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Journal List > J Oncol > v.2010; 2010

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Anticancer Drugs from Marine Flora: An Overview

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Abstract

Marine floras, such as bacteria, actinobacteria, cyanobacteria, fungi, microalgae, seaweeds, mangroves, and other halophytes are extremely important oceanic resources, constituting over 90% of the oceanic biomass. They are taxonomically diverse, largely productive, biologically active, and chemically unique offering a great scope for discovery of new anticancer drugs. The marine floras are rich in medicinally potent chemicals predominantly belonging to polyphenols and sulphated polysaccharides. The chemicals have displayed an array of pharmacological properties especially antioxidant, immunostimulatory, and antitumour activities. The phytochemicals possibly activate macrophages, induce apoptosis, and prevent oxidative damage of DNA, thereby controlling carcinogenesis. In spite of vast resources enriched with chemicals, the marine floras are largely unexplored for anticancer lead compounds. Hence, this paper reviews the works so far conducted on this

aspect with a view to provide a baseline information for promoting the marine flora-based anticancer research in the present context of increasing cancer incidence, deprived of the cheaper, safer, and potent medicines to challenge the dreadful human disease.

1. Introduction

Cancer is a dreadful human disease, increasing with changing life style, nutrition, and global warming. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances. In this context, the natural products derived from medicinal plants have gained significance in the treatment of cancer. According to the WHO, 80% of the world's population primarily those of developing countries rely on plant-derived medicines for the health care [1]. Natural products and their derivatives represent more than 50% of all the drugs in clinical use of the world. Higher plants contribute not less than 25% of the total. Almost 60% of drugs approved for cancer treatment are of natural origin. Fruits and vegetables are the principal sources of vitamins C, B, E, carotenoids, and fibers, and these contribute to the apparent cancer-protective effects of the foods. There is a positive correlation between the increased dietary intake of natural antioxidants and the reduced coronary heart diseases, cancer mortality, as well as longer life expectancy [2, 3]. Herbal drug formulations for the prevention and treatment of cancer appeared in the last three decades, and the interest on natural sources of potential chemotherapeutic agents is continuing.

Antioxidants play an important role in the later stages of cancer development. There is increasing evidence that oxidative processes promote carcinogenesis, although the mechanisms for this are not well understood. The antioxidants may be able to cause the regression of premalignant lesions and inhibit their development into cancer. Preliminary studies have indicated that some antioxidants, particularly β-carotene, may be of benefit in the treatment of precancerous conditions such as oral leukoplakia, possibly a precursor of oral cancer [4]. Several herbs and spices including rosemary, sage, thyme, nutmeg, turmeric, white pepper,

chilli, pepper, ginger, and plenty of other medicinal plants are reportedly exhibiting antioxidant activity [5–7]. Majority of the active antioxidant compounds are flavonoids, isoflavones, flavones, anthocyanins, coumarins, lignans, catechins, and isocatechins. In addition to these, vitamins C and E, *β*-carotene, and *α*-tocopherol present in natural foods, are known to possess antioxidant potential [8–10]. Thus, potential antioxidant and anticancer properties of plant extracts or isolated products of plant origin can possibly be explored for developing the anticancer drugs [11].

From the past few decades, there has been an upsurge in the search for new plant-derived drugs. This process has facilitated to produce remarkably a diverse array of over 1,39,000 natural products, containing medicinally useful terpenoid derivatives, alkaloids, glycosides, polyphenolics, steroids, and so forth. The National Cancer Institute (NCI) of the United States of America (USA) has screened about 1,14,000 extracts from an estimated 35,000 plant samples against a number of tumor systems [12]. Of the 92 anti-cancer drugs commercially available prior to 1983 in the USA and approved world-wide between 1983 and 1994, approximately 62% can be related to natural origin [13]. Some examples include vinblastine and vincristine (*Catharanthus roseus*), epipodophyllotoxin, an isomer of podophyllotoxin (*Podophyllum peltatum* roots), paclitaxel (*Taxus baccata*, *T. brevifolia, T. canadensis*), camptothecin (*Camptotheca acuminata*), homoharringtonine (*Cephalotaxus harringtonia* var. *drupacea*), elliptinium (*Bleekeria vitensis*), flavopiridol (*Dysoxylum binectariferum*), and ipomeanol (*Ipomoea batatas*). The two plant-derived natural products, paclitaxel and camptothecin were estimated to account for nearly one-third of the global anticancer market, respectively to the tune of about $3 and $9 billion, in the year 2002 [14].

Numerous types of bioactive compounds have been isolated from plant sources. Several of them are currently in clinical trials or preclinical trials or undergoing further investigation. Although marine compounds are under-represented in current pharmacopoeia, it is anticipated that the marine

environment will become an invaluable source of novel compounds in the future, as it represents 95% of the biosphere [15]. However, development of marine floral compounds as therapeutic agents is still in its embryonic stage due to lack of an analogous ethno-medical history as compared to terrestrial habitats, together with the relative technical difficulties in collecting the marine floral samples. Over the last few decades, significant efforts have been made, by both pharmaceutical companies and academic institutions, to isolate and identify new marine-derived, natural products especially from faunal species. However, the marine floras are only little unexplored and these works are reviewed here as a baseline data for promoting further research in this field.

2. Uniqueness of Marine Floral Drugs

Marine floras include microflora (bacteria, actinobacteria, cyanobacteria and fungi), microalgae, macroalgae (seaweeds), and flowering plants (mangroves and other halophytes). Occupying almost 71% of globe, the ocean is rich in biodiversity, and the microflora and microalgae alone constitute more than 90% of oceanic biomass [16]. This vast marine floral resource will offer a great scope for discovery of new drugs. It is increasingly recognized that ocean contains a huge number of natural products and novel chemical entities with unique biological activities that may be useful in finding the potential drugs with greater efficacy and specificity for the treatment of human diseases [17]. It cannot be denied that with 3.5 billion years of existence on earth and experience in biosynthesis, the marine microfloras remain nature's best source of chemicals. The marine organisms produce novel chemicals to withstand extreme variations in pressure, salinity, temperature, and so forth, prevailing in their environment, and the chemicals produced are unique in diversity, structural, and functional features [18].

The efforts to extract drugs from the sea started in the late 1960s. However, the systematic investigation began in the mid-1970s. During the decade from 1977 to 1987, about 2500 new metabolites were reported from a variety of marine organisms. These studies have clearly

demonstrated that the marine environment is an excellent source of novel chemicals, not found in terrestrial sources. So far, more than 10,000 compounds have been isolated from marine organisms with hundreds of new compounds are still being discovered every year. About 300 patents on bioactive marine natural products were issued between 1969 and 1999 [18]. Some marine organisms are proved to be the potent sources of drugs. These are mostly invertebrates that include sponges, soft corals, sea fans, sea hares, nudibranchs, bryozoans, and tunicates. It is now believed that microbial floras present in the invertebrates are responsible for the production of medicinal compounds. The search is mostly confined to marine faunal species, and floral species are largely ignored. Some of the compounds derived from marine organisms have antioxidant property and anticancer activities, but they are largely unexplored.

Marine floras have been used for medicinal purposes in India, China, the Near East and Europe, since ancient times. The people of China and Japan have been using seaweeds for consumption. The seaweeds especially brown seaweeds are rich in iodine and hence there is a least incidence of goiter and glandular diseases. History reveals that maritime countries have been using seaweeds as vermifuge, anesthetics and ointment as well as for the treatment of cough, wounds, gout, goiter, venereal disease, and so forth. Sterols and related compounds present in seaweeds have ability to lower blood plasma cholesterol level. Seaweed dietary fibers perform varied range of functions such as antioxidant, antimutagenic, anticoagulant, and antitumor. The seaweeds also play an important role in modification of lipid metabolism in the human body. High intake of calcium, potassium, and sodium is associated with lower mean systolic pressure and lower risk of hypertension. All seaweeds offer an extraordinary level of potassium that is very similar to our natural plasma level. Seaweed extract is interestingly similar to human blood plasma. Two Japanese surgeons have used a novel technique of mixing seaweed compounds with water to substitute whole blood in transfusion and this has been successfully tried in over 100 operations [4].

Although, the use of seaweeds in medicine is not as wide spread as once

it was, the use of seaweed polymer extract in pharmacy, medicine, and biochemistry is well established. Clinical trials are also in progress to make diabetic patients free from injection by introducing insulin secreting "jelly capsule" made of seaweed-derived alginic acid [19]. The capsule renders protection to white blood cells and the patient's immune system. Seaweed gums like carrageenan (extracted from red seaweed) or algin (from brown seaweed) are rich sources of soluble fibers [4].

3. Anticancer Agents from Marine Floras

3.1. Bacteria

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 sarcodictyin), 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 [20, 21] and anticancer substances [22]. The dietary supplements of lactobacilli are reportedly decreasing the induction of experimental colon cancer [23]. They stimulate and modulate the mucosal immune system by reducing the production of proinflammatory cytokines through actions on NFκB pathways, increasing production of anti-inflammatory cytokines such as IL-10 and host defense peptides such as β-defensin 2, enhancing IgA defenses and influencing dendritic cell maturation as well as modulation of cell proliferation and apoptosis through cell responses to short chain fatty acids [24].

Most of the marine animal phyla produce toxins and some studies show that these marine toxins may be produced by marine bacteria associated the animals [25–27]. The microbial toxins are useful in neurophysiological and neuropharmacological studies. For example, bacteria present in *Noctiluca scintillans* are responsible for causing red tides. 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 [28].

Kahalalide F (KF) is a depsipeptide isolated from the mollusk *Elysia rubefescens* from Hawaii and the compound is believed to be synthesized by microbes associated with the animal. KF induces cytotoxicity and blocks the cell cycle in G1 phase in a p53-independent manner. *In vitro*, KF displays activity against solid tumors with an interesting pattern of selectivity in prostate cancer cell lines. In addition, extensive *in vivo* work demonstrates that the agent has activity in breast and colon cancers.

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 [29].

3.2. Actinomycetes

For more than 50 years, the soil-derived actinomycetes of terrestrial origin have provided a major pharmaceutical resource for the discovery of antibiotics and related bioactive compounds. However, marine actinomycetes received only very recent attention. Gutingimycin is a highly polar trioxacarcin derivative from *Streptomyces* species, isolated from sediment of the Laguna de Terminos, Gulf of Mexico [30]. The same *Streptomyces* species also yields trioxacarcins D–F, in addition to the known trioxacarcins A–C [30]. Among the antibiotic-producing microbes, marine actinomycetes within the family Micromonosporaceae are very promising. These microbes are found to be a potent sources of anticancer agents that target proteasome function and their industrial potential is validated by several pharmaceuticals.

Thiocoraline is a novel bioactive depsipeptide isolated from *Micromonospora marina*, a marine microorganism located in the

Mozambique Strait that inhibits RNA synthesis. The bioactive compound is also selectively cytotoxic against lung and colon cancer cell lines as well as melanoma. Interestingly, the compound exerts preferential antiproliferative effects in colon cancer cell lines with defective p53 systems [31]. Thiocoraline represents a model of an anticancer agent acquired from marine microorganisms and illustrates how the problems of drug supply can be overcome by artificial culture.

3.3. Marine Fungi

A rich profile of biologically active metabolites is described from filamentous fungi of terrestrial origin, especially from just three genera: *Penicillium, Aspergillus,* and *Fusarium* [32]. However, the marine fungi are least studied than terrestrial counterparts and other ecological groups. Obligate marine fungi are still an unexplored resource, although, marine facultative fungi, have been studied due to their production of new metabolites which are not found in terrestrial fungi. 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 [33, 34]. A further study of the same fungal species yielded none of the previously found metabolites, but the polyketides, leptosphaerolide, its *o*-dihydroquinone derivative, and leptosphaerodione [35]. This leads to a conclusion that the production of secondary metabolites might be highly dependent on the culture conditions and the origin of the strains. To produce these metabolites and to maximize the potential chemical diversity, they need to be grown in various nutrient-limited media. For example, media for *Penicillium* spp. that are deficient in carbon can produce penicillins, those that are phosphorus-limited can produce cephalosphorins and vancomycin, and those that are nitrogen-limited can produce carbapenems [36].

Marine-derived fungi are known to be a source of antioxidative natural products: (i) Acremonin A from *Acremonium* sp. [37] and (ii) Xanthone

derivative from *Wardomyces anomalus* [38]. 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. Antioxidants delay or prevent oxidative damage and thus they may be useful as therapeutics or food additives.

3.4. Micro Algae

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 [39, 40]. Some of the marine cyanobacteria appear to be potential sources for large-scale production of vitamins (B complex, E) of commercial interest. Scytonemin is a protein serine/threonine kinase inhibitor [41], isolated from the cyanobacterium *Stigonema* 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 [42].

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. 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 [43]. 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 [3, 2 – j] phenanthridine alkaloids which exert their growth inhibitory effects at nanomolar concentrations [43]. 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 [28].

Largazole is unique chemical scaffold with impressive antiproliferative activity derived from *Symploca* sp. [44]. The apratoxins are another class of cyanobacterial compounds that inhibit a variety of cancer cell lines at nanomolar concentrations. The parental compound, apratoxin A, isolated from a strain of *Lyngbya boulloni* shows cytotoxicity to an adenocarcinoma [45]. The coibamide A is a compound derived from a strain of *Leptolyngbya* [46], and it exhibits significant cytotoxicity against NCIH460 lung and mouse neuro-2a cells. The cytotoxicity is a common mechanism of action for many cyanobacterial compounds [47].

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 [49]. Borophycin is related both to the boron containing boromycins isolated from a terrestrial strain of *Streptomyces antibioticus* and to the aplasmomycins isolated from a marine strain of *Strepetomyces griseus* (actinomycetes) [48].

Cryptophycin 1 was first isolated from *Nostoc* sp. ATCC 53789 by researchers at Merck and found to be a potent fungicide. As it was highly toxic, it was disregarded as a natural product lead. Subsequently, the same compound isolated from *Nostoc* sp. GSV 224 exhibited potent cytotoxicity against human tumor cell lines and good activity against a broad spectrum of drug sensitive and drug-resistant murine and human solid tumors [50]. Nevertheless, cryptophycin 1 again appears to be too toxic to become a clinical candidate. This leads to a detailed structure-function study which has resulted in the isolation of cryptophycin 8, a semisynthetic analogue with greater therapeutic efficiency and lower