Review

Biodiversity of Secondary Metabolites Compounds Isolated from Phylum Actinobacteria and Its Therapeutic Applications

Muhammad Mohammed Al-shaibani 1,2, Radin Maya Saphira Radin Mohamed 1,*, Nik Marzuki Sidik 3,*, Hesham Ali El Enshasy 4,5, Adel Al-Gheethi 1,*, Efqan Noman 6, Nabil Ali Al-Mekhlafi 7, and Noraziah Mohamad Zin 2

Abstract: The current review aims to summarise the biodiversity and biosynthesis of novel secondary metabolites compounds, of the phylum Actinobacteria and the diverse range of secondary metabolites produced that vary depending on its ecological environments they inhabit. Actinobacteria creates a wide range of bioactive substances that can be of great value to public health and the pharmaceutical industry. The literature analysis process for this review was conducted using the VOSviewer software tool to visualise the bibliometric networks of the most relevant databases from the Scopus database in the period between 2010 and 22 March 2021. Screening and exploring the available literature relating to the extreme environments and ecosystems that Actinobacteria inhabit aims to identify new strains of this major microorganisms, producing unique novel bioactive compounds. The knowledge gained from these studies is intended to encourage scientists in the natural product discovery field to identify and characterise novel strains containing various bioactive gene clusters with potential clinical applications. It is evident that Actinobacteria adapted to survive in extreme environments represent an important source of a wide range of bioactive compounds. Actinobacteria have a large number of secondary metabolite biosynthetic gene clusters. They can synthesise thousands of subordinate metabolites with different biological actions such as anti-bacterial, anti-parasitic, anti-fungal, anti-virus, anti-cancer and growth-promoting compounds. These are highly significant economically due to their potential applications in the food, nutrition and health industries and thus support our communities’ well-being.

Keywords: microbial ecology; aquatic and marine environments; drug-resistant pathogens; Streptomyces; natural products; VOSviewer software

1. Introduction

Global demand for new chemotherapeutic compounds and antibiotics with high bioactivity and low toxicity has increased recently due to the emergence of life-threatening
microorganisms and multidrug resistance agents among viruses, bacteria and fungi [1]. Additionally, the detection of secondary metabolites molecules with unique modes of action established various therapeutic agents’ strategies for treating many illnesses [2]. To be more specific, endophytic Actinobacteria are microorganisms that represent a new production source of a large number of secondary metabolites, including alkaloids, beta-lactams, sulfonamides, aminoglycosides, glycopeptides, siderophores, quorum-sensing molecules, immunosuppressants, polypeptide macrolides, saccharides, pyrazolo Isoquinolinones, butenolides, nucleosides and degradative enzymes [3]. In fact, it has been reported that more than 10,000 various bioactive compounds have been discovered from Actinobacteria [4].

Endophytic microbes refer to a group of microorganisms, mostly fungi and bacteria, that exist in the host plant’s intracellular space. It usually causes no obvious harmful effect or symptoms of the disease and could produce various associations such as trophobiotic communalistic, mutualistic and symbiotic co-existence [5]. Endophytes in woody plant hosts could exist within host tissues and protect host plants against herbivores and other pathogenic microorganisms [6]. Actinobacteria are a microbial genus of the most antibiotic-producing bacteria with high guanine and cytosine (G + C) content in their genomes, and they are classified into 6 classes, 79 families of 46 orders and 10 fresh families of 16 new orders based on phylogeny using 16S rRNA sequences. The Actinobacterial classes consist of Thermoleophilia, Rubrobacteria, Nitriliruptoria, Coriobacteria, Actinomycetia and Acidomicrobia Salamet. et. al., [7]. Actinobacteria have ubiquitous characteristics. They are present in diverse ecosystems on the earth such as endophytically with plants and in terrestrial and aquatic environments. An abundance of Actinobacteria species have been recorded in ordinary, extraordinary and extreme environments with high or low temperatures, high radiation, acidic/alkaline pH, salinity, low levels of available moisture and nutrients [8].

The genus Streptomyces is a Gram-positive bacteria. It is the largest genus of the phylum Actinobacteria, which has complex growth and can produce various secondary metabolites [8]. In addition, there are more than 800 Streptomyces species that have been found to date (see http://www.bacterio.net/Streptomyces.html (accessed on 20 August 2020)) [9]. Streptomyces is the major microbial genus of the most antibiotic-producing bacteria in the microbial world discovered so far, where streptomycin, gentamycin, rifamycin, chloramphenicol and erythromycin are produced by Streptomyces [10].

Actinobacteria have a large number of secondary metabolite biosynthetic gene clusters. Biosynthetic gene clusters (BGCs) are known as genes comprising locally clustered groups encoding a secondary metabolite biosynthetic pathway. In addition, BGCs contain genes encoding all enzymes required to produce secondary metabolites and pathway-specific regulatory genes. The Actinobacteria have diverse physiology and metabolic flexibility with high potential to produce novel bioactive compounds and enzyme production [11].

The current review aims to summarise the biodiversity, biosynthesis of novel bioactive secondary metabolites, detection of new resources, and strategies to search for potential bioactive compounds producers. In addition, it aims to determine the effects of environments and ecosystem on the phylum Actinobacteria that produce potential bioactive compounds in the pharmaceutical industry market. The VOSviewer software tool was used to visualise bibliometric networks to support Scopus’s prevalent bibliographic databases. This information would be helpful to other scholars who attempt to discover and isolate specific bioactive compounds from phylum Actinobacteria under different ecosystems. Besides their utilisation by people, the perception of the function and distribution of microbial products is regarded as significant to understand microbial families and their impact on biogeochemical cycles.
2. Methods and Protocol

2.1. Study Design and Search Strategy

The methodology of this review was conducted as demonstrated in Figure 1. The process involved six main steps: Step 1 was an identification of the target articles through the Scopus database in the period between 2010 and 22 March 2021 using the general keywords “Actinomycetes” OR “Actinobacteria,” OR “Streptomyces.” The number of articles obtained was n = 70,618. In Step 2, the resulting articles were further screened using more specific keywords, including “Natural Products” OR “Secondary Metabolites” (n = 15,141). Then, in Step 3, from that number of articles, further screening was carried out using more specific keywords, which included antibiotics, anti-fungal, anti-cancer, anti-parasitic, “antimalarial,” OR anti-inflammatory (n = 13,041). In Step 4, from the preceding number of articles, screening was implemented using more precise keywords, such as endophytic, thermophilic, halophilic OR marine (n = 5435 was extracted). Subsequently, in Step 5, from the total number of articles, further screening was considered using more specific keywords, including “mechanism of action” OR “mode of action” (n = 985). Finally, in Step 6, from these articles, the final screening was executed using more specific keywords “drug-resistance” OR “resistant”. The number of articles based on keywords is (n = 436), extracted studies based on related titles was n = 336; reviewed studies out of limitations were n = 31; records excluded based on the validity of the study data and clear contributions were n = 260, and out of limitations were n = 46. Finally, the number of studies included in this review was n = 116. A review scheme was conducted to determine all research documents published only in the English language, presented in Figure 1.

![Figure 1](image_url)
2.2. Data Analysis

The VOSviewer software was used to visualise the bibliometric networks to build assistance for common bibliographic databases from the Scopus database. The most important journals, articles, authors, organisations and states among such articles were identified. Besides this, bibliographic coupling and most utilised keywords in the abstracts with keywords and titles were identified.

The majority of diversity keywords from the reviewed and cited papers based on the Scopus database were *Streptomyces*, Actinobacteria, natural products, primary, secondary metabolites, habitat effects of environments, pharmaceutical industry, as shown in Figure 2A.

This analysis includes diverse secondary metabolite molecules induced by environmental factors such as antibiotic agents, biological products, antineoplastic agent, antifungal, and agent with antimalarial activity, as shown in Figure 2B. The reviewed and cited papers based on the scattered keywords of the antimicrobial isolated from 2010 to 2021 from phylum Actinobacteria were vancomycin, polyketide, tetracycline, cyclopentide, erythromycin, streptomycin, macrolides and amphotericin B, as represented in Figure S1. The percentage of keywords diversification from the Scopus database for *Streptomyces*, Actinobacteria, natural products, primary, secondary metabolites, habitat effects of environments, pharmaceutical industry and anti-infective agents occurrence using VOSviewer software tool to analyse and visualise scientific literature is shown in Figures S2 and S3. The most reviewed and cited papers based on the scattered keywords of the countries for the publication and citation were USA (46 %), UK and India (13% each), Germany (11%), China (6%) and Thailand (3%), while KSA, Egypt, Pakistan, Malaysia had only 2% each, as shown in Figures 2C and S4.
3. Primary and Secondary Metabolites Natural Products

Actinobacteria synthesise diverse metabolite molecules that have key roles in their heterogeneous and complex microenvironments. Natural products, also known as secondary metabolites, are useful compounds developed by microbes. These are not usually needed for natural cell development, but they provide advantages to the cells in other
ways [12]. Such compounds could play roles in inhibition, communication, nutrient acquisition, or other associations with nearby environments or organisms.

Natural products have been utilised for a long time. In fact, the Chinese are amongst users of traditional medicines with more than five thousand plants and microbes’ products in their pharmacopoeia [13]. Therapeutic plant species have been, and are still being, used in traditional medicine in several countries [12]. Primary metabolites are chemicals required for ordinary growth, development and reproduction of organisms as well as maintenance of cellular function, representing the key role in the survival of organisms. Besides this, the primary metabolite plays an active role in the anabolic and catabolic processes in many organisms or cells [14]. The secondary metabolites are substances formed during the end or near the stationary stage of organisms’ development. They are very significant for nutrition and health and are, therefore, economically important [14]. Even though they serve different survival actions in nature, they do not necessarily play a critical role in the growth and development of the organism producing them [15].

4. History of Isolation of Secondary Metabolites from Actinobacteria

Historically, in (1940), Waksman and Woodruff isolated actinomycin D from soil bacteria [16]. Then, Schatz et al. in 1944 [17] isolated streptomycin, an effective antibiotic against tuberculosis. Furthermore, hundreds of various antibiotics were reported from the genus Streptomyces [18]. Actinobacteria are among the secondary metabolites producers and hold high pharmacological and commercial interest. It has great capability to produce secondary metabolites such as immunomodulators [19], antibiotics [20], anti-cancer drugs [21], growth factors [22], anthelmintic enzymes and herbicides [23]. Supplementary Table S1 describes the historical isolation of bioactive compounds from Actinobacteria from the first isolation by Selman Waksman [20].

Several anti-fungal, anti-parasitic, bioactive compounds, growth-promoting compounds and anti-cancer compounds with their chemical classification and application isolated from Actinobacteria and Streptomyces sp. are represented in Supplementary Table S2. The molecular structures of several bioactive compounds isolated from Actinobacteria and Streptomyces are demonstrated in Figures 3–5.
Figure 3. The molecular structure of Actinomycin D; Streptomycin; Gramicidin; Cephamycin C; Fumaramidmycin; and Crisamicins C.
Figure 4. The molecular structure of Simocyclinones D4 and D8; Fistupyrone; Streptocidins A–D; Cedarmycin A and B.
5. Microbial Ecology of Actinobacteria

The diversity of Actinobacteria has been investigated in several special or extreme environments, such as Actinobacteria in terrestrial environments, Actinobacteria in aquatic and marine environments, and thermophilic as well as alkaliphilic and haloalkaliphilic Actinobacteria.

5.1. Actinobacteria in Terrestrial Environments

Terrestrial Actinobacteria have several antimicrobial capabilities, including three active compounds determined as 2,3-heptanediode, butyl propyl ester and cyclohexane with an antimalarial activity isolated from *Streptomyces Suk 08* [24].
The diketopiperazines compounds and chloramphenicol were isolated from *Streptomyces* SUK 25 isolated from the *Zingiber spectabile* plant in Malaysia [25]. Meanwhile, *Streptomyces* sp. CAH29 isolated from the rhizosphere environment can produce tetracycline, possessing potent anti-bacterial and anti-fungal action against *Candida albicans*, methicillin-resistant *Staphylococcus aureus*, *Streptococcus pyogenes* and *Staphylococcus aureus* having 14, 10, 12 and 8 mm inhibition zones, respectively [26]. Besides this, the isolate revealed a marked anti-tumour action with 1.1 μg/mL and IC50 3.3 against colorectal (HCT116) and hepatocellular (HepG2) carcinoma cell lines, respectively [27]. Actinomycin D, which has anti-tumour and anti-bacterial activity, was extracted from *Streptosporangium* sp. (AI-21) at Hardwar district in Uttarakhand state, India [28]. The list of the terrestrial and rhizosphere Actinobacteria isolation and screening for their antimicrobial activity are shown in Table S3.

### 5.2. Actinobacteria in Aquatic and Marine Environments

Marine Actinobacteria are abundant sources for marine drug discovery causal for many bioactive compounds of biomedical appearance. Almost 30 strains of actinomycetes were separated and determined from various families of genus *Streptomyces*. The *Streptomyces* isolates of M93, W108, W38, M72, M71 and M1 are amongst all the chosen strains revealed to show potent antimicrobial action against the multidrug-resistant bacteria (MDRB) [29]. Furthermore, antitumor compounds produced by marine Actinobacteria is reported [30]. Moreover, antimalarial activity was also described from marine Actinobacteria as bioactive compounds [28]. Additionally, from freshwater sediments, 84 Actinobacteria were separated and isolated into a prevalent genus *Streptomyces* as well as eight uncommon genera such as *Micrococcus*, *Kocuria*, *Nocardiosis*, *Promicromonospora*, *Saccharopolyspora*, *Amycolatopsis*, *Prauserella*, and *Rhodococcus*. All strains revealed significant inhibition potentials against yeast pathogens, Gram-negative bacteria and Gram-positive bacteria [5].

Moreover, *Saccharopolyspora* sp. IMA1 was separated from the coral reef environment. Its metabolites existed in aquatic bacterial pathogens *Vibrio vulnificus*, *Vibrio para-hemolyticus* and *Vibrio harveyi*. The IMA1 crude extract revealed excellent antioxidant activity, where 2,2’-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS) has a radical scavenging activity [31]. Almost 52 strains of Actinobacteria were isolated from the marine sediment of the Portuguese coast. The isolates’ greatest fraction were from the genus *Micromonaspora*, from which six *Streptomyces* strains were active against *Candida. albicans*, with minimum inhibitory concentration (MIC) values ranging from 3.90 to 125 μg mL⁻¹ [2].

The list of bioactive compounds isolated from aquatic and marine Actinobacteria are demonstrated in Table 1.

### Table 1. List of bioactive compounds, producers, source of isolation and screening for their bioactivity isolated from aquatic and marine Actinobacteria.

| Bioactive Compound | Producer | Chemical Group | Bioactivity | Source of Isolation | References |
|--------------------|----------|----------------|-------------|---------------------|------------|
| Unknown            | M72, M1, M71, W38, W108 and M93 | N/A | Anti-bacterial | Chenab River Sediments | [29] |
| Lycamycins, spir- | *Streptomyces* sp. | Bisindle pyrrole | Anti-bacterial | Deep sea marine sediment | [32] |
| roindimicins       |          |                |             |                     |            |
| Anandins           | *Streptomyces anandii* | Steroidal Alkaloids | Cytotoxic | Marine sediments from mangrove zone | [33] |
| Paulomycin G       | *Micromonaspora matsuno- | Paulomycin derivatives | Anti-tumor properties | Deep sea marine sediment | [34] |
|                     | matoense |                |             |                     |            |
| Rifamycin B        | *Salinispora* sp. | Polyketides | Anti-bacterial | Sediment | [35] |
| Manzamine A        | *Micromonaspora* sp. | Alkaloid | Antimalarial | Symbiont to sponge Acan-thostrongylophora | [36] |
| Violapyrone B      | *Streptomyces somalicensis* | *a*-pyrone | Anti-bacterial | Deep sea marine sediment | [37] |

Abbreviation: S. = (*Streptomyces*), N/A ; not applicable.
5.3. Thermophilic Actinobacteria

Thermophilic Actinobacteria can withstand temperatures in the range of 40–80 °C [8]. They thrive on organic debris that has decomposed (dead plant and animal materials). Thermophilic Actinobacteria are divided into two types: moderately thermophilic and strictly thermophilic. Certain strains of moderately thermophilic Actinobacteria may develop at temperatures ranging from 37 to 65 °C, whereas some grow between 28 and 60 °C and require 45–55 °C for maximal growth. However, maximum proliferation happens at 55–60 °C.

Thermotolerant Actinobacteria, on the other hand, can withstand temperatures as high as 50 °C [38]. Determining fresh bioactive compounds from taxonomically sole strains of extremotrophic or extremophilic Actinobacteria resulted in the anticipation that mining such groups might provide an alternate dimension to the route of subordinate metabolite resources [39]. Thermotolerant and thermophilic Actinobacteria are unique for having specific metabolic rates and physical features, which are useful in several ecological functions. It was also reported that thermotolerant Actinobacteria like Streptosporangium sp., S. Ianatus, S. Coeruleorubidis, S. Toxytricini and Streptomyces Tauricus, are claimed to inhibit the rhizosphere of several plants in the Kuwait desert during hot seasons [11]. Thermophilic Actinobacteria have not been widely investigated. However, they have developed significant antibiotics like thermomycin from Streptomyces Thermophilus and anthracyclin, an anti-tumour drug created by Streptomyces Refuineus [40].

The Streptomyces strain Al-Dhabi-2 found in Saudi Arabia’s thermophilic region indicated antimicrobial capabilities against pathogenic microorganism [41]. Three strains identified as DJT 15 Streptomyces Thermoviolaceus subsap aptingens, DJT 32 Saccharomonospora Viridis, and DJT 36 Saccharomonospora Glauca exposed inhibitory activity in bioassays with respect to the Enterobacter species (ESKAPE) pathogens, Pseudomonas aeruginosa, Acinetobacter baumannii Klebsiella Pneumoniae, Staphylococcus Aureus and Enterococcus Faecium. Apart from that, DJT 32 and 36 prevented the growth of Aspergillus Fumigatus, a filamentous fungus isolated from the same compost. Azole-resistant human pathogenic strains of Aspergillus Fumigatus were also shown to be inhibited by strain DJT 32 [42].

5.4. Alkaliphilic and Haloalkaliphilic Actinobacteria

An alkaliphilic and mildly halophilic bacterial strain develops optimally at pH ranging from 9.0 to 10.0, with 5–7% (w/v) NaCl [43]. Haloalkaliphilic Actinobacteria Actinobacteria are found in pristine coastal habitat in the saline soil. These unique Actinobacteria Actinobacteria are hereditarily different, developing at high salt concentrations [44]. Alkaliphilic Actinobacteria Actinobacteria are, thus, classified into three main categories: alkali-tolerant Actinobacteria Actinobacteria (developed in the pH range between 6 and 11, abstemiously alkaliphilic (developed in a pH ranging from 7 to 10 but display weak development at pH 7.0), and alkaliphilic (grow optimally at pH 10–11) [11].

Moreover, Streptomyces Clavuligerus (strain Mit-1) was isolated from Mithapur (Western Coast, Gujarat, India) and is described as a salt-tolerant alkaliphilic actinomycete. Note that this strain secreted alkaline protease [45]. Besides this, Thakrar et al. [46] issued the capability to produce protease from the two halo-tolerant and alkaliphilic actinomycetes extracted from the salt-enriched soil of Coastal Gujarat in India. These strains are identified as Nocardiosis Alba OM-4 and Nocardiosis Alba TATA-13. In addition, the phylogeny and multiplicity of the haloalkaliphilic Actinobacteria Actinobacteria study represent a concise and comprehensive account utilising conventional and molecular techniques. This includes the occurrence and cultivation of the marine actinomycetes from the seawater and sediments of pristine coastal habitat in Gujarat (India).

They found that the Actinobacteria Actinobacteria belonged to Prauseria, Streptomyces, Brachybacterium and Nocardiosis [47]. Besides this, the multiplicity of alkali tolerant Actinobacteria Actinobacteria in numerous soils is gathered from various Algerian Sahara areas. Almost 29 alkali-tolerant Actinobacteria Actinobacteria strains were separated by
utilising a complex agar medium. The strains were then tested for non-ribosomal peptide synthetases and genes encoding polyketide synthases, as well as antibiotic behaviour against a broad microorganisms’ variety. They found that some strains can create subordinate metabolites against several pathogenic microbes [19].

A list of bioactive compounds isolated from thermophilic, alkalophilic and haloalkalophilic Actinobacteria is shown in Table 2.

Table 2. List of bioactive compounds from thermophilic, alkalophilic and haloalkalophilic Actinobacteria

| Bioactive Compound | Producer | Chemical Class | References |
|--------------------|----------|----------------|------------|
| Thermomycin        | Streptomyces thermophilus | Polyketide Antibiotic | [40] |
| Anthramycin        | Streptomyces refrineus | Benzodiazepine Alkaloid | [40] |
| Pyridine-2,5-diacetamide | Streptomyces sp. DA3-7 | Antimicrobial aliphatic-aromatic copolyesters | [48] |
| 1, 4-butanediol, adipic acid, & terephthalic acid | Thermomonospora fusca | | [49] |

6. The Important Antibiotics Isolated from Actinobacteria Against Drug-Resistant Pathogens

Yücel and Yamaç [50] showed that extracts from Streptomyces sp. 1492 exhibited antimicrobial activity against MRSA, Vancomycin-resistant Enterobacter faecium (VRE) and Acinetobacter baumannii with 125 μg/mL and 250 to 1000 μg/mL of MICs and MBCs, respectively. From Verrucosispora sp. strains isolated from the Japan Sea’s sediment, Goodfellow and Fiedler [51] identified atrop-abyssomicin C and proximicins A, B and C. It inhibits the formation of p-aminobenzoate during tetrahydrofolate synthesis in Gram-positive bacteria with mithicillin-resistant *Staphylococcus aureus* (MRSA). The *Streptomyces mala-chitofuscus* has anti-fungal action against *Candida albicans* and *Mucor miehei*, as Sajid et al., [52] reported. The spoxazomicins was extracted from *Streptosporangium oxazolinicum* sp. nov., obtained from the root of numerous orchids at Okinawa. The study also isolated spoxazomicins A-C from *Streptosporangium oxazolinicum* K07-0460 (T) with antitrypanosomal activity [53]. Besides this, the alylomycine isolated from *Streptomyces* sp. HCCB10043 show activity against Gram-positive bacteria, among which included *Staphylococcus aureus* [54]. The chlorocatechelins A and B extracted from *Streptomyces* sp. are fresh siderophores encompassing an acyguanidine structure and chlorinated catecholate sets that inhibit various bacteria and fungi [55]. An extremely potent subordinate metabolite formed by endophytic strain is known as *Streptomyces* sp. HUST012. It showed antimicrobial and anti-tumour activities separated from the medicinal plant stems, *Dracaena cochinchinensis* *Lour* [56]. The updated list of antibiotics separated from Actinobacteria is given in Table 3.

The existing literature reported 124 compounds from Actinobacteria with anti-MRSA activity. Several bioactive pharmaceutical compounds generated by Actinobacteria was found to be effective against Vancomycin-resistant *Enterococcus* (VRE), Meticillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant bacterial pathogens strains. Kakadumycin A was isolated from *Streptomyces* sp. NRRL 30566 inhibited the growth of MRSA American Type Culture Collection (ATCC) 33591 four times lower in MIC than vancomycin at a concentration of 0.5 μg/mL compared to the concentration of vancomycin of 2.0 μg/mL, as reported by Castillo, et al., [57]. In addition, polyketide antibiotic SBR-22 comes from a fresh actinomycetes strain, labelled as BT-408, a novel strain of *Streptomyces psammoticus*. The strain showed anti-bacterial activity against MRSA, as documented by Suzathaet, et al., [58]. Besides this, Yooet, et al., [59] isolated laidlomycin from *Streptomyces* CS684 obtained from the soil at Jeonnam, Korea, with potential activity against VRE. Meanwhile, Laidiet, et al., [60] isolated a new actinomycetes strain designated as SK4-6 from
Egyptian soil that demonstrated strong activity against bacteria, including MRSA and Micrococcus luteus. Furthermore, Streptomyces sp. PVRK-1 was isolated from the Manakkudy mangroves in Tamil Nadu, South India. This Streptomyces has been able to produce many small molecules exhibiting potent anti-MRSA activity [43].

Table 3. The list of important producers and chemical classification of antibiotics isolated from Actinobacteria.

| Antibiotic     | Producer                  | Chemical Class | Reference |
|----------------|---------------------------|----------------|-----------|
| Cephamycin C   | Nocardia lactamdurans     | B-Lactam       | [61]      |
| Chlorotetracycline | S. aureofaciens          | Tetracycline   | [62]      |
| Clavulanic acid | S. clavuligerus           | B-Lactam       | [63]      |
| Cycloserine    | S. orchidaceus            | Peptide        | [64]      |
| Daptomycin     | S. roseosporus            | Lipopeptide    | [65]      |
| Daunorubicin   | S. Peucetius              | Peptide        | [66]      |
| FK506          | S.tubercidicus            | Macrolide      | [67]      |
| Fortimicin     | Micromonospora olivaster-| Aminoglycoside | [68]      |
|                | ospora                    |                |           |
| Fosfomycin     | S. fradie                 | Phosphoric acid| [69]      |
| Fumaramidmycin | S. kurzansovii            | Alkaloids      | [70]      |
| Gentamycin     | Micromonospora spp        | Aminoglycoside | [71]      |
| Kanamycin      | S. kanamyceticus          | Aminoglycoside | [72]      |
| Lincomycin     | S. lincolnensis           | Sugar—amide    | [73]      |
| Neomycin       | S. fradie                 | Aminoglycoside | [74]      |
| Nikkomycin     | S. tendae                 | Nucleoside     | [75]      |
| Nocardicin     | Nocardia uniformis        | B-Lactam       | [76]      |
| Novobiocin     | S. neveus                 | Aminocoumarin  | [77]      |
| Oleandomycin   | S. antibioticus           | Macrolide      | [78]      |
| Oxytetracycline| S. rimosus                | Tetracycline   | [79]      |
| Paromomycin    | S.rimosus forma           | Aminoglycoside | [80]      |
| Rifamycin      | Amycolatopsis Ansamycin   | RNA polymerase (PK) | [81] |
| Spiramycin     | S. ambofaciens            | Macrolide (PK) | [82]      |
| Streptomycin   | S. griseus                | Aminoglycoside | [83]      |
| Tetracycline   | S. aureofaciens           | Tetracycline (PK) | [84] |
| Thienamycin    | S. cattleya               | β-Lactam Peptidoglycan | [85] |
| Tobramycin     | S. tenebrarius            | Aminoglycoside | [86]      |
| Vancomycin     | S. orientalis             | Peptidoglycan  | [87]      |

Abbreviation: S. = (Streptomyces).

In addition, Choi et al., [88] claimed that Streptomyces sp. CS392 have anti-bacterial activity against VRE and MRSA. Additionally, the strain Streptomyces sp (VITBRK2) can yield strong antimicrobial activity against VRE and MRSA strains [89]. Moreover, Streptomyces rubrolavundula ICN3 strain displayed potent antimicrobial activity towards MRSA, with a 42 mm inhibition zone. The MIC was 500 μg/mL from the crude extracts, while the cleansed compound was identified as C23 with MIC 2.5 μg/mL in the in vitro assay [90]. Similarly, from a mangrove forest soil on Peninsular Malaysia’s east coast, the MUSC 135T strain was isolated. It can produce broad-spectrum antibiotic bacitracin against MRSA strain ATCC BAA-44 [91]. Correspondingly, from the stems of Dracaena Cochinchnensis Lour plant, Streptomyces sp. HUST012 was isolated, producing two potent antimicrobial compounds towards MRSA ATCC 25923 with MIC of 62.5 and 0.04 μg/mL, identified as SPE-B11.8-B5.4 [56]. Streptomyces sp. KB1 from Ao-Nang, Krabi province, Thailand, contains a compound known as 2,4-Di-tert-butylphenol, an anti-MRSA MIC of 31.15 μg/mL in comparison to vancomycin, with a MIC value of 1.56 μg/mL [92]. Diketopiperazines and chloramphenicol extracted from Streptomyces SUK 25, derived from the Zingiber spectabile root, seem effective towards MRSA [25]. Moreover, Bhaksharee and Kannabiran [93]...
reported the separation of anti-MRSA compounds from *Streptomyces* sp. VITBKA3 strain proteins and cell membrane biosynthesis inhibitors. The strains of *Streptomyces* sp. derived from different environments with potentials in production of anti-MRSA bioactive compounds from 2014 until 2020 is given in Table 4.

**Table 4.** List of anti-MRSA activity of bioactive compounds, producers and their chemical classes isolated from Actinobacteria.

| Antibiotic | Producer | Chemical Class | Reference |
|------------|----------|----------------|-----------|
| Angumicynones A (1); Angumicynones B (2); Angucyclinones analogues compounds 3–8 | *Streptomyces* sp. MC004 | Angucyclic quinones | [94] |
| Watasemycin A (3) | | Thiazostatins | |
| Pulicatin G (4) and aerugine (5) | | Benzyl thiazole and thiazoline | |
| Polypeptide (2-hydroxy-5-((6-hydroxy-4-oxo-4H-pyran-2-yl) methyl)-2-propylchroman-4-one) | *Streptomyces sundaransensis* WR1L18 | N/A | [95] |
| Azalomycin F5 (1) and its four derivative compounds: | *Streptomyces hygroscopicus* var. azalomyceticus | Polyhydroxy macrolide | [96] |
| Gargantulide A | *Streptomyces* sp. A42983 | Macrolactone | [97] |
| New Ikuragamycins: | | | |
| Compound 1: Isoikuragamycin; Compound 2: 28-N-methylkaragamycin; Compound 3: 30-oxo-28-N-methyl-ikuragamycin; Compound 4: Ikuragamycin; Compound 5: MKN-003B; Compound 6: 1H-indole-3-carboxaldehyde; Compound 7: Phenylethanoic acid | *Streptomyces* zhaozhouensis CA-185989 | Compounds 1-4: Pentacyclic tetramic acid macrolactams; Compound 5: Butenolide; Compound 6: Indole; Compound 7: Acetic acid | [98] |
| Pyrrole-Like Structure | *Streptomyces* sp. MN41 | pyrrole | [99] |
| Actinomycins V, X2 and D. | *Streptomyces* antibioticus NBRC 12838² | Actinomycins | [100] |
| Abyssomicin C | Actinobacteria | polyketide | [93] |
| laidomycin | *Streptomyces* sp. C5684 | affecting the metabolism | [89] |
| Neoicreamichins I and II | Nocardia | | [93] |
| Etamycin | Actinomycetes strains CNS-575 | cyclic peptide | [101] |
| Dichloromethane | Actinobacteria (I-400A, B1-T61, M10-77) | N/A | [93] |
| 2, 4-dichloro-5-sulfamoyl benzoic acid (DSBA) | *Streptomyces* sp. VITBRK2 | N/A | [93] |

Abbreviation: S. = (*Streptomyces*), N/A; not applicable.

**7. Production of Enzymes from Actinobacteria**

Both marine and terrestrial Actinobacteria in Table 5 produce a wide range of biologically active enzymes. They can secrete protease, cellulases, lipase, xylanase, pectinase and amylase. These enzymes are vitally important in textile or paper industries, the food industry and fermentation, besides biotechnological application. Consequently, Actinobacteria have been discovered to be a good L-asparaginase source. Various Actinobacteria often those extracted from soils, for example, *Nocardia* sp *Streptomyces* albidoiavus, *S.*
griseus and Streptomyces karnatakensis produce several enzymes [102]. Enzymes like urease, chitinase and catalase are also generated from Actinobacteria [103]. Surprisingly, keratinase, an enzyme that destroys the feathers of poultry chickens, has been successfully produced from Nocardiopsis sp. [104]. Likewise, Actinobacteria separated from goat and chicken gut revealed the existence of numerous enzymes like lipase, phytase, protease and amylase [105].

Table 5. List of enzymes, their producers, uses and application in industry isolated from Actinobacteria.

| Enzyme   | Producer                   | Use                                      | Application in Industry       | References |
|----------|----------------------------|------------------------------------------|-----------------------------|------------|
| Protease | Thermoactinozymes sp.,     | Detergents                               | Detergent                   | [106]      |
|          | Nocardiosis sp., S         | Cheese making                            | Food                        | [106]      |
|          | Pactum, Streptomyces       | Clarification—low-calorie beer            | Brewing                     | [107]      |
|          | Hermoniocalceus, S.sp.     | Dehairing                                | Leather                     | [107]      |
| Cellulase | S. Thermobifida           | Removal of stains                        | Detergent                   | [108]      |
|          | Halotolerans, S. Sp., Ruber| Deinking, modification of fibres         | Paper and pulp              | [108]      |
| Lipase   | S. griseus                | Removal of stains                        | Detergent                   | [109]      |
|          |                            | Stability of dough and conditioning      | Baking                      | [109]      |
|          |                            | Cheese flavouring                        | Dairy                       | [110]      |
| Xylanase | Actinomadura Sp.           | Conditioning of dough                    | Baking                      | [110]      |
|          |                            | Digestibility                            | Animal feed                 | [111]      |
|          |                            | Bleaching                                | Paper and pulp              | [111]      |
| Pectinase | S. lydicus                | Clarification, mashing                   | Beverage                    | [112]      |
|          |                            | Scouring                                 | Textile                     | [113]      |
| Amylase  | S. erumpens                | Deinking, drainage                      | Paper and pulp              | [114]      |
|          |                            | Removal of stains                        | Detergent                   | [114]      |

Abbreviation: S. = (Streptomyces).

8. Mechanism of Bioactive Compounds from Actinobacteria against Drug-Resistant Pathogens

Once scientists provide new antimicrobial drugs, the microorganism starts to adapt themselves against these drugs, which become ineffective at some points. This is primarily due to changes that occur inside the microorganism, especially bacteria, due to the interaction of numerous organisms through their environment and surroundings. These changes may occur for various reasons: mutations, selective pressure, gene transfer and phenotypic change [65]. For example, gene mutation occurs when bacteria reproduce, leading to the development of bacteria with genes that help them resist antibiotics. In addition, the mutation leads to alter the target and modification of the drug-receptor site in the target site [66].

Moreover, selective pressure means that bacteria carrying resistance genes hold up and multiply so that new resistance bacteria become the predominant type. The selective pressure leads to a lack of entry and decreased cell permeability. In addition, it leads to greater exit and active efflux pump [67]. Bacteria unnecessarily replicate to transmit their antibiotic resistance gene. Instead, it is passed across various types of bacteria resistance determinants through horizontal gene transfer making the bacterium resistant [68]. Besides this, phenotypic change suggests that the bacteria can change some of their properties to become more resistant to common antibiotics using the enzymatic inactivation of the antibiotics or by synthesising resistant metabolic pathways [69]. Other mechanisms, by modulation of methicillin-resistance of penicillin-binding protein (PBP2a) synthesis, were regulated by two genes known as Mec1 and MecR1 proteins. When existing, the signalling or regulatory proteins of the plasmid-mediated staphylococcal β-lactamase gene bla-Z system are working.
Furthermore, homogeneous tolerance is based on mutations at a different locus of genetics. Furthermore, other external and internal causes affect the development of methicillin resistance [115]. The mechanism of anti-bacterial resistance is demonstrated in Figure 6.

![Mechanism of Antibiotic Resistance](image)

**Figure 6.** Mechanism of anti-bacterial resistance to avoid killing by antimicrobial molecules. N.B.: BioRender was used to draw these scientific figures.

### 9. Conclusions and Future Prospects

There is a global demand for new chemotherapeutic agents and antibiotics that are extremely active and have low toxicity and environmental effects. The drug resistance in viruses, fungal and bacteria, as well as the emergence of life-threatening microorganisms, have become higher than before. This is due to the wrong usage of dose and time of medication administration, increasing the requirement of new and active compounds that assist and relieve all the aspects of the human condition. Actinobacteria have been isolated from different ecosystems, including several medicinal plants from the terrestrial and rhizosphere environment, hot springs as thermophilic Actinobacteria, deep-sea sediments, marine sponges and alkalines line soil. Several previous published works reported that Actinobacteria are understudied phylogenetic groups with high biosynthetic potential. This type of bacteria was found to have the greatest number of biosynthetic gene clusters in its genomes. There are more opportunities to investigate new resources and other biological characteristics of previously inaccessible natural products extracted from Actinobacteria as interest grows in bioactive molecules from drug formulation with minimal side effects. This group represents the new resource of bioactive compounds due to its ability to grow in multisectoral environments.

This review focused on the emphasis and the connection between finding new resources and novel strategies to search for potential bioactive compounds isolated from phylum Actinobacteria. In addition, this review highlighted some limitations in today’s research regarding a new source for bioactive compounds isolated from Actinobacteria.
For example, most previous publications concentrated only on the endophytic Actinobacteria, excluding other environments such as thermophilic, alkaliophilic and halotolerant Actinobacteria. Note that many other biodiversities and multidisciplinary environments represent important and new resources of potentially bioactive compounds. As a result, it appears that certain new techniques and methodologies for a thorough investigation of bioactive natural compounds are required. This includes, for example, the discovery of novel structure–activity relationships in nature, which has become increasingly important for the synthesis inspiration of natural bioactive product compounds. This results in increased diversity with less complexity and a good knowledge of isolation processes.

To address the challenges of biodiversity and promote future sustainable use of natural resources, a multidisciplinary perspective is required to find, describe and convey nature’s richness. This is necessary for identifying novel bioactive chemicals from Actinobacteria. Moreover, this review summarised the new bioactive compounds isolated from Actinobacteria and their applications in industrial, agricultural and environmental protection, pharmaceutical bioactive compounds and pharmaceutically related biomolecules. This includes superordinate metabolites that act as inhibitory or killing agents against pathogens that affect humans and animals, including resistant bacteria, fungi, viruses and several protozoa. They can also produce an anti-cancer and several enzymes for active degradation and meeting industrial demands worldwide. Therefore, continuous selective isolation and screening studies on the characterisation and identification of novel potential bioactive compounds from Actinobacteria are required. This is to create commercially viable, long-term and cost-effective production methods. Their metabolic flexibility and abundance also provide a novel, strong pathway for the bioremediation of organic wastes and contaminants.

Supplementary Materials: The following are available online. Table S1: Historically isolation of bioactive compounds from Actinobacteria. Table S2: List of antifungal, growth promoting, anti-tumor and antiparasitic bioactive compounds, chemical classification and their application which isolated from Actinobacteria. Table S3: Terrestrial and rhizosphere Actinobacteria isolation and screening for their antimicrobial activity. Figure S1: The spread of reviewed and cited papers based on the scattered keywords of the antimicrobial isolated from phylum Actinobacteria. Figure S2: Percentage of diversity of keywords from the Scopus database for Actinobacteria, Streptomyces, natural products, primary, secondary metabolites, habitat effects of environments, pharmaceutical industry using VOSviewer software tool to analyse and visualise scientific literature. Figure S3: Spread of reviewed and cited papers based on the dispersed keywords of anti-infective agents’ occurrence. Data was extracted using VOSviewer software to analyse and visualise scientific literature. Figure S4: Spread of reviewed and cited papers based on the scattered keywords of the countries for the publication and citation. Data was extracted using VOSviewer software.

Author Contributions: Conceptualisation, methodology and writing—review preparation, M.M.A.-s., R.M.S.R.M. and N.M.S; data validation, H.A.E.E. and N.M.Z.; formal analysis and data curation, E.N., N.A.A.-M. and A.A.-G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the FRGS/1/2020/WAB02/UTHM/03/1, FRGS/1/2017/STG05/UMK/01/1 and Financial support from industrial grant No. R.J130000.7609.4C284 and R.J130000.7609.4C240.

Institutional Review Board Statement: “Not applicable.”

Informed Consent Statement: “Not applicable.”

Data Availability Statement: Supplementary material related to this article can be found in the Supplementary data file.

Acknowledgments: The authors wish to thank The Ministry of Higher Education Malaysia under Fundamental Research Grant Scheme (FRGS) (Ref: FRGS/1/2020/WAB02/UTHM/03/1) under post-doc scheme research for supporting this research. The authors would like to thank the Center for Diagnostic, Therapeutic and Investigative Studies, Faculty of Health Sciences, Universiti Kebangsaan Malaysia and to the Faculty of Agro-based Industry, Universiti Malaysia Kelantan for financial
References

1. Carvalho, I.T.; Santos, L. Antibiotics in the aquatic environments: A review of the European scenario. Environ. Int. 2016, 94, 736–757, doi:10.1016/j.envint.2016.06.025.

2. Ribeiro, I.; Girão, M.; Alexandrino, D.; Ribeiro, T.; Santos, C.; Pereira, F.; Mucha, A.; Urbatziaka, R.; Leão, P.; Carvalho, M. Diversity and Bioactive Potential of Actinobacteria Isolated from a Coastal Marine Sediment in Northern Portugal. Microorganisms 2020, 8, 1691, doi:10.3390/microorganisms8111691.

3. Qi, D.; Zou, L.; Zhou, D.; Chen, Y.; Gao, Z.; Feng, R.; Zhang, M.; Li, K.; Xie, J.; Wang, W. Taxonomy and Broad-Spectrum Antifungal Activity of Streptomyces sp. SCA3-4 Isolated From Rhizosphere Soil of Opuntia stricta. Front. Microbiol. 2019, 10, 1390, doi:10.3389/fmicb.2019.01390.

4. Girão, M.; Ribeiro, I.; Azevedo, I.C.; Pereira, F.; Urbatziaka, R.; Leão, P.; Carvalho, M.F. Actinobacteria Isolated From Laminaria ochroleuca: A Source of New Bioactive Compounds. Front. Microbiol. 2019, 10, 683, doi:10.3389/fmicb.2019.00683.

5. Kandel, S.L.; Joubert, P.M.; Doty, S.L. Bacterial Endophyte Colonization and Distribution within Plants. Microorganisms 2017, 5, 77, doi:10.3390/microorganisms5040077.

6. Frank, A.C.; Güzman, J.P.S.; Shay, J.E. Transmission of Bacterial Endophytes. Microorganisms 2017, 5, 70, doi:10.3390/microorganisms5040070.

7. Salam, N.; Jiao, J.-Y.; Zhang, X.-T.; Li, W.-J. Update on the classification of higher ranks in the phylum Actinobacteria. Int. J. Syst. Evol. Microbiol. 2020, 70, 1331–1355, doi:10.1099/ijsem.0.003920.

8. Passari, A.K.; Chandra, P.; Leo, V.V.; Mishra, V.K.; Kumar, B.; Singh, B.P. Production of potent antimicrobial compounds from Streptomyces cyaneofuscatus associated with fresh water sediment. Front Microbiol. 2017, 8, 68.

9. Li, L.-Y.; Yang, Z.-W.; Asem, M.D.; Fang, B.-Z.; Salam, N.; Alkalihaf, D.H.M.; Hozzein, W.N.; Nie, G.-X.; Li, W.-J. Streptomyces desertaranea sp. nov., a novel actinobacterium isolated from a desert sample. Antonie Leeuwenhoek 2019, 112, 367–374, doi:10.1007/s10482-018-1163-0.

10. Bérdyi, J. Bioactive Microbial Metabolites. J. Antibiott. 2005, 58, 1–26, doi:10.1038/ja.2005.1.

11. Shivlata, L.; Satyanarayana, T. Thermophlic and alkalophilic Actinobacteria: Biology and potential applications. Front. Microbiol. 2015, 6, 1014, doi:10.3389/fmicb.2015.01014.

12. Xin, T.; Su, C.; Lin, Y.; Wang, S.; Xu, Z.; Song, J. Precise species detection of traditional Chinese patent medicine by shotgun metagenomic sequencing. Phytomedicine 2018, 47, 40–47, doi:10.1016/j.phymed.2018.04.048.

13. Ji, H.F.; Li, X.J.; Zhang, H.Y. Natural products and drug discovery. EMBO Rep. 2009, 10, 194–200.

14. Chaudhary, A.K.; Dhakal, D.; Sohung, J.K. An insight into the “omics” based engineering of Streptomyces for second-ary metabolite overproduction. BioMed Res. Int. 2013, 2013, 968518, doi:10.1155/2013/968518.3.

15. Demain, A.L.; Fang, A. The natural functions of secondary metabolites. In History of Modern Biotechnology 1; Springer: Cham, Switzerland, 2000; p. 1–39, doi:10.1007/540-44964-7_1.

16. Waksman, S.A.; Woodruff, H.B. The Soil as a Source of Microorganisms Antagonistic to Disease-Producing Bacteria. J. Bacteriol. 1940, 40, 581–600, doi:10.1128/jb.40.4.581-600.1940.

17. Schatz, A.; Bugle, E.; Waksman, S.A. Streptomyacin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria. Exp. Biol. Med. 1944, 55, 66–69, doi:10.3813/00379727-55-14461.

18. Woodruff, H.B. Selman A. Waksman, Winner of the 1952 Nobel Prize for Physiology or Medicine. Appl. Environ. Microbiol. 2014, 80, 2–8, doi:10.1128/aem.01143-13.

19. Meklat, A.; Bouras, N.; Mokrane, S.; Zitouni, A.; Djemouai, N.; Klenk, H.-P.; Sabaou, N.; Mathieu, F. Isolation, Classifica-tion and Antagonistic Properties of Alkalitolerant Actinobacteria from Algerian Saharan Soils. Geomicrobiol. J. 2020, 37, 826–836, doi:10.1080/01490451.2020.1786865.1.

20. Hoskisson, P.; Fernández-Martinez, L.T. Regulation of specialised metabolites in Actinobacteria—Expanding the paradigms. Environ. Microbiol. Rep. 2018, 10, 231–238, doi:10.1111/1758-2229.12629.

21. Silva, L.J.; Crevelin, E.J.; Souza, D.T.; Júnior, G.L.; De Oliveira, V.M.; Ruiz, A.L.T.G.; Rosa, L.H.; Moraes, L.A.B.; Melo, I.S. Actinobacteria from Antarctica as a source for anticancer discovery. Sci. Rep. 2020, 10, 13870, doi:10.1038/s41598-020-69786-2.

22. Bibb, M.J. Regulation of secondary metabolism in streptomyces. Curr. Opin. Microbiol. 2005, 8, 208–215, doi:10.1016/j.mib.2005.02.016.

23. Busi, S.; Pattnaik, S.S. Current status and applications of Actinobacteria in the production of anticancerous compounds. In New and Future Developments in Microbial Biotechnology and Bioengineering; Elsevier: Amsterdam, The Netherlands, 2018; pp. 137–153, doi:10.1016/b978-0-444-63695-6.00006-X.

24. Zin, N.M.; Remali, J.; Nasrom, M.N.; Ishak, S.A.; Baba, M.S.; Jalil, J. Bioactive compounds fractionated from endophyte Streptomyces SUK 08 with promising ex vivo antimalarial activity. Asian Pac. J. Trop. Biomed. 2017, 7, 1062–1066, doi:10.1016/j.apjtb.2017.10.006.

Conflicts of Interest: The authors declare no conflict of interest.
Molecules 2021, 26, 4504

25. Alshabiani, M.; Jalil, J.; Sidik, N.; Edrada-Ebel, R. and Zin, N.M. Isolation and characterization of cyclo-(tryptophan-prolyl) and chloramphenicol from Streptomyces sp. SUK 25 with anti-thermophilic-resistant Staphylococcus aureus activity. Drug Des. Dev. Ther. 2016, 10, 1817–1827, doi:10.2147/DDDT.S101212.

26. Ozakin, S.; Davis, R.W.; Umile, T.P.; Pirincicoglou, N.; Kizil, M.; Celik, G.; Sen, A.; Minbiole, K.P.C.; Ince, E. The isolation of tetranomycins from terrestrial Streptomyces sp. CAH29: Evaluation of antioxidant, anticancer, and anti-MRSA activity. Med. Chem. Res. 2016, 25, 2872–2881, doi:10.1007/s00044-016-1708-6.

27. Ahmad, R.; El-Gendy, A.; Ahmed, R.R.; Hassan, H.; El-Kabanny, H.M.; Merdasch, A.G. Exploring the Antimicrobial and Anti-Cancer Potential of Streptomyces sp. AGM1-2 Isolated from Egyptian Soil. Front. Microbiol. 2017, 8, 438, doi:10.3389/fmicb.2017.00438.

28. Dimri, A.G.; Chauhan, A.; Aggarwal, M. In vitro antibacterial characterization of Streptosporangiun sp. (AI-21) a new soil isolate against food borne bacteria. Sci. Arch. 2020, I, 25–34, doi:10.4785/sa.2020.1103.

29. Cheema, M.T.; Fatima, A.; Sajjîd, I. Molecular Identification, Bioactivity Screening and Metabolic Fingerprinting of the Actinomycetes of Chenab River Sediments. Br. Microbiol. Res. J. 2016, 17, 1–13, doi:10.9734/bmrij/2016/28805.

30. Kim, J.; Shin, D.; Kim, S.-H.; Park, W.; Shin, Y.; Kim, W.K.; Lee, S.K.; Oh, K.-B.; Shin, J.; Oh, D.-C. Borrelidins C–E: New Anti-Bacterial Macrolides from a Salt-Derived Halophilic Nocardiosis sp. Mar. Drugs 2017, 15, 166, doi:10.3390/md15060166.

31. Krishnamoorthy, M.; Dharmaraj, D.; Rajendran, K.; Karuppiah, K.; Balasubramanian, M.; Ethiraj, K. Pharmacological activities of coral reef associated actinomycetes, Saccharopolyspora sp. IMAU1. Bio catal. Agric. Biotechnol. 2020, 28, 101748, doi:10.1016/j.bcab.2020.101748.

32. Paulus, C.K.; Rebets, B.; Tokovenko, S.; Nadmid, L.P.; Terekhova, M.; Myronovskiy, S.B.; Zotchev, C.; Rückert, S.B.; Zahler, S. New natural products identified by combined genomics-metabolomics profiling of marine Streptomyces sp. MP131-18. Sci. Rep. 2017, 7, 1–11, doi:10.1038/srep42382.

33. Zhang, Y.-M.; Liu, B.-L.; Zheng, X.-H.; Huang, X.-J.; Li, H.-Y.; Zhang, Y.; Zhang, T.-T.; Sun, D.-Y.; Lin, B.-R.; Zhou, G.-X. Anandins A and B, two rare steroidal alkaloids from a marine Streptomyces anandii H41-59. Mar. Drugs 2017, 15, 355, doi:10.3390/md15110355.

34. Sarmentio-Vizzaino, A.; Brañá, A.F.; Pérez-Victoria, J.; Martín, J.; De Pedro, N.; De la Cruz, M.; Díaz, C.; Vicente, F.; Arauñá, J.L.; Reyes, F. et al. A new natural product with cytotoxic activity against tumor cell lines produced by deep-sea sediment derived Micromonospora matsumotoe sp. M-412 from the Avilés Canyon in the Cantabrian Sea. Mar. Drugs 2017, 15, 271, doi:10.3390/md15090271.

35. Yang, N.; Song, F. Bioprospecting of novel and bioactive compounds from marine actinomycetes isolated from South China Sea sediments. Curr. Microbiol. 2018, 75, 142-149, doi:10.1007/s00284-017-1358-z.

36. Waters, A.L.; Peraud, O.; Kasanah, N.; Sims, J.W.; Kothalawala, N.; Anderson, M.A.; Abbas, S.H.; Rao, K.V.; Jupally, V.R.; Kelly, M. An analysis of the sponge Acanthiospongia phylla idgns microbiome yields an Actinomycete that produces the natural product manzamine A. Front. Mar. Sci. 2014, 1, 54, doi:10.3389/fmars.2014.00054.

37. Mahapatra, G.P.; Raman, S.; Nayak, S.; Gouda, S.; Das, G.; Patra, J.K. Metagenomics approaches in discovery and development of new bioactive compounds from marine actinomycetes. Curr. Microbiol. 2020, 77, 645–656, doi:10.1007/s00284-019-10169-5.

38. Nandimath, A.P.; Karad, D.D.; Gupta, S.G.; Kharat, A.S. Consortium inoculum of five thermo-tolerant phosphate solubilising Actinomycetes for multipurpose biofertiliser preparation. Iran J. Microbiol. 2017, 9, 295–304, PMID: 29296275, PMCID: PMC5748449.

39. Mohammadipanah, F.; Wink, J. Actinobacteria from Arid and Desert Habitats: Diversity and Biological Activity. Front. Microbiol. 2016, 6, 1541, doi:10.3389/fmicb.2015.01541.

40. Verma, E.; Chakraborty, S.; Tiwari, B.; Mishra, A.K. Antimicrobial Compounds from Actinobacteria: Synthetic Pathways and Applications. In New and Future Developments in Microbial Biotechnology and Bioengineering; Elsevier: Amsterdam, The Netherlands, 2018; Chapter 19, pp. 277–295, doi:10.1016/B978-0-444-63994-3.00019-9.

41. Al-Dhabi, N.A.; Esmail, G.A.; Duraipandiyar, V.; Arasu, M.V. Chemical profiling of Streptomyces sp. Al-Dhabi-2 recovered from an extreme environment in Saudi Arabia as a novel drug source for medical and industrial applications. Saudi J. Biol. Sci. 2019, 26, 758–766, doi:10.1016/j.sjbs.2019.03.009.

42. Halket, G.; Herron, P.; Munro, C. Isolation of thermophilic Actinobacteria from compost and identification of bioactive compounds with antimicrobial properties. Access Microbiol. 2020, 2, 954, doi:10.1093/acm20/acaa0035.

43. Borsodi, A.K.; Szili-Kovács, T.; Schumann, P.; Prööer, C.; Márialigeti, K.; Tóth, E. Nesterenkonia pannonica sp nov., a novel alkaliphilic and moderately halophilic actinobacterium. Int. J. Syst. Evol. Microbiol. 2017, 67, 4116–4120, doi:10.1099/ijsem.0.022263.

44. Arayes, M.A.; Marboutik, M.E.M.; Sabry, S.A.; Abdella, B. Diversity and characterization of cultivable haloalkaliphilic bacteria from two distinct hypersaline lakes in northern Egypt. Biotechnol. Bioprocess Eng. 2021, 26, 751–761, doi:10.2478/s11756-020-00609-5.

45. Thumar, J.T.; Singh, S.P. Repression of alkaline protease in salt-tolerant alkaliphilic Streptomyces clavuligerus strain Mit-1 under the influence of amino acids in minimal medium. Biotechnol. Bioprocess Eng. 2011, 16, 1180–1186, doi:10.1007/s12257-009-0087-y.

46. Thakrar, F.; Kikani, B.; Sharma, A.; Singh, S. Stability of Alkaline Proteases from Halokaliphilic Actinobacteria Probed by Circular Dichroism Spectroscopy. Appl. Biochem. Micro. 2018, 54, 591–602, doi:10.1134/s003683811800022.

47. Gohel, S.D.; Singh, S.P. Molecular Phylogeny and Diversity of the Salt-Tolerant Alkaliphilic Actinobacteria Inhabiting Coastal Gujarat, India. Geomicrobiol. J. 2018, 35, 775–789, doi:10.1080/01490451.2018.1471107.

48. Nithya, K.; Muthukumar, C; Biswas, B.; Alharbi, N.S.; Kadaikunnan, S.; Khaled, J.M.; Dhanasekaran, D. Desert Actinobacteria as a source of bioactive compounds production with a special emphasis on Pyridine-2,5-diacetamide a new pyridine alkaloid produced by Streptomyces sp. DA3-7. Microbiol. Res. 2018, 207, 116–133, doi:10.1016/j.micres.2017.11.012.
Molecules 2021, 26, 4504

74. Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. Novel antitumor antibiotic phosphine 1. Production, isolation and characterization. J. Antibiot. 1989, 42, 1331–1338, doi:10.7164/antibiotics.42.1331.

75. Schimana, J.; Fiedler, H.-P.; Groth, I.; Submuth, R.; Beil, W.; Walker, M.; Zeeck, A. Simocyclinones, Novel Cytotoxic Angucyclinone Antibiotics Produced by Streptomyces antibioticus Tue 6104. I. Taxonomy, Fermentation, Isolation and Biological Activities. J. Antibiot. 2000, 53, 779–787, doi:10.7164/antibiotics.53.779.

76. Igarashi, Y.; Ogawa, M.; Sato, Y.; Saito, N.; Yoshida, R.; Kunoh, H.; Onaka, H.; Furumai, T. Fistupyrone, a novel inhibitor of the infection of Chinese cabbage from Alternaria brassicicola, from Streptomyces sp. TP-A0569. J. Antibiot. 2000, 53, 1117–1122, doi:10.7164/antibiotics.53.1117.

77. Flinspach, K.; Rückert, C.; Kalinowski, J.; Heide, L.; Apel, A.K. Draft genome sequence of Streptomyces niveus NCIMB 11891, producer of the aminocoumarin antibiotic novobiocin. Genome Announc. 2014, 2, e01146-13, doi:10.1128/genomeA.01146-13.

78. Choi, S.H.; Ryu, M.; Yoon, Y.J.; Kim, D.-M.; Lee, E.Y. Glycosylation of various flavonoids by recombinant oleandomycin glycosyltransferase from Streptomyces antibioticus in batch and repeated batch modes. Biotechnol. Lett. 2012, 34, 499–505, doi:10.1007/s10529-011-0789-z.

79. Yin, S.; Wang, W.; Wang, X.; Zhu, Y.; Jia, X.; Li, S.; Yuan, F.; Zhang, Y.; Yang, K. Identification of a cluster-situated activator of oxytetracycline biosynthesis and manipulation of its expression for improved oxytetracycline production in Streptomyces rimosus. Microb. Cell Fact. 2015, 14, 1–12, doi:10.1186/s13294-015-0231-7.

80. Ogawara, H. Comparison of antibiotic resistance mechanisms in antibiotic-producing and pathogenic bacteria. Molecules 2019, 24, 3430, doi:10.3390/molecules24193430.

81. Ye, F.; Shi, Y.; Zhao, S.; Li, Z.; Wang, H.; Lu, C.; Shen, Y. 8-Deoxy-Rifamycin Derivatives from Amycolatopsis mediterranei S699 Drift Strain. Biomolecules 2020, 10, 1265, doi:10.3390/biom10091265.

82. Thibessard, A.; Haas, D.; Gerbaud, C.; Aigle, B.; Lautru, S.; Permodet, J.-L.; Leblond, P. Complete genome sequence of Streptomyces ambofaciens ATCC 23877, the spiramycin producer. J. Biotechnol. 2015, 214, 117–118, doi:10.1016/j.jbiotec.2015.09.020.

83. Ishigaki, Y.; Akunaga, K.; Yoshida, M.; Horinouchi, S.; Kosono, S.; Ohnishi, Y. Protein acetylation involved in streptomycin biosynthesis in Streptomyces griseus. J. Proteomics. 2017, 155, 63–72, doi:10.1016/j.jprot.2016.12.006.

84. Vastrad, B.M.; Neelagund, S.E. Optimizing the medium conditions for production of tetracycline by solid state fermentation of Streptomyces rimosus NCIMB 2417 using statistical experimental methods. J. Biomol. Eng. 2018, 1, 29–44.

85. Braña, A.F.; Rodríguez, M.; Pahari, P.; Rohr, J.; García, L.A.; Blanco, G. Activation and silencing of secondary metabolites in Streptomyces albus and Streptomyces lividans after transformation with cosmid containing the thienamycin gene cluster from Streptomyces cattleya. Arch. Microbiol. 2014, 196, 345–355, doi:10.1007/s00203-014-0977-z.

86. Hong, W.; Yan, S. Engineering Streptomyces tenebrarius to synthesize single component of carbamoyl tobramycin. Lett. Appl. Microbiol. 2012, 55, 33–39, doi.org/10.1111/j.1472-765X.2012.03254.x.

87. Abdullah, K.G.; Chen, H.J.; Lucas, T.H. Safety of topical vancomycin powder in neurosurgery. Surg. Neurol. Int. 2016, 7; S919–S926, doi:10.4103/2152-7806.195227.

88. Choi, H.J.; Kim, D.W.; Choi, Y.W.; Lee, Y.G.; Lee, Y.-.; Jeong, Y.K.; Joo, W.H. Broad-spectrum In vitro antimicrobial activities of Streptomyces sp. strain BCNU 1001. Biotechnol. Bioprocess Eng. 2012, 17, 576–583, doi:10.1007/s12257-011-0151-2.

89. Rajan, B.M.; Kannabiran, K. Extraction and identification of anti-bacterial secondary metabolites from marine Streptomyces sp. VITBKR2. Int. J. Mol. Cell Med. 2014, 3, 130–137, PMID: 25317399.

90. Kannan, R.R.; Iniyan, A.M.; Vincent; S.G.P. Production of a compound against methicillin resistant Staphylococcus aureus (MRSA) from Streptomyces rubrolavendulae ICNS & its evaluation in zebra fish embryos. Indian J. Med. Res. 2014, 139, 913–920, PMC4165004.

91. Ser, H.-L.; Ab Mutalib, N.-S.; Yin, W.-F.; Chan, K.-G.; Goh, B.H.; Lee, L.-H. Evaluation of Antioxidative and Cytotoxic Activities of Streptomyces pluripotens MUSC 137 Isolated from Mangrove Soil in Malaysia. Front. Microbiol. 2015, 6, 1398, doi:10.3389/fmicb.2015.01398.

92. Chawawisit, K.; Bhoopong, P.; Phupong, W.; Lertcanawanichakul, M. 2, 4-Di-tet-tet-butylphenol, the bioactive compound produced by Streptomyces sp. KB1. J. Appl. Pharm. Sci. 2015, 5, 7–12, doi:10.7324/JAPS.2015.510.S2.

93. Bhakyashree, K.; Kannabiran, K. Actinomycetes mediated targeting of drug resistant MRSA pathogens. J. King Saud Univ. Sci. 2020, 32, 260–264, doi:10.1016/j.jksus.2018.04.034.

94. Kemung, H.M.; Tan, L.T.-H.; Khan, T.M.; Chan, K.-G.; Puspardjaja, P.; Goh, B.-H.; Lee, L.-H. Streptomyces as a prominent resource of future anti-MRSA drugs. Front. Microbiol. 2019, 8, 2221, doi:10.3389/fmicb.2018.02221.

95. Djinni, I.; Defant, A.; Kecha, M.; Mancini, I. Metabolite profile of marine-derived endophytic Streptomyces sundarbasensis WR 1 L 1 S 8 by liquid chromatography–mass spectrometry and evaluation of culture conditions on antibacterial activity and mycelial growth. J. Appl. Microbiol. 2014, 116, 39–50, doi:10.1111/jam.12360.

96. Yuan, G.; Lin, H.; Wang, C.; Hong, K.; Liu, Y.; Li, J. H and 13C assignments of two new macrocyclic lactones isolated from Streptomyces sp. 211726 and revised assignments of azalomycins F3a, F4a and F5a. Magn. Reson. Chem. 2011, 49, 30–37, doi:10.1002/mrc.2697.

97. Rho, J.-R.; Subramaniam, G.; Choi, H.; Kim, E.-H.; Ng, S.P.; Yoganathan, K.; Ng, S.; Buss, A.D.; Butler, M.S.; Gerwick, W.H. Gargantulide A, a complex 52-membered macrolactone showing antibacterial activity from Streptomyces sp. Org. Lett. 2015, 17, 1377–1380, doi:10.1021/acs.orglett.5b00684.
98. Lacret, R.; Oves-Costales, D.; Gómez, C.; Díaz, C.; De la Cruz, M.; Pérez-Victoria, I.; Vicente, F.; Genilloud, O.; Reyes, F. New ikarugamycin derivatives with antifungal and antibacterial properties from Streptomyces zhaohouensis. Mar. Drugs. 2015, 13, 128–140, doi:10.3390/md13010128.

99. Norouzi, H.; Khorasgani, M.R.; Danesh, A. Anti-MRSA activity of a bioactive compound produced by a marine Streptomyces and its optimization using statistical experimental design. Iran. J. Basic Med. Sci. 2019, 22, 1073–1084, doi:10.22038/ijbms.2019.33880.8058.

100. Sharma, M.; R.K. Manhas, R.K. Purification and characterization of actinomycins from Streptomyces strain M7 active against methicillin resistant Staphylococcus aureus and vancomycin resistant Enterococcus. BMC Microbiol. 2019, 19, 1–14, doi:10.1186/s12866-019-1405-y.

101. Haste, N.M.; Thienphrapa, W.; Tran, D.N.; Loesgen, S.; Nam, S.; Jensen, P.; Fencial, W.; Nizet, V.; et al. Activity of the thiopetide antibiotic nosiheptide against contemporary strains of methicillin-resistant Staphylococcus aureus. J. Antimicrob. 2012, 65, 593–598, doi:10.1038/ja.2012.77.

102. Lewin, G.R.; Carlos, C.; Chevrette, M.G.; Horn, H.A.; McDonald, B.R.; Stankey, R.J.; Fox, B.G.; Currie, C.R. Evolution and ecology of Actinobacteria and their bioenergy applications. Frontiers in Microbiol. 2019, 5, 99, doi:10.3390/fmicb.2019.0099.

103. Kaur, T.; Rani, R.; Manhas, R.K. Biocontrol and plant growth promoting potential of phylogenetically new Streptomyces sp. MR14 of rhizospheric origin. AMB Express 2019, 9, 1–14, doi:10.1186/s13568-019-0849-7.

104. Verma, A.; Singh, H.; Anwar, S.; Chattopadhyay, A.; Tiwari, K.K.; Kaur, S.; Dhillon, G.S. Microbial keratinases: Industrial enzymes with waste management potential. Crit. Rev. Biotechnol. 2017, 37, 476–491, doi:10.1080/07388551.2016.1185388.

105. Karimi, S.; Soofiani, N.M.; Lundh, T.; Mabboubi, A.; Kiessling, A.; Taherzadeh, M.J. Evaluation of filamentous fungal biomass cultivated on Vinasse as an alternative nutrient source of fish feed: Protein, lipid, and mineral composition. Fermentation 2019, 5, 99, doi:10.3390/fermentation5040099.

106. Ding, Y.; Yang, Y.; Ren, Y.; Xia, J.; Liu, F.; Li, Y.; Tang, X.-F.; Tang, B. Extracellular production, characterization, and engineering of a polyextremotolerant subtilisin-like protease from feather-degrading Thermoactinomyces vulgaris strain CDF. Front. Microbiol. 2020, 11, doi:10.3389/fmicb.2020.605771.

107. Gaddde, U.D.; Oh, S.; Lillehoj, H.S.; Lillehoj, E.P. Retracted Article: Antibiotic growth promoters virginiamycin and bacitracin methylene disalicylate alter the chicken intestinal metabolome. Sci. Rep. 2018, 8, 3592, doi:10.1038/s41598-018-22004-6.

108. Jiang, C.; Wang, H.; Kang, Q.; Liu, J.; Bai, L. Cloning and Characterization of the Polyether Salinomycin Biosynthesis Gene Cluster of Streptomyces albus XM211. Appl. Environ. Microbiol. 2012, 78, 994–1003, doi:10.1128/aem.06701-11.

109. Vishnupriya, B.; Sundaramoorthi, C.; Kalaivani, M.; Selvam, K. Production of lipase from Streptomyces griseus and evaluation of Bioparameters. Int. J. Chem. Tech. Res. 2010, 2, 1380–1383, doi:10.1007/s132010-011-9457-y.

110. Taibi, Z.; Saoudi, B.; Boudelaa, M.; Trigui, H.; Belghith, H.; Gargouri, A.; Ladjama, A. Purification and biochemical characterization of a highly thermostable xylanase from Actinomadura sp. strain Cpt20 isolated from poultry compost. Appl. Biochem. Biotechnol. 2012, 166, 663–679, doi:10.1007/s12010-011-9457-y.

111. Prakash, D.; Nawani, N.; Prakash, M.; Bodas, M.; Mandal, A.; Khetmalas, M.; Kapadnis, B. Actinomycetes: a repertory of green catalysts with a potential revenue resource. Bioresour. Technol. 2008, 99, 6697–6701, doi:10.1016/j.biortech.2007.10.002.

112. Jacob, N.; Pooma, C.A.; Prema, P. Purification and partial characterization of polygalacturonase from Streptomyces lydicus. Bioresour. Technol. 2020, 27, 3529–3540, doi:10.1016/j.biortech.2020.07.024.

113. Govindaraji, P.K.; Vuppup. Characterisation of pectin and optimization of pectinase enzyme from novel Streptomyces fumi- gatiscleroticus VIT-SP4 for drug delivery and concrete crack-healing applications: An eco-friendly approach. Saudi J. Biol. Sci. 2020, 27, 3529–3540, doi:10.1016/j.sjbs.2020.07.024.

114. Nithya, K.; Muthukumar, C.; Kadaikunnan, S.; Alharbi, N.S.; Khaled, J.M.; Dhanasekaran, D. Purification, characterization, and statistical optimization of a thermostable α-amylase from desert actinobacterium Streptomyces fragilis DA7-7. 3 Biotech, 2017, 7, 1–13, doi:10.1007/s13205-017-0981-5.

115. Uma Maheswari, R. Phenotypic and Genotypic Characterisation of Vancomycin Resistant Staphylococcus aureus among MRSA Isolates in a Tertiary Care Hospital. Master’s Thesis, Tirunelveli Medical College, Tirunelvel, 2019. Available online: http://repository-trmgmu.ac.in/id/eprint/11129 (accessed on 23 August 2019).