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Actinomycetes: Ultimate Potential Source of Bioactive Compounds Production

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ABSTRACT

Every day, increased microbial resistance demands the search for new natural sources that can produce natural and effective antimicrobial compounds. Actinomycetes are attractive microorganisms with an enormous and unlimited potential to produce economically and biotechnologically important metabolites. Approximately 75% of all bioactive compounds produced so far originate from this group of bacteria. Many of these compounds have been successfully isolated and converted into valuable medications and other naturally derived synthetic compounds with antimicrobial and chemotherapeutic properties. The antimicrobial agents produced by this valuable group of prokaryotes were effectively used to rival parasites and other microbes for assets. They include many genera, each with the potential to produce various novel products. For example, one of the leading genera is Streptomyces, which contributes 70% of total antibiotics such as macrolide, aminoglycoside, Rifamycin, Ivermectin, chloramphenicol, and a large number of other medicinally valuable antimicrobial agents. It also includes anticancer agents as well. Similar to Streptomyces, Micromonospora is another major source of antibiotics producing Tetrocarcins, Fortimicins, Antlermicins, Sagamicins, Mutamicins, Verdamicins, Sisomicins, Calicheamicin, and gentamicin. Other rare actinomycetes are potential producers of novel and broad-spectrum antibiotics, including Salinosporamide A, Marinomycin A, Arenimycin, Vancomycin, Abyssomicins, and Proximicins. Due to the expanding studies, data on the production of various metabolites by this unique and outstanding phylum is expanding daily. This review has made an effort to improve the pre-available knowledge on producing and characterizing novel antimicrobial compounds with therapeutic potential from terrestrial and marine actinomycetes.

INTRODUCTION

Over the past three decades, there has been a rise in infections caused by opportunistic microorganisms due to immunocompromising diseases such as organ transplants, tumors, Human immunodeficiency virus (HIV), and other related diseases. Additionally, increasing reports of resistance to existing antimicrobial agents have become a worldwide issue [1]. Antibiotic resistance in pathogenic bacteria is a global problem correlated with morbidity and mortality. Increased multidrug resistance in Gram-negative and -positive pathogenic bacteria has led to difficulty in treatment and even non-treatable infectious diseases with traditional antimicrobial agents. This has prompted the pursuit of novel antibiotic molecules to address this worldwide challenge [2]. Actinomycetes are Gram-positive filamentous bacteria. They are primarily aerobic and possess a high GC content of up to 78% in their DNA. Therefore, they are highly metabolically active microorganisms. They produce metabolic active compounds that are beneficial as nutritional material, antitumor agents, and antimicrobial and immunosuppressive agents [3]. Actinomycetes are a prominent source of natural bioactive compounds. Out of 22,500 metabolites that have been isolated from microbes, 45% belong to this phylum. Among actinomycetes, the genus Streptomyces produces 70% of biologically active metabolites [4]. Actinomycetes have been reported to produce antibiotics of almost every class. Still, few of them are well known, like epoxides, macrolides, β-lactams, peptides, amino-coumarines, aminoglycosides, ansamycines, amino-coumarines, lincosamides and tetracyclines [5]. Natural compounds are the preferred source of antimicrobials with diverse structural and

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chemical properties associated with drug target sites [6]. However, using microbes as a potential cause of biologically active compounds has gained interest in the scientific community for the last two decades. Among microbes, phylum actinobacteria (order-actinomycetales) is a unique and auspicious source of novel and biologically active metabolites with broad-spectrum antimicrobial, anti-tumor activities and also with many other uses [7] (Figure 1).

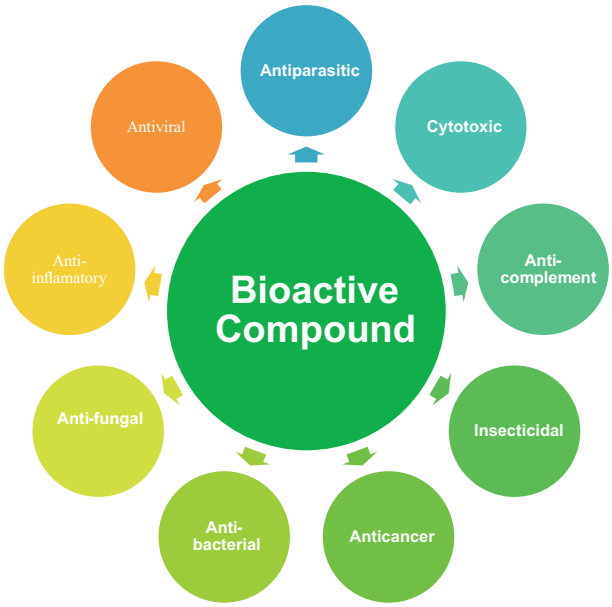

Figure 1: Usefulness of Bioactive Compounds Extracted from Actinomycetes

Approximately 75% of the total bioactive compounds are antitumor agents, immunosuppressive drugs, enzymes, and antibiotics produced by this phylum alone (Table 1).

Table 1: New Novel Bioactive Compounds Extracted from Actinomycetes

Sr. No.	Compounds	Sources	Importance	References
1	Vancomycin	Amycolatopsis Orientalis	Used Against Methicillin-Resistant Staphylococcus Aureus	[8]
2	Tetracycline	Streptomyces Aureofaciens	Inhibits Aminoacyl-TRNA Binding	[9]
3	Chloramphenicol	Streptomyces Venezuelae	Interacts with 50S Subunit, Inhibiting the Activity of Peptidyl Transferase	[10]
4	Erythromycin	Saccaropolyspora Erythraea	Binds with 50S Subunit, Block the Activity of Peptidyl Transferase	[11]
5	Rifampicin	Amycolatopsis Mediterranei	The Main Component of Anti-Tuberculosis Therapy	[12]
6	Novobiocin	Streptomyces Niveus	Inhibits Bacterial DNA Gyrase	[13]
7	Diazepinomicin	Micromonospora Strains	Anticancer Agent Used In Phase II	[14]
8	Salinosporamide A	Salinispora Tropica	Anticancer Agent	[15]
9	FK 506	Streptomyces Tsukubaensis	Antiviral Agent	[16]
10	Ivermectin	Streptomyces Avermitilis	Used to Treat Nematode Infections	[17]
11	Medecamycin	Streptomyces Mycarofaciens	Antibacterial	[18]
12	Rhamnose	Saccharopolyspora Spinosa	Essential Components of Insect Control Agents Like Spinosad	[19]
13	Streptomycin	Streptomyces Sp.	Antibacterial	[20]
14	Lajollamycin	Streptomyces Nodosus	Antibacterial	[21]
15	Amphotericin B	S. Nodosus	Anti-Fungal	[22]
16	Avermictin	Streptomyces Sp.	Antiparasitic	[23]
17	Anthracyclines	Streptomyces Sp.	Anticancer	[24]
18	Chloramphenicol	S. Venezuelae	Antibacterial	[25]
19	Amythiamicins	Amycolatopsis Sp.	Antibacterial	[26]
20	Meilingmycin	Streptomyces Nanchangensis	Antiparasitic	[27]
21	Nanchangmycin	S. Nanchangensis	Insecticidal	[28]
22	Eremomycin	A. Orientalis Sub Sp. Eremomycini	Antibacterial	[29]
23	Daptomycin (Commercialized As Cubicin)	Streptomyces Roseosporus	Antibacterial	[30]
24	Mithramycin	Streptomyces Argillaceus	Anticancer	[31]
25	Aclacinomycin A (Aclarubicin)	Streptomyces Galilaeus	Anti-Cancer	[32]
26	Tetracycline	S. Aureofaciens	Antibacterial	[33]

These bioactive compounds have different modes of action [34] (Figure 2).

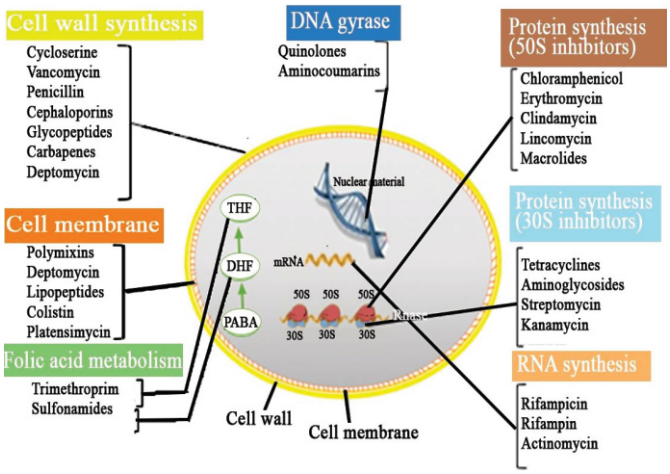

Figure 2: Mode of Action of Most Antibacterial Bioactive Compounds

Actinomycetes exhibit diverse habitats and are found in extreme environments like glaciers, hot springs, and high salt concentrations [35], but are commonly found in soil, marine water, and freshwater and also found as symbiotic

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organisms. Their association with different plants, animals and other organisms has been observed. However, they are categorized as marine or terrestrial based on the ecosystem in which they exist [36]. Terrestrial actinomycetes are commonly called soil actinomycetes. In soil, actinobacteria constitute a significant portion of microbes. According to a rough estimate, approximately 1 million actinomycetes may be obtained from one gram of soil [37]. They play an important role in soil biodegradation, humus formation, nutrient cycles, and inhibit the growth of many plant pathogens in the soil [38]. In contrast, soil actinomycetes have produced a wide variety of novel antibiotics. About 70% of total antibiotics are produced by soil actinomycetes [39]. Actinomycetes, isolated from marine ecosystems, have shown tolerance against NaCl up to 13%, which is very much as compared to actinomycetes isolated from terrestrial environments, which shows no tolerance to this concentration [40]. Moreover, actinomycetes, which were isolated from marine ecosystems, are metabolically more active than terrestrial ones. This is an exclusive adaptation of marine actinomycetes [41]. To understand this unique adaptation of marine actinomycetes, scientists started working on genomic sequencing of these bacteria. Genome sequencing of many novel marine actinomycetes has led to understanding this type of adaptation of marine actinomycetes. It also helped to discover their biosynthetic potential, and it discovered many new broad-spectrum antibiotics [42]. Marine actinomycetes are an attractive source of interesting research and bioactive compounds for most active researchers [43]. The actinomycetes isolated from marine environments have a broad spectrum of antimicrobial activities, including antifungal, antibiotic, toxic, neurotoxic, cytotoxic, antimitotic, antiviral, and antineoplastic. Recently, scientists started considering marine actinomycetes as an admirable probiotic source because marine actinomycetes also showed excellent antibiotic activity against various fatal pathogenic bacteria like Vibrio SP [44]. Study shows compounds extracted from marine actinomycetes with their importance and chemical groups. This is why scientists are now focusing more on marine actinomycetes to extract novel and broad-spectrum bioactive compounds (Table 2).

Table 2: Important Bioactive Compounds Extracted from Marine Actinomycetes

Sr. No.	Compounds	Chemical Form	Significance	Source	References
1	2-Allyloxyphenol	Allyloxyphenol	Antimicrobial Properties: Used in Food Preservation and Oral Disinfection	Derived From Streptomyces Sp.	[45]
2	Glaciapyrroles A, B, and C	Pyrrolosesquiterpenes	Effective Against Bacterial Strains	Isolated From Streptomyces Sp.	[46]
3	Lodopyridone	Alkaloid	Exhibits Antitumor Activity	Found In Saccharomonospora Sp.	[47]
4	Neomarinone	Sesquiterpene	Demonstrates Cytotoxic Effects	Strain CNH099	[48]
5	Saliniketal A, Saliniketal B	Polyketide	Potential in Anticancer Applications	Sourced From Salinispora Arenicola	[49]
6	Abyssomicin C	Polyketide	Known for Antibacterial Capabilities	Found In Verrucosispora	[50]
7	Daryamides	Polyketide	Effective in Anticancer and Antifungal Roles	Originates From Streptomyces Sp.	[51]
8	Actinofuranones A and B	Polyketide	Shows Cytotoxic Activity	Extracted From Streptomyces Sp.	[52]
9	Mechercharmycins	Peptide	Known for Antitumor Effects	Found In Thermoactinomyces Sp.	[53]
10	Saliniketal	Polyketide	Cancer Prevention Potential	From S. Arenicola	[54]
11	Arenimycin	Peptide	Dual Application as an Antimicrobial and Anticancer Agent	From S. Arenicola	[55]
12	Piperazimycins	Peptide	Useful in Cancer Therapy	Derived from Streptomyces Sp.	[53]
13	Dehydroxynocardamine and Desmethyleny-Inocardamine	Peptide	Inhibits Enzyme Sortase B	Sourced from Streptomyces Sp.	[56]
14	Tirandamycins	Dienoyl	Effective Antibacterial Agent	Produced by Streptomyces Sp.	[57]
15	Xanthone IB-00208	Polycyclic	Dual Role: Anticancer and Antibacterial	Isolated from Actinomadura	[58]
16	Piericidins C7 And C8	Piericidin	Known for Anticancer Properties	Found in Streptomyces Sp.	[59]
17	Resistomycin	Quinone	Exhibits Antimicrobial Activity	From Streptomyces Corchorusii AUBN (1) / 7	[60]
18	Proximicins	Aminofuran	Dual Role: Antibacterial and Anticancer	Found in Verrucosispora Sp.	[53]
19	Helquinoline	Quinone	Effective As An Antibacterial Agent	Found in Janibacter Limosus	[61]

Tunicamycin is a bioactive compound isolated from Streptomyces lavendulae DUT 11, a marine actinomycete that showed admirable anti-gastric cancer and breast cancer activity. Both types represent the most significant contributors to cancer-related deaths in the USA and are the most prevalent cause of cancer-related fatalities

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globally [62]. Tunicamycin accumulates unfolded protein in the lumen of the endoplasmic reticulum, thus reducing ER stress. It increases the level of nuclear translocation and CHOP protein expression, suppresses proliferation, reduces invasion, and leads to cell death [63, 64] (Figure 3).

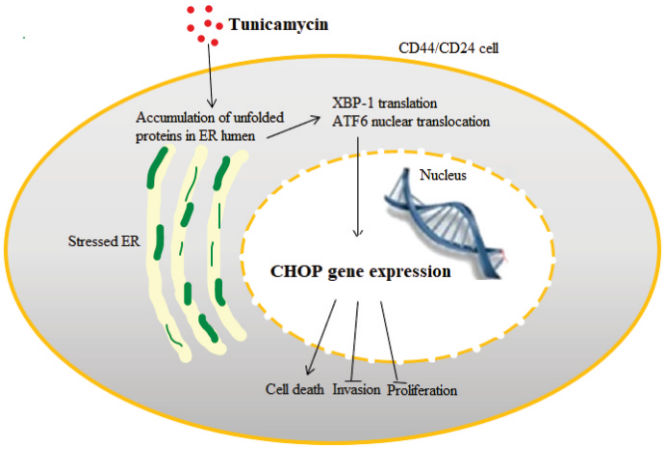

Figure 3: Mechanism of Action of Tunicamycin [65]

Caboxamycin was extracted from Streptomyces sp. NTK937, an obligate marine bacterium. Caboxamycin is a bioactive compound that belongs to the chemical group benzoxazole [66]. This bioactive compound shows potent activity against many pathogenic bacteria, including Staphylococcus lentus, Xanthomas campetris, Staphylococcus epidermis, etc. It also shows activity against the yeast Candida glabrata and the biofilm of Staphylococcus xybsus [67]. Abyssomicin C was identified from marine Verrucosispora sp. in 2004. It dramatically inhibited the synthesis of para-aminobenzoic acid (PABA). PABA is a key factor required for the biosynthesis of folic acid in prokaryotic cells [68]. Abyssomicin C demonstrates significant antibacterial efficacy against methicillin-resistant S. aureus (MRSA) and mycobacteria, which cause tuberculosis by targeting PABA synthesis. Abyssomicin C led to the discovery of next-generation antifolates and first-generation PABA inhibitors [69]. Mechercharmycin A and B were extracted from Thermoactinomyces sp. YM3-251, which is marine-derived. Mechercharmycin A has shown potent antitumor activity and cytotoxic action against human leukaemia and lung cancer, while mechercharmycin B is a linear congener. Crystallographic studies have shown that it is a cyclic peptide that contains four oxazoles and thiazole groups [70]. Pseudopterogorgia, isolated from marine Pseudopterogorgia elisabethae, was found to show intense, potent activity against Mycobacterium tuberculosis. M. tuberculosis is the well-known causative agent of TB. This disease always remains a global threat to the human population and leads to 2 million deaths and more than 9 million infections annually all over the world. Many studies have already reported that Pseudopterogorgia showed potent activity against vancomycin-resistant Enterococcus faecium (VRE) and methicillin-resistant S. aureus (MRSA) bacteria [71]. There are many genera in the phylum of actinobacteria producing novel bioactive compounds, which include Gulosibacter, Actinomadura, Actinomyces, Atopobium, Amycolatopsis, Actinobaculum, Micromonospora, Actinokineospora, Streptomyces, Kitasatospora, Salinispora, Actinomadura [72]. Study shows various genera and the quantity of new bioactive substances extracted from them (Table 3).

Table 3: Different Genera with Several Novel Bioactive Compounds [36]

Actinomycetales Genera	No. of Novel Antibiotics	Actinomycetales Genera	No. of Novel Antibiotics
Streptomyces	8,000	Actinomodura	345
Streptoverticillium	258	Saccharothrix	68
Kitasatosporia	37	Microbiospora	54
Thermoactinomyces	14	Actinosynnema	51
Microellobosporia	11	Micromonospora	740
Microtetraspora/ Nonomuria	26/21	Chainia	30
Actinoplanes	248	Thermomonospora	19
Dactylosporangium	58	Micropolyspora/Faenia	13/3
Saccharopolyspora	131	Nocardiopsis	41
Amycalotopsis/Nocardia	120/357	Nocordia	357
Kibdillosporangium	34	Mycobacterium	57
Psoudonocardia	27	Arthrobacter	25
Amycolata	12	Brevibacterium	17
Streptosporangium	79	Proactinomyces	14
Streptoalloteichus	79	Rhodococcus	13
Spirilospora	11	Actinosporangium	30
Planobispora	10	Microellobosporia	11

Streptomyces is the largest genus of phylum actinomycetes and is known for its novel biological compound production. Among various broad-spectrum antimicrobial compounds, over 70% of bioactive compounds have been isolated from the genus Streptomyces [73]. Many of these compounds have been reported to be important vitamins, alkaloids, and antibiotics. Streptomyces is the only prolific producer of novel biologically active compounds. These compounds include antimicrobial, anti-infective, anticancer agents, antiparasitic, antitumor, antifungals, antivirals, anti-hypertensives, and other critical medicinal compounds [74]. Similarly, Streptomyces nouseri produces nystatin, S. venezuelae produces chloramphenicol, Streptomyces fradiae produces neomycin, Streptomyces peucetius produces Amrubicin, and S. griseus produces streptomycin [75]. Tetracycline is a family of antibiotics that was first discovered in 1940. The application demonstrated efficacy against a range of microorganisms, including both Gram-positive and Gram-negative bacteria, as well as mycoplasmas, chlamydiae, rickettsia, and

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protozoan parasites [76]. Due to its broad-spectrum antimicrobial nature, tetracycline inhibits the protein synthesis mediated by binding with 30S bacterial ribosome. There are many reports that most pathogens have developed resistance to tetracycline [77]. To solve this problem, second-generation (such as minocycline) and third-generation (such as glycylcyclines) antibiotics have been developed [33]. A minocycline derivative, the tigecycline, was isolated from S. aureofaciens. Tigecycline is a novel antimicrobial agent against multidrug-resistant (MDR) pathogens [78]. These include strains resistant to methicillin, such as S. aureus, and those resistant to vancomycin, like enterococci. Tigecycline is structurally related to tetracycline and acts by inhibiting the protein translation in microbes [79]. Erythromycin is another broad-spectrum antibiotic from the genus Streptomyces, which exhibits activity against Gram-negative and Gram-positive bacteria [80]. It consists of a macrocyclic lactam ring to which compounds of sugar and amino are attached. Erythromycin is an alternative to Penicillin and Cephalosporins to treat infections, particularly those caused by β-hemolytic streptococci and pneumococci [81, 82]. Following Streptomyces, Micromonospora is regarded as the second most significant potential source of bioactive chemicals with therapeutic relevance. Out of these compounds, Maximum is aminoglycoside antibiotics. The aminoglycoside group includes mutamicin, neomycin B, gentamicin, fortimicin, antibiotic G-418, antibiotics JI-20, tetrocarcins, calicheamicins, sisomicin, verdamicin, antlermicins, and sagamicin [83, 84]. These medications have been utilized against Gram-positive and Gram-negative bacteria and are bactericidal as opposed to bacteriostatic action. These are also used against eukaryotic organisms, e.g., Protozoa. Another common type of antibiotic is the macrolide, which consists of a 16-, 15-, or 14-membered lactone ring linked to de-oxy sugars such as cladinose and desosamine. The antibacterial spectrum of macrolides is similar to penicillin. It is broad-spectrum; thus, it can be recommended to patients with penicillin allergy to illnesses such as soft-tissue infections and respiratory tract [85, 86]. Gentamicin (GM), which Micromonospora produces, was discovered in 1963 and first introduced into parenteral usage in 1971. Gentamicin is a broad-spectrum aminoglycoside antibiotic. This medication is frequently used to treat pelvic inflammatory disease, intra-abdominal infections, complicated infections, urinary tract infections, sepsis, endocarditis, affecting the skin, bones, and soft tissues, along with other severe infections induced by Gram-negative bacteria [87]. Tetrocarcinsis is a family of novel antibiotics that were isolated from Micromonospora chalcea. The findings demonstrated remarkable efficacy against Gram-positive bacteria and significant antitumor effects through various mechanisms of action. Recent studies have revealed that Tetrocarcins have a unique polycyclic aglycone (tetronolide) that functions in a trans-decalin system and also has tetronate moiety spiro-linked with a cyclohexane ring, which acts by inducing apoptosis in various cancerous cells [88]. Fortimicin is another broad-spectrum antibiotic from the class aminoglycoside. It was extracted from Micromonospora olivasterosporain in 1977. The mechanism works by binding to the 16S rRNA subunit of the 30S bacterial ribosome, thereby inhibiting prokaryotic protein synthesis and preventing the dissociation of 70S ribosomes. This antibiotic is effective against a broad spectrum of Gram-negative and Gram-positive infections [89, 90]. Calicheamicins is known as a novel family of antitumor agents. These compounds exhibit cytotoxic properties and were extracted from Micromonospora echinospora. They show a potency that is at least 1000-fold more significant than that of conventional cytotoxic chemotherapeutics. Calicheamicins bind with DNA in the minor groove, causing double-strand DNA to break, thus leading to cell death, and are more specific in their action than other antitumor agents [31]. Over time, the discovery rate of new novel antibiotics from Streptomyces has decreased; about 70% of antibiotics have been isolated from this genus alone, as discussed earlier. So, it is time to search for novel antibiotics from non-Streptomyces actinomycetes. Uncommon actinomycetes are the strains of the phylum actinomycetes isolated much less frequently than Streptomyces when employing conventional methods [75]. Recently rare actinomycetes are considered excellent potential sources of novel biologically active metabolites. The rare actinomycetes present significant challenges in isolation and cultivation and may possess unique potential for producing novel biologically active metabolites. Until 2005, the exploration for new antimicrobial compounds from rare actinomycetes resulted in the identification of over 2250 novel antimicrobial compounds [91]. Some genera of rare actinomycetes are Marinispora, Actinomadura, Actinoalloteichus, Actinoplanes, Amycolatopsis, Actinokineospora, Acrocarpospora, Actinosynnema, Catenuloplanes, Cryptosporangium, Dactylosporangium, Kibdelosporangium, Kineosporia, Kutzneria, Micro-bispora, Micro-tetraspora, Nocardia, Nonomuraea, Planomonospora, Planobispora, Pseudonocardia, Saccharomonospora, Saccharopolyspora, Saccharothrix, Salinispora, Streptosporangium, Spirilliplanes, Termomonospora, Termobifda, and Virgosporangium [3].

CONCLUSIONS

It was concluded that actinomycetes are a great source of antibiotics. About 45% of the biologically active compounds belong to actinomycetes. Actinomycetes are

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found everywhere in the biosphere. But they are categorized as terrestrial and marine actinomycetes. This is a large bacterial phylum which has more than 30 genera. Some of the actinobacterial genera are prominent like Streptomyces and other genera are known as rare actinomycetes. Almost all actinobacterial genera are known for producing biologically active compounds but Streptomyces are producing about 70% of total compounds that are discovered and isolated from actinomycetes.

Authors Contribution

Conceptualization: NM
Methodology: HK
Formal analysis: HK, NM
Writing review and editing: AT, HJ, RM, IL

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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