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Review Article

BIODIVERSITY OF ACTINOMYCETES AND SECONDARY METABOLITES -A REVIEW.

KALPANA DEVI MOHAN AND USHA RAJAMANICKAM*

Department of Microbiology, Karpagam Academy of Higher Education, Coimbatore, 641 021, Tamil Nadu, India.

Email: usha.anbu09@gmail.com

ABSTRACT

Objectives: Actinomycetes are widely distributed in different habitats and involved in important processes.Therefore, evaluation of their distribution is important in understanding their ecological role very different views of actinobacterial diversity emerge from this paper.There are a tremendous diversity and novelty among the marine actinomycetes present in marine environments. Progress has been made to isolate novel actinomycetes from samples collected at different environments and habitats which include soil, rhizosphere soil, hypersaline soil, marine sediments, earthworm casting, goat faeces, desert, caves and honey bee gut. Among microorganisms, actinomycetes are enthralling resource due to their ability to produce novel bioactive secondary metabolites with antimicrobial activities. They have proven to be an inexhaustive mine of antimicrobial agents, especially those potent against pathogenic organisms. Microbial secondary metabolites, especially those from actinomycetes have been a phenomenal success for the discovery of novel drugs. They produce a wide range of secondary metabolites like antibiotics, pigments, enzymes, anti-inflammatory substances and endophenamines and more than 70% of the naturally derived antibiotics are currently in clinical use. **Conclusion:** They remain a fundamental source of new chemical diversity and an important part of drug discovery. This chapter highlight the bioactive metabolites produces by actinomycetes and their habitats.

Key words: Habitat, Actinomycetes, Secondary metabolites, Enzymes, isolation and Diversity.

INTRODUCTION

Actinomycetes are widely distributed in natural and man-made environments and play an important role in the degradation of organic matter. They are also well known as a rich source of antibiotics and bioactive molecules. Actinomycetes hold a prominent position for their diversity and ability to produce novel substances. They are responsible for the production of about half of the discovered bioactive secondary metabolites, notably antibiotics, antitumor agents, immunosuppressive agents, and enzymes. Because of the excellent track record of actinomycetes in this regard, a significant amount of effort has been focused on the successful isolation of novel actinomycetes from different sources for drug screening programs in the past fifty years [1].

In the past two decades, however, there has been a decline in the discovery of new important compounds from common soil-derived actinomycetes as culture extracts yield unacceptably high numbers of previously described metabolites [2]. Hence, the need for increased exploration of previously unexplored habitats for new actinomycete taxa has become a major focus in the search for the next generation of pharmaceutical agents [3]. Several distinct antibiotics have now been isolated from cultures of actinomycetes. Some, namely, actinomycetin, micromonosporin, mycetin, and actinomyces lysozyme, have been only partly purified, whereas others, including actinomycin, proactinomycin, streptothricin, and streptomycin, have been isolated and crystallized. These substances differ greatly in their chemical structure, antimicrobial properties, toxicity to animals and invivo activity. Some of the antibiotics are produced in simple synthetic media; others are formed in complex organic substrates; still others, like streptomycin, require the presence in the medium of a specific activity factor [4].

Actinomycetes produce and secrete a wide array of biologically active compounds including antibiotics, hydrolytic enzymes, and enzyme inhibitors. They are resistant to desiccation and nutrient stress, by their ability to produce spores. The potential of Actinoplanes campanulatus, Micromonosporachalcea, and Streptomyces spiralis endophytic in cucumber roots, to promote plant growth and to protect seedlings and mature plants of cucumber from diseases caused by Pythiumaphani dermatum, under greenhouse conditions. The author studied the effectiveness of two disease-suppressive Streptomyces spp. to control sugar beet Rhizoctoniasolani damping off under field conditions [5].

Recently, the rate of discovery of new compounds from terrestrial actinomycetes has decreased, whereas the rate of re-isolation of known compounds has increased. Thus, it is crucial that new groups of actinomycetes from unexplored or underexploited habitats be pursued as sources of novel bioactive secondary metabolites [6]. Hence, this paper would review the recent scenario about the diverse actinomycetes and their secondary metabolites.

DISTRIBUTION OF ACTINOMYCETES

Actinomycetes are the most widely distributed group of microorganisms in nature which primarily inhabit the soil. They have provided many important bioactive compounds of high commercial value and continue to be routinely screened for new bioactive compounds. These searches have been remarkably successful and approximately two-thirds of naturally occurring antibiotics, including many of medical importance, have been isolated from actinomycete. Many scientists and pharmaceutical industry have actively involved in isolation and screening of actinomycetes from different untouched habitats, for their production of antibiotics. Majority of the actinomycetes in soil that are potential drug sources remain uncultivable, and therefore inaccessible for novel antibiotic discovery. The majority of actinomycetes are free-living, saprophytic bacteria found widely distributed in soil, water and colonizing plants. Medicinal plants have pharmacological effects can be natural composite sources act as new anti-infectious agent. So, today foremost demand is searching for effective and cheapest improved compound [6].

Niche

Intense screening of actinobacteria especially rare actinomycetes is taking place all over the world. Exploration of actinomycete diversity of Manipur part of the Indo-Myanmar hotspot-holds promise for isolation of biotechnologically significant strains of actinomycetes and, even, novel species.actinomycete genera were obtained, among which Streptomyces, Micromonospora, Actinoplanes, Actinomadura, Nonomuria, Nocardia, and Streptosporangium were the most abundant [7].

Soil

Actinomycetes population has been identified as one of the major group of soil population , which may vary with the soil type. The author reviewed the literature on isolation of actinomycetes and suggested that only 10% of the actinomycetes are isolated from nature [8]. To discover new antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. So we need to screen more and more actinomycetes from different habitats for antimicrobial activity in hope of getting some actinomycetes strains that produce antibiotics that have not been discovered yet and active against drug-resistant pathogens [9]. As basic knowledge of the habitat, physiology, and productivity of molecules of rare actinomycetes increased, ecologically significant properties of actinomycetes assumed significance which made the screening source to expand into uncommon environments.

Rhizosphere soil

There are several dominant groups which are relatively stable in bulk soil and in rhizosphere both in spring and winter season and to a lesser extent between rhizospheres of young and old plants. Actinomycetes are important rhizosphere inhabitants of many plants, where they enhance plant growth and protect the plant roots against attack by phytopathogens [10]. Because of their metabolic diversity, actinomycetes are a great source of lytic enzymes, antibiotics and a great deal of other bioactive metabolites.

Hypersaline soil

Hypersaline habitats are typical extreme environments that include saline lakes, salterns, saline soils, hypersaline soils. Hypersaline soils are the soils for which the conductivity of the saturation extract is more than 18 mm hos/cm at 250 C1. As these soils contains 9 to 23 percent salts, these soils are reached in moderate halophiles.Actinomycetes genera isolated from hypersaline soils were Streptomyces, Streptoverticillium, Micromonospora, Nocardia, Microbispora, Actinoplanes, Planomonospora, Kitasatosporia. Streptomyces albidoflavus, Streptomyces griseoflavus, Streptomyces alboflavus, Streptomyces rimosus showed antifungal activity against Aspergillus niger, Fusarium solani, Candida albicans, Cryptococcus. And Streptomyces rameus, Streptomyces albus, Streptomyces exfoliates, Streptomyces violaceus, Streptomyces fragilis, Streptomyces olivaceiseleroticus, Streptomyces diasticus, Streptomyces albidoflavus, Streptomyces graminifaciens, Streptomyces antibioticus showed antibacterial activity against Escherichia coli, Staphylococcus aureus [11].

Limestone

Limestone is a sedimentary rock composed largely of the minerals calcite and aragonite, which are different crystal forms of calcium carbonate (CaCO3). These are mainly being used as raw materials for the production of cement. Their excavation for the said purpose from the earth leaves behind huge quarries with typical habitat. The harsh climatic conditions in the limestone quarries supposed to be a good niche for detection, which includes isolation and screening of potential isolates as well as novel bioactive molecules. Actinobacteria have the capability to synthesize many different biologically active secondary metabolites such as antibiotics, herbicides, pesticides, antiparasitic, and several enzymes. Of these compounds, antibiotics predominate in therapeutic and commercial importance [12]. Limestone quarries might have in turn led the Actinobacteria to produce their own potential secondary metabolites which are more effective than those produced by another group of microorganisms.

Freshwater

In recent years there has been a growing an awareness of the potential value of freshwater habitat as a source of actinomycetes that produce useful metabolic products. The River water was dominated by representatives of the genus Streptomyces while the River sediments were common by genus Micromonospora.The actinomycetes exhibiting antifungal from this habitat. New sources of antimycotic agent would be welcome, particularly in view of the opportunistic capabilities of yeast and molds in patients afflicted with the terminal disease. It is obvious that agents currently available for the treatment of systematic fungal infections leave much to be desired [13].

Marine sediments

The distribution of actinomycetes in the sea is largely unexplored and the presence of indigenous marine actinomycetes in the oceans remains elusive. This is partly caused by the lack of effort spent in exploring marine actinomycetes, whereas terrestrial actinomycetes have been, until recently, a successful source of novel bioactive metabolites. There is no exception for the cultivation of actinomycetes from the marine environment. Actinomycetes have been detected in unique marine environments, such as in marine organic aggregates and deep-sea gas hydrate reservoirs, where they were found to be the major components of the microbial communities. Actinomycetes isolated from the marine organic aggregates in the Wadden Sea have demonstrated high antagonistic activity within this microbial community. Marine microorganisms which can be grown in culture to yield valuable compounds would be of interest to the pharmaceutical industry [14]. Bona fide actinomycetes not only exist in the oceans, but they are also widely distributed in different marine ecosystems [15].

In previous study author reported Marine bacteria are emerging as an exciting species for the discovery of new classes of therapeutics and it could provide the drugs needed to sustain us for the next 100 years in our battle against drug-resistant infectious diseases [16]. Marine organisms have produced enormous antibiotics for diverse chemical structures. Actinomycetes account for >45% of all bioactive metabolites discovered in nature [17].

Sponges

As a major source of new natural bioactive compounds, marine sponges harbor large amounts of bacteria in their tissues that can amount to 40% of their biomass and it is widely believed that many of sponges products are in fact produced by symbiotic microorganisms [18]. Marine sponges are one of the important components of benthic communities Marine invertebrates have developed highly specific relationships with numerous associated microorganisms and these associations are of recognized ecological and biological importance. Novel actinomycete groups have been found in the Great Barrier Reef sponges Rhopaloeides odorabile, Pseudoceratina clavata and Candidaspongia flabellate, and the Mediterranean sponges Aplysina aerophoba and Theonella swinhoei [19].

Volcanic cave- hot spot

Volcanic caves have been little studied for their potential as sources of novel microbial species and bioactive compounds with new scaffolds. Volcanic cave microbiology from Canada and suggest that this habitat has great potential for the isolation of novel bioactive substances. Beutenbergia cavernae, a new genus of L-lysine-containing actinomycete and Agromyces subbeticus isolated from a cave in southern Spain [20]. Antimicrobial activities against a variety of multidrug-resistant pathogens from volcanic cave actinomycetes isolated in Canada [21].

Desert

The desert biome is regarded as a unique, under-explored source of novel actinobacterial diversity, with a large number of novel bacteria found in soil samples derived from hyper-arid regions of the Atacama Desert. Neilson and her colleagues collected soil samples from three sites across the hyper-arid margin of the Atacama, with the aim of determining the bacterial communities and evaluating the potential functional diversity of these communities within the soils [22]. Due to high levels of oxidation, the soil within the extreme hyper-arid region is depleted in organic material and consists of very low levels of culturable bacteria; therefore, the Yungay region of the Atacama Desert provides a promising setting to investigate the survival of microorganisms in conditions of extreme aridity [23]. Many of these metabolites possess antimicrobial activities and have the potential to be developed as therapeutic agents. It is also believed that the desert soil may harbur a large population of halophilic and alkaliphilic actinomycetes [24].

Insects gut

Insect digestive tracts support communities of symbiotic and transient microorganisms that are increasingly the subjects of studies of microbial diversity and novel bioactive microbial products [25]. In general, insect gut microbiota makes significant contributions to the nutrition of the insect host, as demonstrated in well-studied examples such as termites, cock roaches, wood-feeding beetles, and aphids. Honeybees, Apismellifera, are an interesting model for studies of gut microorganisms because they have a complex digestive tract. Streptomyces sometimes could become dominant in bee guts.They against bee indigenous Bacillus strains, Escherichia coli and two drug-resistant human pathogens. One frequently encountered isolate identified as a species of Nocardiopsis was further characterized and the expression of an antibiotic biosynthetic gene was analyzed [26].

The majority of the bioactivities produced by the actinomycete isolates were specific against several bee indigenous Bacillus strains and two drug-resistant Gram-positive human pathogens. One rare actinomycete isolate from the honeybee gut identified as a strain of N. alba was preliminarily characterized. Production of phenazine-like redox-active molecules by this isolates could contribute to its ability to temporarily survive the anoxic or anaerobic conditions that may occur in honeybee guts [27].

Earthworm castings

The earthworm casting has rarely been explored for actinomycetes having antimicrobial activity and industrial enzymes. The casting activity led to nutrition and enrichment.the earthworm redistribute organic matter with in the soil, increase permeability and microbial activity by its burrowing and feeding activity. The predominant genera was Streptomyces followed by Streptosporangium. Streptomyces from casting that was antagonistic to the common litter and wood degrading fungi.they have wide application in human medicine and veterinary medicines [28].

Goat faeces

Most actinobacteria are not obligate pathogens but true inhabitants of the environment. A symbiotic interaction with actinomycetes is essential for survival and reproduction of many insects. Streptomycetes species appear to protect European beewolf offspring against infection by pathogens. In goat faeces, dominance of Oerskovia and Nocardiopsis.the proportion of strain produced antifungal agents compared to antibacterial agent. Some antibiotics like monensin and flavomycin produced by Streptomyces species have been in use of growth promoting in ruminants [29].

Endophytic actinomycetes

Endophytes are microorganisms that live for the whole or part of their life history inside plant tissues [30]. As a result of these long-held association, endophytic microorganisms and plants have developed good information transfer. Many endophytic actinomycete compounds were used as biocontrol agents like compounds from Nocardia globerula used to control Helminthosporium solani pathogen causes silver scurf disease in potato. The compound from Streptomycetes sp.showed antifungal activity. Ansacarbamitocins were isolated from actinomycetes strain Amycolatopsis CP2808 which belongs to family Pseudonocardiaceae. Ansamitocin is a group of ansamycin antibiotics shows potent antitumor activity [31]. Ansamitocin was isolated from endophytic actinomycetes Nocardia sp

SECONDARY METABOLITES

In general, Gram-negative bacteria are more resistant to antibacterial compounds than Gram-positive bacteria. Several studies showed that the outer cell membrane in Gram- negative bacteria (double membranes) contains many protective mechanisms against antibiotics. The activity of Streptomyces species against Gram-positive bacteria has been widely published but it seems that the activity against Gram-negative bacteria, yeasts and fungi has been rarely reported [32]. Antitumoral activity has also been noted in several strains and species of Streptomyces[33]. Streptomyces is the capacity to produce secondary metabolites including antibiotics and bioactive compounds valued in human and veterinary medicine [32]. A new pyranonaphthoquinone antibiotic, griseusin D was isolated from the cultural fluid of alkalophilic Nocardiopsis sp. which exhibited weak antifungal activity against Alternaria alternate [34].

Antibiotics

Each year thousands of Streptomyces strains are screened by pharmaceutical companies as a source of new antimicrobial compounds [35]. The first antibiotic that was discovered from this genus was Streptothricin which was discovered in 1942. However, the discovery of new Streptomyces strains has substantially decreased over the years, and so has the probability of discovering a new compound [36]. In the present scenario, it is also imperative to isolate new and highly effective antimicrobial compounds as pathogenic microorganisms are developing resistance to existing antibiotics.

The antimycin-A antibiotics are a series of nine-membered dilactones, which were isolated from a number of Streptomyces strains. The antimycins have also other biological properties such as antifungal activity, inhibition of enzymatic activity as well as the ability to induce the death of cancer cells. Houssam M. Atta reported only weak antifungal properties and antiviral and antitumor activities were reported due to the free hydroxy group at C-8. C.B [37].

Salinosporamide A, isolated from the marine+ microbe Salinosporatropica exhibits strong cytotoxicity against melanoma, colon cancer, breast cancer, and non-small cell lung cancer. Salinispora strains are actively growing in some sediment samples indicating that these bacteria are metabolically active in the natural marine environment [38]. It also shows potency 35 times greater than that of omuralide, a powerful anticancer agent with a new way of controlling cancer cell growth [14].

Angucyclines are a group of aromatic polyketides that have a multitude of properties including antibacterial, antitumor, antiviral and enzyme inhibitory activities. Some angucyclines show promising activity even against multidrug resistant cancer cells angucycline biosynthesis, in actinobacteria and environmental samples [39]. To develop new antibiotics for the treatment of antibiotic-resistant pathogens, there has been increasing attention on marine microbial products. Angucyclines are an emerging group of antibiotics that are widely present in actinomycetes and environments [40].

Pigments

Actinomycetes are characterized by the production of various pigments on natural or synthetic media. These pigments are usually described in terms of various shades of blue, violet, red, rose, yellow, green, brown and black. The pigments may be dissolved into the medium or it may be retained in the mycelium. Actinomycetes had known to be produced various kinds of antibiotics and moreover, these antibiotics include many pigments [41]. Melanins are frequently used in medicine, pharmacology, and cosmetics. The highest level of pigment production was detected in Streptomyces virginiae with peptone-yeast extract-iron followed by tyrosine liquid medium.The pigment producing actinomycete strain D10 (Streptomyces hygroscopicus) showed antibacterial activity against the drug-resistant pathogens such as MRSA, VRSA and ESBL strains. The isolated yellowish antibiotic pigment 4-hydroxynitrobenzene from Streptomyces species. The yellow pigment was extracted in chloroform and tested against Bacillus subtilis and Shigella shiga.Microbial pigments are safe for human use, and some even have antibiotic or anticancer properties. Few are also certified as food grade pigments. They are easy to produce as compared to other natural pigments and are economic as well [42]. A major industrially important genus, Streptomycetes has been exploited to produce a wide range of antibiotics. But many Streptomyces species also produce pigments.The capability of these organisms to produce pigments is not a permanent property but can be greatly increased or completely lost under different conditions of nutrition and cultivation. Therefore, it is very essential to develop the correct combination of various culture conditions to enhance the growth and pigment production.Actinorhodin is a biological pigment produced by Streptomyces coelicolor, S.violaceusruber and S. lividans. It is red-blue in color based on the pH. It has found application as an antibiotic compound against Gram-positive bacteria, as an indicator compound in laboratory agents due to its property to exhibit different colours in acid and alkali mediums and lastly, it can be used in the food industry in making beverages, desserts etc, and maybe even in cosmetic industry. The complete scope of this pigment‘s application has not yet been explored.

Enzymes

One-half of Streptomyces parvulus strains newly isolated from soil produce more than 2 units of β-lactamase per ml extra- cellularly and constitutively. It is known that Streptomyces species are nonpathogenic procaryotic cells and produce a great many antibiotics including penicillins and cephalosporins [43]. They catalyze the hydrolysis of the, β-lactam ring of penicillins and cephalosporins to produce penicilloic and cephalosporoic acids. This property is very important when we consider the roles of these enzymes in bacterial resistance to therapeutic penicillins and cephalosporins, because the hydrolysis products have no antibiotic activity [44].

The oncolytic enzyme L- asparaginase is employed in the treatment of a tumor and acute lymphatic leukemia. It is effective anti-lymphoma agents in human is isolated from streptomyces species. Streptomycetes venezuelae able to produce potent fibrinolytic protease (thrombinase) can be used for the treatment of myocardial infection [45].

L-glutaminase is an enzyme produced from Streptomyces olivochromogens is used in enzyme therapy for cancer, especially for acute lymphocytic leukemia. L-glutaminase is in a biosensor for monitoring glutamine level in mammalian and hybridoma cells [46].

Xylanases from Streptomyces albus and Streptomyces chromofuscus have indicated positive bleaching effects in rice straw pulp. Microbispora sp. has been found to be producing hemicellulolytic mannanase enzyme [47]. Laccase was found to show an increase in brightness of eucalyptus kraft pulp in biobleaching studies. The enzyme was able to oxidize veratryl alcohol suggesting the potential of the strain in industrial applications. Veratryl alcohol oxidation and other lignolytic activities have also been demonstrated in Streptomyces viridosporus [48].

The anti-carcinogenic potential of L-asparaginase has received increased awareness in the current years because of its use as an effective therapeutic agent against lymphoblastic leukemia and another kind of cancers .this industrially important L-asparaginase enzyme produced by Streptomycetes parvulus [49].

Anti-inflammatory compounds

Bioactive compounds screened from marine actinomycetes, two compounds such as saphenic acid and lipomycin were found to have anti-inflammatory activity. Micromonospora sp with anti-inflammatory activity along with the antimicrobial activity. S. arenicola also produces the anti-inflammatory metabolites cyclomarin A and C. Swelling was reduced when cyclomarin A was administered topically or intraperitoneally [50].

Endophenazines [51, 45]

One rare actinomycete isolates from the honeybee gut identified as a strain of Nocardia alba was preliminarily characterized. Production of phena zine like redox active molecules by this isolate could contribute to its ability to temporarily survive the anoxic or anaerobic conditions that may occur in honeybee guts [51]. It was thereafter observed that one type of the modified phena- zines, so-called endophenazines, was previously detected as the metabolites of S. anulatus. Microbial metabolites that share an anthranilic acid structural moiety with phenazines, such as actinomycins and quinolones, also have widely known electrochemical properties. In addition, thiols, quinines, and coumarins of microbial origins have noticeable electron transfer capabilities. Phenazines produced by the actinomycetes from honeybee guts probably have structural commonalities even though the producers can be quite different (e.g. Nocardiopsis vs. Streptomyces). Indeed, more actinomycete isolates in our study displayed specific antagonism against a B. marisflavi strain than against other Bacillus strains [45].

Table 1: Showing Novel Metabolites produced by Actinomycetes.

Secondary metabolites	Sources
Antibiotics	*Salinosporatropica, Streptomycetes Acta 1362*
Pigments	*Streptomyces virginiae*
Enzymes	*Streptomyces olivochromogens, Streptomyces parvulus.*
Anti inflammatory compound	*Micromonospora, Streptomyces arenicola*
Endophenazines	*Nocardia alba*

CONCLUSION

The exploitation of actinomycetes as a source for novel secondary metabolites in its infancy. The antagonistic actinomycetes and it supports the evidence that different ecosystem is an important source of biologically active compounds. Actinomycetes can be sources of potent antibacterial agents that can be of value in the treatment of infections. Discovering potent secondary metabolite producer like actinomycetes is an interesting and challenging platform for researchers. In spite of growing under the extreme conditions, members of actinomycete bacteria produce industrially valuable compounds such as enzymes, antibiotics, pigments, and endophenes etc. The different ecological habitats reveal the comprehensive existence of actinobacterial species in specific microbial niches. However, the ecological habitat is underexplored and yet to be investigated for its authentic yet unknown, rare actinomycetes diversity.

REFERENCES

1. Alharbi S.A., Arunachalam C, Murugan A.M and Wainwright M. Antibacterial activity of actinomycetes isolated from terrestrial soil of Saudi Arabia. Journal of Food, Agriculture & Environment, 2012, 10 (2):1093-1097.
2. Mincer T.J., Jensen P.R, Kauffman C.A and Fenical W. Widespread and persistent populations of a major new marine actinomycete taxon in ocean sediments. Appl. Env. Microbiol, 2002, 5005-5011.
3. Bull A.T., Ward A.C and Goodfellow M. Search and discovery strategies for biotechnology: The paradigm shift. Microbiol. Mol. Biol. Rev, 2002, 64:573-606.
4. Waksman S.A., Schatz A and Reynold D.M. Production of antibiotic substances by Actinomycetes. Ann.N.Y. Acad.Sci, 2010, 112-124.
5. Dhanasekaran D., Rajkumar G, Sivamani P, Selvamani S, Panneerselvam A and Thajuddin N. Screening of salt pans Actinomycetes for antibacterial agents. The International Journal of Microbiology, 2005, 2:62–66.
6. Karuppiah P and Mustaffa M. Antibacterial and antioxidant activities of Musa sp. Leaf extracts against multidrug resistant clinical pathogens causing nosocomial infection. Asian Pac J Trop Biomed. 2013, 3(9):737-742.
7. Debananda S., Ningthoujam, Suchitra S and Nimaichand S. Screening of Actinomycete Isolates from Niche Habitats in Manipur for Antibiotic Activity. American Journal of Biochemistry and Biotechnology, 2009, 215-221.
8. Kuster E. And Williams S.T. Production of hydrogen sulphide by Streptomyces and methods for its detection. Appl. Microbiol, 1964, 12: 46-52.
9. Kumar N., Singh R.K, Mishra S.K, Singh A.K and Pachouri U.C. Isolation and screening of soil Actinomycetes as source of antibiotics active against bacteria. International Journal of Microbiology Research, 2010, 2(2):12-16.
10. Gonzalez-Franco A.C., RoblesHernande z , NuñezBarrios A , Strap J.L and Crawford D.L. Molecular and cultural analysis of

seasonal actinomycetes in soils from Artemisia tridentata habitat. International journal of experimental botany, 2009, 78:83-90.
11. Nakade D.B. Biodiversity of Actinomycetes in Hypersaline soils of Kolhapur district and their screening as potential antibiotic producer, India. Research Journal of Recent Sciences, 2012, 1: 317-319.
12. Quadri S.R and Agsar D. Antimicrobial attributes of rare actinobacteria detected from limestone quarries. Int J Pharm Bio Sci, 2012, 3(3): 137 – 147.
13. Rifaat H.M. The biodiversity of Actinomycetes in the River Nile exhibiting antifungal activity. Journal of Mediterranean Ecology, 2003, 4: 3-4.
14. Murti Y and Tarun A. Marine derived pharmaceuticals-development of natural health products from marine biodiversity. International Journal of Chem Tech Research, 2010, 1: 2198-2217.
15. Kin S.L. Discovery of metabolites from marine actinomycetes. Current Opinion in Microbiology, 2006, 9: 245–251.
16. Vimal, Rajan B.M and Kannabiran K. Antimicrobial Activity of Marine Actinomycete, Nocardiopsis sp. VITSVK 5. Asian Journal of Medical Sciences, 2009, 1(2): 57-63.
17. János Bérdy, Bioactive Microbial Metabolites. J. Antibiot, 2005, 58(1):1–26.
18. Ouyang and Yongchang. A method to type the potential angucycline producers in actinomycetes isolated from marine sponges. Antonie van Leeuwenhoek, 2011, 99(4): 807-815.
19. Selvan P., Ravikumar S, Ramu A and Neelakandan P. Antagonistic activity of marine sponge associated Streptomyces sp. Against isolated fish pathogens. Asian Pacific Journal of Tropical Disease, 2012, 724-728.
20. Jurado V., Kroppenstedt R M, Saiz-Jimenez C, Klenk H P, Mouniee D and Laiz L. Hoyosella altamirensis gen.sp. Nov., a new member of the order Actinomycetales isolated from a cave biofilm. Int. J. Syst. Evol. Microbiol, 2009, 59: 3105–3110.
21. Cheeptham N, Sadoway T, Rule D, Watson K, Moote P, Soliman L.C, Azad, Donkor K.K and Horne D. Cure from the cave: volcanic cave actinomycetes and their potential in drug discovery. International Journal of Speleology, 2013, 42 (1): 35-47.
22. Neilson O.M., Nelson J.W, Legatzki W.M, Byrne A and Yu A. Profiling bacterial diversity and taxanomic composition on speleothem surfaces in kartchner caverns. AZ. Microb.Ecol, 2013, 65: 371-383.
23. González I., Ayuso-Sacido A, Anderson A and Genilloud O. Actinomycetes isolated from lichens: evaluation of their diversity and detection of biosynthetic gene sequences. FEMS Microbiol. Ecol, 2005, 54: 401–415.
24. Badji B., Zitouni A, Mathieu F, Lebrihi A and Sabaou N. Antimicrobial compounds produced by Actinomadura sp.AC104 isolated from an Algerian Saharan soil. Can Microbiol, 2006, 52: 373-382.
25. Breznak J.A. Invertebrates—Insects, In Microbial Diversity and Bioprospecting. American Society of Microbiology, 2004, 191-203.
26. Kristufek V., Ravasz K and Pizl. Actinomycete communities in earthworm guts and surrounding soil. Pedobiologia, 1993, 37: 379–384.
27. Teske A., Dhillon A and Sogin MI. Genomic Markers of Ancient Anaerobic Microbial Pathways: Sulfate Reduction, Methanogenesis and Methane Oxidation. Biol. Bull, 2003, 204: 186–191.
28. Kumar R., Biswas K, Soalnki V, Kumar P and Tarafdar A. Actinomycetes: potential bioresource for human welfare: a review. Research Journal of Chemical and Environmental Sciences, 2014, 2(3): 5–16.
29. Tan., Deng Z and Cao L. Isolation and characterization of actinomycetes from healthy goat faeces. Society for Applied Microbiology, Letters in Applied Microbiology, 2009, 49: 248–253.
30. Sachiko H., Akane M, Masafumi S, Tomio N and Hitoshi K. Endophytic actinomycetes and their interactions with host plants. Actinomycetologica, 2006, 26: 72-81.
31. Snipes C.E., Duebelbeis D.O, Olson M, Hahn D.R, Dent W.H et al. The ansacarbamitocins: polar ansamitocin derivatives. J. Nat. Prod, 2007, 70(10): 1578-81.
32. Park H.B., Kwon H.C, Lee C.H and Yang H.O. Glionitrin A, an antibiotic-antitumor metabolite derived from competitive interaction between abandoned mine microbes. J Nat Prod, 2009, 72: 248-252.
33. Bouras N., Meklat A, Toumatia O, Mokrane S, Holtz M.D, Strelkov S.E and Sabaou N. Bioactive potential of a new strain of Streptomyces sp. PP14 isolated from Canadian soil. African Journal of Microbiology Research, 2013, 7(25): 3199-3208.
34. Omura S., Nakagawa A, Yamada H, Hata T, Furusaki A and Watanabe T.C. Structure and biochemical properties of kanamycin A, B, C and D. Chem. Pharm. Bull, 1973, 21: 931-934.
35. Li W.J., Xu P, Schumann P, Zhang Y.Q and Pukall R. Georgenia ruanii sp. Nov., a novel actinobacterium isolated from forest soil in Yunnan (China) and emended description of the genus Georgenis. Int. J. Syst. Evol. Microbiol, 2007, 57: 1424 -1428.
36. Baoxin Z., Xiangjing W and Wensheng X. Optimization of fermentation medium for enhanced production of milbemycin by a mutant of Streptomyces bingchenggensis BC-X-1 using response surface methodology. African Journal of Biotechnology, 2011, 10(37): 7225-7235.
37. Cwala Z., Igbinosa E.O and Okoh A.I. Assessment of antibiotics production potentials in four actinomycetes isolated from aquatic environments of the Eastern Cape Province of South. African Journal of Pharmacy and Pharmacology, 2011, 5(2):118-124.
38. Atta H.M., Dabour S.M and Desoukey S.G. Sparsomycin Antibiotic Production by Streptomyces Sp. AZ-NIOFD1: Taxonomy, Fermentation, Purification and Biological Activities. American- Eurasian J Agric & Environ Sci, 2009, 5: 368-77.
39. Kin S and Lam T. Discovery of novel metabolites from marine actinomycetes. Curr Opin Microbiol, 2006, 9: 245–51.
40. Korynevska A., Heffeter P, Matselyukh B, Elbling L, Micksche M, Stoika R and Berger W. Mechanisms underlying the anticancer activities of the angucycline landomycin. E. Biochem Pharmacol, 2007, 74: 1713–1726.
41. Wawrik B., Kutliev D, Abdivasievna U.A, Kukor J.J, Zylstra G.J and Kerkhof L. Biogeography of actinomycete communities and Type II polyketide synthase genes in soils collected in New Jersey and central Asia. Appl. Environ. Microbiol, 2007,73: 2982–2989.
42. Amal A.M., Abeer K.A, Samia H.M, Nadia A.H, Ahmed K.A and El-Hennawi H.M. Selection of Pigment (Melanin) production in Streptomyces and their application in Printing and Dyeing of Wool Fabrics. Research Journal of Chemical Sciences, 2011, 1(5): 22-28.
43. Sathi Z.S., Sugimoto N, Khalil M.I and Gafur M.A. Isolation of yellowish antibiotic pigment 4-hydroxy nitrobenzene from a strain of Streptomyces. Pak J Biol Sci, 2002, 52: 201–3.
44. Patil P.B., Zeng Y, Coursey T, Houston P, Miller L and Chen S. Isolation and characterization of a Nocardiopsis sp. From honey bee guts. FEMS Microbiol Lett, 2010, 312: 110–118.
45. Dhevagi and Poorani E. Isolation and characterization of L-asparaginase from marine Actinomycetes. Indian Journal of Biotechnology, 2006, 5: 514-520.
46. Amirta K., Nithin J and Devi S. Novel bioactive compounds from mangrove derived Actinomycetes. Innternational Research Journal of Pharmacy, 2012, 3(9): 25-29.
47. Rifaat M., Nagieb Z.A, and Ahmed Y.M. Production of xylanases by Streptomyces species and their bleaching effect on rice straw pulp. Applied Ecology and Environmental Research, 2005, 4 (1): 151–160.
48. Ramachandran S., Krishnan R, Nampoothiri K.M, Szackacs G and Pandey A. Mixed substrate fermentation for the productionof phytase by Rhizopus spp. using oil cakes as substrates. Process Biochemistry, 2005, 40: 1749-1754.
49. Usha R., Mala K.K, Venil C.K and Palaniswamy M. Screening of Actinomycetes from Mangrove Ecosystem for L-asparaginase Activity and Optimization by Response Surface Methodology. Polish Journal of Microbiology, 2011, 60(3): 213–221.

50. Jayaprakashvel M. Therapeutically Active Biomolecules from Marine Actinomycetes. Journal of modern biotechnology, 2012, 1(1): 1–7.

51. Jing Ke. In-situ oxygen profiling and lignin modification in guts of wood-feeding termites. Insect Science, 2010, 17(3): 277-290.