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Review

Hypersaline environments as natural sources of microorganisms with therapeutic potential: review

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Abstract

Hypersaline environments harbor a wide diversity of extremophilic microorganisms, including halophilic archaea, bacteria, and fungi, which have adapted to extreme salinity through unique physiological and molecular mechanisms. These organisms are capable of producing diverse bioactive metabolites with promising biological activities. Such compounds have attracted considerable attention for their potential applications in medicine, particularly in the development of novel therapeutic agents. Several studies have shown that metabolites derived from halophiles may contribute to antimicrobial, antioxidant, anti-inflammatory, and other health-related effects. Furthermore, their involvement in the gut–brain axis and their resilience in extreme conditions make halophiles valuable candidates for biotechnological and pharmaceutical innovations. This review highlights the therapeutic relevance of halophilic microorganisms and emphasizes their emerging role in next-generation biomedicine.

Keywords
Halophilic microorganisms, Bioactive metabolites, Therapeutic potential, Hypersaline environments

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1. Introduction

Hypersaline environments represent aquatic and terrestrial systems characterized by high salinity levels, surpassing those found in seawater (≈35 g/L). They are widely distributed on the planet representing a variety of ecosystems that include: coastal lagoons, salt and soda lakes, salterns (artificial ponds used for salt production), deep-sea brine pools (resulting from salt dissolution during seafloor tectonic processes), brine channels within sea ice, saline soils and fermented food [1, 2]. These environments can be divided into two different types: thalassohaline and athalassohaline, depending on the origin of their water [3]. Thalassohalines environments derive from marine origin, they are characterized by an ionic composition reflecting that of seawater, with a predominance of sodium chloride and neutral to slightly alkaline pH values (pH 7-8). These environments are typified by solar salterns, constituted by a series of shallow ponds in which the seawater is evaporated until the salts are precipitated. On the other hand, in athalassohaline environments, the origin of the water is not marine, its chemical composition results from the dissolution of mineral salt deposits or from concentration due to evaporation of dissolved elements originating from rock weathering, and it sometimes may show extremes of pH as well. The dominant ions in the water composition of these ecosystems may vary, influenced by different factors such as surrounding geology, topography, and climatic conditions [4, 5]. As examples of athalassohaline environments, the Dead Sea characterized by high magnesium, high calcium, relatively low sodium, acidic pH [6].

Hypersaline environments are among the most extreme habitats on earth since they are not only characterized by high salinities but other environmental physicochemical extrema such us high or low temperatures, low nutrient and oxygen availability, high exposure to UV radiation, low water activity, high pressure, extreme pH values, or the presence of heavy metals and toxic compounds [4, 7]. However, despite these harsh conditions, diverse studies in these environments, apparently devoid of life forms, have revealed an enormous quantity and diversity of interesting microorganisms called “Halophiles” [8]. Their ability to withstand high salinity confers them a great metabolic versatility and surprising traits, what reveals a real biotechnological trump. Studies over the last decades showed that several biomolecules produced by these halophilic microorganisms such us: enzymes, exopolysaccharides, halocins, compatible solutes, carotenoids, antimicrobial peptides…etc., showed interesting biological activities which make them very useful and efficient for many pharmaceutical and therapeutic applications [8, 9]. In this review, we describe characteristics and features of halophilic microorganisms and we give their different current and potential applications in pharmaceutical field.

Microorganisms inhabiting hypersaline ecosystems

Halophilic microorganisms are the major inhabitants of hypersaline environment; they are found mostly in the

domain Archaea and Bacteria. Few microbial eukaryotic halophiles like photosynthetic and heterotrophic protists and fungi, and crustacean are frequently observed [10]. Theses microorganisms are characterized by their requirement for sodium ions for their growth and metabolism, with the ability to balance the osmotic pressure and to resist the denaturing effects of salt [11]. Thus, based on the NaCl optimal requirement for growth, the halophiles can be classified into several categories. The most widely adopted classification was proposed by Kushner in 1978 [12] and slightly modified by Oren in 2013 [13]. It divides halophiles into four categories: slight halophiles, moderate halophiles, borderline extreme halophiles and extreme halophiles. In addition, there are halotolerant microorganisms that do not require high salt concentrations for growth, but are able to grow at often high concentrations of NaCl and other salts. Figure 1 presented this classification. It should be noted that various environmental and/or nutritional factors can modify the tolerance parameters and salt requirements of these microorganisms [13].

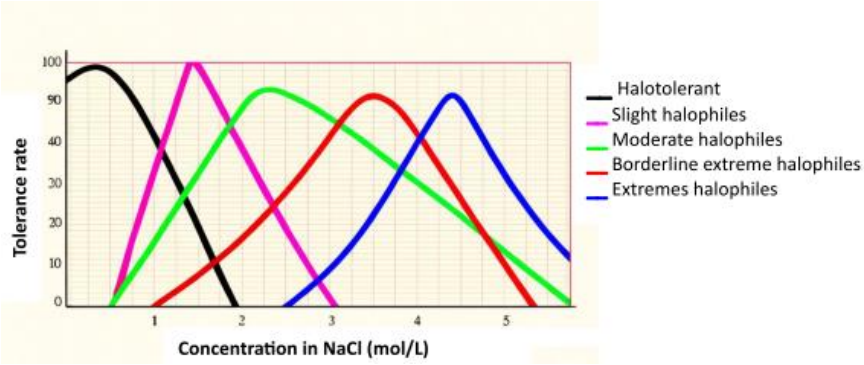

Fig. 1. Halophile's classification

The survival of halophiles in hypersaline environments requires specialized cellular and enzymatic adaptation mechanisms that enable them to grow and cope with osmotic and ionic stress. In fact, osmolarity difference (gradient) between the cell interior and the exterior generates osmotic pressure on the plasma membrane, causing the loss of water to the external medium and cell plasmolysis. In order to prevent plasmolysis, halophiles must maintain the cytoplasm at least isosmotic with respect to the extracellular medium. For that, they have developed two different strategies [11]. The first one, called "salt-in" is based on the intracellular accumulation of potassium and chloride in concentrations equal to or greater than the concentrations of NaCl from the extracellular medium, it is used by a limited number of halophiles, with archaea of the order *Halobacteriales* being the main representative. The second adaptative strategy called "salt-out" is generally used by halophilic bacteria and eukaryotes, it consists of the excluding of salts from the cytoplasm, and the accumulation or the synthesis de novo of compatible solutes like glycine betaine, zwitterionic compounds (in bacteria), glycerol and other polyols (in eukaryotes) [10, 14].

Several metagenomic studies in hypersaline environments revealed that the distribution of halophilic microorganisms is strongly dependent on salinity. An increase in salinity is associated with a decrease in the microbial diversity but an increase in the abundance of prokaryotic microbes showing an extreme halophilic profile [15-18]. For example, a metagenomic study conducted by Ghai et al. [17] on a series of environments representing a range of salinities showed a wide diversity of bacterial taxa at salt concentrations ranging from 3.8 to 6.4% (w/v), while a single taxon became significantly dominant when the saline concentration reaches 37% (w/v). This taxon belongs to the phylum *Euryarchaeota*, encompassing the majority of halophilic archaea, which became dominant when the salinity reaches 19% (w/v). Beyond 24% (w/v) salinity, only a small number of bacteria survive, those of the phylum *Bacteroidetes*, represented mainly by species of the genus *Salinibacter.* The following subsections give relevant information about the most abundant halophilic microbial communities found in hypersaline environments.

2.1. The *Archaea* Domain

Archaea species dominate the microbial populations inhabiting extreme hypersaline ecosystems, with salinities ranging from over 10% to saturation. They are represented by the extremely halophilic aerobic Archaea, also designated as haloarchaea, included within the phylum *Euryarchaeota*, class *Halobacteria*. Until June 2022, 312 species of haloarchaea have been characterized and grouped into 73 genera, three orders and six families: order *Halobacteriales* (families *Halobacteriaceae, Haloarculaceae,* and *Halococcaceae*), order *Haloferacales* (families *Haloferacaceae* and *Halorubraceae*) and order *Natrialbales* (family *Natrialbaceae*) [13, 19]. Halophilic archaea are not only found in the class *Halobacteria*, they are also present among the methanogenic archaea, within the orders *Methanosarcinales* and *Methanomicrobiales*. They are known by their capacity of reduction of carbon dioxide by hydrogen and by splitting of acetate to yield methane and carbon dioxide. However, members of this group cannot grow above 12% (w/v) salinity, probably because the amount of energy obtained in the reaction may be insufficient to supply the additional energy needed for osmotic adaptation [20]. In addition to these methanogenic microorganisms, a third group of halophilic archaea, with very small cells and not-yet-cultured representatives, has recently been discovered through metagenomic studies. They represent a large percentage of the community ($>10^6$ cells/mL representing up to 14%) and constitute a new phylum called *Nanohaloarchaeota* [14].

The general features of halophilic archaea are the low nutritional demands and the high requirements for salt for optimal growth (2–6 M NaCl). Besides, they have a surprisingly large range of degraded carbon sources and metabolic pathways, they can grow on a wide range of substrates including yeast extract, casamino acids, amino acids and simple organic acids such as acetate, succinate, and pyruvate. Some species have the capacity to metabolize pentoses (arabinose, xylulose), hexoses (glucose, fructose), sucrose, and lactose, and others are even capable of degrading aromatic compounds and hydrocarbons [20, 21]. Most members of this group are characterized by their orange and red pigmentation, contributing thus to the red coloration of the brines in hypersaline lakes. This pigmentation is due to the presence of 50-carbon carotenoid pigments (α-bacterioruberin and derivatives), as well as pink retinal pigments like bacteriorhodopsin and halorhodopsin [21].

Haloarchaea lead, in general, an aerobic heterotrophic life style. However, In the absence of oxygen, many species are capable of an alternate lifestyle. Some produce gas vesicles that enable them to migrate vertically to the surface of the brine where oxygen and light concentrations are optimal for growth. While others have the capacity to grow anaerobically by using NO_3^- or other compounds like NO_2^-, ClO_3^- or ClO_4^- as final electron acceptors [14].

2.2. The *Bacteria* Domain

Bacterial populations represent approximately 5–30% of the total microbial community in hypersaline environments, they constitute a highly diverse phylogenetic group showing different types of metabolism. Most are moderate halophiles, thriving optimally at salt concentrations ranging from 50 to 100 g/l but are able to proliferate also at higher salinities, albeit at lower growth rates [14, 22]. Moderately halophilic species include members of the following phyla: *Proteobacteria, Firmicutes, Actinobacteria, Actinomycetes, Bacteriodetes, Cyanobacteria, Tenericutes and Thermotogae* [6]. Members belonging to these phyla constitute a heterogeneous assemblage of microorganisms with diverse physio-biochemical activities and morphological variations. They are aerobic, anaerobic, chemoheterotrophic, photoheterotrophic, and/or photoautotrophic. The class *Gammaproteobacteria* within the phyla *Proteobacteria* contains the largest number of moderately halophilic genera and the members of the family *Halomonadaceae* represented the best studied and most important genera. *Halomonas* and *Chromohalobacter*, belonging to this family are known to be extremely versatile with respect to their adaptability to a wide range of salt concentrations. On the other hand, the best adapted group to various extreme conditions belong to *Cyanobacteria*, photosynthetic bacteria characterized by the presence of chlorophyll and phycobilin pigments. They can prosper in hypersaline (≤ 21% w/v salinity) as well as alkaline lakes. They can also support elevated metal concentrations and tolerate xerophilic conditions [6, 22, 23]. The genus *Salinibacter* with type species *Salinibacter ruber* (phylum *Bacteroidetes*) is the most abundant representative of extremely halophilic bacteria in hypersaline habitats. This bacterium is the first real non-archaeal extreme halophile known, it shares many phenotypic characteristics with haloarchaea, such as aerobic heterotrophic life style in addition to accumulating intracellular potassium as a mechanism of osmoregulation. *Salinibacter* also develops colonies pigmented in orange red due to the presence of a novel C40-carotenoid acyl glycoside compound named salinixanthin and retinal pigments like xanthorodopsin [6, 14].

2.3. The *Eukarya* Domain

Eukaryotic microorganisms represent small fraction of microbial communities inhabiting hypersaline environments, their concentration decrease along a salinity gradient, ranging from approximately 200 morphotypes per liter in marine waters (3.2% (w/v) salinity) to 1–2 morphotypes per liter at the highest salinity levels (30% (w/v) salinity). Microbial eukaryotes that can successfully adapt to and thrive in the highest-salt conditions include different groups like unicellular algae of the genus *Dunaliella*, salt-adapted fungi and yeast, as well as various types of protozoa. There is also a genus of macroorganisms, the brine shrimp *Artemia*, commonly known as the "sea monkey" [6, 24]. Species belonging to the genus *Dunaliella* are the most abundant eukaryotic organisms, they are obligately aerobic, photosynthetic, halotolerant rather than a truly halophilic. However, some species, especially *Dunaliella salina*, are extremely halophilic and can grow even in saturated NaCl [11]. Under stressful conditions such as high light intensity, nutrient limitations, or supra-optimal salinity, *Dunaliella salina* exhibit an orange-red coloration due to the production of large quantities of β-carotene [6].

Fungal species commonly found in hypersaline ecosystems are composed of black and melanised fungi including *Hortaea werneckii, Phaeotheca triangularis* and *Trimmatostroma salinum,* non-melanized yeasts, filamentous genera like *Wallemia*, *Alternaria*, *Scopulariopsis* and species of the genera *Aspergillus*, *Penicillium*, as well as their teleomorphic genera, *Eurotium* and *Emericella* [14, 25]. The most halophilic fungus known is *Wallemia ichthyophaga*, which can grow up to 25% (w/v) salinity [6]. All these fungi are chemoheterotrophs, growing optimally in aerobic conditions on carbohydrates at moderate temperatures and under acidic to neutral pH [11]. Other components of the *Eukarya* domain in hypersaline ecosystems are Amoeboid, ciliate, and flagellate protozoa, which can grow up to NaCl saturation and play a significant role in population control. Among the isolated halophilic protozoa, we found heterotrophic flagellates *Pleurostomum flabellatum* that exhibits optimal growth at 30% (w/v) salt and requires at least 15–20% (w/v), and *Halocafeteria seosinensis* which shows no growth below 7.5% (w/v) salt and reaches its maximum growth rate at 15% (w/v) [6]. We found also the heterotrichous ciliate that acts as a population controller of *Dunaliella salina* in areas with salt concentrations of around 9% (w/v) salt [14].

2.4. Halovirus

Halophilic viruses or haloviruses are the most abundant biological group in hypersaline environments, their amount increases along the salt gradient and exceeds the amount of procaryotic cells at least 10-fold. They are considered to have a crucial role in controlling the abundance of microbial populations in extreme saline ecosystems [26]. Nearly 100 viruses have been described in the scientific literature as predators of halophilic microorganisms. Among these, 90 viruses specifically infect haloarchaea, while the remaining ten have the ability to infect bacteria. However, limited information is available on viruses infecting halophilic eukaryotes and no virus have been described for halophilic fungi or for the green algae *Dunaliella salina*. On the basis of their morphology, halovirus are classified into different families including *Myoviruses*, *Siphoviruses*, *Podoviruses*, Icosahedral viruses, Pleomorphic viruses and Lemon-shaped viruses. *Myoviruses*, *Siphoviruses*, and *Podoviruses*, as well as icosahedral viruses are represented by both archaeal and bacterial haloviruses, while pleomorphic and lemon-shaped haloviruses have only been isolated from archaeal hosts [14, 27].

3. Therapeutic potential of biomolecules from halophilic microorganisms

Halophilic microorganisms are exposed to very strict conditions of growth like extreme salinities, high exposure to UV radiation, extreme pH and temperature values, dry conditions and nutrient scarcity. In response to these hostile conditions, these microorganisms have evolved a highly diversified specialized metabolism. Consequently, they produce various kinds of bioactive molecules with unique structural and functional features such as: carotenoid pigments, biopolymers, bioplastics, retinal proteins, compatible solutes and proteins. Many of these metabolites have been classified as potential therapeutic agents owned to their biological activities [28, 29].

3.1 Carotenoids

Carotenoids are the second most abundant naturally occurring pigments in nature, they are mainly synthesized by plants, to a lesser extent, by bacteria, archaea, algae, and yeasts. They play basic biological roles ranging from serving as accessory pigments in photosynthesis to acting as antioxidants agents, light protectors, and cell membrane stabilizers [30]. Carotenoids are terpenoid pigments made of isoprene residues displaying a conjugated double polyene chain. They are hydrophobic compounds and are generally formed by a skeleton of 40 hydrocarbons (C40 structure) comprised of eight C5 isoprene units. However, there are also C30, C45, and C50 structures containing six, nine, and ten isoprene units, respectively. The latter are exclusively synthesized by bacteria and archaea [14, 31]. Depending on the presence or absence of oxygen in their structures, carotenoids can be classified into two groups: carotenes, which are composed exclusively of carbon and hydrogen atoms in their molecules (e.g. β-carotene or lycopene), and xanthophylls, or oxygenated carotenoids containing several different functional groups such as hydroxyl, carboxyl, epoxy, and carbonyl moieties (e.g. lutein and zeaxanthin) [32].

Carotenoids have received much attention because of their potential beneficial effects on human health. Therefore, they are widely applied in medical, nutraceutical, and pharmaceutical industries [30].

Halophilic microorganisms are a great source of diverse carotenoids including phytoene, β-carotene, lycopene, derivatives of bacterioruberin, and salinixanthin [33]. Most members of the class *Halobacteria* can synthetize a rare C_{50} carotenoids called bacterioruberin (BR) and its derivatives monoanhydrobacterioruberin (MABR), bisanhydrobacterioruberin (BABR) and 2-isopentenyl-3,4-dehydrorhodopin (IDR). In addition, although to a lesser extent, they also synthesize astaxanthin, zeaxanthin, lycopene, and β-carotene. These C_{50} carotenoids show higher antioxidant proprieties due to their longer conjugated double bonds and the presence of a high number of hydroxyl groups. As a consequence of this extraordinary biological function, this rare group of carotenoids is of great interest and could be used in wide range of industrial applications. However, the uses of those these molecules have been poorly explored and none of them has been used at large scale [34, 35]. Collectively, Table 1 gives an overview of some halophilic archaea producing carotenoids with important therapeutic potential.

Table 1. Some halophilic archaea producing carotenoids with important therapeutic potential.

Carotenoids	Producer	Source	Health-beneficial properties	Ref.
BR, BABR, TABR	*Halococcus morrhuae*	Dead Sea	Antioxidant activity	[36]
BR, BABR, TABR	*Halobacterium salinarium*	Salted cowhide, Canada		
	Halobacterium halobium	Solar saltern, Tunisia	Antiproliferative activity against the liver HepG2 cancer cell line, Protection against oxidative stress induced by arachidonic acid and H_2O_2	[37]
BR, MABR, BABR, IDR	*Haloarcula japonica*	Saltern soil, Japan	Antioxidant activity	[38]
BR, MABR, BABR	*Halogeometricum limi*	Marine solarsaltern, China	Antioxidant activity, Antihemolytic activity, Antiproliferative activity against the liver HepG2 cancer cell line	[39]
	Haloplanusvvescus			
	Halopelagius inordinatus		Antioxidant activity, Antihemolytic activity	
	Halogranum rubrum			
	Halogeometricum rufum			
	Haladaptatus litoreus			
	Haloferax volcanii	Dead Sea		
BR	*Natrialba* sp. M6	Wadi El-Natrun, Egypt	Antiviral activity against hepatitis B and C viruses, Antiproliferative activity against colon (Caco-2), breast (MCF-7), liver (HepG-2) and cervical (HeLa) cancer cell lines	[40]
BR, BABR	*Halorubrum* sp. BS2	Bazer Sakra Salt Lake, Algeria	Antioxidant and antibacterial activities	[41]
ND	*Halobacterium halobium*	/	Treatment of skin damage induced by radiotherapy	[42]
BR	*Haloferax volcanii* HVLON3	/	Antioxidant activity, Beneficial effects on sperm cell viability	[43]
BR, MABR, BABR	*Halorubrum* sp. TeSe-85 *Halorubrum* sp. TeSe-85 *Haloarcula* sp. TeSe-89 *Haloarcula* sp. ALT-23 *Haloarcula* sp. TeSe-41 *Haloarcula* sp. TeSe-51	Atacama Salt Lake, Chile	Antioxidant activity, Cholinesterase inhibitory capacity, Anti-proliferative Effect on HaCaT cell line	[44]
BR, MABR, Lycopene	*Halobacterium salinarum*	Solar saltern, Tunisia	Antioxidant activity	[45]
BR, MABR, BABR	*Haloterrigena turkmenica*	Saline soil, Turkmenistan	Antioxidant activity	[46]
BR, MABR, IDR, BABR, β-carotene, Haloxanthine,	*Haloterrigena thermotolerans*K15	Tuz GölüFSASalt Lake, Turkey	Antioxidant activity	[47]

γ-carotene, Lycopene				
BR, BABR, Haloxanthine	*Halogeometricum* sp. ME3	Chott Melghir, Algeria	Antioxidant activity, Antibacterial activity	[35]
BR, MABR	*Haloferax* sp. ME16			
BR, TABR, 3',4'-TH-BABR, 3',4'-DH-MABR	*Haloarcula* sp. BT9	Bethioua Sebkha, Algeria		

Table 1. cont.

Carotenoids	**Producer**	**Source**	**Health-beneficial properties**	**Ref.**
BR	*Haloarcula* sp. A15	Saline environment, Iran	Antiproliferative activity against the breast MCF-7 cancer cell line	[48]
BR, MABR, BABR	*Halorhabdus utahensis*	Utah's Great Salt Lake, United States	Antioxidant activity, Anti-hyaluronidase capacity	[49]
BR, MABR, TABR, BABR, β-carotene, Phytoene, Lycopersene	*Natronococcus* sp. *TC6*	El Golea Sebkha, Algeria	Antioxidant activity, Matrix Metallopeptidase 9 (MMP-9) In Silico Inhibition	[50]
BR, BABR, TABR IDR, Astaxanthin, β-carotene	*Halorubrum tebenquichense* SU10	Uyuni saltern, Bolivia		
BR, MABR, 3',4'-TH-BABR, Haloxanthine	*Halovenus aranensis*	Aran-Bidgol Salt Lake, Iran	Antioxidant activity, Ability to induce the antioxidant gene exression in human primary skin fibroblast cells	[51]
BR, MABR, TABR, BABR	*Haloferax mediterranei* R-4	solarsalt pond, Spain	Antioxidant activity Antiglycemic activity Antilipidemic Activity	[52]
BR, MABR, IDR, BABR	*Haloarcula* sp. E2 *Halorubrum* sp. M5	Salt pans, India	Protective effect against hydrogen peroxide-induced oxidative damage in skin keratinocytes	[53]
BR, MABR, IDR, BABR	*Haloferax marinum*	Seawater, Republic of Korea	Antioxidant activity, DNA damage protective activity Protective effect on skeletal muscle atrophy	[54]
BR, MABR	*Halorubrum* sp. HRM-150	Solar salt, China	Antioxidant activity	[58]
ND	*Halorubrumruber* MBLA0099	Seawater, Republic of Korea	Antioxidant activity Protective effect against hydrogen peroxide-induced oxidative damage in *Caenorhabditis elegans*	[56]
BR	*Halorubrum tebenquichense*	Tebenquiche Lake, Chile	Intestinal barrierrepairing agent.	[57]

(IDR) 2-isopentenyl-3,4-dehydrorhodopin
BABR bisanhydrobacterioruberin; BR bacterioruberin; MABR monoanydrobacterioruberine; TABR trisanhydrobactérioruberin; 3',4'-TH-BABR 3',4'-tetrahydrobisanhydrobacterioruberin; 3′4'-DH-MABR 3',4'-dihydromonoanydrobacterioruberine; ND non identified.

Several studies have also shown that carotenoids produced by halophilic bacteria showed an interesting therapeutic potential. For exemple Rezaeeyan et al. 2017 [58] demonstrated that the carotenoids produced the halotolerant bacterium, *Kocuria* sp. strain QWT-12, isolated from industrial tannery wastewater in Qom, in Iran, had the ability to decrease the viability of seven cancer cell lines belonging to breast (MCF-7, MDA-MB-468, MDA-MB-23), lung (A549) and prostate (PC3, LNCaP, DU145) cancer, without being toxic to the human fibroblast cells line Hu02. In another study, carotenoids from *Halobacillus yeomjeoni* (81-1), *Salinicoccus* sp. (82-1) and *Bacillus amyloliquefaciens* (60-5) has been shown to possess antibacterial activity against *Staphylococcus aureus, Escherichiacoli* and *Bacillus cereus,* respectively [59]. Similarly, carotenoids produced by *Virgibacillus halodenitrificans,* an halophilic bacterium isolated from Wadi El-Natrun Salt Lakes, exhibited inhibitory activity against three pathogenic strains consisting of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Escherichia coli.* They also showed a considerable antifungal effect (inhibition zone > 25 mm) against *Candida albicans* [60]. Fariq et al. [61] found that carotenoids derived from moderately halophilic bacteria *Aquisalibacillus elongatus* MB592*, Salinicoccuss esuvii* MB597, and *Halomonas aquamarina* MB598 displayed substantial antimicrobial activity against the pathogens *Bacillus subtilis, Bacillus pumilus, Enterococcus faecalis, Bacillus cereus, Klebsiella pneumoniae, Alcaligenes faecalis, Pseudomonas geniculata, Enterococcus faecium, Aspergillus fumigatus, Aspergillus favus, Fusarium solani,* and *Mucor* spp. These carotenoids exhibited also a strong antioxidant potential, which was 85% against DPPH$^{\bullet}$.

The halophilic algae *Dunaliella* is considered the richest sources of natural carotenoids including lutein, zeaxanthin and β-carotene. It is the only halophilic organism successfully exploited for the industrial production of carotenoids. Among its species, *Dunaliella salina* has been the most extensively studied, being the most efficient commercial source of natural β-carotene, which can account for up to 14.0% of its total dry weight [62]. Several in vitro and in vivo studies have demonstrated that carotenoids derived from this microalga exhibit strong antioxidant properties which are closely associated with remarkable therapeutic activities such as anticancer, anti-inflammatory and antioxidant ones. For example, invitro studies have shown that carotenoids from *D. salina* exhibited potent cytotoxic activity against breast (MCF7, MDA-MB-231) and liver (HePG2) cancer cell lines [63, 64]. Carotenoids from the same strain has been shown to possess antiproliferative effects on oral carcinoma and fibrosarcoma cells [65, 66]. Similarly, β-carotene extracted from *D. bardawil* was found to exert in vivo anti-inflammatory effect and in vitro antitumor activity on HepG2 and MCF-7 cell lines [67]. Several other studies have also reported anti-inflammatory effects of carotenoids from *Dunaliella* sp [68, 69].

3.2 Bacteriorhodopsin

Bacteriorhodopsin is a 25-kDa retinal-binding protein discovered in the early 1970s in the purple membrane of the halophilic archaeal species *Halobacterium salinarum*. It functions as a light-driven proton pump, capturing photons and using the absorbed energy to transport protons across the cell membrane, thereby generating an electrochemical gradient. Structurally, it consists of seven hydrophobic transmembrane helices that confer remarkable resistance to chemical, thermal, and photochemical degradation, making it suitable for diverse applications in medical and pharmaceutical fields [70,72].

Bacteriorhodopsin has been explored for the development of artificial retinal implants due to its optical properties, which resemble those of natural visual pigments. Its ability to convert light into electrical signals makes it a promising candidate for stimulating retinal neurons in patients with retinal degeneration [73]. Also, owing to its light sensitivity and stability, bacteriorhodopsin has been integrated into immunosensors for the direct, label-free detection of microbial pathogens. These sensors can quantitatively detect bacteria such as *E. coli* by measuring changes in photocurrent upon antigen-antibody interactions, offering thus a sensitive method for microbial detection in clinical diagnostics [74]. Another study suggested the potential of bacteriorhodopsin as a biosensing element for X-ray detection. The researchers designed a flexible sensor integrating bR, capable of real-time monitoring of radiation doses, energy, and dose rates [75].

3.3 Antimicrobial peptides

Antimicrobial peptides (AMPs) are small molecules composed of 12 to 100 amino acids, typically exhibiting an α-helical structure, a positive charge, and amphiphilic properties that enable them to interact with microbial

membranes. Halocins, a specific class of AMPs, are naturally produced and secreted by extreme halophilic archaea into their environment as a defense mechanism. Similarly, bacteria synthesize ribosomally derived peptides known as bacteriocins, also under 100 amino acids in length, which are capable of inhibiting the growth of competing bacterial strains [76]. Bacteriocins have been shown to display a broad spectrum of antimicrobial activity against various antibiotic-resistant planktonic bacteria Table 2. In addition, they have demonstrated inhibitory effects against a wide range of organisms, including yeasts, insects, and even mammalian cells [77].
Halocins are produced by *Halobacteria* during the transition from the exponential to the stationary growth phase. Halocins type H6/H7 derived from *Haloferax gibbonsii* has been shown to inhibit the Na^+/H^+ antiporter in mammalian cells. Notably, halocin H6 has demonstrated cardioprotective effects by reducing infarct size during myocardial ischemia and mitigating reperfusion injury [78] highlighting its potential in advancing therapies related to organ transplantation. Furthermore, halocins H4 and C8 from *Halobacterium* have been observed to induce morphological changes in sensitive rod-shaped cells, transforming them into spherical forms that subsequently undergo lysis [79]. Halotolerant and halophilic fungi have also been reported as a major source of antimicrobial compounds. Among these, *Aspergillus* species are the most prolific producers. *A. protuberus* strain 8Na isolated from the Barents Sea exhibits strong antimicrobial activity against human pathogens, particularly against *Staphylococcus aureus*, the molecule responsible of the activity was identified as Bisvertinolone [80]. *A. flocculosus* and *A. terreus*, isolated from Chinese marine sediments, produce unique antimicrobial metabolites active against *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Candida albican*. These metabolites include new ergosteroids, pyrrole derivatives, and novel compounds like Terrelactone A [81]. Other strains of the *Aspergillus* genus, such as *A. terreus* Tsp22, *A. flavus*, *A. gracilis*, and *A. penicillioides*, have demonstrated antibacterial and antioxidant activities in their crude extracts. However, the specific bioactive compounds responsible for these effects have yet to be identified [9].

Table 2. Examples of halophilic bacteria and their antimicrobial molecules active against human pathogens

Genus	Antimicrobial Activity	Molecule	Ref.
*Nocardiopsis*sp. AJ1	*Staphylococcus aureus,* *Escherichia coli,* *Vibrio parahaemolyticus,* *Pseudomonas aeruginosa,* *Aeromonas hydrophila*	Pyrrolo (1,2-A (pyrazine-1,4-dione, Actinomycin C2 hexahydro-3-(2-methylpropyl)-)	[82]
*Nocardiopsis*sp. HR-4	*Staphylococcus aureus* (MRSA) ATCC 43300, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Micrococcus luteus* ATCC 4698,	(−)-7-deoxy-8-O methyltetrangomycin (−)-8-O-methyltetrangomycin	[83]
*Nocardiopsis*sp. HYJ128	*Salmonella enterica* ATCC 14028	Borrelidin C Borrelidin D	[84]
Nocardiopsisterrae YIM 90022	*Escherichia coli,* *Staphylococcus aureus,* *Bacillus subtilis*	N-acetyl-anthranilicacid p-hydroxybenzoicacid Indole-3-carboxylic acid 4-oxo-1,4-dihydroquinoline-3-carboxamide Cyclo (Leu-Ala) Cyclo (Trp-Gly)	[85]
Nocardiopsisgilva YIM 90087	*Staphylococcus aureus,* *Bacillus subtilis*	6'-Hydroxy-4,2',3',4''-tetramethoxy-p-terphenyl 4,7-bis(4-methoxyphenyl)-6-hydroxy-5-methoxybenzo[d]thiazole	[86]
*Streptomyces*sp. B6921	*Escherichia coli,* *Staphylococcus aureus,* *Bacillus subtilis,* *Streptomyces viridochromogenes*	Himalomycin A Himalomycin B Fridamycin D	[87]
Streptomyces hygroscopicus BDUS 49	*Staphylococcus aureus,* *Escherichia coli,* *Bacillus subtilis,* *Salmonella typhi*	7-Demethoxy rapamycin	[88]
Streptomonospora alba YIM	*Staphylococcus aureus,* *Bacillus cereus* ATCC 4342, *Bacillus anthracis,*	Streptomonomicin (STM)	[89]

	Bacillus subtilis, *Bacillus halodurans,* *Listeria. monocytogenes,* *Enterococcus faecalis,*		

Table 2. cont.

Genus	Antimicrobial Activity	Molecule	Ref.
Paludifilum halophilum SMBg3	*Escherichia coli* BW25113, *Pseudomonas aeruginosa* ATCC 49189 *Staphylococcus aureus* ATCC6538, *Mirococcus luteus* LB 14110, *Listeria ivanovii* BUG 496)	Gramicidin S Cyclo (l -Tyr- l -Pro) Cyclo (l -4-OH-Pro- l -Leu) Cyclo (l -Leu- l -Pro) Cyclo (l -Phe- l -Pro)	[90]
Pseudonocardia endophytica VUK-10	*Staphylococcus aureus* (MTCC 3160), *Escherichia coli* (ATCC 35218), *Bacillus cereus* (MTCC 430), *Staphylococcus epidermis* (MTCC 120), *Streptococcus mutans* (MTCC 497), *Bacillus subtilis* (ATCC 6633), *Pseudomonas aeruginosa* (ATCC 9027), *Bacillus megaterium* (NCIM 2187), *Serratia marcescens* (MTCC 118), *Proteus vulgaris* (MTCC 7299), *Xanthomonas malvacearum* (NCIM 2954) *Xanthomonas campestris* (MTCC 2286), *Salmonella typhi* (ATCC 14028)	3-((1H-indol-6-yl) methyl) hexahydropyrrolo [1,2-a] pyrazine-1,4-dione N-(4-aminocyclooctyl) -3,5-dinitrobenzamide	[91]
Vibrio sp. A1SM3–36-8	*Staphylococcus aureus* (MRSA) ATCC BAA-44, *Bacillus subtilis* ATCC 21556	13-cis-docosenamide	[92]
Bacillus sp. BS3	*Escherichia coli,* *Pseumonas aeruginosa,* *Staphylococcus aureus,*	13-Docosenamide, (Z) 9-Octadecenamide, (Z) Mannosamine	[93]

	Salmonella typhi	2-Octanol, 2-methyl-6-methylene 1,2-Ethanediamine, N,N,N'-N'-tetramethyl- Cylohex-1,4,5-triol-3-one-1-carbo 2-Butanamine, 2-methyl-	
Halomona ssalifodinae MPM-TC	*Pseudomonas aeruginosa* *Vibrio parahaemolyticus,* *Vibrio harveyi,* *Aeromonas hydrophila*	1,1'-Biphenyl]-3-amine Perfluorotributylamine 1-butyl-2-ethyl- cyclopentane, 2-methyl- Hexadecane, 4-(phenylmethyl)- Pyridine Phytol Nonadecane	[94]

Table 2. cont.

Genus	Antimicrobial Activity	Molecule	Reference
Salinispora arenicola	*Mycobacterium lepromatosis,* *Mycobacterium avium,* *Mycobacterium tuberculosis* *Mycobacterium leprae,*	Rifamycin B Rifamycin W Rifamycin S	[95]
Marinispora sp. NPS12745	*Staphylococcus aureus* ATCC 43300-MRSA, *Staphylococcus aureus* ATCC 29213-MSSA, *Staphylococcus epidermidis* ATCC 700582, *Staphylococcus epidermidis* ATCC 700578, *Streptococcus pneumoniae* ATCC 51915-Penicillin resistant, *Streptococcus pneumoniae* ATCC 49619-Penicillin sensitive, *Enterococcus faecium* ATCC 700221-Vancomycin resistant, *Enterococcus faecalis* ATCC 29212-Vancomycin sensitive, *Haemophilus influenzae* ATCC 49766 *Haemophilus influenzae* ATCC 49247,	Lynamicin A Lynamicin B Lynamicin C Lynamicin D Lynamicin E	[96]
Streptomyces nodosus NPS007994	Gram-positive reactionbacteria Drug-sensitive and drug-resistant	Lajollamycin	[97]
*Actinomadura*sp.M048	*Staphylococcus aureus,* *Bacillus subtilis,* *Streptomyces viridochromogenes*	Chandrananimycin A Chandrananimycin B Chandrananimycin C	[98]

3.4 Exopolysaccharides

Exopolysaccharides (EPS) are high molecular weight polymers composed of various carbohydrates as well as organic and inorganic substituents [99]. EPS derived from halophilic bacteria and archaea have demonstrated notable anticancer potential and are being explored as promising components in nanocarrier systems for anticancer drug delivery. For example, the over-sulfated EPS produced by *Halomonas stenophila* strain B100, was found to completely inhibit the proliferation of human T leukemia cells (Jurkatcells) at a concentration of 500 µg/mL in a dose-dependent manner [100]. Another significant finding involves the polysaccharide levan, extracted from *Halomonas smyrnensis* AAD6, along with its chemically modified derivatives (particularly aldehyde-activated levan). These compounds were tested against various human cancer cells lines, including lung (A549), liver (HepG2/C3A), gastric (AGS), and breast (MCF-7) cells, at concentrations ranging from 10 to 1000 µg/mL. The unmodified levan exhibited the highest anticancer effect against AGS gastric cancer cells. However, aldehyde-modified levan showed enhanced anticancer effects across all cell lines. These results clearly suggest that chemical modification of levan with aldehyde groups significantly enhances its antitumor properties, making it a promising candidate for cancer therapy [101].
EPS from halophilic bacteria have also been shown to possess interesting antioxidant properties. For instance [102], isolated a sulfated EPS with a molecular weight of 269 kDa from the marine halophilic strain *Enterobacter* sp. PRIM-26. This EPS demonstrated notable antioxidant activity, exhibiting IC_{50} values of 0.44 mg/mL and 0.33 mg/mL for DPPH and hydroxyl radical scavenging assays, respectively. Another study reported that the exopolysaccharide HMEPS, produced by the marine halophilic bacterium *Halolactibacillus miurensis* exhibited potent antioxidant properties. It demonstrated strong DPPH free radical scavenging activity with an IC_{50} value below 0.10 mg/mL. Additionally, it showed significant reducing power and achieved a superoxide radical scavenging rate of 89.15% at a concentration of 0.5 mg/mL [103].

3.5. Enzymes

Halophilic microorganisms represent an extremely diverse source of valuable enzymes, which are considered polyextremophilic due to their ability to function in high salt concentrations and organic solvents, as well as their tolerance to elevated temperatures and pH variations. [104]. Among these enzymes, l-asparaginase and l-glutaminase, mainly produced by halophilic and halotolerant bacteria, have the ability to inhibit acute lymphoblastic leukemia and other cancer cells [9]. For example, a study conducted on 85 halophilic strains isolated from the hypersaline Urmia Lake in Iran demonstrated that 16 strains exhibited L-asparaginase activity, while 3 strains showed L-glutaminase activity. The majority of L-asparaginase-producing strains belonged to the genus *Bacillus*, whereas L-glutaminase activity was predominantly associated with *Salicola* species [105]. In another investigation involving 110 halophilic bacterial strains obtained from various saline ecosystems in Iran, researchers identified 29 strains producing L-asparaginase, 4 producing L-glutaminase, and 2 strains synthesizing L-arginase. These enzymatically active isolates encompassed a wide range of genera including *Bacillus*, *Dietzia*, *Halobacillus*, *Rhodococcus*, *Pseudomonas*, *Marinobacter*, *Halomonas* and *Idiomarina* [106]. Ghasemi and co-workers [107] evaluated a recombinant L-asparaginase enzyme derived from *Halomonas elongata* strain IBRC M10216 for its anticancer potential. The enzyme was tested against two human leukemia cell lines: Jurkat (lymphoblastic) and U937 (myeloid). This enzyme demonstrated significant cytotoxic activity, with IC_{50} values of 2 and 1 U/mL, respectively. Notably, at these concentrations, the enzyme exhibited no toxic effect on normal human umbilical vein endothelial cells (HUVEC), indicating a degree of therapeutic selectivity. These findings suggest that halophilic bacteria may serve as valuable sources of targeted anticancer agents.

3.6. Compatibles solutes

Halophilic microorganisms have attracted growing interest for their potential role in the treatment of autism spectrum disorder (ASD), particularly through their ability to produce compatible solutes that contribute to host homeostasis [77]. These small organic molecules such as betaine, ectoine, trehalose, and sorbitol enable halophiles to survive in high-salt environments by balancing osmotic pressure and protecting cellular structures [108]. Importantly, these solutes also exert biological effects relevant to human health, including the modulation of immune, gut, and neural signaling pathways. In the context of ASD, which is partially driven by oxidative

stress and disruptions in gut–brain communication, compatible solutes may help mitigate cellular damage by reducing oxidative imbalance and supporting barrier integrity. Furthermore, their involvement in the regulation of the gut–brain axis (GBA) suggests that halophilic microorganisms could influence neurological outcomes by shaping the metabolic and inflammatory environment of the host [77]. Emerging strategies such as fecal microbiota transplantation (FMT) enriched with halophilic strains, or the use of genetically engineered microbes to enhance compatible solute production, represent promising avenues for therapeutic intervention. These findings underscore the significance of compatible solutes as key mediators in the interaction between halophiles and the host, highlighting their potential in microbiome-based approaches to ASD treatment [109].

4. Conclusion

The remarkable adaptability of halophilic microorganisms to extreme saline conditions underscores their untapped potential in medical and therapeutic fields. Their ability to produce a wide range of bioactive metabolites with beneficial biological properties makes them promising resources for novel treatment strategies. From influencing host-microbiota interactions to offering new avenues in drug development and disease modulation, halophiles represent a valuable frontier in biomedicine. Continued exploration of these extremophiles, supported by advanced omics technologies and synthetic biology tools, will not only deepen our understanding of life in extreme environments but also pave the way for innovative solutions to current and emerging health challenges.

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