ejpmr, 2020,7(7), 304-309

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

FROM MARINE ORGANISMS AND PLANTS TO ANTICANCER AGENTS

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Article Received on 10/05/2020 **Article Revised on 30/05/2020** **Article Accepted on 20/06/2020**

ABSTRACT

Marine organisms are potential source of drug discovery. Life has originated from the ocean that cover over 70% of the surface of earth and contain highly ecological, chemical, and biological diversity ranging from microorganism to vertebrates. This diversity has been the source of unique chemical compounds, which hold tremendous pharmaceutical potential. Generally drugs are obtained from the various species of bacteria, virus, algae, sponges, fungi etc. Marine flora and fauna, like algae, bacteria, sponges, fungi, seaweeds, corals, diatoms, ascidian etc. are important resources from oceans, accounting for quite 90% of the entire oceanic biomass. They are taxonomically different with huge productive and are pharmacologically active novel chemical signatures and bid an incredible opportunity for discovery of latest anti-cancer molecules. Ocean contain more than 3,00,000 invertebrates and algal species and rich in flora and fauna. Marine pharmacognosy is not a new area, even the early civilization of Japan, China, Greece and India have explored marine life as source of drug. During the past 35-45 years, Numerous novel compounds are isolated from marine organisms having biological activities like anti-inflammatory, anticoagulant, antiviral, antibacterial, anticancer and cardiovascular compounds. The aim of this review is to stipulate the paths of marine natural products discovery and development, with a special specialise in the compounds that successfully reached the market and particularly watching the approaches tackled by the pharmaceutical and cosmetic companies that succeeded in marketing those products. In this review, we summarized the contributions of marine natural products to treat CANCER via modulation of cancer-related factors involving oxidative stress, inflammation, and cell survival.

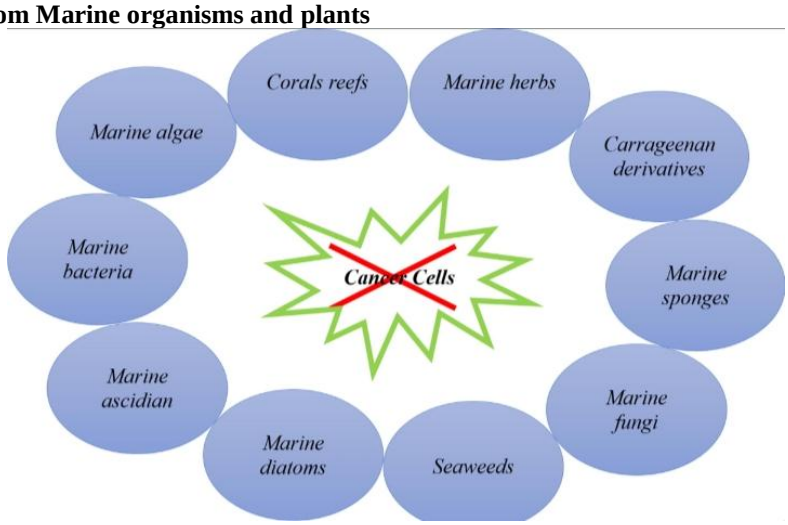
KEYWORDS: Sponges, invertebrates, pharmaceutical, Marine, Modulation.

INTRODUCTION

The discovery of marine organisms being a source of potential medicinal products dates back to the 1940's.[11] When the food and drug administration(FDA) gives approval for ziconotide which was isolated from a cone snail in 2004 came through, it was evident that the natural products obtained from the marine sources could be a possible way to obtain new entities of immense therapeutic value. Natural products (NP) are usually small molecules, with a molecular weight below 3000 Dalton, which are produced by a biological source such as plants, animals and microorganisms, but it's occurrence may be limited to a particular taxonomic family, genus, species or even organism.[3] The basic scientific achievement in oceonography is possible due to hybridization(Two or more skeletons into single compound).[4] The hybridization strategy has been used to identify further opportunities to overcome certain limitations, such as structural complexity, scarcity problems, poor solubility, severe toxicity, and weak potency of marine natural products for advanced development in drug discovery.

Several molecules derived from marine sources have proven to be beneficial in combating disease like cancer by either preventing the proliferation of cancerous cells or by being enhancers of apoptosis in cancerous cell lines present in humans. Highly sulfated polysaccharides possess tremendous anti-viral activity.[12] The first marine anti-cancer drug found in coral reefs was 'Cytosar-U' which is used to treat leukemia and lymphoma by killing cancer cells. It works by disrupting DNA synthesis in these cells.[16] Coral reefs belong to the phylum Cnidaria and provide a habitat for a wide variety of underwater organisms. Corals have many anticarcinogenic properties and can be immensely used as an excellent target for cancer research.[15] Secondary bioactive metabolites derived from marine algae include brominated phenols, nitrogen-containing heterocyclics, kainic acids, phenazine derivatives, amines, sterols, sulfated polysaccharides and prostaglandins. All these compounds display a wide range of pharmacological activities like anti-oxidant, immuno-stimulatory and anti-tumour potential.[14] Marine algae act as potent antioxidant due to their significant reactive oxygen species scavenging activity which in-turn might be responsible for anticarcinogenic property.[13]

Anticancer Agents from Marine organisms and plants



CHARACTERIZATION OF MARINE DRUGS

The major obstacles for higher understanding of marine metabolites chemistry and composition are sampling difficulties. A separation methodology is usally used with MS to enhance resolution and selectivity, in hyphenated techniques such as LC-MS, LC-MS/MS, GC-MS, pyrolysis-GC-MS, and direct temperature-resolved MS (DT-MS) methods.[20,21,22,23] MS has been mainly used in past studies for identifying and quantifying the specific fractions or trace components within the marine organisms.[24] LC-HRMS is extremely sensitive and can detect compounds present at very low quantities, there are certain classes of compounds that cannot be detected by MS; they may not form ions at all, or ion formation may be suppressed or they are not able to be eluted from the column to be detected.[25] with the ongoing advancement in marine chemistry, new tools have been employed, e.g., metabolomics, to examine marine products from different perspectives.[19]

FROM MARINE ORGANISMS TO ANTICANCER DRUG

99% of all marine bacteria cannot be cultured but can synthesize many fascinating natural products that are potential drug leads.[18] There are more than 22,000 known microbial secondary metabolites, 70% of which are produced by actinomycetes, 20% by fungi, 7% by Bacillus spp. and 1–2% by other bacteria.[25] There are few examples of marine antineoplastic agents that have reached clinical phase trials. For instance, bryostatin 1, ET-743 and dolastatin 10. The bryostatin 1 has recently entered phase II clinical trial against melanoma, non-Hodgkin's lymphoma, renal cancer and colorectal cancer.[26,27,28]

FROM MARINE PLANTS TO ANTICANCER DRUGS

Over 90% of marine plant species are algae.[29] There are two types of algae i.e. macroalgae and microalgae. Because of great chemical diversity in marine plants, including marine algae and mangroves, products isolated from these plants have been shown various pharmacological activities.

Macroalgae are also know as seaweeds. An alcoholic extract of the red alga Acanthophora spicifera was supplemented to mice treated with Ehrlich's ascites carcinoma cells, and to exhibit anti-tumor activity at an oral dose of 100 and 200 mg/kg.[30] The anti-proliferative effect of fucoidan, isolated from Ascophyllum nodosum was demonstrated against sigmoid colon adenocarcinoma cells (COLO320 DM), in comparison to fibroblasts (hamster kidney fibroblast CCL39.[31] Condriamide-A, isolated from Chondria sp., showed a cytotoxic effect at a dose of 0.5 µg/mL against KB cells and 5 µg/mL against LOVO cells (colon cancer).[32] Sulfated polysaccharides purified from the brown alga Eclonia cava selectively and dose-dependently suppressed the proliferation of murine colon carcinoma (CT-26) and human leukemic monocyte lymphoma (U-937) cell lines.[33]

Cyanobacteria, also known as blue-green algae. This are sources of more than 400 novel metabolites, particularly unique, biologically active peptide and polyketide metabolites.[34] Cynobacterias are effective at either killing cancer cells by inducing apoptotic death or affecting cell signaling via activation of the protein kinase c family. Two cyanobacteria-derived anti-microtubule agents, i.e., dolastatin 10 and curacin A, have been clinically evaluated for the treatment of cancer and to serve as lead structures for the synthesis of a number of synthetic analogs/derivatives.[35] Various strains of cyanobacteria exhibited apoptotic activity against acute myeloid leukemia cells without affecting non-malignant cells, e.g., hepatocytes and cardiomyoblasts.[36] Apratoxins represent are another class of cyanobacterial compounds that inhibited a variety of cancer cell lines at nanomolar dose levels. Scytonemin is present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. This compound regulates mitotic spindle formation as well as enzyme kinases involved in cell

cycle control, and to also inhibit the proliferation of human fibroblasts and endothelial cells.[37] The parental compound, apratoxin A, isolated from a strain of Lyngbya boulloni, exhibited cytotoxicity against adenocarcinoma.[38]

FROM MARINE BACTERIA TO ANTICANCER DRUGS

Marine Pseudomonas-derived bioactive substances are diverse and include pyrroles, pseudopeptides, pyrrolidinedione, benzaldehyde, quinoline, quinolone, phloroglucinol, phenazine, phenanthrene, phthalate, andrimid, moiramides, zafrin and bushrin.[39] Discodermolide, bryostatins, sarcodictyin, and eleutherobin are among the most effective anticancer drugs produced mainly by marine bacteria.[40] Lactobacilli exhibited chemopreventive effects against colon cancer and melanoma cancer.[41] The marine-derived Halomonas spp. strain GWS-BW-H8hM was reported to inhibit the growth of HM02 (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma) and MCF7 cell lines to induce apoptosis via cell cycle arrest compared to actinomycin D.[42,43] Highly heterogeneous polymers, i.e., exopolysaccharides (EPSs) and sulfated EPSs isolated from H. stenophila inhabiting a hypersaline environment have also been reported for their pro-apoptotic effects on T-leukemia cells. Only tumor cells were found susceptible to apoptosis induced by the sulphated EPS (B100S), whilst primary T cells were resistant.[44] The isolation of cytotoxic hydroxyphenylpyrrole dicarboxylic acids, i.e., 3-(4-hydroxyphenyl)-4-phenylpyrrole-2,5-dicarboxylic acid (HPPD-1), 3,4-di-(4-hydroxy-phenyl) pyrrole-2,5-dicarboxylic acid (HPPD-2) and the indole derivatives 3-(hydroxyacetyl)-indole, indole-3-carboxylic acid, indole-3-carboxaldehyde, and indole-3-acetic acid, from a marine Halomonas sp. has also been reported.[45] HPPD-1 and HPPD-2 exhibited potent antitumor activities via the inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA) induced activation of Epstein–Barr virus early antigen.[46] The two most active extracts were obtained from isolates of Sulfitobacter pontiacus (P1-17B (1E)) and Halomonas axialensis (P5-16B (5E)), that inhibited the growth of HeLa and DU145 cells by 50–70%.[47]

FROM MARINE FUNGI TO ANTICANCER AGENTS

Marine-derived fungi represent a rich and promising source of novel anticancer agents.[48,49] Antioxidative effects against free radical reactions associated with atherosclerosis, dementia, and cancer were exhibited by acremonin A from Acremonium spp.[50], and a xanthone derivative from Wardomyces anomalus.[51] The anticancer activity of 14 anthracenedione derivatives of secondary metabolites of the mangrove endophytic fungi Halorosellinia spp. and Guignardia spp. has been reported.[52] The 14 anthracenedione derivatives were found to function via apoptosis induction.[53]

ADVANTAGES

Marine natural products have been particularly highlighted for their extraordinary bioactivity under highly diluted conditions.[5,6] Variety of marine molecules shows unique structural features and exhibit various types of biological activities.

LIMITATIONS

1) Many of Marine compounds are highly toxic in nature in mammalian system. Cautions should always been taken in handling of marine organisms.
2) Some marine compounds are highly irritating causes immediate itching and ash formation. Ex- Fibularia nolitangers, Tedania ignis (Fire sponge).
3) The unmet needs from natural resources occasionally leads to samples being obtained via chemical synthesis, and it usually remains difficult to satisfy substantial supply requirements.[7,8,9]
4) The highly complex structure of marine natural products frequently makes it very difficult to modify or synthesize them on a large scale.[10]

CONCLUSION

Natural product obtained from marine organisms are act as chemical weapons and are extremely potent inhibitors of physiological processes. It is clear that marine products are promising in providing a platform for improving the anti-cancer therapeutic strategies. According to the maximum reports on the mechanism of action of marine products is inhibiting tumor growth both in vitro and in vivo suggest it is mediated via apoptosis, necrosis, and lysis of the tumor cells. The Marine ecosystem is not only productive to discover novel entities but it is also a tool to identify the new cellular targets for therapeutic intervention. Marine product are truly benifical for treatment of various diseases but it has some limitations and in order to overcome the limitations SAR, structural simplification, development of synthetic route and medicinal chemistry approach have been studied thus far. With the arrival of recent development and use of technologically advanced computer aided sophisticated analytical instruments have turn this novel dream like fiction into reality.

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