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THERAPEUTIC POTENCY OF ANTICANCER PEPTIDES DERIVED FROM MARINE ORGANISM

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ABSTRACT

Nature has been instrumental as a source of therapeutics. Since the oceans cover more than 70% of the earth surface and the marine environment is highly diverse, it is very much likely that marine organisms would be a wonderful source of biologically active molecules. Over the past decade, several new therapeutic agents derived from marine sources have entered preclinical and clinical trials. This field has expanded significantly as a result of improvements in the technology of deep-sea collection, extraction and large-scale production through aquaculture and synthesis. The collection of the marine therapeutics includes molecules with antibiotic, antiviral, antiphrastic, analgesic and anticancer activity. This review focuses on the latest studies and critical research in this field and evidences the immense potential of marine organisms as sources of bioactive peptides and other anticancer biomolecules. Various anticancer compounds with diverse modes of action, such as, anti-proliferative, antioxidant, anti-microtubule have been isolated from marine sources. Traditional chemotherapeutic agents have a range of side effects like fatigue, gastrointestinal distress and depression of immune system which introduces the necessity of natural anticancer drug discovery. Recent researches have been focused on peptides from marine animal sources, since they have been found as secondary metabolites from sponges, ascidians, tunicates and molluscs. The structural characteristics of these peptides include various unusual amino acid residues which may be responsible for their bioactivity. Purified peptides from these sources have been shown to have antioxidant activity and cytotoxic effect on several human cancers such as pancreatic, breast, bladder and non-small-cell lung cancer. These characteristics imply that the use of peptides and others biomolecules from marine sources has potential for the prevention and treatment of cancer and they might also be useful as molecular models in anticancer drug research.

KEYWORDS: Biologically active molecules, peptides, chemotherapeutic agents.

INTRODUCTION

Nature has been playing an important role in providing therapeutic entities since ancient time for treating and preventing human disease. The vast source of nature includes terrestrial and marine plant, microorganism, vertebrates and invertebrates etc. it is importnt to consider that the major anti-infective, anticancer, analgesics and immunosuppressive compounds are of natural origine. in terms of evolution and biodiversity the sea appears to be supirior to the terrestrial ecosystem. as marine species comprise approximately a half of the total biodiversity, they are offering a vast source from which useful therapeutics can be discovered. over the past decade, marine organisms have been recognized as an untapped resource for novel bioactive compounds. Marine floras have been used for medicinal purposes in India, China, the Near East and Europe, since ancient time. **C**hinese pharmacopia recommends seaweed based recipies for a number of physiological disorders. such as pain,abscesses, menstrual difficulties and cancer. seaweed remidies are also used by the San Bias Indians in Panama and Romans attributed medicinal effects to some marine animals. During the last 25 years, natural products derived from marine organism has been the focus of many investigations, specially for cancer. Marine derived biomolecules such as peptides, enzymes, enzyme inhibitors, lipids has potential for the prevention and treatment for cancer and they might be useful as molecular models in drug

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research. Purified peptides from these source have been shown to have cytotoxic effects on several human cancers such as poancreatic, breast, bladder and lung cancer. The objective of this study is to find out new ways to combat cancer emerging from modern research area on marine biodiversities and to gain a broader understanding of the mechanism of cancer and the factors involved in discovery and theraputic uses of anticancer drug. This review focuses on the latest studies and evidences the immense potency of marine organism as anticancer biomolecule sources.

THERAPEUTIC AGENTS FROM MARINE SOURCES

Marine organisms are rich source of chemical products. In recent years, a renaissance has occurred in marine pharmacology. Emerging evidence suggests that marine natural products, specially the secondary metabolites from marine organisms, are far more likely to yield potential anticancer drugs than terrestrial sources.

Bacteria

Marine microorganisms are a rich source of new genes, exploitation of which is likely to lead to the discovery of new drugs and therapeutic approaches. Only a few marine bacteria can be isolated under laboratory conditions and there is an urgent need to develop new culture techniques to isolate slow-growing bacteria and also to isolate the bacteria that are unique in production of novel natural products. Of them, secondary metabolites produced by marine bacteria have yielded pharmaceutical products [1] such as novel anti-inflammatory agents (e.g., *Seudopterosins*, *Topsentins*, *Scytonemin* and *Manoalide*), anticancer agents (e.g., *Bryostatins*, *Discodermolide*, *Eleutherobin* and *Sarcodictyin*) and antibiotics (e.g., *Marinone*). Anti-Parasitic compound *Valinomycin* is isolated from *Streptomyces sp.* strains of Mediterranean Sea.

Cyanobacteria

The cyanobacteria population comprises [2] 150 genera and about 2000 species of considerable diversity. The potency of marine cyanobacteria as anticancer agents is the most explored among all marine derived chemicals. Besides cytotoxicity in tumor cell lines, several compounds have emerged as templates for the development of new anticancer drugs. However, they are also found to induce anti-inflammatory and antibacterial activities. Well studied species of marine cyanobacteria includes *Nostoc*, *Calothrix*, *Lyngbya*, *Symploca* etc [3].

Invertebrates

Soft corals are likely to be rich sources of biologically active secondary metabolites. Recent experiments show that methanol extracts of two *Nephthea* (*Alcyonacea*, *Nephtheidae*) species of soft coral have exhibited anticancer properties [4,5]. Tunicates are group of marine organism which is member of *Tunicata*, sub-phylum of Chordata. They are particularly abundant along coastal regions. Although ascidians are considered as group members of tunicates, but recent evidence suggests that they are not [6]. There are several ascidian species that produce bioactive anticancer peptides, steroid and anti-oxidants with novel structures.

Fungi

Marine derived fungi provide plenty of structurally unique and biologically active secondary metabolites. The *Anthracenedione* derivatives acting as the potent anticancer agents screened from the mangrove [7] endophytic fungus *Halorosellinia sp.* and *Guignardia sp.* for example, *Cytarabine*, an antileukemic drug and *Trabectedin*, an agent for treating soft tissue sarcoma are developed from marine fungi sources [8]. Besides, marine-derived fungi are known to be a source of antioxidative natural products such as *Acremonin A* from *Acremonium sp.* and *Xanthone* derivative from *Wardomyces anomalus* [9]. Reactions of free radicals, such as superoxide radical, hydroxyl radical, peroxyl radical and other reactive oxygen and nitrogen are associated with diseases such as atherosclerosis, dementia and cancer. Antioxidants delay or prevent oxidative damage and thus they may be useful as therapeutics or food additives. Different types of *Cephalosporins* are isolated from marine fungi which are being used as antibiotic [10].

Sponge

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Approximately 10,000 sponges have been found worldwide [11] and most of them live in marine environments [12]. Marine sponges have yielded over 70 novel compounds to date that exhibit significant inhibitory activity towards a range of protein kinases. A range of bioactive compounds has been found in about 11 sponge genera. Three of these genera (*Haliclona, Petrosia* and *Discodemia*) produce influential anticancer and anti-inflammatory agents [13]. These compounds possess a wide spectrum of biological activities. However, it is difficult to isolate them in sufficient quantity for pharmacological testing.

Mollusk

Mollusks are species that have a wide range of uses in pharmacology. Different types of linear, cyclic and conjugated peptides are found as therapeutically potent anticancer biomolecules from cone snail and other shelled organisms [14], such as *Kahalalides, Dolastatins, Ziconotide, Bursatellanin, Keenamides* etc.

Table 1: Therapeutically important biomolecules from marine organisms

SOURCE	COMPOUND	BIOACTIVITY
Bacteria	Valinomycin	Anti-Parasitic
Cyanobacteria	Calothrixin A and B	Antimalarial
Cyanobacteria	Curacao extracts	Antiproliferative
Fungi	Cephalosporins	Antibiotic
Fungi	Antioxidants	Atherosclerosis, dementia
Soft coral	Methanol extracts	Anticancer
Sponge	Kuanoniamines	Growth inhibitor
Sponge	Steroid	Inflammation, asthma
Sponge	Ara-c	Antiviral
Cone snail	Conotoxins	Chronic pain

ANTICANCER PEPTIDES FROM MARINE ORGANISMS

Today, more than 60% of the anticancer drugs commercially available are of natural origin [15]. The relevance of the sea as a tool to discover novel anticancer compounds was validated by the discovery, development and marketing approval of isolated marine derived bioactive compounds. The available results clearly anticipated the potential of the marine ecosystem in cancer therapy. During the last decade about 2500 new metabolites with antiproliferative activity have been reported. A recent review has discussed 68 new marine derived anticancer chemical entities, most of them with undetermined modes of action [16]. The identification of new targets for therapeutic intervention in cancer is instrumental to improve the physiological condition of cancer patients. The clinical results generated with a number of marine derived compounds such as the *Dolastatins, Didemnin B, Aplidine* have been recently reviewed [17]. Most of the natural products of interest to the pharmaceutical industry are secondary metabolites, but there is a growing interest in products of primary metabolites such as various marine lipids, enzymes complex heteropolysaccharides and different types of peptides. Although different type of anticancer bio-molecules are obtained from various types of marine organism this manuscript critically summarizes the developmental status of marine derived peptides from different micro and macro organism.

Cyanobacterial derivatives

Marine cyanobacteria have been considered as an important source of structurally diverse and biologically active natural products. Different types of peptides are isolated from a wide variety of marine cyanobacteria which induces anticancer effects on various human cell lines. The cytotoxic effects of marine cyanobacterial compounds on human tumor cell lines are the most studied, with some compounds producing effects at a minimum range. For example, *Apratoxin A* (Fig. 1a) is cyclic depsipeptide extracted from *Lyngbya*

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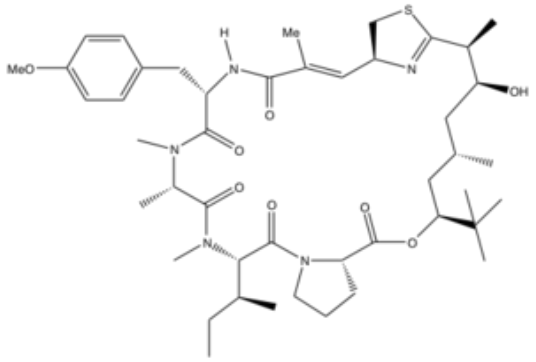
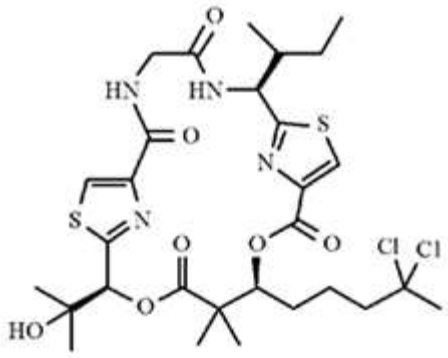
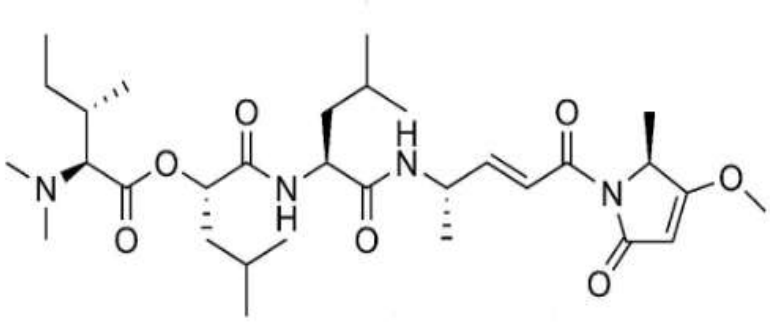
majuscula which exhibit cytotoxic effects on Human HeLa cervical carcinoma cells by cell cycle inhibition [18]. Similar mechanism has been observed by cyclic depsipeptide *Coibamide A* which is isolated from *Leptolyngbya sp.* on Human lung cancer cell line [19] and *Lyngbyabellin B* (Fig. 1b) isolated from *Lyngbya majuscula* on Human Burkitt lymphoma cells [20]. Linear Pentapeptide *Dolastatin 10* and *Symplostatin 1* (Fig. 1c) are isolated from *Symploca sp.* which show cytotoxic effect on human lung cancer cell line and Human breast carcinoma cell line by both Bcl-2 phosphorylation and Caspase-3 protein activation [21,22]. Besides, there are also different types of anticancer peptides isolated from *Lyngbya sp.* and *Nostoc sp*, which shows their activity against cancer on different cell lines through microfilament disruption, secretory pathway inhibition etc [23].



a. Apratoxin



b. Lyngbyabellin B



c. Symplostatin 1

Figure 1: Cyanobacterial anticancer derivatives

Tunicate and Ascidia derivatives

Different types of tunicates and ascidia are inhabitants of sea floor. They produce complex antitumor compounds that are estimated as more effective than any other cancer medicine now in use. One of these potent compounds is *Didemnin* which was isolated first from the Caribbean tunicate *Tridemnum solidum* [24]. But later on it has also been extracted from other species of the same genus [25]. Among various *Didemnin*, *Didemnin B* (Fig. 2a) has the most potent antitumor and antiproliferative activity against human prostatic cancer cell lines [24]. *Didemnin B* is the first marine peptide to enter into clinical trial as a potent anticancer drug [26]. This is a cyclic depsipeptide which exerts antitumor activity via protein synthesis inhibition [27]. However, high toxicity, poor solubility and short life span led to the discontinuation of clinical trials of *Didemnin B* [26].

Aplidine (Fig. 2b) is a cyclodepsipeptide isolated from the tunicate *Aplidium albicans*. It has been shown to have potent anticancer activity against a variety of human cancer cell lines, such as breast,

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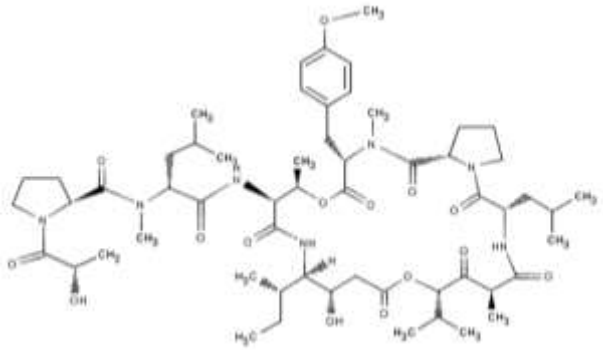
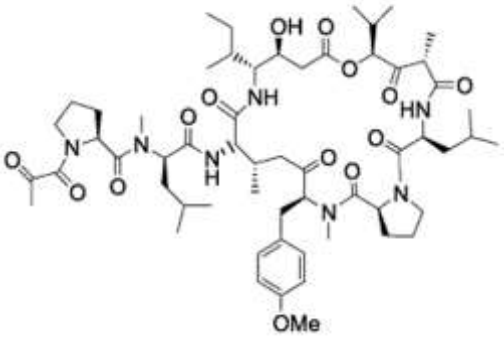
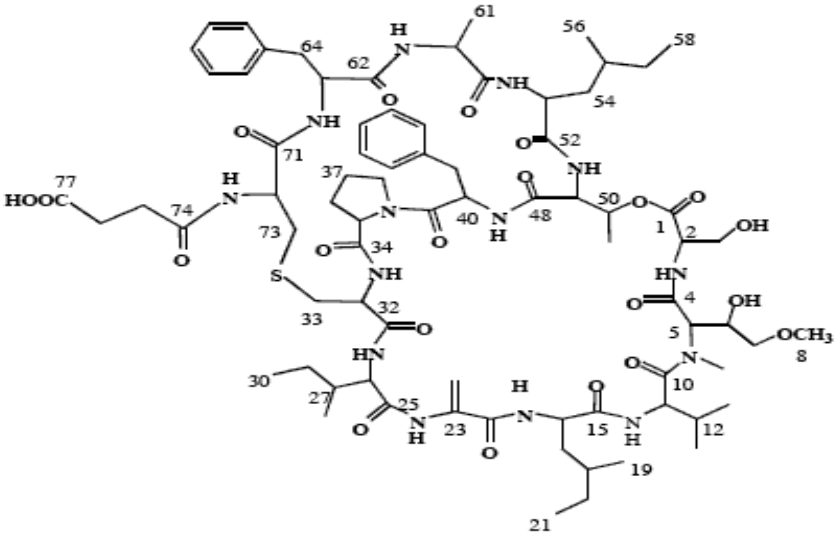
melanoma and lung cancers [28]. It is appeared that these cancer cells are sensitive to low concentrations of this compound. *Aplidine*'s mode of action involves several pathways; that's why *Aplidine* is described as multifactorial apoptosis inducer. The compound induces rapid cell cycle arrest at G1-G2 and inhibition of protein synthesis, thus introduce apoptosis of cancer cells [29]. *Aplidine* also inhibits the expression of the vascular endothelial growth factor gene, having antiangiogenic effects [30]. However, *Aplidine* is appeared as more active than *Didemnin* in preclinical models and so far has not shown evidence of life threatening neuromascular toxicity [28,29,31].



a. Didemnin B



b. Aplidine



c. Vitilevuamide

Figure 2: Anticancer derivatives from Tunicate and Ascidia

Another ascidia derivative is *Vitilevuamide* (Fig. 2c) which is a cyclic peptide isolated from the ascidians *Didemnum cuculiferum*. It is a tubulin interactive agent. Vitilevuamide inhibit tubulin polymerization and can arrest the cell cycle of target cells in the G2/M phase [32,33]. *Tamandarins* A and B are also cytotoxic depsipeptides from a marine Ascidian of the family *Didemnidae*, which was evaluated against various human cancer cell lines. *Mollamide* is a cyclodepsipeptide obtained from the ascidian *Didemnum molle* and it has shown cytotoxicity against a range of cell lines like human lung carcinoma and human colon carcinoma [34,35,36]. *Trunkamide A* is a cyclopeptide with a tiazoline ring similar to *Mollamide* obtained from

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ascidians of the genus *Lissoclinum*, for which antitumor activity under preclinical trials has been observed [34,37].

Fungi derivatives

Marine derived fungi provide plenty of structurally unique and biologically active secondary metabolites. As part of ongoing research on marine biodiversity for cancer treatment marine fungi have been proved to be a rich source. Two novel cyclodepsipeptides *Scopularide A* and *B* are found in marine fungi *Scopulariopsis brevicaulis* [38]. Although they are also isolated from marine sponge *Tethya aurantium*, both of them significantly inhibit growth of pancreatic tumor cell and colon tumor cell line, through an yet unknown mechanism. *Sansalvamide A* (Fig. 3) is a structurally unique cyclic depsipeptide isolated from various marine fungi. It exhibits cytotoxic activities against different types of cell line like pancreatic, colon, breast and prostate sarcoma as well as melanoma which suggest it as a potent anticancer therapeutic agent [39]. The exact mechanism is unknown; but recent study shows an interaction between heat shock protein (HSP90) and client cancer protein in mammalian cell line. *Sansalvamide A* binds to N-middle domain of HSP90 and allosterically inhibits protein complex formation which is necessary to promote tumor growth [39].

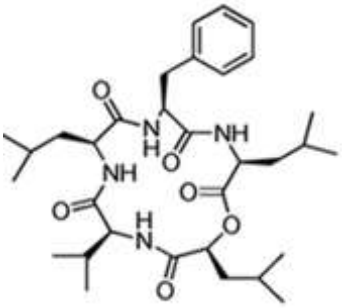

Figure 3: Sansalvamide A, anticancer peptide from marine fungi

Sponge derivatives

There are a number of research studies on bioactive peptides from sponges, where most of them are cyclodepsipeptides. Cyclopeptides are secondary metabolites with unusual amino acids and non-amino acid moieties. These compounds possess a wide spectrum of biological activities; however, it is difficult to isolate them in sufficient quantity for pharmacological testing.

Jaspamide (Fig. 4a) is a cyclic depsipeptide isolated from sponges of the genus *Jaspis* and *Hemiastrella*. It possesses a 15-carbon macrocyclic ring which contains three amino acid residues. It has been proved that this is a bioactive compound inducing apoptosis in human promyelocytic leukemia cell line and T cells in brain tumor by Caspase-3 activation and decreasing in Bcl-2 protein expression [40,41,42]. *Hemiasterlins* are oligopeptides isolated from two distinct genera (*Auletta*; *Siphonochalina*) of sponge. There are three different *Hemiasterlins* with drug development potential (*Hemiasterlin, Hemiasterlin A, Hemiasterlin C*) exhibit cytotoxic and antitubulin activity. Mitotic inhibition occurs through binding to tubulin at the peptide region in a manner similar to *Dolastatin* [43,44].

Geodiamolide H (Fig. 4b) is a cyclic peptide isolated from a Brazilian Sponge *Geodia corticostylifera* have demonstrated antiproliferative activity against breast cancer cells by altering the actin cytoskeleton [45]. *Arenastatin A* (Fig. 4c) is a cyclodepsipeptide isolated from *Dysidia arenaria* that have demonstrated potent cytotoxicity against different cells [24]. Nine new cyclodepsipeptides, *Homophymines B–E* and *A1–E1* (Fig. 4d) isolated from the sponge *Homophymia sp.* have shown very potent cytotoxic activity in nM range. This activity has been reported against several human cancer cell lines with moderate selectivity against human prostate and ovarian carcinoma. *Homophymines A1–E1* exerts stronger potency than the corresponding *A–E* [46,47].

Discodermin tetradecapeptides are another group of cytotoxic peptides obtained from sponges of the genus *Discodermia sp.* containing 13–14 known and rare amino acids as a chain, with a macrocyclic ring constituted by lactonization of a threonine unit with the carboxy terminal. *Discodermins A–H* is being tested against human lung cell line showing cytotoxicity [24]. *Papuamides A–D* (Fig. 4e) are isolated from sponges of the genus *Theonella*, are the first marine-derived peptides reported to inhibit the infection of human T-lymphoblastoid cells by HIV-1 *in vitro* [24, 48].

Phakellistatins (Fig. 4f) are cyclic heptapeptides isolated from the Western Indian Ocean sponge *Phakellia carteri* [49]. This compound inhibits leukemia cell growth. Another related compound,

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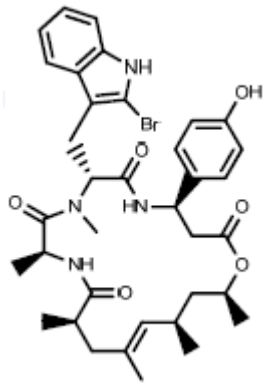
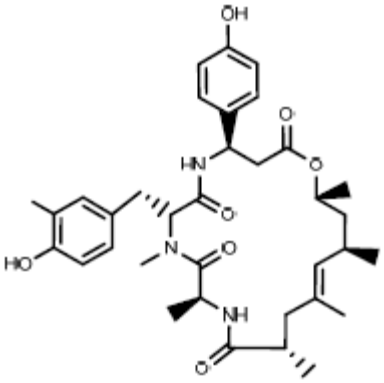
Phakellistatin 13 from sponge *Phakellia fusca* was cytotoxic against the human hepatoma cell line . Synthetic specimens of *Phakellistatin* are found to be chemically but not biologically identical to the natural products. The reason might be a conformational difference, especially around the proline residue [37,50].

Mollusk derivatives

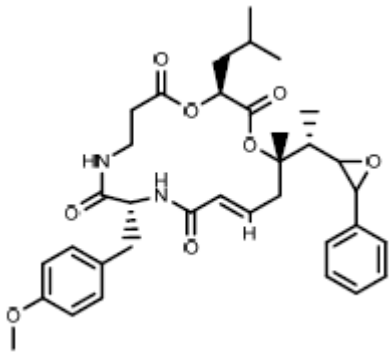
Mollusks are species that have a wide range of uses in pharmacology. Cone snails belonging to the genus *Conus* are a valuable source of active peptides named conotoxins. They consist of a mixture of peptides with short chains of amino acids (8–35) rich in disulfide. *Ziconotide* is a 25 amino acid peptide with three disulphide bonds; and is present in the venom of the predatory Indo-Pacific marine mollusk, *Conus magus.* It possesses remarkable analgesic activity, which has proved to be 1000 times more active than morphine in animal models of nociceptive pain [51]. Studies have postulated that these peptides could be of interest in the treatment of cancer. *Keenamide A* is a cytotoxic cyclic hexapeptide isolated from the mollusk *Pleurobranchus*



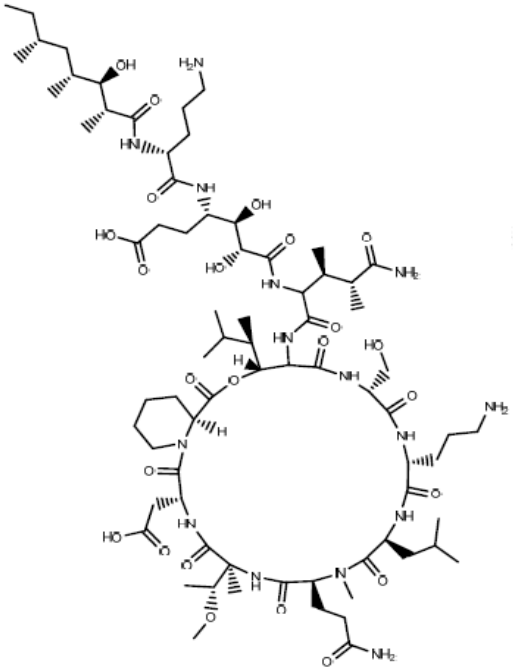
a. Jaspamide



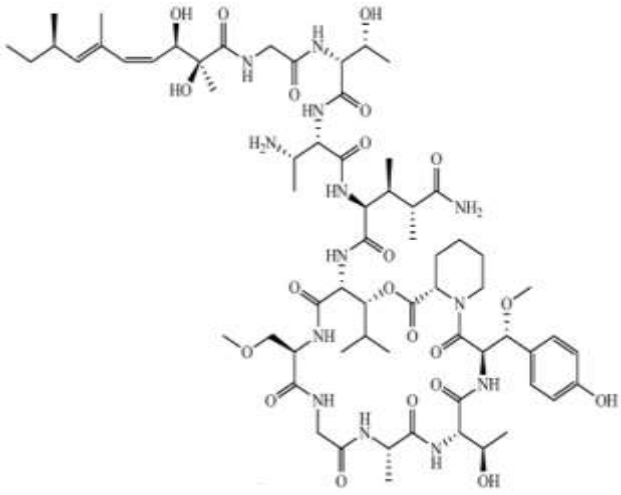
b. Geodiamolide H



c. Arenastatin A



d. Homophymines



e. Papuamide

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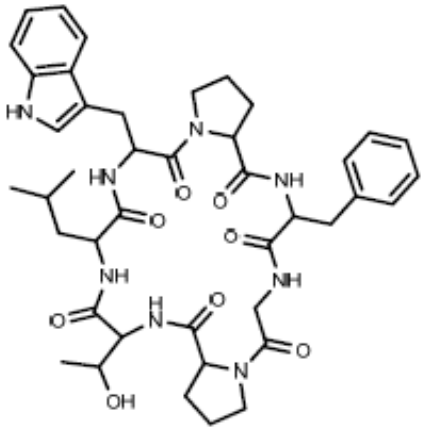

f. Phakellistatin

Figure 4: Anticancer peptides from marine Sponge

forskalii, which elicits antitumor activity via unknown mechanisms. This compound exhibited significant activity against different type of tumor cell lines [52].

Sea hare, a shelled organism, produces bioactive metabolites used in the treatment of cancerous tumors. The *Dolastatins* are cytotoxic cyclic and linear peptides derived from the sea hare, *Dolabella auricularia*, a mollusk found in the Indian Ocean. *Dolastatins 10* and *15* are small peptides. *Dolastatin 10* (Fig. 5a) was selected for clinical trials because of its favourable preclinical profile [53]. It inhibits microtubule assembly and tubulin polymerization, causing cells to accumulate that are arrested in metaphase [54,55,56] and is extremely potent *in vitro*. *Dolastatin 10* caused bone-marrow toxicity in initial clinical trials, as well as local irritation at the injection site and mild peripheral neuropathy. *Dolastatin 10* is an antineoplastic substance proven against several cancer cell lines and has been evaluated in various phase I clinical trials reporting good tolerability and identifying myelosuppression as the dose limiting toxicity. Other side effects observed were peripheral sensory neuropathies, pain, swelling, and erythematic at the injection site. Complexity and low yield of chemical synthesis of *Dolastatins*, together with low water solubility, have been significant obstacles to broader clinical evaluation [55].

Kahalalides is a family of peptides isolated from the sacoglossan mollusk *Elysia rufescens*. Among these, *Kahalalide F* (Fig. 5b) is a dehydroamino-butyric acid-containing peptide. This is known to exhibit interesting antitumor activity [57]. *Kahalalide F* has shown *in vitro* and *in vivo* selectivity for prostate-derived cell lines and tumors [58,59]. It has been observed that *Kahalalide F* induces disturbances in lysosomal function that might lead to intracellular acidification and cell death [57]. This biomolecule also appears to inhibit the expression of certain specific genes that are involved in DNA replication and cell proliferation, thereby inhibiting tumor spreading and growth. Extensive experiments show that this compound has a potent activity on non-small cell lung cancer, melanoma, androgen-independent prostate cancer, hepatocellular carcinoma, colon cancer and breast cancer [60].

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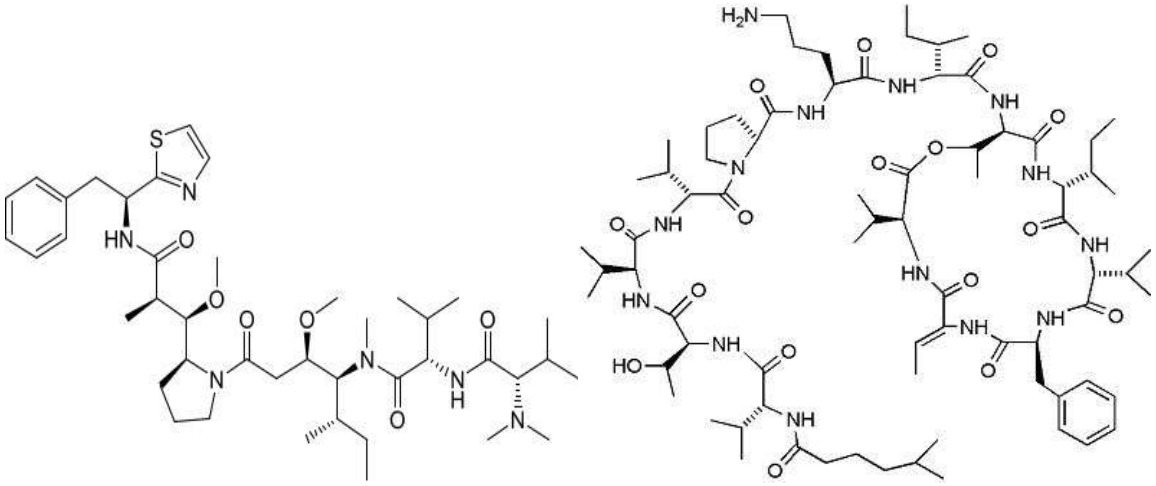

a. Dolastatin 10 b. Kahalalide

Figure 5: Marine mollusk anticancer derivatives

NECESSITY OF MARINE ANTICANCER DRUG

Once a cancer diagnosis is confirmed, it is determined how to treat it. Conventionally, there are three ways to treat cancer; these are Chemotherapy, radiation, surgery and hormone therapy. Any of these or combination of these is used to treat cancer. In chemotherapy chemical agents or drug is administered to body orally or more commonly by intravenous injection. Chemotherapy has many side effects as it targets a wide area of the body frequently. Various parts of body which grows or replicates regularly like hair, bone-marrow, nail, cells of digestive system are badly affected. By radiation and surgery there is an immense possibility of increasing invasion of cancer rather than decreasing. Hormone therapy involves removal of organ to increase or decrease hormone production or administration of drug to induce hormone production. Hormone therapy exerts several side effects. Such as blood clots, change in appetites, fluid retention, hot flashes, nausea, tiredness, weight gain etc. Besides, conventional cancer chemotherapy has the limitation of multidrug resistance (MDR) caused by over expression of integral membrane transporters which can efflux intracellular anticancer drugs thus decreasing drug accumulation [56]. MDR cells are resistant to cytotoxic effects of various structurally and mechanistically unrelated chemotherapeutic

Table 2: Marine bioactive peptides with anticancer potential & their sources

COMPOUND	SOURCE	ORGANISM	BIOACTIVITY
Aplidine	Ascidia	*Aplidium albicans*	Antitumor
Arenastatin A	Sponge	*Dysidea arenaria*	Antitubulin
Didemnin	Ascidia	*Tridemnum sp.*	Antitumor
Dolastatin	Mollusk	*Dolabella auricularia*	Antineoplastic
Geodiamolide H	Sponge	*Geodia sp.*	Antiprolfierative
Homophymines.	Sponge	*Homophymia sp.*	Antitumor
Jaspamide	Sponge	*Jaspis sp.*	Antiproliferative
Kahalalide F	Mollusk	*Elysia rufescens,*	Antitubulin
Keenamide A	Mollusk	*Pleurobranchus forskalii*	Antitumor
Mollamide	Ascidia	*Didemnum molle*	Antiproliferative
Tamandarins A & B	Ascidia	*Didemnum sp.*	Antitumor

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agents. Developing new anticancer drugs that are efficient to MDR cells is a feasible strategy to overcome MDR. But, marine drugs which are available in market for cancer treatment (*Cytarabine*, *Ara-c*, *Trabectedine*) have less side effects. A list of available drug that is conventionally used for treating different type of cancer and relevant marine peptides which have potency on respected area are given here.

Table 3: Conventional drug used in cancer treatment and relevant marine peptides with anticancer potential

	Conventional Drug	Mode of action	Marine peptides	Mode of Action	Status
BREAST CANCER	Letrezol (Femara)	Decreasing hormone	Dolastatin 10	Bcl-2 phosphorylation	Phase II
	Tamoxifen (Nolvadex)	Receptor blocking	Kahalalide F	Apoptosis inducer	Phase I
LEUKEMIA	Imatinib (Gleevec)	Kinase inhibitor	Papuamides A and B	Inhibition of infection	Phase II
	Dasatinib (Sprycel)	Inhibition of protein production			
PROSTATE CANCER	Bicalutamide (Casodex)	Anti androgen	Homophymines	Unknown	Phase I
	Leuprolide (Lupron)	Reducing hormone production	Didemnin B	Apoptosis	Phase I

THE ADVANTAGES AND CHALLENGES IN DEVELOPMENT OF MARINE DERIVED THERAPEUTICS

It is important to emphasize the complexity of the different steps and areas that are involved during the development of a given marine derived candidate. There are several reasons for which marine resources have drawn attention for anticancer drug discovery. Marine peptides have inherent activity, largely unexplored and ability to revolute against challenges. Marine peptides are structurally diverse, have wide spectrum of therapeutic action, low bio-deposition rate in body tissues and are highly specific to targets. Marine derived peptides also possess reduced risk of unwanted adverse side-reactions. As marine peptides are composed of metabolically and allergenically tolerable amino acids, they are generally safe and non-toxic. Besides their use as active ingredients, marine peptides also have the ability to be used as excipients in drug formulations for modification of biological activity, targeted delivery or transport across cellular membranes. There are also a number of issues that have to be considered from the earliest stages of development when a marine chemical entity is selected for clinical development. The issues involve sourcing, technological and scientific difficulties, legal uncertainty etc.

CONCLUSION

Nature has supplied several active anticancer agents which have significantly improved the management of many types of human cancers. These marine-derived compounds are extremely potent in culture, with inhibitory concentrations generally in the nanogram range. One can speculate that these organisms require potency and rapid penetration of cellular membranes for protection against predators, since their aquatic environment will rapidly dilute their poisons. The challenge of identifying new anticancer agents in the oceans has been taken up by a group of scientists who have formed a worldwide collaboration to investigate the organisms found on coral reefs and in deep ocean thermal events. This field is also expanding thanks to advances in deep-sea collection techniques, aquaculture, and the technology needed to extract nucleic acids from biological materials. The manipulation of microbial biosynthetic pathways through genetic engineering has also led to the production of interesting new molecules. These living organisms represent a rich reservoir of genetic and metabolic diversity, which is ready to be

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exploited and which will certainly make anticancer drug discovery even more challenging in the next few years.

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