current industrial manufacturing process of Trabectedinis by synthetic fermentation of cyanosafracin B from *Pseudomonas fluorescens* which has made mass production of the low yield drug much more feasible (Cuevas C et al, 2000).

III. Biotechnology

The identification of gene locus for existing compounds by whole genome sequencing can pave way for discovery of newer compounds. Genome mining is an emerging method for drug discovery that can be used as an predictive tool for chemical structure of existing compounds (Challis GL, 2008, Lane AL, Moore BS, 2011).

Table 3: List of marine compounds undergoing clinical trials

Sourced from - http://marinepharmacology.midwestern.edu/clinPipeline.htm

Trial status	Compound name	Marine organism	Chemical class	Molecular target	Disease/area
Phase III	Piltidepsin	Tunicate	Desipeptide	Rac1 and JNK activation	Cancer: Multiple Myeloma, Leukemia, Lymphoma
	Tetrodoxin	Pufferfish	Guanidinium alkaloid	Sodium Channel	Pain: Chronic Pain
Phase II	ABT-414 EGFRvIII MMAF	Mollusk/ cyanobacterium	ADC (MMAF)	EGFR and microtubules	Cancer: Glioblastoma Multiforme, Squamous Cell Tumors
	DMXBA	Worm	Alkaloid	α7nicotinic acetylcholine receptor	Schizophrenia, Alzheimer Disease, Attention Deficit Hyperactivity Disorder, Endotoxemia, Sepsis,Vagal Activity
	Glembatumumab Vedotin (CDX-011)	Mollusk/ cyanobacterium	ADC (MMAE)	GPNMB and microtubules	Cancer: Metastatic breast cancer, Metastatic melanoma, Triple negative breast cancer
	AGS-16C3F	Mollusk/ cyanobacterium	ADC (MMAF)	ENPP3 and microtubules	Cancer: Carcinoma, Renal Cell, Renal Cell Carcinoma With Clear Cell Histology, Renal Cell Carcinoma With Non-Clear Cell Histology, Renal Cell
Phase I/II	Lifastuzumab vedotin DNIB0600A	Mollusk/ cyanobacterium	ADC (MMAE)	NaPi2b and microtubules	Cancer: Non-Small Cell Lung Cancer, Ovarian Cancer; Epithelial Tumors
	Pinatuzumab vedotin (DCDT-2980S)	Mollusk/ cyanobacterium	ADC (MMAE)	CD22 and microtubules	Cancer: Non-Hodgkin lymphoma, Chronic lymphocytic leukemia, Lymphoma, B-Cell, lymphoma, Follicular
	Polatuzumab vedotin (DCDS-4501A)	Mollusk/ cyanobacterium	ADC (MMAE)	CD79b and microtubules	Cancer: Non-Hodgkin lymphoma, Chronic lymphocytic leukemia, Lymphoma, B-Cell

Trial status	Compound name	Marine organism	Chemical class	Molecular target	Disease/area
Phase I	GSK2857916	Mollusk/ cyanobacterium	ADC (MMAF)	BCMA	Cancer: Multiple Myeloma
	ASG-67E	Mollusk/ cyanobacterium	ADC (MMAE)	CD37 and microtubules	Cancer: Refractory Lymphoid Malignancy; Relapsed Lymphoid Malignancy
	ASG-15ME	Mollusk/ cyanobacterium	ADC (MMAE)	SLITRK6 and microtubules	Cancer: Metastatic Urothelial Cancer
	ASG-22ME	Mollusk/ cyanobacterium	ADC (MMAE)	Nectin-4 and microtubules	Cancer: Tumors; Medical Oncology; Neoplasms; Metastatic Urothelial Cancer
	Bryostatin	Bryozoan	Macrolide lactone	Protein kinase C	Melanoma, Renal Cell Cancer, Lymphoma,Pancreatic Cancer, Gastric Cancer
	DSTP3086S	Mollusk/ cyanobacterium	ADC (MMAE)	STEAP1 and microtubules	Cancer: Prostate Cancer
	HuMax®-TF-ADC	Mollusk/ cyanobacterium	ADC (MMAE)	Tissue Factor and microtubules	Cancer: Ovary Cancer , Cervix Cancer, Endometrium Cancer, Bladder Cancer, Prostate Cancer , Head and
	Marizomib (Salinosporamide A; NPI-0052)	Bacterium	Beta-lactone-gamma lactam	20S proteasome	Cancer: Non-Small Cell Lung Cancer, Pancreatic Cancer, Melanoma, Multiple myeloma
	MLN-0264	Mollusk/ cyanobacterium	ADC (MMAE)	GCC and microtublues	Cancer: Advanced Gastrointestinal Malignancies
	PM060184	Sponge	Polyketide	Minor groove of DNA	Cancer: Solid Tumors
	SGN-CD19A	Mollusk/ cyanobacterium	ADC (MMAF)	CD19 and microtubules	Cancer: Burkitt Lymphoma, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma
	SGN-LIV1A	Mollusk/ cyanobacterium	ADC (MMAE)	LIV-1 and microtubules	Cancer: Breast Cancer

CONCLUSION

The marine environment offers a unique opportunity for drug discovery owing to the characteristic properties of bioactive compounds obtained from the sea and also due to the fact that even today a vast majority of the seas and oceans have yet to be fully explored. As evident from the emergence of a long list of effective drugs from marine sources, the clinical drug pipeline also holds several promising molecules that will be making it's way to phase III trials and marketing phase. The major setback of marine drug discovery which is the supply problem, can now be efficiently tackled using sophisticated technology starting right from the stages of sample collection, through High Throughput Screening methods and semisynthetic to synthetic methods of industrial mass production.

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Abbreviations:

ADC: Antibody Drug Conjugate;

CD: Cluster of Differentiation;

EGFR: Epidermal Growth Factor Receptor;

ENPP3: EctonucleotidePyrophosphatase/Phosphodiesterase Family Member 3;

ETBR: Endothelin B Receptor;

FDA: Food and Drug Administration;

GCC: GuanylylCyclase C;

GPNMB: Glycoprotein nonmetastatic B;

JNK: c-Jun N-terminal protein kinases;

LIV-1: Zinc transporter SLC39A6;

MMAE: Monomethylauristatin E;

MMAF: Monomethylauristatin F;

NA: Not Available;

NaPi2b: Sodium-Dependent Phosphate Transport Protein 2b;

PSMA: Prostate-Specific Membrane Antigen;

RAC1: Ras-related C3 botulinum toxin substrate 1;

SLITRK6: SLIT and NTRK-like protein 6;

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