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REVIEW ARTICLE

Biodiversity and potential applications of halophilic archaeal secondary metabolites

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Abstract

Halophilic archaea inhabit extreme ecosystem so their enzymes are also resist to multiple extreme condition which can be utilize as biotechnological application. Pigments, enzymes and secondary metabolites produce by haloarchaea microorganism shows a potential to use in biomedicines, pharmacy and biotechnology process. Several biocompounds produced by haloarchaea like halocins, PHAs/PHBs, carotenoids and enzymes are of high biotechnology interest. Some haloarchaeal species can produce carotenoids, which can be genetically modified or can improve the cultivation parameters to get the high yield product. This haloarchaeal carotenoids show a potential use in biomedicine and by the help of a biotechnological process, its production can be done at large scale. Many halophilic enzymes like esterases, lipases, proteases and glycosyl hydrolases could be used in biotechnological application Halophilic bacteria and highly halophilic archaea which are aerobic or called as haloarchaea, assume a significant role in the industry with a huge number of applications like in food products fermentation, preservatives, cosmetics, manufacturing of bioplastics, artificial retinas, photoelectric devices, holograms, biosensors, etc.

Keywords: biocompounds; biotechnological applications; eco-system; extreme

Introduction

Halophilic archaea dominate the Earth's many hypersaline environments such as salt lakes, underground salt deposits and solar salterns (1-3). These microbes can survive under low water activity and can permit sodium chloride (NaCl) brine at saturation; even salt crystals (halite) are added in the fluid (4). Extremely halotolerant and halophilic microbes can be established in each of the three areas of life: Archaea, Bacteria and Eukarya. In some ecosystems, halophile microorganisms live in huge numbers that their closeness can be viewed without the requirement for a magnifying instrument. The brackish water of saltern crystallizer lakes globally is shaded pink-red by Eucarya (*Dunaliella salina*), Bacteria (Salinibacter) and Archaea (Haloquadratum and further delegates of the Halobacteriales) (5). According to the requirement for salt components, halophiles are classified into the groups including slightly halophiles (2–5 % NaCl), moderately halophiles (5-20 % NaCl) and extremely halophiles (20-30 % NaCl) while strains grow in 0–5 % salinity are considered halotolerant microorganisms (6). The period of genomics has not passed either by the halophiles: recently the total sequence of the genome of the principal halophile (the Archaeon *Halobacterium salinarum*) has been published (7). To adapt to excessive saline conditions, halophilic microorganisms have established several biochemical strategies, including compatible solute synthesis to support cell structure and function (8). These solutes (e.g., ectoine) plus other compounds (hydrolases, exopolysaccharides, biosurfactants, bacteriorhodopsins) maintained by halophilic microorganisms, which are positively to the industry. Other than these physiological and metabolic highlights, halophilic microbes are known to assume fundamental roles in degrading and transforming organic toxins and waste in saline wastewaters and in fish sauces fermentation (9). In the previous few years, the microorganism variety of such environments of hypersaline has been broadly investigated by utilizing both culture-independent and culture-dependent methods and the halophilic prokaryotes has been found in a large range of saline situation in the several geographical locations like salt lakes, marine salterns and saline soils (10, 11). Enzymes maintained by halophilic microorganisms have an ideal environment under exponentially high concentrations of salt, as concentrations of potassium chloride (KCl) of approximately 4 M or concentrations of NaCl higher than 5 M. These enzymes have some extra amino acids which supply large negative charge on the surfaces of the enzymes (12). Discovery of enzymatic abilities of halophilic microorganisms can accelerate the industrial processes and meet the increasing demands for biocatalysts. The charge of surface area of halophilic enzymes plays a significant role in solvent-enzyme interaction. A halophilic α-amylase isolated from *Alicyclobacillus acidocaldarius* contained a negative charge on the surface area that contributed to the stability improvement in salty circumstances (13). The halophilic members in genera *Bacillus*, *Halomonas*, *Salinovibrio*, *Chromohalobacter* and *Salinicoccus* have been identified with potential in production of types of exoenzymes under hypersaline habitats (14). Thus, the enzymatic effect is enhanced during biofuel production. *Sagittula stellata*, a marine aerobic bacterium, was the first halophilic strain with the capacity to break down lignin into smaller units (15).

Diversity of halophytes

Hypersaline conditions are found in an enormous variety of terrestrial and aquatic ecosystems. They are occupied by microbes that are halotolerant yet additionally halophilic microbes extending from halophiles of moderate with greater development rates in media containing somewhere in the range of 0.5 M and 2.5 M NaCl to utmost halophiles with greater development rates in media containing over 2.5 M NaCl (16). We know anaerobic as well as aerobic chemoautotrophic, halophiles, phototrophic and heterotrophic types, to convert a huge substrate variety (17). Among the halophiles we also encounter "polyextremophilic" types, adapted to grow at a combination of extremes, for example, of salt and alkaline conditions (a commonly found combination), salt and low pH (relatively rare), or salt and high temperatures; we even know some anaerobic halophilic thermoalkaliphilic bacteria (18). Microorganisms able to grow at salt concentrations up to NaCl saturation (> 300 g/l salt) are all over present at the small subunit rRNA-based tree of life. Thus, three red-pigmented organisms are frequently found in salt-saturated saltern crystallizer ponds worldwide: The *D. salina* alga which is unicellular (Chlorophyceae, Eucarya), the *Haloquadratum walsbyi* which is a square archaeon (Halobacteriales, Euryarchaeota) and *Salinibacter ruber* (Bacteroidetes, Bacteria) (19). Among the utmost halophiles, the aerobic Archaea of the Halobacteriaceae family have the most studied. This family, the only family described in the order Halobacteriales, is prokaryotes that require salt and is a group of phylogenetically coherent (20). Most of the over a hundred species described grow optimally above 150 g/l salt and no development is acquired in its absence. Most of the species even lyse at salt concentrations which are below 100 g/l. Within the domain bacteria we find halophiles in several phyla, notably in the *Cyanobacteria*, the *Gammaproteobacteria*, the *Firmicutes* and the *Bacteroidetes*. The best-known group of halophilic or highly halotolerant types within the Bacteria is probably the family Halomonadaceae (*Gammaproteobacteria*), in which thus far about 70 species of versatile aerobic heterotrophs with a broad salinity range were described (21). Within the Firmicutes we also find the order *Halanaerobiales* with two families, the *Halanaerobiaceae* and the *Halobacteroidaceae*, consisting entirely of anaerobic halophilic, generally fermentative bacteria (22).

The general characteristics of microbes of halophilic are the minimum nourishing needs and resistance to excessive concentrations of salt with the ability to adjust the osmotic pressure of the environment (23). Their systems of haloadaptation depend on the intracellular stockpiling of KCl over 37 % (5 M) (salt-in strategy) or the gathering of solutes that is compatible (salt-out strategy) to keep the sodium balance into the cytoplasm and neutralize the osmotic pressure of the outside condition given by the high saltiness (24). They are physiologically differing; for the most part, oxygen consuming and too heterotrophic, chemoautotrophic, phototrophic and anaerobic.

The considerable metabolic adaptability of halophilic microbes, their low wholesome needs and their hereditary machineries of adjustment to brutal conditions, similar to supplement starvation, drying up, high ionic strength and high solar radiation, make them promising competitors and a plan for drug discovery (25).

Halophilic microorganisms are accepted makers of retinal proteins, carotenoid pigments, hydrolytic enzymes and perfect solutes as biofertilizers, biopolymers and macromolecules stabilizers (26). Halophilic bacteria and highly halophilic oxygen-consuming archaea, or called as haloarchaea, assume a crucial role in the industry with a huge number of uses like biosensors, holograms, artificial retinas, photoelectric devices, manufacturing of bioplastics, preservatives, cosmetics, fermented food products, etc.

The microbes may dwell everywhere in the universe, even in extreme conditions like pH, salinity, pressure and temperature. The microbes that survive in a saline environment are considered halo-tolerant and those microbes whose growth is favored in a saline condition are halophiles (Table 1, Supplementary Data). The environments having a concentration of NaCl approaching saturation are considered hypersaline environments, populated with halotolerant microbes. The halophilic archaea (or the haloarchaea) are known to be extremophiles that dominate in hypersaline environments (Table 2, Supplementary Data) in large populations. The highly halophilic archaea belong to the family Halobacteriaceae. They are heterophilic and dominate in hypersaline environments with their ability to sustain in, by balancing osmotic potentials. The master plan to assist in high salt concentrations is: (i) losing water from cytoplasm and (ii) assembling osmolytes in cytoplasm. In the first strategy, the microbes have a high concentration of salts (like NaCl, KCl) in the cytoplasm by water loss to maintain osmolarity with the environment. In the second strategy, the microbes accumulate solutes (like amino acids, sugars) to survive in a hypersaline environment. The adaptations like high Guanine Cytosine (GC) content in DNA and glycosylated proteins in membranes also play an important role in their survival (27). The haloarchaea are diverse in pigmentations (like purple, red) due to carotenoid/ carotenoid derivatives and cell shapes (like rods, spherical or pleomorphic) (28). The diversity of haloarchaea could be marked based on morphology, culture, conserved sequences and rDNA sequencing. The classification of halophilic archaea is summarized in Table 3, Supplementary Data.

Adaptations of the Halophilic Archaea

For survival of halophilic archaea in extreme saline conditions, the changes in metabolic pathways could be seen as adaptation. Such adaptation leads to a change in the production of some metabolites, which could be of interest for large-scale production. The better understanding of the physiology, metabolism and molecular biology in halophilic archaea could pave the way for production of several commercially important compounds. Various compounds are isolated from the culture of halophilic archaea and are being described from diverse species. Some of these are carotenoids (phytoene, lycopene and β-carotene), enzymes (Glycosyl hydrolases, Proteases, Esterases, lipases, Cellulases and chitinases), polyesters (Polyhydroxyalkanoates) and bacteriocin-like peptides (halocins). The details of the source organisms and potential roles of those compounds are provided in Table 4, Supplementary Data.

Bioethanol/Biobutanol

Production of bioethanol via different enzymes from different biomasses is more nature-friendly and more favored than other processes. Lignocellulosic biomass or other plant biomasses are renewable materials, consisting mainly of cellulose, hemicelluloses, lignin and starch. Production of bioethanol from biomass comprises of four major steps, including pretreatment of biomass, hydrolysis of enzyme, fermentation process and distillation (29). To perform a fermentation process, it is important to preprocess this biomass under the highest pH or at a high temperature condition. The salt concentration and resulting pH make the nearby environment similar to alkaline–saline lakes. Hydrolyzed biomass produced reduced sugars, which are then transformed by microbial action to ethanol (7).

Acetyl-Coenzyme A is a central metabolite that can be used as a substrate for the production of ethanol (8). *Pyrococcus furiosus,* a thermophilic archaeon, was recently used to demonstrate the pathway for the production of ethanol from acetate (13). Carbohydrates can be metabolized by *P. furiosus* at a near 100 °C temperature to primarily H_2, CO_2 and acetate. Heterologous expression of the AdhA gene from Thermo anaerobacter species strain X514 (T. X514) in *P. furiosus* up to 78 °C temperature can be used for the production of ethanol (13). AOR (aldehyde oxidoreductase) of *P. furiosus* is ferredoxin-dependent, which generates a substrate that is acetaldehyde for AdhA. Acetaldehyde oxidizes by this enzyme for detoxification purposes (6). In anaerobic and aerobic environments, the halophilic bacterium strain F of species *Nesterenkonia* that is isolated from Aran-Bidgol, which is a hypersaline Iran, can produce ethanol, butanol and acetone.

Archaeocins

Bacteriocins are antimicrobial proteins and peptides which are widely produced by bacteria and have been utilized in many industries. From haloarchaea, an antibiotic peptide named archaeocins, which is an antibiotic peptide, is being widely found and more recently from the *Sulfolobus* genus sulfolobicins. Amongst haloarchaea the production of halocin is thought to be near universal and as a result within these molecules there is a great deal of diversity (30). Based on size, halocins can be classified into two classes: the microhalocins, which are smaller than 3.6 kDa and the halocins, which are larger than 35 kDa (28). The antimicrobial action of these halocins can likewise run, with some halocins having a limited scope of action influencing just close family members, instead of an all the more extensively dynamic A4 halocin fit for repressing the development of *Sulfolobus solfataricus,* an agent of another phylum of archaea (31). Halocin producing strains are particularly used in the industry of textile, in the tanning process where a considerable amount of salt is used. At these conditions, there can be damage of the product by halophiles, including some haloarchaea growth and this unwanted growth can be prevented by halocins (1).

Metabolites

Metabolites produced by Archaea are diketopiperazines, archaeocins, polyhydroxyalkanoates, exopolysaccharides, Acyl homoserine lactones, phenazines, Carotenoids, biosurfactants (26).

Diketopiperazines

Diketopiperazines (DKPs) have only recently been identified in a haloarchaeon, *Haloterrigena hispanica* and have been observed in many bacteria from a wide range of environments, it is also occasionally referred to as cyclic dipeptides (32). It is currently unknown how many archaea produce DKPs, but it is suggested that *Natronococcus occultus* is one of the potential makers because of a biosensor that can be enacted by DKPs or Acyl-homoserine lactones (AHLs) (32). Synthesis of DKPs in bacteria takes place using one of these pathways, by a novel class of enzymes called CDPS (cyclic dipeptide synthases) or the NRPS (nonribosomal peptide synthesis) (15). At present, there are no functional nonribosomal peptide synthesis gene clusters or cyclic dipeptide synthase genes identified in archaea. DKPs have a plethora of bioactivities that are useful or potentially significant for medical and industrial purposes, including antibacterial, antifungal and antiviral as well as antitumor activities (33).

Exopolysaccharides and Polyhydroxyalkanoates

EPS (Exopolysaccharides) are released and produced by many different microbes, including archaea; it is a carbohydrate of high molecular weight. EPS is thought to give an organism assurance against a few natural insults, for example ultraviolet radiation, predation, or desiccation (34). Production of EPS in archaea has been essentially investigated within the thermophile and halophile groups (35). Molecules of EPS have various industrial applications, for example utilized in the food industry as emulsifying or gelling agents. Various bacterial molecules of EPS, for example dextran, curdlan and xanthan are being industrially produced despite some of these being delivered by pathogens, for example, *Alcaligenes faecalis* (36). EPS producing *Haloferax* species could be utilized to expel substantial metal contamination from a condition high in salt (36). The polyhydroxyalkanoates (PHAs) is a polymer that is insoluble in water utilized as a method for energy and carbon storage in archaea and bacteria. Polyhydroxyalkanoates (PHAs) have gotten extensive consideration in biotechnology as a potential option in contrast to plastics that are based on petrochemical because of their biodegradability and auxiliary properties (25).

Carotenoids

Carotenoids are generally found in haloarchaea that are naturally occurring pigments and are liable for the unmistakable rosy pigmentation of the living beings. Carotenoids are broadly utilized as coloring agents and food enhancement (25). The carotenoids' role is still being researched in human health; however, identified its some potential benefits, such as the prevention of disorders such as cancer, chronic diseases, chronic heart disease and osteoporosis (37, 38). Halophilic archaea grow in extreme conditions. For example, *H. salinarum* shows amassing of C50 carotenoids (5). Only three biosynthetic pathways of cyclic C50 carotenoids, the ε-cyclic C50 carotenoid decaprenoxanthin in *Corynebacterium glutamicum* (39), the βcyclic C50 carotenoid 2,2' bis-(4-hydroxy-3-methybut-2-enyl)- β, β carotene in *Dietzia* sp. strain CQ4 and the γ-cyclic C50 carotenoid (36).

Phenazines

Phenazines are a large class of redox-active secondary metabolites produced by many Gram-positive (e.g. Streptomyces) and Gram-negative bacteria (e.g. Pseudomonas), or by archaeal Methanosarcina species. The center structure of phenazines is a pyrazine ring (1,4-diazabenzene)showingtwoannulatedbenzenes (40).

The biosynthesis of phenazines in bacteria typically stems from non-ribosomal peptide synthesis, a process responsible for many secondary metabolites and natural products, though as mentioned above there are no known non-ribosomal peptide synthetases (NRPS) systems detected in archaea (26). Phenazines can both give and accept electrons, relying on their relative redox potential to other electron transfer molecules. ROS (Reactive oxygen species) formation is a significant method of activity of phenazines and can be helpful to the host, for example through hindrance of pathogenic organisms or inconvenience by obstruction with ordinary cell capacities.

Effect of nutrition and physical factors on their production

Halophilic archaea are present in hypersaline environments and their enzymes are stable at low water activity. Carotenoid pigment is an isoprenoid compound that can be produced from halophilic archaea. Carotenoids are extracted by disrupting the cells within the sight of water. The cell wall of Archaea contains glycoproteins, proteins and polysaccharides. High concentration sodium ions bind to the sulfate group in the cell wall, which helps to maintain the stability. Cell lysis happens when there is a weakening of sodium particles and thus negative charges on the superficial level begin to repulse. Some halophilic archaea can be used in the production of lipids (for food additives), liposomes (for visualizing delivery system in cancer cells), bacteriorhodopsin (for voltaic cells synthesis). *Haloferax mediterranei* ATCC 33500 produces more pigments at a low salt condition about 15 % than at a high condition. *H. salinarum* ATCC 33170 does not produce any carotenoid pigment at a low salt condition than at a high salt medium. *Haloferax volcanii* strain shows that archaea can produce more carotenoids in low salt content media.

Halobacterium salinarium ATCC 33170 shows an increase in pigment production by an increase in glucose concentration, but the effect of glycerol on pigment formation decreases. In many microorganisms, the oxygen and light can act as an inducer. In *Haloferax alexandrius* TM and *Haloferax Salinarum* ATCC 33170 strains, there is no difference in the pigment production when there is the presence or absence of light. There is a demand of magnesium and sulfate ions for the creation and development of carotenoid by *Haloferax alexandrius.* Effect of temperature in carotenoid production can alter the concentration of enzymes involved. Halophilic archaea at the neutral pH maintain their gradient, pH of a microorganism controls the macromolecules stability. Carboxyl ester hydrolases production of a halophilic archaea is active at a high amount of salt, high temperature and low water activity (23).

Pharmacological Significance

Halophilic microbes like archaea have a potential for antimicrobial activity which can be directly used as a drug or can help in drug discovery. *H. salifodinae* MPM-TC secondary metabolites can be used as an antiviral drug which can act against shrimp viruses (41). These extremophiles can be used against multi-drug resistant bacteria and can develop a new molecule as biomedicine. The property of these microbes, like adaptation in harsh conditions and low nutrient requirement can be used in drug discovery. They have several bioactive compounds can be produced with the help of the gene encoding process by bioinformatic tools. In 1982, from the few individuals of the genus *Halobacterium,* the first antimicrobial compound was produced, named halocin. Haloarchaea produce antimicrobial peptides, proteins and extracellular polymeric substances which can be utilized to prevent imminent risk for hospitalized patients. *H. salifodinae* MPM-TC isolated from Tamil Nadu, India shows antiviral and antibacterial activity. The bioactive molecules produced by some organisms and used as an anticancer natural product can be easily manipulated by these microorganisms to produce a new antitumor natural product. The halophilic microorganisms live in a hypersaline condition and their metabolites can be considered as to act against cancer cell viability with less side effects. The use of *Halomonas stenophila* strain B100 in a dose-response method can be used to completely stop the human T leukemia cell proliferation with the over-sulfated exopolysaccharide. Without damaging the healthy fibroblast cells, *H. salinarum* IBRC M10715 shows the strong cytotoxic impact on prostate cancer cell lines. Haloarchaea have the potential to produce carotenoids which shoe antioxidant activity (29). They are also resistant to radiation and able to withstand without the loss of viability by detoxifying the radiation with deleterious effect. *H. salinarum* which lives in an extreme salty environment is resistant to high dose of ultra violet radiation. It detoxifies the free radicals due to the presence of intracellular salt like KCl and DNA is repaired due to the presence of multiple copies of the chromosome set (42).

Potential application

Halophiles can survive in an extreme saline environment with water loss because of the osmoregulatory balance. They can cope with the high salt concentration by accumulating salt in the cytoplasm or by accumulating compatible solutes like 2-sulfotrehalose inside the cell. Halophilic microbes can adapt to the condition by predominating the residues of amino acid on the surface of halophilic proteins and many genes are salt resistant. Due to haloarchaea features, it has a potential application in biotechnology like producing hydrolytic enzymes under hypersaline conditions, which can be utilized in extending the range of already available biocatalysts. Production by the help of enzyme can decrease the secondary reactions and show no dangerous effect on the environment (14). Extremophilic enzymes, also known as extremozymes, can live in a harsh conditions and can be used in various biotechnological and industrial processes to catalyze the reaction. Halophilic archaea inhabit extreme ecosystems so their enzymes are also resistant to multiple extreme conditions which can be utilized as a biotechnological application (36). Under the extreme condition, many unwanted or contaminated biomolecules and proteins will get inactivated and hence may not need purification or sterilization. Many enzymes can work at minimum water activity, so the problems like solubility of water-insoluble substrate and unwanted water-related reaction will not occur, therefore it will be easy to get a desirable product. Enzyme produced from halophilic microorganisms may serve as a protein model to study the structural and functional features of proteins that have stability and activity under extreme salt conditions. Immobilizing of biocatalyst can increase enzyme stability, improve tolerance to organic solvent, quality of enzyme products and its activity (7). Peptide molecules like archaea's and secondary metabolites like acyl homoserine lactones produced by archaea can be used for biotechnological purposes. Metabolites like archaeon's and diketopiperazines show a great biotechnological potential and use in the cosmetic and food industry (26).

Several bio compounds produced by haloarchaea like halocins, PHAs/PHBs, carotenoids and enzymes are of high biotechnology interest. Some haloarchaeal species can produce carotenoids which can be genetically modified or can improve the cultivation parameters to get the high yield product. This halo archaeal carotenoids show a potential use in biomedicine and by the help of a biotechnological process, its production can be done at large scale. Many halophilic enzymes like esterases, lipases, proteases and glycosyl hydrolases could be used in biotechnological applications. Starch hydrolyzing enzymes found in the family of glycosyl hydrolases are used in detergent and food industries. Amylase of *Haloarcula* sp. can show its activity when salt is not present, which acts as a potential candidate for industrial application. Enzyme from *H. utahensis,* for example, cellulose can be utilized in biofuel production. *H. halobium* produces proteases, which is a heart of the global market as used to produce silk, leather, detergent, food, agrochemical and pharmaceutical products. *Haloarcula marismortui* produces lipases and esterases, which have application in cosmetic, detergent modification, paper and textile industries, food modification and lipid rich waste water pretreatment. Pigments, enzymes and secondary metabolites produced by haloarchaea microorganisms show a potential to be used in biomedicines, pharmacy and biotechnology processes (30). Halophilic archaea show plant growth promoting activity due to its unique adaptation in drastic conditions and help to grow the crops in varying extreme conditions (12).

Conclusion

Haloarchaea is a group of microbes that shows tremendous metabolic features. Since the last few decades, various types of new haloarchaea have been discovered by culturable or non-culturable techniques. It has been seen that the increasing number of haloarchaea is very useful, as they can withstand various ecological and environmental conditions. Various haloarchaeal species produce metabolites of very high interest that have potential applications in the emerging field of biotechnology. And also, the carotenoids are very efficient in terms of antimicrobials, antioxidants and various types of food colorants. It also shows anticancer properties, which in the future will help in the treatment of cancer. Among all the carotenoids, bacterioruberin produced by haloarchaea shows higher antioxidant activity than most of the above-mentioned carotenoids from plants, yeast, or algae. Despite having so many tremendous properties, it still needs to be explored more to identify other features of haloarchaea to continue specialized research and advantages for the welfare of the environment (Table 5 & 6, Supplementary data).

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Authors' contributions

MS conceptualized the study and wrote the manuscript, SB and SP edited the manuscript, SS and ND finalized the manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this research article.

Ethical issues: None

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