Marine Microorganisms: Potential Resources of Biomolecules of Human Healthcare Importance

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The oceans cover over 70% of the earth's surface and contain an extraordinary diversity of life. The microscopic organisms in salt water in the sea are referred as marine microorganisms. Marine microorganisms are named on the basis of ecological group (ocean) and not on the basis of taxonomic classification. As per the report of Bowler *et. al.* (2009) the current estimate of global oceanic microflora is composed of 3.6×10^{29} bacterial cells, 1.3×10^{28} archaeal cells and 4×10^{30} viruses. Marine microbes inhabit different environments of the ocean such as polar ice, hydrothermal vent, deep sea, coral reef, mangroves, etc., and their presence and ecological role vary according to the environmental conditions where they persist. Hence, marine environment is considered as a treasure for scientists / researchers to explore unique chemical entities. Researchers consider marine microbes as an alternative source of marine natural products.

Marine microorganisms in drug development

In 1967, a small symposium was held in Rhode Island, USA, with the ambitious title "Drugs from the Sea". The catchphrase of the symposium title has endured over the decades as a metaphor for drug development from marine natural products, though the first genuine drug from the sea was a long time coming. The need for novel substances for the treatment of severe human diseases such as cancer, microbial infections and inflammatory processes, combined with the recognition that marine organisms provide a rich source of such substances support the intensive search for new molecules from marine organisms. In the past, often algae and marine invertebrates have been investigated. However, modern marine biotechnology has moved its focus to microbes and encompasses the discovery of new pharmaceuticals from marine microbes.

Marine microorganisms and their role in production of bioactive compounds

Diverse marine microbial community produces compounds with unique structural characteristics and these compounds possess broad spectrum of pharmaceutical properties such as:

- Antimicrobial
- Anti-tuberculosis
- Antiviral
- Antiparasitic
- Antheimintic
- Antimalarial
- Antiprotozoal
- Anticoagulant
- Antiplatelet
- Anti-inflammatory
- Antidiabetic
- Antitumor
- Anticancer
- Cytotoxic
- Cytostatic

These activities by secondary metabolites are collectively called as bioactive property. Particularly marine Actinobacteria has shown to produce these wide range of secondary metabolites. Each strain of Actinobacteria is likely to have the genetic potential for the production of 10-20 secondary metabolites. More than half of the molecules currently in the marine drug development projects are likely to be produced by microorganisms. Food-grade metabolites which possess promising pharmaceutical properties have been isolated from marine microbes and there would be a clear potential to develop those active ingredients as modern nutraceuticals and functional food. It shall be noted that there are many constraints associated with marine natural products and one among them is adequate quantity of metabolites. Currently, only a small portion of microbial diversity has been cultivated in the laboratory and the presence of other microbes is only minimal. Marine environment is a virtually unexplored source of bioactive metabolites.

Harnessing marine microbes for biomolecules

Many different approaches have been used to cultivate uncultured bacteria. Indications of the common presence of Actinomycetes in marine habitats have increased efforts to discover new taxa and thus new metabolites. In recent years, newly discovered bioactive metabolites have encouraged growing interest in marine Actinomycetes in parallel with the need for new antibiotics. Natural products in general play an important role in the development of drugs. 63% of new drugs were classified as naturally derived (unmodified natural product, modified natural product, or synthetic compound with a natural product as pharmacophore).

Covering the period from January 1981 to the middle of October 2008, 68% of anti-infectives (antibacterial, antifungal, antiparasitic, and antiviral) and 63% of drugs used in cancer treatment, respectively, were naturally derived. Mimicking the natural habitats of microorganisms in the laboratory is important for their successful isolation. Although some of the isolation methods of Actinomycetes from terrestrial samples are used to isolate their marine counterparts, different approaches for reaching different species and metabolites are being tested. Only few marine natural products entered preclinical or clinical trials, although a large number has been described from marine biota and many have reached advanced states of applied research studies (Figures 1 and 2). Genera of Actinobacteria include Streptomyces, Actinomyces, Arthrobacter, Corynebacterium, Frankia, Micrococcus, Micromonospora and so on.

- Epi-fluorescence microscopy and rRNA sequencing strategies revealed enormous diversity than plate counting.
- <1% fraction is cultivable. "Great plate anomaly" discrepancy between the total viable cell count and the cell count of culturable cells were attributed
    - i. Cell damage by oxidative stress
    - ii. Formation of viable but non-culturable cells
    - iii. Inhibition by high substrate concentrations
    - iv. Induction of lysogenic phages upon starvation
    - v. Lack of cell–cell communication in laboratory media
- Culture- dependent method
    - i Extinction culturing method
    - ii. *In vitro* simulation models
    - iii. High-throughput cultivation methods
- Culture- independent method
- Metagenomic approach

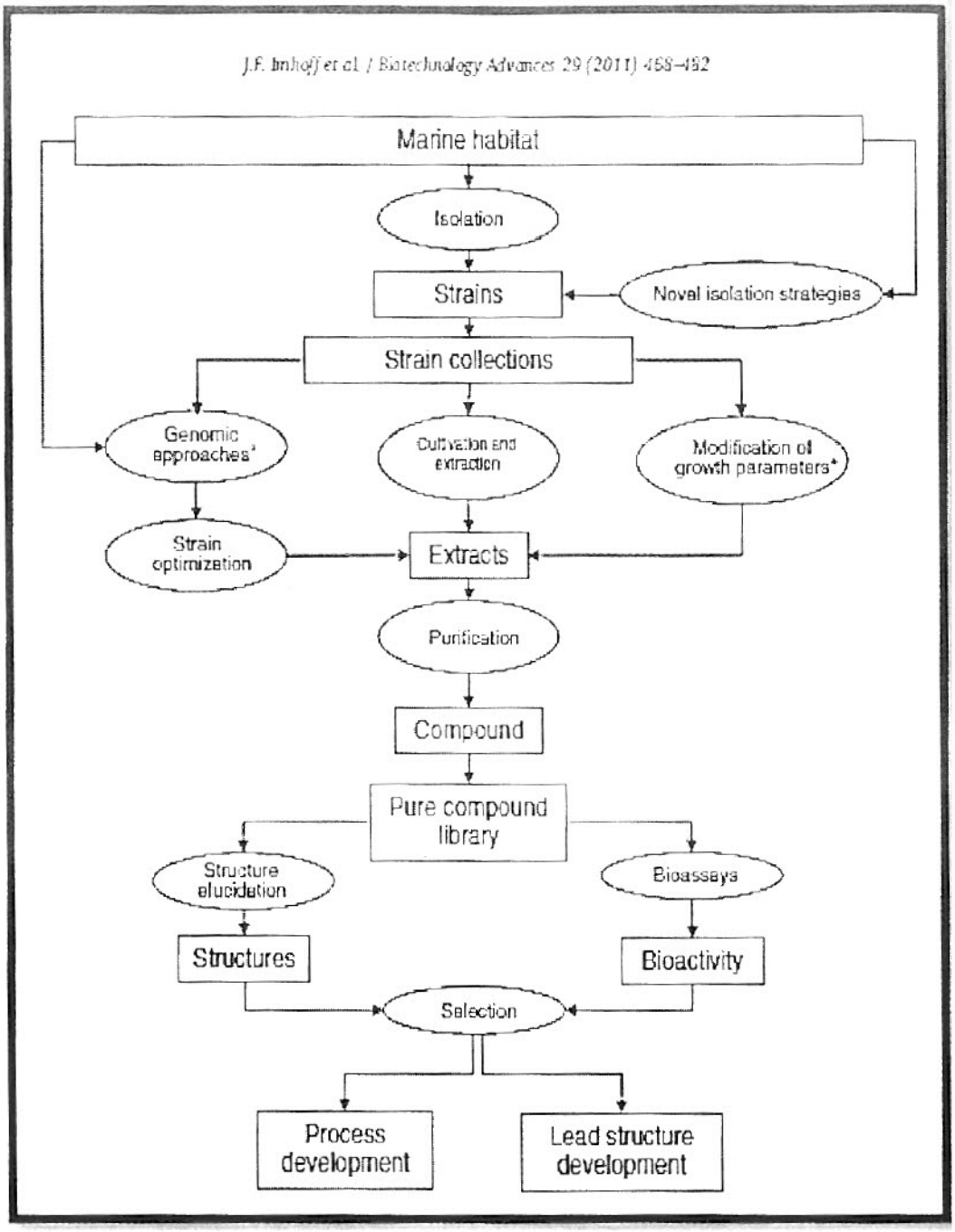

Fig. 1. New drug discovery approaches

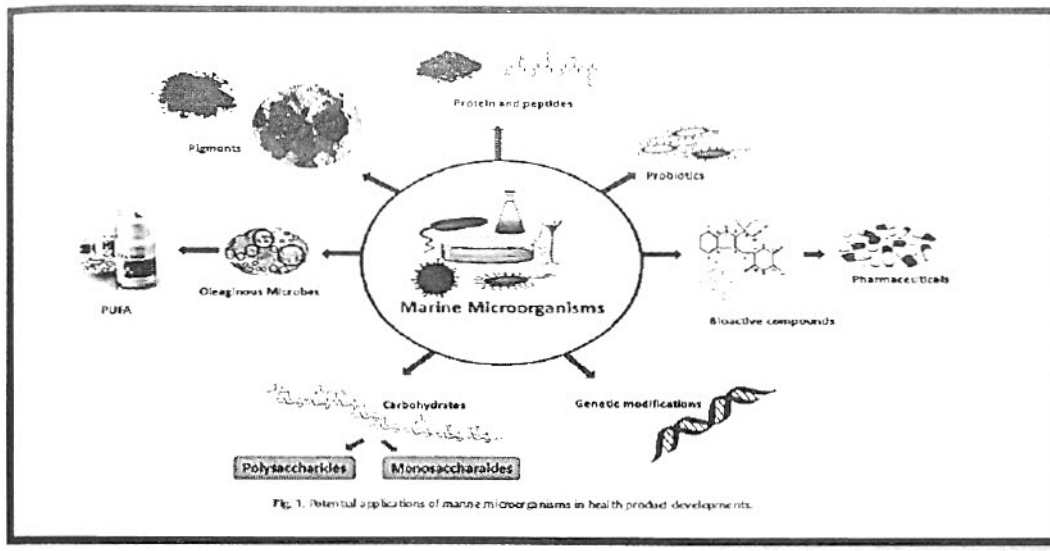

Fig. 1. Potential applications of marine microorganisms in health product developments.

Fig. 2. Potential health benefit-secondary metabolites from Actinomyces (Drugs)

Numerous new compounds have been isolated and many were found with interesting biological activities, most of which were derived from sponges, corals and other marine invertebrates. Recovery rates of less than 1 g of substances such as halichondrin, ecteinascidin or bryostatin obtained from a ton of sponges, ascidia or bryozoa, respectively, as well as widely unsolved problems with the mariculture of most marine macroorganisms make it extremely difficult to produce substances in amounts sufficient for further studies. Alternative production processes solves these problems for several substances. Only few marine natural products entered pre-clinical or clinical trials, although a large number has been described from marine biota and many have reached advanced stages of applied research studies.

Actinobacteria, which are the prolific producers of antibiotics and important suppliers to the pharmaceutical industry, can produce a wide variety of secondary metabolites. It is only more recently that marine Actinobacteria have become recognized as a source of novel antibiotics and anti-cancer agents with unusual structures and properties. Marine Actinobacteria are the best sources of secondary metabolites and most of these compounds are derived from the single genus Streptomyces, whose species are distributed widely in the marine and terrestrial habitats (Tables 1 and 2). In fact, the genus Streptomyces alone accounts for a remarkable 80% of the Actinobacterial natural products reported to-date, a biosynthetic capacity that remains without rival in the microbial world.

Table 1. Potential and application of marine microbes in the production of natural products and in marine biotechnology

Substance produced	Name of the organism	Application in human health care
Antibacterial activity		
Abyssomicins	Verrucosispora sp	Antibacterial
Bonactin	Streptomyces sp.	Antifungal
Chlorodihydroquinones	Streptomyces sp.	Anticancer
Diazepinomicin	Micromonosproa sp.	Anticancer; Anti-inflammatory
Marinomycins	Marinispora	Antifungal; Anticancer
Antifungal activity		
Chandrananimycin	Actinomadura sp.	Antialgal; antibacterial; anticancer
1-Hydroxy-1-norresistomycin	*Streptomyces chinaensis*	Antibacterial
Antitumor activity		
Arenimycin	*Salinispora arenicola*	Antibacterial
Staurosporinone	Streptomyces sp.	Phycotoxicity
Cytotoxic activity		
Pyridinium	Amycolatopsis alba	Antimicrobial
Albidopyrone	Streptomyces sp.	Cytotoxic (inhibitor of protein–tyrosine phosphatise)
Cytostatic activity		
Proximicins	Verrucosispora sp	Antitumor
Anti-inflammatory activity		
Cyclomarins	Streptomyces sp. *Salinispora arenicola*	Anti-inflammatory

Anti-parasitic activity		
Avermectins	*Streptomyces avermitilis*	Anti-parasitic
Anti-malarial activity		
Trioxacarcin	Streptomyces sp.	Antibacterial; antitumor
Anti-viral activity		
Benzastatin C	*Streptomyces nitrosporeus*	
Antioxidant activity		
Dermacozines A-G	Dermacoccus	Antitumor; Antiprotozoal
2-Allyloxyphenol	Streptomyces sp	Antimicrobial
Anti-angiogenesis activity		
Streptopyrrolidine	Streptomyces sp.	

Genera of Actinobacteria include Streptomyces, Actinomyces, Arthrobacter, Corynebacterium, Frankia, Micrococcus, Micromonospora and several others. Secondary metabolites produced by the marine Actinobacteria possess a wide range of biological activities. Actinobacteria comprise about 10% of the bacteria colonizing marine aggregates and can be isolated from marine sediments.

The fidelity of these enzymes also differed and one enzyme, that from the marine thermophile *Pyrococcus furiosus*, named Pfu was found to have superior copying fidelity and is now a widely used PCR reagent. *P. furiosus* was isolated from geothermally heated marine sediments on Vulcano island, Italy and is a good example of marine biodiversity providing useful solutions to analytical methods. Green fluorescent protein (GFP) from a jellyfish can be used to tag and study biological molecules under the microscope *in vivo*.

Table 2. Bioactive compounds extracted from microorganisms (bacteria, fungi and thraustochytrids) from different marine habitats

Important groups	Bioactive Compounds	Action	Source Microorganisms	Habitat
Anti-Aging Products				
Polysaccharides	EPS	Emulsifying, thickening, absorption and gel formation and anti-wrinkles	Marine fungi and bacteria such as *Agrobacterium* sp., *Alcaligenes faecalis*, *Xanthomonas campestris*, *Bacillus* sp., *Zymonas mobilis*, *Eduarsiella tarda* and *Aureobasidium pullulans*, *Alteromonas macleodii*, *Pseudoalteromonas* sp.	Different marine environments, including extreme ecosystems. *Pseudoalteromonas* sp., isolated from antarctic waters
	HE 800	Structurally analogous to hyaluronic acid	*Vibrio diabolicus*	Deep-sea hydrotermal vents
PUFAs	DHA, EPA and omega-3 fatty acids	Soft tissue repair, skin nourishment and stimulation of collagen production	Marine fungi (i.e., *Trichoderma* sp., *Rhodotorula mucilaginosa* AMCQ8A), bacteria (i.e., *Moritella dasanensis*, *Vibrio* sp., *Pseudomona* ssp. *Shewanella* sp. and *Colwellia* sp.) and	Thraustochytrids isolated from seawater and sediments from tropical and temperate to polar ecosystems, in particular organically enriched systems (e.g., estuaries, leaves of mangrove forests); bacteria

Important groups	Bioactive Compounds	Action	Source Microorganisms	Habitat
			thraustochytrids (in particular *Schizochytrium*, *Aurantiochytrium* and *Ulkenia*)	and fungi isolated from coastal to deep-sea habitats
Antioxidant Compounds				
MAAs		Antioxidant activity and scavenging activity of superoxide anions	Marine fungi and bacteria	Coastal and open-ocean systems, deep-sea, hypersaline, Arctic and Antarctic ecosystems and others
Carotenoids	Astaxanthin	Antioxidant activity	Marine fungi bacteria and thraustochytrids	Coastal and open-ocean systems, deep-sea, hypersaline, Arctic and Antarctic ecosystems and others
	Saproxanthin and myxol	Reinforce biological membranes, decreasing permeability to oxygen and enhancing protection	Marine bacteria family Flavobacteriaceae	Antartic marine habitats

Important groups	Bioactive Compounds	Action	Source Microorganisms	Habitat
		against oxidation		
Phenols	Hydroquinone derivatives (e.g., wentiquinone, ethyl 4-(3,4-dihydroxybenzamido)-butanoate)	Anti-oxidant activity	Marine fungi *Acremonium* sp. and *Aspergillus wentii* N48	Coastal systems, isolated from brown algae
Isobenzofuranone derivative	4,5,6-trihydroxy-7-methylphthalide	Radical scavenging activity	Marine fungus, *Epicoccum* sp.	Coastal systems, isolated from brown algae *Fucus vesiculosus*
Exopolysaccharides	EPS2	Radical scavenging activity	Marine fungus *Keissleriella* sp. YS 4108	Marine sediments
Diketopiperazine alkaloids	Golmaenone and related alkaloids	Radical scavenging activity and UV-A screening function	Marine fungus *Aspergillus* sp.	Isolated from the surface of the marine red alga *Lomentaria catenata*
Dioxopiperazine alkaloids	Dihydroxyisoechinulin A and related echinulin	Radical scavenging activity and UV-A screening function	Marine fungus *Aspergillus* sp.	Isolated from the surface of the marine red alga *Lomentaria catenata*

Important groups	Bioactive Compounds	Action	Source Microorganisms	Habitat
Antimicrobial Products				
Polysaccharides	Chitin, chitosan and their derivatives	Antimicrobial activity	Marine fungi such as zygomycetes, chytridiomycetes, ascomycetes, basidiomycetes	Coastal and open-ocean systems, deep-sea, hypersaline, Arctic and Antarctic ecosystems and others
Carotenoids	Astaxanthin	Antimicrobial activity, anti-wrinkle and anti-acne effects	Marine bacteria, fungi and thraustochytrids	Coastal and open-ocean systems, deep-sea, hypersaline, Arctic and Antarctic ecosystems and others
Parabens	4-hydroxybenzoate alkyl esters	Preventing the growth of yeasts, molds and gram-positive bacteria	The marine bacterial strain, A4B-17, genus Microbulbifer	Isolated from an Ascidian

Conclusion

About 23,000 antibiotics have been discovered from microorganisms. It has been estimated that approximately 10,000 of them have been isolated from Actinobacteria. Actinobacteria, mainly the genus *Streptomyces*, can produce a wide variety of secondary metabolites such as bioactive compounds, including antibiotics. The group has an enormous biosynthetic potential that remains unchallenged among other microbial groups. The immense diversity, along with its under-utilization is the fundamental reason for attracting the researchers toward discovering novel metabolites. In ocean there are more than 100 different microbial phyla and up to a billion kinds of marine microbes makes oceans treasures for biomolecules producing microbes. As of now researchers explored only less than 1%. More than 50% of the biomolecules are from marine origin. The need of the hour is various approaches for the selective isolation of diverse microbes with diverse biological activity and use them for healthcare benefits and to treat hitherto difficult to cure dreaded diseases.