



Bioprospecting Potential of Marine Microbial Natural Bioactive Compounds

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Abstract

The ocean is considered to be an immense reservoir of biological and microbial diversity on the planet. In marine biospheres, microbial communities are ecologically significant as intermediaries of energy. By decomposing the dead as well as decaying organic matter with the assistance of microbial communities, it plays an indispensable role in nutrient regeneration cycles of marine ecosystems. Marine environments associated with microorganisms such as bacteria, fungi and bacterial virus have renowned potential to produce novel bioactive natural products and chemically diverse secondary metabolites like antibiotics, antifungal, antiviral, antitumor, anticancer and also different hydrolyzing enzymes, namely, protease, lipase, amylase, chitinase, etc. Hence, the bioprospecting for these compounds is of greater importance. Numerous effective and efficient application of marine microbial metabolites contribute to the fields of pharmaceuticals, biotechnological, agricultural, cosmetics industries, and so on. This review attempts to summarize the present status of bioprospecting marine microorganisms and their role in natural product discovery.

Keywords: Natural Products, Marine Bacteria, Fungi, Bacterial Virus, Enzyme

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Introduction

The oceans cover more than 70% of our blue planet, and biological evolution began several million years earlier on land.¹ Still, the oceans and the marine organisms have not been adequately explored.² The targeted and precise exploration for bioactive secondary metabolites as well as genes with marine organisms for the purpose to be used as products is called marine bioprospecting,³ which has an extensive range of applications *viz*, medicine, cosmetics, molecular probes, enzymes, agrichemicals, nutritional supplements, etc.⁴ Bioprospecting is performed on the marine organisms; including microorganisms like bacteria, viruses, fungi, and larger organisms such as sea plants, fish and shellfish.⁴⁻⁷ Marine bioprospecting provides opportunities to utilize resources from the sea in a sustainable way.⁸ Due to the remarkable performance in biogeochemical processes of marine environment, bacteria, fungus and virus communities are considered as an important ecological component throughout the ocean.⁹ Different types of enzymes, amino-acids, antibiotics, vitamins and alcohols can be produced

commercially by making use of elite microorganisms.¹⁰⁻¹² In recycling of various life-saving ingredients such as, oxygen, nitrogen, carbon, sulphur, phosphorus, etc., microorganisms play a vital role and are also able to hydrolyze different hydrocarbons.¹³⁻¹⁶ In the last century, a very large number of pathogenic microbes have isolated from various sources and their biocontrol measures have been identified by certain microbes. It is estimated that about half of the biomass on earth is microbial life.^{8,17,18} Microbial activity is extensive in nature and varies from the development of various types of infectious diseases in plants, animals, and human to the synthesis bioactive compounds, bioleaching of heavy metals, biodegradation of organic and recalcitrant compounds, and also enhancing soil fertility.¹⁹ Many of the potential pharmaceutical candidates have been explored from marine-derived microorganisms.²⁰⁻²² At different phase of pharmaceuticals development, pharmaceutical companies utilize marine organism dependent classical knowledge.²³ As compared to the estimated microbial communities, the availability of potential marine microorganisms is still poor.

For this reason, discovery of fresh potential microbes from intriguing environments such as coral reefs ecosystems for the retrieval of new marine microorganisms is time demanding. This approach might help in exploring a bunch of potential microbial symbionts with the presence of metabolite secreting capabilities.²⁴ During the last hundreds of years, different types of potential bioactive natural products have been explored from terrestrial microbial communities.²⁵ It has also been recorded in recent decades that the volume of new natural products from terrestrial microbes has significantly diminished. This means, research on the untapped elite marine microbial communities as well as resources may enhance the rates of exploring new era of bioactive natural products.²⁶ Specifically, screening of bioactive natural products producing marine microbes are very much important for exploring their biotechnological potential.²⁷ Keeping this view in mind the main objectives of this review was to explore the bioprospecting marine microorganisms and to find out antimicrobial compounds and other metabolites produced by marine microorganisms.

Marine Bioprospecting

Marine bioprospecting can be defined as “the systematic inquiry for interesting and novel genes, metabolites, molecules, and organisms from the marine environment that might be useful to the society and have economic potential to commercial product development”.²⁸ Marine bioprospecting is compatible with comprehensive sectors and activities, like pharmaceutical, agricultural, biotechnology, cosmetics industries, bioremediation, biodegradation, health, biomonitoring, mining, fuel production from biomass, pulp and paper processing, etc.²⁹ During extreme survival condition, marine microorganisms produce various types of bioactive compounds to accomplish their defense, offence, and signaling mechanisms. Now a days, bioprospecting of marine biogenetic resources has increased manifold compared to terrestrial biogenetic resources.³⁰ Thus it holds promises for drug development and higher probability of commercial success.³¹

The Scope of Marine Bioprospecting

Investigators started bioprospecting cruises since the early 1990s for the sampling and commercialization of new marine biotech products.³² According to the Convention on Biological Diversity (CBD), the “marine bioprospecting basically consists of procuring and examining marine derived biological samples and identifying potentially commercial products developed from marine genetic materials”.³³ However, enzyme bioprospecting is a research method for the discovery of novel biocatalysts.³⁴ Marine organisms such as microbes, plants or animals represent the enzyme source.³⁵ Marine enzymes may have novel chemical and stereo-chemical properties. Leary et al³⁶ reported the scientific and commercial interests of marine genetic resource. Research on bio-markers is also an important field of marine bioprospecting because of its ability to pollution monitoring.³⁷ Study on marine microorganisms having novel physiological characters might be a dynamic tool for exploring potential enzymes.³⁵ Till now, scientists are able to extract some potential enzymes namely; cellulose, peroxidase, protease and chitinase from promising marine bacteria in *in vitro* conditions.³⁸ Variation in the number of new marine natural products from 2010 to 2019 are presented in Figure 1.

Antibiotic Activity of Potential Marine Bacteria

Due to misuse of antibiotics in humans and animals, many pathogenic bacteria are becoming resistant to a multiple group of antibiotics and is becoming one of the major threats to the world.³⁹ The necessity for new potential antibiotics has stimulated the exploration of untapped marine environments for novel bioactive natural products. Numerous marine invertebrates as well as macroalgae were the primary source of marine natural products²⁶ and have successfully provided numerous bioactive compounds.⁴⁰ Moreover, marine-derived bacteria, roughly in total of 1×10^{29} cells in the marine environment,⁴¹ have played a major role as marine bioprospecting by contributing up to 38% of enlisted natural products annually.⁴² In 2010, marine bacteria contribute to

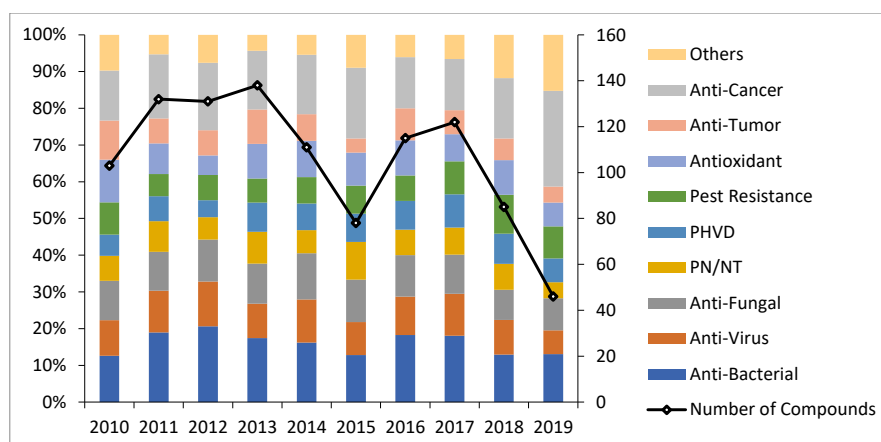


Figure 1. Variation in the Number and Proportion of the 10 Bioactive Compound Groups Isolated From Different Types of Marine Sources, 2010–2019 (PHVD: Prevention of heart and vascular disease, PN/NT: Protection of neurons/neurotoxicity).

about one-fifth of new compounds in the list of microbial metabolites database, AntiBase.⁴³

The prokaryotic and prokaryote–eukaryote symbiotic relation in nutrient-rich environments and complex niches⁴⁴ create a competitive habitat that can be selected for screening potential bioactive microorganisms.²⁴ Accordingly, a large number of antibiotic-producing bacterial strains discover from different eukaryotic hosts, including corals, sponges, macroalgae, zooplankton, bryozoans, mollusks, fish, etc.⁴¹ Although marine bacteria from several taxonomic groups can produce antibiotics, but Actinobacteria, Gammaproteobacteria and Alphaproteobacteria group associated bacteria contribute to a huge amount of antibiotics compared to others (Figure 2).³⁴ Surprisingly, marine bacterial antibiotics have identical chemical scaffolds rather than terrestrial sources.

Marine Habitat as a Source of Enzymes

The metabolic activity of marine enzymes is dependent on the ecological features of their habitat. Conventional enzymes are fully degraded under the inflexible situations in which thermophilic enzymes can successfully operate. One of the latest biotechnological issues is the synthesis and production of polyhydroxy-alkanoates by halophilic marine microorganisms.⁴⁶ Because of reducing water activity, the organic and salt tolerance nature is very often noticed in halophilic enzymes.³¹ The enhancement of thermostability in marine microbes can be observed.⁴⁷ Thermostability is higher in marine microbes than in freshwater species. The osmoregulation depends on the synthesis and aggregation of compatible solutes without interfering the nature of enzymes. In marine animals, D-alanine is engaged in the response of osmotic stress.⁴⁸ Besides, extremophilic archae derived enzymes are resistant to extreme proteolytic attack and also have higher stability towards temperature, pressure and solvents.¹⁹ The potential biotechnological applications of the piezophiles are examined in contrast with those of other extremophiles.⁴⁹ Pressure regulated operons in barophiles have a relationship between high temperature, pressure and microorganisms growth.⁴⁴ Several studies have

been performed for screening antimicrobial compounds producing microorganisms isolated from different types of natural sources such as in sediments,⁵⁰ hydrothermal vents,⁵¹ eukaryotic marine organisms,⁵² plants,⁵³ and seawater.⁵⁴ This comprehensive screening approach has successfully isolated and identified promising improved antibiotics.⁵¹ Several studies have revealed that marine sediments harbor diversified microbial communities and have the potential to produce different polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS) enzymes with antibacterial and antitumor activity (Table 1).

Marine Actinomycetes Symbionts as a Source of Prolific Marine Natural Products

Numerous number of marine microorganisms continuously degrade various materials within the marine ecosystem.⁶⁴ Besides, marine actinobacteria play a vital role in contributing to the breakdown as well as recycling organic compounds in the surrounding marine environments.⁶⁵ In pharmaceuticals and cosmetics industries, marine microbial metabolites also remain as a vital resource. Among all the potential resources of bioactive natural products, marine-derived bacteria have proven to be precisely prolific resources accounting for most of the explored bioactive compounds.⁶⁶ Among all the bacterial phyla, only five of them are able to produce diversified bioactive natural products.⁶⁷ Surprisingly, Actinobacteria which belong to the order of Actinomycetales (also known as actinomycetes) consist of a diversified range of Gram-positive bacteria,⁶⁸ account for almost 7000 of the bioactive natural products recorded in the Natural Products Dictionary. The genus *Streptomyces* alone accounts for 80% of the total actinomycetes in the world and contributes a lion's share in producing promising antibiotics.⁶⁸ Feling et al⁶⁹ recommended extension of the research for discovering new marine actinomycetes and their potential metabolites. Several studies have been carried out to isolate actinomycetes from marine environments and several genera have been reported.⁶⁴ From the marine habitat, *Actinomycetes*, *Actinopolyspora*, *Micro-monospora*, *Micropolyspora*, *Nocardia*, *Rhodococcus*,

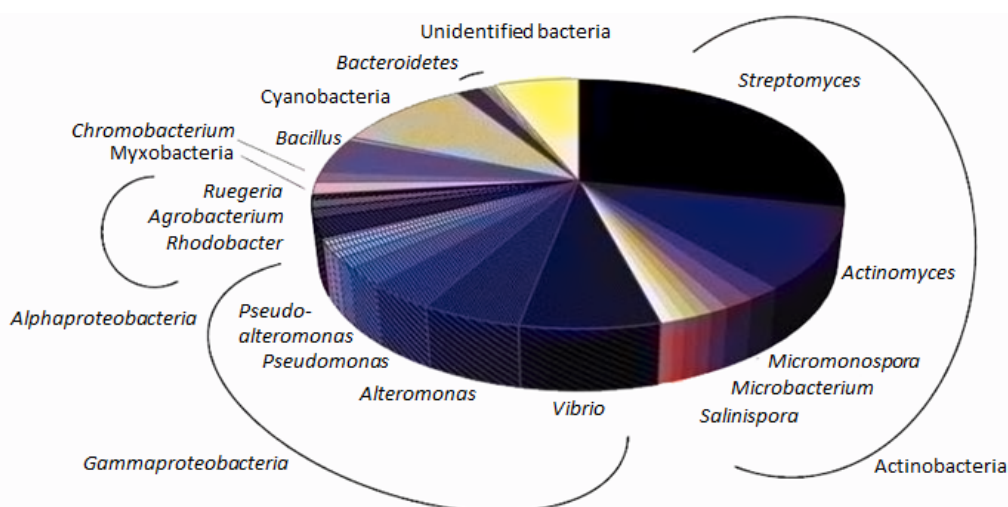


Figure 2. Distribution of Antibiotic Producing Marine Bacteria Under Their Corresponding Taxonomic Group.⁴⁵

Streptomyces, *Streptosporangium* and *Streptoverticillium* have been reported so far. They are capable of producing many bioactive compounds, including different types of antibiotics. These antibiotics have unique features compared to terrestrial ones.⁶⁵ Marine actinomycetes have different physiological, biochemical and molecular characteristics than terrestrial actinomycetes which have the potential to produce a variety of biologically active enzymes.⁴⁰ The utilization of marine-derived actinomycetes bacteria, as a source for promising bioactive natural products, and the exploration rate of novel secondary metabolites from them has recently surpassed compared to terrestrial counterparts.⁶⁶ In this aspect, more attention and systematic investigation is needed on novel antibiotic producing actinomycetes.⁶⁸ This means it will be easy to discover more potential metabolites with a higher hit rate from marine environment. A list of potential metabolites produced by marine actinomycetes symbionts within 2013 to 2019 are presented in Table 2.

Marine actinomycetes also produce a number of other economically important enzymes that have not been listed in Table 2 such as peroxidases, dextranase, laccases, nitrile hydratase, cutinase and alginate lyases (Table 3). Actinomycetes are also one of the common cellulase producing microorganisms. The starch degrading amyolytic enzymes, namely, amylase has great importance in agricultural, industrial and biotechnological applications like fermentation of food, textile and also paper industries.¹²⁴ Lipase has a wide range of applications in various sectors such as, food, pharmaceutical, oleochemical, cosmetics, detergent industries and also in diagnostic purposes.¹²⁵ It also has application in biopolymers and biodiesel synthesis.⁸

Marine Bacterium as a Source of Protease Inhibitor

Protease inhibitors (PIs) have been widely used as highly potential antiretroviral therapy applied for the treatment of abnormally active protease mediated diseases and have also been used in the field of agriculture as well as fisheries.¹³⁸ Nowadays, they have been isolated from marine microorganisms. PIs producing marine bacterium (*Pseudoalteromonas sagamiensis*) have been isolated, identified and characterized from neritic seawater of Japan which are able to produce PIs only in the presence of saline water. This strain simultaneously produces simple peptides named marinostatin and a glycoprotein named monastatin

as PIs.

Coral Reef Associated Fungal Symbionts as a Source of Natural Products

Fungi are widely distributed in marine environments and are found in almost all kinds of living and dead organic matter. In compared to marine bacteria, the fungal distribution in the marine environment is comparatively limited. Investigations demonstrated that different types of marine sponge, coral, marine algae harbor different species of marine fungi such as, *Aspergillus*, *Penicillium*, *Fusarium*, *Trichoderma*, *Phoma*, and *Acremonium*.^{139,140} However, marine fungi are vital sources of metabolites due to their complex genetic background, chemo-diversity and high yield of natural products.¹⁴¹ As compared to their high species biodiversity, the discovery rate of marine habitats associated with novel fungi is still insufficient.^{24,142} Likewise, the global marine fungal diversity and their distribution pattern is not explored completely. The possibilities of isolating new fungal strains under various taxonomic groups from marine samples remain high.¹⁴³ Previously, an active metabolite sorbicillactone A, which was active against the human leukemia cell line, was discovered from a marine fungal isolate *Penicillium chrysogenum*.¹⁴⁴ Till now, marine organisms associated with fungi have contributed a significant proportion among the discovered elite bioactive natural products. Continuous research on this field have explored a large number of novel metabolic compounds such as, the alkaloids, macrolides, terpenoids, peptide derivatives, and so on from the marine-derived coral reef associated fungal strains. Up till now, about 8600 bioactive compounds are isolated from marine fungi.¹⁴⁵ Among all the marine derived fungi, the *Aspergillus* sp. fungi contribute about 31% of the total natural products of the marine fungal communities.¹⁴¹ Meanwhile, marine fungi have exclusive significance to be an important resource for pharmaceutical industries.¹⁴⁶ Potential natural products isolated from marine sponge associated fungi are presented in Table 4.

Potential Applications of Marine Bacterial Viruses

Viruses are the dominant component of most of the aquatic ecosystems and are more common in the marine environment. Virus population biodiversity is almost unexplored.^{161,162} Viral growth is abundant in deep sea sediments and controlled by complex interactions with both biotic and abiotic

Table 1. Bioactive Compounds Derived from Marine Microbes

Enzyme	Bioactive Compound	Producing Species	Activity
PKS	Bryostatin ⁵⁵	<i>Candidatus Endobugula sertula</i>	Antitumor
	Macrolactin ⁵⁶	<i>Bacillus amyloliquefaciens</i>	Antibacterial
	Mupirocin ⁵⁷	<i>Pseudomonads fluorescens</i>	Antibacterial
	Salinilactam A ⁵⁸	<i>Salinispora pacifica</i>	Antitumor
	Pederin ⁵⁹	<i>Paederus fuscipes</i>	Antitumor
NRPS	Surfactin ⁶⁰	<i>Bacillus subtilis</i>	Antibacterial
	Bacitracin ⁶¹	<i>Bacillus</i> spp.	Antibacterial
	Retimycin ⁶²	<i>Salinispora arenicola</i>	Antitumor
	Salinosporamide K ⁶³	<i>Salinispora pacifica</i>	Antitumor

Table 2. Novel Bioactive Compounds Produced by Marine-derived Actinomycetes within 2013 to 2019

Source Strain	Compound	Chemical Group	Activity
<i>Actinoalloteichus cyanogriseus</i> ⁷⁰	Cyanogramide	Spirocyclic alkaloid	Multidrug-resistance reversing activity
<i>Actinoalloteichus cyanogriseus</i> ⁷¹	Cyanogrisides E–H	Acyclic bipyridine glycosides	Cytotoxicity
<i>Actinokineospora</i> sp. ⁵²	Actinosporins A and B	O-glycosylated angucyclines	Active against <i>Trypanosoma brucei</i>
<i>Actinomadura</i> sp. ⁷²	Halomaduronones A–D	Halogenated electrophilic pyrones	Potent Nrf2-ARE activation
<i>Actinomadura</i> sp. ⁷³	Forazoline A	Polyketides	Anti-candida activity
<i>Actinomycetospora chloral</i> ⁷⁴	Thiasporines A–C	Thiazine and Thiazole Derivatives	Cytotoxicity
<i>Amycolatopsis</i> sp. ⁷⁵	Amycolactam	Indole alkaloids	Cytotoxicity
<i>Amycolatopsis</i> sp. ⁷⁵	Amycocyclopiazonic acid	Cyclopiazonic acid	Modest cytotoxicity
<i>Amycolatopsis</i> sp. ⁷⁵	Amycofuran	Benzofuran glycoside	Modest cytotoxicity
<i>Dermacoccus abyssi</i> ⁷⁶	Dermacozines H–J	Heteroaromatic phenazines	Radical scavenging activity
<i>Kribbella</i> sp. ⁷⁷	Kribellosides A–D	Alkyl glyceryl ethers	Antifungal and RNA 5'-triphosphatase inhibitor
<i>Microbacterium sediminis</i> ⁷⁸	Microbacterins A and B	Peptaibols	Potent cytotoxic activity
<i>Microbacterium</i> sp. ⁷⁹	Microindolinone A	Novel indole	No anti-allergic and anti-proliferative activities
<i>Micrococcus</i> sp. ⁸⁰	Microluside A	O-glycosylated xanthone	Antibacterial activity
<i>Micromonospora carbonacea</i> ⁸¹	Tetrocarcin Q	Spirotetronate glycoside	Moderate antibacterial activity
<i>Micromonospora harpali</i> ⁸²	22-dehydroxymethyl-kijanolidide	Spirotetronate glycoside	No antibacterial activity
<i>Micromonospora harpali</i> ⁸²	8-hydroxy-22-dehydroxymethyl-kijanolidide	Spirotetronate glycoside	No antibacterial activity
<i>Micromonospora harpali</i> ⁸²	Microsporanates A–F	Spirotetronate glycoside	Antibacterial activity
<i>Micromonospora harpali</i> ⁸²	Tetrocarcin P	Spirotetronate glycoside	Antibacterial activity
<i>Micromonospora matsumotoense</i> ⁸³	Paulomycin G	Glycosylated paulomycins	Strong cytotoxic activity
<i>Micromonospora</i> sp. ⁸⁴	Levantilide C	20-membered macrolide	Antiproliferative activity
<i>Micromonospora</i> sp. ⁸⁵	Micromonolactam	Polyene macrocyclic lactam	No antimicrobial activity
<i>Micromonospora</i> sp. ⁸⁶	Butremycin	Polycyclic tetramic acid macrolactams	Weak antibacterial activity
<i>Micromonospora</i> sp. ⁸⁷	5'-Methylthioinosine	Protonated aromatic tautomer	No antibacterial activity
<i>Micromonospora</i> sp. ⁸⁸	MBJ-0003	Hydroxamate	Moderate cytotoxicity
<i>Micromonospora</i> sp. ⁸⁹	Isopimara-2-one-3-ol-8,15-diene	Pimarane Diterpene	Weak cytotoxicity
<i>Micromonospora</i> sp. ⁸⁹	Lagumycin B, Dehydrorabelomycin, Phenanthroviridone, WS-5995 A	Angucyclines	Cytotoxicity
<i>Micromonospora</i> sp. ⁹⁰	Micromonohalimane A and B	Halimane-type diterpenoids	Modest antibacterial activity against MRSA, bacteriostatic
<i>Micromonospora</i> sp. ⁹¹	Quinoline alkaloid	Alkaloid	Antibacterial activity
<i>Micromonospora</i> sp. ⁹²	1,4-dioxane derivative	Dioxane	Antibacterial activity
<i>Nesterenkonia flava</i> ⁹³	Nesterenkoniane	Novel cyclic ether	Anti-allergic activity
<i>Nocardia alba</i> ⁹⁴	(Z)-1-((1-hydroxypenta-2,4-dien-1-yl)oxy)anthracene-9,10-dione	glycopeptide	Antiviral
<i>Nocardioopsis alba</i> ⁹⁵	Isomethoxyneihumicin	Lactam-lactim tautomers	Strong cytotoxicity
<i>Nocardioopsis</i> sp. ⁹⁶	Nocardioopsins C and D	Prolinyl-macrolactam polyketides	Not specified
<i>Nocardioopsis</i> sp. ⁹⁶	Nocardiopyrone A	α -pyrone polyketide	Not specified
<i>Nocardioopsis</i> sp. ⁹⁷	Nocardiamide A and B	Cyclic hexapeptides	Antimicrobial activity
<i>Nocardioopsis</i> sp. ⁴⁵	Nocapyrones H–J	α -pyrones	Pro-inflammatory factor, stronger inhibitory effect on nitric oxide
<i>Nocardioopsis</i> sp. ⁹⁸	Nocapyrone R	α -pyrones	No cytotoxicity
<i>Nocardioopsis</i> sp. ⁹⁹	Diketopiperazine 1	Diketopiperazine	Sterol O-acyltransferase inhibitor
<i>Nocardioopsis</i> sp. ¹⁰⁰	Nocarimidazoles A and B	4-aminoimidazole alkaloids	Weak antibacterial activity
<i>Nocardioopsis</i> sp. ⁹²	Compounds 1–12	Benzamides, Indoles	Antibacterial, antifungal and cytotoxic activities

Table 2. Continues

Source Strain	Compound	Chemical Group	Activity
<i>Nocardiopsis</i> sp. ¹⁰¹	Nocapyrones O–S	α -pyrones	Cytotoxicity
<i>Nocardiopsis</i> sp. ¹⁰²	Nocazines F and G	Diketopiperazine	Excellent cytotoxicity
<i>Nocardiopsis</i> spp. ¹⁰³	α -pyrones 1–8	α -pyrones	Moderate antibacterial activity
<i>Nocardiopsis</i> sp. ¹⁰⁴	α -pyrone	Polyketides	Antibacterial activities
<i>Nocardiopsis</i> sp. ¹⁰⁵	1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane	Nonane	Antioxident
<i>Pseudonocardia carboxydivorans</i> ⁸³	Branimycins B and C	Macrolide	Antibacterial activities
<i>Pseudonocardia</i> sp. ¹⁰⁶	Pseudonocardides A–G	γ -butyrolactones	Antibacterial and cytotoxic activities
<i>Pseudonocardia</i> sp. ¹⁰⁷	Curvularin macrolides 1–5	Macrolides	Antibacterial and cytotoxic activities
<i>Rubrobacter radiotolerans</i> ¹⁰⁸	Dimeric indole derivatives 1 and 2	Dimeric indoles	Acetylcholinesterase (AChE) inhibitory activity
<i>Saccharomonospora</i> sp. ¹⁰⁹	Saccharomonopyrones A–C	α -pyrones	Weak antioxidant activity
<i>Saccharopolyspora</i> sp. ¹¹⁰	1,2-naphthoquinone	Naphthalene derivative	No cytotoxicity
<i>Saccharothrix</i> sp. ¹¹¹	Saccharothrixones A–D	Aromatic polyketides	Cytotoxic activity
<i>Salinispora pacifica</i> ¹¹²	Cyanosporasides C–F	Polyketides	Not specified
<i>Salinospora</i> sp. ¹¹³	Salinipostins A–K	Bicyclic Phosphotriesters	Antimalarial activity
<i>Serinicoccus</i> sp. ¹¹⁴	Seriniquinone	Quinones	Anticancer agent
<i>Solwaspora</i> sp. ¹¹⁵	Solwaric acids A and B	Trialkyl-substituted aromatic acids	Antibacterial activity against MDR pathogens
<i>Streptomonospora</i> sp. ¹¹⁶	Marinopyrones A–D	α -pyrones	Inhibition of NO production
<i>Streptomyces bacillaris</i> ¹¹⁷	2,6-di- <i>tert</i> -butylphenol	Phenolics	Antibacterial activities
<i>Streptomyces bacillaris</i> ¹¹⁷	1H, 5H, pyrrolo (1' 2':3, 4) imidazo	Alkaloid	Antibacterial activities
<i>Streptomyces bacillaris</i> ¹¹⁷	1,4-benzenediol, 2,5-bis(1,1-dimethylethyl)	Quinolone	Antibacterial activities
<i>Streptomyces coeruleorubidus</i> ¹¹⁸	Bis (2-Ethylhexyl) Phthalate	Phthalates	Antibacterial and anticancer activities
<i>Streptomyces</i> sp. ¹¹⁹	3'-epi-N-Acetyl-holyrine A	Indolocarbazole	Antibacterial activities
<i>Streptomyces</i> sp. ¹²⁰	4- 2(acetylamino)ethoxy	Carboxyl group	Antibacterial and antioxidant
<i>Streptomyces</i> sp. ¹²¹	3-methylpyridazine	Methylpyridine	Antibacterial activities
<i>Streptomyces</i> sp. ¹²¹	n-hexadecanoic acid	Palmitic acid	Antibacterial activities
<i>Streptomyces</i> sp. ¹²¹	indazol-4-one	Alkaloid	Antibacterial activities
<i>Streptomyces</i> sp. ¹²¹	3a-methyl-6-((4-methylphenyl) sul	Phenolics	Antibacterial activities
<i>Verrucosipora</i> sp. ⁸⁶	Butrepyrazinone	Pyrazinone	No antibacterial activity
<i>Verrucosipora</i> sp. ¹²²	Glycerol 1-hydroxy-2,5-dimethyl benzoate	Salicylic derivative	Anti-MRSA activity
<i>Williamsia</i> sp. ¹²³	3-benzyl-3 α ,4 β -dihydroxypentan-2-one	Phenolics	Not specified

factors, including the metabolic state of bacteria and supply of virus from the water column.¹⁶³ The viral abundance influences the existence of bacteria and phytoplankton diversity.¹⁶⁴ Viruses have played a key role in the production of dimethyl-sulphide which is formed by the hydrolysis of dimethyl sulphoniopropionate.¹⁶⁵ Viruses have also great roles in Carbon budgets. Marine-derived viruses influence the composition of their communities and are considered as significant forces behind biogeochemical cycles.¹⁶⁶ In the marine environment, the distribution of viruses plays notable roles via exchanging their genetic material among marine bacteria by means of viral attack. It also helps in the cycle of marine food chain, disseminate various types of viral toxin and play a role in controlling the diversity of

microbial species.¹⁶⁷ Due to the application of viruses during phage therapy,¹⁶⁸ bacterial infection treatment¹⁶⁹ as well as recombinant protein production¹⁷⁰ increases the interest of revealing the unexplored marine viruses. In the field of nanomedicine, marine viruses have been recognized as important tools.¹⁷¹ Some potential bacterial virus with their host and isolation source are presented in Table 5.

Conclusions

This review highlighted the importance of marine microorganisms since they are the sources of various types of bioactive natural products such as, antibiotics, biocatalysts and others potential metabolites. Marine microbial communities also have greater potential to produce hydrolyzing enzymes

Table 3. Commercially Important Enzymes Produced by Marine Actinomycetes, Their Characteristics and Potential Uses

Enzyme	Producing Species	Industrial Usage
Amylase	<i>Streptomyces erumpens</i> ¹²⁶	Detergent
	<i>Thermobifida fusca</i> ¹²⁷	Paper and pulp
Protease	<i>Streptomyces pactum</i> ¹²⁸	Pharmaceutical, Leather
	<i>Streptomyces thermoviolaceus</i> ¹²⁹	Detergent, Food, Brewing
Cellulase	<i>Streptomyces ruber</i> ¹³⁰	Detergent
	<i>Thermobifida halotolerans</i> ¹³¹	Paper and pulp
Chitinase	<i>Streptomyces thermoviolaceus</i> ¹³²	Textile
	<i>Nocardiopsis prasina</i> ¹³³	Leather
Lipase	<i>Streptomyces exfoliates</i> ¹³⁴	Paper and pulp
	<i>Nocardiopsis alba</i> ¹³⁵	Detergent
Pectinase	<i>Streptomyces lydicus</i> ¹³⁶	Beverage, Textile
Keratinase	<i>Actinomadura keratinolytica</i> ¹³⁷	Leather

Table 4: Potential Metabolites Harvested from Sponge Associated Marine Fungi

No.	Fungus	Source	Metabolites	Activity
1	<i>Aspergillus niger</i> ¹⁴⁷⁻¹⁴⁹	<i>Hyrtios</i> sp.	Asperazine	Antileukemic
2	<i>Trichoderma harzianum</i> ¹⁵⁰	<i>Halichondria okadai</i>	Trichodenones	Anticancer
3	<i>Exophiala pisciphila</i> ^{151, 152}	<i>Mycale adhaerens</i>	Exophilin A	Antibacterial
4	<i>Emericella variegata</i> ¹⁵³	<i>Haliclona valliculata</i>	Evariquinone	Antiproliferative
5	<i>Aspergillus flavipes</i> ¹⁵⁴	<i>Anthopleura xanthogrammica</i>	Flavicerebroside A	Cytotoxic
6	<i>Aspergillus niger</i> ¹⁵⁵	<i>Aplidium</i> sp.	Yanuthone A	Antimicrobial
7	<i>Gymnascella dankaliensis</i> ¹⁵⁶	<i>Halichondria japonica</i>	Gymnastatin F	Cytotoxic
8	<i>Aspergillus versicolor</i> ^{157, 158}	<i>Xestospongia exigua</i>	Aspergillitine	Antibacterial
9	<i>Microsphaeropsis</i> sp. ¹⁵⁹	<i>Myxilla incrustans</i>	Microsphaeropsin	Antifungal
10	<i>Penicillium chrysogenum</i> ¹⁶⁰	<i>Ircinia fasciculata</i>	Sorbicillactone A	Cytotoxic

Table 5. Potential Marine Bacterial-Virus Discovered from the World's Marine Environment

Sl	Bacteriophages	Bacterial Host	Isolation Source
1	Cyanophages ¹⁷²	<i>Synechococcus</i> sp.	Bermuda, Mass and United Kingdom
2	Marine phages ¹⁷³	<i>Vibrio parahaemolyticus</i>	Florida (Tampa Bay)
3	Lysogens or Bacteriocinogens ¹⁷⁴	<i>Vibrio</i> spp., <i>Vibrio harveyi</i>	Marine environment
4	Marine actinophages ¹⁷⁵	Actinomycetes	Mangrove sediments
5	Coliphage ¹⁷⁶	<i>Escherichia coli</i>	Sea foods

specifically protease, lipase, amylase, chitinase etc. Marine fungi and virus also play a crucial role in the balance of ecosystems by synthesizing diversified potential natural products. Marine microbial natural products possess diverse bioactivities. In the field of natural products discovery, more advanced research is recommended to reveal the unexploited bioprospecting marine microorganisms.

Authors' Contributions

SIP and BCM have searched and contributed in writing this article. SIP, RE, MH, AB and MAHB have designed the paper structure and contributed to editing and revising the article. All authors read and

approved the final manuscript.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

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