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Review Article
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SALINE WATERS: A POTENTIAL SOURCE OF ACTINOMYCETES POSSESSING ANTIBACTERIAL ACTIVITY

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ABSTRACT

Microorganisms growing in saline environments represent an important source of biologically active compounds. Such environments are distributed all over the world and mainly include oceans, coastal and deep sea locations, soda lakes, soda deserts as well as artificial salterns. Many antibacterial, antifungal, anti-tumor, cytotoxic and photo protective compounds have been isolated till date from these areas. This unique environment is still in its infancy for isolation of new microbes that can produce pharmaceutically valuable metabolites. From ancient times actinomycetes are known to produce secondary metabolites that are being used to treat many infections. Many new species of actinomycetes that have not yet been cultured under laboratory conditions are expected to occur in these environments, and they can be a source of drugs with novel chemistry and promising potential. This review aims to consolidate the reports on antagonistic actinomycetes from different types of saline environments. It will help to open up new possibilities of isolating uncommon genera of actinomycetes from saline systems producing valuable metabolites.

KEY WORDS

Antibacterial compounds, Extreme environments, Marine microbes, Secondary metabolites

INTRODUCTION

About 75% of the earth is covered with seawater and it harbours enormous microbial diversity present in the coastal and offshore regions, in water surface and abyssal depths, in specialized ecosystems like hot thermal vents, tropical coral reef ecosystems, estuaries, lagoons, salt pans, backwaters and mangroves. Such saline waters are characterized by presence of dissolved solutes and alkaline pH where native microbes are under a number of intense ecological pressures. Microorganisms found in these saline sites require high salt (NaCl) concentrations for their growth and are referred as halophiles. They encompass distinctive physiological properties that can be used for production of enzymes, bioactive compounds, osmoprotectants and many polymers [1].

Pathogenic bacteria are expanding their resistance mechanisms to the already existing antibiotics hence there is an urgent need of bringing out novel antibiotics. In spite of chemical synthesis and engineered biosynthesis of antimicrobials, natural microbial products are the most promising source of the future antibiotics to be developed. Actinomycetes are the most important prokaryotes both economically and biotechnologically in this respect and according to mathematical models, above 105 new antibiotics can be discovered from them [2]. They are responsible for the production of about half of the discovered bioactive secondary metabolites [3] that includes antitumor agents [4], antibiotics [3,5] and immunosuppressive agents [6].

Among actinomycetes, *Streptomyces* is the most dominating genus covering around 80% of total

antibiotic produced, and *Micromonospora* ranks second after it [7]. Many natural antimicrobial compounds are microbial secondary metabolites of low molecular weight. They are not essential for normal growth of an organism and are not necessarily expressed continuously. Moreover their production is often limited to a narrow set of species within a phylogenetic group. On the basis of their chemical structure and physical properties they can be classified into one or more of the following groups like alkaloids, aliphatic, aromatic, terpenoids, polyketides, and heteroaromatic organic acids, steroids, saponins, resins peptides, and phenols. Many of these secondary metabolites, including antibiotics serve survival functions for the organisms producing them [8]. In this review we focus on actinomycetes producing antibacterial compounds identified from saline waters and sediments of marine ecosystem and salt lakes many of which are novel in nature.

MARINE ECOSYSTEM

Marine environments possess many unique features different from other aquatic environments. It contains dissolved compounds as sodium chloride (NaCl) that makes up about 85% of the solids in seawater and the remaining 15% includes sulfate, calcium, potassium, magnesium, bicarbonate, borate, strontium, bromide, fluoride and others. The average salinity of seawater is about 35 ppt. which stays relatively constant throughout the ocean varying between 33 and 37 ppt. Most marine life cannot adapt to significant changes in the salinity of their environment. This feature allows microorganisms to produce different bioactive compounds then their terrestrial counterparts [9]. They adapt themselves to grow in saline environment by producing compatible solutes (e.g., polyols, amino acids) and increasing concentration of cytoplasmic ions [10]. Marine sediments, surface waters, mangrooves, delta regions as well as bodies of marine animals as sponges provide an important source from where actinomycetes can be isolated for production of their unique metabolites.

Marine sediments

Streptomyces spp. BD21-2 isolated from a shallow-water sediment sample collected from Kailua Beach, Oahu, Hawaii produced an antimicrobial ester bonactin that showed antimicrobial activity against Gram-positive and Gram-negative bacteria [11]. Two quinone antibiotics, himalomycins A and B were found to be present in ethyl acetate extract of *Streptomyces spp.* B6921 isolated from coastal site of Mauritius (Indian Ocean) that showed activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis,* and *Streptomyces viridochromogenes* (Tü 57) [12]. *Verrucosispora* strain AB-18-032, isolated from bottom of Japanese Sea was found to produce, a polycyclic polyketide abyssomicin C. It targets p-amino benzoate (PABA) biosynthesis and therefore inhibits folic acid biosynthesis in clinical isolates of multidrug-resistant (MDR) bacteria and vancomycin-resistant *S. aureus* [13]. Sub tidal sediment samples collected from the Bismarck and the Solomon Sea off the coast of Papua New Guinea revealed the presence of 102 actinomycetes along with two new genera of family *Micromonosporaceae* that showed activity against MDR Gram-positive bacteria [14]**.** The *Streptomyces* species (NPS008187) isolated from sediment of Alaska Sea, also showed antibacterial activity attributed to the presence of three new pyrrolosesquiterpenes, glyciapyrroles A, B and C [15]. *Streptomyces* strain B8005 and B4842 from sediment of the Laguna de Terminos at the Gulf of Mexico were reported [16] for antibacterial activity. Strain B8005 was found to produce three antibiotics, resistomycin, tetracenomycin and resistoflavin that act against *E. coli*, *S. viridochromogenes* (Tü 57), *S. aureus*, *Candida albicans*, *Mucor miehei*, and the microalga *Chlorella vulgaris*. The inhibitory activity of strain B4842 against *B. subtilis, S. aureus*, *E. coli*, and *C. albicans* was attributed to the presence of resistoflavin methyl ether and resistomycin in the extract.

Sediment samples collected from California, located along pacific coast of United States were reported to be rich in antagonistic actinomycete *Streptomyces nodosus* (NPS007994). Isolated from Scripps Canyon, La Jolla, California, this strain showed antimicrobial activity against both drug-sensitive and resistant Gram-positive bacteria which is attributed to the presence of lajollamycin antibiotic [17]. In an another study the presence of *Streptomyces* strain CNQ-418 producing marinopyrroles was also reported from La Jolla, (California) that showed potent activities against

methicillin resistant *S. aureus* (MRSA) [18]. *Marinispora,* a novel strain of a marine actinomycete was isolated from another coast of San Diego (South California) which produced broad spectrum lynamicins that showed activity against both Gram-positive and Gram-negative bacteria and was found be effective against MRSA and vancomycin-resistant *Enterococcus faecium* [19].

The *Streptomyces* species Merv8102 isolated from sediment samples of Paltium coast on the Mediterranean Sea of Egypt produced a novel triazolopyrimidine antibiotic, essramycin that showed antibacterial activity against Gram-positive and Gram-negative bacteria [20]. Marine sediment samples from different places at Anyer, a town in Banten province of Indonesia situated on West Coast, Java showed the presence of twenty nine actinomycetes isolates that produced active compound against Gram-positive and Gram-negative bacteria [21]. Sediment samples collected from near the sea side in Bigeum Island, South west coast in South Korea also revealed the presence of actinomycetes colonies of which majority of isolates belonging to the genus *Streptomyces* showed antimicrobial activity [22].

South India is also known to be rich in actinomycetes diversity and is continuously explored for the isolation of antagonistic actinomycetes. Fifty one strains of antagonistic actinomycetes from the littoral sediments of Parangipettai (South India) were reported of which eleven strains showed good antibiotic activity and were identified as members of genus *Streptomyces* and *Nocardia* [23]. A halophilic *Actinopolyspora* species AH1 isolated from Alibag coast, Maharashtra, India showed antibacterial activity against *B. subtilis, S. aureus, Staphylococcus epidermidis*, and antifungal activities against *Fusarium oxysporum, Aspergillus niger, A. fumigatus*, *A. flavus*, *Trichoderma and Penicillium* species [24].

Many sediment samples collected from regions around Bay of Bengal also revealed the presence of antagonistic actinomycetes. Eighty strains of actinomycetes from the sediments off the Bay of Bengal near Machilipatnam were isolated, of which seven isolates exhibited broad-spectrum antimicrobial activity [25]. *Streptomyces chinaensis* AUBN$_1$/7 was reported to produce 1-hydroxy-1-norresistomycin and resistoflavin that showed weak antibacterial activities against Gram-positive and Gram-negative bacteria and also showed cytotoxicity against cell lines HepG2 (hepatic carcinoma) and HMO2 (gastric adenocarcinoma) [26]. In 2005, isolation of eighty eight actinomycetes from areas near islands of the Andaman Coast of the Bay of Bengal were reported, of which most promising antibacterial activity was shown by *Streptomyces*, *Micromonospora*, *Nocardia*, *Streptoverticilium* and *Saccharopolyspora*. *Streptomyces* species BT 606 and BT 652 was active against *Pseudomonas aeruginosa* and *S. aureus* [27]. In another study the presence of antagonistic *Streptomyces* as dominating genus was also reported from Andaman Coast [28]. Marine actinomycete, *Nocardiopsis* sp. VITSVK 5 (FJ973467) was isolated from samples collected at the Puducherry coast on East of South India and tested for its antibacterial activity in three different solvent extracts. It was reported that the petroleum ether extract showed significant activity against *E. coli, P. aeruginosa, Klebsiella pneumoniae, E. faecalis*, *Bacillus cereus* and *S. aureus*. The ethyl acetate and chloroform extract showed antifungal activity [29]. In an another study fifty actinomycete strains were isolated from sediments of Puducherry coast, and were screened for antimicrobial, cytotoxicity and hemolytic activity against selected bacterial and fungal pathogens. It was reported that 24% of isolates belonging to genera *Streptomyces, Micromonospora, Actinopolyspora* and *Saccharopolyspora* showed significant antimicrobial activity against *B. subtilis, S. aureus, E. coli* and *K. pneumoniae* [30]. *Streptomyces* was found to be dominant genus among seventy eight isolates of marine sediments collected from Bay of Bengal near Pudimadaka coast of Andhra Pradesh, India. Promising antibacterial and antifungal activities were shown by isolates of the genus *Rhodococcus* and *Streptomyces* [31]. Actinomycete strain DVR D4 identified as *Amycolatopsis alba* from marine sediment samples from Visakhapatnam coast of Bay of Bengal, produced a cytotoxic compound, identified as pyridinium salt antibiotic, 1-(10-aminodecyl) pyridinium. It not only showed potent cytotoxic activity against a few cell lines *in vitro* but also exhibited antibacterial activities against Gram-positive and Gram-negative bacteria [32]. *Streptomyces coeruleorubidus* spp. was also isolated

from a similar environment of Visakhapatnam coast that exhibited broad spectrum of antimicrobial activity against the pathogenic bacteria and fungi [33].

Sea and Coastal waters

Surface waters of sea and coast are also important sources of antagonistic actinomycetes. *Janibacter limosus,* an isolate from North Sea, a marginal sea of Atlantic Ocean showed high biological activity against *S. viridochromogenes* and *S. aureus*. Its ethyl acetate extract was found to compose of two new natural products, a tetrahydroquinoline derivative identified as helquinoline and the N-acetylkynuramine along with other known secondary metabolites [34]. Water samples from Antarctic locations, especially from Terra Nova Bay (Ross Sea), were found to be rich in actinomycetes that express antagonistic activity against *E. coli* and *Proteus mirabilis, Micrococcus luteus* and *B. subtilis* [35]. Eighty percent of the *Streptomyces* isolated from the Waters of the Asen fjord in the Trondheim fjord and Steinvikholmen (a small islet) in Norway also revealed antagonistic activity against Gram-negative, and Gram-positive bacteria in their DMSO extracts [36].

An antagonistic *Streptomyces marinensis* producing neomycin (B&C) complex, was isolated from the Visakhapatnam coast of India [37]. Sixty strains of actinomycetes from the Bay of Bengal near Kakinada coast were tested for antibacterial activity and it was found that 18.3% of the isolates exhibited potent activity [38]. Three strains of halophilic actinomycetes *Streptomyces*, *Actinompolyspora* and *Nocardia* isolated from coastal water samples of Dhanushkodi, Rathnapuram district, India showed antimicrobial activity against human pathogens like *S. aureus*, *P. aeruginosa*, *Salmonella typhi*, *Vibrio cholerae*, *Klebsiella* species and *Aspergillus* [39]. *Streptomyces rochei* isolated from sea water samples of Vishakhapatnam coast of Bay of Bengal, India was found to have broad spectrum activity against pathogenic bacteria and fungi [40]. Presence of antagonistic actinomycetes was also reported from marine environment located at Karrwar, west coast of India [41]. In a study one hundred and seven marine actinomycetes were reported from seawater and near sea shore sediment of Konkan coast, Maharashtra. It was found that some of isolates showed potent activity against *B. subtilis*, *S. aureus*, *E. coli and Proteus vulgaris* etc [42].

Mangrove Regions

Mangrove forests are among one of the world's most productive tropical ecosystems that protect coastal zones from erosion, and provide food and shelter for a large number of commercially valuable fin and shell-fishes. They are harboring enormous microbial diversity and are now exploited for the production of many bioactive compounds. Members of *Streptomyces*, *Micromonospora*, *Sacharomonospora*, *Actinomadura* and *Nocardiopsis* were reported from mangrove sediments in Zhangzhou, Fujian, China. These isolates exhibited antimicrobial activity against *E. coli*, *S. aureus*, *B. subtilis*, *C. albicans* and *Rhizoctonia solani* as well as also showed antitumor activities for BEL7402, A549 and HL60 tumor cells [43].

Indian mangroves covers an area of about 6,740 sq.km [44] that occupies 7% of the total Indian coastline and 70% of it occurs on the east coast especially towards south. The Sundarbans on the delta of the Ganges, Brahmaputra and Meghna rivers on the Bay of Bengal, India has the largest area of 4,250 sq. km approximately which forms the largest block of mangroves of the world taken together with Bangladesh. These mangrove forests are characterized by moderate to highly saline water and are a potent source for the isolation of antibiotic-producing actinomycetes [45]. An actinomycete isolated from the Sundarbans region showed potent antimicrobial activity against Gram-negative and positive bacteria including MDR bacteria like MRSA, molds, and yeast [46]. Three hundred and fifty actinomycetes were isolated from southern, northern and eastern regions of Sundarbans. Among them *Streptomyces* was found to be dominant. All the isolates were tested for antibacterial activities against Gram-positive bacteria like *S. aureus*, *M. luteus*, *Arthrobacter protophormiae*, *Bacillus pumilus*, *B. subtilis, Lactococcus lactis*, and *Mycobacterium smegmatis* and Gram-negative strains that included *K. pneumoniae*, *Serratia marcescens*, *P. mirabilis*, *P. aeruginosa*, *E. coli.* About fifty percent of isolates were active against at least one of the test bacteria and 58.33% of the isolates showed higher antibacterial activity when cultured in natural

seawater [47]. Fifty five actinomycetes were isolated from soil sample of Karanjal region in Sundarbans and were found to be *Actinomyces*, *Nocardia*, *Streptomyces* and *Micromonospora.* They were effective against one or more Gram-negative pathogenic bacteria such as *Shigella boydii*, *S. flexneri, S. sonnei*, *S. dysenterriae*, *V. cholerae, S. typhi*, *Plesiomonas*, *Pseudomonas, Hafnia* spp., and *E. coli* [48].

Pichavaram mangrove forest located between the Vellar and Coleroon estuaries, Tamil Nadu, India [49] was also studied for the presence antagonistic actinomycetes. *Streptomyces roseolilacinus* and other actinomycetes were isolated from different sites of Pitchavaram mangrove ecosystem. These isolates showed activity against human pathogens as *C. albicans, P. vulgaris, S. aureus* and *K. pnemoniae* [50]. In an another study about 50% of the actinomycetes isolates from the similar sites showed activity against *S. aureus* followed by *V. cholerae, B. subtilis, P. vulgaris, E. coli, K. pneumoniae* and *S. typhi* [51]. Two marine actinomycetes were also isolated from sediment samples collected from the Manakudi mangrove estuary of Arabian Sea, Tamil Nadu, and India. They exhibited antagonistic activity against the MRSA, *Enterobacter* species, *S. typhi, B. subtilis, K. pneumoniae*, *P. vulgaris* and *P. aeruginosa* [52].

The Vellar estuary is situated at Porto Novo about 75 km south of Pondicherry, South India. Forty strains of actinobacteria isolated from their sediments were studied for antagonistic activity against *B. subtilis, P. vulgaris, S. flexneri, K. pneumoniae, V. cholerae* and *S. aureus* of which 22.5% were found to be active [53]. In 2009, isolation of actinomycetes that produced bioactive compounds from Vellar Estuary was also reported. These isolates strongly inhibited the growth of both Gram-positive and Gram-negative bacteria and yeast [54]. Sediment samples collected from Muthupet mangrove ecosystem situated along the Southeast coast of India, showed the presence of actinomycetes having antagonistic activity against human pathogens like, *E. coli, Pseudomonas* spp., *Klebsiella* spp. and *Bacillus* spp. [55]. *Streptomyces* isolated from mangrove regions in local area of Visakhapatnam, south east of India also showed antimicrobial activity against many pathogens [56].

The Andaman and Nicobar Islands, located in the northeast Indian Ocean, occupy 966 sq. km of mangrove cover. In a study carried out, isolation of forty two bioactive actinomycetes from mangrove sediments of Andaman and Nicobar Islands, India were reported. They were evaluated for their antibacterial activity against pathogenic bacteria *S. aureus*, *K. pneumoniae, B. subtilis* and *S. typhi.* Among all the tested isolates, antibacterial metabolite production was shown by twenty two species [57].

Twelve percent of India's Mangroves lies on the west coast. Marine soil samples collected from Calicut mangrove of West Coast of Kerala, India showed the presence of twenty four actinomycetes of which, *Streptomyces sp*. RM42 possessed broad spectrum of antimicrobial activity, due to a compound similar to cephalexine, a semi synthetic derivative of cephalosporin C [58].

SALT LAKES AND SOLAR SALTERNS

Hyper saline waters of salt lakes can be divided in two types. They are called as thalassohaline, if their composition is similar to that of sea water. However, if their composition reflects the composition of the surrounding geology, topography and climatic conditions, often particularly influenced by the dissolution of mineral deposits then the water is called as athalassohaline. Examples of thalassohaline environments are solar salterns, used for the natural evaporation of sea water for the production of salt where as examples of athalassohaline waters are the Dead Sea, Great Salt Lake, some cold hypersaline lakes in Antarctica or alkaline lakes, particularly East African lakes, like Lake Magadi or the lakes of Wadi Natrun, soda lakes and soda deserts [59, 60]. Various promising antagonistic strains of actinomycetes have been reported from these environments.

Lake Bardawil located along the northern shore of Sinai, Egypt was reported to be rich in *Streptomyces* species and the isolate *Streptomyces viridiviolaceus* exhibited antimicrobial activities against *Corynebacterium michiganese* B-33, *E. coli*, pathogenic *Edwardsiella tarda*, *Staphylococcus* spp. *and Pseudomonas solanacearum* B-3212 [61]. Twenty three strains of halophilic actinomycetes isolated from a salt lake Hami in Xinjiang, China showed antibacterial activity towards *B. subtilis* and other pathogens [62]. Water samples from salt lakes of Bay

of Bengal, India starting from Pulicat Lake to Kanyakumari were reported to be rich in actinomycetes. Of the total two hundred and eight isolates, fifty three percent exhibited antimicrobial activity against human pathogens as *S. epidermidis*, *B. subtilis*, *P.aeruginosa*, *E. coli* and *C. albicans* whereas seventy two percent of isolates showed antifungal activity against two plant pathogens [63].

Solar salt pans consist of a series of inter linked pans of different salinity due to evaporation of seawater. Salinity in these ponds reaches as high as 400 psu during the peak salt-producing season and as low as 5 psu during the monsoons. Marine salt pans in Goa are multi-pond systems interconnected to each other and have a discontinuous salinity gradient. These ponds have a continuous inflow of sea water which is evaporated for the commercial production of sodium chloride. The actinomycetes isolated from crystallizer ponds of the salt pans of Batim and Ribandar, Goa, India were tested for antibacterial activity against human pathogens and it was found that they produced antimicrobial compounds [64].

Marakkanam located at Southern coast of India in Tamil Nadu has large areas of salt pans with salinity of 32-38 parts per thousand. Actinobacteria that showed broad spectrum antibacterial activity were isolated from this site [65]. *Streptomyces* species isolated from Ennore saltern, Tamil Nadu also exhibited promising antagonistic activity against *E. coli*, *P. aeruginosa*, *A. flavus* and *A. fumigatus* [66]. *Streptoverticillium album* was reported to be dominant actinomycetes species in soil samples of salt pan environment of Kodiakarai, Vedaranyam, Nagapattinam, and Tamilnadu. It showed antibacterial activity against three human pathogens, *S. aureus, K. pneumoniae* and *E. coli* [67].

Soil from the salt pan regions of Cuddalore and Parangipettai (Porto-novo) revealed the presence of *Streptomyces* and *Saccharomonospora* which showed promising antimicrobial activity against *E. coli, K. pneumoniae, P. aeruginosa, V. cholerae, S. typhi, S. aureus,* and *Shigella dysenteriae* [68]. In an another report, sediment samples collected from the salt pans of Marrakanam and Puducherry coast of Bay of Bengal, India showed the presence of *Streptomyces* VITSVK9 spp. Active against *B. subtilis*, *E. coli*, *K. pneumoniae, A. niger*, *A. fumigatus* and *C. albicans* [69]. A moderately halophilic *Nocardiopsis* species JAJ16 isolated from salt pan soil was reported to show antibacterial activity against bacteria such as *S. aureus, B. subtilis, S. typhi*, MRSA, *K. pneumoniae*, *Enterobacter* sp. and *P. aeruginosa.* The antifungal activity was also reported against fungi *C. albicans*, *A. flavus* and *F. oxysporum* [70].

CONCLUSION

Organisms growing in halophilic environments have unique physiological and structural characteristics which enable them to survive in extreme conditions of, salinity, pH, pressure and temperature and they are capable of producing novel secondary metabolites not observed in terrestrial microorganisms [71]. Due to their distinct chemical structures, these secondary metabolites can serve as the basis for the synthesis of new drugs [72]. Traditionally access to the microbial diversity of actinomycetes in the environment has been focused on intensive sampling from a wide diversity of geographical locations and habitats. Large numbers of samples were processed empirically by general isolation methods, which resulted in recurrent isolation of the predominant species in these habitats [73]. This has led to a decreased probability of isolating novel compounds from already explored terrestrial habitats. Thus now the efforts are on discovering novel metabolites from unexplored extreme habitats and in this regard halophilic habitats prove to be promising. Use of modern techniques like metagenomics will be helpful to identify uncultured microbes of interest. Development of new isolation strategies in the recovery of actinomycetes from these environments is of immense importance for ensuring success in this field and we hope that in near future many novel antibacterial compounds will be isolated for the benefit of mankind.

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