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INFLUENCE OF CULTURAL PARAMETERS ON THE PRODUCTION OF BIOACTIVE METABOLITES BY STREPTOMYCES RECTIVERTICILLATUS VJMS-8 ISOLATED FROM SOUTH COASTAL REGIONS OF ANDHRA PRADESH, INDIA

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Keywords:

Marine ecosystem, *Streptomyces rectiverticillatus* VJMS-8, Optimization, Bioactive metabolites

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ABSTRACT: Adaptation of marine actinobacteria to extreme climatic conditions such as high salinity, high pressure and high temperature has modified their physiological conditions to survive and elaborate novel bioactive metabolites. Among the different actinobacterial strains isolated from coastal regions of Guntur District, Andhra Pradesh, India, one potent strain with broad-spectrum antagonistic activity was found and identified as *Streptomyces rectiverticillatus* VJMS-8. Attempts were made to optimize the cultural parameters for an enhanced yield of antimicrobial metabolite production. Production of bioactive metabolites by the strain was high in tryptone yeast extract dextrose broth as compared to the other media tested. The strain utilized galactose and tryptone as good carbon and nitrogen sources for the elaboration of bioactive metabolites. The optimum temperature and pH for bioactive metabolite production by the strain were recorded as 35 °C and 7.0, respectively. NaCl @ 5% supported high production of bioactive metabolites. The secondary metabolites produced by the strain grown under optimal conditions exhibited high antagonistic activity against a variety of gram-positive and gram-negative bacteria as well as fungi.

INTRODUCTION: Microbes naturally produce defensive chemicals as a habit of challenging with other species for limited resources and survival, which are known as antimicrobials. These microbes are miniature chemical factories having the ability to produce a variety of raw materials used as substrates in to a series of treasure added products. Marine microorganisms have been recognized as a relevant source of secondary metabolites with the potential to regulate the pathogens [1, 2].

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These marine forms have the potential to integrate to extreme life environments, overcome the stress barriers and survive by modifying their biochemical potential with the generation of novel metabolites. The marine Actinobacteria, especially *Streptomyces* spp. are known as notable factories for the evolution of many biologically active compounds that are useful as antibacterials, antifungals, anti-virals, anti-thrombotics, immune-modifiers, anti-tumor drugs and enzyme inhibitors in many fields especially in medicine [3-7].

The exploration of marine actinobacteria as a source of potential novel metabolites has inspired the suspicion that marine forms will prove to be as fruitful as those isolated from terrestrial habitats [8]. Usually, the marine environmental conditions are extremely different from the terrestrial environment

[9], and these are having different characteristics from their terrestrial counterparts; therefore might produce different types of bioactive compounds. Furthermore, marine representatives of the *Phyla actinobacteria* (Order *Actinomycetales*) are pleasant, bodacious filamentous gram-positive bacteria having high GC content in their DNA.

Actinobacteria are unusual as antibiotic producers, building three-quarters of all known products especially *Streptomyces* produced many antibiotics and other classes of biologically active secondary metabolites and covered around 80% of total antibiotic production as compared with other genera. Approximately 289 secondary metabolites from the marine-derived genus of *Streptomyces* are reputed in the marinlit database, overlaying a broad variety of chemical structures, including peptides, macrolides, lactones, indoles, terpenes and quinines [10]. These compounds unfold an extensive range of industrially profitable activities such as cytotoxic, antibacterial, antifungal, anti-malarial [11, 12] anti-cancer, immune-suppressant [13] anti-inflammatory, antihelmintic, herbicide, enzyme and others [14, 15].

The novel actinobacteria are also remarkable for their production of pigments, extracellular enzymes and the terpenoid compounds that give soil its characteristic odor. These marine actinobacteria are a virtually infinite source of novel compounds with many therapeutic properties. Further, the innovation of novel antibiotic and non-antibiotic lead molecules over microbial secondary metabolite screening is becoming increasingly important [16].

Looking at the wide importance of Actinobacteria in various fields, the present study was undertaken to isolate Actinobacteria from sea sediment samples of coastal regions of Guntur district, Andhra Pradesh, India. On screening of all forty strains isolated from the coastal zones for antimicrobial activity, one potential Actino-bacterium was obtained. Colony morphology, gram staining and biochemical tests revealed the identity of organisms as *Streptomyces* sp. Growth media and incubating conditions have a very strong influence on secondary metabolite production. Secondary metabolism is regulated by factors like carbon sources, nitrogen sources, NaCl, trace elements and different parameters like temperature, pH and incubating time intervals [17]. Optimization of physicochemical parameters like incubation period, temperature, pH, carbon as well as nitrogen sources and varied concentration of salinity was performed for improving the antimicrobial metabolite production by *Streptomyces rectiverticillatus* VJMS-8.

MATERIALS AND METHODS:

Collection of Marine Sediment Samples: Marine sediment samples were collected at a depth of 6-10 cm from different regions of Guntur District located near the South Coast of Andhra Pradesh, India. They were air-dried and pretreated with calcium carbonate (1:1 w/w) followed by drying at 45 ºC for 1 h, in order to reduce the contamination with bacteria and molds [18, 19].

Isolation of Actinobacteria Strains: International Streptomyces project ISP-2 (Yeast extract-malt extract-dextrose agar-YMD) medium was prepared, sterilized and poured into petri plates under aseptic conditions. Antibiotics such as streptomycin and nystatin were added to the media just before pouring into petri plates. Soil dilution plate technique was used for the isolation and enumeration of Actinobacterial strains [20]. Marine soil (1 g) samples pretreated with calcium carbonate were suspended in 100 ml of sterile distilled water followed by serial dilutions from 10^{-1} to 10^{-6}. 0.1 ml of the desired dilution of the sample was spread on different petri dishes. After incubation of the plates at 35 °C for 10 days, actinobacterial strains were isolated by observing the characteristics like tough, leathery colonies partially embedded into the agar [21] and maintained on YMD slants at 4 °C. A total of 40 distinct actinobacterial strains were picked and screened for their potential antagonistic activity. One promising strain with potential activity was identified a *Streptomyces rectiverticillatus* VJMS-8.

Taxonomic Studies of Actinobacterial Strain: Cultural and molecular (16S rRNA gene sequencing) characteristics of the strain VJMS-8 were studied. Different ISP media *viz.*, ISP-1 (Tryptone-yeast extract agar), ISP-2 (Yeast extract malt extract dextrose agar), ISP-3 (Oatmeal agar), ISP-4 (Inorganic salts starch agar), ISP-5 (Glycerol-asparagine salts agar), ISP-6 (Peptone yeast extract iron agar medium) and ISP-7

(Tyrosine agar), as well as non ISP media like Czapek-Dox, Glucose tryptone and Nutrient agar with initial pH 7.0, were employed to monitor the characteristic features of the organisms [22] cultural characters including growth, the colour of the aerial and substrate mycelia with their pigmentation were also recorded. The biomass accumulation and bioactive metabolite production by the strain were determined after 8 days of incubation. The medium in which the strain exhibited maximum bioactive metabolite production was fixed for further studies.

Nutritional Parameters Affecting the Production of Antimicrobial Metabolites:

Growth Pattern and Effect of Incubation Time on Biomass and Bioactive Metabolite Production: Growth pattern of the *Streptomyces rectiverticillatus* VJMS-8 and its antimicrobial activity against gram-positive bacteria (*Bacillus megaterium*, *Streptococcus mutans* and *Staphylococcus aureus*), gram-negative bacteria (*Escherchia coli*, *Klebisella pneumoniae*, *Xanthomonas campestris* and *Pseudomonas aeruginosa*) and fungi (*Aspergillus flavus, Candida albicans*, and *Penicillium citrinum*) were recorded in ISP-2 medium for 8 days. The strain was inoculated into 250 ml flasks containing 100 ml YMD broth and incubated at 35 °C for optimum yields on a rotary shaker at 120 rpm. At every 24 h interval, dry weight of the biomass of the strain and production of antimicrobial metabolites were determined the stationary phase of the strain extended from 144 h to 168 h of incubation. Biomass was measured as dry weight of the cell mass (mg/100 ml culture medium). The supernatant was extracted with ethyl acetate, vacuum dried in a rotavapor followed by testing the residues (1 mg/ml) for antimicrobial activity against bacteria and fungi through agar well diffusion method [23].

Influence of Culture Media on Biomass and Bioactive Metabolite Production: Effect of growth media on the production of antimicrobial metabolites was studied by culturing the strain separately in different liquid broths *viz*., ISP-1 (Tryptone-yeast extract broth), ISP-2 (Yeast extract malt extract dextrose broth), ISP-3 (Oatmeal broth), ISP-4 (Inorganic salts starch broth), ISP-5 (Glycerol-asparagine salts broth), as well as non ISP media like Czapek-Dox and nutrient media. The efficiency of the secondary metabolites of the strain was recorded as antimicrobial potential against gram-positive, gram-negative bacteria and fungi by employing agar well diffusion assay. The medium in which the strain elaborates maximum levels of antimicrobials was studied individually and fixed for further studies [24].

Influence of Initial pH and Incubation Temperature on Biomass and Bioactive Metabolite Production: Influence of initial pH on growth and bioactive metabolite production of the strain was determined by adjusting the pH of production medium from [5-9]. The optimal pH achieved at this step was used for further study [25]. Similarly, the optimum temperature for growth and bioactive metabolite yield was measured by incubating the production medium at temperatures ranging from 20-40 ºC, while maintaining all other conditions at optimum levels [26].

Influence of Sodium Chloride Tolerance on Biomass and Bioactive Metabolite Production: The influence of salinity on growth and bioactive metabolite production by the strain was recorded by culturing the strain in the fermentation medium amended with different concentrations of NaCl (0-12%) at optimum pH and temperature for six days. The salt concentration in which the strain exhibits optimum levels of bioactive metabolites was fixed for further studies.

Influence of Carbon and Nitrogen Sources on Biomass and Bioactive Metabolite Production: Various carbon sources such as dextrose, galactose, dulcitol, maltose, mannitol, starch, sucrose, lactose, fructose, cellulose and sorbitol @1% were added to the optimized medium by replacing the carbon source.

The influence of varying concentrations of the best carbon source (0.5-2.0%) on the growth and bioactive metabolite production was also examined. Likewise, the impact of different nitrogen sources on the yield of antimicrobials of the strain was studied by supplementing the nitrogen source in the medium with different nitrogen sources like peptone, glycine, urea, methionine, glutamine, asparagine, cystiene, L-arginine, ammonium sulphate, tryptone and sodium pyruvate in the optimized medium by replacing the nitrogen source. Further, the impact of different levels of

optimized nitrogen source (0.5-2.0%) was studied to enhance antimicrobial metabolite production [27].

Influence of Minerals on Biomass and Bioactive Metabolite Production: To evaluate the influence of minerals on growth and bioactive metabolite production, the optimized medium with superior carbon and nitrogen sources was amended separately with different minerals such as K_2HPO_4, KCl, $MgSO_4$, $ZnSo_4$, $CaCl_2$, $NaNo_3$, $FeSO_4$, $MnCl_2$ each at a concentration of 0.5% (w/v).

Test Organisms: The antimicrobial metabolites produced by the strain under optimized conditions were tested against bacteria (*Staphylococcus aureus* (MTCC 3160), *Bacillus megaterium* (NCIM 2187), *Streptococcus mutans* (MTCC 497), *Xanthomonas campestris* (MTCC 2286), *Klebisella pneumoniae* (MTCC 109), *Pseudomonas aeruginosa* (ATCC 9027) and *Escherichia coli* (ATCC 9027)) and fungi (*Aspergillus flavus* (ATCC 189), *Candida albicans* (MTCC 183) and *Penicillium citrinum* (MTCC 6849)) using agar plate diffusion assay.

Statistical Analysis: Statistical data were recorded for the biomass of the strain and antimicrobial metabolite production by using a one-way analysis of variance (ANOVA).

Nucleotide Sequence Accession Number: The 16S rRNA gene (rDNA) sequence of the strain VJMS-8 has been deposited in the NCBI Gen Bank with the accession no. MG309763.

RESULTS AND DISCUSSION:

Growth Pattern and Antimicrobial Profile of the Strain: The growth curve and antimicrobial profile of *Streptomyces rectiverticillatus* VJMS-8 were studied at regular intervals up to 8 days in batch culture. The stationary phase of the strain extended from 144 h to 168 h of incubation **Fig. 1**. The secondary metabolites obtained from 6-day-old culture showed high antimicrobial activity against the test microbes. Munaganti *et al.*, (2015) noted the production of antimicrobial metabolites from 5-day-old culture of *Rhodococcus erythropolis* VL-RK-05 [28]. Manideepa *et al.*, (2015) reported that 5-day old-culture extracts of *Streptomyces cellulosae* VJDS-7 exhibited high antagonistic activity [29]. Naragani *et al.*, (2014) reported that 5-day old-culture extracts of *Streptomyces violaceoruber* VLK-4 evidenced the production of antimicrobial compounds [30]. The secondary metabolites obtained from the 4-day-old culture of Nocardia Levis MK-VL-113 isolated from laterite soils of Guntur showed high antimicrobial activity against the test microbes [31].

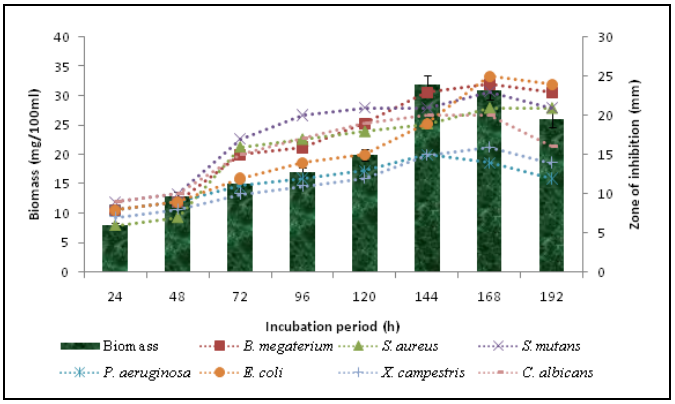

FIG. 1: INFLUENCE OF INCUBATION PERIOD ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

Influence of Culture Media on Biomass and Bioactive Metabolite Production: The influence of different media on the production of biomass and bioactive metabolites was recorded in **Fig. 2**. Among the media tested, tryptone yeast extract broth supported the production of bioactive metabolites followed by yeast extract malt extract dextrose broth and the production of biomass was also high in some broth. Oskay *et al.*, showed that the activity of actinomycete isolates could be increased or decreased remarkably under different cultural conditions [32]. Reported that Thornton's medium increased biomass and bioactive metabolite production of *Streptomyces* sp. 201.

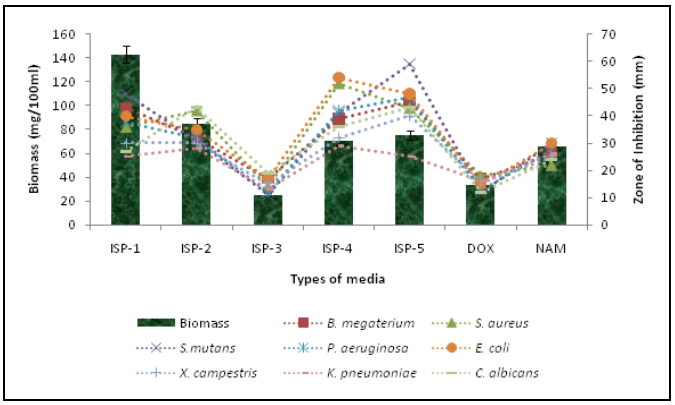

FIG. 2: INFLUENCE OF CULTURE MEDIA ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

Influence of Initial pH and Incubation Temperature on Biomass and Bioactive Metabolite Production: The various environ-mental requirements influence growth and bioactive metabolite production by actinomycetes. Maximum growth and antimicrobial metabolite production were obtained at pH 7 **Fig. 3**. The actinobacterial strains like *Streptomyces tendae* [33], *Streptomyces afghaniensis* VPTS334 and *Streptomyces malaysiensis* [35] showed an optimum level of antibiotic production at 7.0 pH.

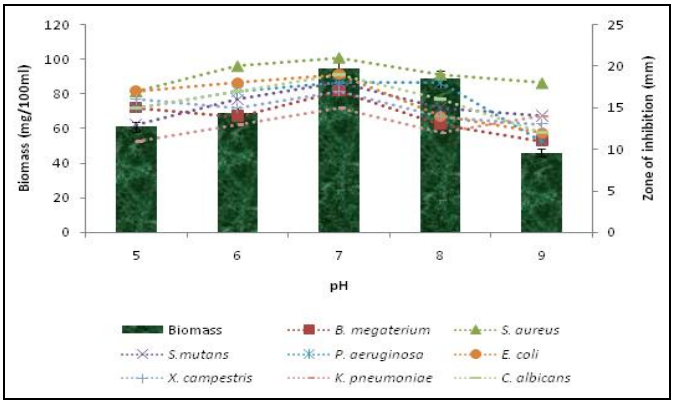

FIG. 3: INFLUENCE OF pH ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

The influence of temperature on the biomass and bioactive metabolite production of the strain is presented in **Fig. 4**. Good growth, as well as antimicrobial metabolite production was obtained at 35 °C. The organism appeared to be mesophilic in terms of its optimum temperature for growth. Several strains of actinobacteria belonging to the genus *Streptomyces* including *Streptomyces albidoflavus* [36], *Streptomyces parvus* [37] and *Streptomyces tritolerans* [38] showed optimum levels of antibiotic production at 35 ºC.

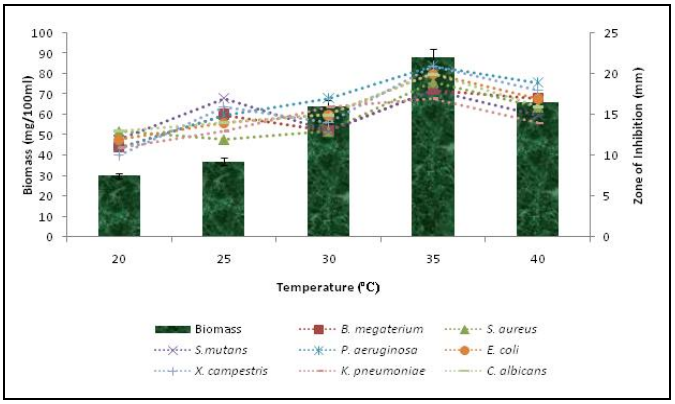

FIG. 4: INFLUENCE OF TEMPERATURE ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

Influence of Sodium Chloride on Biomass and Bioactive Metabolite Production: Optimum salt requirement for bioactive metabolite production was examined by supplementary the production medium with different salt concentrations ranging from 0-12%.

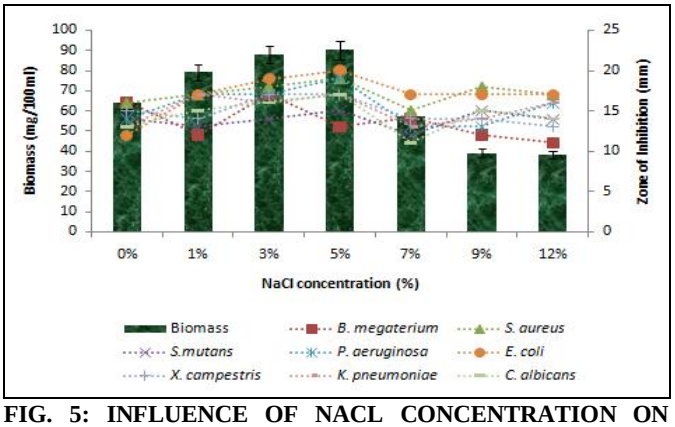

FIG. 5: INFLUENCE OF NACL CONCENTRATION ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

NaCl at the concentration of 5% was found to be optimum for maximum growth as well as anti-microbial compound production by *Streptomyces rectiverticillatus* VJMS-8 **Fig. 5**. Further, increase in salt concentration reduced the antimicrobial agent biosynthesis. The requirement of NaCl for the production of bioactive metabolites seems to be different among actinomycete strains.

Optimum NaCl concentration for maximum growth as well as antimicrobial metabolite production, was reported to be 5% for Streptomyces VITSVK939 and *Streptomyces gulbargensis* [40].

Influence of Carbon Sources on Biomass and Bioactive Metabolite Production: Effect of different carbon sources were evaluated for their impact on growth and antimicrobial metabolite production **Fig. 6**. Among the various carbon sources tested, galactose was the best one for bioactive metabolite production.

Maltose, as the best carbon source for antibiotic production, was reported in *Streptomyces rochei* G164. [41] Kavitha *et al.*, (2009) reported that *Nocardia levis* MK-VL_113 isolated from laterite soils of Acharya Nagarjuna University utilized sucrose as the sole carbon source for antibiotic

production. As galactose was the most preferred carbon source for biomass and bioactive metabolite production by the strain, different levels of galactose (0.5-2.0%) were tested to determine the optimal concentration for bioactive metabolite production **Fig. 7**. Galactose@ 1.0% supplemented in the medium promoted the bioactive metabolite production.

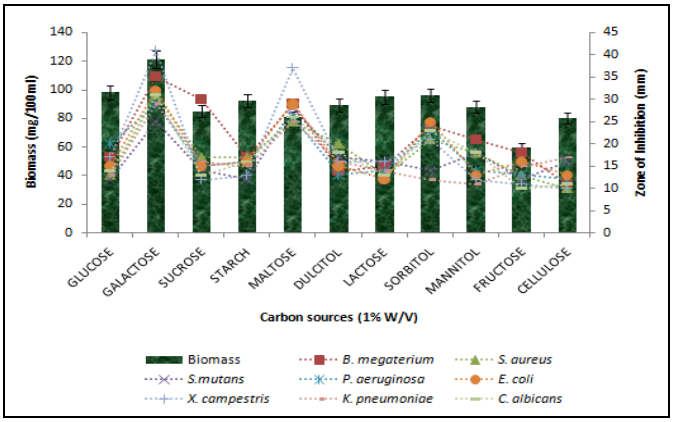

FIG. 6: INFLUENCE OF CARBON SOURCES ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTI-CILLATUS* VJMS-8. Data are stati-stically analyzed and found significant at 5%

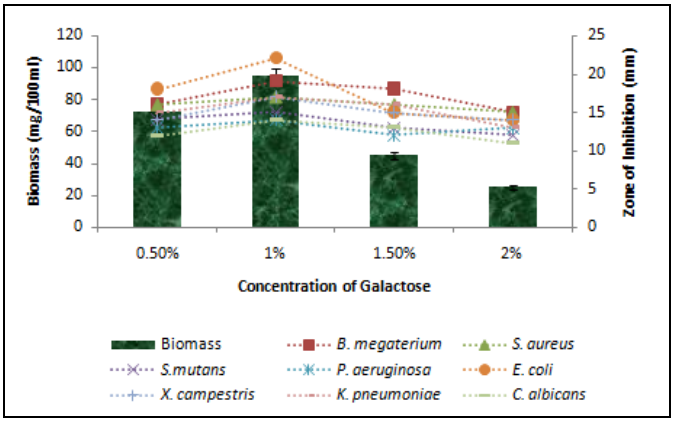

FIG. 7: INFLUENCE OF GALACTOSE CONCENTRATION ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTI-CILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

Influence of Nitrogen Sources on Biomass and Bioactive Metabolite Production: Different nitrogen sources were found to have a significant effect on growth and secondary metabolite production by *Streptomyces rectiverticillatus* VJMS-8. Maximum antimicrobial activity was obtained in culture filtrates supplemented with tryptone followed by peptone and glutamine, whereas biomass was found to be increased with glutamine followed by peptone and tryptone **Fig. 8**. Tryptone (1%) supported high metabolite production, **Fig. 9**. Growth and antibiotic production were found to be governed by nitrogen sources [42], and the utilization of nitrogen sources for the production of bioactive metabolites seems to be different among Actinomycete strains.

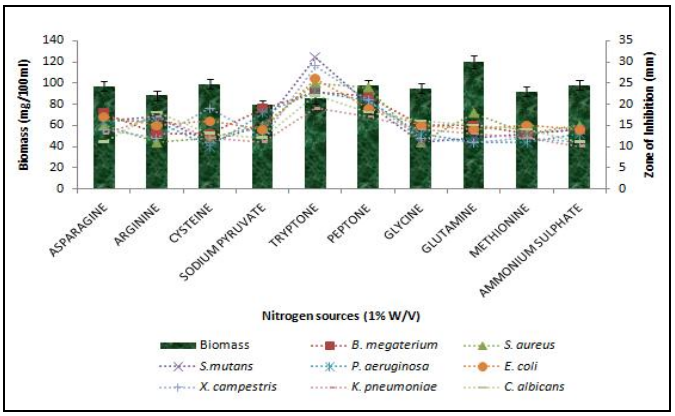

FIG. 8: INFLUENCE OF DIFFERENT NITROGEN SOURCES ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

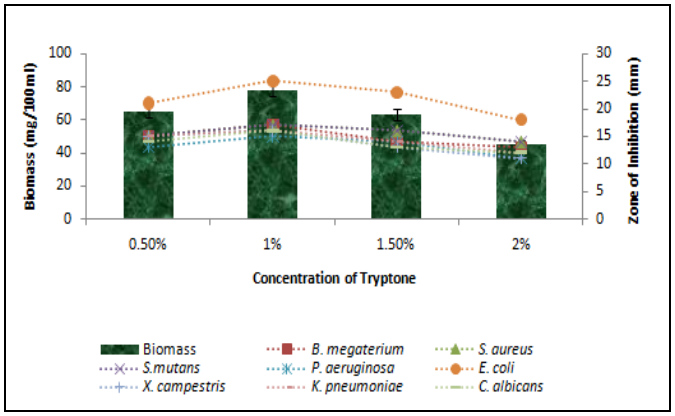

FIG. 9: INFLUENCE OF TRYPTONE CONCENTRATION ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY STREPTOMYCES RECTIVERTI-CILLATUS VJMS-8. Data are stati-stically analyzed and found significant at 5%

Influence of Minerals on Biomass and Bioactive Metabolite Production: The influence of minerals on biomass and bioactive metabolite production by the strain is represented in **Fig. 10**. K_2HPO_4 enhanced the production of biomass and antimicrobial metabolites. In contrast, the production of bioactive metabolites was very low with $CaCl_2$ followed by $MnCl_2$. Majumdar and Majumdar (1967) reported the maximum yield of neomycin by Streptomyces fradiae with K_2HPO_4 and least with $ZnSO_4$ [43]. Ripa *et al.*, [27] reported that among different minerals

tested, K_2HPO_4 showed a positive influence on antibiotic production by Streptomyces RUPA-08PR.

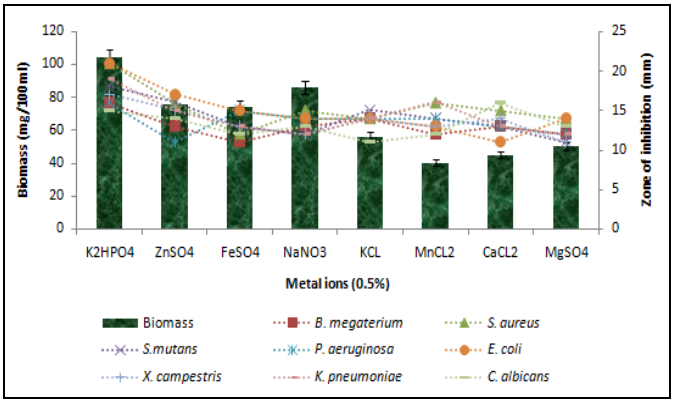

FIG. 10: INFLUENCE OF DIFFERENT METAL IONS ON BIOMASS AND BIOACTIVE METABOLITE PRODUCTION BY *STREPTOMYCES RECTIVERTICILLATUS* VJMS-8. Data are statistically analyzed and found significant at 5%

CONCLUSION: In the present study *Streptomyces rectiverticillatus* VJMS-8 isolated from coastal region of Guntur District exhibited high antimicrobial activity when cultured in modified ISP-2 broth with galactose 1%, Tryptone 1% NaCl 5% and K_2HPO_4 0.5%, with pH 7.0 and incubated at 35 ºC for 144 h. Among the bacteria tested, *Staphylococcus aureus* and *Escherichia coli* were highly sensitive to the metabolites followed by *Xanthomonas campestris*, *Streptococcus mutans* and *Bacillus megaterium* while *Candida albicans* exhibited high sensitivity followed by *Aspergillus flavus* and *Penicillium citrinum* with respect to fungi.

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CONFLICTS OF INTEREST: We declare that we have no conflicts of interest.

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