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REVIEW ON ANTICANCER AGENTS FROM THE DEEP OF OCEAN

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ABSTRACT

Cancer remains one of the major threats to human health worldwide with its high mortality rates. Approximately,19.3 million new cancer cases and almost 10.0 million cancer deaths, were estimated each year worldwide. Lung and breast cancer are the most frequently diagnosed cancers worldwide and are the leading causes of cancer-related death in men and women respectively. There are so many therapies for cancer such as radiation therapy, chemotherapy, Surgery, targeted therapy, immunotherapy, hormone therapy, bone marrow transplant etc. plays major role to treat cancer. However, it is not able to avoid repetition of tumor, side effects of therapies as well as drug opposition. There are various cancers which cannot be controlled well with the help of currently available drugs. Along with terrestrial resources the marine environment is recently emerged. Marine-derived drugs belong to wide variety of chemical classes including terpenes, alkaloids, polyketides, peptides, cyclodepsipeptides, shikimates, hydroxyphenylactic Acid derivatives etc. These agents have the potential to inhibit the humantumor cell growth via in-vivo as well as in vitro cancer cell mechanisms. Marine environment represents diverse resource for novel anticancer drugs. There are various properties seen in marine compounds from antibacterial, antidiabetic, antiviral, anti-inflammatory to anticancer. This review provides an overview on the development of marine-derived compounds for cancer therapy along with its possible scope in future. We also discuss about the commercial, potential marine-derived anticancer compounds Along with drugs that are in different phasesof clinical trials.

KEYWORDS: Marine-derived compounds, anti-cancer, *Molusca*, Marine fungi, Marine sponges.

INTRODUCTION

The ocean cover more than 70% of Earth's surface and content over 200000 invertebrates and algal species and fauna and flora. Marine fauna and flora play a significant role in as a source of new molecular entity. During last few decades numerous novel compounds have been isolated from marine organisms having biological activity. Several compounds with anticancer and cytotoxic activities have been isolated from various Marine sources such as a sponge gorgonian coral sea algae sea hares and cucumbers.[1]

Nature has played abundant role in providing chemically active metabolite which causes effective therapeutic activity. Text reveal many of the therapeutic anticancer agents are derived from Marine origin and its various uses also.[2] Marine drugs are secondary metabolites and can be used to fight against different kinds of infectious diseases but many of the times Marine microbes are difficult to find in deepof the ocean. In 1970s Molecular Biology has evolved and by the end of 1990s, has progressed in the entire world. David Newman, Director Of Natural Product Division at US National Cancer institute in Bethesda, Maryland, started to work on producing genes. They started to work on the ability to grow microbes. Synthetic chemist started to work on total synthesis and structure of genes. Though scarcity of new drugs on the market, Marine Drug Discovery still attracts newcomers.[3]

Marine environment has produced treasure of medicinal agents with great biodiversity and unique chemical biodiversity. Cancer is the second most leading cause of mortality which causes 10 million deaths in the 2020. In the past decades great effort has been taken by scientist to study the pathogenesis of cancer and sure Marine drugs for cancer has been developed.[4] Marine plants, and microbes have you want a unique portfolio of chemicals to defend themselves and red communication scientist are keen to know more about this novel compounds.[5] Cancer group of more than hundred diseases which can be developed for most everywhere in the body. Uncontrolled growth of cells coupled with malignant behavior such as inversion and metastasis. From last 30 to 40 years this chemotherapy drugs are used to treat the malignancy. These drugs can affect on different functioning of cell at different stages, which finally leads to the death.[6]

Till the date, there about, 60% of approved drugs for

cancer treatment from Marine origin. For the preventing or delaying cancer development ,these drugs may fight against more than one stages of the cancer. As the marine microbes, plants and animals posses antimutagenic and anticarcinogenic functions.[7] In 2019, Cytarabine, a very first marine derived anticancer drug has completed 50 years of developing. The scientific and medical community have celebrated 50th anniversary of the Cytarabine [aka ara- C cytosar-U®]. This drug is derived firstly from marine sponge. It has good anticarcinogenic property which blocks DNA polymerase function.[8] According to conventional allopathic medicine, there are over 150 types of cancer that can be categorized in five main types of cancer is as per fig. no.1-.

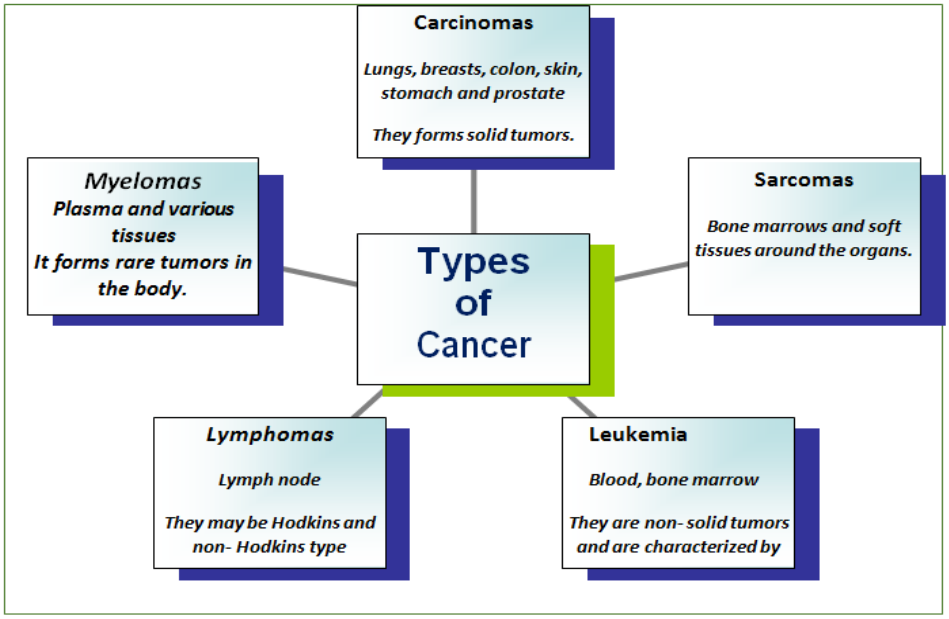

Fig. 1: Types of cancer.[9]

Table 1: Sources of Marine Natural Products in Clinical Trials.[10]

Sr. No.	Sources	% Drug	Examples
1	Sponges	28.6	Hemiasterlin A and B, E 7974 , HTI 286
2	Molluska	20.4	Dolastatin 10, Dolastatin 15, TZT – 1027 [Auristatun PE or soblidotine], Tasidotin [ILX 651] Cematodin [LU103793]
3	Chordata	-	Didemnin B, Plitidepsin, Dehydtodidemni B
4	Fungi	8.2	Higher fungi like basidiomycetes, endophytic fungi and filamentous fungi such as leptosphaerin,, leptosphaerolide and leptosphaerodione from the lignicolous fungus *Leptosphaeria oraemaris [*Pleosporaceae]
5	Algae	14.3	Cyanobacteria [Blue-green algae] and other algaes of more than 400 novel metabolites are bioogically active peptide and polyketide that kills cancer cell or reduce its proliferation.

There is a substantial progress in biological, immunotherapy and the significant improvements in the modern drug design and manufacturing. This discovery have made for the cure the cancer, which is our achievable goal. Cure and prolonged survival have already been attained for different malignancies. Such as lymphomas, testicular cancer and childhood lymphoblastic leukemia.

The marine territories is rich in biodiversity. There is various majour source for isolation of drug that exhibits pharmacological activity that described in table no. 1.

LITERATURE REVIEW

Terrestrial animals and plants have been every time a key source of natural products. From Millennium human begins to withdraw active ingredients from terrestrial plants and animals to treat disorders. With the advancing of drug discovery , it is more and more too much effort to develop new molecular structure of drugs from terrestrial animals and plants which cannot be deal with the expanding declaration or threat to human life and health. Therefore, “asking for drugs from sea” has become a keyto find new drug sources.[11] In recent years ,marine natural product exploration has renounced a significant number of drug applicants. Majority of these molecules are remain in preclinical or early clinical development.[12] The marine natural products are used not only for anticancer property but also antibacterial, antifungal, anti-Inflammatory, analgesic, neuroprotective and animal arial properties.[13] Nowadays, some newly derived anticancer small peptides and their immitatives

from ocean organisms have been broadly applied to clinical research. About 49 marine derived active substance or their Derivatives have been approved for the market or entered clinical trials globally. There are 11 kinds of marine drugs are authorized by European and American authorities in which the four drugs are used as anticancer Property: Cytosar – U, Yondelis, Halverson and Adcetric The marine domain is a vital biological kingdom with the abundant source of novel effective proteins and peptides. Also, it is graduallyrepresenting a essential field of drug development.[14]

In this review, research progress of marine derived anticancer agents from marine microalgae, cyanobacteria, sponges, tunicates, Mollusca and soft corals have been included and also the information about the drugs which posses antiproliferative property.

Marine Anticancer Agents

In the world, cancer is most complicated disease which may be expressed by network medications. In this review, compilation of marine drug sources which are used as anticancer agents are Marizomib, Plinabulin Enapotamab vedotin, Coibamide A, Tisotumab vedotin, Plocabulin, Ladiratuzumab vedotin, AGS- 16C3F, Pli0tidepsin, Bryostatin, Pectenotoxin – 2, Lurbinectedin, Belantamab Mafodotin, Enfortumab vedotin, Polatuzumab vedotin, Trabectedin, Brentuximab vedotin, Eribulin Mesylate, Cytarabine. These are summarized in table no.2.

1) Marizomib

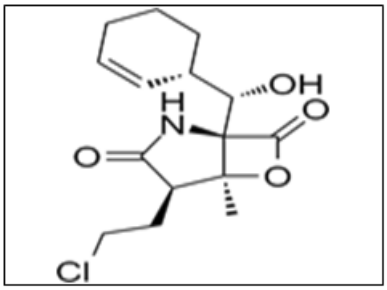

Fig. 2: Marizomib.

Marizomib is an actinomycets having gram positive bacteria with a high G + C ratio in their DNA as shown in fig. no 2.[15] Marizomib or Salinosporamide A or NPI – 0052 is a proteasome inhibitor derivedfrom the marine actinobacterium salinospora tropica belonging to family Salinosporamide and represents a promising clinical agent in the treatment of haematologic malignancies.[16] Marizomib is phase I stage of development. In the clinical trial of Marizomib having relapsed or refractory multiple myeloma. The binding of NPI – 0052 is irreversible and the Beta lacton is active moiety of Marizomib.[17] Molecular target of Marizomib is a monochlorinated 20s proteasome inhibitor in clinical trials for the treatment of cancer.[18] Marizomib is irreversible inhibitor which inhibits all three subunits of the proteasome beta-5, beta-1, beta-2. Currently the Marizomib is not approved by US food and drug administration.[19]

2] Plinabulin

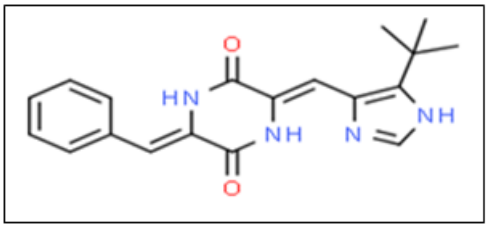

Fig. 3: Plinabulin.

Plinabulin having aspergillus species having Chemical Class is alkaloid from the source marine Fungus and the molecular target of plinabulin is alpha beta tubulin protein which is given in fig. no 3. Plinabulin i.e. NPI-2358 is used to treat non-small cell lung cancer, brain tumors and it is now going through phase III clinical trials. It is also strong anti-microtubule agent. Plinabulin has preclinical data shows favorable safety and antitumor activity profiles and evaluate the safety, pharmacokinetics and biological activity of plinabulin in patients with advanced malignancies.

3] Enapotamab vedotin

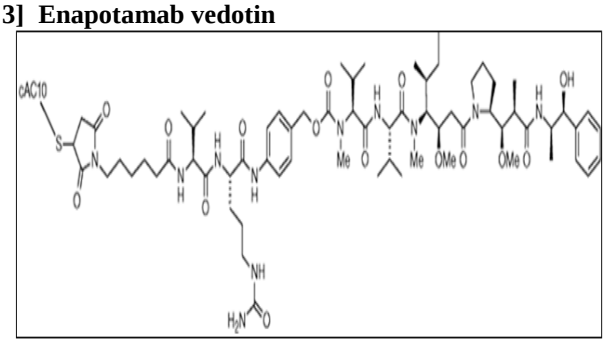

Fig. 4: Enapotamab vedotin.

Enapotamab vedotin is a anticancer marine drug used to treat ovarian cancer, cervical cancer and endometrial cancer in which molecular target is AXL – RTK /Nectin-4 having species Molluska/ Cyanobactspecific and its structure given in fig. no. 4. Enapotamab vedotin [HuMax-AXL] is a novel ADC conjugating with a human AXL- specific IgG1 and MMAE, and currently it is in phase II clinical trials.[20- 23]

4] Coibamide A

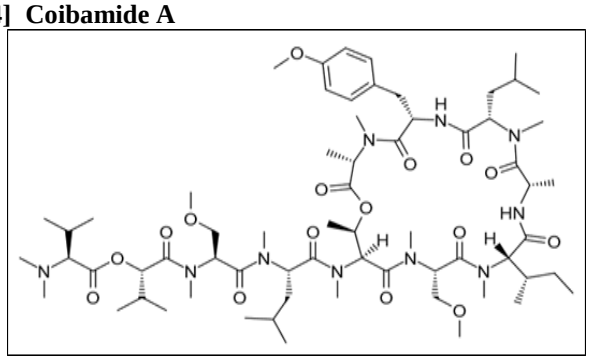

Fig. 5: Coibamide A.

Coibamide A is new, potent anti – proliferative despepetide which is Cyanobacterium source is shown in fig. no 5. The molecular target of Coibamide A is NCI – H460 lung cancer clinical trials.[24] Coibamide A had indicated a strong cytotoxic effect in case of NCI – H460 lung cancer cell lines when utilized in nanomolar concentrations. Apart from that, it caused upregulation of G1 cells in dosedependent method. In recent past, it was tested against particular 60 cell lines for colon, breast and ovarian malignant tumor cells of human. It was additionally established to be extra effective against MDA– MB – 231 cell line.[25] Coibamide A is a powerful cancer cell contagion and one of a preferred group of natural products that obstruct protein entry within the secretory pathway by a direct inhibition of the Sec61 protein translocan. In currently survey we evaluated the effect of Coibamide A against human epidermal growth factor receptor[HER, ErbB] proteins in the case of breast and lung cancer cell types. Even if Coibamide A inhibits biogenesis of a vast range of Sec61 substrate Protein in a presumed substrate non – selective manner.[26]

5] Tisotumab vedotin

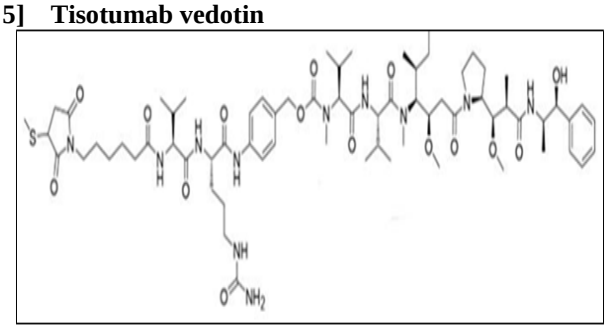

Fig. 6: Tisotumab vedotin.

Tisotumab vedotin in fig. no. 6 is an antibody drug conjugate which target tissue factor as well as the microtubule disrupting agent monomethyl auristatin E [MMAE]. Its main source is cynobacterium. Tissue Factor [TF] is actively expressed in solid tumors and is thought to promote to tumor progression by rectifying tumor growth , neoangiogenesis and metastatic potential through local activation of coagulation and protease activated receptor – 2 [PAR-2] signaling. Tisotumab vedotin was already displayed to activate cytotoxicity through MMAE and Fc – dependent Mechanisms. In addition, Tisotumab vedotin repressed PAR-2 signalling in TF – Positive tumor cells.[27] Tisotumab vedotin concluded a convenient assurance profile and reassuring antitumor activity in patients with formerly treated recurrent or metastatic cervical cancer. In cervical cancer TF acts as potential target, as it is generally highly conveyed and identical with poor prognosis. A first – in – class investigational antibody drug conjugate targeting TF is Tisotumab vedotin , has demonstrated refreshing activity in solid tumors. Here the report data from cervical cancer cohort of Innova TV201 phase I/ II study [NCT02001623].[28] On the basis of phase II trial result of Tisotumab vedotin is approved by USA for the treatment of metastatic cervical cancer with disease progression on or after chemotherapy.[29]

6] Plocabulin

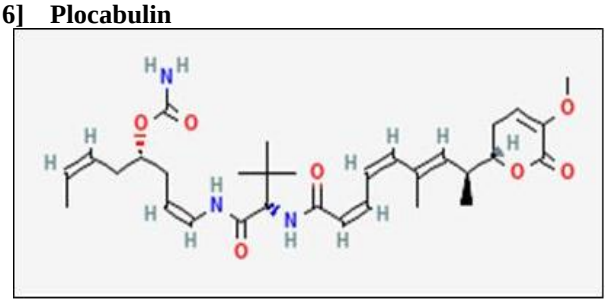

Fig. 7: Plocabulin.

Plocabulin [PM060184] basically deserted from the marine sponge , is a polyketide acts as new tubulin binding agent as shown in fig. no. 7 and now which is under in phase II clinical tests. It is used to treat solid tumors. It is a novel marine derived microtubule inhibitor that acts as an antitumor agents.[30] The molecular target of Plocabulin is minor groove of DNA and which is not approved.[31] Plocabulin compound is recently formed by total synthesis and concealed by interpretation in clinical studies having patients with leading cancer diseases. In recent past was published that Plocabulin presents the highest obvious affinities among tubulin binding agents and that is determine tubulin dimers at a new binding site.[32]

7] Ladiratuzumab vedotin

It is from Mollusk/ Cyanobacterium marine organism. The chemical class of Ladiratuzumab vedotin is ADC[MMAE]. The molecular target of Ladiratuzumab vedotin is LIV-1 and microtubules. It is used to treat breast cancer.[33] Ladiratuzumab vedotin [LV] is an investigational anti-LIV-1 antibody drug conjugate with a protease – cleavable linker to monomethyl auristatin E [MMAE]. LIV – 1 is extremely conveyed in metastatic triple negative breast cancer [TNBC]. LV mediated delivery of MMAE drives antitumor activity over cytotoxic cell assassination and has been exhibited to cause immunodeficiency cell death [ICD]. LV monotherapy has concluded supportive action in TNBC.[34] Ladiratuzumab vedotin is not approved to date by US – FDA.[35]

8] Cytarabine

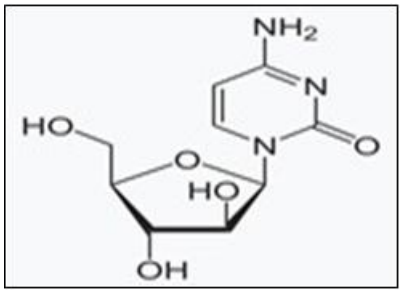

Fig. 8: Cytarabine.

In 1969, the food and Drug Administration [FDA] approved marine-derived compound, cytarabine [Ara-C, Cytosar-U], a synthetic pyrimidine nucleoside as a first-line drug against leukemia.[36] Leukemia is a cancer of

white blood cells [WBCs] that is characterized by the dysfunctional proliferation as well as excessive immatured leukocytes, which cause a lack of normal WBCs and, thus various symptoms occurs such as fatigue, fever, frequent infections, bleeding or bruising or even death.

According to Global Cancer Statistics 2020, an estimated 0.5 million new cases of leukemia along with 0.3 million deaths happen worldwide. Cytarabine in fig. no. 8 was first isolated from a marine spong Tethya Crypta. After being administered into plasma, cytarabine get converted into active form cytarabine triphosphate by the action of deoxycytidine kinase within the cell. Then the competition of cytarabine triphosphate for the DNA polymerase enzyme inhibits the synthesis of DNA. Further, the drug produces cytotoxicity in the cell through incorporation into DNA and RNA. Cytarabine produces it's effects mainly on the cell which are actively dividing by blocking the progression of the cell from G-1 phase to the S phase. These overall results in the death of the actively dividing cells.

9] Brentuximab vedotin

It is an antibody-drug conjugate [ADC] of CD30-specific monoclonal antibody brentuximab with the antimitotically active monomethyl auristatin E [MMAE], which is a synthetic analog of dolastatin-10, produced by cynobacteria symbiotic to sea hare Dolabella auricularia. One year later, after eribulin mesylate's approval, brentuximab vedotin, was first approved in 2011 for the treatment of anaplastic large T-cell systemic malignant lymphomas as well as Hodgkins lymphomas. It act by binding to CD30 [antibody] and inhibition of tubulin polymerization [MMAE]. In 2012 Adcetris® or Brentuximab vedotin was approved for the treatment of Hodgkins lymphoma is a type of cancer that is distinguished by thehigh expression of CD30.

10] Trabectidine

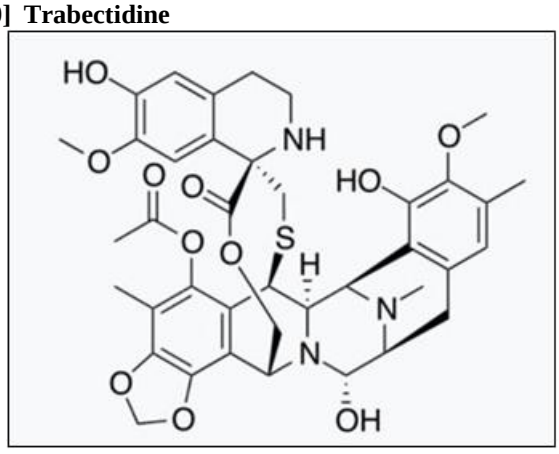

Fig. 9: Trabectidine.

Trabectidine [ET-743, Yondelis], first approved in 2015 for the treatment of soft tissue sarcoma as well as ovarian cancer. Unlike previous marine drugs trabectedine [Yondelis], the natural alkaloid as shown in fig. no.9 was initially isolated from marine tunicates exerts its anticancer functions through many different mechanisms. Firstly, it binds to the minor groove of DNA double strand. Secondly, it can cause cell cycle arrest by distrupting microtubules and then interfering with late S and G2 phases of cell cycle. It is also capable of inducing degradation of the RNA polymerase ll [RNA Pll]. It can also modulate the tumor microenvironment by inhibiting the release of cytokines with its various anticancer mechanisms and potent effects.

11] Eribulin mesylate

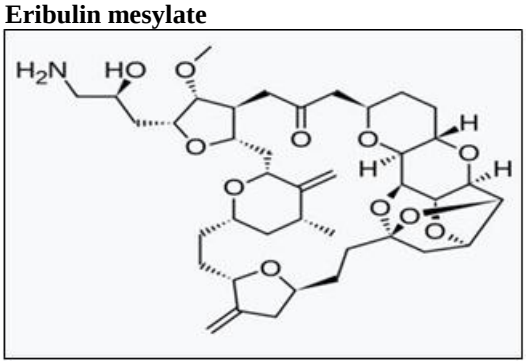

Fig. 10: Eribulin mesylate.

Spongian macrolide Eribulin mesylate or Halaven as given in fig. no.10, was first approved in 2010 by the Food and Drug Administration [FDA] for the treatment of metastatic breast cancer and in 2016, it become the second line of treatment for liposarcoma therapy [40In preclinical studies, eribulinhas shown antitumor activity in different types of cancer, such as head and neck cancer, non-small cell lung cancer [NSCLC], ovarian cancer, pancreatic cancer, colon cancer, melanoma, glioblastoma as well as small cell lung cancer. Tumor metastasis is inhibited by eribulin by inhibiting epithelial-mesenchymal transition [EMT] and inducing mesenchymal-epithelial transition [MET]. It is a synthetic derivative of marine product halichondrin B. It acts as a non-taxane microtube-targeted drug. Eribulin mesylate can supress the centromere's dynamics as well as arrest mitosis through the binding to tubulins andmicrotubules in the interphase and hence cause proliferative inhibition as well as apoptosis of cancer cells.

12] Plitidepsin

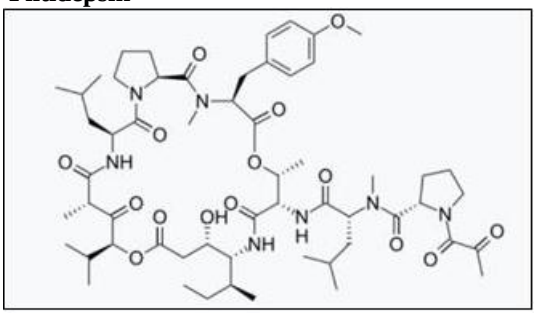

Fig. 11: Plitidepsin.

Plitidepsin [dehydrodidemnin B, Aplidin], is an ascidian depsipeptide first approved in Australia in 2018 for the

treatment of lymphoma, multiple myeloma as well as leukemia. It is a natural compound which is isolated from Aplidium albican and it has strong antitumor activity with low toxicity which is as shown in fig. no 11. The mechanism of Plitidepsin was achieved through targeting eukaryotic elongation factor 1A2 [eEF1A2] and then inducing cancer cell apoptosis. The target of Plitidepsin, eEF1A2, is one of the two isoforms of the protein elongation factor eukaryotic elongation factor 1 [eEF1A]. As an elongation factor protein, eEF1A can mediate aminoacyl tRNA recruitment to the ribosome during the translation. It exhibits anticancer effects by inducing cell apoptosis in multiple myeloma, ovarian cancer, pancreatic cancer, plasmacytoma and prostate cancer. Moreover, Plitidepsin can cause apoptosis via G1 and G2/M arresting and can also inhibit the cell cycle and sustained activation of the Racl/JNK pathway.[36-42]

13] Polatuzumab vedotin

The drug polatuzumab vedotin was approved by the Food and Drug Administration [FDA] in 2019 for the treatment of non-Hodgkin lymphomas, B-cell lymphomas, and chronic lymphocytic leukemia.[43] It is an antibody-drug conjugate [ADC] that consists of monomethyl auristatin E [MMAE] an analogue of dolastatin-10, which is a peptide toxin of symbiotic marine cynobacteria conjugated with the CD76b-specific monoclonal antibody polatuzumab. The antibody provides a specific delivery of monomethyl auristatin E [MMAE] to cancer-cells, where following the proteolytic ADC cleavage and release of the ``warhead'' molecule [MMAE], an inhibition of tubulin polymerization leading to the cancer cells death.[44]

14] Enfortumab vedotin

Enfortumab vedotin is an antibody-drug conjugate [ADC] directed against Nectin-4, an extracellular adhesion protein which was approved by the Food and Drug Administration for the treatment of metastatic urothelial cancer. It is highly expressed on the surface of many epithelial cancers, such as lung cancer, breast cancer, bladder cancer and pancreatic cancer. Nectin-4 attached to a chemotherapeutic microtubule disrupting agent, monomethyl auristatin E [MMAE] offers enfortumab vedotin the ability to target the nectin-4-positive cells and then induce cell death through MMAE.[45]

15] AGS 16C3F

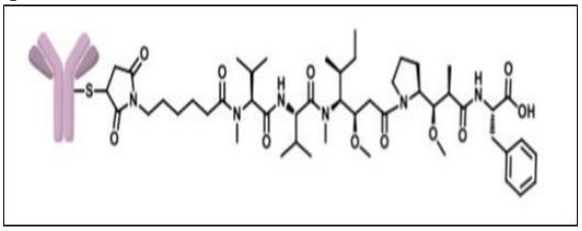

Fig. 12: AGS 16C3F.

AGS- 16C3F in fig. no.12 is a novel anticancer agent derived from Mollusk [Cyanobacterium] which generally used for treatment of renal and liver carcinomas. AGS-16C3F is established by Agensys and Astellas Pharma.AGS-16C3F, ADC which targets ENPP3 [D203a] conjugates with Monomethyl Auristatin-F [MMAF].[A]AGS-16C3F further known as AGS16M8F. It is an ADC belonging to the human IgG2k monoclonal antibody [AGS-16] which is associated with MMAF. This MMAF is a potent microtubule inhibitor having potential antineoplastic activity.[46]

AGS-16C3F is a MMAF by a non-cleavable maleimido caproyl [mc] linker. At the cell surface of ENPP3 extracellular nucleotides are catalysed and contribute to the pathophysiology of cancer with increasing tumor invasion. Preclinical trials observations conclude that AGS-16C3F have high affinity towards molecular target i.e.ENPP3 which observed on the surface of renal, hepatocellular and chronic nucleogenous leukemia cells.[47]

In addition, antitumor activity is also observed. However, in phase-II trials AGS-16C3F combined with axitinib in 84 patients who earlier treated with metastatic renal cell carcinoma [mRCC].[48] The study concluded that AGS-16C3F was well tolerated with clinical activity at 1.8mg/kg every 3 weeks and then this 1.8mg/kg dose was found to be suggested for phase-II trials. This combination of AGS-16C3F with axitinib was failed to reach its primary and secondary endpoints and this is the reason of discontinuation of AGS-16C3F.[49]

16] Pectenotoxin-2[50-53]

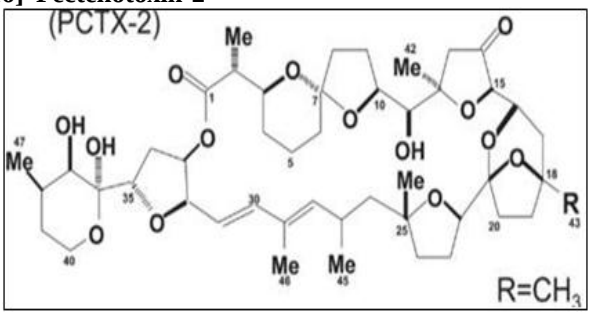

Fig. 12: Pectenotoxin-2.

Pectenotoxin-2 is a polyether lactone which belongs to neutral class of diarrhetic shellfish poisoning [DSP] toxins. In between the class of natural toxins, pectenotoxin-2 had been combined with DSP because they coincide with okadaic acid and dinophysis toxins in their chemical structures as givenin fig. no. 12. They are always synchronize in the shellfish contaminated with dsp toxins.

This has been clearly expressed and identified in Dinophysis fortii which are composed in northern Adriatic Sea[Emillia Romagna Coasts].This is the first time in Europe that such toxins are emerged and reported. At the recent studies, it has been observed that pectenotoxin-2 have affinity towards G-actin, pectenotoxin-2 binds towards unique binding site of G-

actin with respect to each other well known marine derived actin- targeting agents and it also capping the portion of a non-muscle actin filament that points towards the site of attachment on cell membrane which is called barbed end. This capping of barbed end is without filament severing properties.

Pectenotoxin-2 has been found in different toxins like dinoflagellates D. fortii, D. accuminsta, D. norvegica, D. rotundata and D. accuta. Pectenotoxin-2 in bivalves is observed by algae and metabolisedby two processes.

Method no. 01- Hydrolysis:Pectenotoxin-2 undergoes hydrolysis and produces pectenotoxin-2 seco acid compound. Further this compound undergoes acylation process and gives 37-O-acyl PTX-2SA, 33- O- acyl PTX- 2SA and 11-O- acyl PTX- 2SA.

Method:02-Oxidation: Pectenotoxin-2 undergoes stepwise oxidation and gives pectenotoxin-1which is a alcohol, this compound further undergoes oxidation and gives pectenotoxin-3 which is an aldehyde molecule which further oxidised and gives pectenotoxin-6 which is an carboxylic acid.[51]

Targeted Organs: Apart from other actin- disrupting agents, pectenotoxin-2 has been stated to having selective toxicity towards P53 mutant and P53 null cancers which includes varients that are highly chemoresistant.

17] Bryostatin-1

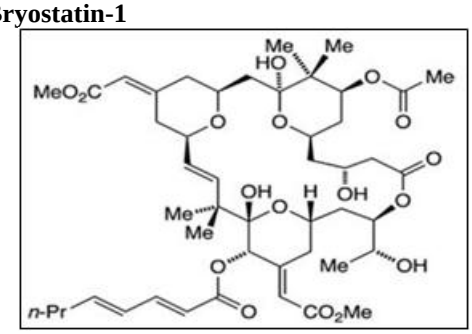

Fig. 13: Bryostatin-1.

Bryostatin-1 is an antineoplastic agent obtained from bryozoan Bugula neritina. Bryostatin-1 binds to enzyme protein kinase-C[PKC] and performs various biological activities likewise angiogenesis, growth inhibition, induction of cell hippocampal synapses, memory, spatial learning, etc.It is a prospective drug to treat strokes. As bryostatin-1 leads to activation of protein kinase-C [PKC] isoenzymes at nanomolar concentrations.Hence,it is a powerful PKC agonist. To achieve cognitive, restorative and antidepressant effects appropriate doses should be given in pharmacological studies of bryostatinstin-1.

It belongs to class of highly oxygenated macrolides possesing a 20 membered macrolactone ring with wide range having biological activity like enhance the cytotoxicity of other agents which is clinicallyproven as shown in fig no. 13. Biological activities of bryostatinstibs becomes a great research group for study of marine environment. Reduction of neurotoxic amyloid accumulation and tau proteins hyperphoshorylation may involved in underlying pharmacological mechanism. Bryostatin-1 have a potent activity as a drug acting on CNS. Modulation of PKC represents a novel approach to cancer therapy by altering the expression of surface antigens in cancerous cells. This results to enhancing their sensitivity to immune or other antigen targeted treatment strategies.

Bryostatin-1 potently increases the effect in many hematological and solid tumor cell lines.[58] To yield a 28gm of Bryostatin-1, there is neccecity to harvest 12 tons of Bugula neritina. For the total synthesis of Bryostatin-1, recently new method has been invented. But it is not attainable for large scale production in case of set design of 'Bryologues' which are simpler analogue of Bryostatins.[54- 58]

Table 02: Summary on marine anticancer agent.[15-58]

Sr. No.	Compound name	Marine Organism	Chemical class	Molecular Target	Cancer Type
1]	Marizomib	Actinobacteria	Beta- lactone	20s Proteasome inhibitor	Myeloma
2]	Plinabulin	Fungus	Alkaloid	Alpha - beta tubulin protein	Small cell lung cancer, Brain tumors.
3]	Enapotamab vedotin	Mollusk/ Cyanobacterium	ADC [MMAE]	AXL-RTK/ Nactin-4	Ovarian cancer, Cervical cancer, Endometrial cancer.
4]	Coibamide A	Cyanobacterium	Anti- proliferative depsipeptide	Sec61 substrate protein	Lung cancer, Breast cancer, Ovarian Malignant tumor.
5]	Tisotumab Vedotin	Mollusk/ Cyanobacterium	ADC[MMAE]	Tissue factor	Metastatic cervical cancer.
6]	Plocabulin	Sponge	Polyketide	Microtubule inhibitor ,	Solid tumors

				Minor groove of DNA.	
7]	Ladiratuzumab vedotin	Mollusk/Cyanobacterium	ADC[MMAE]	Microtubules	Breast Cancer
8]	Cytarabine	Sponge	Nucleoside	DNA Polymerase	Leukemia
9]	Eribulin	Sponge	Macrolide	Microtubules.	Metastatic Breast cancer
10]	Brentuximab Vedotin	Mollusk/Cyanobacterium	ADC[MMAE]	CD30, Microtubules	Anaplastic large T-cell systemic Malignant lymphoma, Hodgkin's Disease
11]	Trabectidine	Tunicate	Alkaloid	Minor groove of DNA	Soft tissue sarcoma and Ovarian cancer
12]	Plitidepsin	Tunicate	Desipeptide	eEF1A2	Multiple Myeloma, Leukemia, Lymphoma.
13]	Polatuzumab Vedotin	Mollusk/Cyanobacterium	ADC[MMAF]	CD76b, Microtubules	Non-hodgkins lymphoma, Chroniclymphocyti leukemia, lymphoma.
14]	Enfortumab Vedotin	Mollusk/Cyanobacterium	ADC[MMAE]	Nectin-4	Metastatic Urothelial cancer
15]	Ags 16 C3F	Sponge	ADC[MMAF]	ENPP3	Tumor
16]	Pectenotoxin-2	Sponge	Macrolactone	Cdc 25c	Tumor necrosis
17]	Bryostatin-1	Invertebrate *Bugula neritina*.	Macrocyclic lactone	Protein kinase	Non-hodgkins lymphoma, Cervical cancer

DISCUSSION

The review highlights the discovery of marine organisms having anticancer property, novel chemical structures and chemical properties. Activity prevention of tumor formation and related compounds induces apoptosis and cytotoxicities were tackled. For the purpose, the study of marine population having bioactive metabolites with anticancer property has been studied.[10] The diversification of biological substances from marine environment virtually complement to marine domain are crucial of anticancer agents.

Marine derived cancers in deriving new anticancer agents have dominant role to expanding knowledge about medicinal agents obtained from marine organisms which targets various events of carcinomas processes.[23] This context implied that these anticancer agents acts by both preventive as well as therapeutic intercession. At clinical level, there is alliance of biologists,chemists, toxicologists, medical and 'omics' experts which jointly collaborates in the initial stages deliberately rely upon national as well as international scientific funding resources, also have a open access to data from previous research activities.[9] It is comprehensible that marine products are hopeful in providing a platform to improve anti- cancer therapeutic strategies. Despite the fact that more definite exploration are crucial to encounter through most common challenges in chemical utility. Fundamentally, sponge derived active metabolites should be exploited with combination of innovative technologies which could expand new province of applications that will influence remarkably on biotechnology. With proceeding progress of drug discovery, it becomes more strenous to obtain new active metabolite from terrestrial sources, with cannot be contend with expansion of threat to mankind and their wellness.[42]

The natural products obtained from enzymatic process ande these are furnished by 3-dimensional structural features which is responsible to conjugate with binding sites, having substantial specificity as well as unique biodiversity.[57] Several perspective towards the enhancement of natural products uncovering programmes with the improved number of natural products derived drugs making to the market. These natural products have been used in mankind maladies and put down a strong foundation on which present pharmacology has been erected.These chemotherapeutic agents have astonishing influence on the field of pharmacy, with allowing the extension of knowledge and for their clinical importance in cancer pharmacology.[59]

As cancer is one of the most life-threatening disease, and therefore, putting a question of 'why to looking forward towards anticancer drugs from the deep of ocean?' which flatter a solution to discover a new marine anticacer entities.[46] Continual innovation of deep sea mining technology, extraction as well as separation technology provide hope and new opportunities for the discovery of marine anticancer agents.from terrestrial sources of marine compounds mankind has been started to extract active molecular moiety since a millennium.As the field of marine fauna and flora is explored widely and becomes an interesting research area for study purpose to aquire a new anticancer leads.[35]

CONCLUSIONS

Current review paper concise about several novel marine drugs that can be clinically useful and incorporated for treatment of various neoplastic disorder. These drugs exert different mechanism of action to cure cancer by either killing cancer cells or by retarding their proliferation. Hence, these biomolecules can be helpful

as futuristic accessibility for combinational cancer chemotherapy of marine derived drugs. Also, these drugs can be continued for medicinal research to cure other body disorders. This review enlightens some antineoplastic agent that can be also evaluated for antineoplastic effect which is emerging revolution in cancer chemotherapy.

CONFLICTS OF INTEREST

All authors contributed equally. There is no conflicts of interest.

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