An Overview on Diversity, Characteristics, and Biotechnological Applications of Hypersaline Actinomycetes

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***Abstract* - Microorganisms that grow in saltwater environments are an important source of bioactive compounds, and such environments are common throughout the world primarily in seas, coastal and deep-sea regions, alkaline lakes, soda deserts, and artificial salt pans. The hypersaline environment is the most characteristic extreme environment, including high salt, alkalinity and hypoxia, and is the most important physicochemical parameters affecting biodiversity. Many reports reveal the predominance of microorganisms, including actinomycetes, in a variety of high-salt environments such as salt lakes, oceans, sunbathing, salt water, and salt pans. Despite the importance of the physiological adaptation of these actinomycetes, they are the least explored, especially in the local and sub local regions of the world. Actinomycetes obtained from a high salt environment are metabolically very active and stable and have industrially important values such as antibiotics, anticancer agents, cytotoxicity, neurotoxicity, antifungal, antiviral and antitumor activity. With this background, this chapter describes diversity, properties, in vitro culture methods, biological activity, and potential uses for highly salted actinomycetes.**

***Index Terms* - Actinomycetes, Hypersaline environment, Biodiversity, Halophilic, Applications.**

I.INTRODUCTION

Hypersaline environment is one that is more salty than seawater, has highly variable total salt and ionic composition, and differs in many other aspects such as temperature, pressure, and nutritional status. They range from temporary drops on the surface of the leaves to Jamaican-sized salt pans; and from sunbaked salina to darkly buried evaporites. Not surprisingly, there are a great variety of organisms that can be described as halophilic bacteria (salt lovers). Salt is one of the main factors affecting the composition of communities, and some hypersaline environments are one of the most diverse ecosystems on the planet.

High salt concentrations attenuate some microbial processes while enhancing others, and so it is imperative that they are considered when modelling global biogeochemical cycles. Furthermore, the tenacity of extreme halophiles, coupled with the preserving properties of salt, makes them ideal candidates for investigating long-term survival. Hypersaline habitats are present all over the globe in the form of saline soil, saline water and salted food. These hypersaline habitats are widely distributed and can be found at sea level in arid and semiarid regions, both as naturally occurring or human-made salterns. Among the natural ones, sabkhas ("salt-flat" in Arabic) are a good example but are only occasionally studied. Hypersaline habitats can be classified based on the extremity, adaptability and geological and geographical location of the area.

In this review of literature study we mainly aimed to capture diversity, focusing largely on those organisms that grow optimally at a salinity of more than 100 g^{-1} (approximately three times more saline than seawater), which is mainly, but not exclusively, the realm of microorganisms, and concentrating primarily on their ecology and physiology. Further, we described characteristics, and biotechnological applications of hypersaline actinomycetes.

II. BIODIVERSITY OF MICROFLORA IN HYPERSALINE ENVIRONMENT

Most environmental studies were carried out on aquatic habitats, represented by saline lakes and solar salterns designed for the commercial production of salt. However, other habitats include saline soils, salted foods and other products, hides, and deep-sea brine pools *(e.g.,* Lakes Thetis and Kryos).[1-3] Salt proportions are different from seawater. Thalassohaline habitats are typified by solar salterns, which are constituted by a series of shallow ponds in which the seawater is evaporated until the salts are precipitated. However, not all salts precipitate at the same concentration, since this depends on their solubility. Thus, salterns are thalassohaline only up to the salinities when the first salts precipitated. Most a thalassohaline habitats are terminal lakes containing various salts, and dependent on the geology and geographic location of their fresh waters traverse.[1] Halophilic microorganisms are classically categorized on the basis of their optimal growth in different salt concentrations. The two main groups are the extreme halophiles (optimal growth above 15% NaCl) and moderate halophiles (optimal growth 3–15% NaCl). In contrast, slight halophiles are able to grow optimally in media with 1–3% NaCl.[1,4]

Classification is based on data obtained in laboratory media and conditions, but optimal growth may be influenced by factors such as temperature or media composition. Ideally, categorization should be based on the environmental conditions at which they naturally live instead of laboratory ones. Cellular life in hypersaline habitats is dominated by prokaryotes (archaea and bacteria), with a few microbial eukaryotes, such as photosynthetic and heterotrophic protists and fungi, and the crustacean Artemia salina.[1,4-7] Also, viruses are a significant part of the community.[8,9] The use of culture independent techniques typically demonstrated that the most abundant species in saturated brines are the square haloarchaeon Haloquadratum walsbyi and Salinibacter ruber though there are notable exceptions.[10,11] Recent *in-situ* analyses of several hypersaline habitats discovered a new archaeal class called Nanohaloarchaea,[12] and also provided insight into the isolation of some abundant previously uncultivated microbes, such as the recently described gamma proteobacterium *Spiribacter salinus*.[13-15] The presence of novel, abundant and previously unsuspected microbial groups was detected, including a group of low-GC Actinobacteria related to freshwater strains, a euryarchaeon named *Candidatus haloredivivus* which has the lowest GC content described for any euryarchaeon, a high-GC euryarchaeon and a gammaproteobacterium related to Alkalilimnicola and Nitrococcus.[13] Single-cell genome analyses have also indicated that new bacteroidetes groups, different from Salinibacter, might be abundant in these salterns.[16] Only organisms that can grow above 100 g NaCl were considered.

Microbial resources have made an incredible contribution to the antibiotic drug discovery and development process over the last seven decades.[17] In particular, actinomycetes are the most important source of bioactive natural compounds with a long track record of producing novel molecules, including several commercially important drugs like Streptomycin, Gentamicin, Vancomycin, Clindamycin, Erythromycin, Amphotericin, Rifampicin, and Tetracycline. More novel molecules with potential therapeutic applications are still on the row to be discovered from these actinomycetes.[18] In recent decades, isolation and exploitation of actinomycetes for novel compounds from conventional environments have led to rediscovery of known compounds.[19,20] However, diverse actinomycetes from poorly studied unusual environments promises a raise in the prospect of discovering novel compounds with potential activities that can be developed as a resource for drug discovery.[21-27] In this respect, current actinomycetes isolation programs are reoriented toward largely unexplored, unusual and extreme environments like hypersaline marine environments, extreme inland saline zones, volcanic zones, hyperarids and glaciers.[25,26] There are several reports on inhabitance of microorganisms including actinomycetes in diverse hypersaline environments such as salt lakes,[28,29] solar salterns,[30,31] salt mines,[32] and brine wells.[33] However, these hypersaline environments remain largely unexplored as a source of novel actinomycetes in many tropical and subtropical regions throughout the world. In a recent review reported by Hamedi et al described that actinomycetes form a stable, metabolically active and persistent population in various marine hypersaline ecosystem and it is accepted that halophilic actinomycetes will provide a valuable resource for novel products of industrial interest, including antimicrobial, cytotoxic, neurotoxic, antimitotic, antiviral and antineoplastic activities. Series of bioactive metabolites like Pyrostatins, Salinosporamides, Abyssomicins, Trioxacarcin A, Gutingimycin, Sporolides, Marinomycins, Himalomycins, Diazepinomicin, Helquinoline, Lajollamycin, Tetrodotoxin, Mechercharmycins, Cyanosporasides, Erythronolides, and Ammosamide D have been reported from this physiological group of actinomycetes.[25]

In continued efforts to discover novel natural products from new extremophilic actinomycetes, Zhao et al discovered new linear polyketides, actinopolysporins A, B, and C, as well as the known antitneoplastic antibiotic tubercidin from the halophilic actinomycete *Actinopolyspora erythraea* YIM 90600.[34] Actinomycetes isolated from marine environments have been mainly assigned to a few genera including Micromonospora, Rhodococcus and Streptomyces.[35] Nevertheless, actinomycetes form a stable, metabolically active and persistent population in various marine ecosystems, and culture-dependent studies have revealed members of the genera Dietzia, Rhodococcus, Streptomyces, Micromonospora, Salinispora, Marinophilus, Solwaraspora, Salinibacterium, Aeromicrobium, Gordonia, Microbacterium, Mycobacterium, Nocardiopsis, Pseudonocardia, Actinomadura, Saccharopolyspora, Streptosporangium, Nonomuraea, Williamsia and Verrucosispora.[35-39] Also, one of the artificial saline environments, in which the presence of halotolerant actinomycetes has been investigated is decayed monuments in which high concentrations of hygroscopic salts, including carbonates, chlorides, nitrates, sulfates, etc., are present.[40]

III. PROMINENCE OF ACTINOMYCETES

Actinomycetes, one of the most diverse groups of filamentous bacteria, are well recognized for their metabolic versatility. The bioactive potential of these bacteria facilitates their survival even in distress and unfavourable ecological conditions. This special issue is dedicated to the importance of multitude of primary and secondary metabolites produced by actinomycetes. The importance of large repertory of enzymes from actinomycetes and their potential in replacing chemical catalysts is discussed. Successful commercialization of these enzymes is an important step towards revolutionizing “green technology.” Reduction in the cost of enzyme production is demonstrated by production of endoglucanases from *Streptomyces* sp. on low-cost substrates. Such low-cost production initiatives can be extended to other enzymes and metabolites. Novel properties like thermal and ionic stabilities and a better turnover make these systems infallible and regenerative. The activity of enzymes from actinomycetes is not confined to substrate conversion alone but broadened to biocontrol of quorum-sensing-dependent phytopathogens, as mediated by acyl-homoserine-lactone-degrading enzymes from endophytic actinomycetes.

Unexplored environments often appeal to researchers in the hope of accruing novel bacteria, a continuous quest which has actually led to discovery of unusually industrious microbes. Antimicrobial potential of actinobacteria isolated from the integument of *Trachymyrmex* fungus-growing ants is on par with commercial antimicrobials, clearly manifesting a new explorable niche “actinobacterial symbionts of plants and animals.” The term “antimicrobials” often leads our thoughts to “medicine-related” but it's “environment-related” applications are less contrived. *Streptomyces lunalinharesii* produces antimicrobial substances against sulfate-reducing bacteria commonly responsible for corrosion in the petroleum industry, with an ability to replace the existing biocides. Making the best out of the already good can be achieved for actinomycetes by strain improvement. Advanced microarray-driven reverse engineering strategies for the understanding and modulation of independently functioning regulatory pathways can allow these microfactories to overproduce important antibiotics.

In a nutshell, actinomycetes offer the most promising synthesizers of many industrially and commercially meaningful metabolites. Novel and unexplored habitats may offer bacterial assemblages not reached hitherto. An integration of newer habitats, screening, and improvement technologies can offer promising candidates for biotechnology and health-related applications.

IV. CHARACTERISTICS OF ACTINOMYCETES

Actinomycetes are distinguished on the basis of development of more often than not by branching threads or rods (Figure 2). Hypersaline environments attracted the interest of early microbiologists by the second half of the nineteenth century. Occasional spoilage of salt-cured hides and food gave evidence that, although high concentrations of inorganic salts represent too extreme a condition for most microorganisms, other microorganisms can cope and thrive under such circumstances.

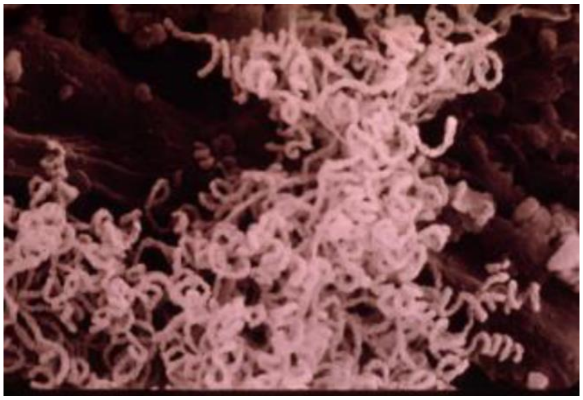

Figure 2: Structure of actinomycetes

V. INIMITABILITY OF HYPERSALINE ACTINOMYCETES

Recently, Actinomycetes have been reported from wide variety of geographical ranges, different ecological conditions and extreme environments. Organisms growing in unusual habitats have unique physiological and biochemical characteristics, producing niche specific secondary metabolites which enable them to thrive in such extreme conditions of higher salinity, pH, pressure and temperature. Previous studies on the chemical structure and composition of marine Actinomycetes has revealed that they possess novel secondary metabolites, active against human tumours and other diseases.[41] The discovery of widespread populations of *Salinispora* (formerly *Salinospora*)- an obligate marine actinomycete genus from the ocean sediments by Fenical's research group was a breakthrough.[38]

Later, *Salinispora* strains were isolated from sponges of some ocean reefs like the sponge, *Pseudo ceratinaclavata* inhabiting Great Barrier Reef. Novel actinomycetes have also been reported from other Great Barrier Reef sponges like *Rhopaloeides odorabile*, *Pseudo ceratinaclavata* and *Candida spongiaflabellate* and sponges inhabiting the Mediterranean Sea like *Aplysina aerophoba* and *Theonella swinhoei.*[42] Actinomycetes isolated from these sponges are uncommon; belong to *Gordoniaceae, Micrococceae* and *Dermatophilaceae* families. This sponge associated actinomycetes produce novel bioactive metabolites.[43] Actinomycetes inhabit either in isolation under deep sea floor and marine snow or in association with marine invertebrates and form an exclusive group of these unique ecosystems. The actinomycetes adapted themselves to these high pressure and low temperature unique ecosystems and produced an enormous reservoir of secondary metabolites to be exploited for practical biomedical applications.

VI. BIOTECHNOLOGICAL APPLICATIONS

Other biomolecules and activities of halophilic actinomycetes that are promising for biotechnological applications are embracing polymers, single cell protein (SCP), removing phosphate from saline environments, enzyme inhibitors, novel drugs etc... Enzyme inhibitors have received increasing attention as useful tools for the study of enzyme structures and reaction mechanisms and in pharmacology. Different types of enzyme inhibitors, *viz.* a-glucosidase, N-acetyl-a-D-glucosaminidase, pyroglutamyl peptidase or a-amylase inhibitors are reported from marine actinomycetes.[44] Actinomycetes are known to enhance the growth of juvenile fish, shrimp and prawn and they can be considered as SCP.[45] Pigments of halophilic microorganisms can be used for food coloring. Among the pigments isolated from halophilic actinomycetes are yellow-red carotenoid pigments which are produced by the halophile *Nesterenkonia halobia*.[46] Neurotoxins are also among actinomycete metabolites with biotechnological potential such as antitumor activity, pain suppression or use in anesthesia. A tetrodotoxin-producing actinomycete, which was determined to be most closely related to *Nocardiopsis dassonvillei*, has been isolated from pufferfish ovaries.[47]

Diseases constitute a significant threat in the life of humans; over 30,000 diseases have been described clinically. Nevertheless, only less than one third of these can be treated.[24] There is an urgent need to obtain new therapeutic agents to cover this medical requirement. Natural products are able to fulfil medical needs through the discovery of novel therapeutic compounds.[48] In this regard, investigations on halophilic actinomycetes during recent years have led to the development of numerous isolated therapeutic substances, including anticancer, antitumor, anti-inflammatory, antioxidant, and antimalarial substances.[49] Salinosporamide A is a novel anticancer substance isolated from the marine actinomycete *Salinispora tropica*. Its chemical structure is bicyclic beta-lactone gammalactam. The mode of action of salinosporamide A is the inhibition of proteasome, which leads to induced apoptosis in multiple myeloma cells.[50] Nereus Pharmaceuticals, Inc., has developed salinosporamide A under the name NPI-0052 for the treatment of cancer in humans, which represents the first clinical anticancer agent candidate for the treatment of cancer produced by halophilic actinomycetes.[24] Lodopyridone is an anticancer agent obtained from the marine actinomycete *Saccharomonospora* sp.[51] Lodopyridone exhibited anticancer activity against the human colon adenocarcinoma cell line HCT-116 with an IC50 of 3.6 µM. Cyclomarin A is a novel anti-inflammatory agent isolated from halophilic *Streptomyces* sp. It is a cyclic heptapeptide and possesses potent anti-inflammatory activity in both *in-vivo* and *in-vitro* assays. Trioxacarcin is a new antimalarial substance isolated from marine *Streptomyces* sp.[52] Trioxacarcin has been tested for antimalarial activity. Results showed extremely high antiplasmodial activity against the pathogen of malaria in comparison to the artemisinin drug, the most effective drug against malaria. Actinosporins C and D are novel antioxidants produced by the sponge-associated actinomycete *Actinokineospora* sp. strain EG49 isolated from the marine sponge *Spheciospongia vagabunda*.[53] Actinosporins C and D showed (at 1.25 µM) a significant antioxidant and protective capacity from the genomic damage induced by hydrogen peroxide in the human promyelocytic (HL-60) cell line.

V. SUMMARY

Studies on the discovery of various natural compounds from salt-tolerant and salt-tolerant actinomycetes inhabiting hypersaline environments have shown that this physiological group has the enormous ability to produce a variety of secondary metabolites with varying activities. The hypersaline environment is of great interest as a habitat for new actinomycetes and is a potential source of new metabolites, therapeutic compounds, enzymes, and other chemicals. Among them, the use of highly salted actinomycetes for medically and industrially important metabolites and enzymes is gaining increasing attention in the scientific community. Numerous new compounds and enzymes from hypersaline actinomycetes have been isolated and characterized from different geographic regions of the world. Hypersaline actinomycetes also serve as an excellent model for producing important metabolites and enzymes involved in stress responses. In addition, the new properties of this type of highly salted actinomycetes and their ability to grow on a large scale make them potentially valuable for biotechnology applications.

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