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REVIEW ARTICLE OPEN ACCESS

Salt Tolerant Microbes (Active Metabolites) Mediated Nanoparticle: Drug Delivery and Future Prospects

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Abstract

Salt Tolerant Microbes are a group of microorganisms that grow, develop, and survive in extremely high salt concentrations. Based on their tolerance level they generally grow up optimally at pH values beyond 9.0, but the growth is inhibited at the pH value that is most closely associated with neutral 6.5. They have minimal dietary needs and a good salt quantity that is high enough to osmotic pressure. They can produce biological metabolites that have certain actions such as antibacterial, antifungal, antioxidant, and anticancer. We discussed in this article various pharmaceutical formulations of salt-tolerant microbes, every formulation shows the specific pharmacological actions like anti-cancer activity, anti-oxidant activity, and anti-microbial activity, and also discusses methods for the biosynthesis of salt-tolerant microbes' nanoparticles.

Keywords: Salt Tolerant Microbes, Nanoparticles, Metabolites, Microorganism

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INTRODUCTION

Salt-tolerant microbes are divided into three main categories i.e., Mild, Moderate, and High. Salt Tolerant Microbes require levels of sodium chloride above 3% in salt water.[1] Several factors affect the tolerance criteria like growth medium, pH, temperature, and salt concentration. They generally grow up optimally at pH values beyond 9.0, but the growth is inhibited at the pH value that is most closely associated with neutral 6.5.[2,3] The general mechanism followed by Salt Tolerant microbes for surviving in varying saline conditions.

They have minimal dietary needs and a good salt quantity that is high enough for osmotic pressure.[4] The processes of their halo adaptation (halophilic bacteria can maintain growth and development under salinity conditions) on the internal storage of KCl (potassium chloride) approximately 37% or maintain the equilibrium of sodium ions in the cell plasma and resist the osmotic pressure of the outside surroundings caused by the excessive salinity.

These organisms act on an osmoregulatory mechanism that helps them to grow in acute concentration by balancing ion exchange with the surroundings and their tolerance along with surviving for a long-life span brings the Salt Tolerant Microbes into a new era of development.[5-8]

Hypersaline regions offer several possibilities for the production of additional metabolites with industrially relevant bioactivities.[9,10]

The secondary metabolites produced by the Salt Tolerant Microbes show properties against drug-resistant bacteria. Using these metabolites with the help of nanotechnology will be used as a powerful tool in pharmaceutical sciences.[11-13]

They can produce biological metabolites that have certain actions such as antibacterial, antifungal, antioxidant, and anticancer. The overuse of basically antibiotic drugs has resulted in the development of drug resistance (DR), which reduces or eliminates their efficacy.[14,15] The DR is shown in the human body (Cancer cells and micro-organisms). So, to overcome DR issues

Table 1. Various nano-formulations of Salt Tolerant Microbes

Targeted delivery	Salt Tolerant Microbes	Nano-formulations	Ref.
Anticancer	*Archaeal halophile*	nanoparticles synthesis, and gas vesicles	29
	Haloarchaea	Silver nanoparticles	
	Halomonas elongata.	Selenium nanoparticles (antibacterial and antioxidant)	
	Ideomarina species	Selenium nanoparticles	
Antimicrobial	*Halophilic Archaea*	Encapsulation of carotenoids isolated from halophilic Archaea in oil-in-water (O/W) nano- and micro-emu	30, 31
	Chromohalobacter salexigens, Halobacillus halophilus, and *Halomonas elongate*	Ectoine nasal spray	
	Archaeal Salt Tolerant	Nanoparticles synthesis, and gas vesicles	
	Microbes *Halophilic*	Gas vesicle nanoparticles	
	archaeon Extremophilic	Silver nanoparticles	
	bacterium-A30	Silver nanoparticles	
	Archaebacteria, actinomycetes, *cyanobacteria,* and fungi.		
Antioxidants	*Streptomyces Marietta, Bacillus subtilis, Bacillus tequilensis, and Bacillus Haynes*	Methanolic extract of halophilic bacterial strain	32, 33, 34
	Haloferax volcanii BBK2, Haloarcula japonica BS2, and Halogeometricum borinquense E3	Nanoneedles and selenium nanospheres	

advanced technologies have been introduced example drug-resistant strains using biomaterials and metabolites. The challenge is to overcome the difficulties related to drug resistance not only in animals and environmental aspects but also in humans. Two types of genes are responsible for resistance, where the first is horizontal gene transfer (HGT) and the second is genes that are already encoded in the bacterial genome that can give antibiotic resistance by mutation and activation of mobile elements. The recent drug resistance example is third-generation cephalosporin caused by a mutation in genes encoding penicillin-inactivating enzyme. The invention of new medications is necessary to overcome DR issues for better treatment and the Salt Tolerant Microbes (active metabolites) nanoparticles attracted a lot of attention. Some examples of DR have been observed in clinical strains against various antibiotics, affecting both gram-negative and gram-positive bacteria. Resistance is perceived in *Haemophilus influenza* to ampicillin, in *Helicobacter pylori* to clarithromycin and in *Staphylococcus aureus* shows intermediate resistance to vancomycin. *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae* to aminoglycosides and quinolone, *Enterobacteriaceae* to cephalosporins and carbapenems. Furthermore, *Enterococcus faecium* exhibits resistance to cephalosporin and vancomycin, whereas *Streptococcus pneumoniae* discerns resistance to penicillin. Unexpectedly, the quorum-sensing mechanism of *Pseudomonas aeruginosa* led to the development of fluconazole resistance in *Candida albicans*. In response to these challenges, there has been a growing interest in utilizing halophilic biomolecules to combat DR bacteria.[16- 20]

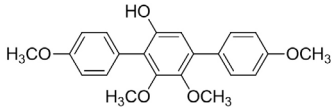
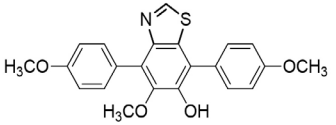
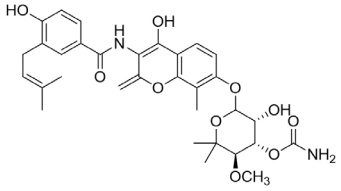
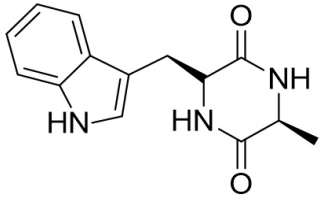
Table 2. Methodology and Key Findings (application) of Biosynthesized Nano-particles

No.	Methods	Key- findings	Ref.
1.	Dynamic aggregation with radiation-induced cross-linking	Drug carrier	35-39
2.	Genetically encoded synthesis in *E. coli*	Treatment of cancer-conjugated drug	40, 41
3.	Electrospraying	Doxorubicin drug delivery model: ph-responsive drug	42-46
4.	Ionic gelatin	Delivery of hydrophobic bioactive compounds	47
5.	Redox reaction	Anti-cancer treatment	48
6.	One pot synthesis	Platinum drugs delivery to cancerous cells	49, 50
7.	Lyophilization	Treatment of breast cancer	51
8.	Ring-opening polymerization	Drug delivery for prostate carcinoma	52
9.	Self-assembly	Biosensors	52

Table 3. Anti-cancer activity of a few Active Metabolites of Salt Tolerant Microbes with targeted deliveries

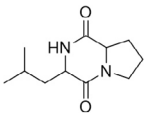
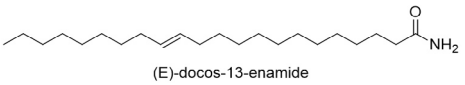
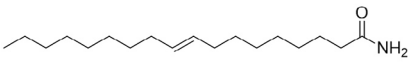
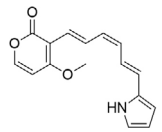
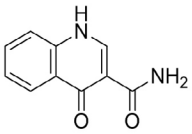
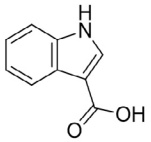
No.	Salt Tolerant Organism	Metabolite	Targeted Delivery	Ref.
1.	*Bacillus* species	3-Methyl-2(2-isopropyl) furan	Cervical carcinoma	53
2.	*Nocardiopsis* species HYJ128	Borrelidin C, Borrelidin D	Stomach and leukemia carcinoma	54
3.	*Streptomyces* sp.	Salternamide A	Colorectal and gastric cancer	55
4.	*Streptomyces* species WH26	Naphthomycin	Lung adenocarcinoma, cervical carcinoma	56
5.	*Nocardiopsis* species	Methyltetrangomycin	Liver cancer	56

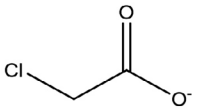
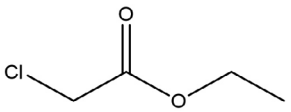
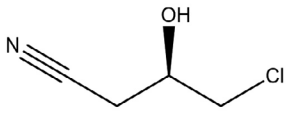
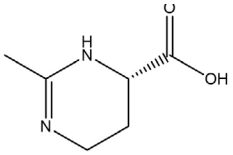
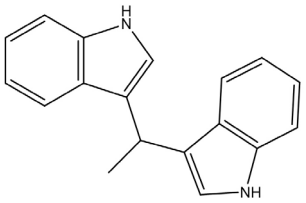
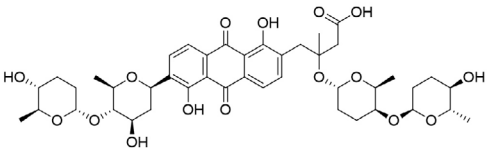
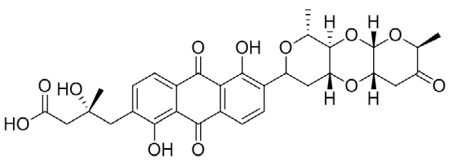
Table 4. Active metabolites of Halophilic micro-organisms responsible for anti-oxidant activity

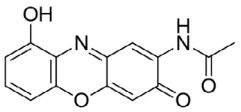
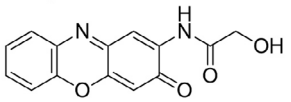
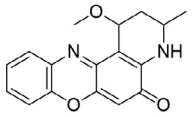
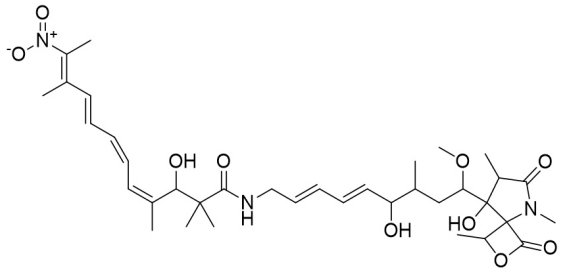
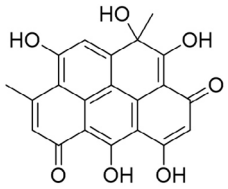
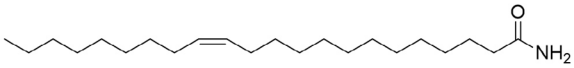
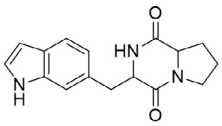
Salt Tolerant Microbes	Structure/ metabolite	Antioxidant assay	Free radical cleavage capacity	Ref.
Nocardiopsis gilva YIM 90087		DPPH / ABTS	54.9±2.0% at 2 mg/mL in DPPH 68.6±1.0 at 1 mg/mL in ABTS	57
		DPPH / ABTS	14.3 ± 1.5% at 4 mg/mL 28.4±2.7 at 2 mg/mL in ABTS	
		DPPH/ ABTS	47.7±0.9% at 2 mg/mL 78.2±3.7 at 0.5 mg/mL in ABTS	
		ABTS	54.6±0.6% at 2 mg/mL	
Halophilic Archaea	C50 carotenoids	EPR spectroscopy	43.17±1.79 of microemulsion and 66.08±0.25 of Nanoemulsion (5 min) 82.38±0.13 of microemulsion and 87.98±2.13 of Nanoemulsion (30 min)	57

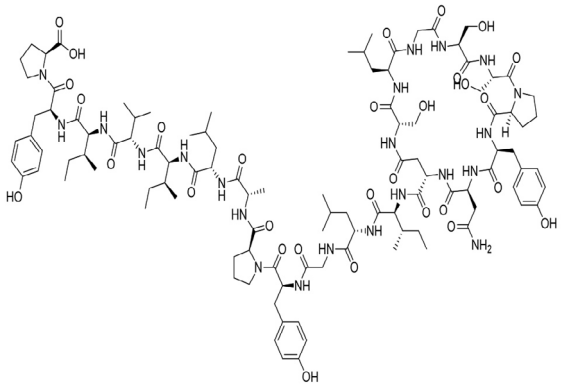
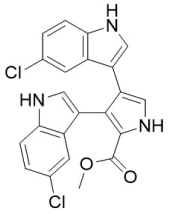
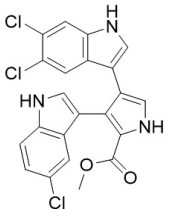
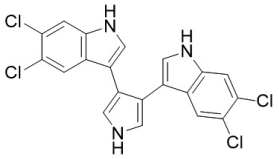
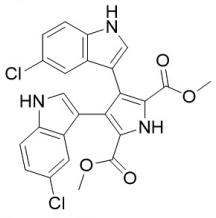
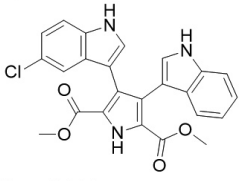
Haloterrigena turkmenica	Carotenoids (BR, MABR, and BABR)	DPPH / FRAP	66.8%±1.2 with DPPH 0.067±0.008 at 0.2 µg with FRAR	57
Halomonas nitroreducens strain WB1	EPS (glucose, mannose, galactose, rhamnose, arabinose)	Hydroxyl radical scavenging activity, DPPH radical scavenging activity	5.0 mg/ml show 83.3%	58
Phialosimplex species	-	DPPH, OH-, b-carotene antioxidant	450.92±6.73 (mg/ml), 390.97±3.97 (mg/ml), 36.59±2.94(mg/ml) respectively	58
Nesterenkonia species	HJ01pe	DPPH, ABTS	37.7±1.7 and 16.2±0.5 respectively	58
Staphylococcus Arlette *Bacillus subtilis* *Bacillus tequilensis* *Bacillus Hayne*	-	ABTS, nitric oxide, phosphomolybdenum, FRAP, and DPPH	86.34±0.007 mM TE/g extract with ABTS 64.79±0.004 µg/ml with nitric oxide 1.69±0.024 mg AAE/g extract with phosphomolybdenum 28.19±0.012 mM Fe (II) E/mg with FRAP 5.48 mg/ml with DPHH	59
Haloarcula species	-	ABTS	95.6± 0.1 at 200 004 µg/ml	59
Halorubrum species HRM-150	bacterioruberin(84.12 %), followedby mono anhydr-obacterioruberin(15.13 %) and carotenoid extract	2,2-azinobis-3-ethyl-b enzo-thiazole-6-sulfonicacid, 2,2-diphenyl-1-picrylhydrazyl, and hydroxylradicals.	Bacterioruberin shows better antioxidant activity	59
Aspergillus terreus Tsp22	Crude extracellularcompounds	-	-	60
Aspergillus flavus, Aspergillus gracilis, Aspergillus penicilliosis				
Halogeometricum limi strain RO1-6 *Haloplanus vescus* strain RO5-8	-	1,1-diphenyl-2-picrylhydrazyl radical scavenging assay.	-	60

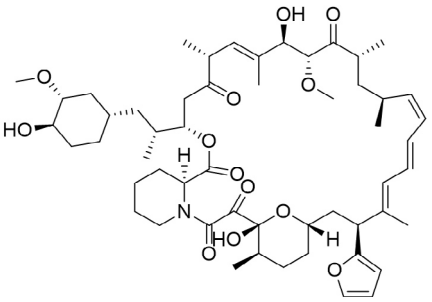
Table 5. Salt Tolerant Microbes metabolites examples with antimicrobial activities

No	Salt Tolerant Microbes Organisms	Metabolite	Activity	Ref.
1	Nocardiopsis species	 Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl)	Antibacterial	61
2	*Bacillus subtilis*	 (E)-docos-13-enamide  octadec-9-enamide	Antibacterial, antifungal	61
3	*Aspergillus flocculosus*	 4-methoxy-3-[(1E,3Z,5E)-6-(1H-pyrrol-2-yl)hexa-1,3,5-trienyl]pyran-2-one	Antibacterial	61
4	*Bacillus subtilis*	Glycoprotein	Antibacterial, antifungal	62
5	*Norcardiopsosis terrae*	Quinoloid alkaloid,  4-oxo-1,4-dihydroquinoline-3-carboxamide  Indole-3-carboxylic acid	Antibacterial and anticancer	62
6	*Halomonas salaria*	Amylase Protease 8-anilinonaphthalene-1-sulfonic acid (lipase) (2S, 3R,4S,5S,6R)-2-[(2R,3S,4R, 5R,6S)-4,5-dihydroxy-2-(hydroxymethyl)-6 [(2R,3S, 4R,5R,6R)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxyoxan-3-yl]oxy-6-(hydroxymethyl)oxane-3, 4,5-triol (cellulase) Pectinase DNAase	Antimicrobial	62

7	*Actinomyces* species	 2-chloroacetate  ethyl 2-chloroacetate  (3R)-4-chloro-3-hydroxybutanenitrile	Antimicrobial	62
8	*Bacillus subtilis*	Carotenoids Polyhydroxy alkanoates	Antibacterial	63
9	*Halomonaselongata*	 (6S)-2-methyl-1,4,5,6-tetrahydropyrimidine-6-carboxylic acid	Antimicrobial	63
10	*Halobacilluskarajiensis*	Peptide furanomycin	Antimicrobial	63
11	*Vibrio parahaemolyticus* B2	 3-[1-(1H-indol-3-yl)ethyl]-1H-indole Himalomycin A	Antimicrobial	63
12	*Streptomyces* species B6921	 himalomycin B  Fridamycin D	Antimicrobial	64

13	*Actinomadura* species M048	 N-(9-hydroxy-3-oxophenoxazin-2-yl)acetamide Chandrananimycin A  2-hydroxy-N-(3-oxophenoxazin-2-yl)acetamide Chandrananimycin B  1-methoxy-3-methyl-1,2,3,4-tetrahydropyrido[3,2-a]phenoxazin-5-one Chandrananimycin C	Antimicrobial	64
14	*Streptomyces nodosus* NPS007994	Nitro-tetraene Spiro-beta-lactone-gamma-lactum  Lajollamycin	Antimicrobial	64
15	*Steptomyces chibaensis species* AUBN1/7	 1-Hydroxy-1- norresistomycin	Antimicrobial	64
16	Vibriosp. A1SM3-36-8	 13-cis-docosenamide	Antibacterial	65
17	*Pseudonocardia endophytica* VHK-10	 3-((1H-indol-6-yl) methyl) hexahydropyrrolo (1,2-a) pyrazine-1,4-dione	Antimicrobial	66
18	*Halobacilluskarajiensis, Alkalibacillus almallahensis*	Peptide furanomycin	Antimicrobial	66

19	*Steptomonosporaalba*	 (Streptomonomicin)	Antibacterial	67
20	*Streptomyces* species CNQ-418	Marinopyrroles A Marinopyyroles B  Lynamicin A  Lynamicin B	Antibacterial	67
21	*Marinispora* species NPS12745	 Lynamicin C  Lynamicin D  Lynamicin E	Antimicrobial	68,69

22	*Streptomyces hygroscopicus* BDUS 49	 7-Demethoxy-7-(2-furyl) rapamycin	Antimicrobial	69

Nano formulation of existing salt tolerant microbes for the targeted diseases

Several factors are required for the biosynthesis and formulation of bioactive metabolites for example uniform size, high purity, and composition for synthesis through selected techniques.[21,22]

Various existing nanoformulations of Salt Tolerant Microbes with different targeted delivery like anticancer, antimicrobial, and antioxidant are discussed in Table 1.

Different methods for preparing nanoparticles with key findings are discussed in Table 2.

Currently, the nano-formulation of Salt Tolerant Microbes' active metabolites is considered a scientific tool in the pharmaceutical field. The current approach is focused on treating antibiotic resistance. The study suggests that the metabolite of Salt Tolerant Microbes produced due to the lack of nutrients, starvation, dehydration, UV-rays, and imbalanced ion concentration makes them deserving candidates for drug discovery. Some examples are also discussed like Anti-cancer activity (Table 3), and anti-oxidant activity (Table 4) in the table we also discuss some tests of anti-oxidant activity like DPPH stands as 2,2-diphenyl-1-picrylhydrazyl is a chemical compound commonly used to measure the antioxidant properties of a substance. The principle behind the DPPH assay is to determine antioxidant properties, through which antioxidant substances will neutralize the free radical of DPPH. ABTS stands for (2,2-casino-bis (3-ethylbenzothiazoline-6-sulfonic acid)), and it measures the ability of antioxidants to scavenge free radicals and prevent oxidation. It observed the reduction of the blue-green color of the solution. The nitric oxide test is used to measure the antioxidant activity of a substance. Nitric oxide is a free radical on which different substances are tested to determine their antioxidant properties by using various methods such as the Griess reagent method.

Anti-microbial activity (Table 5) of a few Active Metabolites of Salt Tolerant Microbes with targeted deliveries. The production of carotenoid colors, retinal amino acids, hydrolytic enzymes, and suitable solutes like macromolecule stabilizing agents, biopolymers, and biofertilizers by halophilic microbes is well known. The production of bioplastics, artificial retinas, photoelectric devices, holograms, biological sensors, and other products uses salt-tolerant microbes and extremely halophilic aerobic archaea, also known as haloarchaea, plays a significant role in the industry.[23-28]

Future perspective

Public health is currently at risk due to the widespread development of antibiotic resistance. Millions of lives have been saved by antibiotics over the years, yet overuse of these drugs has resulted in the development of multi-drug resistant (MDR), which reduces or eliminates their efficacy. Antibiotic resistance has recently reached critical levels, indicating a rise in fatality in the healthy community and a near-term concern for hospitalized patients. In actuality, problems with MDR infections can cause the majority of patient deaths. The exploitation of all organic and environmentally friendly assets, including major environments as an opportunity for new antibiotic discoveries, is being prompted by the urgent need to develop new antimicrobial medicines that are

effective and safe. In 1982, Rodriguez-Valeraetal reported the discovery of the first antibacterial substances produced by salt-tolerated microbes. Halocin is the name given to compounds released by numerous Halobacterium species that can lyse and kill the local microbiota. Haloarchaea synthesize peptides and antimicrobial peptides (AMPs) known as halocins. Although some halocins play an ecological and environmental role, less research has been done on how they interact with human infections.[70]

The clinical significance of salt-tolerated microorganisms is rarely described in the race against time, and antimicrobial intervention against the most significant risk category of human pathogens is lacking. *Staphylococcus aureus*, *Klebsiella pneumoniae, Acinetobacter baumannii, Enterococcus faecium*, and *Pseudomonas aeruginosa* are still potential pathogens.[71]

In the generation of advancement, nanotechnology has been proven as the speedily evolving field that deals with the size of material 1 to 100 nm in diameter. biomolecules like proteins, nucleic acid, lipids, and polysaccharides are proven to be found in nature and can be used in the development of nanoparticles because they possess their individual properties. To develop distinctive works of art and purpose biomolecules can be engineered with nanoparticles which can result in a Novel Biomolecule Nanoparticle hybrid. So far, there are limited articles available for biomolecule nanoparticles and Salt Tolerant Microbes that can be persuaded for the creation of drug-resistant bacteria to make a variety of antibacterial drugs and anti-cancer drugs. hence, contemporary information on the technology and current trends in an individual field is required. the present review is about the Salt Tolerant Microbes and the metabolites formed by them and integrating them with nanotechnology to form biological nanoparticles which can be considered as new trends in the field of medicine and pharmaceutical field.[72]

CONCLUSION

As this review proceeds, the study focuses on the Salt Tolerant Microbes, their origin, and the mechanism through which they survive in extreme saline conditions. along with they also produce bioactive agents with significant uses and applications in the pharmaceutical and healthcare area. Salt Tolerant Microbes show diverse significance in the production of bioactive compounds that show therapeutic properties such as antioxidant, antimicrobial, and anti-cancer. Due to their more distinctive properties, these can be considered novel drugs. A further highlight is to focus the beam toward the integration and conjugation of these bioactive substances with nanoparticles for novel perception. The nanotechnology to form salt-tolerant microbes-mediated nanoparticles can be considered a new trend in the pharmaceutical field. This study will also be helpful in the MDR of antibiotics in the pharmaceutical field.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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