ANO IMPLICATION OF ACTINOMYCETES ON HUMAN WELL-BEING: A REVIEW

ALI MOHAMMED ABDULLAH BAWAZIR1, PALAKSHA2, MANJULA SHANTARAM2*

1Department of Studies and Research in Microbiology, Post Graduate Centre, Mangalore University, Jnana Kaveri, Chikka Aluvara, Kodagu 571232, Karnataka, India, 2Department of Studies and Research in Biochemistry, Post Graduate Centre, Mangalore University, Jnana Kaveri, Chikka Aluvara, Kodagu 571232, Karnataka, India

Email: manjula59@gmail.com

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ABSTRACT

This review conceptualizes about the actinomycetes and its contribution to human health by playing a key role as bioactive secondary metabolites, such as enzymes, antibiotics and pigments, leading to their diverse applications and use in various industries. These searches have been uncommonly successful, and around 66% of naturally happening antibiotics, including many medically important, have been isolated from actinomycetes. The speedy occurrence of antimicrobial resistance among pathogens has led to a renewed interest to search for novel antimicrobial agents, but these antibiotics are not enough for the treatment of all diseases because there is a berserk requirement for a novel actinomycetes to combat against the antibiotic-resistant strains of pathogens and microorganisms, which are rapidly expanding bit by bit. Actinomycetes are the important providers to the pharmaceutical and other industries and are well known for their capacity to produce secondary metabolites many of which are active against pathogenic microorganisms.

Keywords: Actinomycetes, Antibiotics, Natural pigments, Enzymes

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INTRODUCTION

The presence of actinomycetes has been known for over hundred years. For much of the time they were seen as a foreign group of organisms with an attraction to both bacteria and fungi. However, the study of their fine structure and chemical composition started in the 1950s, having confirmed their prokaryotic nature. They now create the order actinomycetes and their removal from the mycologists, has ruined the effective reach. Their difference in status paralleled that of the blue-green growth to the cyanobacteria but it was accepted more rapidly and less bitterly. It is not easy to give a short, accurate definition of actinomycetes. They are frequently described as bacteria which have the ability to form branching hyphae at some stage of their development. However, this attribute is unconvincing and it often requires the imagination to believe it [1].

The name "actinomycetes" was derived from Greek "aktis" (a ray) and "mikes" (fungus) and has features of both bacteria and fungi [2]. Actinomycetes are soil organisms which have features common to bacteria and fungi and however possess sufficient distinctive features to delimit them into a distinct group. They were initially erroneously classified as fungi since they have true aerial hyphae and form spores, both of which are thought to be fungal characteristics [3]. Actinomycetes are characterized as microscopic organisms that can shape spreading hyphae at some phase of their advancement [4]. They are characterized by having a high guanine and cytosine content in their deoxyribonucleic acid [5]. The actinomycetes are a group of microbes which possess many significant and interesting features. They have given many important bioactive compounds of high commercial value and continue to be routinely screened for new bioactive substances.

These searches have been uncommonly successful, and around 66% of naturally happening antibiotics, including many of medical significance, have been isolated from actinomycetes [6]. One result of intense screening programs carried out over the past several years is that there is a developing issue of "rediscovery" of definitely known bioactive compounds [7]. This pattern appears to suggest that the effortlessly open microorganisms in soil had been depleted and there is a need to look for unutilized microorganisms from unexplored sources [8].

One way to approach with this issue is to extend the source of actinomycetes via ecological evaluations of environments other than earthly soils. There is also a growing interest in the non-streptomycete actinomycetes as sources of novel compounds [7]. It is likely that the assorted variety of secondary metabolites depends pretty much on the isolation source, viz. the environment of the producers [8]. Based on the above beliefs, new actinomycetes strains that create active compounds have been as of late removed from novel sources including saline, sea, mangrove woodlands and specialty natural surroundings, for example, caves, bee hives, pristine forests, lakes, rivers and other wetlands [9-12]. To cope with the demand for new pharmaceutical compounds and to resist the antibiotic-resistant pathogens.

Goals of novel actinomycetes research towards contribution to the human health

The war continues between antibiotics and resistant bacteria. More the scientists produce new and effective antibiotics, more frequent will be the bacteria changing their genetic mutations and adjusting their defenses, according to the components of the new antibiotic and win it, every time. To solve the problem of antimicrobial resistance there is a need for the discovery of new drugs, which is a critical element in a coordinated response to antimicrobial resistance. The resistance of bacteria to antibiotics is one of the global health and economic problems, prompting researchers to look for new antibiotics to overcome resistant bacterial strains that increase morbidity and epidemics. Health experts estimate that nearly 90,000 people die each year from antibiotic-resistant bacteria in the United States, and hospital-acquired disease develops in more than 2 million people annually, and that three-quarters of these occur as a result of at least one adverse common antibiotic. Antibiotic-resistant bacteria make the patient stay in the hospital for more than 74,040, more than the treatment costs for a sensitive strain, ie., patients with Staphylococcus aureus methicillin resistance and may cost up to $ 4,000 more than the cost of treating patients with an antibiotic-resistant S. aureus strain. The cost of treatment with multidrug-resistant TB bacteria is $ 180,000 or more and the cost of treatment for sensitive strains is $ 2,000. In general, the total cost associated with antibiotic-resistant bacteria is estimated at $ 45 billion per year in the United States [1].
There is a post for new anti-infection agents to treat ailments via looking for different sources, for example, actinomycetes to confine crude anti-infection agents. Since, now 66% of the anti-infection agents utilized as a part of medication are recently separated from actinomycetes and numerous more are of therapeutic significance, having been secluded from it [6].

Screening of actinomycetes for the generation of new anti-infection agents has been seriously taken after a long time by researchers. Actinomycetes have been utilized as a part of numerous fields including agriculture, veterinary and pharmaceutical industry. Actinomycetes can integrate various naturally dynamic optional metabolites, for example, anti-infection agents, herbicides, pesticides, hostile to parasites, and catalysis like cellulase and xylanase which are utilized as a part of waste treatment [14].

The proceeding with accomplishment of a biotechnologist in the hunt of microbial metabolites as antimicrobial mixes (anti-infection agents) is helpful in battling human, creature and plant illnesses for fortifying the conviction that microorganisms constitute a limitless supply of mixes with pharmacological, physiological, medicinal or rural applications [15].

Antibiotic drug discovery is an indispensable process to combat aggressive ability of pathogenic microorganisms and emerging infectious diseases against health and well-being of people throughout the world [16]. According to the updated and expanded data on natural products presented by Newman and Cragg [17], the utility of natural products as sources of novel structures is still alive and the anti-infective area depends on natural products and their structures. The natural products with pharmaceutical importance are largely produced from primary and secondary metabolism of plants and microorganisms. Microbial natural products have made an incredible contribution to the antibiotic drug discovery and subsequent progress into a medicine in the 1940s laid the foundation for development of microbial natural products as drugs [19, 20]. Afterwards, according to Waksman’s resulting reports of actinomycin, streptomycin, and streptomycin in 1940, 1942 and 1943 respectively, actinomycetes was introduced as a source of antibiotics [21-23]. At the end of the 20th century, diversified actinobacterial natural products had found wide utilization in clinical field as antibacterial, antifungal, antiparasitic, and anticancer agents [24]. According to Berdy [25], out of all studies of bioactive compounds of microbial origin, 45% are produced by actinomycetes. Moreover, 90% approximately of all antibiotics utilized as drugs isolated from the actinomycetes and they are as yet being principal natural antibiotic producers [26]. Since the report of streptomycin from the strains of Streptomyces griseus, there has been a fast acceleration in antibiotic discovery from the genus Streptomyces (biggest genus of Actinobacteria). Subsequently, members of this genus have become renowned as a prime source of natural antibiotics [27, 28]. It has been evidenced by continuing production of string of commercially important antibiotics like doxycycline, erythromycin, fosfomycin, lincomycin, neomycin, streptomycin, and tetracycline from industrially-important members of the genus Streptomyces [29]. However, the possibility of novel antimicrobials leads from these special actinomycetes has as of late dwindled upon the rediscovery of known compounds [30] and the focus of current microbial drug discovery programs being reoriented toward other promising microbial resources. Other side of the coin, emergence of new infectious diseases and antibiotic resistance provoked in earlier infectious diseases has raised the need for novel antibiotics. Against this background, uncommon actinomycetes (non-streptomycetes) are by and by isolated from different habitats and genuinely examined for antibiotic discovery programs. The rare actinomycetes are generally viewed as strains of actinomycetes whose isolation frequency by traditional methods is significantly lesser than that of streptomycete strains [31]. According to Tiwari and Gupta [32], this non-streptomycete actinomycetes group include diverse bioactive secondary metabolite producing members under following genera: Actinomadura, Actinoplanes, Amycolatopsis, Dactylosporangium, Kibdelosporangium, Kitasatospora, Microbispora, Planomonospora, Planobispora, Salinispora, Streptosporangium, and Verrucosipilis. The studies have furthermore been expanded by recent studies of bioactive compounds from individuals from other rare generators, Nonomuraea [33-35], Actinomaduraeichii [36, 37], Pseudonocardia [38-40], and Saccharothrix [41-43]. Furthermore, basic information about the habitats, physiology and secondary metabolite diversity of the rare actinomycetes have continuously increased [31]. Out of in excess of eight thousand antimicrobial products portrayed in the ABL database, 16% created by strains have a place with uncommon genera of actinomycetes [44]. Allocation of the novel actinomycetes has been observed to be very wide in terrestrial and aquatic environments [31]. Isolation techniques have turned out to be vital as these uncommon actinomycetes utilize slow growth while quickly growing streptomycetes and fungal strains dominate in ordinary actinomycetes isolation methods. Different isolation methods have to be used for getting diverse actinomycetes from different sources. These methods use a variety of pretreatment techniques and enrichment techniques along with selective isolation medium improved with specific antimicrobial agents [45]. In 2013, Tiwari and Gupta [46], have reviewed almost all the selective isolation methods that have been developed for date to isolation of rare actinomycetes. In fact, all the isolation methods are designed to favor the growth of rare actinomycetes while suppressing the growth of undesired microorganisms. In recent times, much care has been given to isolating rare actinomycetes from diverse previously unexplored common as well as uncommon extreme environments. Numerous rare actinomycetes have been isolated from variety of soil samples [31; 47-50], plant materials [51-53], marine sources [54-57], extreme saline zones [58], volcanic zones [59], hyper arids [60], glaciers [61,62], and much more. Therefore, a variety of uncommon actinomycetes accessible for current antimicrobial medication screening programs has increased. In the review article of Tiwari and Gupta [46] there are reports of isolation of uncommon actinomycetes from various natural habitats throughout the world. It is disclosed that a surprising assortment of uncommon actinomycetes colonize in diverse, previously unexplored natural habitats. Finally, rare actinomycetes are being detected as highly prospective sources of bioactive compounds. Ways have already been sketched to reach these rare microorganisms but steps should be taken with specific isolation strategies [16]. The developed disclosures of novel bioactive compounds from these uncommon actinomycetes (non-streptomycetes) clearly opine that these organisms contribute to the antibiotic drug discovery programs [16].

Importance of actinomycetes

Enzymes

Different genera of Actinomycetes have been reported to create a wide cluster of potential industrial enzymes that can be utilized as a part of biotechnological applications and specific biomedical fields [63]. Proceeding advances in sequencing technology and bioinformatics apparatus make it conceivable to think about the microbial enzyme production by utilizing proteomics andmetaproteomics [64]. Microbial enzymes assume a key part as metabolic catalysts, promoting their different applications and use in different industries. The steady look for novel microbial enzymes has prompted an act of ad-lib in the industrial procedures which is the key pay off growth. Actinomycetes form a noteworthy group of microbial populations in the soil, plant tissues, and marine environments. Actinomycetes produce numerous significant extracellular enzymes which can break down a assortment of organic materials. Enzymes produced by actinomycetes and used in various industries are cellulases, proteases, amylases, lipases, xylanases, chitinases, cutinases and pectinases (table 1). Actinomycetes distinguished from the extreme environments are known to be makers of novel enzymes with incredible industrial potential [65]. Actinomycetes have been consistently considered and utilized for the production of amylases, cellulases, proteases, chitinases, xylanases and pectinases. This audit production of industrially important enzymes by actinomycetes, their qualities and industrial uses (applications in biomedicine, food, cleanser, mash and paper, agribusiness, material, and waste administration) are commendable.
Table 1: Significant enzymes produced by actinomycetes

| Enzyme       | Producing strain                       | Industrial application                                      | Reference |
|--------------|---------------------------------------|------------------------------------------------------------|-----------|
| Cellulase    | Streptomyces ruber Thermobifida halotolerans | Detergent, Paper and pulp                                  | [66-67]   |
| Protease     | Streptomyces pactum and Streptomyces thermoviolaceus | Pharmaceutical, Leather, Food and detergents                | [68-69]   |
| Keratinase   | Actinomadura keratinilytica and Streptomyces erumpens | Leather and detergents                                     | [70]      |
| Amylase      | Thermobifida fusca and Streptomyces overmilitis | Paper, pulp, textile, food, brewing and distilling industries | [71-72]   |
| Xylanase     | Streptomyces spp. and Actinomadura sp. | Paper, pulp and Animal feed                                | [73-74]   |
| Lipase       | Nocardiosis alba Streptomyces esculentiae | Detergent industries, foodstuff, oleochemical              | [75-76]   |
| Chitinase    | Streptomyces thermoviolaceus, Nocardiosis prasina, Streptomyces hygroscopicus and Streptomyces aureofaciens | Textile and Leather                                        | [77-78]   |
| Pectinase    | Streptomyces lydicus                   | Beverage and Textile                                       | [79-81]   |
| L-asparaginase | Streptomyces griseus, S. karnatakensis, S. albidoflavus and S. hygroscopicus | Therapeutic agent in the cure of certain human cancers, mostly in acute lymphoblastic leukemia | [82]      |

Antibiotics

The discovery of actinomycin was soon replaced by that of streptomycin which is most likely best known for its utilization in the control of tuberculosis. Numerous other medically helpful antibiotics are still being used. Although the greater part of these antibiotics began from streptomycetes, other genera, for example, Actinoplanes, Actinomadura, and Micromonospora, likewise deliver helpful or possibly valuable antibiotics. In spite of the fact that the rate of return has diminished as of late, new antibiotics and other valuable metabolites from actinomycetes are yet to be found. This will be represented by β-lactamase inhibitors, for example, clavulanic acid from Streptomyces clavuligerus [83], which has been economically produced to surmount bacterial resistance to existing β-lactam antibiotics. The capacity of actinomycetes to create valuable secondary metabolites stays amazing; in spite of the fact that the purposes behind this and biological importance of such products are as yet not clear [84]. Moreover, it is a continuous effort to look into new ecological housing for novel actinomycetes. Target coordinated screening is being utilized for screening of antibiotic-producing actinomycetes. Molecular biology methods have helped on a huge scale in finding new antibiotics from actinomycetes. The significance of actinomycetes in modern biosynthesis has catalyzed many parts of essential research on these microbes. The streptomycetes, are the most productive well spring of new antibiotics [25, 65, 86]. Actinomycetes are at present known to deliver more than 10,000 bioactive compounds, 7,600 of which have been isolated from streptomycetes and 2,500 from non-streptomycetes, prominently from the so-called rare actinomycetes [87]. In spite of this astounding productivity, it has been assessed that only tiny part of the aggregate number of antimicrobial compounds which actinomycetes can produce have been found to date [88]. Sacrificial numbers of bioactive microbial metabolites have appeared in table 1.1.

Table 2: Estimated number of bioactive microbial metabolites as indicated by their producers and bioactivities [25]

| Source | Antibiotics | Bioactive metabolites |
|--------|-------------|-----------------------|
|        | Total       | (with other Activity)  | No antibiotic activity | (antibiotics plus other bioactivities) | Total bioactive metabolites |
| **Bacteria:** | 2900 | 780 | 900 | 1680 | 3800 |
| Eubacteriales | 2170 | 570 | 580 | 1150 | 2750 |
| Bacillus sp. | 795 | 235 | 66 | 300 | 860 |
| Pseudomonas sp. | 610 | 185 | 185 | 370 | 795 |
| Mycobacteria | 400 | 130 | 10 | 140 | 410 |
| Cyanoacteria | 300 | 80 | 340 | 420 | 640 |
| **Actinomycetes:** | 8700 | 2400 | 1400 | 3800 | 10100 |
| Streptomyces sp. | 6550 | 1920 | 1080 | 3000 | 7630 |
| Rare actinomycetes | 2250 | 580 | 220 | 800 | 2470 |
| **Fungi:** | 4900 | 2300 | 3700 | 6000 | 8600 |
| Microsopic fungi | 3770 | 2070 | 2600 | 4750 | 6450 |
| Penicillium/Aspergillus | 1000 | 450 | 950 | 1400 | 1950 |
| Basidiomycetes | 1050 | 200 | 950 | 1150 | 2000 |
| Yeats | 105 | 35 | 70 | 140 | |
| Slime moulds | 30 | 5 | 20 | 25 | 60 |
| **Total** | 16500 | 5500 | 6000 | 11500 | 22600 |
Table 3: Antibiotics isolated from actinomycete genera, as described in the antibiotic database of the Journal of Antibiotics [6]

| Actinomyocyte                                      | AG | ML | AML | BLA | PEP | GP | ANC | TC | NUC | POL | QN |
|----------------------------------------------------|----|----|-----|-----|-----|----|-----|----|-----|-----|----|
| Streptomyces                                       |    |    |     |     |     |    |     |    |     |     |    |
| Other actinomycetes:                               |    |    |     |     |     |    |     |    |     |     |    |
| Actinomadura                                       |    |    |     |     |     |    |     |    |     |     |    |
| Actinoplanes                                       |    |    |     |     |     |    |     |    |     |     |    |
| Actinosynnema                                      |    |    |     |     |     |    |     |    |     |     |    |
| Ampullariella                                      |    |    |     |     |     |    |     |    |     |     |    |
| Amycolatosis                                       |    |    |     |     |     |    |     |    |     |     |    |
| Dactylosporangium                                  |    |    |     |     |     |    |     |    |     |     |    |
| Kibdelosporangium                                 |    |    |     |     |     |    |     |    |     |     |    |
| Kitasatospora                                      |    |    |     |     |     |    |     |    |     |     |    |
| Microbiosa                                         |    |    |     |     |     |    |     |    |     |     |    |
| Micromonomospora                                   |    |    |     |     |     |    |     |    |     |     |    |
| Microtetraspora                                    |    |    |     |     |     |    |     |    |     |     |    |
| Nocardia                                           |    |    |     |     |     |    |     |    |     |     |    |
| Nocardiosis                                        |    |    |     |     |     |    |     |    |     |     |    |
| Nonomuraea                                         |    |    |     |     |     |    |     |    |     |     |    |
| Pseudonocardia                                     |    |    |     |     |     |    |     |    |     |     |    |
| Rhodococcus                                        |    |    |     |     |     |    |     |    |     |     |    |
| Saccharomonospora                                  |    |    |     |     |     |    |     |    |     |     |    |
| Saccharopolyspora                                  |    |    |     |     |     |    |     |    |     |     |    |
| Saccharothrix                                      |    |    |     |     |     |    |     |    |     |     |    |
| Streptoaelliteaus                                  |    |    |     |     |     |    |     |    |     |     |    |
| Streptosporangium                                  |    |    |     |     |     |    |     |    |     |     |    |
| Thermomonospora                                    |    |    |     |     |     |    |     |    |     |     |    |

AG: aminoglycoside; ML: macrolide; AML: ansamacrolide; BLA: β-lactam; PEP: peptide; GP: glycopeptides; ANC: anthracycline; TC: tetracycline; NUC: nucleotide; POL: polyene; QN: quinine: Production

Natural pigments

Several microscopic organisms will just produce their pigments under certain environmental conditions. Different species produce pigment as the colonies age or when a particular nutrient is available in the media. Pigments can help recognize microscopic pigment as the colonies age or when a particular nutrient is under certain environmental conditions. Different species produce pigments that are soluble in fat. To decide this, one can expect some of a pigmented colony and shake it in oil. In the event that the oil becomes pigmented, the pigment is fat soluble. Natural pigments are a superior substitute to chemical dyes utilized in the industries and research centers. Out of the numerous types of Streptomyces available universally in the soil, S. coelicolor and S. violaceoruber produce an important red-blue anti-toxin actinorhodin and associated compounds like α-, β-, ε-, actinorhodin collectively known as Actinorhodin-related "Blue Pigments". These pigments have an extensive variety of utilization in the scientific, medical and industrial sector [102]. Microorganisms can create distinctive colors, for example, those carotenoids, melanins, flavins, quinones, prodigiosins, monacins, violins or indigos. The temperature of the nursery is the primary factor that relies upon the pigment-producing actinomycetes from soil were also described by Selvameenal et al. [112] and the actinomycetes have a potential for pigment-producing activity along with antimicrobial activities. Many industries are using the natural pigment producing actinomycete. The study concluded that actinomycetes have the ability of diffusible pigment-production on different agar media, can open doors for food colors and beverage, in the pharmaceutical industry, and can be included in cosmetic industries.

Biological control

It is well understood that actinomycetes carry out various activities in soil: degradation of organic matter; hindrance or stimulation of different microorganisms and plant; conversion of the chemical compound, for example, herbicides and other horticulturally valuable compound and numerous different activities that can only be estimated [114]. Soil actinomycetes have fluctuating degrees of the inhibitory movement against particular fungi and by and large decrease soil fungal populace [115].

Streptomyces spp. has been appeared to have characteristics, which make them beneficial as biocontrol operators’ soil-borne fungal plant pathogens. These qualities incorporate the production of various sort of secondary metabolites and biologically active substances of high commercial value such as enzymes which degrade the fungal cell divisor straight-forwardly and antibiotics.
They are one of the major contributors to the biological buffering of the soil and have roles in the decomposition of organic matter conducive to crop production [1, 116].

**Plant growth enhancement**

The free-living actinomycetes have been in the improvement of plant development, where that more actinomycetes isolated from the rhizosphere of pine produced B vitamins, since mycorrhizae require these vitamins and are known to upgrade the growth of the plants. It was recommended that actinomycetes may in this indirectly contribute to plant development stimulation [117].

In another investigation, actinomycetes, added to the soil to control black rot of peanuts caused by *Cylindrocladium crotalariae*, did not increase control of the disease, but did, in some cases measurably increase plant development [110].

**Biotechnology**

The consideration given to the actinomycetes in biotechnological applications is a characteristic consequence of the immense metabolic assorted variety of these living beings and their long relationship with the earth and needs of people. Other valuable activities of actinomycetes identified with biotechnology is their gene expression activity which is becoming an active research region [119].

**Waste management**

Wastes from food processing transactions contain the huge measure of starch [120]. Amyloytic actinomycetes may be utilized for bioconversion of such wastes. A few mesophilic streptomycetes strains have been appeared to create amylase that hydrolyse starch and crude starch granules to maltose [121]. The amylases of thermophilic actinomycete have more mercantile potential than those of mesophilic Streptomyces e.g. *Thermoactinomycetes vulgaris* is a good producer of a heat stable, highly active amylase.

Cyanide and other dangerous metals are produced on the industrial scale for use in the metal extraction, electroplating, and steel industry. In nature cyanide can be acclimatized or detoxified by plants. Certain microorganisms likewise can decompose cyanide to formamide, in nature cyanide can be acclimatized or detoxified by plants. Certain microorganisms likewise can decompose cyanide to formamide, certain microorganisms likewise can decompose cyanide to formamide, certain microorganisms likewise can decompose cyanide to formamide.

**CONCLUSION**

Actinomycetes are of great importance since they have the ability to contribute to human well-being through the production of antimicrobial agents and other industrial products like enzymes, drugs and natural pigments. Actinomycetes are at present known to deliver more than 10,000 bioactive compounds, 7,600 of which have been isolated from streptomycetes and 2,500 from non-streptomycetes, prominently from the so-called rare actinomycetes.

**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally

**CONFLICT OF INTERESTS**

Declared none

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Shantaram et al. Int J Pharm Pharm Sci, Vol 11, Issue 5, 11-18
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