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Streptomycetes: Characteristics and Their Antimicrobial Activities

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Abstract

The Streptomycetes are gram positive bacteria with a filamentous form that present in a wide variety of soil including composts, water and plants. The most characteristic of Streptomycetes is the ability to produce secondary metabolites such as antibiotics. They produce over two-thirds of the clinically useful antibiotics of natural origin (e.g., neomycin and chloramphenicol**.** Another characteristic of Streptomycetes is making of an extensive branching substrate and aerial mycelium.Carbon and nitrogen sources, oxygen, pH, temperature, ions and some precursors can affect production of antibiotics. This review also addresses the different methods to study the antimicrobial activity of *Streptomyces sp.* Because of increasing microbial resistance to general antibiotics and inability to control infectious disease has given an impetus for continuous search of novel antibiotics all the word.

Key words: Streptomyces, soil, PH, Antibiotics

Introduction

First time the genus *Streptomyces* was introduced by Waksman and Henrici in 1943 (Williams et al., 1983) .Genus *Streptomyces* belongs to the Streptomycetaceae family (Arai, 1997). In general Streptomycetaceae family can be distinguished by physiological and morphological characteristics, chemical composition of cell walls, type of peptidoglycan, phospholipids, fatty acids chains, percentage of GC content , 16 SrRNA analysis and DNA-DNA hybridization (Korn-Wendisch & Kutzner, 1992). Streptomycetaceae family are in Actionobacteria phylum and Actinomycetales order within the classis Actinobacteria and the genus *Streptomyces* is the sole member of this family (Anderson & Wellington 2001). In terms of number and variety of identified species, *Streptomyces* represents one of the largest taxonomic items of recognized *Actinomycetes* (Bhattacharyya , pal, & Sen, 1998). They are distinguished as gram-positive bacteria, aerobic, non-Acid- Fast and with a high GC content more than 70% (Dehnad, Parsa Yeganeh, Bakhshi, & Mokhtarzadeh, 2010). Streptomycetes can grow in different environments (Maleki, Dehnad, Hanifian, & Khani, 2013). They produce layer of aerial hyphae that can differentiate into a chain spores (Korn-Wendisch & Kutzner, 1992). More than 500 species of the genus *Streptomyces* have been described and nearly two third of the naturally occurring antibiotics are produced by Streptomycetes (Mohanraj & Sekar, 2013).

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Characteristics of Streptomycetes

Streptomyces is the largest genus of Actinobacteria and the type genus of the family Streptomycetaceae (Hong et al., 2009). Over 500 species of *Streptomyces* bacteria have been described *(Lee , Jung, & Hwang, 2005).Streptomyces* species are chemoorganotrophic, filamentous gram-positive bacteria but not acid-alcohol fast, not fungi and occur in the same habitats as fungi and are superficially similar (Ikeda et al., 2003). They have genomes with high GC content 69-78% (Kavitha, Vijayalakshmi, Sudhakar, & Narasimha, 2010).The filaments and spores are very small usually 1 µm or less in diameter (Willemse, Borst, Waal, Bisseling, & Wezel, 2011). The spores are formed by the fragmentation of the filaments and are borne in straight, wavy, or helical chains (Chater, 1993). The colonies are slow-growing and often have a soil-like odour because of production of a volatile metabolite, geosmin (Jüttner & Watson, 2007). Firstly colonies are relatively smooth surfaced but later they develop a weft of aerial mycelium that may appear floccose, granular, powdery, or velvety (Ambarwati, Sembiring, & Soegihardjo, 2012). They produce a wide variety of pigments responsible for the colour of the vegetative and aerlial mycelia(Flärdh & Buttner, 2009). *Streptomyces* species are nonmotile, catalase positive, reduce nitrates to nitrites and degrade adenine, esculin, casein, gelatin, hypoxanthine, starch, and L-tyrosine(Smaoui, Mathieu, Fguira, Merlina, & Mellouli, 2011). The cell wall peptidoglycan contains major amounts of L- diaminopimelic acid (L-DAP). They have no mycolic acids,contain major amounts of saturated, iso- and anteiso-fatty acids, possess either hexa- or octahydrogenated menaquinones with nine isoprene units as the major isoprenolog, and have complex polar lipid patterns that typically contain diphosphatidyl glycerol,phosphatidyl ethanolamine,phospha-tidyl inositol, and phosphatidyl inositol mannosides (Cummins & Harris, 1958).

The life cycle of Streptomycetes

The life cycle of Streptomycetes starts when a spore settles in a nutrient rich medium. This stimulates the spore to exist its dormant state and undergo germination and form germ tubes. Germ tubes grow by tip elongation and the cells don't undergo binary fission. Through extension and branching the germ tubes give rise to a network of filaments which grow into and across the surface of an agar plate. This network is called the substrate mycelium (Flärdh & Buttner, 2009). As the colony continues to grow, the mycelium in the center of the colony starts to differentiate. Differentiation results in the formation of a new cell type, the aerial hyphae. When heaven word growth of the spiraling, multi- genomic aerial hyphae stops, the aerial hyphae undergo synchronous cell division giving rise to monoploid compartments each of which will develop in to a resistant spore (Kieser , Bibb, Buttner, Chater, & Hopwood, 2000) .The life cycle of a *Streptomyces* sp. has been studied by the Robinow HC1-Giemsa method of nuclear staining, and is described in the subsequent manner: (1) initial nuclear division phase; (2) primary mycelium; (3) secondary mycelium (Including aerial); (4) the formation of spores. The primary mycelium develop after the initial nuclear division phase and produce side divisions, then later gave rise to single swellings in the hyphae. These swellings grow to form large round cells, each of which contain many nuclei. The secondary mycelium develops, a part of which become aerial and terminates in the form of chains of spores (Mc Gregor 1954).

Streptomycetes habitats

Although streptomycetes widely distributed in soil, water and other natural environments (Seong, Choi, & Baik, 2001),(Singh, Baruah, & Bora 2006).The population of them in an ecosystem are determined by

numerous physical, chemical and biological factors(Kharat, Kharat, & Hardikar, 2009). Identification of novel ecological systems is therefore crucial for the discovery of novel Streptomycetes (Wang, Zhang, Ruan, Wang, & Ali, 1999).

Streptomycetes make 40% of soil bacteria (Boone, Castenholtz, & Garrity, 2001). Under dry and alkaline conditions *Streptomyces sp.* are the numerous microbial population in soil and because of their filamentous form, they cause the strength of soil texture and protect it from wind and rained eradication (Vetsigian & Roy Kishony, 2011). The percentage of *Streptomyces sp*. in total microbial population has positive correlation with the depth of soil and they can even be obtained from the horizon C of the soil (Kim, Seong, Jeon, Bae, & Goodfellow, 2004). Distribution of Streptomycetes in water and soil, depends on food stress, temperature, pH, moisture,salinity, soil texture and climate (Locci, 1989). Although soil is the most important Streptomycetes habitat (Mokrane, Bouras, Sabaou, & Mathieu, 2013), other habitats are:

Hay and other organic material: Mesophilic and Thermophilic *Streptomyces sp.* can degrade many natural substrates, cotton textiles, plastics, rubber and paper (Subbarao 1999). Most of streptomycetes subjected as indigenous microbes isolated from soil and had successfully capability to growth remove and use different organic compound (Rahmansyah, Agustiyani, Julistiono, & Dewi, 2012). Streptomycetes are capable to produce degrade Cellulose, lignocellulose, chitin and different organic compounds in biogeochemical cycles (Horn, Vaaje-Kolstad, Westereng, & Eijsink, 2012).

Fresh water and marine habitats : In addition to drinking water systems with drainage after heavy rainfall (Rowbotham & Cross, 1977). The isolation of Streptomecetes from marine environments has been an abundant area of investigation in the past decade(Remya & Vijayakumar, 2008). Of the marine inhabitants studied, marine invertebrates, particularly sponges, are of excessive interest for discovering novel Streptomecetes (Selvakumar, Arun, Suguna , Kumar, & Dhevendaran 2010). In recent times, the marine derived actinomycetes have become documented as a source of novel antibiotic and anticancer agent (Baskaran, Vijayakumar, & Mohan, 2011).

-***Plants***: Streptomycetes play a minor role as plant pathogens such as *Streptomyces scabies, S.ipomoea, S.turgidiscabies, S.aureofaciens, S.acidiscabies* and *S.tumescans* causing gall potato, soil rot or pox, pitted scab, netted scab, gall potato in acidic soil and root gall respectively (Fatope , Al-kindi, & Abdulnour 2000). In the other hand some species of *Streptomyces* act as biological control (Rugthaworn 2007). Biological control is an environmentally sound and effective means of reducing or mitigating pests and pest effects through the use of microorganisms. For example biological control of sunflower stem rot (Baniasadi 2009) , (Aghighi , Shahidi Bonjar, & Saadoun, 2004) and potato common scab (Kalantarzadeh 2006).

- ***Animal and humans*:** Although a small number of clinical Streptomycetes have been isolated so far, their role as pathogens and infectious disease cannot be ignored (Korn-Wendisch & Kutzner, 1992). Streptomycetes are uncommon pathogens, though infections in humans, such as mycetoma, can be caused by *Streptomyces somaliensis* and *Streptomyces sudanensis* (Quintana et al., 2008).

Streptomycetes requirements

Streptomycetes are aerobes, chemoorganotrophic bacteria and they need organic carbon source, inorganic nitrogen sources, and mineral salts and don't need vitamins and growth factors (Lee & Demain 1997). *Streptomyces* requirements has been investigated by kutzner (Kuster & Williams, 1964).

Most of *Streptomyces sp*. are mesophile and grow in temperatures 10-37℃ (Deeble, Fazeli , Cove , & Baumberg 2005) ,(James & Edwards, 1989) but three species *Streptomyces thermonitrificans, S.thermovulgaris* and *S.thermoflavus* are thermophile and grow in temperature 45-55℃ (Srivibool, Kurakami, Sukchotiratanac, & Tokuyamab, 2004). Streptomycetes grow in pH 6.5-8.0 (Cabello , Gonzalez , & Genilloud 2003). Streptomycetes are not only more resistant to drought and form arthrospore but also require less moisture than other bacterial and are very sensitive to water logged conditions(Subbarao 1999) . Some of reports described that drained soils (sandy loam, calcareous) have more *Streptomyces* than heavy clay soils (Sujatha, RajuB, & Ramana, 2005).

Streptomycetes metabolites

A primary metabolite is a kind of metabolite that is directly involved in normal growth, development, and reproduction. It usually performs a physiological function in the organism. A primary metabolite is typically present in many organism or cell (Demain 1980). Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of an organism (Shomurat, Yoshida, Amano, Kojina, & Niida, 1979). Therefore secondary metabolites differ from primary metabolites (e.g. amino acids and nucleotides) in four manner: 1) they are not essential for growth, 2) their production is dependent on growth conditions liked type of culture media, 3) they are often produced as groups of closely related molecules, and 4) it is often possible to overproduce these components (Drew & Demain, 1977).The most important characteristic of Streptomycetes is the ability to produce secondary metabolites with antibacterial, antifungal, antiviral and antitumoral properties. Two species of *Streptomyces* by the name of *Streptomyces griseus* and *Streptomyces coelicolor* are used for industrial production of Streptomycin and novel antibiotics such as dihydrogranticin respectively. Doxorubicin as anticancer agents (Mukhtar, Ijaz , & Ul-Haq, 2012) and Rapamycin as immunomodulatory agents are Secondary metabolites produced by *Streptomycete*s (Ying & Marta, 2001).Another metabolite of *Streptomycetes* known as the 'Geosmin'and sidrophore are responsible for the earthy odor (Sanglier, Haag , Huck , & Fehr, 1993). However volatile product secreted by *Streptomyces* may also be responsible for the specific smell (Bais, Nimbekar, Wanjari1, & Timande, 2012).

Streptomycetes and antibiotics

Streptomycetes have high potential to produce secondary metabolite such as antibiotics (MCIntyre, 2002), anthelminthic enzymes, herbicides (Kariminik & Baniasadi, 2010), anti- cancer drugs (Berdy, 2005) , growth factors like vitamin B12 (Bibb, 2005) and immune- modulators (Mann, 2001) . Louis Pasteur was one of the pioneers of modern antibiotics knowledge, in 19th century (Gray & Jacobs 2003). He found that, some of microorganisms are able to kill other microorganisms. Penicillin was the first antibiotic that discovered by Alexander Fleming from *Penicillium notatum* in 1929 (Silva & Anne, 2004). The history of antibiotics obtained from *Streptomyces* sp. began with the discovery of Streptothricin in 1942(Sanglier et al., 1993), and the discovery of Streptomycin in 1943 (Schats, Bugie , & Waksman, 1994), and then scientists intensified the search for other antibiotics within the genus(Watve, Tichoo, MM, & Bhole, 2001). The most productive years of antibiotic discovery were between 1945 and 1960 (Watve *et al.*, 2001). In 1949 Rachel Brown extracted the first antibiotic for treatment of fungal disease called Nystatin from *Streptomyces noursei* (Orna, 2001). They produce over two-thirds of the clinically useful antibiotics of natural origin (e.g., neomycin and chloramphenicol). Today, 80% of the antibiotics are derived from

Streptomyces sp.(Kharat *et al.,* 2009). Some of antibiotics has listed in table 1. Of the clinically useful antibiotics, more than 50% are derived from *Streptomyces* (Keiser *et al*., 2000).

Because of microbial resistance, despite the success of the discovery and production of antibiotics, infectious diseases still seem the second agent of death in the world (Nikaido, 2009). The resistance may be due to genetic changes such as mutation or acquisition of resistance factors such as plasmids through horizontal genetic transfer (Wright 2010). In the other hand some physiological state of the bacteria such as biofilm formation can induce antibiotic resistance and also microorganisms related to chronic and recurrent infections usually are resistant to antibiotics (Hassan et al., 2011). As a result, scientists are trying to change to existing antibiotics or discover new agents that are more effective and stable to inactivating enzyme produced by resistant bacteria (Garza-Ramos, Silva-Sánchez , & Martínez-Romero, 2009).Granaticin is a pigmented and pH sensitive antibiotic which produce by *Streptomyces thermoviolaceus*. Granaticin is specially synthesized at temperatures as high as 55 °C but optimally at 45 °C. *Streptomyces thermoviolaceus* possesses a termotolerant polypeptide pathway. Although the rate of production of the secondary metabolite is fastest at 37 °C the yield is not as high as that seen at 45 °C. We attribute this to a preference for producing biomass at 37 °C and there is an inverse relationship between cell yield and titre of antibiotic over the temperature range 30 to 50°C (James & Edwards, 1989),(Procópioa, Silvaa, Martinsa, Azevedoa, & Araújob, 2012) .

Table 1. List of some antibiotics produced by *Streptomyces sp.*

Streptomyces sp.	Antibiotic	*Streptomyces sp.*	Antibiotic
S. orchidaccus	Cycloserin	*S.erythraeus*	Erythromycin
S.oriantalis	Vancomycin	*S.vensuella*	Chloramphenicol
S.fradiae	Neomycin, Actinomycin, Fosfomycin, Dekamycin	*S.aureofaciens*	Chlortetracycline, Dimethylchlor tetracycline
S.nodosus	Amphotricin B	*S.ambofaciens*	Spiramycin
S.noursei	Nistatin	*S.avermitilis*	Avermicin
S.mediterranei	Rifampin	*S.alboniger*	Puromycin
S.griseus	Streptomycin	*S.niveus*	Novobicin
S.knanamyceticus	Kanamycin	*S.platensis*	Platenmycin
S.tenebrarius	Tobramycin	*S.roseosporus*	Daptomycin
S.spectabilis	Spectinomycin	*S.ribosidificus*	Ribostamycin
S.viridifaciens	Tetracycline	*S.garyphalus*	Cycloserine
S.lincolensis	Lincomycin, Clindamycin	*S.vinaceus*	Viomycin
S.rimosus	Oxytetracyclin	*S.clavuligerus*	Cephalosporin

Antibacterial activity of Streptomycetes

Sampling

According to the many investigations, it is better to do the sampling from various parts of the soil from depth of 5 to 10 cm (Shahidi Bonjar, 2004). Streptomycetes exist in different types of soil and the surface

layer of soil is more numerous because of their strict aerobic metabolism. *Streptomyces* population is more in alkaline soils, compost, river's mud and riverbeds (Kariminik & Baniasadi, 2010). Their concentration in soil depends on physical properties, organic matter content, pH, moisture, soil reactions and soil texture (Nonoh et al., 2010). Streptomycetes are highly tolerant to salinity and that's why many species are found in salty soil and marine(Selvakumar et al., 2010).

Nutrient requirements for antibiotic production

Streptomycetes can grow on Muller-Hinton agar, Trypticase soy agar, and Nutrient agar with calcium chloride (Busti & Yushi, 2006).Carbon and nitrogen sources , oxygen,pH,temperature,ions and some precursors can affect production of antibiotics (Rafieenia, 2013).

Carbon: Some investigators reported that glucose decreases antibiotic production because of suppressing the enzymes involved in antibiotic biosynthesis and can be related to effect of growth rate on antibiotic biosynthesis (Lounes, Lebrihi, Benslimane, Lefebvre , & Germain, 1996) , (Lounes et al., 1996). Polysaccharides such as starch and glycerol are commonly the best carbon sources as they support a slow growth rate that is appropriate for antibiotic production(Jonsbu, McIntyre, & Neilson 2002). Slavica Ilić *et al* showed the use of new carbon and can lead to the best microbial growth and antibiotic production .The maximum production of some antibiotics was in the culture media with glucose and lactose, while the minimum antibiotic production was observed in the medium with ribose(Ilić, Konstantinović, Veljković, Savić , & Gojgić-Cvijović, 2010). (Jonsbu et al., 2002)

Nitrogen: Several studies have showed that antibiotic synthesis related to type and concentration of nitrogen source in culture media (Rafieenia, 2013). Simple and inorganic nitrogen sources usually decrease antibiotic production(Young & Kempe, 1985). Complex nitrogen sources such as soybean meal, corn steep liquor and yeast extract can increase antibiotic production which can be attributed to slow breakdown of these compounds in the medium. Slavica Ilić *et al* found that replacement of soybean as nitrogen source with isatin-Schiff bases (isatin-3-thiosemicarbazone - ITC, isatin-3-semicarbazone - ISC and isatin-3-phenylhydrazone – IPH;) increased the level of antibiotic production (Ilić et al., 2010).

Rate of growth: Bacterial growth in exponential phase, which has the optimum growth rate, can effect on more antibiotic production (Sejiny, 1991). The biosynthesis of antibiotics is a particular possessions of microorganisms and depends on growth conditions (Young & Kempe, 1985). These microorganisms use a wide range of substrates for growth; however, many of these substrates can have a negative effect on the production of secondary metabolites. Under several nutrient limitations, the production of secondary metabolites will be higher than non-limiting nutrient conditions (Sejiny, 1991).

Minerals: Minerals such as phosphorus (Martin, 2004), potassium, iron, zinc and manganese in trace increase level of antibiotic production (Gesheva , Ivanova , & Genava 2005). Many secondary metabolites are produced only when phosphate is the growth limiting nutrient. It has been shown that antibiotic synthesis starts after decrease of phosphate source(Martin, 2004).

Oxygen: Streptomycetes are aerobic bacteria. Thus appropriate oxygen has a great influence on their growth and antibiotic production(Wang et al., 1999).

pH: Most antibiotics are optimally produced in pH close to 7.0(Saadoun , Momani, Malkawi, & Mohammad, 1999).

***Precursors*:** Precursors such as amino acids and Short-chain fatty acids are the precursors of some antibiotics and added to media in industrial processes(Tang, Zhang , & Hutchinson, 1994).

Ions: Divalent ions as Mn2+, Cu2+, Fe2+ usually stimulate antibiotic biosynthesis (Gesheva et al., 2005).

Antibacterial activity protocols.

There are many different techniques for investigation of antimicrobial properties.

Cross streak method

Agar plates are prepared and inoculated with Streptomyces isolates by a single streak in the center of petridishes and incubated at 30 ℃ for 7 days. The plates were then inoculated with the test bacteria by a single streak at 90° angles to the Streptomyces isolates and incubated at 37℃ for 24 hr. Antibacterial activity is recorded by zone of inhibition (Kumar, Preetam Raj, Duraipandiyan, & Ignacimuthu, 2012).

Agar overlay method

In this method, Streptomyces isolates are spot inoculated in medium for 7 days in 30℃. Following incubation, one ml of chloroform is added to arrest the growth of inoculated isolates and after 40 minutes they are overlaid with 7 ml of semisolid nutrient agar (0.7%) inoculated with 0.1 ml of overnight culture of tested bacteria. Plates are incubated for 24 hours at 37 ℃ and zone of inhibition is measured in millimeters (Sahin & Ugur, 2003).

Disc Diffusion assay

The *Streptomyces* isolates are inoculated as submerged culture in 500 ml Erlenmeyer flasks containing 100 ml of broth Streptomyces medium and incubated in shake incubator at 200 rpm in 30 ℃ for 5 days. The cultures are centrifuged for 15 minutes in 1500 rpm. The culture filtrates are extracted with ethyl acetate solvent (1:1 v/v) and shacked for 20 minutes. The supernatant organic layer are collected and evaporated in Rotary evaporator system at 40℃ . A crude and dry extract obtained, are suspended in ethyl acetate at a concentration of 1mg/ml for antibacterial studies. Sterile blank discs - 6mm in diameter- are saturated with 50 ml suspension, dried and placed on to the plates previously inoculated with tested bacterial. The plates are incubated for 24 hours in optimum temperature of bacterial and zone of inhibition are measured. The inhibitory effects are evaluated by the measurement of inhibition zone diameter(Gebreyohannes, Moges, Sahile, & Raja, 2013) and (Manivasagan et al., 2009).

Agar well diffusion assay

250 ml Erlenmeyer flasks containing 150 ml sterile starch casein nitrate broth are aseptically inoculated with the spore suspension of Streptomyces isolates and incubated aerobically at 30 ℃ for 10 days. After incubation, the contents in the flasks are filtered through sterile what man paper No.1 the culture filtrates are centrifuged and supernatant and ethyl acetate (1:1 v/v) is used for solvent extraction, and agitated for 30 minutes. Solvent layer is removed and the supernatant is twice extracted with ethyl acetate and then the ethyl acetate layer evaporated by Rotary evaporator at 40 ℃ to dryness. The bacterial isolates are grown on with 1.5×10^{8}/ ml equal 0.5 McFarland solvent, Nutrient agar plate using sterile cotton swabs.

Wells of 6 mm diameter are punched in the inoculated plates. Ethyl acetate extracts (5 mg/ml of 25% dimethyl sulfoxide) are filled in wells. The plates are incubated at optimum temperature of bacteria for 24 hours. The inhibition zones formed around the wells are measured in millimeters (Pallavi et al., 2013).

References

Aghighi , S., Shahidi Bonjar, G., & Saadoun, I. (2004). First report of antifungal properties of a new Strain of Streptomyces plicatus (strain101) against four Iranian phytopathogenic isolates of Verticillium dahliae, a new horizon in biocontrol agents. Biotechnology, 3(1), 90-97.

Ambarwati, A., Sembiring, L., & Soegihardjo, C. (2012). Antibiotic produced by streptomycetes associated with rhizosphere of purple nut sedge (Cyperus rotundus L.) in Surakarta, Indonesia. African Journal of Microbiology Research, 6(1), 52-57.

Anderson , A. S., & Wellington , E. M. (2001). The taxonomy of streptomyces and related genera. International Journal of Systematic and Evolutionary Microbiology, 51, 797-814.

Arai, T. (1997). What are Actinomycetes? Atlas of Actinomycetes',The Society for Actinomycetes Japan (SAJ), Asakura Publishing Co., Ltd., Japan, 176-191

Bais, Y., Nimbekar, T., Wanjari1, B., & Timande, S. (2012). Isolation of antibacterial compound from marine soil actinomycetes. International Journal of Biomedical and Advance Research, 3(3), 193-196.

Baniasadi , F. (2009). Biological control of Sclerotinia sclerotiorum , by use of soil actinomycetes isolates American J of Agricultural and Biological Sciences, 4(2), 146-151.

Baskaran, R., Vijayakumar, R., & Mohan, P. M. (2011). Enrichment method for the isolation of bioactive actinomycetes from mangrove sediments of Andaman Islands, India. Malaysian Journal of Microbiology, 7(1), 26-32.

Berdy, J. (2005). Bioactive microbial metabolites: a personal view. J Antibiot, 58(1), 126.

Bhattacharyya , B., pal, S., & Sen, S. (1998). Anitibiotic production by Streptomyces hygroscopicus D1.5 , cultural effect. Rev.microbial. , 29(3), 254-257.

Bibb, M. (2005). Regulation of secondary metabolism in Streptomycetes. Curr Opin Microbiol 8, 208-215.

Boone, R., Castenholtz, R., & Garrity, G. (2001). Bergey's manual of systematic bacteriology'. Springer-Verlag. New York, Berlin Heidelberg,, . 1, 163-164.

Busti, E., & Yushi, O. (2006). Media conditions for growthing Actinomycetes Microbial Res, 424-427.

Cabello , A., Gonzalez , A., & Genilloud , O. (2003). Patterns of antimicrobial activities from soil Actinomycetes isolated under different conditions of pH. Salinity journal of Applied microbiology, 95(4), 814-823.

Chater, K. (1993). Genetics of Differentiation in Streptomyces. Annual Review of Microbiology, 47, 685-711.

Cummins , C., & Harris, H. (1958). Studies on the cell-Wall composition and taxonomy of Actinomycetales and related groups. J. gen. Microbiol., 18, 173-189.

Deeble, V., Fazeli , M., Cove , J., & Baumberg , S. (2005). Effects of temperature on production of antibiotics in Streptomyces griseus. Journal of antibiotics, 171-178.

Dehnad, A., Parsa Yeganeh, L., Bakhshi, R., & Mokhtarzadeh, A. (2010). Investigation antibacterial activity of Streptomycetes isolates from soil samples, West of Iran. African Journal of Microbiology Research, 4(16), 1685-1693.

Demain , A. (1980). Microbial production of primary metabolites Naturwissenschaften, 67(12), 582-587.

Drew, S., & Demain, A. (1977). Effect of primary metabolites on secondary metabolism. Annual Review of Microbiology, 31, 343-356.

Fatope , M., Al-kindi, M., & Abdulnour , O. (2000). Research trends: Natural products as pest, microbial disease and tumor control agents. Sci. Technol, 55-71.

Flärdh, K., & Buttner, M. (2009). Streptomyces morphogenetics: dissecting differentiation in a filamentous bacterium. Nature Review, 7, 36-49.

Garza-Ramos, U., Silva-Sánchez , J., & Martínez-Romero, E. (2009). Genetics and genomics for the study of bacterial resistance. Galud Pública Mex, 51, 439–446.

Gebreyohannes, G., Moges, F., Sahile, S., & Raja, N. (2013). Isolation and characterization of potential antibiotic producing actinomycetes from water and sediments of Lake Tana, Ethiopia. Asian Pac J Trop Biomed., 3(6), 426–435.

Gesheva , V., Ivanova , V., & Genava , R. (2005). Effects of nutrients on the production of microbial antibiotic by Streptomyces hygroscopicus. Microbial Res, 160(3), 243-248.

Gray , W., & Jacobs , F. (2003). Penicillin: the first miracle drug. Journal of Drug

390-396.

Hassan, A., Usman , J., Kaleem, F., Omair, M., Khalid, A., & Iqbal, M. (2011). Evaluation of different detection methods of biofilm formation in the clinical isolates. Braz J Infect Dis., 15, 305–311.

Hong, K., Gao, A., Xie, Q., Gao, H., zhuang, L., Yu, H.,Mand Ruan, J. (2009). Actinomycetes for marine drug discovery isolation from Mangrove soils and plants in china microbiological research. Mar Drugs., 7(1), 24-44.

Horn, S., Vaaje-Kolstad, G., Westereng, B., & Eijsink, V. (2012). Novel enzymes for the degradation of cellulose. Biotechnology for Biofuels 5(45), 1-12.

Ikeda , H., Ishikawa , J., Hanamoto , A., Shinose , M., Ikuchi, H., Shiba, T., . . . Omura , S. (2003). Complete genome sequence and comparative analysis of the industrial microorganism Streptomyces avermitilis. Nature Biotechnology 21, 526- 531.

Ilić, S., Konstantinović, S., Veljković, V., Savić , D., & Gojgić-Cvijović, G. (2010). The impact of different carbon and nitrogen sources on antibiotic production by Streptomyces hygroscopicus CH-7. Current research,Technology and Education topics in Applied Microbiology and Microbial Biotechnology, 2, 1337-1342.

James, P., & Edwards, C. (1989). The effects of temperature on growth and production of the antibiotic granaticin by thermotolerant streptomycete. J. Gen microbiology 135, 1997-2003.

Jonsbu, E., McIntyre, M., & Neilson , J. (2002). The influence of carbon sources and morphology on nystatin production by Streptomyces noursei. J. Biotechnol., 95(2), 133-144.

Jüttner, F., & Watson, S. (2007). Biochemical and ecological control of geosmin and 2-methylisoborneol in source waters. Appl. Environ. Microbiol., 73(14), 4395-4406

Kalantarzadeh , M. (2006). Antagonistic potential of two native Streptomyces strains in biocontrol of the major causals of common scab of potato in Iran. Asian J of Plant Sciences, , 5(1), 5-8.

Kariminik, A., & Baniasadi, F. (2010). Pageantagonistic activity of Actinomycetes on some gram negative and gram positive bacteria. World Applied Sciences Journal 8(7), 828-832.

Kavitha, A., Vijayalakshmi, M., Sudhakar, P., & Narasimha, G. (2010). Screening of Actinomycete strains for the production ofantifungal metabolite. African Journal of Microbiology Research, 4(1), 27-32.

Kharat, K., Kharat, A., & Hardikar, B. (2009). Antimicrobial and cytotoxic activity of Streptomyces sp. from Lonar Lake. African Journal of Biotechnology, 8(23), 6645-6648.

Kieser , T., Bibb, M., Buttner, M., Chater, K., & Hopwood, D. (2000). General Introduction to Actinomycete Biology. In: Practical streptomyces Genetics. The John Innes Foundation, Crowes, Norwich, England,. 1-21.

Kim, S., Seong, C., Jeon, S., Bae, K., & Goodfellow, M. (2004). Taxonomic study of neutrotolerant acidophilic actinomycetes isolated from soil and description of Streptomyces yeochonensis sp. nov. . International Journal of Systematic and Evolutionary Microbiology, 54(1), 211-212`214.

Korn-Wendisch , F., & Kutzner, H. (1992). The family Streptomycetaceae In: 'The prokaryotes (2 ed Edn),(Eds A Balows, HG Truper, M Dworkin, W Harder and KH Schleifer), Springer-Verlag: New York,. 2, 923-995.

Kumar, P., Preetam Raj, J., Duraipandiyan, V., & Ignacimuthu, S. (2012). Antibacterial activity of some actinomycetes from Tamil Nadu, India. Asian Pac J Trop Biomed 2(12), 936-943.

Kuster, E., & Williams, S. (1964). Selection of media for isolation of Streptomycetes. Nature, 202(4935), 928-929.

Lee , J., Jung, H., & Hwang, B. (2005). Streptomyces koyangensis sp. nov., a novel actinomycete that produces 4-phenyl-3-butenoic acid Int J Syst Evol Microbiol, 55, 257-262.

Lee, M., & Demain , A. (1997). Effects of nitrogen source on production of antibiotics Journal of Microbiology, 412-422.

Locci, R. (1989). Streptomyces and related genera. Bergeys manual of systematic bacteriology. Baltimore: Williams & Wilkns Company. 2344-2508.

Lounes, A., Lebrihi, A., Benslimane, C., Lefebvre , G., & Germain, P. (1996). Regulation of spiramycin synthesis in Streptomyces ambofaciens: effects of glucose and inorganic phosphate. Appl. Microbiol. Biotechnol, 45(1-2), 204-211.

Maleki, H., Dehnad, A., Hanifian, S., & Khani, S. (2013). Isolation and molecular identification of Streptomyces spp. with antibacterial activity from northwest of Iran. BioImpacts, 3(3), 129-134.

Manivasagan, P., Gnanam, S., Sivakumar, K., Thangaradjou, T., Vijayalakshmi, S., & Balasubramanian, T. (2009). Antimicrobial and cytotoxic activities of an actinobacteria (Streptomyces Sp. PM-32) isolated from an offshore sediments of the Bay of Bengal in Tamilnadu. Advances in Biological Research 3(5-6), 231-236.

Mann, J. (2001). Natural products as immunosuppressive agents. NatProd Rep, 18, 417-430.

Martin, J. F. (2004). Phosphate control of the biosynthesis antibiotics and other secondary metabolites is mediated by the PhoR-PhoP system: an unfinished story. J. Bacteriol., 186(16), 5197-5201.

Mc Gregor , J. (1954). Nuclear division and the life cycle in a Streptomyces sp. J. gen .Microbiol 11, 52-56.

MCIntyre, J. (2002). Antibiotic drugs. Journal of Antibiotics 34, 356-370.

Mohanraj, G., & Sekar, T. (2013). Isolation and screening of actinomycetes from marine sediments for their potential to produce antimicrobials Int. J. LifeSc. Bt & Pharm. Res, 2(3), 115-126.

Mokrane, S., Bouras, N., Sabaou, N., & Mathieu, F. (2013). Actinomycetes from saline and non-saline soils of Saharan palm groves: Taxonomy, ecology and antagonistic properties. African Journal of Microbiology Research, 7(20), 2167-2178.

Mukhtar, H., Ijaz , S., & Ul-Haq, I. (2012). Production of antitumor antibiotic by Streptomyces capoamus Pak. J. Bot.,, 44(1), 445-452.

Nikaido, H. (2009). Multidrug Resistance in bacteria. Annu Rev Biochem, 78, 119–146.

Nonoh, J., Lwande, W., Masiga, D., Herrmann, R., Presnail, J., Schepers, E., . . . Boga, H. (2010). Isolation and characterization of Streptomyces species with antifungal activity from selected national parks in Kenya. African Journal of Microbiology Research, 4(9), 856-864.

Orna, M. (2001). Women chemists in the national inventors hall of fame:Their remarkable lives and their awaer-winning research Bull. Hist. Chem., 34(1), 50-60.

Pallavi , S., Manasa, M., Kambar, Y., Asha, M., Chaithra, M., Vivek, M., . . . Mallikarjun, N. (2013). Anti-Staphylococcus aureus and Anti-yeast activity of Streptomyces species isolated from rhizosphere soil of Sahyadri Science College, Shivamogga, Karnataka. Asian Journal of Biomedical and Pharmaceutical Sciences, 3(24), 7-11.

Procópioa, R., Silvaa, I., Martinsa, M., Azevedoa, J., & Araújob, J. (2012). Antibiotics produced by Streptomyces. The Brazilian Journal of infectious diseases, 16(5), 466-471.

Quintana, E., Wierzbicka, K., Pawel Mackiewicz , Osman , A., Fahal, A., Hamid, M., . . . Goodfellow, M. (2008). Streptomyces sudanensis sp. nov., a new pathogen isolated from patients with actinomycetoma. Antonie van Leeuwenhoek, 93, 305–313.

Rafieenia, R. (2013). Effect of nutrients and culture conditions on antibiotic synthesis in Streptomycetes. Asian Journal of Pharmaceutical and Health Sciences, 3(3), 810-821.

Rahmansyah, M., Agustiyani, D., Julistiono, H., & Dewi, T. (2012). Groeth and adaptation of four Streptomyces isolates in the media containing propoxur ARPN Journal of Agricultural and Biological Science, 7(9), 773-781.

Remya, M., & Vijayakumar, R. (2008). Isolation characterization of marine antagonistic actinomycetes from west coxst of india. Medicine and Biology, 15, 13-19.

Rowbotham , T. J., & Cross, T. (1977). Ecology of Rhodococcus coprophilus and associated Actinomycetes in fresh water and agricultural habitats. Journal of General Microbiology, 100(2), 231-240.

Rugthaworn , P. (2007). A search and improvement of actinomycete strains for biologhcal control of plant pathogens Kasetsart J, 41, 248-254.

Saadoun , I., Momani, A., Malkawi, H., & Mohammad, M. (1999). Isolation, identification and analysis of antibacterial activity of soil streptomycetes isolates from north Jordan. Microbios, 100, 41-46.

Sahin, N., & Ugur, A. (2003). Investigation of the antimicrobial activity of some Streptomyces isolates. Turk J Biol, 27, 79-84.

Sanglier, J., Haag , H., Huck , T., & Fehr, T. (1993). Novel bioactive compounds from actinomycetes. Res Microbiol. , 144(8), 661-663.

Schats, A., Bugie , E., & Waksman, S. (1994). Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. Proceeding of Society for Exprimental Biology and Medicine,, 55, 66-69.

Sejiny, M. (1991). Growth phrases of some antibiotics producing Streptomyces and their identification. J.K.A.U.Sci, 3, 21-29.

Selvakumar, D., Arun, K., Suguna , S., Kumar, D., & Dhevendaran , K. (2010). Bioactive potential of Streptomyces against fish and shellfish pathogens. IRAN. J. MICROBIOL., 2(3), 157-164.

Seong, C., Choi, J., & Baik, K. (2001). An improved selective isolation of rare Actinomycetes from forest soil. The Journal of Microbiology, 39(1), 17-23.

Shahidi Bonjar, G. (2004). Screening for antibacterial properties of some Iranian plants against two strains of Escherichia coli. Asian Journal of Plant Sciences, 3, 310-314.

Shomurat, T., Yoshida, J., Amano, S., Kojina, M., & Niida, T. (1979). Studies on actinomycetal producing antibiotics only in agar culture. I. Screening taxonomy and morphology – productivity relationship of Streptomyces halstedii, strain SF. J Antibiot, 32, 427-435.

Silva, M., & Anne, D. (2004). The best penicillin for resistant bacteria Journal of antibiotics, 48, 562-569.

Singh, L., Baruah, I., & Bora , T. (2006). Actinomycetes of Loktak habitat: isolation and screening for antimicrobial activities. Biotechnology 5(2), 217-221.

Smaoui, S., Mathieu, F., Fguira, L., Merlina, G., & Mellouli, L. (2011). Taxonomy and antimicrobial activities of a new Streptomyces sp. TN17 isolated in the soil from an Oasis in Tunis. Arch. Biol. Sci., Belgrade, 63(4), 1047-1056.

Srivibool, R., Kurakami, K., Sukchotiratanac, M., & Tokuyamab, S. (2004). Coastal soil actinomycetes: Thermotolerant strains producing N-Acylamino acid racemase. Science Asia 30, 123-126.

Subbarao , N. (1999). Soil Microbiology (4th edition). Science Publishers, Inc: USA. 279-283.

Sujatha, P., RajuB, & Ramana, T. (2005). Actinomycetes of Loktak habitat: isolation and screening for antimicrobial activities. Mirobiological Research, 160, 119-126.

Tang, L., Zhang , Y., & Hutchinson, C. (1994). Amino acid catabolism and antibiotic synthesis: valine is a source of precursors for macrolide biosynthesis in Streptomyces ambofaciens and Streptomyces fradiae J. Bacteriol., 176(19), 6107-6119

Vetsigian, K., & Roy Kishony, R. (2011). Structure and evolution of Streptomyces interaction networks in soil and in silico. PLoS Biology, 9(10), e1001184.

Wang, Y., Zhang, Z. S., Ruan, J., Wang, Y. M., & Ali, S. (1999). Investigation of actinomycete diversity in the tropical rainforests of Singapore. J. Ind. Microbiol. Biotechnol., 23, 178-187.

Watve, M., Tichoo, R., MM, J., & Bhole, B. (2001). How many antibiotics are produced by the genus streptomyces? Arch Microbiol, 176, 386-390.

Willemse, J., Borst, J., Waal, E., Bisseling, T., & Wezel, G. (2011). Positive control of cell division: FtsZ is recruited by SsgB during sporulation of Streptomyces Genes & Dev., 25, 89-99.

Williams , S., Goodfellow, M., Alderson, G., Wellington, E., Sneath , P., & Sackin, M. (1983). Numerical classification of Streptomyces and related genera. Journal of General Microbiology,, 129, 1743-1813.

Wright , G. (2010). Antibiotic resistance in the environment: a link to the clinic? Curr Opin Microbiol, 13, 589–594.

Ying , Y., & Marta, M. (2001). Effects of L-lysine on production of rapamycine. Journal of Drugs, 102-105.

Young, M., & Kempe, L. (1985). Effects of phosphate, glucose, and mmonium on cell Growth and lincomycin production by Streptomyces irncohensis in chemically defined media. Biotechnology and Bioengineering, 55(2), 327-333.