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Review Article

Encouraging Leads from Marine Sources for Cancer Therapy - A Review Approach

N. Srinivasan[1,*], S. Dhanalakshmi[2], P. Pandian[1]

ABSTRACT

Cancer is one of the dreadful illnesses that cause mortality in many individuals around the world. Present cancer treatments generally include surgery, radiation therapy with chemotherapy. One of the primary sources of anticancer drugs are natural products that exhibit impressive potential in medicines. Plant and microbial secondary metabolites are an important source for cancer drug development. The ocean has an immense collection of flora and fauna overflowing with natural compounds having potent pharmaceutical significance. Marine bioprospecting has just started recently hence, marine ecosystem has not yet been explored properly. Nearly 68 percent of the drugs derived from marine sources are utilized for cancer and the remaining are utilized for inflammation, pain relief etc. Ongoing advancement in synthetic processes has helped in solving the limitations caused due to the complicated structure of natural products. Unlimited potent sources of compounds that can be isolated having diverse structures are found in the marine biodiversity. Only 1% of the marine microorganisms have been distinguished till now. Coral reefs and mangrove ecosystem have been focused for bioprospecting on the grounds that they have an elevated level of biodiversity. This review focuses on pharmacologically active anti-cancer leads discovered from marine ecosystem. The review has also tried to describe the structure and mechanism of action of marketed drugs and future prospects of marine anti-cancer drugs.

Key words: Natural sources, Marine sponges, Algae, Anti-cancer activity.

N. Srinivasan[1,*], S.Dhanalakshmi[2], P.Pandian[1]

[1]Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, Chidambaram – 608002, INDIA.
[2]Department of Pharmacognosy, Faculty of Pharmacy, Dr.M.G.R Educational and Research Institute (Deemed to be University), Chennai - 600 077, INDIA.

Correspondence

N. Srinivasan

Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, Chidambaram – 608002, INDIA.

E-mail: seenu301@gmail.com

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INTRODUCTIONS

Cancer has been one of the major causes of mortality and morbidity globally and is expected to rise about 70 % over the next two decades.[1]It is estimated that over 8.8million people are dying of cancer every year.[2] Cancer cells grow in all the tissues of body and initiate their growth and the spread to other tissues and organs. Lungs, prostrate, liver and stomach are commonly affected regions in men whereas in cases of women, breast, cervix, lungs and stomach are the most affected regions.[3] Treatment of the illness involves surgical procedures for removal of biomass, radiation followed by chemotherapy to prevent further development of cancer. Given the economic problem and mortality associated with cancer, there is an urgent need for more effective therapeutics.

Natural products have gained more attention in recent years for the treatment of human ailments considering their biological and eco-friendly properties in targeting infected sites with less toxicity to normal cells.[4] Hence, lot of advancements for cancer and other lethal diseases are directly correlated with discovering drugs from natural sources. Therapeutic products from nature offer promising source for investigation of new antagonistic chemical classes with novel mechanism of action.[5,6]

The first marine organism to be studied for its chemical components is the Caribbean sponge, *Cryptotethya crypta*. Biotechnology emerged as a study with drug discovery for improving health-care during 1980s and researches has been improving with advanced tools for development of pharmaceutical leads.[7]Here is an overview of significance of marine sources for cancer therapy and anti-tumour lead molecules.

ADVANTAGES AND DISADVANTAGES OF MARINE SOURCES

Advantages of Marine sponge and Fungi

Marine environment have produced many compounds that have potential activity against cancer. Alkaloids, Flavonoids, polysaccharides etc isolated from marine sources are said to have potential activity against cancer. Cytarabine, a marine natural product was extracted from a sponge. It has been found that marine sponges have compounds made by bacteria, hence these bacterial symbionts are said to be the origin of the drugs. Thicoraline, a compound extracted from a marine microorganism stops RNA production and is cytotoxic against several cancer lines. This also stops cell growth in colon cancer cell lines. Metabolites produced by marine fungi are said to have anticancer effects and are not found in terrestrial fungi. Over half of the marine cyanobacteria can be utilized for isolating bioactive compounds that have efficacy in initiating cancer cell death or intervene in the cell signalling process by activating protein kinase. Seaweeds producing metabolites have exhibited activity against cancer too.

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Aplidine, an antitumor marine compound is used for Acute Lymphocytic Leukemia. Curacin A extracted from a marine cyanobacterium has potential activity against cancer. Dolastatins, eleuthrobin, cephalostatin are some other agents against cancer isolated from marine resources. Synthetic analogues of Dolastatins obtained from *Dollabela auricularia* have antitumor activity. They stop the growth of abnormal mass of tissues from accumulating, arrest cell cycle at metaphase in various cancer cell lines and initiate cell death in lymphoma cells.[8]

The coral shows specifically important anticancer features. So, various compounds fighting against cancer are from coral origin.[9] Nitrogenous diterpene analogues have been extracted from the coral and were used to fight several cancer cell line and stops tumour proliferation by 50%.[10]

Disadvantages

A few disadvantages of these compounds must be taken into account, like its production in low amounts, the possible toxins and inorganic salts found from this source, the variety of chemical compounds found in the organism and the presence of non-specific drug targets. For *in vitro* screening measures, limited quantities are required, but in pre-clinical investigations many grams to kilograms are frequently needed for testing.[11] Generally when a marine organism produces toxins, it is said to produce a lot of significant compounds as well.[12] So, more focus should be put on extracting the potent contaminants so as to make marine concentrates good with *in vitro* testing having high efficacy. Controlled aquaculture could maintain a strategic distance from the issue of exhausting the marine ecosystem and could be an achievable alternative to deliver the necessary biomass for production in higher amounts.[13]

SELECTION OF MARINE ORGANISM FOR DRUG DISCOVERY

Demand for novel drugs is in an exponential phase due to changing environment and increase in population. Drug scientists are looking out for new sources to discover effective drugs in order to tackle need of novel therapeutics. Marine environment is biologically diverse and offers variety of resources such as aquatic animals and plants. 32 out of 33 of known animal phyla are derived from ocean where 15 are exclusively found in aquatic environment.[14] Hence, there is immense scope for new pharmaceutical leads with antimicrobial, anticancer, antimalarial properties etc. in the marine ecosystem. These resources are been explored for medicinal purposes since ancient times. One of the classic examples of products that are marine derived is fish oil which is used since old ages.[15]

Marine derived medicines are been used for human ailments from around 5000 years ago. The Chinese emperor Fu His, during 2953 BCE imposed fish-derived medicines.[16] Hippocrates in 400 BCE identified sponges with antibiotic properties and ordered his soldiers to dress their wounds with them.[17] Brown algae were used for curing inflammation during 65 CE and the discharges of the marine fish*Torpedo nobiliana* were used during 41 CE to treat headaches. Later on Galen identified that the mucilage covering the thallus of algae possessed anti-inflammatory property.[18] The Canon of Medicine has mentioned 23 difference marine sources with therapeutic functions.[19]It has a list of marine flora and fauna including algae, crustaceans like *Cancer marina*, *Crangon vulgaris*; the sponge, *Spongia officinalis*; echinoderm, *Echinus marinus*; mollusks such as *Cypraea moneta*, *Sepia officinalis*, *Aplysia* sp.; the reptile, *Chelonia mydas*; mammal, *Monodon monoceros* and the fish, *Anguilla* sp. Chapman has quoted the use of seaweed-based therapeutics during 1590 CE by Chinese physicians.

Marine based ethnomedicines are presently used in Netherlands, Brazil, California, Mexico, and Africa and in many regions worldwide for therapeutics.[20,21] Glasswort is used for diuretic medication.[22]Mangroves for myriad ailment[23]shrimps for asthma.[24] Marine sponges, fishes, corals, tunicates, molluscs and marine microbes are resources of such biologically active components.[25] Natural products with novel mechanism of therapeutic action for treatment of human diseases like cancer could generally be found in marine ecosystem. Marine pharmacology focuses on screening of such potential substances from marine organisms are unique genetically and also in synthesis of biochemical compounds.[26,27] So far more than 13,000 molecules have been identified from marine sources where 3000 possessed active pharmacological properties.[28] Marine natural products have no primary function with growth of a species as they are basically secondary metabolites that are not generated by regular biological pathways and could be utilized by humans with only minimum manipulation.[29] Ala-genintiocin is a broad-spectrum thiopeptide antibiotic recently identified from marine-derived a *Streptomyces* sp.[30] Nearly thirty percentage of marine derived products have been identified from marine sponges.[31,32] The discovery of ribo-pentosyl nucleosides from marine sponges is remarkable and is the first naturally occurring nucleoside with sugars other than ribose and deoxyribose.[33]

MARINE SOURCES WITH ANTICANCER POTENTIAL

Ocean constitutes seventy percentage of global area and are biologically rich with almost ninety percentage of this area covered by microflora offering greater possibility for novel drug discovery.[34] Natural products from flora of marine origin emerged during 19th century and has great potential to yield novel principles for cancer therapy. Nearly 22,000 secondary metabolites derived from nature are of marine origin. Bio-active molecules from marine sources for instance microbes (bacteria, actinomycetes, cyanobacteria, fungi), algae (microalgae and macroalgae like seaweeds), flowering plants like mangroves and invertebrates like sponges, corals, nudibranchs, tunicates etc have been evaluated for bio-activity against different types of cell masses at every stage of cancer progression.[35] Cytarbine, Eribulinn, Mesylate, Brentuximab vendotin and Trabactidine are examples of marine-derived anti-tumour drugs used for the treatment of ovarian cancer, leukemia, breast cancer and sarcoma.[36]

Marine bacteria

Marine derived *Lactobacillus* spp. are reported to possess anti-cancer activity against colon cancer.[37] Bacteria derived from the mollusc *Elysiarubefescens* produced Mactrolactin-A which could inhibit cancer cells of B16-F10 murine melanoma model.[38]Diverse active biological components for instance Pyrroles, Pseudopeptides, Phenazine, Quinolone, Phthalate etc. have been isolated from Pseudomonas of marine origin.[39]

Marine actinomycetes

Actinomycetes are known to be the largest secondary metabolite producers and they include the following genera: *Streptomyces*, *Micromonospora*, *Salinispora*, *Rhodococcus* etc. Seventy five percentage of the actinomycete-derived active leads are from *Streptomyces* spp.[40,41] Trioxacarcins A-C were extracted from *Streptomyces* spp. with anti-cancer activity in lung cancer cell line.[42]

Marine fungi

Many pharmaceutically active anti-cancer lead molecules such as Leptosphaerinm Lignicolous, Leptosphaerodioneetc have been identified from marine derived basidiomycetes, endophytic and filamentous fungi[43]. Marine fungi *Acremonium* spp. produced Acremonin A and *Wardomyces anomalus* yielded a xanthone derivative both showing anti-cancer properties.[44] *Aspergillus glaucus*, a marine filamentous fungus was used to isolate a compound Aspergiolide-A with cytotoxicity against diverse cancer cell lines.

Marine microalgae[45]

Marine cyanobacteria are well-known for screening bioactive molecules many of them are active against cancer cells inducing apoptosis. Activities towards human HeLa tumour cells were detected in vitro in the extracts of Calothrix cells. Calothrixin A and B were able to inhibit cancer cells in nanomolar concentrations.[46] An antiproliferative compound Curacin-A is been isolated from *Lyngbya majuscula*. This compound also inhibited breast, renal and colon cancer cell lines. *Lyngbya boulloni* derived compounds Apratoxin-A and Coibamide A showed activity against adenocarcinoma.[47] Recently Cryptophycin, Borophycin and Cyanovirin were identified from Nostoc spp. with potent cytotoxicity on epidermoid carcinoma and adenocarcinoma human cell lines.[48]

Marine macroalgae

Seaweeds are marine macroalgae which are predominant sources of vitamins, minerals and proteins. *Palmaria palmate* is an edible seaweed with capability to inhibit proliferation of tumour cells.[49] Dose-dependent suppression of cancer cells were noticed with sulphated polysaccharides produced from algal species.[50] Anti-cancer properties were also identified in the seaweeds *Padina boergesenii*, *Gracilaria foliifera*, *Ulva reticulate* and *Acanthophora spicifera* derived alcoholic extracts.[51]

Marine Sponges

Sponges have contributed to approximately thirty percentage of biological products identified from nature so far. Discovery of Spongothymidine and Spongouridine from *Tethya crypta* is considered as a breakthrough in discovery of biologically active natural compounds from sponges. This discovery led to the identification of the anticancer compound Arabinoside. Eribulin is an active breast cancer drug which is a synthetic derivative of Halichondrin B initially isolated from a marine sponge *Halichondria okadai*.[52,53]

Mangroves[54]

Mangroves comprise almost ninety percentage of marine plants and are well-distinguished in producing natural compounds with anti-microbial, anti-inflammatory, analgesic and cytotoxic properties. An anti-sarcoma sulphur containing alkaloid is reported from a mangrove plant *Bruguiera sexangula*. Tannin from mangroves were found to possess activity against human lung cancer. 2-Benzoxazoline derivative from *Acanthus ilicifolius* is identified to have anticancer as well as antiviral properties. The extract of *Ceriops decandra* successfully prevented buccal carcinogenesis.

Anti-cancer compounds derived from marine sources and mechanism of action[55]

Many marine-derived antineoplastic agents were reported to show potent growth inhibition *in vitro* and in murine models *in vivo*. Cytosine arabinoside, Trabectedin, derivative of Halichondrin B and Brentuximabvedotin have so far been approved for human use. Bryostatin 1 (clinical trial phase II), a tetrahydroisoquinilone alkaloid (ET-743) (phase I) and Dolastatin 10 (phase II) are two marine derived agents that have entered clinical trial phases. The anticancer compounds and targeting cancer cells from marine sources are listed in Table 1. Bryostatin 1 is in clinical phase II for its therapeutic use against melanoma, renal, colorectal and lymphoma. The alkaloid ET-743 is reported to show anti-proliferative activity.

Cytarabine[56,57]

Ara C or cytosine arabinoside is a chemotherapy drug utilized to cure different forms of leukemia like Acute Lymphotic Leukemia (ALL), Acute Myelogenous Leukemia (AML). It is injected intravenously, or into the cerebrospinal fluid. Cytosine Arabinoside is basically a Cytosine base and an arabinose sugar. The mechanism of action of this compound is because of its fast conversion to Cytosine Arabinoside Triphosphate that harms the DNA and arrests the cell cycle at S phase hindering DNA synthesis.

Trabectidin[58]

Trabectidin is a synthetic antineoplastic compound. It is isolated from the Carribean marine organism *Ecteinascidia turbinadata*. It gets attached to the minor groove of DNA, arresting the cell cycle & stops cell growth. It intervenes with the transcription coupled nucleotide excision repair pathway. It also stops the development of G2 to M phase of the cell cycle and also stops activated gene transcription. Trabectidin has shown action *in vitro* and *in vivo* for a variety of tumour cell lines, human xenografts, melanoma, ovarian, prostate and non-small cell lung cancer.

Halichondrin-B[23,59,60]

This compound is a macrocyclic polyether initially extracted from the marine organism *Halichondria okadai* received in 1986. Its main target is tubulin and the microtubules liable for the development and

Table 1: List of anticancer compounds and targeting cancer cells from marine sources.

Marine source	Active compound	Used to treat specific cancer type/cell line	Reference
Marine sponge	Halenaquinone (HQ)	Molt 4, DLD-1K562 and MDA-MB-231cell lines	75
Marine actinomycete	Salinosporamide A	melanoma, pancreatic carcinoma, or NSCLC	76
Antarctic fungus	HDN-1	lung cancer cell lines	77
Marine sponge	Panicein A hydroquinone	melanoma cells	23
Marine cyanobacterium	Biselyngbyaside (BLSs-1)	HeLa cells	78
Marine red alga	BDDPM	hepatoma carcinoma cell	79
Red-Alga associated bacterium	Diacetoxyscirpenol (DAS)	lung cancer cell lines A549	80
Marine sponge	Pyrroloiminoquinone alkaloids	colon and prostatic carcinoma	40
Cyanobacteria	Aplysiatoxin (ATX)	Leukemia and breast cancer cells	81
Marine bacterium	Chromopeptide A	prostate cancer cell lines PC3	82
Mangrove	ZWM026	lung cancer cells	83
Red Sea soft coral	Pachycladin A	breast cancer cell lines, cervical cancer HeLa cells	84
Bryozoan	Bryostatin-1	Sarcoma, melanoma, ovaria, cervical cancer	85
Tunicate *Applidium albicans*	Plitidepsin	Multiple myeloma	86

appropriate working of the mitotic spindle. This has been found to restrain the growth of cancer cells with high potential, and research shows that it arrests cell cycle from G2 to M phase by having activity on tubulin or microtubules, that is presently in phase III of clinical stages is an analogue of this compound that has a modified structure compared to the Halichondrin B but has the same power to treat breast cancer.

Brentuximab vendotin[61]

Brentuximab Vendotin also called Adcetris, is an anticancer drug made up of an Anti- CD30 antibody connected by a linker to a possible, synthetic drug, mono methylauristatin-E (MMAE). It was accepted in March 2018 by the Food and Drug Administration (FDA) and can be used as medication along with chemotherapy for patients with stage IV clinical Hodgkin lymphoma (CHL). It arrests cell cycle development from G2 to M phase by destroying the cytosolic microtubule network, stopping cancer cell growth and multiplication hence causing death of tumor cells. Its side effects include Neutropenia, Fatigue, Peripheral sensory neuropathy etc. It is mainly utilized as medication for relapsed Hodgkin Lymphoma (HL) and Anaplastic large lymphoma (ALCL).

Dolastatin-10[27,61]

This compound is a pentapeptide derived from the marine organism *Dolabella auricularia*. Its mode of action includes the hindrance of tubulin polymerization and nucleotide exchange. It also hinders the tubulin dependent guanosine triphosphate hydrolysis. It is a possible non-competitive impeder of vincristine getting attached to tubulin stopping mitosis. This compound additionally initiates tumor cell death by indulging bcl-2, an oncoprotein that is over expressed in some cancers. Dolastatin 10 additionally has impact on improving the attachment of colchicines to tubulin.

Eribulin[62]

Eribulin is a synthetic anticancer agent used to treat metastatic breast cancer. This compound is extracted from Japanese marine organism *Halichondria okadai*. It mode of action is it intervenes with the microtubular growth finally resulting in apoptosis following mitotic blockage. It stops cell cycle development at G2 to M phase and causes tumor suppression. The compound was accepted by the US Food and Drug Administration (FDA) on end of 2010 for metastatic breast cancer. There are two Eribulin based products under research and development. One is a liposomal formulation and another one is an antibody medication combination therapy. They are used as medication for solid tumor cell lines.

Didemnin B[63,64]

This compound is a cyclic depsipeptide derived from the Caribbean tunicate *Didemnum cyanophora*. This compound is a powerful antiviral drug for both DNA and RNA viruses for example Herpes Simplex Virus type 1, a powerful immunosuppressant which has possible effectiveness in skin graft and is extremely cytotoxic. It has powerful effect for murine leukemia cells as well. It has finished stage II of human clinical preliminaries for Adenocarcinoma of the kidney epithelial ovarian cancer and metastatic breast cancer. But because of the high level of toxicity in the drug and high rate of anaphylactic responses in patients trials were ended.

Psammaplins from Verongid sponges[65,66,67]

Psammaplin-A (PSA) is an anticancer agent derived from Poecillastra and Jaspis species. *Psammaplinaplysilla* sea sponges belong to the same species and Psammaplin-A was first derived from it. Psammaplin-A comprises of an even disulfide and a cystamine linker functionalized on the two sides with tyrosine-derived alpha hydroxyiminoazyl moieties. Psammaplin A has been exhibited to hinder the multiplication of leukemia cells by the initiation of cell death like the development of Bap-1 null cells while making it less toxic to human neuroblastomal SKN cells. This drug is responsible for cell cycle arrest and the initiation of cell death in various human tumor cells.

Dolastatin 15[68,69]

This compound is a seven subunit depsipeptide which is isolated from *Dolabella auricularia*, is a possible antimitotic drug fundamentally similar to the drug Dolastatin 10, acquired from the same marine organism. Dolastatin 15 is an anti-neoplastic pseudopeptide that represses tubulin dependent GTP hydrolysis to tubulin yet has been found attached to the RZX/MAY region. The drug has a mechanism of action where it initiates cell death by BCl-2 phosphorylation in various cancer cell types and also a weak tubulin.

Ziconotide[70,71]

Ziconotide is the synthetic drug like N- conopeptide MVIIA, found in the venom of *Conus magus*, a marine organism. Ziconotide has potential antinociceptive effects. It specifically binds to the N- type voltage sensitive calcium channels on neurons stopping neurotransmission from primary nociceptive afferents resulting in pain relief.

Ecteinascidin-743[72]

It is used as an anticancer agent for liposarcoma and leiomyosarcoma which cannot be removed by surgery or spread to different parts of the body. It is a type of alkylating agent and also known as Trabectidin. The method of activity of Ecteinascidin-743, a marine tetrahydroisoquinoline alkaloid extracted from *Ecteinascidia turbinata* has been found to have powerful antitumor action in pre-clinical systems and promising results in phase I clinical stage.

Current Scope and Future Prospects of Marine Organism in Cancer Therapeutics[73,74]

Though marketed cancer drugs are less in number, diverse marine derived compounds with anti-carcinogenic properties are under clinical trials. High toxicity and low efficacy of active principles is the main constraint existing between discoveries and marketing of drug candidates. Six drugs were approved in this decade due to the development of modern screening techniques in isolating drug leads from unexplored marine origin. Several research institutions worldwide have involved in marine pharmacology research. Though there are challenges in drug discovery, several screening strategies are being planned in order to extract anti-cancer principles from marine sources. Hence, several novel drugs with new target mechanism for the treatment of various types of human cancers need to be identified to tackle rising tumour conditions in humans.

CONCLUSION

Anti-cancer activities have been reported in marine resources including microbes, algae, invertebrates, water and sediments. The compounds extracted from these flora showed diverse activity *in vitro* towards lung, breast, bladder, renal, lymphoid, melanoma and sarcoma cell lines. The mechanism of inhibition such as necrosis, lysis and apoptosis of cancer cells of these marine-derived compounds have also been described. Development in cancer science and natural products have paved way for discovering new active therapeutics. We have discussed in this review, the importance of marine sources in discovering novel bioactive lead compounds, advantages and disadvantages in exploring aquatic resources, list of commercially available drugs and mechanism of action, and also active anti-proliferative secondary metabolites. Though, further detailed studies on this area are needed, marine environment is undoubtedly a promising source for developing novel pharmacological leads.

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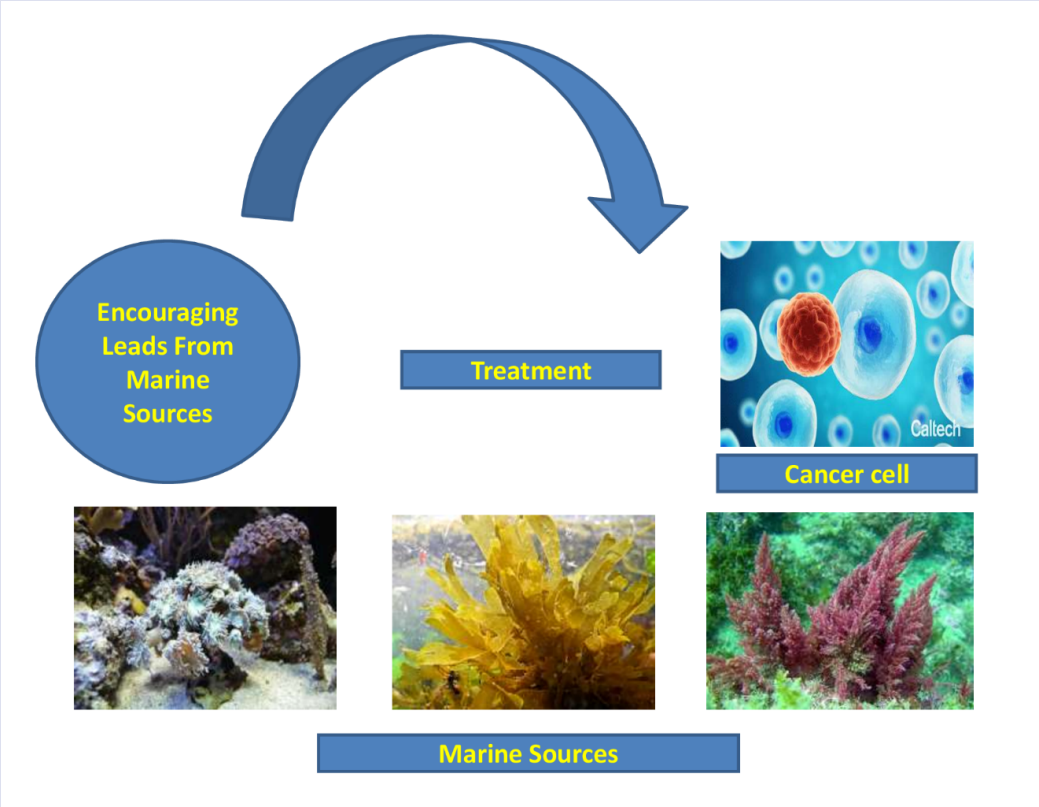
GRAPHICAL ABSTRACT



ABOUT AUTHORS

N. Srinivasan is currently working as Assistant Professor in Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalai Nagar, graduated and post-graduated from The Tamil Nadu Dr. M.G.R Medical university, Chennai and Ph.D from Annamalai University. His research is mainly in the field of Liver protective agents from natural sources. His research attention is isolation of metabolites from medicinal plants and study about its biological properties.

P. Pandian is working as an Associate Professor in the Department of pharmacy, Annamalai University. He received his B.Pharm degree and M.Pharm in industrial pharmacy and his Ph.d in pharmacy from Annamalai University, Annamalai nagar, india in 1999, 2001 and 2016 respectively. His research topic include in Marine pharmacology and Herbal technology.

S. Dhanalakshmi, working as Assistant Professor Under Faculty of Pharmacy, Dr.M.G.R Educational and Research Institute,Chennai – 600 077. Her Specialist area of interest is Herbal Formulation and Marine drug development. She received Young Educator and Research Award, on Teachers Day Celebration in the year of 2019. Currently working in the area of Endometrial cancer research by using marine source.

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