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Antimicrobial potential of *Streptomyces* sp. to the Gram positive and Gram negative pathogens

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ABSTRACT

Background: The occurrence of drug resistant infectious disease causing microbial pathogens was highly spreaded because of the wide level application of the commercially available antimicrobial agents. However, the eradication of the microbial pathogens was of huge demand. Although, many antimicrobial compounds were commercially available in the market however the spreading of the pathogens were hugely increased. Actinomycetes produce various secondary metabolites against pathogenic bacteria and fungi. The present investigation aimed to study the antimicrobial potential of the *Streptomyces* sp. towards infectious diseases causing pathogens.
Methods: Culture dependable isolation techniques were followed for the isolation of the active actinomycetes isolates and the antimicrobial properties of the actinomcyetes were detected by primary screening techniques using modified starch casein agar medium. The active isolate was confirmed by various biochemical and morphological techniques.
Results: In this study, 10 actinomycetes were isolated and later five were selected for secondary screening and noted significant activity against *Enterobacter aerogenes* and *Proteus mirabilis*. Among the selected *Streptomyces* sp., ES2 showed potent activity against selected microbes and was identified as *Streptomyces* sp. The studied isolates were resisitant towards streptomycin (10 μg), ampicillin (50 μg) and ciprofloxacin (5 μg). The organic solvent extracts of the promising isolate ES2 prononunced comparatively better inhibitory properties towards the studied pathogenic bacteria.
Conclusion: Overall, the present study evidenced that the actinomycetes were promising candidate for the eradication of the pathogenic strains.

Introduction

Actinomycetes are Gram positive, saprophytic, free living, filamentous bacteria and are very important source for the production of various antibiotics [1–3]. They belong to the order Actinomycetales and are found in marine, estuarine environment, soil and freshwater [4,5]. Actinobacteria were generally considered as an intermediate group between fungi and bacteria [6–9] and these actinomycetes are the most economically important microbes. Actinomycetes from the environmental samples were known for the wide level production of chemically diverse secondary metabolites such as alkaloids, flavanoids, terpernoids, and also known for recycling organic wastes in various environments. Actinobacteria are noteworthy as important antibiotic producers, making three quarters of all well known commercially available antibiotics. They are highly responsible for the production of many antibiotics, antitumor agents, immune suppressive agents and various enzymes. Among the actinobacteria, *Streptomyces* accounted for more than 80% of the total antibiotic products, followed by *Actinopolyspora* and *Micromonospora* which are rare actinobacteria with less than one-tenth of *Streptomyces* population. It was estimated that about 42% of commercial metabolites are known to be produced by various actinomycetes, 16% by fungal strains and the remaining from bacterial source. These organisms produce secondary metabolites and release into the environment. They have broad spectrum biological activities such as antifungal, antibacterial, antiparasitic, antiviral, immunosuppressive, insecticidal, antitumor, antioxidant, anti-inflammatory, diabetogenic and enzyme inhibition. The dis-

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covery of antibiotics had a significant impact on the control of various infectious diseases and the development of pharma industry.

The invention of broad spectrum antibiotic such as, streptomycin made much more attention towards screening of various novel antibiotics from these organisms. These have been frequently exploited for the production of novel antibiotics from various sources [10]. Actinomycetes have potentials to synthesize antimicrobial metabolities such as, beta-lactams, polyketides, glycopeptides, macrolides, tetracycline, aminoglycosides, polyenes and actinomycins. In actinomycetes, *Streptomyces* is the important genus and has more than 1000 species have been elucidated [11–13]. About 70% of the naturally available antibiotics are synthesized by *Streptomyces* sp. actinomycetes are potential producers of metabolites with anti-parasite, antimicrobial, antitumor, antiviral activity, and other pharmaceutically useful compounds. Actinomycetes from marine origin are the important source of antimicrobial compounds as the physical factors of the sea are totally different from the terrestrial environment [15]. Marine sediments are promising sources for various *Actinomycetes* species, including *Streptomyces* sp. Also, actinomycetes from new taxa or unique environmental niches are still very useful for novel drug discovery. Many researchers have identified various antibiotics from *Streptomyces* sp. in marine and estuarine environment [14–20]. The marine *Streptomyces* sp. and rare actinomycetes produce various enzyme inhibitors, anticancer compounds and antibiotics. The novel secondary metabolites such as, Abyssomicin C has been isolated from *Verrucosispora* sp., which showed potent inhibitory effect on para aminobenzoic acid synthesis [21,22]. Also, an anticancer molecule, Salinosporamide A was isolated from *Salinispora* sp. [23] and marinopyrroles was characterized from *Streptomyces* sp. [24]. The marine and estuarine actinomycetes, especially, *Streptomyces* sp. proved that the estuarine ecosystem is an excellent source for analyzing diverse actinomycetes with novel biological properties.The present study aimed to identify the promising actinomycetes strain from the environmental samples with antibiotic production cababilities.

Materials and methods

Sample collection

In this study soil samples were collected from the estuary in Tamil Nadu, India. A total of five samplings were made in five different locations for the isolation of potent *Streptomyces* species for the production of antibiotics.

Isolation of actinomycetes

Serial dilution method using Starch Casein Agar medium (Himedia, Mumbai, India) was followed for the isolation of the strains. Briefely, serial dilution was made upto 10^{-7} and spread on Starch Casein Agar plates. After incubation, the colonies with powdery texture, folded and branching filaments without or with aerial mycelia were subcultured on SCA slants. The slants were kept at 4 °C until further use.

Selection of actinomycetes and maintenance

Ten actinomycetes isolates were initially selected based on their colony morphology. They were subcultured using streak plate method using SCA culture medium and incubated for 8 days at room temperature (28 ± 2 °C) and pure culture was obtained. Pure cultures of these actinomycetes isolates were named as, ES1, ES2, ES3, ES4, ES5, ES6, ES7, ES8, ES9, and ES10.

Initial screening of actinomycetes for the production of antimicrobial agents

Primary screening was performed as suggested by Al-Dhabi et al. [25] with little modifications. Double layer method was followed for the screening of actinomycetes.

Morphological and 16S rRNA gene levelcharacterization of potent Streptomyces *sp*

A cultural characteristic of potent isolated strain was examined by the visible observation of 14-day old culture which was grown on AIM medium. Micro-morphology, sporulation and spore chain morphology of the colonies were observed under light microscopy and colony morphology was registered with respect to colony, substrate and aerial mycelium, branching and the nature of the colony was observed after 7 days and 14 days intervals. The sensitivity and resistant pattern of the isolates were tested against different antibiotics such as amikacin (30 μg), streptomycin (10 μg), carbenicillin (50 μg),ampicillin (50 μg),imipenem (10 μg), ticarcillin (75 μg), ciprofloxacin (5 μg),nalidixic acid (50 μg) and cefpodoxime (10 μg) by disc diffusion techniques. The 16S rRNA gene level characterization has been studied by PCR amplification and sequencing.

Submerged fermentation for the production of secondary metabolities by actinomycetes

In this study five actinomycetes isolates were selected for secondary screening experiments grown on culture medium (g/l: soybean meal, 10; $MgSO_4.7H_2O$; $CaCO_3$, 0.5; NaCl, 3; $(NH_4)_2HPO_4$, 0.5; K_2HPO_4, 1; and medium pH 7.0 ± 0.2), and incubated for six days at 28 °C. The cellular growth was assessed by clumps, turbidity, aggregates, visible pellets in the culture medium. The fermented medium was centrifuged at 10,000 rpm for 10 min. The supernatant was extracted twice with ethyl acetate (double volume) and the combined organic layers were evaporated to obtain the ethyl acetate extract. Antimicrobial activity of the actinomycetes was compared with commercial antibiotics.

Biosynthesis of secondary metabolites by Actinomycetes *species in solid substrate fermentation*

Spores (10^7/ml) of *Streptomyces* strains were inoculated in the starch casein agar plates at optimum temperature and pH and incubated for 7 days. After one week, the culture medium was cut into small pieces aseptically and kept in Erlenmeyer flask (500 ml) containng 200 ml ethyl acetate. It was kept on shaker and left for overnight at room temperature. Then remaining agar pieces were further extracted with 200 ml ethyl acetate separately. The crude extract was filtered using Whatman No 1 filter paper as suggested by Bizuye et al. [26]. Finally organic solvent was evaporated and the crude extracts were concentrated.

Screening of actinomycetes by well diffusion method

In the present study antibacterial activity of the isolates was carried out by agar plate diffusion assay against five pathogenic bacteria such as, *E. coli*, *P. aeruginosa*, *B. subtilis*, *E. aerogenes* and *P. mirabilis*.

Results and discussion

Screening of actinomycetes from estuary

Inspite of the success of developing novel drugs, and development of upstream and downstream process, infectious diseases still

Table 1
Priliminary screening of actinomycetes isolates for antimicrobial properties using cross-streak method.

	Test bacteria				
Isolates	*E. coli*	*P. aeruginosa*	*B. subtilis*	*E. aerogenes*	*P. mirabilis*
ES1	–	+	–	+	–
ES2	+	+	+	+	+
ES3	–	+	–	+	–
ES4	+	+	+	+	+
ES5	+	+	+	+	+
ES6	+	–	+	+	–
ES7	–	–	–	–	–
ES8	+	+	+	+	+
ES9	+	+	+	+	+
ES10	–	–	+	–	+

Table 2
Secondary screening of actinomycetes isolates for antimicrobial properties using disc diffusion method.

Sample ID	*Bacillus*	*S. aureus*	*P. aeruginosa*	*Enterobacter* sps.	*E. coli*
ES2	19	26	18	22	21
ES4	18	24	20	20	20
ES5	21	27	21	24	15
ES8	20	26	18	22	19
ES9	17	23	21	15	16
Standard	20	29	18	23	13

remain the leading cause of death world wide [27]. In this study initially 10 Actinomycetes were isolated and tested for its antibacterial efficacy (Table 1). These, five actinomycetes were selected for the production of antimicrobial agent against *E. coli*, *P. aeruginosa*, *B. subtilis*, *E. aerogenes* and *P. mirabilis*. Ethyl acetate extract of the selected five actinomycetes showed broad spectrum antibacterial activity. This result is in good agreement with the results of Gebreyohannas et al. [27]. Among the ten actinomycetes isolates, five actinomycetes synthesized excellent quantities of antimicrobial agents (Table 2). Among the isolates, potent organism (ES2) was Gram-positive, negative to Indole production test, positive to methyl red-test, Voges–Proskauer test, negative to starch and casein hydrolysis, and nitrate reduction test, negative to carbohydrate fermentation and hydrogen sulphide production. The results of cultural characteristics features and morphology of strain ES2 suggested that this isolate belonged to *Streptomyces* sp. [28]. In addition, the antibacterial sensitivity pattens of the isolates against the different standard antibiotics were displayed in Table 3. The studied isolates showed resisitant towards streptomycin (10 μg), ampicillin (50 μg) and ciprofloxacin (5 μg), whereas the other antibiotics activity inhibited the growth of the studied isolates. The resistant pattern of the isolates towards the common antibiotics such as streptomycin was the ideal characterisitics of *Streptomyces* species. Actinomycetes from estuarine origin showed the synthesis of various antimicrobial agents. Of the actinomycetes, *Streptomyces*

Table 4
Molecular level identification of the potent antimicrobial strains.

Isolates name	16S rRNA gene (BP)	Similarity	Similar strain
ES2	1445	100 %	*Streptomyces radiopugnans*
ES4	1440	99.67%	*Streptomyces atacamensis strain C60*
ES5	1507	100 %	*Streptomyces fenghuangensis*
ES8	1452	100 %	*Streptomyces verrucosisporus*
ES9	1373	100 %	*Streptomyces mangrovi*

showed potential activity against various bacteria and fungi. These *Streptomyces* are well adapted to the marine ecosystem and are able to produce various novel bioactive compounds. The isolation and cultivation of novel microorganisms of under explored habitats is still useful for the exploration of novel compounds [29]. Microbes have to initially adapt and evolve to resist various stress conditions, thus, have the ability to synthesis of new biochemical agents to carryout special bioactivities and biofunctions [30]. The molecular level identification of the strains from the estuary authenticated that all the selected isolates shared similarity to the antibacterial actinomcyetes group. The isolate ES2 showed 100% similarity towards *Streptomyces radiopugnans* and the isolate ES2 shared 99.97% to *Streptomyces atacamensis* strain C60 (Table 4). Simmilarly, the other strains such as ES5, ES8 and ES9 clearly showed similarity towards *Streptomyces fenghuangensi, Streptomyces verrucosisporus* and *Streptomyces mangrove* respectively.

Antibacterial activity of seconday metabolites from actinomycetes

The selected five actinomycetes were cultured in submerged fermentation and solid state fermentation and the crude extract showed antibacterial activity. All five actinobacterial isolates showed inhibitory activities against selected pathogens. Among the five actinomycetes isolates, the strain ES2 showed more activity against the bacterial pathogens. The antibacterial profile of culture extract of actinomycetes against selected pathogenic bacteria was shown in Fig. 1. Recent studies indicated that the potential of various marine actinomycetes, specifically, *Streptomyces* sp. as a potential resource of novel bioactive secondary metabolites. The isolated *Streptomyces* sp. from mangrove sediments was able to produce types of secondary metabolites, including antifungal, anticancer, antibacterial and anti HIV [31–34]. It was also reported that Streptomyces specis were known for secreting various compounds for killing various clinical pathogens [34–36]

Five out of the ten actinomycetes strains showed activity against all of tested pathogenic Gram-positive and Gram-negative bacteria. The strain ES2 exhibited strong antibacterial activity

Table 3
Antibiotic sensitivity pattern of the different actinomcyetes against the commercially available antibiotics.

Different antimicrobial compounds	Inhibition zone (diameter in mm)				
	Isolate ES2	Isolate ES4	Isolate ES5	Isolate ES8	Isolate ES9
Amikacin (30 μg)	10	12	15	15	NA
Streptomycin (10 μg)	R	R	R	R	R
Carbenicillin (50 μg)	21	32	17	18	–
Ampicillin (50 μg)	R	R	R	R	R
Imipenem (10 μg)	17	12	10	24	29
Ticarcillin (75 μg)	18	31	43	12	15
Ciprofloxacin (5 μg)	S	S	S	S	S
Nalidixic acid (50 μg)	R	R	R	R	R
Cefpodoxime (10 μg)	15	S	S	S	S

S: sentive; R: resisitant; – no results noted.

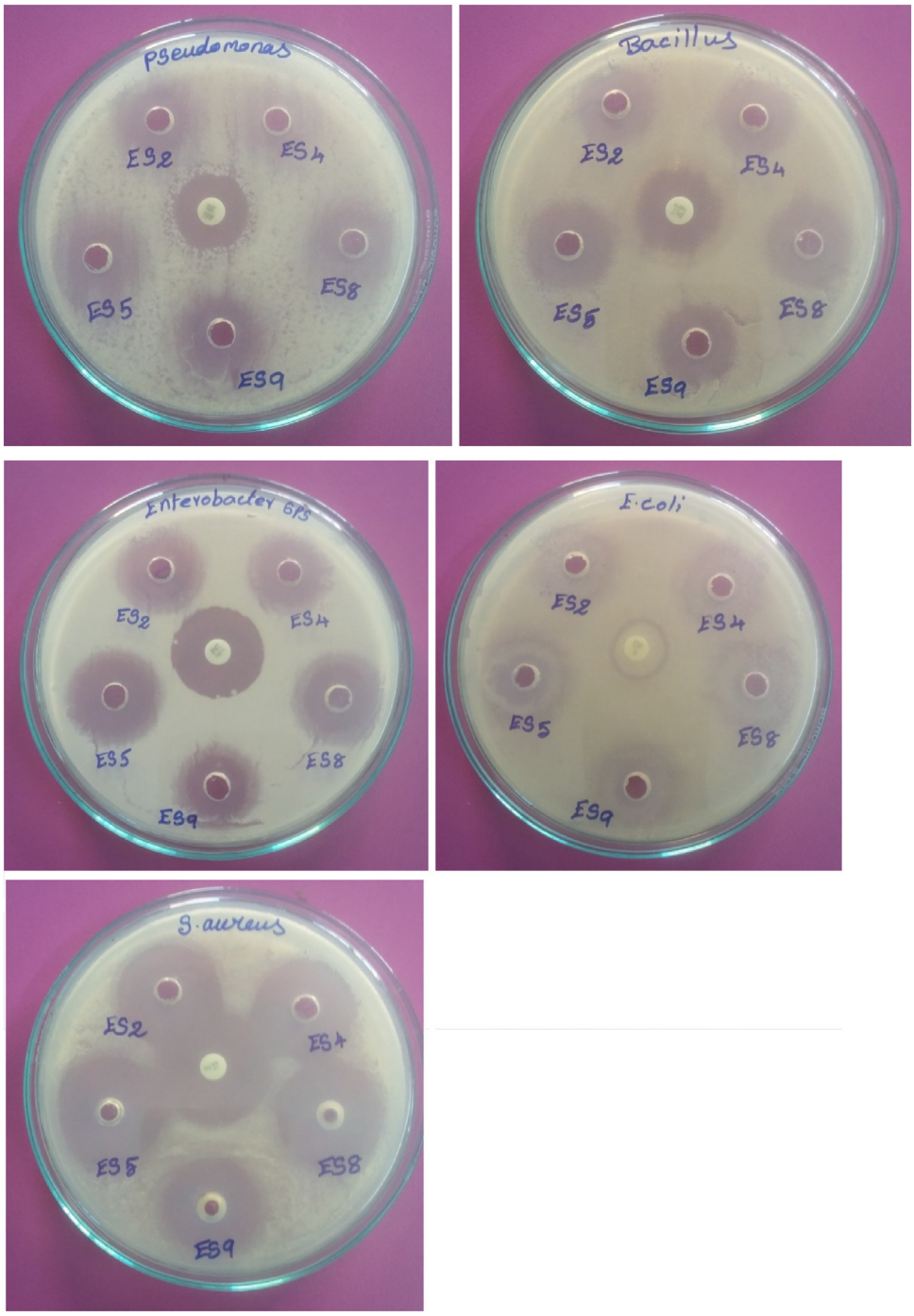

Fig. 1. Antimicrobial activity of cell free extract against test bacteria by well disc diffusion method.

against *E. coli* (19 mm), *P. aeruginosa* (26 mm), *B. subtilis* (18 mm), *E. aerogenes* (22 mm) and *P. mirabilis* (21 mm). Previous studies also revealed that members of the genus *Streptomyces* isolated from the aquatic and terrestrial environments are responsible for the production of various secondary metabolites production [37,38]. The crude extract of *Streptomyces* sp. showed high activity against Gram-positive and Gram-negative bacteria suggests that the environmental factors also influence on secondary metabolites production. Recently *Streptomyces* species isolated from various environments showed potent anti MRSA activity. These organisms may produce a high molecular weight glycopeptide with novel anti-MRSA activity [39–42]. Hence, screening of various actinomycetes for the production of new drug is a continuous process which should be effective against present day's antibiotic resistant pathogenic bacteria. Actinomycetes have been proved as important sources of various useful secondary metabolites [43]. Freshwater and marine environment have been proven as interesting resources for developing novel and potent lead molecules having antimicrobial properties. Also, recent investication indicated that the protential of marine Actinomyctes, especially, *Streptomyces* sp. as a sustainable and useful source of novel bioactive compounds [43–47]. Hence, the findings of this study revealed that the estuarine *Streptomyces* sp. with antibiotic substances production cabability was an important application.

Conclusion

In conclusion, multiple drug resistant bacteria pose a serious threat world wide. *Streptomyces* species have played a critical role as a source of various lead molecules against many pathogenic bacteria. Also, *Streptomyces* species from unexplored regions like estuary which are likely to yield novel antibacterial agents. From this study, it is very clear that *Streptomyces* sp. ES2 could be a promising microorganism for the development of novel antibacterial drug against a wide range of pathogenic bacteria.

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Competing interests

None declared.

Ethical approval

Not required.

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