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A REVIEW ON DIVERSITY AND ANTIMICROBIAL METABOLITES FROM HALOPHILIC BACTERIA

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ABSTRACT: Microorganisms that live their life in places with high salt concentrations are known as Halophiles. Halophilic bacteria play a majority role in hypersaline environments than other microorganisms. These Halophiles are having intense strategies of adaptation and tolerate them to sustain their survival in the saline extreme, such adaptation in hypersaline environments makes them to give unique attention to the researcher for their biological properties. The diversity of halophiles bacteria incorporates aerobic and anaerobic phototrophs, aerobic heterotrophs, fermenters, denitrifies, sulfate reducers, and methanogens. The biotechnological important of the halophilic bacteria, such as producing a Novel bioactive compounds, industrially important enzyme, Bio-surfactants, Stabilizers Exopolysacharides, Probiotics *etc*. Secondary metabolites are organic compounds produced by bacteria, fungi, or plants which are not directly involved in the normal growth, development, or reproduction of the organism. Some common examples of secondary metabolites include ergot alkaloids, antibiotics, naphthalenes, nucleosides, phenazines, quinolines, terpenoids, peptides, and growth factors.

INTRODUCTION: Hypersaline environments contain higher salt concentrations, and now a day's these environments are largely used for the study of microbial diversity and ecology [1], whereas halophiles are a group of indigenous, salt-loving microorganisms that inhabit hypersaline environments such as salt packs, brines, bodies of saltwater, mud, and industries using salt as a preservative; until recently investigations in this field were supported mainly by salt pans.

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Besides, the hypersaline environments have low dissolved oxygen concentration, low or high temperatures, high pH values, solar irradiation, *etc*. The parameters overall make the condition stressful for the microorganisms; henceforth they resist the denaturing effects of the salts with the capacity to balance the osmotic pressure of the saline environment.

Halophilic and extremely halotolerant microorganisms can be found in three domains of life: Archaea, Bacteria, and Eucarya. Halophilic microorganisms include extremely halophilic and methanogenic archaea, cyanobacteria, green and purple bacteria, sulfur-oxidizing bacteria, anaerobic fermentative, homoacetogenic, sulfate-reducing bacteria and Gram-negative and Gram-positive heterotrophic bacteria.

In addition, some algae, protozoa, fungi, and a few higher organisms have adapted to life in high salinity [2]. Halophiles are organisms defines that have an optimal growth above 3% salt concentration; if the optimal growth occurs between 3 and 15% salt, they are regarded as moderate halophiles and when it occurs above 15% and up to halite saturation (34%), they are regarded as extreme halophiles.

Halophiles have developed two different adaptive strategies to cope up with the osmotic pressure induced by the high NaCl concentration they tend to inhabit. The halobacteria and some extremely halophilic bacteria accumulate inorganic ions in the cytoplasm (K^+, Na^+, Cl) to balance the osmotic pressure of the medium, and they have developed specific proteins that are stable and active in the presence of salts. In contrast, moderate halophiles accumulate in high amount in the cytoplasm as specific organic osmolytes, which functions as osmoprotectants, providing osmotic balance without interfering with the normal metabolism of the cell [3]. Apart from this, they accumulate one or more compatible solutes by using a variety of osmoregulatory methods [1, 4].

Although salt has been a valuable resource and required for all life forms [3], proposed the classification of microorganisms, whose response to salinity (NaCl) *viz.*, non-halophilic microorganisms, <0.2 M (~1%) salt; slight halophiles, 0.2-0.5 M (~1%) salt; moderate halophiles, 0.5-2.5 M (~3-15%) salt; borderline extreme halophiles, 1.5-4.0 M (~9-23%) salt; and extreme halophiles, 2.5-5.2 M (~15-32%) salt [5]. In contrast, non-halophiles grow optimally in less than 0.2 M NaCl concentrations. This review will be focused on the diversity and biotechnological applications of the novel metabolites and unique bioactive enzymes from halophiles. The adaptation for living in such hypersaline environments gives rise to these extremophiles, which builds in advantages between them to get exploited more from a biotechnological point of view. In recent years, halophilic organisms are mainly isolated from saline environments, such as salt lakes, marine solar salterns, saline soils, and marine sediments. However, halophile bacteria have also been isolated from some non-common places, for example, textile effluents, halophytes, mine tailings as well as processed foods.

Diversity: Gibbons, described the three genera of extremely halophilic bacteria: Halobacterium, Halococcus, and Haloarcula [6]. In the genus, Halobacterium, or more species have been described. Halococcus is the second genus of the family Halobacteriaceae [6]. So far, four species have been validated under the genus, Halococcus namely, *Halococcus morrhuae* Approved list (IJSB 30:225-420, 1980). *Halococcus turkmenicus* [7]. *Halococcus saccharolyticus* [8] and *Halococcus salifodinae* [9]. The family Halomonadaceae of the class Gammaproteobacteria consists mostly of marine and moderately halophilic bacteria with rather diverse phenotypic characteristics [10]. A total of nine genera have included in the family Halomonadaceae; out of which, six are halophilic bacteria (Halomonas, Chromohalobacter, Modicisalibacter, Cobetia, Kushneria, and Salinicola) and three are non-halophilic bacteria (Zymobacter, Halotalea, and Carnimonas), which showed heterogeneity during the study of phylogeny and phenotypic characters [11]. The genus Halomonas is the type genus of the family, Halomonadaceae, and it has been studied with the genus Chromohalobacter as a model organism of halophilism [12].

The genus Halomonas and Halomonas type subspecies to accommodate a group of Gram-negative and rod-shaped bacteria that grow on a wide range of salt concentrations from 0.1 to 32.5% (w/v) NaCl was later placed under the family Halomonadaceae [13]. To date, the genus Halomonas comprises 58 species, including the recently described *Halomonas zhanjiangensis* [14]. *Halomonas ilicicola*, *Halomonas fontilapidosi* [15], *Halomonas xinjiangensis* [16], *Halomonas hamiltonii* [17], *Halomonas johnsoniae*, *Halomonas stevensii* [18]. *Halomonas andesensis* [19]. Halomonas sinaiensis [20], *Halomonas beimenensis* [21], Halomona sramblicola and *Halomonas smyrnensis* [22]. The members of this genus were isolated from various saline habitats, such as salt lakes, saline sand, salt soil (including soil contaminated with crude oil), saline wells, solar salterns, saline wetland, and marine (including deep-sea) environments. In addition, some Halomonas species were isolated from animals, mineral pools, traditional Korean fermented seafood, mural paintings as well as artificial sewage installations [23, 24]. A novel Halomonas like strain designated YIM-C248T was isolated from a sediment sample collected from the

Dachaidamu salt lake in Qaidam Basin in Qinghai, northeast China, where the water temperature was 18 ºC with pH 6.4-7.8 and salinity of (w/v) [14]. In the course of investigating the microbial diversity of salt Lakes in Xinjiang, two Halomonas like organisms were isolated from sediments of aiding salt Lake in Xinjiang [25].

The genus Virgibacillus was first proposed and emended by Heyndrickx. At the time of writing, the genus comprised 25 recognized species, namely, *Virgibacillus pantothenticus*, *Virgibacillus proomii*, *Virgibacillus carmonensis*, *Virgibacillus necropolis*, *Virgibacillus marismortui*, *Virgibacillus salexigens*, *Virgibacillus carmonensis*, *Virgibacillus halodenitrificans*, Virgibacillus dokdonensis [26], *Virgibacillus koreensis*, *Virgibacillus olivae* [27], *Virgibacillus halophilus*, *Virgibacillus chiguensis* [23], *Virgibacillus kekensis* [14] and *Virgibacillus salaries* [28], *V. Arcticus* [29], *V. salinus* [30], V. sediment [14], *V. byusanensis* [31], *V. xinjiangensis* [32]. *V. Soli* [30] and *V. Subterraneus* [21], *Virgibacillus alimentarius* [17], *Virgibacillus albus* [33, 14] isolated a moderately halophilic bacterium *Virgibacillus litoralis* from saline soil and isolated a moderately halophilic strain, from Naozhou Island, Leizhou Bay, South China Sea [34].

In India, halophilic Bacteria have been reported from the Extreme environment of the coastal regions of Maharashtra, Gujarat, Tamil Nadu, Goa, and the desert state of Rajasthan. The bacteria reported from these locations (*e.g.*, Alkalibacillus sp. A1, Virgibacillus sp. V1, and Actinopolyspora sp. AH1) are halo-alkaliphilic in nature and exhibit optimal growth in the presence of 5–20% NaCl and pH 8–10 [35]. The genus Halobacillus was originally described by Springto accommodate two novel species [36], *Halobacillus litoralis* and *Halobacillus trueperi* and the transfer of *Sporosarcina halophila* [37] to Halobacillus as *Halobacillus halophilus*. At present, this genus comprises 18 recognized species, including the recently described H. halophilus, H. litoralis and *H. Trueperi* [38], H. Salinus [39], H. Karajensis [40], *H. Locisalis*, H. aidingensis and H. Dabanensis, H. Yeomjeoni , H. Campisalis [31], H. profundi and H. Kuroshimensis [41], H. faecis, H. mangrovei [42], H. alkaliphilus [20], H. Naozhouensis H. Salsuginis [15] and H. Seohaensis [28], The Halobacillus genus comprises moderate halophiles which can grow and produce enzymes over a very wide range of salinities, making them very attractive for research and for screening of novel enzymes with unusual properties [2]. The genus Halobacillus can be differentiated clearly from other related genera by having a cell-wall peptidoglycan type based on L-Orn–D-Asp [36, 43, 31] with the exception of Halobacillus campisalis [39], H. Seohaensis [44] and H. Naozhouensis [14] having the cell-wall type

meso-diaminopimelic acid (meso-DAP). During an investigation of the microbial diversity of the Xiangli Salt Mine in Hunan Province, China, a novel Halobacillus like strain was isolated and designated as JSM 071077T, which contains meso-DAP in its cell-wall peptidoglycan as the diamino acid [39]. The genus Marinobacter, within the class Gammaproteo bacteria, family Alteromonadaceae, currently includes 33 species that are isolated mainly from saline or hypersaline environment [44]. Some extremely halophiles, archaeal and bacterial isolates were identified in Chott El Jerid, a hypersaline lake in the south of Tunisia, assessment of 68 partial 16S rRNA analyzed by amplified rDNA restriction analysis (ARDRA) revealed 15 different bacterial and archaeal taxonomic groups.

Based on ARDRA results, phenotypic and hydrolytic activity tests, 20 archaeal and 6 bacterial isolates were selected for sequencing and as members of the genera: Salicola, Bacillus, Halorubrum, Natrinema, and Haloterrigena. Bacterial and archaeal aerobic communities were recovered from sediments from the shallow El-Djerid salt lake in Tunisia, and their salinity gradient distribution was established. Six samples for physicochemical and microbiological analyses were obtained from 6 saline sites in the lake for physico-chemical and microbiological analyses. All samples studied were considered hypersaline with NaCl concentration ranging from 150 to 260 g/L. A specific halophilic microbial community was recovered from each site, and characterization of isolated microorganisms was performed *via* both phenotypic and phylogenetic approaches. Only one extreme halophilic organism, domain Archaea, was isolated from site 4 only, whereas organisms in the domain Bacteria were recovered from the five remaining sampling sites that contained up to 250 g/L NaCl. Members of the domain Bacteria belonged to genera Salicola, Pontibacillus, Halomonas, Marinococcus, and Halobacillus, whereas the only member of domain Archaea isolated belonged to the genus Halorubrum [45]. Boyadzhieva isolated 20 morphologically different moderately halophilic and two halotolerant strains affiliated with 11 species from eight genera referred to the phyla Proteobacteria, Firmicutes, and Actinobacteria [46]. Gram-negative bacteria belonged to the genera Halomonas, Chromohalobacter, Salinivibrio, Cobetia, and Nesiotobacter, and gram-positive strains were representatives of the genera Virgibacillus, Salinicoccus, and Brevibacterium. Totally 152 halophilic bacteria were isolated from Yuncheng Salt Lake, China. Phylogenetic analysis based on 16S rRNA gene sequence comparisons revealed that thirty-four strains were related to the phylum Firmicutes and belonged to three families, Bacillaceae, Clostridiaceae and Staphylococcaceae. The other strains were identified as the members of Halomonadaceae and Idiomarinaceae, which belonged to the phylum γ-Proteobacteria [47]. Lnès Quadri isolated 102 extremely halophilic strains isolated from hypersaline environments of the Algerian Sahara [48].

Novel Metabolites: Halophiles have attracted many researchers because of their wide range of adaptability to a saline environment and their potentially promising applications as well. They are the primary sources of various compatible solutes, stable enzymes (DNAses, lipases, amylases, and proteases), bacteriorhodopsin, polymers, β-carotene and other organic substances of interest [49, 50, 51]. According to Kindzierski, broad-spectrum diversity of various compounds, which mimics as a compatible solute from halophilic bacteria, makes the strategy difficult in understanding the withstand of salt tolerance task [4]. The understanding of the various pathways that produce certain compatible solutes by knowing about the metabolic network involved is considered challenging work. Since ancient times up to now, there has been a continued battle between humans and pathogens that cause infections such as bubonic plague, tuberculosis, malaria, HIV, and so on. A wide variety of diseases and medical problems represent a challenging threat to humans, who since ancient times have been searching for natural compounds from plants, animals, and other sources to treat them. Although the process of finding effective treatments against fatal diseases is difficult, extensive searches for natural bioactive compounds have previously yielded some successful results. The isolation and identification of specific natural compounds led to the development of medicine, and human learned to separate the isolates into medicinal drugs, which could be used to treat different diseases and poisonous substances. Statistically, at least 50% of the existing drugs that used to treat human illnesses were derived from natural products and most of which are obtained from terrestrial organisms.

However, due to continuous and exhaustive research, land-based natural bioactive compounds have become increasingly difficult to find. Instead, water-based natural compounds have become a more promising source, not only from a pharmacological point of view but also for industrial and commercial applications. Unlike terrestrial organism that produces material in comparatively better yields, the collection and processing of the compounds from marine source ranges from grossly impractical to the utterly impossible due to availability in micro quantities [52]. Hence, the elucidation of the absolute structure of such active compounds is essential so that one can attempt their synthesis in order to provide sufficient scope for evaluating and exploiting these compounds for the benefit of mankind.

Antimicrobial activity among marine bacteria is a well-known phenomenon and demonstrated in a number of studies [53]. Since late 1940s, Microbiologists and Pharmacologists have been focusing on marine bacteria as potent sources for new antibiotic discovery and development [54]. Members of Halorubrum and Haloferax have been identified as the preponderant halocin-producing genera, the cross-domanin antimicrobial action was observed against bacterial members of the genera Halomonas, Rhodovibrio, Salisaeta or Pontibacillus, all isolated from hypersaline samples [55]. The ability to produce multiple antibiotics probably helps to suppress diverse microbial competitors. The halophilic bacteria were not much explored for the production of such active compounds. Two sulfonolipids (SL1 and SL2) isolated from the lipid extract of the halophile, Salisaeta longa, and those sulfonolipids have sulfonate sphingoid base, which is an analogue of capnine [56, 57, 58].

The capnine of extremely halophilic bacteriodetes has the specific name of halocapnine. Similarly, two antimicrobial compounds, glycolipids and lipopeptides by halophilic Antarctic Nocardioides sp [59]. Actinoalloteichus sp. AH97 produced two bioactive compounds; (hydrophilic) aminoglycosidic compound and (hydrophobic) dioctylphthalate [60]. Other examples are pigments such as prodigiosin isolated from Vibrio spp., that exhibit antimicrobial activity [61] and diketopiperazines (DKPs) from Streptomyces spp., Bacillus spp. and Nocardiopsis spp [62].

Halophiles can be developed as a new source of bioactive compounds [10]. However, little is known about bioactivities screened from the moderately halophilic bacteria and some antitumor and antimicrobial substances have been isolated from moderately and extremely halophilic bacteria. Bacteria from salt pans have a potential resource for antibacterial metabolites [63]. Halocins, the proteinaceous antimicrobial compounds were discovered from several extremely halophilic Archaea [64]. Three new cyclopeptides (halolitoralin A–C) isolated from a marine sediment-derived Halobacillus litoralis YS3106 showed moderate antifungal activities [65]. Antimicrobial activities of two novel halophilic Saccharomonospora strains have been isolated in Algerian Sahara soils [60]. Studies also showed that some bacterial strains of Bacillus isolated from different hypersaline soils could inhibit certain plant pathogenic fungi [66]. Phylogenetic analysis and screening of antimicrobial and cytotoxic activities of moderately halophilic bacteria isolated from the Weihai Solar Saltern were carried out in China [54]. Various filamentous fungi isolated from hypersaline conditions inhabit a large variety of different ecological habitats [67]. Competition selected fungi have the ability to produce various secondary metabolites [68,] and different extracellular enzymes have a wide range of applications in agrochemical, food, and pharmaceutical industries [69].

GC-MS analysis of the halophilic Halomonas sp. BS4 contains polymers, fatty acids, and other compounds including 1, 2-Ethanediamine N, N, N', N'-tetra, 8-Methyl-6-nonenamide, (Z)-9-octadecenamide, etc. But, interestingly there are not many studies that have directed towards halophilic bacteria for the compound analysis [70], the production of novel methyl-branched fatty acids in a halophilic bacterium [71]. There are many research articles published on antibiotic production by halophilic actinomycetes [72]. Similarly, Pseudo alteromonas piscicida PG-02, a moderately halophilic bacterium reported to have the ability to produce antibiotic compounds with broad-spectrum antibacterial activity [69] but its antibacterial activity against MRSA was comparable with vancomycin, which is the last reported antibiotic against this pathogen. Recently, Sawale discovered partial structures of a bioactive compound of CH_3, O=C, C-H, CH_2, group C-N stretching with substituted benzene ring isolated from halophilic Bacillus pumilus strain [51, 73].

Halophilic bacterial strains exhibited higher antimicrobial activity in Gram-negative bacteria than Gram-positive bacteria. These results were not consistent with previous studies; wherein Gram-positive bacteria were more susceptible to antibiotics than Gram-negative bacteria [74]. However, the study corroborates with the findings of Chen [49, 21]. The antibacterial and antifungal assays of halophiles (crude extract) have shown that the marine environments represent a potential source of new antimicrobial and antifungal agents.

The marine environments and mangrove rhizosphere have an enormous diversity of all aerobic as well as facultative anaerobic bacteria [75]. A large proportion of the bioactive natural products reported over the past two decades were derived from marine macro and microorganisms. Several of these compounds were reported to be pharmacologically active and interesting candidates for the drug industry as anticancer, anti-inflammatory or analgesic agents [76, 77], besides antitumor and antimicrobial compounds have been reported from moderately and extremely halophilic microorganisms including archaeal proteinaceous antimicrobials (i.e halocins) that have been isolated from several extremely halophilic archaea such as Natrinema sp [78]. Antimicrobial of bio-pigments by Aquisalibacillus elongatus MB592, Salinicoccus sesuvii MB597, and Halomonas aquamarina MB598 isolated from Khewra Salt Range, Pakistan [79]. Hypersaline environment and halophilic bacteria are the promising resource for antimicrobial compounds, and which is immense importance for the discovery in the future.

Thus, the saline environments could be largely underexplored ecological niches for the discovery of bioactive metabolites and these halophilic microorganisms are potential sources for a broad range of new therapeutic compounds [69]. The current estimate that 90% of the biosynthetic capacity of micro-organisms is yet to be discovered highlights the importance of research in microbial diversity and in the discovery of bioactive principles as keys to unlocking the metabolic potential of microbes [80].

The antimicrobial characteristics of novel bacterial isolate Paenibacilllus sp. SMB1 from a halo-alkaline lake in India. They have inhibitory activity against indicator bacteria and found that four novel species were able to prevent the growth of test strains studied *in-vitro* [81].

CONCLUSION: The Diversity of halophilic archaea and bacteria were widely present in an extreme environment. These halophiles from extreme environments are exemplified as great sources for identifying industrially important enzymes and novel biomolecules with unique properties to treat various kinds of diseases.

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