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AN OVERVIEW ON ANTICANCER DRUGS FROM MARINE SOURCE

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ABSTRACT

The last decade has seen an ever evolving strategy for the screening and discovery of new anticancer leads from nature, and this is proving effective. In part, the need for this continuing evolution has been stimulated by a desire to develop novel and less toxic therapies for cancer treatment. Hence, new approaches are needed which truly show the genetic and biochemical ability of a particular cell type to synthesize a metabolite of interest by the natural marine floras. Marine natural source are the most important bioactive leads possess medicinally potent chemicals, especially antioxidant, immunostimulatory, and antitumour activities. Marine sources such as bacteria, actinobacteria, cyanobacteria, fungi, microalgae, seaweeds and other halophytes are extremely important oceanic resources, constituting over 90% of the oceanic biomass. The marine floras are largely explored for the anticancer lead compounds. In recent past, numerous marine anticancer compounds have been isolated, characterized, identified and are under trials for human use. In this review we have tried to compile about marine-derived com-pounds anticancer biological activities of diverse flora and their underlying mechanisms and explored utilization for the malignant growth treatments over the deadful disease cancer.

KEYWORDS:– Marine naturals, anticancer, microalgae, actinomycetes, sea weeds, corals reefs.

INTRODUCTION

Cancer is one of the most life-threatening diseases worldwide. Over 1,000,000 new cases and 65,000 deaths are estimated globally, with an incidence rate around two times higher among men than women.[1] The highest incidence rates were reported with increased risk is

associated with age, and an unhealthy lifestyle**.** The incidence of cancer continues to increase due to environmental changes and life style modernization. The progress in biological, immunotherapy and the substantial improvements in modern drug design and manufacturing have made the discovery of a cure for cancer a motive goals. Natural products represent an available source of new drugs, drug leads and chemical entities.[2] Approximately 80% of the approved chemotherapeutic drugs,[3] and more than half of all drugs are based on bioactive natural products.[4] Eighty-seven percent of human diseases, including cancer, are treated using natural products.[5] Natural bioactive molecules exhibit cytotoxic effects by attacking macromolecules expressed by cancer cells, such as those in oncogenic signal transduction pathways.[6] A significant number of marine-derived metabolites act as antitumor agents via potent growth inhibition of human tumor cells both in vitro, in vivo (in murine) models and in cancer clinical trials.[7] Advanced technology and extensive research on marine natural products have led to the discovery of a new generation of anticancer drugs currently used in clinical trials.

Marine organisms are a great resource of marine natural products which can be used to treat life threatening diseases/disorders like cancer and acquired immune deficiency syndrome. Marine natural products include a wide variety of secondary bioactive metabolites, peptides, sulfated polysaccharides, sterols, carotenoids and derivatives obtained from chitin, chitosan and chi-to oligosaccharides. Sulfated polysaccharides obtained from different types of marine algae show a remarkable activity against cancer and AIDS. Plants, fungi, algae and microorganism's synthesis coloring pigments known as carotenoids which have advantageous effects in preventing diseases like cancer, cardiovascular and some other acute/chronic diseases.

1. Marine algae as anti-cancer agents

Various algae present in marine water bodies possess several essential nutrients like lipids, minerals, proteins, fiber, fatty acids, polysaccharides, vitamins and many essential amino acids. Marine algae are a rich source of many bioactive molecules which are reported to have many pharmacological properties including anticancer action. Marine blue-green algae (Cyanobacteria) are considered to be one of the potential organisms which can be the richest sources of known and novel bioactive compounds including toxins with potential for pharmaceutical applications[1] More than 50% of the marine cyanobacteria are potentially exploitable for extracting bioactive substances which are effective in either killing the cancer

cells by inducing apoptotic death, or affecting the cell signaling through activation of the members of protein kinase-c family of signaling enzymes.

Scytonemin is a protein serine/threonine kinase inhibitor, isolated from the cyanobacterium *St igonema* sp. and this compound is a yellow-green ultraviolet sunscreen pigment, known to be present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. Scytonemin regulates mitotic spindle formation as well as enzyme kinases involved in cell cycle control and the compound also inhibits proliferation of human fibroblasts and endothelial cells. Thus scytonemin may provide an excellent drug as protein kinase inhibitors to have antiproliferative and anti-inflammatory activities. The cell extracts of *Calothrix* isolates inhibit the growth *in vitro* of a chloroquine-resistant strain of the malarial parasite, *Plasmodium falciparum,* and of human HeLa cancer cells in a dose-dependent manner. Bioassay directed fractions of the extracts have led to their isolation and structural characterization of Calothrixin A (I) and B (II), pentacyclic metabolites with an indole. Another compound, Curacin-A, isolated from the organic extracts of Curacao collections of *Lyngbya majuscula* is an exceptionally potent antiproliferative agent as it inhibits the polymerization of the tubulin and it also displays the inhibitory activity selectively on colon, renal, and breast cancer-derived cell lines. In recent times, the most significant discoveries are of borophycin, cryptophycin 1 & 8, and cyanovirin. Borophycin is a boron-containing metabolite, isolated from marine cyanobacterial strains of *Nostoc linckia* and *N. spongiaeforme* var. *tenue.*[48] The compound exhibits potent cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma (KB) cell lines.

2. Marine bacteria as anti-cancer agent

Marine microorganisms are a source of new genes, and exploitation of which is likely to lead to the discovery of new drugs and targets. Secondary metabolites produced by marine bacteria have yielded pharmaceutical products such as novel anti-inflammatory agents e.g., pseudopterosins, topsentins, scytonemin, and manoalide, anticancer agents e.g, bryostatins, discodermolide, eleutherobin, and sarcodictyne and antibiotics e.g, marinone. The contribution of probiotic bacteria, such as lactobacilli and bifidobacteria, is mainly in the control of pathogenic microbes, through production of antibacterial protein namely, bacteriocin[8,9] and anticancer substances.[10] The dietary supplements of lactobacilli are reportedly decreasing the induction of experimental colon cancer.[11] The major metabolite,

macrolactin-A, inhibits B16-F10 murine melanoma cancer cells, mammalian herpes simplex virus (HSV) (types I and II), and protects T lymphocytes against human immunodeficiency virus (HIV) replication.

3. Marine Fungi as anticancer

A rich profile of biologically active metabolites is described from filamentous fungi of terrestrial origin, especially from just three genera: *Penicillium, Aspergillus,* and *Fusarium.* Recently more interest has been generated on studying biologically active metabolites from higher fungi (Basidiomycetes), endophytic fungi and filamentous fungi from marine habitats, the symbiotic lichens. In one study, the lignicolous fungus *Leptosphaeria oraemaris* (Pleosporaceae) yielded leptosphaerin. Marine-derived fungi are known to be a source of antioxidative natural products: (i) Acremonin A from *Acremonium* sp. and (ii) Xanthone derivative from *Wardomyces anomalus* Reactions of free radicals, such as super-oxide radical, hydroxyl radical, peroxyl radical and other reactive oxygen and nitrogen are associated with diseases such as atherosclerosis, dementia, and cancer.

4. Marine actinomycetes as anticancer

It include members of the genera Dietzia, Rhodococcus,[12] Streptomyces[13] Salinispora, and Marinispora.[14-15] Actinomycetes are undoubtedly the largest producers of secondary metabolites among marine microorganisms.[16] Actinomycete-isolated secondary metabolites account for ca. 45% (~10,000 compounds) of the total known anti-microbial metabolites. Actinomycetes, Streptomyces and Micromonosporaceae are good candidates for the isolation of potent growth-inhibiting compounds and novel antitumor agents. In the exploration of marine-derived actinomycetes as sources of antitumor compounds, lucentamycins A-D, which are 3-methyl-4-ethylideneproline-containing peptides were isolated from Nocardiopsis lucentensis (strain CNR-712). Lucentamycins A and B exhibited significant in vitro cytotoxicity against HCT-116 human colon carcinoma using MTS assay with IC50 = 0.20 and 11 µM, respectively. Thicoraline, a depsipeptide isolated from Micromonospora marina, displayed cytotoxic activity against both LOVO and SW620 human colon cancer cell lines with IC50 of 15 nM and 500 nM, respectively in vitro. Trioxacarcins A-C extracted from Streptomyces species showed high anti-tumor activity against lung cell line. Macrodiolide tartrolon D, extracted from Streptomyces sp. MDG-04-17-069, exhibited strong cytotoxic activity against three human tumor cell lines, viz., lung (A549), colon (HT29), and breast (MDA-MB-231) cancer.

5. Coral reefs as anticancer

Sarcophyton is one of the most widely distributed soft coral genera in the tropical and sub-tropical oceans, and approximately 30 species from this genus have been collected and tested for the presence of bioactive secondary metabolites, i.e., fatty acids (arachidonic, eicosapentaenoic, docosahexaenoic acids) that showed cytotoxic activity against brine shrimp in dose-dependent manner (LC50 of 96.7 ppm) . Among the most important components of soft coral are cembranoids, which are present at high concentrations (up to 5% dry weight). Cembranoids have an impact on biological activities, i.e., ichthyotoxic, cytotoxic, anti-inflammatory, and antagonistic activity. In vitro cytotoxicity testing showed that furano-cembranoids and decaryiol isolated from Nephthea spp. and Sarcophyton cherbonnieri are effective against several tumor cell lines (gastric epithelial, breast and liver). In addition, Mar. Drugs 2019, 17, 491 11 of 31 crassumolide C isolated for the first time from (the soft coral Lobophytum crissum) was found to inhibit the accumulation of the pro-inflammatory proteins iNOS and COX-2 at 10 µM, as well has a cytotoxic effect toward Ca9-22 cancer cells.

Table 1: List of compounds isolated from marine sources with potential anticancer effect.

Compound Name/ Class	Main source	Type of cancer	Mechanism
Fucoidan/Polysaccharides	Ascophyllum nodosum, algea	Colon cancer	Inhibit the proliferation of arterial smooth muscle cells.
Apratoxin A/Peptide	Lyngbya boulloni, bacteria	Cervical cancer	Cell cycle inhibition
Lyngbyabellin B/p Peptide	Lyngbya majuscule, bacteria	Burkitt lymphoma cancer	Inhibit of cell growth
Chondroitin-4-sulphate/Polysaccharides	Cucumaria frondosa, sea cucumber	-	-
Sansalvamide A/Peptide	Marine fungi	Pancreatic, colon, breast and prostate cancers	Inhibits protein complex formation
Phlorofucofuroecol A/Polyphenol	Brown seaweeds	Cancer	Not reported
Phloroglucinol/polyphenol	Brown seaweed	Colon cancer	Induce DNA damage, and cell death at 300 µM
Apratoxins	Cyanobacteria	Cancer	Inhibit a variety of cancer cell lines
Condriamide A	Chondria sp	Tumor	Cytotoxic

CONCLUSION

The technological innovation and scientific advances provided a baseline for exploring a great scope of the chemically unique, biologically active, and taxonomically diverse marine floras. 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. We discussed the pharmaceutical prospects and the chemical space properties that provided crucial insights and valuable knowledge on the largely unexplored marine flora-based anticancer leads. Although more detailed investigations are essential to meet the most common challenges of the clinical utility, it is clear that marine products are promising in providing a platform for improving the anti-cancer therapeutic strategies.

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