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Aquatic Ecosystems: A Review on Prospecting of Anticancer Molecules from Fungi and Other Microbes

Mukesh Chander[1,*], Jasmeet Kaur[2]

Abstract

Marine biota; namely, actinomycetes, bacteria, fungi, microalgae, green algae, oceanic weeds, mangroves, and other extremophiles constitute about 90% of the oceanic biomass. The organisms are taxonomically diverse, biologically productive/active, and biochemically unique. These unique biochemiques may act as a great source for the discovery of new bioactive molecules, including anticancer drugs. The marines produce medicinally potent biochemicals; namely, sulfated saccharides, polyphenols, and, sterols. Only a few of these alkaloids have been studied for their pharmacological properties; namely, antitumor, immunostimulatory, and antioxidative activities. The phytochemicals may probably interact with macrophages, initiating cell death and prevent mutational damage to DNA, reducing event of carcinogenesis. Peptides are bioactive products, which are inherent to many marine species. These marine peptides are of immense nutraceutical and medicinal importance as they have broad range of bioactivities, including microbicidal, antiviral, antimelanoma, antioxidative, cardioprotective, immunomodulatory, analgesic, anti-anxiety, anti-diabetic, appetite suppressing, and neuroprotective activities which have attracted the attention of the pharmaceutical industry, which attempts to modify them for treatment, cure, and prevention of various diseases. Some of these peptides and their derivatives are highly valuable commercially and developed as pharmaceutical and nutraceuticals commercially. The marine habitat, little explored, may act as a potential source of novel bioactive compounds acting as prospective and potent biopharmaceuticals. The biologically and the artificially synthesized/modified form of these chemicals may prove as novel therapeutic agents. The recent progress in technology and deep-sea exploration missions have made the drug discovery from oceanic sources a reality, resulting in screening, isolation, and modification of drugs capable of curing cancer, Parkinson's, Alzheimer's, and various other uncurable disorders and diseases. The available technology and use of modern gadgets have brought the depths of ocean within human approach and now marine resource like sponges, corals, etc., can be studied for their potential utilization in biopharmaceutical industry. In future, various types of bioactive compounds discovered for treating the diseases and these marine bioactive compounds are very beneficial and have no side effects.

Keywords: Antioxidant, antitumor, bioactive molecules, biopharmaceuticals, microbes

***Author for Correspondence**
Mukesh Chander
E-mail: mukeshchander76@yahoo.co.in

[1]Assistant Professor, Department of Biotechnology, Khalsa College (Autonomous), Amritsar, Punjab, India
[2]Student, Department of Biotechnology, Khalsa College (Autonomous), Amritsar, Punjab, India

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INTRODUCTION

The earth surface has about 70% of oceans inhabiting versatile and unexplored ecological, chemical, and biological diversity [1]. The inhabitants of these ecosystems may prove to be endless source for obtaining novel drugs and antibiotics to treat diseases. Many antitumor compounds have been derived from microbial sources and further used in advanced drug discovery. The marine macroalgae have been reported to be used as medicines in traditional healing systems [2, 3]. The marine sponges also

contain bioactive chemicals of potential medical importance. Holothurians toxins possess and showed antitumor activity in mice. At the start of 20th century, identification of bioactive compounds was carried out using traditional qualitative techniques. With advent of technology, researchers now rely on latest downstream processing methods; namely, ASE (Accelerated Solvent Extraction), aqueous two phase isolation system, SFE (Super-critical Fluid Extraction), affinity portioning systems, PLE (pressurized hot-water extraction, ultrasound assisted extraction, etc., for marine metabolite's isolation [4]. Cytarabine or Ara-C (cytosine arabinoside) was the first marine derived anticancer compound developed for clinical use to treat myelocytic leukemia and non-Hodgkin lymphoma [3]. As a result, findings of new bactericidal molecules such as quinolones, sulfonamides, and oxazolidinones, have helped the physicians to effectively control bacterial pathogens [5]. Dehydrotyrosyl and Dehydrodopyl (peptides or small proteins) compounds have been reported from a broad range of invertebrate phyla [1–112].

Along with producing bioactive compounds marine algae and macroalgae have been used as functional food ingredients too.

The studies have reported the variable bioactivities of these metabolites, including antibiosis, modulation of host-defense activities, enzyme inactivation, anti-sepsis, and strengthening of human immune system, etc. [6]. Novel compounds like Sepastianines A and B (pyridoacridine alkaloids) isolated from the cytolyses dellechiae and dilemmas, an antitumor compound, known as bryostains isolated primarily from the bryozoans, from some sponges and tunicates [7]. The metabolites of marine bacteria also used as Taq DNA polymerase used as antitumor agents, anti-inflammatory agents. Macrolactin A-F, which inhibits murine cancerous cell growth in *in-vitro* tests and also inhibits human herpes simplex virus (HSV; Type 1 and Type 2) and human immune deficiency virus (HIV) replication. These compounds showed anti-viral activity against influenza virus, MDCK cell line (Martin Darby Canine Kidney cells), Helper simplex virus (HSV), and Vero cell lines [8]. Ara A has been reported to be the only compound having therapeutic activity. The two Salinamides; namely, A and B, isolated from marine actinomycete isolated from the surface of jelly fish have strong anti-inflammatory activity [9]. The marine sponges have also been reported to be anti-inflammatory, antitumor, immune, or neurosupressive, antiviral, antimalarial, antibiotic, or antifouling with their variety of therapeutics [10].

Bioactive compounds obtained from medicinal plants have been studied to modulate host–microbe interaction (synergistic) in favor of the host. The peptides obtained from single-cell protein (SCP) of marine yeast G7a can effectively inhibit angiotensin converting enzyme activity [11]. The ocean hides great potential for providing nutritional supplements, raw materials for cosmetics, nutraceuticals, and agricultural practices. Each of these bioproducts may have a strong potential commercial value [12]. The actinomycetes have 45%, fungi 38%, and prokaryotic bacteria 17% share in providing these supplements. The consumption of these natural metabolites has enhanced the average life term from 47 to 74 years (in men) and 80 years (in women). Sir Alexander Fleming discovered penicillin in 1928. This discovery further, motivated the discovery of chloramphenicol and streptomycin. The screening programs were then started to obtain anticancer drugs, anti-viral, anti-mycobacterial, antimalarial, and anti-parasitic molecules. However, the study was done on terrestrial ecosystems, with a scant work done on marine biota [13, 14].

A bioactive 'Salinosporamide A' of marine bacterial origin has been put to clinical trial phase. Initially, it has been promising in treating myelomas resistant to drug action and other main types of cancers [15]. The sequencing of genomes (microbial chromosomal DNA) is used to create genomic libraries. The large-genomic DNA fragments directly isolated from the sample and cloned in vector. (Figure 1) the microorganisms can be engineered easily than mammalian and plant cells to modify metabolic pathways, leading to production of structurally more diverse analogs such as polypeptides and non-ribosomal peptides. The larger part of such compounds has been used as anti-myeloma, anti-tumor molecules. A study has shown that nearly 67% of these marine metabolites have cytotoxic activity [16].

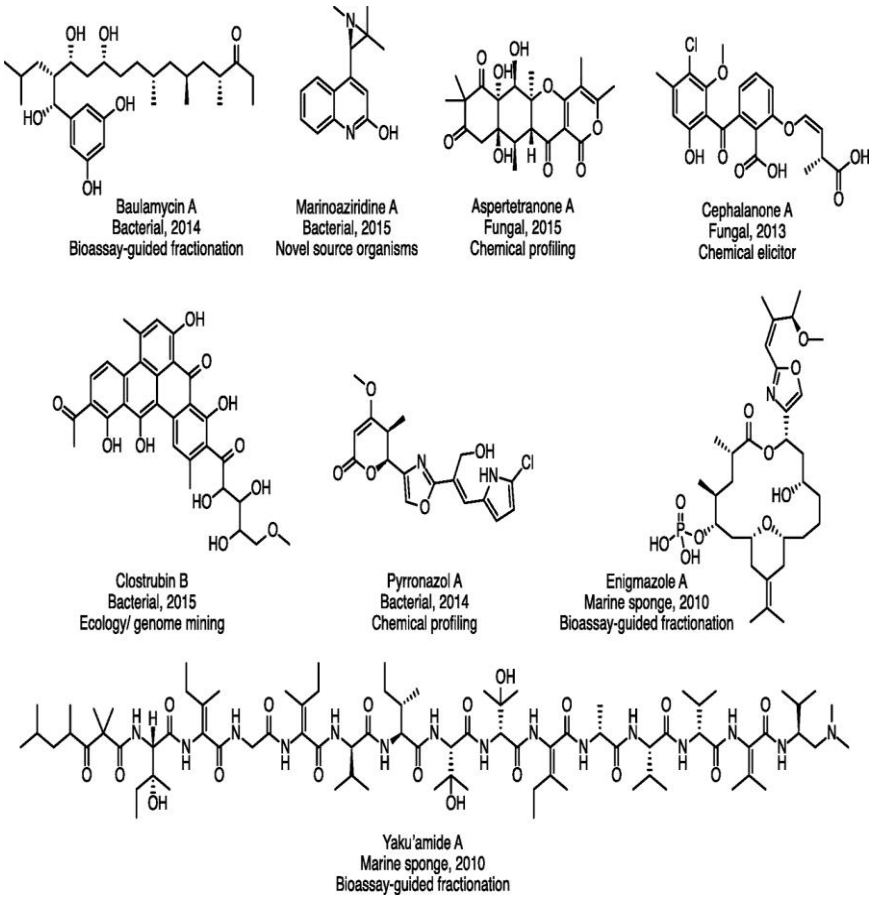

Figure 1. Structure of antimicrobial secondary metabolites from marine bacteria or fungi.

About 30,000 biochemicals of marine origin have been discovered till date; with nearly 1000 additions each year. These are structurally novel complex and actively diverse from the pre-existing molecules. The commercialized marine products, include agar, carrageenan, fish-liver oil (vitamins A, D), and polyunsaturated fatty acids (PUFAs), viz. Eicosa-pentanoic (EPA) and docosahexaenoic acid (DHA). The world register of marine species counts recently about 240,000 known species [17]. At least 90% of marine species remain undescribed by science, may yield chemicals having potential to become drug, medicinal products, experimental tools, or food supplements [18]. The search for new alkaloids/aliphatic molecules has shown a decreasing trend. However, research leading to discovery of anti-inflammatory, antifungal, antiviral, analgetic molecules has been getting more importance [19]. The use of modern analytical instruments (LC, GLC, HPLC, LC+MS, NMR) helped the researchers a lot in screening and isolation of novel compounds. In future, genome data mining may prove to be a highly useful research tool. Bioinformatics analysis is necessary to identify the biosynthetic gene clusters. The authors have reported bioprocess-based cultivation for macro and microalgae, invertebrate cells, marine fungi, and several bacteria [20].

BACTERIA AND FUNGI: SOURCE OF BIOACTIVITY

The research and development leading to findings of unexplored marine products may prove to be beneficial in biomedical/clinical research, semi-synthetic drug designing, and raw materials chemical drug synthesis [21]. A few of these drugs have undergone the clinical trials and now awaiting FDA approval for mass human consumption [22]. In recent times, the increased demand for compounds having role as pharmaceutical raw materials or as synthetic material for cosmetics, chemicals, drugs, and personal care products, the natural product discovery programs took a boost [23]. After the end of the First World War, pharma companies planned screening programs aiming for discovery of new bioactive biomolecules, such as cholesterol biosynthesis inhibitors [24].

New Bioactive Natural Products from Marine Organism

The marine water is a complex mixture and may contains approximately less than a million bacterial cells per milliliter [25]. These bacteria carry a higher probability of being a source of secondary metabolites [26]. In the year 2007, 961 new compounds were isolated from marine microbes with an increase of 24% in comparison that found in 2006 [27].

Secondary Metabolites with Biocidal Activity

The discovery of penicillin in 1920's boosted the terrestrial bacteria and fungi-based research for screening novel bioactive substances. The colonies of *Brevibacillus laterosporus* PNG276 (native of Papua) [28], produced 'tauramamide' along with two new lipopeptide isomers in laboratory conditions. Another novel lip peptide 'Aura amide' showed antimicrobial activities. It contains two Dextrose (+) amino acids and its N-terminus has an acyl group [21]. Bacteria (strain NPS008920) belonging to genus Marinispora was screened from water sediments of Cocos Lagoon, Guam. The *Marinispora* sp. yielded four bioactive compounds, namely, Lipoxazolidinones (A, B, C) and H12. These were tested for their bactericidal activity against Gram (+) and Gram (–) bacteria. The compounds showed wide-spectrum activity, killing tester bacteria and two antibiotic resistant cultures of *Haemophillus influenzae* [29]. Another study reported the weak-microbicidal activity of aqueous extracts of 12 seaweed against MSSA. (Methicillin-sensitive *Staphylococcus aureus*). A new actinomycete, NPS12745, has recently isolated and reported from the coast of San Diego, USA. The phylogenetic analysis of the 16s RNA subunit of NPS 12745 confirmed that it is a new species of the marine actinomycete genus *Marinespora*. This microbe synthesized bisindole pyrroles and lynamicins (chlorinated compounds). The bisindole pyrrole includes an isomer (chrompyrrolic acid) that has been also reported in *Chromobactrium vilocerum* [30].

Secondary Metabolites: Cytoxicity and Related Activities

The aquatic ecosystems have been explored for their natural products having anti-cancer and cytotoxic activities. The researchers isolated 'thiocoraline', a bioactive depsipeptide from the hyphal culture of marine bacterium *Micromonospora marina.* It was isolated from the coral in the Indian Ocean [31]. It synthesized a curvularin macrolide, 'apralactone'. The isolated compounds were tested against human myeloma/tumor cell lines, including those causing benign and malignant tumor types. A group of scientists screened a fungus *Spicellum roseum*, from the sponge *Ectyplasia perox.* The isolation was done from the waters of Dominica Island, of Caribbean. This fungus was bioprospected and two new cyclohexadepsipeptides (spicellamide and spicellamide) were isolated from its culture medium. The biosynthetic peptides were cytotoxic against rat neuroblastoma B104 cell line as determined by the Blue Cell Viability Assay [32].

Chemical research of culture broth extracts from the fungus of marine origin *Massarina* sp. (strain CNT-016), isolated from a sample of marine mud on the Palau island, produced spiromasaritone and masariphenone as novel metabolites in their stationary growth phase. The isolated compounds were actively arresting the growth of colon carcinoma cell line of man [HCT (Hematocrit)-116]. In general, the aliquots were able to restrict the growth of Hematocrit feebly, with no significant activity against *Candida albicans* or *S. aureus* was detected [33]. The fungus *Aspergillus ustus* was isolated from *Suberites domuncula*, a sponge of the Adriatic Sea. This fungi grew luxuriantly on biomalt agar and barley agar medium.

In past, about 400 plant species have been reported to produce antidiabetic phytomolecules [8]. However, aquatic microbes have got a little attention for screening of their antidiabetic properties. A fungus *Cosmospora* SF-5060, was screened from coastal waters of Gejae Island, South Korea. It produced a compound '*aquastatin A*' with very high-protein tyrosine phosphatase 1B (PTP1B) enzyme inhibition activity (EC_{50}). The PTP1B modulates tyrosine phosphorylation-controlled metabolic events. The PTP1B, an intracellular PTP (non-receptor type), repress insulin- and leptin-receptor regulated signaling pathways. Thus, its inhibition potential may be used in designing effective therapy for diabetes (Type-II) and obesity (Figure 2) [35].

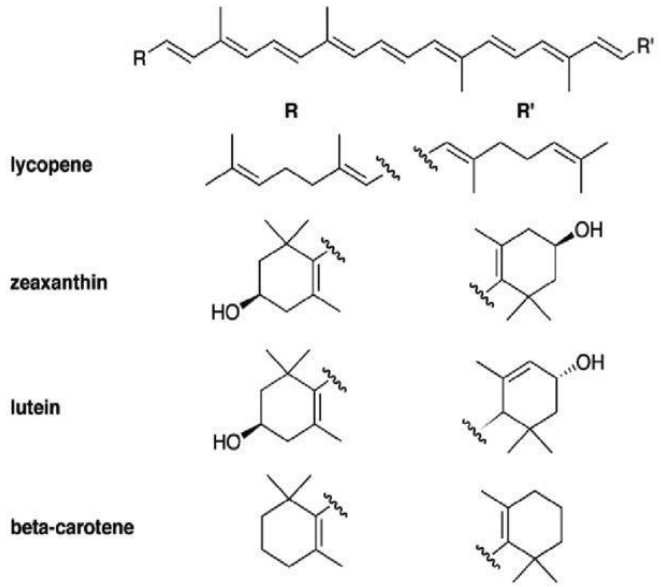

Figure 2. Structures of cytotoxic secondary metabolites.

AQUATIC PLANTS: PRODUCTION OF ANTICANCER DRUGS

The biosynthetic products and their analogs constitute about half of all therapeutics or drugs used in clinical practices worldwide. The vegetables/fruits being rich in vitamins (C, B, and E), carotenoids, lycopene, and fibers, apparently impart cancer-protective properties to the foods. Antioxidants have been reported to be inducing apoptosis in final stages of cancer [30]. Several herbs and species, including rosemary, sage, thyme, nutmeg, turmeric, chili, ginger, and other medicinal plants are important in exhibiting antioxidant activity [4]. The most important antioxidant compounds are anthocyanins, catechins, coumarins, flavonoids, flavones, isoflavones, isocatechins, and lignans. The antioxidant potential of food is dependent upon its carotene content, vitamin C, and tocopherols. The antimutagenic and antioxidative potential of plant extract may act as building blocks for designing anticancer drugs [36]. In USA, the National Cancer Research Institute (NCI) has isolated about 114,000 aliquots from about 35,000 plants. These extracts have been characterized for their anti-tumor action under various physicochemical conditions. However, isolation of such therapeutic agents from aquatic zones has not got the much-desired thrust. A few research institutes in collaboration with pharmaceutical companies have initiated the marine exploration to isolate and identify new natural products from faunal species; namely, microbes, microalgae, seaweeds, mangroves, and aquatic life forms [12]. Marine organism constitutes a new gene pool that may lead to the invention of new drugs and antibiotics. These metabolites may have extensive anti-inflammatory (e.g., topsentins, scytonemin), anticancer (e.g., bryostanins, discodermolide), and microbicidal activities [28]. All of these bio-active compounds with potential for therapeutical applications have been isolated from one or more marine namely fungi, macro-algae, cyanobacteria, planktons, etc. [18].

For a long time, seaweeds have been collected from the sea for obtaining biomolecules (protein, peptides, vitamins) and minerals with potent anticarcinogenic activity. The seaweeds also accumulate high concentration of antimicrobial polyphenols/catechins in their cytoplasm. Mangroves have been reportedly used as medicines to treat the human diseases. Marine plants have a great prospect to be used as nutraceuticals and may also fulfill the requirement of food and nutrition for human beings. Seaweeds are used for human consumption and also as medicines.

Secondary Metabolites from Bacteria

Among the various marine microorganisms, the bacteria have highest potential to be tapped as a source of novel drugs and bioactive molecules, including novel anti-inflammatory agents (e.g., pseudopterosins, topsentins, scytonemin), anticancer agents (e.g. bryostanins discodermolide, sacrodictyin), and antibiotics (e.g., Marinone) [37].

The *Lactobacilli* and *Bifidobacteria* constitute probiotic bacteria, having strong antagonistic activity against pathogenic microbes. These probioforms produce antibacterial protein; namely, bacteriocin, which has bactericidal and anticancer properties. The researchers have shown that the intake of *Lactobacilli* as dietary supplements decrease the chances of colon cancer. The microbial toxins of marines have been found to be useful in curing neurophysiological and neuropharmacological ailments. Red tides caused by bacteria present in *Nactiluca scintillans*. The major metabolite, macrolacine-A, inhibits B16-F10 melanoma, HSV (Type 1 and Type 2) and protects T-lymphocytes against HIV replication.

A depsipeptide 'Kahalalide F' (KF), isolated from the mollusk *Elysia rubefescens* found in island waters of Hawaii. KF induces the cytotoxicity and restricts the cell cycle in late phase (G1). KF also display anti-tumor activity against benign tumor and has shown promising results in biocontrol of prostate cancer cell lines [38].

Actinomycetes

The terrestrial actinomycetes have proved to be the largest resource for the screening of novel biocidal and related compounds. (Figure 3) However, marine exploration for actinomycetes is still lagging behind. 'Gutingimycin', a polar trioxacarcin derivative from *Streptomyces* sp., isolated from Gulf of Mexico has a broad killing spectrum against Gram positive and negative pathogenic bacteria [47].

The microbes have been found to be sources of antitumor and anticancer molecules that can inactivate proteasome function preventing cancer. 'Thiocaraline', a bioactive depsipeptide isolated from *M. marina*, in Mozambique, can inhibit RNA synthesis. Their cytotoxic bioactivity can restrict the malignant growth of lung and colon cell lines [38]. The compounds can revert the mutations in defective p53 system of the colon cancer cells (Table 1).

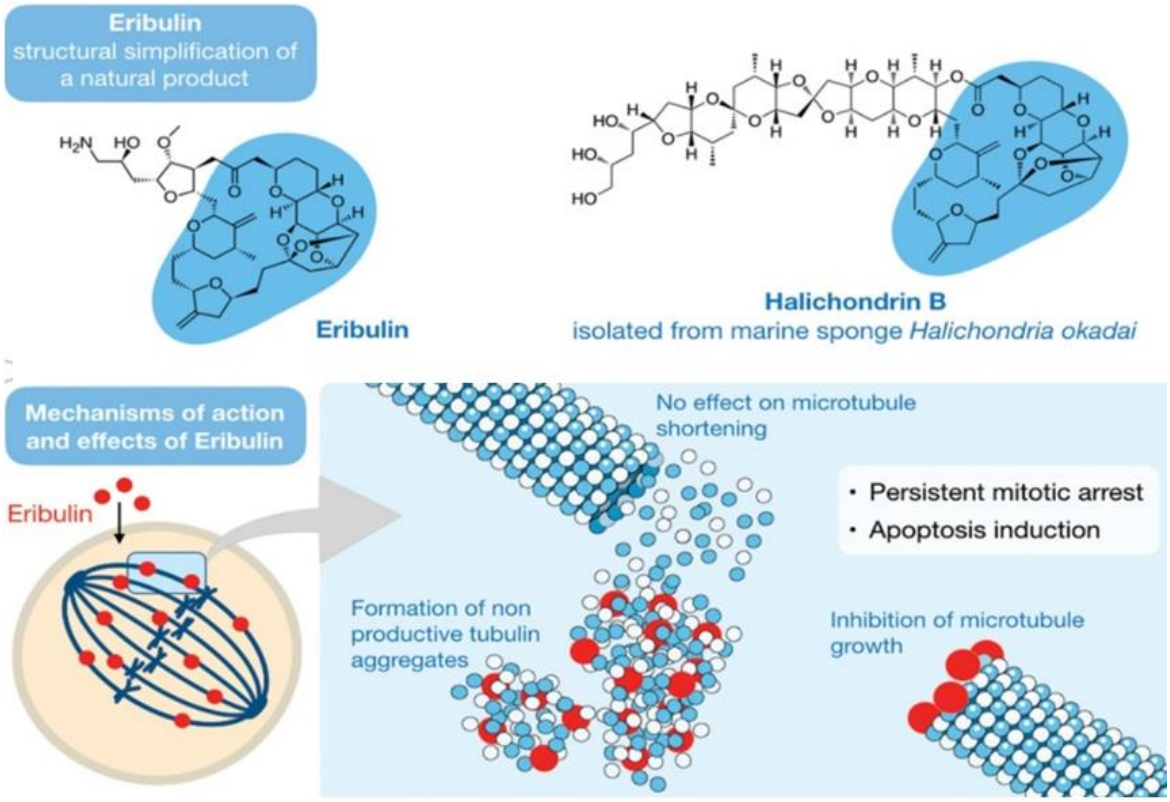

Figure 3. Chemical structures of Eribulin mesylate and Halichondrin-B of sponge *Halichondria okadai*. The anticancer mechanism of Eribulin mesylate cells in cancer.

Table 1. Distribution of biological activities in marine microorganisms.

Biological Activities	Bacteria Origin	Fungi Origin
Anti-tumor	Alcyonarian (2), algae (1), fish (1), mollusk (2)	Alga (6), fish (2), mollusk (1)
Anti-bacterial	Algae (3), mollusk (1), sediment (8), sponge (4)	Sediment (2), sponge (5)
Anti-viral	Sediment (2)	Phanerogame (1)
Anti-fungal	---------	Alga (1), wood (1)
Anti-inflammatory	Jellyfish (1)	Crab (1)
Enzymatic inhibition	Mollusk (1), sediment (1)	Sponge (10), wood (1)

Aquatic Fungi

The terrestrial filamentous fungi have been the prime source of bio-active molecules in the past. These belong to three genera, namely, *Aspergillus*, *Fusarium*, and *Penicillium* [39]. In the recent past, focus of research has shifted towards higher fungi, including endophytic and filamentous fungi of marine habitats. The production of secondary metabolites in artificial growth conditions by these microbes require accurate simulation of natural oceanic habitats. Hence, to achieve maximum biomass and metabolite productivity various nutrient limited media needed to be used. For instance, Penicillin is produced by *Penicillium* sp. only in carbon limiting media (Figure 2). If the same media has phosphorous limitation, cephalosporins, and vancomycin are produced. Following is the two classes of marine fungi-based commercialized antioxidative products:

1. Acremonin (*Acremonium* sp.);
2. Xanthone (*Wardomyces anomalus*)

The free radicals of different types (super-oxide, hydroxyl, peroxyl, ROS) have been reported to be causing atherosclerosis, cancer, dementia, and neuralgia [11]. Antioxidants protect cell from oxidative stress and has potential therapeutic effect on human body.

Table 2. Chemical classes and activities observed in marine fungi.

Microorganism	PW	Chemical Classes	Activities
Aspergillus • Fish • Algae • Sponge	 N TER N	Fumiquinazoline Sesquiterpenes Nitrobenzoate Indolediketopiperazine Clorolactono	 Cytotoxic Antitumoral
Leptosphaeria • Brown algae • Sea grass	 N AC	Indolediketopiperazine Clorolactono Heptoquinone	 Cytotoxic Anti-dopamine
Penicillium • Fish • Green alga • Offshore sediment	 N N AC	Acyclic peptides Indole Aromatic lactones	 Cytotoxic Cytotoxic Inhibitor of cellular growth
Phoma • Crab shell	 TER	Diterpene	 PAF antagonist

PW = Pathway, N = Nitrogenated compound, AC = Acetate-derived compound,
TER = Terpenoid.

Microalgae

The marine cyanobacteria or microalgae have inherent potential to produce novel bioactive compounds, such as toxins and steroids with possible pharmaceutical applications [40]. Their microbial metabolites can be used as precursors for commercial synthesis of different vitamins (B-complex, E). A protein serine/threonine kinase inhibitor, 'Scytonemin' has been purified from culture medium of *Stigonema* sp. It is yellow-green to ultra-violet colored pigment, found in extracellular sheaths of different blue-green algae. Scytonemin regulates enzyme kinases and mitotic spindle

formation during cell cycle and can also inhibit uncontrolled growth of human fibroblast and endothelial cells; an excellent protein inhibitor with antiproliferative and anti-inflammatory actions [41]. The marine cyanobacterial metabolites have been studied and found to be either killing the cancer cells (apoptosis), or inhibiting the protein kinase-C activity (signaling enzymes). An antiproliferative compound 'Curacin –A', has been procured from media aliquots of *Lyngbya majuscula*. By inhibiting the condensation of the tubulin it inhibits proliferation of colon, rectal, renal, and breast cancer cell lines [42]. 'Apratoxin – A' found in culture extracts of *Lyngbya boulloni* has shown cytotoxicity to adenocarcinoma of different glandular tissues. The 'Coibamide A', secreted by *Lepto lyngbya* displays strong cytotoxic activity against lung (NCIH46 lines) and mouse cancer (Neuro-2A) cells [43]. Borophycin is boron-containing metabolite obtained from marine *Nostoc linckia* and *N. spongiaeform.* A marine actinomycetes *Strepetomyces griseus* produced 'aplasmomycins', similar to structure and biocidal activity of that of Boromycins [43]. 'Cryptophycin 1' separated from culture extracts of *Nostoc* sp. (Ref: ATCC 53789) by researchers at Merck Inc. has strong fungicidal activity. The similar metabolite obtained from *Nostoc* sp. GSV224 was cytotoxic against human tumor cell lines [44].

Macroalgae (Seaweed)

Seaweeds produce epicatechin, polyphenols, protein, gallic acid, iodine, vitamins, and minerals along with some important anticancer metabolites [45]. In recent past, researchers have described *Palmaria palmata* as an effective antioxidant, inhibiting glandular neoplasia. The seaweeds of marine origin, that is, *Acanthaphora spicifera*, *Ulva reticulata*, *Gracilaria* sp., and *Padina boergesenii* of the Manner Gulf biosynthesize compounds with reported cytotoxic activity. Algae have immunomodulating and antitumor activities. *Sargassum thunbergii* culture extract has antitumor activity and inhibit tumorigenesis in the rat (13762MAT-mammary adeno cancer cell). The bio-active 'Fucoidan' obtained from *Ascophyllum nodosum* has an anti-nodulatory effect on both normal and malignant cells, including fibroblasts [46] with additional antitumor and fibrinolytic properties. Stylopoldione, of *Stypodium* sp., can effectively stop mitotic spindle formation and hence act as potent cytotoxic metabolite. Similarly, compound Condriamide-A (*Chondria* sp.), Caulerpenyne (*Caulera* sp.) are cytotoxic towards colorectal and nasopharyngeal cancer cells. The brown algae *Eclonia cava* upon hydrolysis liberate enzymes and water-soluble antioxidants [47].

Mangroves and Other Higher Plants

A total of sixteen mangrove plants were explored for their metabolites and possible possession of anticancer drugs. A sulfur alkaloid, 'Brugine' of *Bruguiera sexangula* inhibited growth of sarcoma 180 cell lines and lung carcinoma [48]. A carbohydrate derivative of 2-benzoxazoline of *Acanthus ilicifolius* possessed antitumor and antiviral activities. A crude aliquot obtained from mangrove plant *Ceriops decandra* prevents the hamster buccal pouch carcinoma caused by dimethyl benzo[a]anthracene. It also enhances the probiotic bacteria (*Lactobacilli* sp.) in buccal cavity of the animals.

Phytochemical Constituents of Marine Plants

Marine flora possesses biologically active and medicinally important chemicals. Polysaccharides and polyphenols are important and useful group of compounds that are applicable for their bio-activities. The 40,680 different species of phytoplankton and marine algae (of Rhodophyta, Phaeophyta, Chlorophyta) and 71 other mangrove plant species have been studied in a recent oceanic exploration. They produce essential fatty acids, carotenoids, trace minerals, vitamins, enzymes, amino acids, etc. [12, 49].

Polyphenols

The plant polyphenols scavenge free radical and are antimicrobial and anticancer agents [24]. Marine plants viz. seaweeds, grass, and mangroves have high concentrations of these polyphenols. The inclusion of these seafoods in dietary intake may result in reduction in coronary heart ailments, cancer mortality, and death rate. They are natural metal ligands with high-antioxidant activity prevent a variety of toxin-induced organ dysfunctions [50].

Osmundea pinnatifida, a marine red algae possess antimould, antimicrobial, and antioxidant activities as it has flavonoid, polyphenols, and phloroglucinol [51]. The edible seaweeds also have a list of potentially bioactive metabolites; namely, phlorotannins in addition to the preceding ones. One such seaweeds *P. palmata* produce antioxidants that have been proved to be cytotoxic to cancer cells. These anticancer activities of these compounds are attributed to restricting the cell division at telophase stage of mitosis. The division is restricted by reducing the mitotic index and/or the colony formation by proliferating carcinoma [13, 52].

The authors have suggested that the use of phytochemicals (carotenes, xanthans, polyphenols, lignans, and flavonoids) as food supplement in daily diet improve metabolic activities. These activities play a vital role in neutralizing ROS. These biomolecules may regulate ionic/mineral/nutrient efflux, and influx in cell membranes of tumor, thus inhibiting growth [16, 53].

Polysaccharides

The polysaccharides along with glycans form a class group of major biochemicals of marines. The most common being monosaccharides, the amino sugars (D+ glucosamine, N-acetylneuraminic acid, and D+galactosamine), simple sugar acids (glucuronic and iduronic acids), and algal heteropolysaccharides (alginates, agar, etc). The red algae of genera *Gelidium* and *Gracilaria* produce agar-agar, which gave strength to the algal cell walls [16, 21, 37, 54]. It is formed by polymerization of galactose, while the carrageenan are formed by condensation of galectin [55]. The algal polysaccharide's bioactivity has been attributed to presence of sulfate groups. The sulfur moiety may promote the immune response and enhance the anti-carcinoma activities of macrophages, WBC, and natural killer cell. The elevated activity of T-helper cell will further activate cytotoxic T-cell, which has been reported to be strongly cytotoxic to tumor cells. These moieties on adsorption to T-lymphocytes, further enhance T-cell proliferation [56]. *Pseudomonas* sp., was screened for 'B-1', a sulfated polysaccharide. This polysaccharide increased death rate of human leukemic cells *in vitro*. Similarly, 'PI-88', an oligosaccharide induced early apoptosis of pancreatic carcinoma cells. Internalized sulfated glycosaminogycans interfere with transcription function and induce the apoptosis of marine melanoma cells.

Fucoidan is a unique polysaccharide obtained from cell wall of brown algae. It has been reported to restrict growth of human lymphoma HS-Sultan cell lines by apoptosis. The cell death has been attributed to activation of caspase-3 and inhibition of extracellular signal-regulated kinase activity [42]. Fucoidans restricts the rate of cellular processes and effectivity of binding proteins (adhesion proteins, growth factors, cytokines, etc.) resulting in cessation of cell growth. These bio-molecules can further mitigate and retard events of angiogenesis, tumor, or cancer cell metastasis and atherosclerosis. The fucoidans have been studied for their anticoagulating, antithrombosis, antiviral, anticarcinoma, anti-edematous, HDL reducing, antioxidant status [58]. The studies have observed that addition of sulfur to bioprocess involved in fucoidan's synthesis results in increased bio-active potential of final metabolite [34, 42].

Alkaloids

Meissner, in 1819 characterized these 'alkali-like' compounds found of plant origin. Various organic amines and chlorinated ring nitrogen chemicals are also named as alkaloids [59]. Morphine was the first plant alkaloid purified in 1805 by Kappelmeier. In 1950, hordenine was the first isolated aquatic alkaloid of marine algae [60]. These compounds/alkaloids may change normal enzymatic or metabolic activities in human beings. For example, anticancer alkaloids 'taxol' of *Taxus brevifolia*. Camptothecin and derivatives, are under clinical trials in USA. *Camptotheca acuminata* was bio-prospected to obtain these alkaloids. The marine algae alkaloids may be classified in three groups:

- phenylethylamine alkaloids;
- indole; and
- halogenated alkaloids and other alkaloids.

Structurally, the alkaloids are isolated from marine algae mostly belong to phenylethylamine and indole groups. Marine drugs are focused on finding new drugs for cancer treatment. These are two derivatives; lophocladine A and lophocladine B obtained from an algae *Lophocladia* sp., have been reported to be cytotoxic to cancer cell lines [7, 29, 31, 49].

MECHANISM FOR THE ANTICANCER ACTIVITY OF MARINE PLANTS

Any damage to DNA structure leads to cancer. A mutagenic marker can estimate risk of genetic mutation leading to cancer and also in evaluation the affectivity of chemoprevention. However, DNA has innate mechanism of SOS repair to nullify most of damage [60].

Antioxidants

The human DNA has various methods and mechanisms to defend itself from free radical damage and mutations caused by ROS. Various defenses act in coordination with each other in different cellular structures. This defense mechanism is dependent on superoxide dismutase (Sod), glutathione peroxidase (GPx), and catalase enzymes. Biochemicals such as vitamin E, C, and carotenoids also have radical-scavenging potential. During normal conditions, the high concentration of SOD reduces the superoxide levels to a low. Hence, the synthesis of peroxynitrite is also inhibited [61]. The antioxidant depletes the glutathione (GSH) in aerobic tissues. It is obtained from sulfhydryl-containing amino acids. Nutrition vitalize the body's immunity against free radicals. The minerals including copper, manganese, and zinc are important part of structure and catalytic sites of these enzymes. Vitamin E do not increase the transformation rate of any enzyme; however, it provides strength to lipids and phospholipid of cell membranes and enhances immunity. Vitamin E has other metabolic functions viz. modulation of gene expression and subsiding inflammatory responses [62].

Apoptosis

Apoptosis involves complex cellular reactions, changes in signaling pathways resulting in cell death. The imbalance in activity of anti- and pro-apoptotic proteins, starts programmed cell cessation. The decreased expression of caspases may also cause decreased apoptosis [64, 65]. Some researchers have endorsed the anti-tumorigenic potential of curcumin and resveratrol. These phytochemicals can activate the macrophages and initiate apoptosis by enhancing the activity of macrophage and T-lymphocyte [3, 18, 66]. The fucoidans can enhance the repair of cancer cells while lowering the lymphocyte degradation rate. Fucoidan can further increase the production of interleukin-1 (IL-1). Thus speeding up the activity of T-lymphocytes, macrophage, and NK cells [67].

Marine Food: Nutritional Aspect

The 'plant- based' diets has higher dosage of nutrients, dietary fiber, and low-HDL/energy density [67]. The colored vegetables, fruits, and nuts have anticancer properties. The Seaweeds are the aquatic equivalents and when consumed by man, provide nutritional components that have medicinal values to subside variety of diseases (tuberculosis, colds, influenza, cancer). The seaweeds have high concentration of vitamins, flavonoids, pigments, riboflavin, and minerals [19, 31, 67], with the quantities exceeding that in similar mass of land plants [68].

APPLICATIONS IN CANCER TREATMENT

Natural metabolites and their analogs contribute greatly in alternative cancer management. These antineoplastic analogs used therapeutically, include vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, taxotere, and cabazitaxel (Jevtan); podophyllotoxin and analogs etoposide (Etopophos), teniposide (Vumon), and belotecan (Camptobell); and camptothecin and analogs topotecan (Hycamtin) and irinotecan (Camptosar). The terrestrial microbes also produce such drugs; namely, anthracyclines doxorubicin (Doxil, Adriamycin), daunorubicin (Cerubidine), and epirubicin (Ellence); the glycopeptide bleomycin (Blenoxane); and the non-ribosomal peptide dactinomycin (Cosmegen) (1, 22, 34, 69). However, only 2% of marine plants have been studied for their antineoplastic metabolites. There remains a vast biota to be explored for study of their bioactive molecules.

Cytarabine (Cytosar)-Debuting Marine Compounds in Cancer Field

Werner Bergmann, a professor and researcher of Yale University lead an oceanic expedition and published several papers in mid-1900's; namely, 'contributions to the study of marine products'. The highest recognized part was the discovery of the arabinonucleosides (spongouridine and spongothymidine) from the sponge *Cryptotethya crypta* (*Tectitethya crypta*) of the Caribbean [5, 70]. This finding changed the concept that nucleosides are biologically only if it had ribose or deoxyribose bound to them. An antimetabolite drug is one that is structurally similar to that of a natural drug. However, it does not have the ability to express or preserve its function and hence does not regulate normal cell metabolism [5, 71]. Thus, stalling the growth, even in the cancer cell. For instance, the cytarabine triphosphate when bind to DNA, cleaves phosphodiester bond between the two pentose molecules, and terminates DNA synthesis [24].

Cytarabine was approved by FDA for its clinical use in 1969. It has been used reliably for management of leukemia, nodular tissues, myeloma, and non-Hodgkin's lymphoma. The synthetic analog of cytarabine, 'adenine arabinose', was modified to synthesize 'vidarabine' or 'Ara-A'. It has been used for treatment of HSV and *Varicella zoster* infections [72].

Trabectedin (Yondelis) – Overcoming the Supply Problem

The Caribbean ascidians have been known for their anticancer activity since 1960s. However, species level studies of different genera were completed in late 1980's [52, 73]. The study explored 'trabectedin' as the most abundant of the six isomers of Ecteinascidin-743. It inhibited the DNA alkylation in myeloma, causing inactivation of cancer cell replication. Trabectedin was synthesized in lab for the first time in 1996. It was a complex and laborious process giving a very low yield of trabectedin. The same authors reported a simple process with improved product yield; however, still the higher demand of it could not be fulfilled.

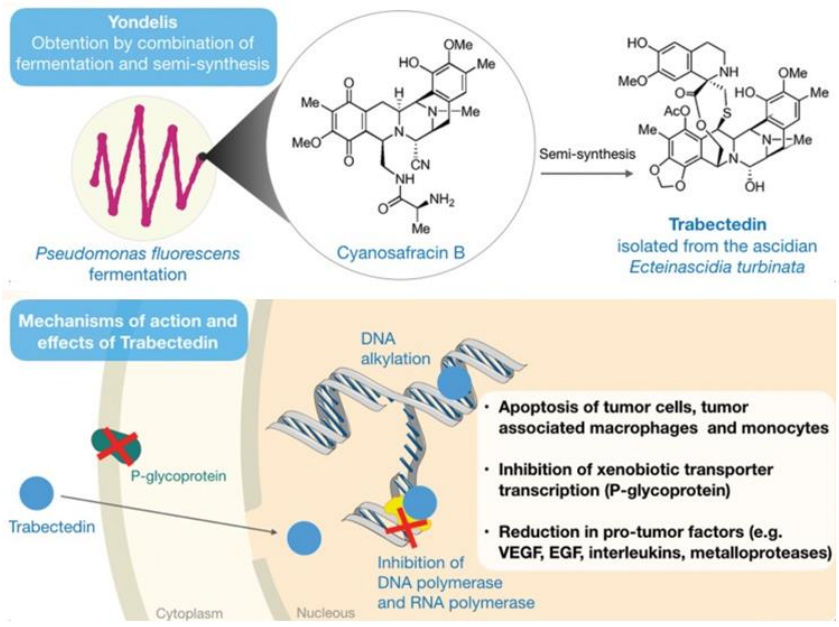

Figure 4. Trabectedin of *Ecteinascidia turbinate*, its effect and mode of action.

It displaced the DNA strands from its normal stereochemical positions to the opposite folds of the alkylation site. Hence, it prevented the RNA polymerase II activity, thus terminating DNA synthesis. The yondelis affects the transcription in myeloma resulting in lowering in production of chaperones (heat shock proteins-HSPs) [74]. This drug modifies the tumor microenvironment (TME). The TME has nontumor cells (macrophages), which communicate with myeloma/tumor cells. These macrophages may promote growth, proliferation, and metastasis of tumor cells. Hence, these TME

cells become resistant to chemotherapy. However, trabectedin disintegrates this association and induce apoptosis in these cells [52].

The mariculture of ascidian for the production of trabectedin using *Ecteinascidia turbinata* under natural ecological circumstances, was very low. The need of higher supply of trabectedin lead to bioprocess development using an intermediate cyanosafracin B to produce trabectedin using the bacterium *Pseudomonas fluorescens* (Figure 4) [74–80].

Eribulin Mesylate (Halaven)-Understand Structure Activity Relationship

Eribulin mesylate, a semi-synthetic growth suppressant has been reported to be a strong antimitotic compound. It can alter microtubule dynamics when administered in a very low dose. This compound target tubulin and arrest the elongation of microtubules. The cell mitosis is terminated that leads to death of carcinoma. Eribulin was developed by a Japanese pharma company, Eisai [75].

MARINE PEPTIDES: BIOACTIVITIES AND APPLICATIONS

Marine species, the half of the total global biota, have proved to be potential resources of new bioactive compounds. Peptides constitute a vital group of important bioactive marine products [65, 76]. Their strong bioactivities do include antitumor, antidiabetic, neuroprotective, and cardioprotective capacities. Bioactive peptides have been described for their neurotoxic/cardiotoxic, cardiotonic, antiviral, antitumor, and antimicrobial behavior in some earlier studies [76].

Bioactive peptides may be supplemented in nutraceutical products. These peptides gain full bioactivity only after their gastrointestinal digestion (Figure 5) [77–81].

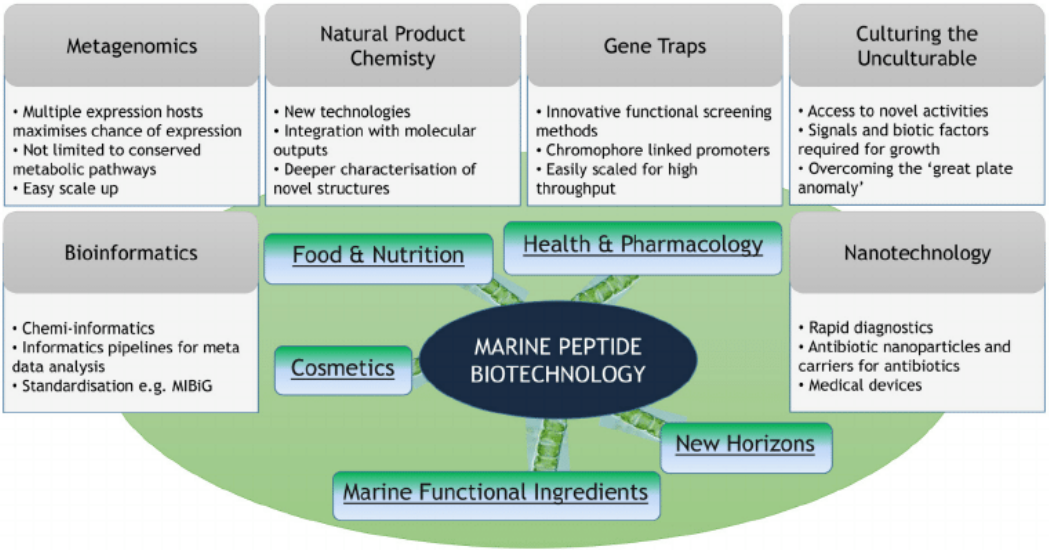

Figure 5. Marine peptides used in different fields of technology.

Antimicrobial peptides (AMPs) strengthen innate immunity and act as 'host defensive peptides'. They carry positive charge and have high-cysteine content. The AMPs inhibits the growth of various Gram + and Gram – pathogenic bacteria [99]. The aquatic AMPs are structurally diverse and significantly differ from the one produced by land species [77]. These peptides also have anti-mold properties (Table 3) [100–103].

The sponges predominantly produce antiviral peptides. These antiviral metabolites have cyclic or linear in structure and have atypical amino acids attachment to their terminals. They block the virus entry in host, inhibition viral cytopathy, and perform viral neutralization to defend host. These cyclic peptides of *Siliquariaspongia mirabilis* inhibited growth of HIV-1. Mirabamides A–C suppressed proliferation in *C. albicans* and *B. subtilis* [78].

These peptides can be subdivided in four types:

1. linear depsipeptides;
2. cyclic depsipeptides;
3. linear peptides; and
4. marine protein hydrolysates.

Table 3. Marine peptides sources and applications.

Compound	Natural Products/Derivatives	Sources	Applications
Ziconotide	Natural products	Wcenotoxin from *Conus magus*	Analgesics
Brentuximab vedotin	Derivatives	Dolastain 10 from *Dalbello euricularia*	Cancer treatment
Glembatumumab vedotin	Derivatives	Dolastain 10 from *Dalbello euricularia*	Cancer treatment
Katsuobushi oligopeptides	Natural products	Pentapeptide from hydrolysate of *Dride bonito*	Anti hypersenstive
Dermo chlorella	Natural products	Oligopeptides extract from *Chlorella vulgares*	Skin toner and firm

The depsipeptides may have atypical amino acids carrying post-translational modifications such as *N*- and *O*-methylation or carboxylation. These depsipeptides include devastating 10 dolastatin 15, hemiasterlin, monomethyl auristatin, and HTI-286 [51, 72]. The depsipeptides exert cytotoxicity by stopping tubulin polymerization [73], stopping cell cycle [74], and inducing early apoptosis [76, 79].

The hydrolysate obtained from Atlantic Cod promoted and stimulated the microbicidal power of phagocytes [74, 82]. Use of fermented marine fish-protein and Chum-salmon protein hydrolysate activated T-helper raise levels of cytokines and enhanced cytotoxic activity of the NK cells in mice [76].

These peptides have been studied to be anti-diabetic in nature. It reduced the glucose levels in blood, activated lower levels of insulin, and improved insulin sensitivity index in the diabetics. The study was conducted on Chinese patients with Type-II diabetes. The patients were given marine collagen peptides obtained from fish hydrolysate for 45–60 days (Figure 6) [67, 81].

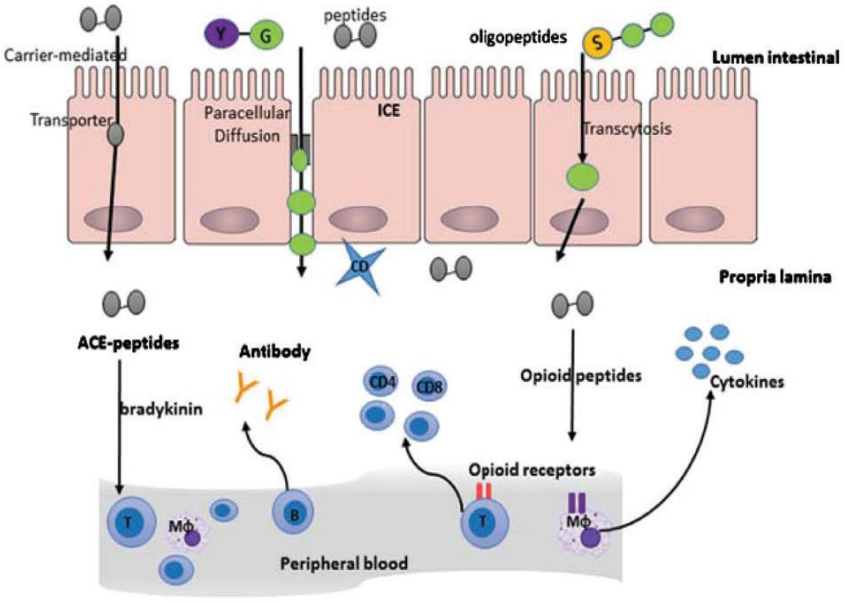

Figure 6. Mechanism of immunomodulatory peptides or binding of receptor to the CD4 or CD8.

ANTIBACTERIAL SPECTRUM OF AQUATIC BACTERIA AGAINST MULTIDRUG RESISTANT HUMAN PATHOGEN

Infectious disease agents such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, *S. aureus*, *Acinetobacter baumannii*, and *Enterobacter cloaceae*, became a serious health problem in many developing countries, including Indonesia [80], because they led into morbidity and high mortality in human. In recent years, that pathogen bacterial became into organisms resistant to multiple antibiotics, or also called the Multi Drug Resistant (MDR). The increasing number of victims has reported. Moreover, these problems led to higher maintenance costs and only a few hospitals that could solved this problem. The emergence of discovery the never antibiotics were needed with a promise for combating MDR strain [79].

Screening for Antibacterial Activities against MDR Pathogen Bacteria

The microbicidal activity of isolate associated with sponge was conducted by testing it against test pathogens; namely, *P. aeruginosa*, *K. pneumonia*, *E. coli*, *S. aureus*, *A. baumannii*, *and E. cloaceae* [8].

Extraction of Bioactive Metabolites

The screened actinomycetes were cultured in 500 ml marine broth and grown for 10–15 days at 28°C in an orbital shaker (200–250 rpm). Afterwards, culture was centrifuged at 4000g for 10 minutes. The biomass free supernatant was mixed with equal volume of ethyl acetate and kept still overnight. The upper aqueous layer with bioactive compound was retrieved and kept in watch glass. The extract was kept in an oven at 40°C for 4 hours (Figure 7) [80].

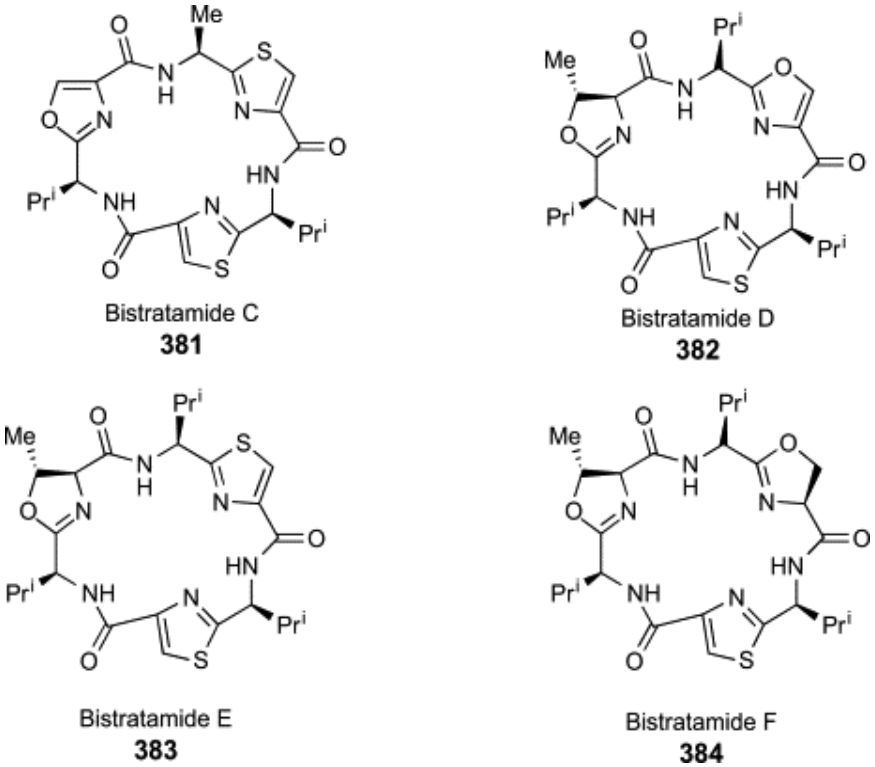

Figure 7. Chemical structures of bioactive compounds isolated from marine sponge.

SIVER NANOPARTICLE SYNTHEIS BY MARINE BACTERIUM: ACTIVITY AGAINST UTI PATHOGENS

Silver has bio-restricting properties and may be used as microbicidal agent against several pathogens [82–88]. The Ag^{2+} ions and related compounds are toxic to microbes [89]. Since ancient times, the silver foil has been used as a medicine and food additive in India [90]. In 1700; $AgNO_3$ was

used for the treatment of UTI, venereal diseases, salivary glands fistula, and abscesses. In early 19th century powdered silver particles were used to heal surface of wounds by physicians. A study elaborated the bacterial synthesis of silver nanoparticles using marine *Bacillus* sp. NJYRK. A number of techniques are available to synthesize and confirm formation of nanoparticles. UV-vis spectroscopy, X-ray diffraction, electron microscopy, Fourier Transform Infrared spectroscopy (FTIR spectroscopy), are the extensively used one. The microbicidal potential of silver nanoparticles was assayed against UTI pathogens [88–93]. The antibiotic inhibitory concentration test confirmed that 10 g/ml of silver nanoparticles can inhibit the growth of UTI pathogens. These particles retain their microbicidal (Figure 8) activity in shampoos, detergent, soaps, shoes, cosmetic products, toothpaste, engineered gloves, face masks, textiles, water bacteriological filters, High Efficiency Particulate Air (HEPA) filters, etc. [92–100].

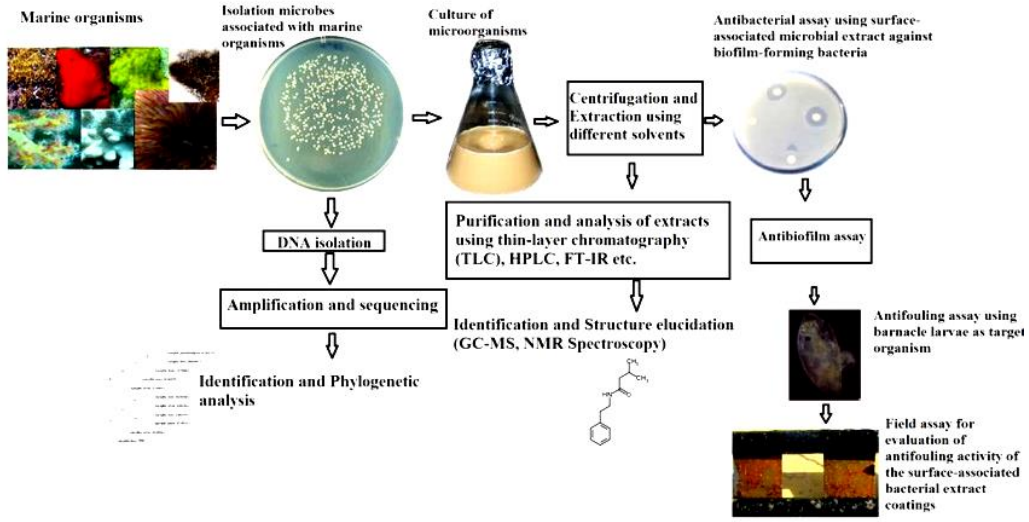

Figure 8. Schematic diagram showing the steps involved in isolation and identification of natural product antifouling compounds from the microbes associated with marine microorganisms.

BIOSYNTHESIS OF SILVER NANOPARTICLES

A recent study outlined the biosynthesis of Ag nanoparticles in an economic way (Figure 8) [93]. The UTI pathogens like *E. coli*, *Enterobacter*, *Shigella* sp., were collected from clinical laboratory and kept at 4°C.

The bacterial culture (100 µl) was spread plated on nutrient agar plates. The well of 4 mm were dug in these plated with cavity borer. The marked wells were filled with 5, 10, and 15 g/ml silver nanoparticles [8, 24, 94]. The plates were kept in an incubator at 37°C overnight. The zone of inhibition (in mm) was measured by authors in all plates [101]. The minimal inhibitory concentrations of these particles were also assayed using the similar procedure (Figure 9).

THERAPEUTIC ROLE OF BIOACTIVE COMPOUNDS FROM NON-CONVENTIONAL MARINE SOURCES

Marine sponges of genera Ircinia have terpenoids with potent pharmaceutical activity. These terpenes generate tetronic acid having microbicidal, analgesic, and anticancer activity [102]. The marine sponges produce halogenated alkaloids as bioactive secondary metabolites marine sponges have potential therapeutic effects [52, 65, 103–106]. The sponge *Dalbergia nigra* and *Ircinia ramosa* have metabolite with antiviral and CNS stimulatory activities [107]. Caribbean sponge named *Tethya crypta* produce marine drugs namely spongothymidine and spongouridine. Deep-sea sponges maintain ecological balance in oceanic biosphere as by the deep-sea corals [76, 82, 108].

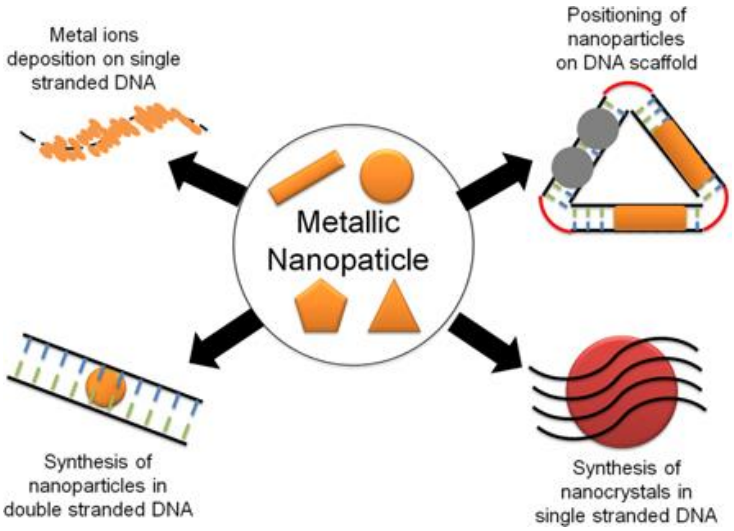

Figure 9. A schematic representation of biosynthesis of metallic nanoparticles.

MARINE BIOACTIVE COMPOUNDS AND THEIR HEALTH BENEFITS

Importance of Seafood

Any form of sea life regarded as food by humans is called sea food, including fish, shellfish, mussel, oyster, scallop, abalone, snail, crab, shrimp, and lobster, etc. [67, 109].

Seafood is tasty, nutritious, and easily available worldwide. Marine products have been identified as being rich in proteins, all the essential amino acids, PUFAs, Calcium, Iodine, vitamins, and many other nutrients [110]. The vastness of oceans accounts for their high level of biodiversity and a logical target for looking for natural products from its lower and higher life forms. Each form is unique as a species and because of their life under different conditions, such as salinity, pressure, temperature, and illumination, they potentially contain different natural products**.**

Sterols from Spirulina

The algal sterols (C_{28} and C_{29} sterols) are essential raw materials for biosynthesis of some important biomolecules such as vitamins, for example, ergosterol for synthesis of vitamin D_2 and cortisone [106]. *Spirulina* has been reported to produce 'clionasterol' a sterol associated with formation of plasminogen-activating factor in endothelial cells of vascular system. The different brown and red algae have been cultivated at commercial level to produce Sargasterol and Fucosterol [107].

Health Benefits of Seafood as a Source of Antioxidants

Synthetic antioxidants viz. butylated hydroxy anisole/toluene, 3^o-butylhydroquinone, etc., have been generally used for human consumption. However, strict medical regulation in developed countries forbid use of these synthetic compounds due to their health hazards. The Eicosa-Hexanoic acid derived from omega-6 PUFAs is fish oil based antioxidant. It has pro-inflammatory and immunogenic properties. However, eicosanoids derived from omega-3 PUFAs (EPA and DHA) have been reported to be anti-inflammatory. Unfortunately, the ratio of omega-6 PUFAs is higher in our diets in comparison with omega-3 PUFAs [106, 108, 112]. Use of EPA and DHA rich diet is beneficial in management of arthritis by subsiding inflammation better than the nonsteroidal anti-inflammatory drugs (NSAID). For that reason, the increase of the (DHA + EPA)/AA ratio deceases the inflammatory mediators. The omega-3 fatty acids are also known to inhibit the activity of the pro-inflammatory transcription factor nuclear factor κB (NF-κB), which induces the expression of many pro-inflammatory genes that encode adhesion molecules (for example, intercellular adhesion molecule 1), cytokines, chemokines, and other effectors of the innate immune response [68, 79]. Different research has been conducted on patients with rheumatoid arthritis (RA), which is an autoimmune disease characterized by flare-ups of arthritis involving ball-and-socket joints (Figure 10).

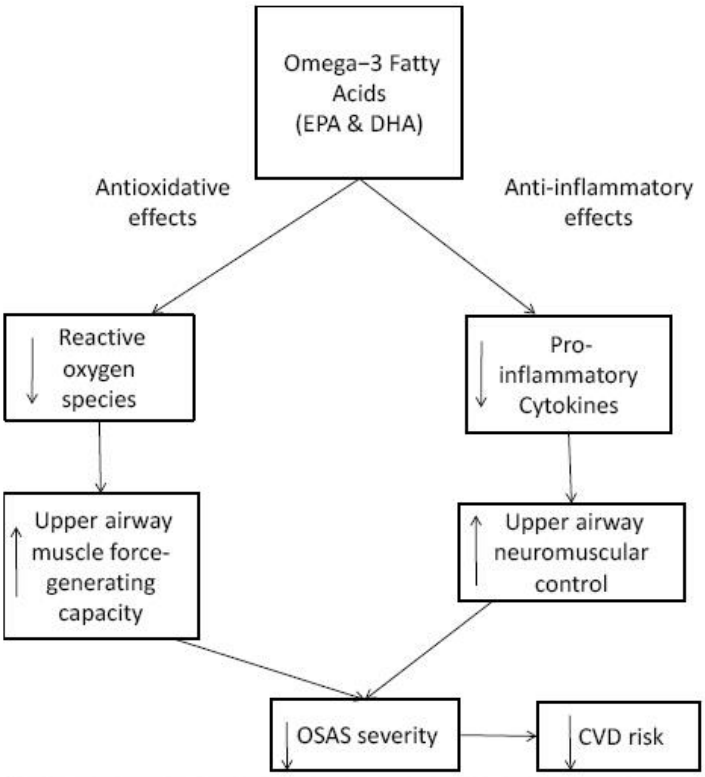

Figure 10. Flow chart indicates the possible mechanisms through which the marine omega 3 fatty acids may improve OSAS severity and reduce CVD risk.

CONCLUSION

Marine-derived micro and macrobiota constitute a rewarding resource of novel metabolites with potential pharmaceutical, therapeutical, antimicrobial, and nutraceutical potential. Increasing use of pesticides, insecticides, advent of industrial pollution, malnutrition, and various other factors have alarmingly increased the occurrence of cancer. The marine bioactive compounds may also act as precursor for synthesis of semi-synthetic drug reducing the side effects to human beings. The marines can provide an alternative to the terrestrial microbes in providing potent, cheaper, novel, and safer anticancer/bioactive molecules. Because of their broad spectrum of bioactivities (discussed in detail in preceding text) mariners have potential applications in the different industries at the scale up levels. Biosynthesized metal nanoparticles have potent and high-antibacterial activities with minimum side effects to human patients. Marine resources offer important bioactive molecules that have advantages on the human body. The marine metabolites may find their application in fields of drug designing, cosmetic making, and food industries. The sea, still less explored, may be an enormous source for unlimited metabolites useful to mankind.

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