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Marine Resources for Marine-Derived Drugs: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The oceans are the world's most important sources of biological activity, water, and biomass production. They supply food, oxygen, and other natural products critical for human existence, and interactions between the oceans and the climate. The oceans serve as the world's greatest reservoir of biodiversity, including marine mammals, fish, crustaceans, molluscs, and countless species of zoophytoplankton. The ocean is a key source of organisms that are beginning to provide new and potent drugs for the treatment of human disease, as well as new products that use in biotechnology. Ocean can support human health, through providing new sources of drugs to treat human disease. Bioactive metabolites derived from marine organisms provide a rich source of chemical diversity that can contribute to design and development of new and potentially useful pharmaceutical agents. The marine ecosystem possesses efficient pharmaceutical materials to identify, isolate and characterize new compounds suitable for therapeutic purposes. Marine sponges, tunicates, fishes, soft corals, nudibranchs, sea hares, molluscs, echinoderms, bryozoans,

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prawns, shells, sea slugs, and marine microorganisms are sources of bioactive compounds. The current review is designed to collate all currently available data about the marine drugs with respect to sources, classification, chemical classes, metabolites of marine algae, fungi, bacteria and invertebrates, techniques for separation and isolation, and examples. This review aims to provide a holistic, multidisciplinary account of the current state of affairs on this topic.

Keywords: Biodiversity; cancer; mangroves; marine bioactive metabolites; marine organisms; pharmaceuticals; seaweeds.

1. INTRODUCTION

"World's oceans cover about 70% of the earth's surface and represent 28 major animal phyla. Marine compounds are underrepresented in routine clinical practice. On the other hand, aquatic environment may become a potentially valuable source of novel compounds" [1]. "Drug discovery based on marine biodiversity has been a relatively rapid growing field over the last five decades"

Biodiversity provides the foundation in nature for the production of diverse chemical compounds now used to treat human disease. Today, about one-half of all cancer drug discovery focuses on marine organisms, and over 6,000 structurally unprecedented and highly bioactive metabolites have been isolated from marine plants and animals" [2-4].

According to Pomponi [5], marine plants, animals, and microbes produce unique chemicals and metabolites for their defence, reproduction, and communication. These metabolites also interact with receptors and enzymes involved in human disease processes. They also prevent the cells of other organisms from growing and dividing. Therefore, they may also be effective in inhibiting the uncontrolled growth of cancer cells [6].

Jimenez et al [7] reported that, "7 marine-based pharmaceuticals have been approved for marketing, 23 compounds are in clinical trials and over one thousand compounds isolated from marine organisms are undergoing preclinical studies". "4 compounds derived from marine organisms like cytarabine, trabectedin, eribulin mesylate and the conjugated antibody brentuximab vedotin are used in the treatment of cancer" [8, 9].

"Marine organisms (algae, bacteria, molluscs, soft corals and sponges) produce chemical compounds with beneficial medical and industrial uses. These chemicals and natural products can be developed as pharmaceuticals, nutritional supplements, medical diagnostics, cosmetics, agricultural chemicals (pesticides and herbicides), enzymes and chemical probes for disease research, and for many other applications" [10, 11].

Montalvao [12] reported that "extracts from microalgae showed the antimicrobial results against *Staphylococcus aureus* and fungus *Candida albicans"*. Ciavatta et al [13] stated that, "bryozoans are a source of many pharmacologically important bioactive compounds, which acts as anticancer agents and treatments for brain diseases" [14].

Bhakuni and Rawat [15] noted that "marine natural products exhibit biological activity. Bioactive metabolites of marine flora include brominated phenols, oxygen heterocyclics, nitrogen heterocyclics, sulphur nitrogen heterocyclics, sterols, terpenoids, polysaccharides, peptides and proteins". "These compounds were isolated from marine algae, fungi, bacteria, sponges, jelly fish, sea anemones, corals, bryozoans, molluscs, echinoderms, tunicates and crustaceans. Marine fauna yields bioactive metabolites such as steroids, terpenoids, isoprenoids, nonisoprenoids, quinones, brominated compounds, nitrogen heterocyclics, and nitrogen sulphur heterocyclics" [3, 16,17].

Vinothkumar and Parameswaran [18] summarised that "marine organisms produce secondary metabolites as a technique of chemical defence to live in a highly competitive environment". "Because of recent advances in underwater exploration, natural products chemistry, genome mining and bioassays have led to the search for novel biomolecules from underexploited habitat. As a result, more than 70% of marine metabolites were obtained from marine sponges, corals and microorganisms" [19-21].

Table 1. Structure of the review paper

Section	Details
I	Introduction and Current status of Marine Bioactive Metabolites
II	Literature Search Methods
III	Sources of Marine Natural Products (MNP)
IV	Classification of Bioactive Metabolites based on Therapeutic Category
V	Classes of Marine Natural Products
VI	Bioactive Metabolites of Marine Algae, Fungi and Bacteria
VII	Bioactive Metabolites of Marine Invertebrates
VIII	Bioactive Metabolites of Marine Sponges
IX	Techniques for Separation and Isolation of Bioactive Metabolites
X	Examples of Marine drugs

Lindequist [22] stated that "marine organisms produce specific secondary metabolites as an important adaption to survive in the sea. These metabolites possess biological activities which can be possible drugs for human". "Marine organisms such as the sponges; corals and jellies; sea stars; molluscs; polychaetes; moss animals; flatworms; acorn worms; lamp shells; crustaceans; and vertebrates have been the most important source of bioactive metabolites" [23-25].

"Marine derived pharmaceuticals were used as sources of chemical diversity in drug discovery programs. Marine biotechnology is an emerging field to develop and produce new products in the pharmaceutical industry. Though many compounds were isolated from marine organisms and their biological activities were assessed, those that have either been marketed or are under development are very few" [26, 27].

Lomartire and Gonçalves [28] pointed that, "species of marine algae or seaweeds (phylum Ochrophyta, Rhodophyta and Chlorophyta) are valuable for the food, cosmetic, pharmaceutical and nutraceutical industries; and also used to treat several diseases". "Compounds from seaweeds exhibit antioxidant, antimicrobial, and antiviral activities; and are used for beneficial properties for human health. Due to their non-toxic, edible, cheap and easy culturing properties, macroalgae could replace synthetic compounds with those of natural origin" [29, 30].

Bhatia et al [31] have shown that, "marine drugs are abundant in number, have diverse structures with mechanisms of action, and have scope for the discovery of new drugs for better treatment and management of several acute to chronic diseases". "They show approaches in the treatment of chronic diseases such as cancer, diabetes, neurodegenerative diseases, and cardiovascular disorders"

Marine floras include microflora (bacteria, actinobacteria, cyanobacteria and fungi), microalgae, macroalgae (seaweeds), and flowering plants (mangroves and other halophytes). This vast marine floral resource offers a great scope for discovery of new drugs" [32]. "Mangroves extracts have shown inhibitory activity against human, animal and plant pathogens. They also produce bioactive compounds that show antibacterial activity against pathogenic bacterial strains and control microbial growth. Mangrove extracts is also the sources of mosquito larvicides, antifungal, antiviral, anti-cancer and anti-diabetic compounds" [33].

The aim of current study is to briefly review recent research on drug discovery based on marine organisms. This review provides information applicable to marine drugs with respect to sources, classification, chemical classes, metabolites of marine algae, fungi, bacteria and invertebrates, techniques for separation and isolation, and examples of marine drugs.

2. LITERATURE SEARCH METHODS

The review was carried out through extensive literature search, using website databases, and online search tools, such as EMBASE, Google Scholar, Medline, NCBI, PubMed, Science Direct, Scopus, and Web of Science databases. Data and information was collected from the thorough study of the journal articles, research papers, reports and various literatures. This review paper analysed a total of 38 research articles published in reputed journals. The keywords used for reviewing the literature were the ones that refer to the issues concerning the

'marine bioactive compounds/marine drugs'. For literature search, keyword "marine bioactive compounds/marine drugs" is combined with: sources, classification, chemical classes, metabolites of marine algae, fungi, bacteria, invertebrates and sponges, techniques for separation and isolation, and examples.

3. SOURCES OF MARINE NATURAL PRODUCTS

Avhad and Bhangale [34] noted that, "the organisms producing MNP are divided into three major biological classes such as: marine microorganisms (bacteria, fungi, cyanobacteria, phytoplankton), marine algae (macro-algae/seaweeds: green, brown and red algae) and micro algae (blue green algae, dinoflagellates, bacillariophyta/diatoms), and marine invertebrates (bryozoans, coelenterates, corals, echinoderms, molluscs, sponges, and tunicates)" (Fig.1 and Fig. 2, Table 2).

4. CLASSIFICATION OF BIOACTIVE METABOLITES BASED ON THERAPEUTIC CATEGORY

According to Shadenet al [21] and Lindequist [22], the therapeutic category, marine bioactive metabolites can be classified into various types such as: analgesic, antibacterial, anticancer, anti-inflammatory, antimalarial, antimicrobial, anti-parasitic, antiviral, bone grafting, ca2+-ATPase and histone deacetylase inhibitor, enzyme, molecular probe, and neuro-protective (Table3).

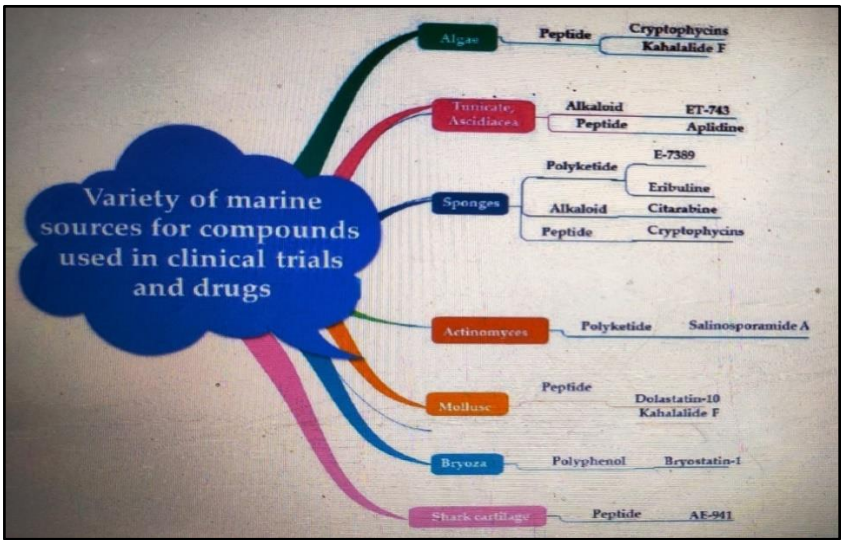

Fig. 1. Sources and chemical nature of marine bioactive metabolites
(Source: [21])

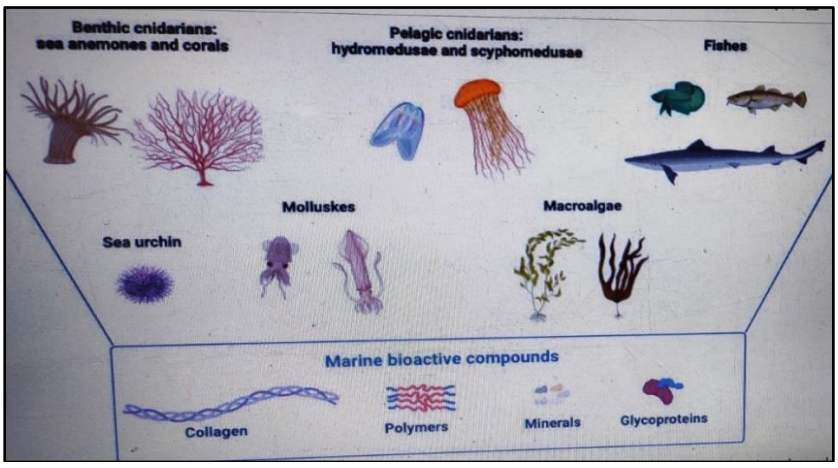

Fig. 2. Sources of marine bioactive compounds
(Source: [35])

Table 2. Sources of marine natural products

Organisms	Examples	Potential Medicinal Applications
Marine snails	Cone snails	Diabetes, chronic pain, Other human illnesses.
	Gastropods snail (Slime snail/ mucus snail)	Treatment of Human skin: Acne, wrinkles and scars, healing of injured skin. Hydration, anti-ageing, dry skin and stretch marks. Protection from free radicals, calms the skin, heals damaged tissues, and restores moisture. Stimulation of collagen and elastin synthesis. Anti-cancer properties and strengthen immune system.
Marine corals	Octocorals (Sea fans, sea pens, soft corals)	Tissue scaffolds, bone implants, Antibacterial, anti-inflammatory and drug delivery agents, Aesthetic and other medical implementations
Marine algae (Phaeophyta, Chlorophyta *rhodophyta*)	Brown, Green and Red algae *Corallina officinalis*	Avoiding malignancies (breast cancer and lung cancer) Used as a food colouring. Control the production of skin oil.
Marine Sponges	*Hyrtios erectus*, *Cryptotethya crypta*	Nucleosides used as building blocks for the creation of: Ara-A: Antiviral medicine, Ara-C: First anticancer drug generated from marine sources
Tunicates	Ascidians, tunicates and sea squirts	Bioactive secondary metabolites with potential uses in biomedicine. Produce potential compounds with anti-bacterial and anti-cancer properties.

Table 3. Classification of bioactive metabolites based on therapeutic category

Therapeutic category	Drugs	Source
Analgesic	Ziconotide (Prialt)	*Conus magus*
Antibacterial	Eicosapentaenoic acid	*Phaeodactylum tricornutum*
Anticancer	Squalimine	Shark
	Bryostatins 1 and 2	*Bugula neritina*
Anti-inflammatory	Topsentin	*Spongosporites ruetzleri*
	Tsitsixenicin A	*Capenella thyrsoidea*
Antimalarial	Manzamine A	*Haliclona sp.*
	Axisonitrile 3	*Acanthella klethra*
Antimicrobial	Cephalosporins Istamycin	*Cephalosporium acremonium*

Therapeutic category	Drugs	Source
		Streptomyces tenjimariensi
Anti-parasitic	α-Kainic acid	*Digenia simplex*
Antiviral	Didemnin B Avarol and Avarone	*Tridemnum sp.* *Disidea avara*
Bone grafting	Orthopedic implants	Coral (Family *Isididae*)
Ca^{2+}-ATPase and histone deacetylase inhibitor	Speradine A	*Aspergillus tamari*
Enzyme Molecular probe	Polyketide synthase Okadaic acid	*Pseudoceratina clavata* *Prorocentrum belizeanum*
Neuroprotective	Extracts of South Indian green seaweed	*Ulva reticulata*

Table 4. Classes of marine natural products

MNP	Definition	Subclasses	Occurrence	Examples	Activity
Alkaloids	Cyclic organic compounds containing nitrogen in a negative oxidation state.	Indole, Pyrrole, Pyridoacrine, Isoquinoline, Gadinine, Aminoimidazole, Sterol alkaloids	Sponges (*Agelas, Axinella, Acanthella, Hymeniacidon, Pseudoaxinyssa*), Tunicates	Oroidin, Nagelamide J, Nagelamide A, Trabectedin	Antimicrobial, Anticancer,
Peptides	Specific protein fragments that act as sources of amino acids and Nitrogen.		Tunicate (*Tridemnum solidum*), Marine sponge (*Discodermia Kiiensis*), Marine cone snail	Didemnin B, Discodermin A, Ziconotide,	Antitumor, Antiproliferative, Antimicrobial, Treatment of chronic pain in spinal cord injury
Polyketides	Low molecular weight compounds assembled via sequential condensations of small carboxylic acids.	Polyethers, Polyenes, Polyphenols, Macrolides, Polyols,	Sponges (*Spirastrella spinispirulifera* and *Hyrtios*), Fungus (*Penicillium* sp),	Eribulin (Halichondrin B), Spongistatin 1, Macrolides, Brefeldin A, Brefeldin C, 7-oxobrefeldin A,	Anticancer, Antimicrobial,
Polysaccharides	Heteropolysaccharides	Agar, Alginates, Agarose, Carrageenans, Fucoidans	Microalgae, Macroalgae, Red seaweeds (Rhodophyta)	Carrageenan,	Anticoagulant, Antitumor, Anticancer, Antibiotic, Antioxidant, Anti-inflammatory Antiviral
Terpenes/	Derived from a five-carbon	Monoterpenes (C10),	Seaweeds (*Laurencia obtuse,*	Manoalide	Antibacterial, Cytotoxic

MNP	Definition	Subclasses	Occurrence	Examples	Activity
Terpenoids	isoprene structure with several functional groups (e.g., isonitrile, dichloroimine, halogenated, isocyanate)	Sesquiterpenes (C15), Diterpenes (C20), Sesterpenes (C25), Triterpenes (C30, steroids), Tetraterpenes (C40, carotenoids)	*Laurencia microcladia*)		

Table 5. Bioactive metabolites of marine algae, fungi and bacteria

Organism	Bioactive metabolite	Occurrence	Activity
Marine Algae	Brominated phenols, (2,3-dibromobenzyl alcohol, 4,5-disulphate dipotassium salt)	Green, brown and red algae, *Symphyocladia gracilis, Rhodomela larix, Polysiphonia lanosa*	Antibacterial, Antifungal
	Brominated Oxygen Heterocyclics (Laurencin, Laureatin, Prelaureatin, Bromofucin)	Red algae (*Laurencia glandulifera, L. nipponica*)	Larvicidal
	Nitrogen Heterocyclics (Domoic acid)	Algae, *Chondria armata*	Antihelmintic (Ascaris and Pinworms)
	Kainic acids	Red algae (*Digenea simplex*, *Corallina officinalis, Digenea*)	Antihelmintic (Ascaris)
	Guanidine derivatives	Marine plankton (*Gonyaulax catenella*), Butter clam (*Californian mussel*)	Neurotropic
	Phenazine derivatives (Caulerpin)	Algae (*Caulerpa lamourouxii, C. sertularioides*)	Anaesthetic
	Amino acids and Amines (Laminine) (Methylamine, Dimethylamine)	Algae (*Laminaria angustata* and *Chondria amata*)	Pharmacological agent
	Sterols (22-Dehydrocholesterol, Demosterol)	Red algae (*Rhodymenia palmata, Porphyra purpurea, P. umbilicalis*)	Reduce blood cholesterol level.
	Sulfated Polysaccharides (Carrageenan, Agar, Agarose, Furcellaran, Alginic acid, Laminarin)	Seaweed (*Chondrus, Eucheuma, Gigartina, Iridea*)	Treatment of gastric and duodenal ulcers.
Marine Bacteria and Fungi	Cephalosporin C, Cephalosporin P, Cephalothin, Prodigiosin	Bacteria (*Pseudomonas piscicida*, *P. bromoutilis*), Fungus (*Cephalosporium acremonium*)	Antibiotic, Antiviral, Antifungal, Anti-yeast, Antimicrobial,

Table 6. Bioactive metabolites of marine invertebrates

Organism	Bioactive metabolite	Occurrence	Activity
Brominated compounds	Aplysin-19, Aplysin-20, Dibromophakellin, Aerothionin,	Marine Sponge (*Dysidea herbacea*, *Verongia cauliformis*) Sea hare (*Aplysia kurodai*), Marine hemichordate (*Balano glossus*)	Antibacterial, Antimicrobial, Antibiotic
Isoprenoids	Furoventalene	Sea fan (*Gorgonia ventalina*)	Antibiotic
Prostaglandins	15-epi-PGA_2, PGA_2, $PGA_{2\alpha}$	Gorgonian (*Plexaura homomalla*)	Fertility control, Labour induction, Renal physiology
Quinones	Naphthaquinones, Rhodocomatulin	Marine fauna	Antimicrobial
Steroids	Crustecdysone, Deoxycrustecdysone, Callinecdysone A, Steroid hormones, Sterols, Saponins,	Crustacean (*Cragon vulgaris*) Crayfish (*Jasus lalandei*) Marine crab (*Callinectes sapidus*), Holothurian (*Halodeima grisea*, *H. vagabunda*)	Neuromuscular, Anticancer, Antibiotic, Cytotoxic, Chemotherapeutic
Terpenoids	Crassin acetate, Eunicin	Gorgonian (*Eunicea mammosa*), Horny corals (*Pseudoplexaura porosa, P. wagenaari*)	Antibiotic, Antibacterial,

Table 7. Bioactive metabolites of marine sponges

Types of Sponge	Bioactive metabolite	Activity
Acanthella spp.	Kalihinol A	Antibiotic
Agelas nakamurai (Okinawan sea sponge)	Agelasidine-A, Keramadine Agelasidine B and Agelasidine C	Antimicrobial Antibiotic
Disidea pallescens	Ent-chromazonarol	
Dysidea arenaria	Arenarol, Arenarone, Illimaquinone	
Dysidea fragilis	Nakafuran-8, Nakafuran-9	Antifeedant
Dysidea species	Hydroxy sterol	
Dysidea, Euryspongia and *Siphonodictyon*	Furanoid sesquiterpenoids	
Halichondria mooriei	Halistanol	Antibacterial
Halichondria panicea	Panicein A, -B1, -B2, -B3, -C	
Hyrtios eubamma	Puupehenone	

Types of Sponge	Bioactive metabolite	Activity
Latrunculia magnifica Marine sponges	Latrunculin A to D Siphonodictyal-A, Siphonodictyal-B	Cytotoxic
Phyllospongia foliascens (Pacific sponge)	Phyllofolactore A and Phyllofoloctone	Antifungal, Antiinflammatory
Plakina spp.	Plakinamine A, Plakinamine B	Antimicrobial
Smenospongia echina	Sesquiterpene phenol	Antimicrobial
Spongia officinalis	Tetracyclic furanoditerpenes	Antifungal, Antimicrobial
Spongia officinalis (Bath sponge)	Terpenoids	
Toxadocia zumi	Sterols	Antimicrobial
Xestospongia exigua (Australian sponge)	Xestospongin A, B, C and D	Antimicrobial

Table 8. Marine drugs with source and use for treatment

Marine Drugs	Source	Use/Treatment
Brentuximab Vedotin	Indian Ocean gastropod (*Dolabella auriculria*)	Anticancer
Cytarabine (Cytosar) (Cytosine arabinoside or Arabinosyl cytosine, Ara-C)	Caribbean sponge (*Tectitethya cript*) (*Cryptotethya crypta*)	Types of leukemia (Acute myelocytic leukemia, Lymphocytic leukemia, Meningeal leukemia, Chronic myelogenous leukemia)
DMXBA (GTS-21) [3-(2,4-dimethoxybenzylidene)-anabaseine]	Marine worms of Phylum Nemertea	Schizophrenic patients
Elisidepsin (PM02734)	Marine fauna of Kahalalide family	Antitumor, Cytotoxic
Eribulin mesylate (E7389), Halichondrin B	Marine sponges (*Halichondria okadai*)	Irreversible antimitotic activity, Cell death.
Marizomib (Salinosporamides A)	Marine Actinomycete (*Salinispora tropica*)	Anticancer
Omega vit -369	Marine fishes (Mackerel, Herring, Tuna, Salmon)	Reduce discomfort and swelling, Prevent blood clotting
Plitidepsin (Aplidine)	*Aplidium albicans*	Anticancer
PM00104 (Zalypsis)	Pacific Nudibranch (*Jorunna funebris*)	Antitumor
Trabectedin	Caribbean ascidian (*Ecteinascidia turbinate*)	Anticancer, Soft-tissue sarcoma, Platinum-sensitive ovarian cancer
Vidarabine (Adenine arabinoside, Ara-A or Arabinofuranosyladenine)	Caribbean sponge (*Tethya crypta*)	Antiviral, Recurrent epithelial keratitis, Acute kerato-conjunctivitis, Superficial keratitis,
Ziconotide (PRIALT)	Venom of marine snail (*Conus magus*)	Analgesic, Relieve chronic pain,

5. CLASSES OF MARINE NATURAL PRODUCTS

Avhad et al [34] and Montalvao [12] reported that the MNP divided into seven classes based on their chemical structure. These classes include Alkaloids, Ethers (including ketals), Peptides, Phenols (including quinones), Steroids (including steroidal saponins), Strigolactones, and Terpenes/Terpenoids.

6. BIOACTIVE METABOLITES OF MARINE ALGAE, FUNGI AND BACTERIA

Bhakuni and Rawat [15] reported that marine algae, fungi and bacteria generate various types of bioactive metabolites having varying occurrence and biological activity (Table 5).

7. BIOACTIVE METABOLITES OF MARINE INVERTEBRATES

According to Bhakuni and Rawat [15], "among invertebrates, bioactive metabolites have been generated by marine sponges, jelly fish, sea anemones, corals, bryozoans, molluscs, echinoderms, tunicates and crustaceans". "Various bioactive metabolites isolated from marine invertebrates include, brominated compounds, isoprenoids, nitrogen heterocyclics, nitrogen sulphur heterocyclics, nonisoprenoids, prostaglandins, quinones, steroids, and terpenoids" [15] (Table 6).

8. BIOACTIVE METABOLITES OF MARINE SPONGES

Marine sponges are a good source of bioactive metabolites such as: Halistanol, Sterols, Hydroxy sterol, Plakinamine A, Plakinamine B, Furanoid sesquiterpenoids, Nakafuran-8, Nakafuran-9, Agelasidine-A, B, and C; Arenarol, Arenarone, Illimaquinone, Ent-chromazonarol, Kalihinol A, Keramadine, Latrunculin A to D, Panicein A, -B1, -B2, -B3, -C; Phyllofolactore A and Phyllofoloctone, Puupehenone, Sesquiterpene phenol, Siphonodictyal-A, Siphonodictyal-B, Terpenoids, Tetracyclic furanoditerpenes, and Xestospongin A, B, C and D [10] (Table 7).

9. TECHNIQUES FOR SEPARATION AND ISOLATION OF BIOACTIVE METABOLITES

"Bioactive secondary metabolites produced by marine organisms consist of mixture of several classes of compounds. Chemically, these compounds could be divided into amino acids, peptides, nucleosides, alkaloids, terpenoids, sterols, saponins, and polycyclic ethers. A broad separation of the mixture of metabolites can be achieved by fractionation with organic solvents" [26].

"Various separation techniques used includes separation of water soluble constituents either by desalting, ion-exchange chromatography, reverse-phase (RP) columns, high/medium pressure chromatography, or combination of ion-exchange and size-exclusion chromatography. Mixture of metabolites can also be separated by following bioassay directed fractionation, general fractionation, or isolation procedures for amino acids and simple peptides, peptides, nucleosides, cytokinins, and alkaloids" [8].

10. EXAMPLES OF MARINE DRUGS

Avhad et al [34], [31], and Navgire [25] reported that, at present various categories of marine drugs were used for treatment of different ailments of human. Commonly used marine drugs include: brentuximab vedotin, cytarabine, DMXBA, elisidepsin, eribulin mesylate, marizomib, omega vit -369, plitidepsin, PM00104, trabectedin, vidarabine, and ziconotide. Different marine drugs with their source and application for treatment of human diseases are shown in Table 8 [36].

11. CONCLUSION

The review indicates that in recent years the systematic research has led to the isolation, identification and characterization of many new bioactive metabolites of pharmaceutical. They are used for the treatment of various ailments such as increased levels of cholesterol, viral and protozoan infections, inflammation, and cancer etc. It is recommended that, more basic and applied research should be conducted on to discover more substances used in pharmaceutical industry. We aim in this review to bring attention of researchers those interesting in bioactive compounds for developing the pharmaceutical materials.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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