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Der Pharmacia Lettre, 2018, 10 [8]: 78-85
[http://scholarsresearchlibrary.com/archive.html]

ISSN 0975-5071
USA CODEN: DPLEB4

Present Status and Future Perspectives of Marine Actinobacterial Metabolites

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ABSTRACT

The purpose of this review was to describe the status of research on marine actinobacteria yielding pharmaceutically active secondary metabolites and other important bioproducts. Marine actinobacteria are the most economically and biotechnologically priceless prokaryotes. The major genera of actinobacteria include Streptomyces, Actinomyces, Frankia, Micrococcus, Micromonospora and several others. Secondary metabolites produced by the marine actinobacteria possess a wide range of biological activities. As the search for discovery of rare and new actinomycetes is continuous and is getting significant interest to drug discovery because the development of new and potent therapeutic agents is needing to act against resistance pathogens. For the detection and isolation of bioactive actinomycetes, improved cultivation methods and recent insights in molecular technologies are essential. In this context in this review we have described the modern methods in cultivation of marine actinobacteria and about the marine environmental metabolites. In addition, nanotechnological approaches for Production of Bioactive compounds from Marine Actinobacteria are also provided.

Keywords: Marine Actinobacteria, Bioactive metabolites, Isolation and cultivation, Modern molecular techniques and Nanotechnological approaches.

INTRODUCTION

Marine Biotechnology which includes a vast and high biodiversity zone as a rich source of marine derived products is getting fast and important attention in the sector of global biotechnology. It is estimated that the global market for Marine Biotechnology, their products and processes may reach US$ 4.8 billion by 2020. Currently, marine derived products have wide impact and can be used for production of antibiotics, pharmaceutically active compounds and several other metabolites in the fields of food, agriculture and cosmetic industries. The other successful application of marine biotechnology is marine drugs. The research and development of marine microbes is projected for the treatment of multi drug resistant bacteria and to obtain novel compounds with antibacterial and anticancer activity. The search for new drugs and novel marine organisms from deep sea was started since 1960s and extended the research in the mid-1970s. The discovery of a variety of marine organisms and extraction of about 2500 novel metabolites from these sources was done during the time between 1977 to 1987. Up to now nearly more than 10,000 compounds have been isolated from marine organisms and still being investing every year.

About 70% of the world's surface is covered with oceans and these are an important resource for the bioprospection of novel marine microorganisms. The phylum Actinobacteria represents the largest reservoir of marine organisms and provides 40% of the bioactive secondary metabolites [1-3]. The genus *Streptomyces* contributing to nearly 80% of actinobacteria isolated from deep seas [4] and along with this genus other new taxa have been identified through molecular ecology studies and actinobacterial operational taxonomic units (OTUs) [5,6]. The capability and uniqueness of marine organisms is different from terrestrial microorganisms in having prominent metabolic, physiological and biochemical activities that made optimal and potential to produce novel metabolites [7,8]. In addition, presence of huge gene clusters and genes that code for polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS) explored actinobacteria to produce medicinally important metabolites [9]. As marine actinobacteria are economically priceless prokaryotes and a good source of unique secondary metabolites the present review was focused in future prospective of marine actinobacteria for the discovery of new metabolites for delivering therapeutic and other essential leads with distinct biological activities.

MATERIAL AND METHODS

Isolation of marine bacteria

Isolation of marine actinobaceria from deep sea sediments was routinely done by culture dependent methods [10]. Due to special growth requirements and culture conditions <2% of bacteria can be isolated by conventional techniques [11] or may

remain "viable but not culturable" (VBNC) strains [12]. To overcome these drawbacks and to replace laborious microscopic techniques recent and advance techniques like genomics, proteomics, bioinformatics and using high-throughput sequencing approaches are necessary. Limited Previous studies had employed robust technologies in identification of marine bacteria by genetic fingerprinting [13], DNA-DNA hybridization techniques [14], and the construction of metagenomic library and sequencing [15] (Ki sand et al., 2012), next generation sequencing (NGS) [16] and nanopore sequencing [17]. The coupled metagenomics and meta transcriptomic analysis were successfully used for determining the microbial communities in deep sea water of the North Pacific Ocean [18]. Other new sophisticated techniques like hollow-fiber membrane chamber (HFMC) and I Chip for in situ cultivation of previously unculturable microbial species opened novel and facile bacterial cultivation platforms [19,20]. Thus, the combination of both culture dependent (grow and isolate) and culture independent (analysis of nucleic acids and proteins) approaches have revolutionized the characterization and isolation of diverse marine organisms including rare actinobacteria [21,22].

LITERATURE REVIEW

Several studies were carried out and had isolated various strains of actinobacteria from different marine environments. Zhang and Prieto-Davó et al., had identified 9 actinobacterial genera from deep Arctic marine surface sediments Salinispora spp from deep marine sediments of Canary Basin and South Pacific Gyre [23,24] and some more actinobacteria abundantly from Arctic Ocean by Jorgensen et al., Inagaki et al., [25,26] from Atlantic Ocean by Schauer et al., [27] from pacific ocean by Inagaki et al., [26].

Bioactive metabolites from Actinobacteria

Among the various marine actinobacterial genera, *Actinomadura*, *Actinoplanes*, *Amycolatopsis*, *Marinispora*, *Micromonospora*, *Nocardiopsis*, *Saccharopolyspora*, *Salinispora*, *Streptomyces* and *Verrucosispora* are the major potential producers of commercially important bioactive natural products. Among these, *Streptomyces* spp. ranks first with a large number of bioactive natural products. Among all marine actinobacteria, *Streptomyces* strain is the major producer of several bioactive and pharmaceutical compounds. Marine actinobacteria are known to produce several kinds of Halogenated Terpenes (Hemiterpenoid, Tetraterpenoid), Steroids and sterols (Isofucosterol, Clionasterol, etc.,), Polyphenols (Phloroglucinol, Eckol, etc.,), Polyketides (Griseorhodin A, Daryamides etc.,), peptides (Mechercharmycin B, Thiocoraline, etc.,) quinones (Himalomycin A, Tetracenomycin D, etc.,), Macrolides (Chalcomycin, Glyciapyrroles A, etc.,), Terpenes (Azamerone, Neomarinone, etc.,), Alkaloids (Aburatubolactams A, Bohemamine, etc.,), Indole compounds (Caboxamycin, Streptochlorin, etc.,),

Pyrroloiminoquinone, Butenolides, Benzoxazole, Piericidins, Methylpyridine, Trioxacarcins, Marinopyrroles, Manumycin derivatives, Triazolopyrimidine, Macrocyclic lactam, Sisomicin, and Esters.

Recent insights in procurement of bioactive metabolites

Progressive research in exploring novel metabolites from actinobacteria is increasing with coupled advancement in molecular and analytical tools. With biological and chemical methods, it is possible to tune and construct superior analogs of biomolecules by the modification of structural and functional properties. The application of cutting edge translational research in synthesis or transferred biomolecule have wide application in clinicals or in industries. Dhakal and Song, had laid the foundation for rational integration of biological processes and chemical techniques [28,29]. Salinosporamide A (Marizomib) is a highly effective compound which is a structural/functional diversified and successes in phase trails derived from marine actinobacteria [30,31]. The biosynthetic mechanism and structural diversification of Nocardioazine B from *Nocardiopsis* sp. CMB-M0232 was well understood by the analysis of genome sequencing and mass spectroscopy [32]. Thus, the innovative methods can assist in efficient production of bioactive molecules from potent strains.

Nanotechnological approach for production of bioactive compounds from marine actinobacteria

The advent of Nanotechnology has paved way for developing novel ways to merge different disciplines to achieve novel solutions for the betterment of humankind [33] Nanoparticles are the zero or one-dimensional nanoparticles in the size range of 1-100 nm. These nanoparticles have unique and beneficial properties in this size domain [34]. In attention to the green synthesis, several researchers exploited the use of nature provided microbes, marine microbes and plants etc. for the synthesis of nanoparticles [35]. Marine actinobacteria also played a significant r ole in the formation of nanoparticles like silver, gold, germanium, silicates and other metal oxides [36]. Importantly, the *Shewanella oneidensis* MR-1 has involved in the conversion of uranium metal to uranium dioxide (UO_2) nanoparticles. The pH-dependent oxidoreductases of the microbes were involved in the catalytic reduction of soluble metal complexes [37]. However, nanotechnology can be used for enhancing the production of marine actinobacteria assisted bioactive compounds than just preparing nanoparticles using them.

RESULTS AND DISCUSSION

Nanoparticles show the unique and novel properties due to their higher surface area and surface energy. As the size decreases, the surface area increases which is very useful for enzyme immobilization. The enzymes released or the enzymatic activity to process the marine actinobacteria will be helpful by coating enzymes on the nanoparticles surface [38]. Nanoparticles with magnetic

properties such as iron oxide nanoparticles are highly beneficial [39]. The ability to precipitate these nanoparticles in external magnetic field will help in controlling the reaction products and enzyme reactivity's. In addition, the immobilization will enhance the enzyme efficacy and their long-time use without degradation or degeneration effecting their catalytic activity.

The viability and accessibility of the marine actinobacteria shall be monitored by incubating the bacteria with gold nanoparticles. Gold nanoparticles has specific detectable ability for Surface Enhanced Raman Spectroscopy (SERS) [40]. In addition, the carbonaceous materials such as calcareous lamina, siliceous spicules [41] etc., produced by the marine sponges and the actinobacteria associated with the sponges are helpful in devising novel bioengineering and tissue engineering applications. The calcium [42] and silicate [43] materials are widely employed as osteogenic markers for enhanced osteogenesis in bone tissue engineering. The encapsulation of these nanoparticles in polymers and fabricating biocompatible grafts will be useful in bone tissue regeneration. The integration of the nanotechnology in enhancing the production of pharmaceutical agents form the marine actinobacteria is a unique strategy. Rather than the preparation of nanoparticles using microbes, the utilization of nanoparticles or Bio/Synthetic polymeric nanospheres for the better growth of microbes for increased production of the bioactive agents is very effective to reduce the cost and for the effectiveness in mass production of actinobacteria. The encapsulation of marine actinobacteria inside the nanospheres can serve as nanoreactors in a growth media that can grow in more mass and increased production inside a bioreactor. The production can be controlled by removing these particles whenever needed. The present strategy will be more effective in enhancing the production of the pharmaceutical bioactive compounds which also helps in easy harvest without losing microbes.

CONCLUSION

It may be concluded from this review that the marine actinobacteria are the most economically and biotechnologically sources for bioactive metabolites. The cultivation of marine actinobacteria by modern molecular techniques and nanotechnological approaches for production of Bioactive compounds from marine actinobacteria were also provided in this study.

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