microbiology research

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Review

Streptomyces: Still the Biggest Producer of New Natural Secondary Metabolites, a Current Perspective

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Abstract: There is a real consensus that new antibiotics are urgently needed and are the best chance for combating antibiotic resistance. The phylum Actinobacteria is one of the main producers of new antibiotics, with a recent paradigm shift whereby rare actinomycetes have been increasingly targeted as a source of new secondary metabolites for the discovery of new antibiotics. However, this review shows that the genus *Streptomyces* is still the largest current producer of new and innovative secondary metabolites. Between January 2015 and December 2020, a significantly high number of novel *Streptomyces* spp. have been isolated from different environments, including extreme environments, symbionts, terrestrial soils, sediments and also from marine environments, mainly from marine invertebrates and marine sediments. This review highlights 135 new species of *Streptomyces* during this 6-year period with 108 new species of *Streptomyces* from the terrestrial environment and 27 new species from marine sources. A brief summary of the different pre-treatment methods used for the successful isolation of some of the new species of *Streptomyces* is also discussed, as well as the biological activities of the isolated secondary metabolites. A total of 279 new secondary metabolites have been recorded from 121 species of *Streptomyces* which exhibit diverse biological activity. The greatest number of new secondary metabolites originated from the terrestrial-sourced *Streptomyces* spp.

Keywords: streptomycetes; *Streptomyces*; extreme environments; actinobacteria; microbial natural products

Citation: Donald, L.; Pipite, A.; Subramani, R.; Owen, J.; Keyzers, R.A.; Taufa, T. *Streptomyces*: Still the Biggest Producer of New Natural Secondary Metabolites, a Current Perspective. *Microbiol. Res.* **2022**, *13*, 418–465. https://doi.org/10.3390/microbiolres13030031

Academic Editor: Mireille Fouillaud

Received: 3 June 2022
Accepted: 29 June 2022
Published: 1 July 2022

1. Introduction

Indiscriminate use of antibiotics has led to a rise in antimicrobial resistance [1]. This dramatically increases the demands for research and discovery of new drugs and antibiotics. Natural products isolated from microorganisms as well as their semi-synthetic derivatives and synthetic analogues have historically been one of the most important sources of antibiotics [2]. Nature includes a large number of microbial species including at least 1.5 million fungi and as many as 5×10^{12} distinct microbial species [1]. However, only a small fraction of about 250,000 to 300,000 living species, mainly in oceans and rainforests, have been identified and documented [1,3]. Worryingly, over the past few decades, there has been a significant decrease in the discovery of new natural product-derived medicines from 20 to 30 approved drugs per decade to only 3 to 4 newly marketed drugs, which has triggered many uncertainties in the medical industries [1]. This decline in translation from

discovery to the clinic seems to be due to a decrease in screening efforts rather than a lack of new compounds [1]. For example, of the 18 largest pharmaceutical companies, 15 have withdrawn from antibiotic research [4]. Therefore, the need to produce new antibiotics has driven researchers to put more effort into finding new and novel natural products from untouched and under-explored habitats [5].

The phylum Actinobacteria is one of the main producers of biologically active products with medical, industrial and agricultural applications [6]. This phylum constitutes one of the largest of the 30 major phyla classified in the Domain Bacteria. There are 6 classes, 18 orders, 14 suborders, 63 families and 374 genera recorded in this phylum, with *Streptomyces* as the largest genus of this phylum [7]. Similar to other genera of Actinobacteria, *Streptomyces* are Gram-positive bacteria with a GC content of 69–78% [8] and with physiologically characteristics that resemble those of many fungal species [9]. They belong to the family Streptomycetaceae and the order Streptomycetales [10]. Approximately 39% of Actinobacteria have been sources of new natural products, of which around 80% are from the genus *Streptomyces* [11].

The genus *Streptomyces* was first discovered as a widespread source of antibiotics in 1943. Subsequently, more than 800 *Streptomyces* spp. with validly published names have been registered so far [7]. Rediscovery of known secondary metabolites from *Streptomyces* species has redirected scientists to the discovery of rare actinomycetes with claims that *Streptomyces* species are no longer an important biological resource for new antibiotics [12,13]. Environmental conditions and different habitats strongly contribute to the diversity and production of natural bioactive compounds [14]. In this review paper, "Streptomycetes" is used to refer to soil and marine microorganisms classified as *Streptomyces* spp. from the phylum Actinobacteria in the order Actinomycetales and the family Streptomycetaceae [7]. Streptomycetes are ubiquitous in terrestrial and marine environments with the highest recorded diversity in terrestrial habitats [15]. Whatever the habitats, the natural products produced by Streptomycetes under normal and extreme conditions exhibit great structural diversity and significant biological activity [16,17]. Since techniques for the isolation of Streptomycetes are well understood, this genus has been frequently isolated. Consequently, genus *Streptomyces* produces the highest number of natural products compared to other genera of Actinobacteria.

An interesting recent study by Laskaris et al. (2021) on "*Streptomyces*, Greek Habitats and Novel Pharmaceuticals: A Promising Challenge" did an excellent job of reporting compounds from Greek Streptomyces including antibiotics, antitumor compounds, biofilm inhibitors, antiparasitics, bacterial toxin production inhibitors and antioxidants [18]. Their work showed that Streptomyces is still a large current producer of bioactive compounds.

In this review, we support their conclusion and present practical ideas, and encouraging results to help researchers meet challenges preventing progress to find novel antibiotics from natural environment. Here, we summarize new *Streptomyces* species and natural bioactive compounds from various sources and from 2015 to 2020. We describe culture conditions and molecular biology protocols to help in their isolation and characterization.

2. Hidden Potential of Streptomyces: Metagenomic Insights and Evidence

Metagenomics studies have shown that a high number of *Streptomyces* spp. and other genera of Actinobacteria from environmental samples remain unculturable under normal laboratory condition [19]. These are referred to as viable but not culturable (VBNC) [12]. Even the potential of cultured *Streptomyces* spp. to produce bioactive secondary metabolites is not fully realized as environmental factors (pH, temperature, incubation time) have profound effects on antibiotic production [20]. The development of genome sequencing methods and in silico genome mining tools have revolutionized the bioactive screening approach in Actinobacteria [21]. Genome mining showed that one *Streptomyces* strain possessed 25–70 Biosynthetic Gene Clusters (BGCs), most of which are cryptic (Silent BGC) and were not expressed under normal laboratory conditions [22,23]. This suggests that the chemical abilities possessed by a single bacterium to combat pathogens is poorly studied. Guerrero-Garzon et al. (2020) reported that 10 strains of *Streptomyces* spp. isolated from

the marine sponge *Antho dichotoma* has limited bioactivity, however, using draft genomes, pronounced biosynthetic gene clusters were recorded of which all the strains harbor between 7.1 Mb to 10 Mb which encodes at least 28 to 36 BGCs per genome [24]. Additionally, genome quality and genome completeness remain vital for accurate analyses in genome mining and in silico identification of BGCs [25,26]. A study by Belknap et al. (2020) stated that genome mining not only revealed the potential novel secondary metabolite BGCs but also show that *Streptomyces* strains that are considered the same species can have high variation in the BGCs with potential derivatives of natural products [27]. Liu et al. (2020) also used a genome mining approach on *Streptomyces* strain YINM00001 and reported fifty-two putative secondary metabolites biosynthetic gene clusters which included cycloheximide, dynactin, warkmycin, and anthramycin biosynthetic gene clusters that are responsible for the strong antifungal and antibacterial activity of the strain [28]. Genome mining also reveals that *Streptomyces* spp. can harbor resistance genes to pathogens which is useful to combat the escalating issue of drug resistant pathogens and these resistance genes can easily be transferred between *Streptomyces* spp. [29]. Current perspectives of genome mining unveil the unimaginable amount of cryptic smBGCs (secondary metabolite biosynthetic gene clusters) in *Streptomyces* spp. genomes [30]. Further, securing a high-quality and close *Streptomyces* genome sequence is essential to precisely predict their smBGCs and their functional annotation [25,26]. When exploring the evolutionary dynamics of smBGCs from lineage divergence of *Streptomyces* sister taxa, it was revealed that the sister taxa strains contain 310 distinct smBGCs belonging to 22 different gene cluster classes [31]. Moreover, genome mining enables the engineering of genes by integrating regulatory genes and codons which can optimize the production of secondary metabolites and deletion of negative regulatory gene [32]. Thus, the full potential of *Streptomyces* spp. as a source of bioactive secondary metabolites is yet to be explored.

In terms of activating these silent cryptic genes in vitro, researchers should be made aware that a single BGC can lead to one or more secondary metabolites [33]. In addition, as secondary metabolites have different roles from primary metabolites, they are mainly produced under stressed, unusual or extreme conditions [31]. Understanding these concepts may help researchers in designing culture-based conditions that help them overcome challenges that impede progress in the search for new antibiotics from natural and extreme environments.

This review summarizes these culture-based methods by reviewing a large number of Streptomycetes studies from various environments.

3. Novel *Streptomyces* Species Isolated from Terrestrial Environments

Streptomyces can be found in a variety of terrestrial habitats, including extreme environments, gastrointestinal commensals with insects, and living in symbiosis with plants, fungi, and animals [34]. They are also highly abundant in soils and sediments [11,35].

3.1. Isolation Methods

Streptomycetes are ubiquitous in nature and have colonized a wide range of ecologically important terrestrial habitats. To isolate Streptomycete species from environmental samples, sophisticated research techniques and correlated studies are needed to mimic the native environmental conditions. A diverse suite of isolation methods has been used to successfully isolate new strains of Streptomycetes [36]. These include different methods of pre-treatment, the use of specific selective media under specific laboratory conditions, the use of supplements, and modification of the incubation time and temperature [37–40]. In particular, it is important to understand the physiological and biochemical conditions of the sampled environment. However, some bacterial cells cannot be cultured using culture-dependent methods or modern laboratory techniques and are referred to as "viable but not culturable" (VBNC) [41]. For this, high throughput sequencing metagenomic studies have shown that a large number of microbial communities remain unculturable from environmental samples [42].

3.2. Extreme Environments

Extreme environments are characterized by high salinity, high or low pH, arid conditions, low nutrient and oxygen content, high or low temperatures, and high exposure to UV rays, and which would be detrimental to "normal" conditions as required for human survival [43]. In recent years, researchers have focused more on the extreme environment as a potent source of new species of Streptomycetes with biological activity [44]. This group of bacteria has the ability to survive under multiple such conditions (polyextremophilic) because they possess distinctive adaptive characteristics such as the production of specific enzymes, switching between different metabolic modes (i.e., heterotrophy and autotrophy) and antibiosis [39].

Thirty-six new strains of *Streptomyces* were reported from various extreme environments between 2015 and 2020 (Table 1). In order to isolate new strains of Streptomycetes from these samples collected from these environments, it is essential to consider various factors such as pH, temperature, nutrients required, as well as the use of pre-treatments. Culturing *Streptomyces* from samples collected from these environments does not necessarily require extreme conditions to obtain new *Streptomyces* spp. [45]. The pretreatments applied activate the endospores, which grow on the isolation media [46,47].

The culture media is supplemented with nutrients and other supplements to support bacterial growth. The isolation of *Streptomyces* spp. from an extreme environment is effective when different carbon sources (glycerol, soluble starch, glucose, trehalose, carboxy-methylcellulose, humic acid and dextrose) are supplemented with culture media for the successful isolation of novel *Streptomyces* spp. [37,40,48–54] as indicated in Table 1. Carbon–nitrogen sources can also be added to the isolation media; casein [55,56], peptone [8,57], malt extract [58] and yeast extract [53,58,59]. The isolation media can be supplemented by $K_2Cr_2O_7$ [54,60–64], nalidixic acid, nystatin, cycloheximide, rifampicin, and tetracycline [37,38,40,49,51,53,55,56,58,59,65–69] to inhibit the growth of unwanted bacteria and fungi (See Tables 1 and S1).

Selective pretreatment is carried out to eliminate Gram-negative, fastidious bacteria and unwanted microorganisms [12]. There are different pre-treatment methods used for environmental samples, including chemical pretreatment, physical pretreatment, and heating. Samples from extreme environments are subjected to various chemical pretreatments, including the addition of chemicals to the samples and dilution with deionized water. Physical treatments have also been applied to samples, which involves shaking the sample on a rotary shaker or a tumble shaker and heat treatment of the sample involving wet heat treatment or dry heat treatment. *Streptomyces* spores are very resistant to exogenous chemicals and temperature extremes due to the complex chemical compositions of their cell wall [70]. This is advantageous when performing pretreatments to selectively isolate *Streptomyces* spp. Some of the commonly used pretreatments for the isolation of *Streptomyces* from an extreme terrestrial environment include distilled water with added NaCl [38,52,71,72], air-drying [53,64,68] pretreatment by ultrasound [56,69] and agitation on a rotary stirrer [37,40,54,57,66,69]. Dry heat treatment and wet heat treatment are the most frequently used pretreatments. Notably, a combination of physical and chemical treatment [66] or two different physical treatment methods [69] have been shown to be significant and effectively isolate strains of *Streptomyces*. On the other hand, there are samples from extreme environments, which are not subjected to any pretreatment [51,54,60,61,65,73].

Table 1. Novel *Streptomyces* spp. reported from extreme environments between 2015 and 2020.

Strain	Nature of the Sample	Isolation Medium	Country	Reference
Streptomyces boncukensis sp. nov.	Saltern soil	Starch Casein agar, pH 7.0–7.2, supplemented with filter-sterilized cycloheximide (50 μg mL^{-1}) and 3% NaCl	Turkey	[38]
Streptomyces taklimakanensis sp. nov.	Desert	Gauze's No. 1 medium [1] supplemented with Nystatin (100 mg mL^{-1}) and nalidixic acid (50 mg mL^{-1})	North-West China	[40]
Streptomyces alkaliterrae sp. nov.	Alkaline soil close to Soda lake	Starch casein agar adjusted to pH 8.5 with 1N NaOH and supplemented with 5% (*w/v*) sodium chloride and cycloheximide and nystatin (each at 50 μg mL^{-1})	India	[37]
Streptomyces cahuitamycinicus sp. nov	Desert soil	Minimal medium supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (10 μg mL^{-1})	Turkmenistan	[53]
Streptomyces acidicola sp. nov.	Soil from peat swamp forest	Humic acid vitamin (HV) agar supplemented with nalidixic acid (25 μg mL^{-1}) and nystatin (50 μg mL^{-1})	Thailand	[51]
Streptomyces harenosi sp. nov.	Sand dunes	Actinomycete isolation agar (HiMedia), pH 7.3	Indonesia	[74]
Streptomyces tibetensis sp. nov.	Acid sandy soil sample	ISP medium 7 adjusted to pH 7.3 at 25 °C supplemented with an inhibitor solution containing $K_2Cr_2O_7$ (25 mg mL^{-1}), calcium propionate (30 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	China	[66]
Streptomyces abyssomicinicus sp. nov.	Rock soil sample	Humic acid vitamin agar	Mexico	[50]
Streptomyces altiplanensis sp. nov.	Arid soil samples	Starch Casein Agar within the pH range of 7.0–7.2, supplemented with 50 μg mL^{-1} nyastatin and 50 μg mL^{-1} cycloheximide	Chile	[65]
Streptomyces cyaneochromogenes sp. nov.	Soil sampled at a manganese contaminated area	Gause's synthetic medium [1], supplemented with 0.04 g $K_2Cr_2O_7$	China	[64]
Streptomyces huasconensis sp. nov.	Arid soil samples	Starch Casein agar within the pH range of 7.0–7.2	Chile	[48]
Streptomyces cadmiisoli sp. nov.	Cadmium-contaminated soil	Modified proline agar medium, supplemented with 2.0–3.0 mL $K_2Cr_2O_7$ solution (1.775 g L^{-1}) in a 100 mL medium + Gause's synthetic agar medium no.1	China	[61]
Streptomyces fodineus sp. nov.	Acidic mine area soil	Acidified (pH 5) starch-Casein Agar supplemented with cycloheximide and nystatin, each at 50 μg mL^{-1}	Korea	[49]

Table 1. *Cont.*

Strain	Nature of the Sample	Isolation Medium	Country	Reference
Streptomyces dengpaensis sp. nov	Desert soil	ISP 7 medium (HiMedia) supplemented with inhibitor solution containing $K_2Cr_2O_7$ (25 mg mL^{-1}), calcium propionate (30 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	China	[67]
Streptomyces durbertensis sp. nov.	Saline–alkali soil	CMKA medium [1] supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North-East China	[69]
Streptomyces polaris sp. nov.	Frozen soil	Humic acid vitamin (HV) agar supplemented with $K_2Cr_2O_7$ (50 mg L^{-1})	High Arctic	[60]
Streptomyces septentrionalis sp. nov.				
Streptomyces desertarenae sp. nov.	Desert Soil	Reasoner's 2A (R2A; BD) agar adjusted to pH 7.0.	China	[57]
Streptomyces manganisoli sp. nov.	Manganese-polluted soil	Modified proline agar medium, supplemented with 2.0–3.0 mL $K_2Cr_2O_7$ solution (1.775 g L^{-1}) in a 100 mL medium	China	[63]
Streptomyces salilacus sp. nov.	Salt lake sediment	ISP (International Streptomyces Project) medium 4 supplemented with 1.5% (*w/v*) NaCl	China	[52]
Streptomyces sediminis sp. nov.	Crater lake sediments	ISP 2 medium supplemented with 10 mg L^{-1} tetracycline with (50 µg mL^{-1}) of nystatin and (5 µg mL^{-1}) of rifampicin	Turkey	[58]
Streptomyces asenjonii sp. nov.	Hyper-arid Atacama desert soils	Humic acid vitamin (HV) agar	Chile, Peru, South America	[73]
Streptomyces aridus sp. nov.	Subsurface soil of Atacama desert	Glucose-yeast extract agar (HiMedia) supplemented with cycloheximide and nystatin (each at 25 µg mL^{-1})	Chile, Peru, South America	[59]
Streptomyces jeddahensis sp. nov.	Desert soil	Mineral salt medium (MSM)	Saudi Arabia	[71]
Streptomyces caldifontis sp. nov.	Hot water spring sediment	Starch casein agar medium supplemented with 25 µg mL^{-1} nystatin	Pakistan	[55]
Streptomyces daqingensis sp. nov.	Saline–alkaline soil	CMKA medium [2] supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North-East China	[56]
Streptomyces actinomycinicus sp. nov.	Soil of a peat swamp forest	Humic acid vitamin (HV) agar supplemented with nalidixic acid (25 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	Thailand	[68]
Streptomyces luozhongensis sp. nov.	Desert soil	Gauze's No. 1 medium [2] pH 7.2, supplemented with 2.0–3.0 mL of $K_2Cr_2O_7$ solution (1.775 g L^{-1}) in a 100 mL medium at pH 7.2	Lop Nur, Xinjiang, North-West China	[54]

Table 1. *Cont.*

Strain	Nature of the Sample	Isolation Medium	Country	Reference
Streptomyces xiangtanensis sp. nov.	Soil near Xiangtan Manganese mine	Gauze's synthetic medium [1] adjusted to pH 7.2, supplemented with 2.0–3.0 mL of $K_2Cr_2O_7$ solution (1.775 g/L) in a 100 mL medium	Central-South China	[62]
Streptomyces arcticus sp. nov.	Frozen soil	Mineral agar 1 Gause medium supplemented with $K_2Cr_2O_7$ (50 mg L^{-1})	Arctic	[75]
Streptomyces canalis sp. nov.	Hypersaline soilsample	B7 medium supplemented with 1.5% (*w*/*v*) NaCl	China	[72]
Streptomyces alkaliphilus sp. nov.	Saline lake sediment	Solid basal medium, Horikoshi 1 supplemented with 100 mL of sterilized 10% Na_2CO_3	Kenya	[76]
Streptomyces lonarensis sp. nov.	Lake sediments (alkaline salt water meteorite lake)	Medium for the isolation of alkalophilic actinomycetes at pH 10.0 or 11.0 (after autoclaving) . Na_2CO_3, or NaOH were separately sterilized and used for adjusting the pH	India	[8]

Refer to Supplementary Table S1 for the composition of each media. The superscript ([1,2]) on some media indicates slight changes in the amount of ingredients used.

3.3. Symbionts

Microorganisms are the most common symbiotic partners of eukaryotes. They live either in mutualism with the host organism or may be parasitic to the host organism [77]. Streptomycetes are not only free species, but have also evolved to live in symbiosis with other animals, fungi and plants [78]. Similar to extreme conditions, *Streptomyces* have developed specific adaptive strategies and it is therefore very important to have knowledge of the sample environment to successfully isolate them [78]. In addition, it is important to know the different environmental factors such as pH, temperature, specific nutrients necessary for the preparation of isolation media [12].

Different parts of plants are sampled for the isolation of Streptomycetes, including tree bark [79], leaf litter [80], bulbil [81], roots [82–84], stem [85–87], fruits [88], seeds [89] and phylloplane [90] (Table 2). Mosses have also been recorded as a source of novel *Streptomyces* spp. [91]. Studies have proven that *Streptomyces* are very important for the growth and development of plants as they play an important role in nutrient uptake, have high absorption of tropospheric di-hydrogen and they also play an important role in forests by actively participating in biodegradation of biopolymers, which increases the fertility of forests soil [92].

Humic acid vitamin agar is typically used to isolate new *Streptomyces* spp. from plant samples [70,77–83]. There are also other isolation media that have been used for isolation, including potato dextrose agar [93] and vitamin arginine agar [88] (Table 2). Different carbon sources have been used in these isolation media, including humic acid, glucose, dextrose, methanol and starch. The main sources of carbon–nitrogen in isolation media are beef or yeast extracts. Additionally, supplements such as nalidixic acid and cycloheximide may be added to the medium to reduce fungal and fastidious bacterial growth as shown in (Table 2).

Plant samples are often pretreated using a range of chemical, physical and thermal methods. Chemical pretreatment includes different concentrations of NaCl [82,88], sodium hypochlorite [89], Lodewyckx pretreatment [81] and hydrogen peroxide [81]. The only heat treatment applied is air-drying, which involves spreading the sample evenly on clean sheets and leaving it at room temperature to remove moisture from the sample [79,83].

This pretreatment is effective because desiccation selectively kills other common bacteria and fungi and activates *Streptomyces* spores [94]. In addition, sonic oscillation can also be applied [80].

Additionally, fungi and lichens are also a source of new Streptomycetes. For example, symbiotic Streptomycetes that reside on fungus farming ants are beneficial because they protect the fungal garden and ants against pathogenic fungi [78]. Streptomycetes have also been shown to suppress phytopathogenic fungi [95]. Streptomycetes are mutually important for fungi because they promote mycorrhizal symbiosis [96], which indirectly benefits plants. For successful isolation of Streptomycetes from fungal samples, vitamin arginine agar [97] and potato dextrose agar [98] (Table 2) were used. No pretreatment was applied to isolate the new Streptomycetes from fungi from the data reviewed.

Table 2. Novel *Streptomyces* spp. reported from plants and Fungi between 2015 and 2020.

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces bauhiniae sp. nov.	Tree bark of *Bauhinia variegata* Linn	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (25 μg mL^{-1})	Thailand	[79]
Streptomyces fuscigenes sp. nov.	Bamboo (*Sasa borealis*) litter	Bennett's Agar adjusted to pH 7.3 with NaOH and supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (20 μg mL^{-1}) at pH 5.5	Republic of Korea	[80]
Streptomyces dioscori sp. nov.	Bulbil of *Dioscorea bulbifera* L.	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (25 mg L^{-1})	South-West China	[81]
Streptomyces carminius sp. nov.	Roots of *Sophora alopecuroides*	Gauze's No. 1 medium [3] at pH 7.5	North-West China	[84]
Streptomyces geranii sp. nov.	Root of *Geranium carolinianum Linn*	Humic acid vitamin (HV) agar supplemented with nystatin (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[83]
Streptomyces populi sp. nov.	Stem of *Populus adenopoda*	Humic acid vitamin (HV) agar supplemented with nalidixic acid (25 mg L^{-1}) and cycloheximide (50 mg L^{-1})	China	[87]
Streptomyces lichenis sp. nov.	Lichen sample	Arginine-vitamin (AV) agar	Thailand	[97]
Streptomyces roietensis sp. nov.	Surface-sterilized stem of jasmine rice, *Oryza sativa* KDML 105	Humic acid vitamin (HV) agar	Thailand	[85]
Streptomyces capparidis sp. nov.	Fruits of *Capparis spinosa*	Tap water-yeast extract (TWYE) witin the pH range of 7.0–7.2 supplemented with 3% (*w/v*) NaCl	China	[88]
Streptomyces ginkgonis sp. nov.	Aril of a seed of *Ginkgo biloba*	Gause's Synthetic agar medium [2] supplemented with streptomycin sulphate (10 μg mL^{-1}) and actidione (50 μg mL^{-1})	Yangling, China	[89]
Streptomyces tremellae sp. nov.	Culture of mushroom *Tremella fuciformis*	Potato dextrose agar (PDA) medium (200 gpotato tissue, 20 g glucose, 20 g agar and 1000 mL deionized water, pH 5.6); cycloheximide (100 μg mL^{-1})	China	[98]

Table 2. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces polygonati sp. nov.	Root of *Polygonatum odoratum* (Mill.)	Humic acid-vitamin agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[82]
Streptomyces pini sp. nov.	Phylloplane of pine (*Pinus sylvestris* L.) needle-like leaves	Ammonium mineral salts medium amended with 0.5% (*v*/*v*) methanol as carbon source and cycloheximide (10 µg mL^{-1})	India	[90]
Streptomyces phyllanthi sp. nov.	Stem of *Phyllanthus amarus*	Yeast extract-malt extract medium (ISP2 medium) supplemented with 10 µg L^{-1} tetracycline	Thailand	[86]
Streptomyces bryophytorum sp. nov.	Moss (Bryophyta)	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North China	[91]

Refer to Supplementary Table S1 for the composition of each media. The superscript (^{2,3}) on some media indicates slight changes in the amount of ingredients used.

Furthermore, several studies have shown that insects are also an important host of *Streptomyces*. They are beneficial for the insect microbiome because they influence the production of metabolites and the biosynthetic potential to inhibit and resist pathogens [99]. The main areas of insects that studies generally focus on are the intestinal region [100,101], the cuticle [102], and the head region [93,103–106] (Table 3). Studies have shown that Streptomycetes live in symbiosis with insects and strengthen their defensive mechanism by producing chemicals for ecological adaptation [99]. For example, endosymbiotic *Streptomyces* live in the antennal glands of female solitary wasps, where they are secreted as a white matter that the larvae absorb and wrap around their cocoon as a defense mechanism [107].

As with other samples, to isolate Streptomycetes from insects, different carbon sources (humic acid, starch, methylcellulose and oats) can be added to the isolation media [93,100,102,106] as well as cycloheximide and nalidixic acid have been the main supplements in isolation settings [102–106]. Unlike samples from plants and extreme environments, only two different pretreatment procedures have been applied to insect-derived samples from the data collected, which include physical pretreatment where the sample was shaken in a rotary shaker at 180 r.p.m. at 28 °C for 30 min [102–106], or a chemical pre-treatment where samples were surface sterilized in 70% ethanol [100].

Table 3. Novel *Streptomyces* spp. reported from insects and other animals between 2015 and 2020.

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces smaragdinus sp. nov.	Gut of the fungus-farming termite *Macrotermes natalensis*	Chitin agar supplemented with 0.05 g L^{-1} cycloheximide	South Africa	[101]
Streptomyces buecherae sp. nov.	Femaloe cave myotis bat (*Myotis velifer*)	ISP 2 Medium	New Mexico	[108]
Streptomyces corynorhini sp. nov.	Male Townsend's big-eared bat	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}), nalidixic acid (50 mg L^{-1}), trimethoprim (50 mg L^{-1})	New Mexico	[109]

Table 3. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces capitiformicae sp. nov.	Head of an ant (*Camponotus japonicus* Mayr)	Sodium succinate-asparagine agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid 20 mg L^{-1}	China	[104]
Streptomyces lasiicapitis sp. nov.	Head of an ant(*Lasius fuliginosus* L.)	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[106]
Streptomyces camponoti sp. nov.	Cuticle of *Camponotus japonicus* Mayr	Gause's synthetic agar no. 1 [1] adjusted to pH 7.2 supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	Harbin, Heilongjiang, China	[102]
Streptomyces cuticulae sp. nov.				
Streptomyces amphotericinicus sp. nov.	Head of an ant	Sodium succinate-asparagine agar pH 7.2, supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	Harbin, Heilongjiang, China	[103]
Streptomyces kronopolitis sp. nov.	Millipede (*Kronopolites svenhedind* Verhoeff)	Gause's Synthetic Agar No. 1 [1] supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[110]
Streptomyces camponoticapitis sp. nov.	Head of an ant (*Camponotus japonicus* Mayr)	Tap Water Yeast Extract Agar (TWYE)[2] supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[105]
Streptomyces formicae sp. nov.	Head of *Camponotus japonicus* Mayr ant	Gause's synthetic agar no. 1 [1] supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[93]
Streptomyces fractus sp. nov.	Gut of a South African termite	Medium II at pH 7, supplemented with 50µg mL^{-1} cycloheximide and 10 µg mL^{-1} nalidixic acid	South Africa	[100]

Refer to Supplementary Table S1 for the composition of each media. The superscript ([1]) on some media indicates slight changes in the amount of ingredients used.

3.4. Soil and Sediments

Actinomycetes represent up to 50% of the total population of Actinobacteria found in the soil (varies on different soil) [111]. They play a major role in the soil by biodegrading biopolymers such as lignocellulose, cellulose and hemicellulose [112–114]. *Streptomyces* also play an important role in biogeochemical cycles due to their high ability to produce the enzyme hydrogenase, which actively participates in the hydrogen cycle [92]. In addition, *Streptomyces* also influence the structure of soil microbial communities [115]; they are involved in the decomposition of plant litter and the formation of organic matter in the soil [116], as well as weathering of rocks [117]. New strains of Streptomycetes have been isolated from different soil samples, including rhizospheric soil [118–120], free soil [121–123], forest soil [124–126], wetland soil [127], and the sediments and the soil of the savannah. There were 16 new *Streptomyces* spp. isolated and reported from the rhizosphere (Table 4), which underlines the importance of *Streptomyces* spp. to plants. *Streptomyces* in the rhizosphere are essential for plant growth and development as they enhance root and shoot growth, biological nitrogen fixation, mineral solubilization, and they also serve as biological control agents against insects, pests and pathogens [10].

For the preferential isolation of Streptomycetes from soil, a number of isolation methods have been reported to enhance the growth of *Streptomyces*. Different isolation agars that could selectively isolate *Streptomyces* spp. have been used. Humic acid vitamin agar is prolific in the isolation of novel *Streptomyces* spp. isolates (Table 4). Other commonly used isolation media include starch casein agar and Gauze synthetic agar (Table 4).

Table 4. Novel *Streptomyces* spp. reported from terrestrial soil samples between 2015 and 2020.

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces triticiradicis sp. nov.	Rhizosphere soil of wheat (*Triticum aestivum* L.)	cellulose-proline agar (CPA) supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	Central China	[128]
Streptomyces coryli sp. nov	Soil from a commercial hazelnutorchard	Stevenson's medium no. 3 adjusted to pH 7.0 and supplemented with cycloheximide (50 µg mL^{-1}), nalidixic acid (10 µg mL^{-1}), nystatin (50 µg mL^{-1}) and novobiocin (10 µg mL^{-1})	Turkey	[129]
Streptomyces paludis sp. nov.	Alpine wetland soil	Gause's synthetic agar medium [2] adjusted pH 7.2	China	[130]
Streptomyces boluensis sp. nov.	Lake sediment	M1 agar supplemented with filter-sterilized cycloheximide (50 mg mL^{-1}) and rifampicin (5 mg mL^{-1})	Turkey	[131]
Streptomyces roseicoloratus sp. nov.	Soil in cotton fields	GJ medium adjusted to pH 7.0–7.5	North-West China	[132]
Streptomyces soli sp. nov.	Birch forest soil	Streptomyces Project 2 (ISP2) medium (yeast extract–malt extract agar) adjusted to pH 7.2 supplemented with 10 mg L^{-1} tetracycline	China	[133]
Streptomyces albicerus sp. nov.	River sediment	Glycerol-arginine medium adjusted to pH 7.5 and supplemented with 100 µL of 50 mg mL^{-1} $K_2Cr_2O_7$ in a 100 mL medium to reduce fungal contamination	China	[134]
Streptomyces inhibens sp. nov.	Rhizosphere soil of wheat (*Triticum aestivum* L.)	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North-East China.	[118]
Streptomyces dangxiongensis sp. nov.	Grass soil	Gause's synthetic agar medium [2] adjusted to pH 7.2 and supplemented with nalidixic acid (25 µg mL^{-1})	China	[135]
Streptomyces rhizosphaericola sp. nov.	Brazilian Cerrado biome (wheat rhizosphere)	Glucose Yeast Extract Agar (GYEA) –HiMedia	Brazil	[119]
Streptomyces sporangiiformans sp. nov.	Soil collected from Mount Song	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[136]

Table 4. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces monticola sp. nov.	Soil from Mount Song	Sodium succinate-asparagine agar adjusted to pH 7.2 and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[137]
Streptomyces tritici sp. nov.	Rhizosphere soil of wheat (*Triticum aestivum* L.)	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 µg L^{-1}) and nalidixic acid (20 µg L^{-1})	Central China	[120]
Streptomyces venetus sp. nov.	Rhizosphere soil of an oil palm (*Elaeis guineensis*)	Starch casein agar (SCA) adjusted to pH 7.0–7.2 supplemented with nalidixic acid (25 µg mL^{-1}) and cycloheximide (50 µg mL^{-1})	Thailand	[138]
Streptomyces xiangluensis sp. nov.	Soil from Xianglu Mountain	Sodium succinate-asparagine agar adjusted to pH 7.2 and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[139]
Streptomyces urticae sp. nov.	Rhizosphere soilof *Urtica urens* L.	Cellulose proline agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	northeast China	[140]
Streptomyces tunisialbus sp. nov.	Tunisian rhizosphere soil of *Lavandula officinalis*	Glucose yeast-malt extract agar (DSMZ medium 65)	Tunisia (North America)	[141]
Streptomyces flavalbus sp. nov.	Rhizosphere of maize (*Zea mays* L.)	Humic acid vitamin (HV) agar supplemented with nystatin (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North-East China	[142]
Streptomyces lutosisoli sp. nov.	Muddy soil from stream	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North-East China	[143]
Streptomyces boninensis sp. nov.	Soil	Humic acid vitamin (HV) agar supplemented benlate (final conc. 25 µg mL^{-1} (*w/v*)) and nalidixic acid (final conc. 25 µg mL^{-1} (*w/v*))	Japan	[123]
Streptomyces triticisoli sp. nov.	Rhizosphere soil of wheat	Gause's Synthetic Agar No. 1 [2] adjusted to pH 7.2 supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[144]
Streptomyces cerasinus sp. nov.	Soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 µg mL^{-1}) and nalidixic acid (25 µg mL^{-1})	Thailand	[121]
Streptomyces solisilvae sp. nov.	Tropical forest soil	Starch–casein–nitrate agar within the pH range of 7.0–7.2 and supplemented with cycloheximide (50 µg mL^{-1}), nystatin (50 µg mL^{-1}) and nalidixic acid (20 µg mL^{-1})	China	[126]

Table 4. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces thermoalkaliphilus sp. nov.	Soil of a tropical rainforest	Humic acid vitamin (HV) agar	China	[145]
Streptomyces swartbergensis sp. nov.	Soil collected from the banks of the Gamka river	MC agar pH 7.4	South Africa	[146]
Streptomyces luteus sp. nov.	Soil	Mannitol-casein acid hydrolysis (GW1) medium prepared with 5% (*w/v*) NaCl	Southern China	[122]
Streptomyces xylanilyticus sp. nov.	Soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (25 μg mL^{-1})	Thailand	[147]
Streptomyces odonnellii sp. nov.	Soil savanna	Malt extract–yeast extract–glucose-agar medium pH 7.0	Brazil	[148]
Streptomyces fuscichromogenes sp. nov.	Soil from a tropical rain forest	Yeast extract-malt extract agar (ISP 2) supplemented with 10 mg L^{-1} tetracycline	China	[149]
Streptomyces krungchingensis sp. nov.	Soil collected from Krung Ching Waterfall National Park	Starch casein nitrate agar within the pH range of 7.0–7.2 and supplemented with nystatin (25 mg L^{-1}) and tetracycline (10 mg L^{-1})	Thailand	[150]
Streptomyces rhizosphaerihabitans sp. nov.	Rhizosphere soil and humus layer from bamboo forest	Starch casein agar at pH 5.5 adjusted with HCl	Korea	[151]
Streptomyces adustus sp. nov.				
Streptomyces indoligenes sp. nov.	Rhizosphere soil of *Populus euphratica*	Gause's synthetic agar medium [2] adjusted to pH 7.2	China	[152]
Streptomyces yangpuensis sp. nov.	Soil	Gause's synthetic agar medium [2] adjusted to pH 7.2	China	[116]
Streptomyces xinjiangensis sp. nov.	Soil	Reasoner's 2A (R2A) agar medium at pH 7.2; adjust with crystalline K_2HPO_4orK_2HPO_4 before adding agar	China	[153]
Streptomyces alfalfae sp. nov.	Rhizosphere soil in an alfalfa field	International Streptomyces Project 2 (ISP2) supplemented with 10 mg L^{-1} tetracycline	China	[154]
Streptomyces palmae sp. nov.	Oil palm (*Elaeis guineensis*) rhizosphere soil	Starch casein agar (SCA) within the pH range of 7.0–7.2 supplemented with nalidixic acid (25 μg mL^{-1}) and cycloheximide (50 μg mL^{-1})	Thailand	[155]
Streptomyces gamaensis sp. nov.	Tropical soil	Gause's synthetic agar No. 1 adjusted to pH 7.2 and supplemented with nystatin (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	Gama, Chad	[156]
Streptomyces andamanensis sp. nov.	Soil	Starch casein nitrate agar plates (HiMedia) supplemented with 25 mg mL^{-1} nystatin	Thailand	[157]

Table 4. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces lacrimifluminis sp. nov.	Soil from river bank	Gause's synthetic agar medium [3] adjusted to pH 7.2 supplemented with nalidixic acid (25 μg mL^{-1})	China	[158]
Streptomyces olivicoloratus sp. nov.	Forest soil	HV agar adjusted to pH 7.2 and supplemented with 50 mg mL^{-1} filter-sterilized cycloheximide, 50 mg mL^{-1} nystatin and 0.5 mg mL^{-1} rifampicin	Korea	[159]
Streptomonospora halotoleransans sp. nov.	Muddy soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	China	[160]
Streptomyces tyrosinilyticus sp. nov.	River sediment	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	North China	[161]
Streptomyces albiflavescens sp. nov.	Rainforest soil	ISP 2 medium with 10 mg L^{-1} tetracycline	South-West China	[124]
Streptomyces polymachus sp. nov.	Forest soil	Humic acid vitamin (HV) agar	South Korea	[125]
Streptomyces maoxianensis sp. nov.	Pine forest soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	South-West China	[162]
Streptomyces rubrisoli sp. nov.	Red soil	Modified mineral-medium agar containing 0.5% sorbitol supplemented with cycloheximide, nystatin, nalidixic acid (each at 50 μg mL^{-1}), and novobiocin (at 25 μg mL^{-1})	China	[163]
Streptomyces gilvifuscus sp. nov.	Forest soil	Humic acid vitamin (HV) agar	Republic of Korea	[164]
Streptomyces lushanensis sp. nov.	Soil from mount Lushan	ISP media	China	[165]
Streptomyces bambusae sp. nov.	Bamboo rhizosphere soil	Humic acid vitamin agar (HV agar) adjusted to pH 7.2 and supplemented with filter-sterilized cycloheximide (50 μg mL^{-1}), nystatin (50 μg mL^{-1}), and rifampicin (0.5 μg mL^{-1})	Republic of Korea	[166]
Streptomyces sasae sp. nov.	Rhizosphere soil of bamboo (*Sasa borealis*)	Starch casein agar adjusted to pH 8.5	Republic of Korea	[167]

Refer to Supplementary Table S1 for the composition of each media. The superscript ([2,3]) on some media indicates slight changes in the amount of ingredients used.

Different pretreatment techniques have also been applied to samples, such as ultrasonic treatment [140], orbital shaking [166] and water bath sonication [163], and are crucial to activate Streptomycete spores and inhibit the growth of unwanted microbes [168] (Table 5). Subjecting the sample to heat treatment for 1 h at 120 °C [146] is an important pre-treatment because actinomycete spores, including Streptomycetes, are more resistant to desiccation than other facultative and Gram–negative anaerobic bacteria [94]. In addition, the selective isolation of actinobacteria by suspending the sample in 1.5% phenol for 30 min is a chemical

pretreatment used [138] that disrupts the cell wall of other common bacteria and fungi and improves the growth of *Streptomyces* [94]. Furthermore, treatment of samples by air-drying for a week [121,130,147] or two [129,136] is a commonly used pretreatment method (Table 5). Moreover, different carbon sources (cellulose, glucose, chitin, starch, dextrose, mannitol and proteose) and combined nitrogen-carbon sources (casein, yeast extract, malt extract, tryptone and peptone) have been added to the media for successful isolation of Streptomycetes [128,129,133,136] from soil sediments (see Table 4 and Supplementary Notes on Supplementary Table S1). Highlighted data shows that soil and sediment are the main source of new *Streptomyces* spp. in the terrestrial environment (Figure 1), followed by the extreme environment and other symbionts.

Table 5. Different pre-treatments employed for the isolation of novel *Streptomyces* spp. terrestrial samples between 2015 and 2020.

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
Heat Treatment				
Heated at 120 °C for 15 min	Arid, non-saline soil sample (sand dunes)	Actinomycete isolation agar (HiMedia), pH 7.3	45 °C for up to 14 days	[74]
One gram of soil was suspended in 1.5% (*w/v*) phenol solution and incubated at room temperature for 30 min	Soil from peat swamp forest	Humic acid vitamin (HV) agar supplemented with nalidixic acid (25 μg mL^{-1}) and nystatin (50 μg mL^{-1})	30 °C for 14 days	[51]
Air-dried at room temperature for 14 days and suspended with strength Ringer's solution	Soil sample from a commercial hazelnutorchard	Stevenson's medium no. 3 supplemented with cycloheximide (50 μg mL^{-1}), nalidixic acid (10 μg mL^{-1}), nystatin (50 μg mL^{-1}) and novobiocin (10 μg mL^{-1})	28 °C for 21 days.	[129]
Heating at 55 °C for 6 min in a thermo-regulated bath	Arid soil samples	Starch Casein agar within the pH range of 7.0–7.2	28 °C for 14–21 days	[48]
	Atacama desert soil	Starch Casein Agar within the pH range of 7.0–7.2, supplemented with 50 μg mL^{-1} nyastatin and 50 μg mL^{-1} cycloheximide	28 °C for 14 days	[65]
Heated at 60 °C for 20 min	Acidic mine area soil	Acidified (pH 5) Starch-Casein Agar supplemented withcycloheximide and nystatin, each at 50 μg mL^{-1}	30 °C for 14 days	[49]
Heated at 85 °C for 15 min	Rock soil sample	Humic acid vitamin agar	28 °C for three weeks	[50]
Wet heat (20 min, 60 °C)	Crater lake sediments	ISP 2 medium supplemented with 10 mg/L tetracycline, nystatin (50 μg/mL) and rifampicin (5 mg mL^{-1})	28 °C for 14 days	[58]
Heat treated at 120 °C for 1 h	Soil from the banks of Gamka river	MC agar adjusted to pH 7.4	30 °C for 21 days	[146]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
Pre-heated at 55 °C for 20 min, was incubated at 28 °C for 21 days	Hot water spring soil	Starch casein agar medium within the pH range of 7.0–7.2 supplemented with 25 μg mL^{-1} nystatin	28 °C for 2 weeks	[55]
Pre-heated suspension 60 °C for 20 min	Lake sediment	M1 agar supplemented with filter-sterilized cycloheximide (50 mg mL^{-1}) and rifampicin (5 mg mL^{-1})	28 °C for 21 days	[131]
Dried at 55 °C for 48 hrs.	Soil sample near Xiangtan manganese mine	Gause's synthetic medium [1] adjusted to pH 7.2 and supplemented with 2.0–3.0 mL of $K_2Cr_2O_7$ solution (1.775 g L^{-1}) in a 100 mL medium	30 °C after incubation for 7–12 days	[62]
Heated at 55 °C in a water bath for 5 min	Soil	Starch casein nitrate agar plates (HiMedia) supplemented with 25 mg mL^{-1} nystatin	28 °C for 14 days	[157]
Air-dried at room temperature for 14 days	Desert soil	Minimal medium within the pH range of 7.5–8.0 supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (10 μg mL^{-1})	28 days at 28 °C	[53]
	Soil from mount Song	Sodium succinate-asparagine agar pH 7.2 supplemented with cycloheximide (50 mg L^{-1}) and Nalidixic acid (20 mg L^{-1}).	28 °C for 21 days	[137]
	Soil collected from mount Song	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 28 days	[136]
Air-dried at room temperature for 7 days	Soil of a peat swamp forest	Humic acid vitamin (HV) agar supplemented with nalidixic acid (25 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	30 °C for 4 days	[68]
	Soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (25 μg mL^{-1}),	30 °C for 3 weeks.	[121]
	Soil	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (25 μg mL^{-1})	30 °C for 3 weeks	[147]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
	Tree bark of *Bauhinia variegata* Linn	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 µg mL^{-1}) and nalidixic acid (25 µg mL^{-1})	30 °C for 3 weeks	[79]
Air-dried at room temperature for a week	Soil sampled at a manganese-contaminated field	Gause's synthetic medium [1] supplemented with 0.04 g $K_2Cr_2O_7$	28 °C for 7–14 days	[64]
	Alpine wetland soil	Gause's synthetic medium [2] adjusted to pH 7.2	28 °C for 21 days	[130]
Air-dried at room temperature for 48 h	Root of *Geranium carolinianum* Linn	Water–yeast extract agar supplemented with actidione (50 mg L^{-1}) and nalidixic acid (25 mg L^{-1})	28 °C for 2–6 weeks	[83]
Air-dried	Soil of a tropical rainforest	Humic acid vitamin (HV) agar	50 °C in the dark for 5 days	[145]
Air-dried at room temperature	Forestsoil	Humic acid vitamin (HV) agar	28 °C for 3 weeks	[164]
Air-dried for 72 hrs and then incubated at 40 °C for 16 hrs.	Forest soil	Humic acid vitamin (HV) agar	28 °C for 3 weeks	[125]
Heated to 40 °C for 16 hrs.	Forest soil	HV agar supplemented with 50 mgL^{-1} cycloheximide at pH 7.2 and starch-casein agar at pH 7.2 and supplemented with 50 mg mL^{-1} filter-sterilized cycloheximide, 50 mg mL^{-1} nystatin and 0.5 mg mL^{-1} rifampicin	28 °C for 3 weeks	[159]
Physical treatment				
Shaken at 250 r.p.m. in 100 mL of sterile water with glass beads for 30 min at 20 °C	Rhizosphere soil of wheat (*Triticum aestivum* L.)	Cellulose-proline agar (CPA) supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 3 weeks	[128]
Mixed on a tumble shaker for an hour	Alkaline soil adjacent to a meteoric alkaline soda lake	Starch casein agar adjusted to pH 8.5 with 1N NaOH and supplemented with 5% (*w/v*) NaCl and cycloheximide and nystatin (each at 50 µg mL^{-1})	28 °C for 4 weeks	[37]
Shaken at 180 r.p.m. overnight	Desert	Gauze's No. 1 medium [1] supplemented with Nystatin (100 mg mL^{-1}) and nalidixic acid (50 mg mL^{-1}) which had been filter sterilized (0.22 µm pore) before being added to 45 °C molten agar	28 °C for 21 days	[40]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
1 g of soil was diluted in 50 m of 1 g L^{-1} 3-morpholinopropanesulfoinc acid solution with 0.2 g l-1 $CaCO_3$. The resulting soil suspension was shaken at 180 r.p.m. min^{-1} at 30 °C for 1 hr	Acid sandy soil	ISP medium 7 pH adjusted to 7.3 at 25 °C supplemented with an inhibitor solution containing $K_2Cr_2O_7$ (25 mg mL^{-1}), calcium propionate (30 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	30 °C for 14 days	[66]
Sonic oscillator (Sonics Vibra-Cell VCX750) for 40 s at 30 W in 9 mL sterilized water	Bamboo (*Sasa borealis*) litter	Bennett's Agar supplemented with cycloheximide (50 µg mL^{-1}) and nalidixic acid (20 µg mL^{-1}) at pH 5.5	28 °C for 2 weeks	[80]
Shaken at 180 r.p.m. at 30 °C for 1 hr	Desert soil	ISP 7 medium (HiMedia) supplemented with $K_2Cr_2O_7$ (25 mg mL^{-1}), calcium propionate (30 mg mL^{-1}) and cycloheximide (50 mg mL^{-1})	30 °C for 7 days	[67]
Incubation in an orbital shaker at 37 °C, 200 r.p.m. for 1 hr.	Desert Soil	Reasoner's 2A (R2A; BD) agar adjusted to pH 7.0.	37 °C for 7 days	[57]
Suspended in distilled water (2 mL) followed by an ultrasonic treatment (160 W) for 3 min + soil suspension was incubated at 28 °C and 250 r.p.m. on a rotary shaker for 30 min	Rhizosphere soil of *Urtica urens* L.	Cellulose proline agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1}).	28 °C for 21 days	[140]
Ultrasonic treatment (160W) for 3 min followed by incubation of soil sample at 28 °C and 250 r.p.m. on a rotary shaker for 20 min	Saline–alkali soil	CMKA medium supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 14 days	[69]
Shaking on a rotary shaker at 180 r.p.m. at 28 °C for 30 min	Cuticle of *Camponotus japonicus* Mayr	Gause's synthetic agar no. 1 adjusted to pH 7.2 and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1}).	28 °C for 21 days	[102]
	Head of an ant	sodium succinate-asparagine agar at pH 7.2 and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1}).		[103]
	Head of an ant (*Camponotus japonicus* Mayr)	sodium succinate-asparagine agar at pH 7.2 and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})		[104]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
	Head of an ant (*Camponotus japonicus* Mayr)	Tap Water Yeast Extract Agar (TWYE)) supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})		[105]
	Head of an ant (*Lasius fuliginous* L.)	Humic acid vitamin (HV) agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 21 days	[106]
Kept in an orbital shaker (28 °C, 180 r.p.m.) for 1 hr.	Soil	Reasoner′s 2A (R2A) agar medium at pH 7.2; adjust with crystalline K_2HPO_4 orK_2HPO_4	28 °C for 14 days	[153]
Shaken on a rotary shaker at 250 r.p.m. at 28 °C for 30 min	Millipede (*Kronopolites svenhedind* Verhoeff)	Gause's Synthetic Agar No. 1 at pH 7.2. supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 21 days	[110]
	Rhizosphere soil of wheat			[144]
Ultrasonic treatment (160 W) for 3 min + incubation at 28 °C and 250 r.p.m. on a rotary shaker for 20 min	Saline–alkaline soil	CMKA medium prepared with 10 % (*w/v*) NaCl and supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 14 days	[56]
500l sterile water with shaking on a rotary shaker at 180 r.p.m at 28 °C for 30 min	Head of *Camponotus japonicus* Mayr ant	Gause's synthetic agar no. 1 [2] supplemented with cycloheximide(50 mg L^{-1}) and nalidixic acid (20 mg L^{-1}).	28 °C for 21 days	[93]
Water bath sonicator for 2 min at 30 °C	Red soil	Modified mineral-medium agar containing 0.5 % sorbitol supplemented with cycloheximide, nystatin, nalidixic acid (each at 50 µg mL^{-1}), and novobiocin (at 25 µg mL^{-1})	28 °C for 3–4 weeks	[163]
Orbital shaking at 120 r.p.m. for 2 weeks	Bamboo rhizosphere soil	Humic acid vitamin agar (HV agar) at pH 7.2 and starch-casein agar supplemented with filter-sterilized µg mL^{-1} cycloheximide (50 µg mL^{-1}), nystatin (50 µg mL^{-1}), and rifampicin (0.5 µg mL^{-1})	28 °C for 2 weeks	[166]
Chemical Treatment				
Lodewyckx pretreat–ment method	Bulbil of *Dioscorea bulbifera* L.	Humic acid vitamin (HV) agar containing cycloheximide (50 mg L^{-1}) and nalidixic acid (25 mg L^{-1})	28 °C for 2–6 weeks	[81]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
3% NaCl	Saltern soil	Starch Casein agar within the pH range of 7.0–7.2 supplemented with filter-sterilized cycloheximide (50 µg mL^{-1}) and 3% NaCl	28 °C for 30 days	[38]
1.5% (*w/v*) NaCl	Salt lake sediment	ISP (International Streptomyces Project) medium 4 prepared with 1.5% (*w/v*) NaCl	28 °C for 5 days	[52]
One gram of soil was suspended in 9 mL 1.5% (*v/v*) Phenol for 30 min	Rhizosphere soil of an oil palm (*Elaeis guineensis*)	Starch casein agar (SCA) wthin the pHrange 7.0–7.2 supplemented with nalidixic acid (25 μg mL^{-1}) and cycloheximide (50 µg mL^{-1})	30 °C for 14 days	[138]
Suspended and diluted with a solution [0.38% K_2HPO_4, 0.12% KH_2PO_4, 0.51% $MgSO_4.H_2O$, 0.25% NaCl, 0.005% $Fe_2(SO_4)_3.H_2O$, 0.005% $MnSO_4.5H_2O$]	Soil	Humic acid vitamin (HV) agar supplemented benlate [final conc. 25 µg mL^{-1} (*w/v*)] and nalidixic acid [final conc. 25 µg mL^{-1} (*w/v*)]	27 °C for 3 weeks	[123]
2–3 cm stem section excised with sterile scalpel, washed in 20% (1.05% for roots) hydrogen peroxide (10 min) and rinsed 4x in sterile 0.02 M potassium phosphate buffer	Stem of *Populus adenopoda*	Humic acid vitamin (HV) agar containing nalidixic acid (25 mg L^{-1}) and cycloheximide (50 mg L^{-1})	28 °C for 2–6 weeks	[87]
Seeds were surface sterilized withserial washes of 75% ethanol for 1 min, 10% sodium hypochlorite for 5 min and several rinses with distilled water	Aril of a seed of *Ginkgo biloba*	Gause's Synthetic agar medium [2]at pH 7.2. supplemented with streptomycinsulphate (10 µg mL^{-1}) and actidione (50 µg mL^{-1})	28 °C for 21 days	[89]
5% NaCl	Subsurface soil sample of Atacama desert	Glucose-yeast extract agar (HiMedia) supplemented with cycloheximide and nystatin (each at 25 µg mL^{-1})	28 °C for 14 days	[59]
Suspended in 1 mL sterile saline (0.9% NaCl)	Desert soil	Mineral salt medium (MSM) agar containing Nile Red (0.5 µg mL^{-1})	30 °C for five days	[71]
3% (*w/v*) NaCl	Fruits of *Capparis spinosa*	Tap water-yeast extract (TWYE) agarwithin the pH range of 7.0–7.2 supplemented with 3% (*w/v*) NaCl	30 °C for 2–6weeks	[88]

Table 5. *Cont.*

Pre-Treatment	Terrestrial Source	Isolation Medium	Incubation Time/ Temperature	References
Subjected to a seven-step surface sterilization procedure: a 60 s wash in sterile tap water containing cycloheximide (100 mg L^{-1}) and nalidixic acid (20 mg L^{-1}), followed by a wash in sterile water, a 5 min wash in 5% (*v/v*) NaCl, a 10 min wash in 2.5% (*w/v*) $Na_2S_2O_3$, a 5 min wash in 75% (*v/v*) ethanol, a wash in sterile water and a final rinse in 10% (*w/v*) $NaHCO_3$ for 10 min, and then the rinsed root sample was Dried at 100 °C for 15 min.	Root of *Polygonatumodoratum* (Mill.)	Humic acid-vitamin agar supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C fro 14 days	[82]
1.5% (*w/v*) NaCl	Hypersaline soil sample	B7 medium prepared with 1.5% (*w/v*) NaCl	37 °C for 10 days	[72]
10% (*w/v*) NaCl	Saline alkaline soil	CMKA medium supplemented with cycloheximide (50 mg L^{-1}) and nalidixic acid (20 mg L^{-1})	28 °C for 14 days	[56]
Surface sterilized in 70% ethanol for 2 min before being washed twice in sterile distilled H_2O	Gut of a South African termite	Medium II at pH 7.0 supplemented 50 µg mL^{-1} cycloheximide and 10 µg mL^{-1} nalidixic acid	30 °C 4 weeks	[100]

Refer to Supplementary Table S1 for the composition of each media. The superscript (^{1,2}) on some media indicates slight changes in the amount of ingredients used.

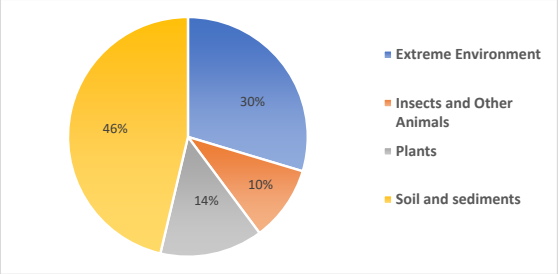

Figure 1. Distribution of new *Streptomyces* spp. sampled from different terrestrial sources. Soils and sediments sources provide 46% of the new *Streptomyces* spp., 30% from extreme environments, 14% from plants and 10% originated from insects.

To summarize, the data collected have shown that soil and sediments are prominent sources of novel *Streptomyces* spp. from the terrestrial environment as shown in Figure 1 below, followed by extreme environments and other symbionts.

4. Novel Streptomycetes Species Isolated from Marine Environments

Despite the fact that marine Actinobacteria are less studied than terrestrial Actinobacteria, studies have revealed that marine sources of Actinomycetes harbor some of the most important bioactive metabolites for industrial and medical applications [12,169]. However, it is still not clear whether these organisms, in particular *Streptomyces* spp., are also present

in terrestrial sources or exclusive to marine environments [170,171]. Several studies have found that actinobacterial spores are generally dormant and wash away from terrestrial ecosystems in runoff and rivers to the ocean floor and remain dormant [171]. There, at the bottom of the ocean, they will often be exposed to harsh conditions such as high pressure, high salinity and nutrient deficiency. As a result, they will evolve genetically over time and produce a secondary metabolite profile distinct from terrestrial actinobacteria [171]. However, to date, knowledge about the chemistry, distribution and biodiversity of marine *Streptomyces* and other genera of marine Actinobacteria is still limited [172]. In addition, marine ecosystems are extremely dynamic and it is very difficult to access varying ocean depths for sampling [173]. However, after the development of SCUBA, microbial ocean studies accelerated for the discovery of new drugs [173]. Marine *Streptomyces* are not only found in seawater and sediments, but also in a wide range of biological sources, including sponges, algae, corals, fish, jellyfish and mangroves [174]. In this review, only two marine sources were reported as sources of new *Streptomyces* spp. namely marine invertebrates and sediments.

4.1. Isolation Methods

Actinobacteria adapt well and successfully colonize different marine ecosystems where they exhibit a wide range of morphologically, physiologically and metabolic diversity. Marine *Streptomyces* may require special growth conditions, which require knowledge and experience to prepare isolation media. To mimic such marine environments, researchers must have in-depth knowledge of the different abiotic factors in the sampled environment to successfully isolate new marine Streptomycetes. Since marine habitats are halophilic environments, salt supplements are important ingredients that are added to the isolation medium to provide osmotic values similar to seawater [175]. In addition, the NaCl added to the medium serves to protect the halophilic bacterial cells from changes in osmotic pressure between the external and internal environment of the bacteria [176]. Similar to the terrestrial environment, culture independent studies using high throughput sequencing are used to study marine microbial communities that are not culturable in the laboratory. At the same time, the knowledge gained over time from these culture independent studies on the morphological and physical characteristics of marine Streptomycetes has led to better strategies for growth and culture media to recover these previously uncultured *Streptomyces* [36,177].

4.2. Invertebrates

About 89% of organisms living in the marine environment are invertebrates [178]. This is clearly reflected by the high number of microbial symbionts associated with this group. These microbial symbionts have produced medically important natural products and studies have shown that Actinomycetes are the most prolific producers of marine novel antibiotics with about 80% of reported compounds from marines' microorganisms originating from actinomycetes [178]. This can be seen by the great diversity of actinobacteria colonizing marine habitats. *Streptomyces* are also known to be abundant in marine habitats [167,173]. For successful isolation of marine *Streptomyces*, different concentrations of sodium salts were added to the medium of different marine samples. Some of the isolation media supplemented, 50% (*v/v*) sea water [179,180], 3% NaCl [181,182] and even up to 70% seawater can be added to the growth media [183]. In addition, isolation media are made specifically to isolate *Streptomycetes* spp. from marine samples [182]. In addition to humic acid isolation agar [179,184], other isolation agars such as actinomycete isolation agar [181], inorganic salt-starch agar [183] and starch and casein [180] have also been used to isolate new Streptomycetes from the marine environment. In comparison, humic acid and starch are the only two sources of carbon supplemented reported for us for the isolation of marine invertebrate Streptomyces [179,181,182]. Among these supplements, casein is the main source of carbon-nitrogen [180–182]. Other isolation media have been summarized in Table 6. Notably, a sample underwent chemical pretreatment using 3% NaCl [184]. Three

percent NaCl has proven to be the optimum concentration that supports actinobacterial growth compared to concentrations lower or higher than 3% [185]. Moreover, the addition of NaCl to the medium selectively inhibits other fastidious microbes by altering the ionic strength of the medium, thus generating an osmotic shock for the microbes resulting in dehydration and growth retardation resulting in cell death [186,187]. Furthermore, NaCl addition also disrupts the solubility of oxygen by disrupting enzymatic functions, thus reducing the growth rate of fastidious bacteria and fungi [188].

Table 6. Novel *Streptomyces* spp. reported from marine vertebrates and invertebrates between 2015 and 2020.

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces reniochalinae sp. nov. *Streptomyces diacarni* sp. nov.	LHW50302^T from *Reniochalina stalagmitis* LHW51701^T from *Diacarnus megaspinorhabdosa*	Streptomyces Isolation Medium agar plates containing 3% sea salt (*w/v*), 50 mg L^{-1} cycloheximide and 25 mg L^{-1} nalidixic acid.	China	[182]
Streptomyces tirandamycinicus sp. nov.	Marine sponge	Humic acid vitamin (HV) agar prepared with 50% (*v/v*) seawater and supplemented with $K_2Cr_2O_7$ (100 mg L^{-1})	China	[179]
Streptomyces zhaozhouensis subsp. *mycale* subsp. nov.	Marine sponge (*Mycale* sp.)	Actinomycetes Isolation Agar (HiMedia) supplemented with 1% sponge extract and gentamycin (2 mg 100 mL^{-1}), cycloheximide (2.5 mg 100 mL^{-1}), and amphotericin B (1 mg 100 mL^{-1}).	India	[181]
Streptomyces atlanticus sp. nov.	Marine sponge *(Aplysina fulva)*	Humic acid vitamin (HV) agar amended with 3% NaCl, nystatin (100 µg mL^{-1}), cycloheximide (100 µg mL^{-1}) and nalidixic acid (50 µg mL^{-1})	Brazil	[184]
Streptomyces hyaluromycini sp. nov.	Tunicate (*Molgula manhattensis*)	Inorganic salts−starch agar (ISP 4) supplemented with cycloheximide (25 mg mL^{-1}), potassium dichromate (50 mg mL^{-1}) and nystatin (50 mg mL^{-1}) supplemented with nalidixic acid (20 mg L^{-1}) and cycloheximide (50 mg L^{-1})	Japan	[183]
Streptomyces bohaiensis sp. nov.	Young *Scomberomorus niphonius* in (long, slender, laterally flattened, pelagic fish with longitudinal dark spots on the sides and ~ 15 cm in fork length)	Oatmeal agar international Streptomyces project (ISP 3) (HiMedia) containing nalidixic acid (25 mg L^{-1}) and cycloheximide (50 mg L^{-1})	China	[189]
Streptomyces spongiicola sp. nov.	Marine sponge	Starch casein nitrate agar at pH 7.0–7.2, prepared with 50% (*v/v*) seawater and supplemented with actidione (50 mg mL^{-1}), nystatin (50 mg mL^{-1}) and nalidixic acid (20 mg mL^{-1}).	China	[180]

Refer to Supplementary Table S1 for the composition of each media.

4.3. Sediments

Marine sediments represent 63.5% of the Earth's surface [190], constituting inorganic and organic products from erosion of landmasses, volcanic activities and biochemical activities in the ocean [191]. Apparently, this ecosystem is the most under-sampled marine habitat [192], presumably due to the inaccessibility of the deep-sea floor. Marine sediments have a remarkable diversity of microbial communities constituting approximately 0.18–3.6% of the Earth's total living biomass [193,194].

In this context, sediments refer to shallow- [195] to deep-water sediments [196], sandy beaches [197] and mangrove sediments [34,198,199] (Table 7). Reports have suggested

that these habitats harbor a great number of microbial species, which are still under-explored [12,172]. This is clearly reflected from the data collected at the time of writing where deep-sea sediments are the least sampled for *Streptomyces* (Table 7) compared to sediments from mangrove forests. A total of 20 new *Streptomyces* species were isolated from marine sediments between 2015 and 2020 (Table 7) Microorganisms in seawater play an important role in the marine food chain by recycling and breaking down organic matter and other biochemical processes [200]. From this study, 11 out of 20 new *Streptomycetes* spp. from marine sediments were isolated from mangrove habitats (Table 7).

Streptomycetes from marine sediment samples were isolated using several isolation media. One of the most widely used media is the International *Streptomyces* Project (ISP2) media [34,201–204] (Table 7). As seen with marine invertebrate-derived samples, NaCl is also an important ingredient in the isolation medium of marine sediments. These sodium sources include both fresh and aged seawater [196,199] or NaCl solution [205,206] to give the medium an ionic strength similar to that of the sampled environment. In addition, different carbon sources (chitin, dextrose, glucose and soluble starch) combined with carbon-nitrogen sources (casein, peptone, malt extract, yeast extract and tryptone) were added to the medium to successfully isolate them. Furthermore, the media were also supplemented with nystatin and cycloheximide [196,197,199,204,207–210].

Table 7. Novel *Streptomyces* spp. from marine sediments between 2015 and 2020.

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces marianii sp.	Subtidal marine sediment	Gause's inorganic agar media (pH 7.2–7.4) supplemented with 75 mg mL^{-1} of cycloheximide and 25 mg mL^{-1} of nystatin	India	[196]
Streptomyces otsuchiensis sp. nov.	Marine sediment	Bushnell–Haas medium supplemented with 1.0% (*w*/*v*) pre − sterilized olive oil by dry − heat sterilization at 135 °C for 5 hrs and 3.0% (*w*/*v*) NaCl	Japan	[205]
Streptomyces nigra sp. nov.	Rhizosphere soil *Avicennia marina*	Modified ZoBell 2216E agar plates (HiMedia)	China	[211]
Streptomyces caeni sp. nov.	Mangrove mud	Inorganic salts/starch [International Streptomyces Project (ISP) 4]. Final pH adjusted to 7.2 at 25 °C that had been made with 70% aged seawater in distilled water (instead of pure distilled water), and supplemented with cycloheximide (25 mg mL^{-1}), potassium dichromate (50 mg mL^{-1}) and nystatin (50 mg mL^{-1})	China	[199]
Streptomyces qaidamensis sp. nov.	Sand	Gause's synthetic agar medium [2] at pH 7.2 supplemented with nalidixic acid (25 µg mL^{-1})	China	[197]
Streptomyces monashensis sp. nov.	Mangrove soil	ISP2 agar	Malaysia	[34]
Streptomyces euryhalinus sp. nov.	Sediment in a mangrove forest	Enrichment medium at pH 7.5	India	[198]
Streptomyces colonosanans sp. nov.	Sediment in mangrove soil	ISP 2 medium supplemented with cycloheximide (50 µg mL^{-1}) and nalidixic (20 µg mL^{-1})	Malaysia	[201]
Streptomyces kalpinensis sp. nov.	Salt water beach	GW1 medium	China	[195]
Streptomyces humi sp. nov.	Mangrove soil	ISP 2 medium supplemented with cycloheximide (25 µg mL^{-1}) and nystatin (10 µg mL^{-1})	Malaysia	[206]

Table 7. *Cont.*

Strain	Nature of Sample	Isolation Medium	Country	Reference
Streptomyces litoralis sp. nov.	Salt water beach	GW1 medium prepared with 5% (*w/v*) NaCl	China	[212]
Streptomyces ovatisporus sp. nov.	Marine sediments collected at a depth of 42 m	Non-sporulating medium within the pH range of 7.2–7.4 and supplemented with filter-sterilized rifampicin (5 μg mL^{-1}) and nystatin (50 μ g mL^{-1})	Turkey	[204]
Streptomyces chitinivorans sp. nov.	Brackish sediment of a fish dumping yard in Chilika lake	Colloidal Chitin agar (CCA) medium supplemented with nystatin (50 mg L^{-1})	India	[208]
Streptomyces verrucosisporus sp. nov.	Marine sediments	Seawater– proline supplemented with cycloheximide (50 μg mL^{-1}) and nalidixic acid (25 μg mL^{-1})	Thailand	[207]
Streptomyces antioxidans sp. nov.	Mangrove forest soil	ISP 2 supplemented with cycloheximide (25 μg mL^{-1}) and nystatin (10 μ g mL^{-1})	Malaysia	[213]
Streptomyces malaysiense sp. nov.	Mangrove soil	ISP 2 agar supplemented with cycloheximide (25 μ g mL^{-1}) and nystatin (10 μ g mL^{-1})	Malaysia	[202]
Streptomyces lonarensis sp. nov.	Lake sediment	Beef extract-yeast extract-glucose agar medium adjusted to a pH between 8 and 10 with addition of an appropriate amount of 10% sterile Na_2CO_3 solution	India	[8]
Streptomyces gilvigriseus sp. nov.	Mangrove sediments	ISP 2 supplemented supplemented with cycloheximide (25 μg mL^{-1}) and nystatin (10 μg mL^{-1})	Malaysia	[203]
Streptomyces mangrovisoli sp. nov.	Mangrove sediments	ISP 2 supplemented with cycloheximide (25 μ g mL^{-1}) and nystatin (10 μ g mL^{-1})	Malaysia	[209]
Streptomyces mangrovi sp. nov.	Mangrove sediments	SM3 agar (Gauze's medium) 2 at pH 7.0 and supplemented with filter sterilized solutions of cycloheximide (50 μ g mL^{-1}), nalidixic acid (10 μ g mL^{-1}), novobiocin (10 μ g mL^{-1}) and Nystatin (50 μ g mL^{-1}).] supplemented with sterile seawater (3.3%, *w/v*)	Egypt	[210]

Refer to Supplementary Table S1 for the composition of each media. The superscript (^{2}) on some media indicates slight changes in the amount of ingredients used.

More than 70% of the new *Streptomyces* spp. were isolated from marine sediments and only 7 (29%) of the new *Streptomyces* spp. from the marine environment were isolated from marine invertebrates (Figure 2).

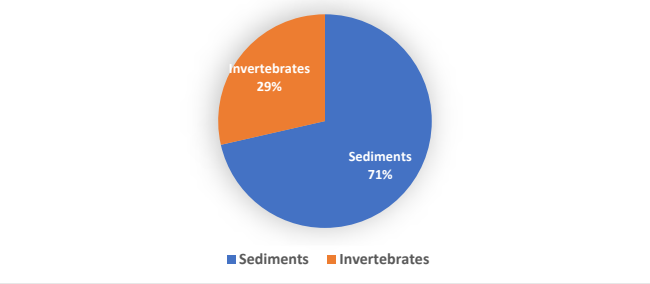

Figure 2. Marine sources of novel *Streptomyces* spp. between 2015 and 2020 shows 71% of the total novel *Streptomyces* spp. originated from sediments and 29% were isolated from marine invertebrates.

The pre-treatment of samples is also an important procedure for marine sediments, with heat being the most commonly applied pre-treatment (Table 8). Of the 27 novel *Streptomyces* spp. isolated from marine samples, less than half of the samples, constituting only 11 new *Streptomyces* spp., have undergone some form of pre-treatment. The pre-treatments carried out were either treatment by the wet method [201,208,213] or by dry heat [199,207]. Chemical pre-treatment is used when a source of sodium is added such as 3% NaCl [205] or 3.3% seawater [210]. Sodium modifies the tonicity of the isolation medium and thus selectively inhibits the growth of unwanted microbes [186].

Table 8. Pretreatment Method for isolation of novel *Streptomyces* spp. From marine sources between 2015–2020.

Pre-Treatment	Marine Source	Isolation Medium	Incubation Time/ Temperature	References
Heat Treatment				
Heated at 55 °C for 6 min, then suspended in 100 mL sterile aged seawaterand stirred for 30 min.	Mangrove mud	Inorganic salts/starch [International Streptomyces Project (ISP) 4]$^{-}$ Final pH adjusted to 7.2 at 25 °C that had been made with 70% aged seawater in distilled water (instead of pure distilled water), and supplemented with cycloheximide (25 mg mL^{-1}), potassium dichromate (50 mg mL^{-1}) and nystatin (50 mg mL^{-1})	28 °C for 7 days	[199]
Wet heat in sterilized water for 15 min at 50 °C	Sediment in mangrove soil	ISP 2 medium supplemented with cycloheximide(50 µ g mL^{-1}) and nalidixic (20 µ g mL^{-1})	28 °C for 14 days.	[201]
Wet heat in sterilized water (15 min at 50 °C) using a water bath	Mangrove sediment	ISP 2 medium supplemented with cycloheximide (25 µ g mL^{-1}) and nystatin (10 µ g mL^{-1})	28 °C for 7–14 days	[206]
	Brackish sediment of a fish dumping yard in Chilika lake	Colloidal Chitin agar (CCA) medium supplemented with nystatin (50 mg L^{-1})	30 °C for 7 days	[208]
Air-dried at room temperature for 7 days	Marine sediments	Seawater– proline medium supplemented with cycloheximide (50 µg mL^{-1}) and nalidixic acid (25 µg mL^{-1})	28 °C for 2–3 weeks	[207]
Wet heat in sterilizedwater (15 min at 50 °C)	Mangrove Forest soil	ISP 2 supplemented with cycloheximide (25 µ g mL^{-1}) and nystatin (10 µ g mL^{-1})	28 °C for 14 days	[213] [209]
	Mangrove sediments	ISP 2 supplemented supplemented with cycloheximide (25 µg mL^{-1}) and nyastatin (10 µg mL^{-1})	28 °C for 14 days	[203]
Supplemented with sterile seawater (3.3%, *w*/*v*) after incubation at 28 °C for 4 weeks *textfollowing* inoculationwith a pre − heated suspension (60 °C for 15 min)	Sediments around the mangrove plant *Avicennia mariana*	SM3 agar (Gauze's medium 2) at pH 7.0 supplemented with filter sterilized solutions of cycloheximide (50 µ g mL^{-1}), nalidixic acid (10 µ g mL^{-1}), novobiocin (10 µ g mL^{-1}) and nystatin (50 µ g mL^{-1}) and supplemented with sterile seawater (3.3%, *w*/*v*)	28 °C for 4 weeks	[210]
Chemical Treatment				
3.0% (*w*/*v*) NaCl solution	Marine sediment	Bushnell–Haas Medium supplemented with 1.0% (*w*/*v*) pre − sterilized olive oil by dry − heat sterilization at 135 °C for 5 h and 3.0% (*w*/*v*) NaCl	27 °C for 2 weeks	[205]
	Marine sponge (*Aplysina fulva*)	Humic acid vitamin (HV) agar amended with 3% NaCl, nystatin (100 µ g mL^{-1}), cycloheximide (100 µ g mL^{-1}) and nalidixic acid (50 µ g mL^{-1})	28 °C for 21 days	[184]

Refer to Supplementary Table S1 for the composition of each media.

5. Summary

In summary, the data collected have shown that terrestrial environment has been the source of a higher number of novel *Streptomyces* spp. (80%) compared to the marine environment (20%) as shown in Figure 3.

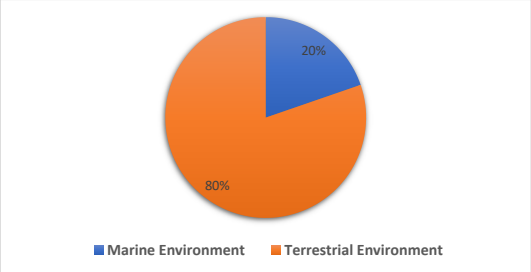

Figure 3. Distribution of novel *Streptomyces* spp. recorded in terrestrial and marine environment between 2015 and 2020, with 80% sourced from terrestrial environments and 20% reported from the marine environment.

6. Streptomyces as Source of Antibiotics

Streptomyces spp. have the genetic capacity to produce an average of 30 secondary metabolites [99], making them the most prolific producers of antibiotics. This genus produces about 80% of the total antibiotics sourced from the phylum Actinobacteria [11,16] and produces two thirds of the antibiotics from natural sources that are currently available for public use [7]. The production of secondary metabolites by Streptomycetes is abundant; when resources are limited, they produce aerial hyphae, which divide into spores that can withstand adverse conditions [214]. This is an important factor for successful colonization by Streptomycetes in normal and extreme environments. Strepomycete secondary metabolites protect the vegetative bacterial cell by sequestering heavy metals such as iron, protecting against UV rays, inhibiting other competitors and playing a major role in quorum sensing [15,99].

The discovery of Streptomycetes as a source of antibiotics began in 1940 when the antibiotic actinomycin, commonly used as chemotherapeutic agent for the treatment of a variety of cancers, was discovered, filling the void left by penicillin that was ineffective against tuberculosis and certain Gram–negative pathogens [215]. Two years later, streptothricin was isolated from *Streptomyces lavendulae* [216] followed by streptomycin from *Streptomyces griseus* [217]. Approximately 12,400 bioactive compounds used clinically and in agriculture were produced by the genus *Streptomyces* throughout the years, such as the immunosuppressive tacrolimus produced by *S. tsukubaensis*, the anti-tumor platenolides were obtained from *S. platensis*, and the insecticide avermectin, as a few examples [6,218]. However, there was a sharp decline in the discovery of such bioactive compounds from 1985 to 2006 [2]. In addition, in the past 30 years, only two *Streptomyces*-sourced antibiotics have been approved for clinical treatment of systemic infections [16]. This has led researchers to focus their attention on the production of bioactive compounds from other genera of actinobacteria, commonly referred to as "rare Actinomycetes" [219]. A recent study has shown that *Streptomyces* spp. are no longer considered a potential source of new antibiotics given that no compound isolated from Streptomycetes underwent clinical trials between 2007 and mid-2013 [12], while three compounds isolated from rare marine Actinomycetes are currently undergoing clinical trials [12]. However, data collected from 2015 to 2020 show that a high number of new secondary metabolites were isolated from Streptomycete species. A total of 279 new natural products with diverse bioactivities were discovered from 121 *Streptomyces* spp. between 2015 and 2020.

6.1. Terrestial Streptomyces as a Source of Antibiotics

Actinomycetes from terrestrial environments produce a large number of bioactive compounds. The data collected showed that despite the decrease in bioactive compounds isolated from Streptomycetes in terrestrial samples, a high number of new secondary metabolites are still isolated from this environment. Seventy-three terrestrial *Streptomyces* spp. were isolated between 2015 and 2020 as sources of 173 new bioactive compounds, the majority of which show significant antibiotic bioactivity.

6.2. Marine Streptomyces as a Source of Antibiotics

Marine natural products (MNPs) are also a prolific source of novel antibiotics [220]. Actinomycete sources alone account for approximately 80% of novel antibiotics derived from the marine environment [178]. Studies targeting specific and understudied marine microbial phyla can result in a greater likelihood of finding specific marine compounds, since most compounds isolated from marine microorganisms are closely related to compounds isolated from terrestrial microorganisms [221]. Unfortunately, the marine environment is one of the most under-explored environments, but still holds as a promising source of new and innovative natural products [220], which is clearly illustrated in Figure 4. Nair et al. (2020), highlighting the urgent need to explore marine habitats for new microbial bioactive compounds [220]. A total of 106 new bioactive compounds have been discovered from 48 *Streptomyces* spp. sourced from the marine environment between 2015 and 2020.

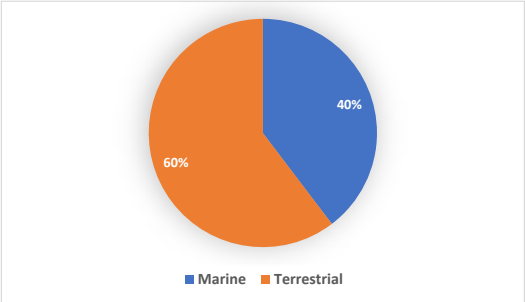

Figure 4. Distribution of *Streptomyces* spp. with novel/new natural products from terrestrial and marine environment between 2015 and 2020. The terrestrial *Streptomyces* spp. were the source of 60% of novel/new natural products while marine *Streptomyces* spp. were sources of only 40% of novel/new natural products.

6.3. New Compounds from Streptomyces spp. with Bioactivity

All new compounds from *Streptomyces* spp. as reported between 2015 and 2020 are reviewed below. Despite the fact that a high number of new compounds were reported during the timeframe covered by this review, only a selection of the structures with significant biological activity as stated in their respective articles are presented.

6.4. Antibacterial Activity

Infections by pathogenic bacteria are a leading cause of death worldwide. Unfortunately, the resistance to antibiotics acquired by pathogenic bacteria has led to an increasing number of untreatable bacterial diseases [220]. Thus, the need to scour natural habitats for new antibacterial compounds has increased. Between 2015 and 2020, 92 new compounds were reported from 39 *Streptomyces* spp. with antibacterial activity against a wide range of bacterial pathogens, including two of the multidrug-resistant pathogens (Table 9). This shows that *Streptomyces* spp. are undoubtedly still the current leading producer of antibacterial agents. Figure 5 showed some examples of new compounds isolated from *Streptomyces* spp. with significant antibacterial activity.

Table 9. Novel/new antibacterial bioactive compounds isolated from *Streptomyces* spp. between 2015 and 2020.

Novel/New Antibacterial Compound	Chemical Class	Antibacterial Activity	Sample Environment	Ref.
Terrestrial Source				
1-Hydroxy-7-oxolavanucyanin and Δ (7″,8″)-6″-hydroxynaphthomevalin	Phenazine/terpene hybrid	G+	Soil	[222]
Krisynomycin B and C	Cyclic Depsipeptide	G+	Desert Sand	[223]
Meliponamycin A and B	Cyclic Hexadepsipeptide	G+	Bees	[224]
Picolinamycin	Pyrimidine alkaloid	G+	Soil	[225]

Table 9. *Cont.*

Novel/New Antibacterial Compound	Chemical Class	Antibacterial Activity	Sample Environment	Ref.
Nybomycin D	Quinoline	G+	Acid mine soil	[226]
Pentaminomycin C–E	Cyclic pentapeptide	G+	Fungi	[227]
Nalidixic acid 1	Quinolone	G-	Rhizospheric soil	[228]
Quinomycin I and J	Cyclic depsipeptide	G+	Mount soil	[229]
Puromycin B–E	Amino-nucleoside	G+	Soil	[230]
Abyssomicin M−X	Spirotetronate polyketide	G+	Soil	[231]
Streptoone A	Linear polyketide	G+	Soil	[232]
Asenjonamide A–C	β-diketone	G+ & G-	Desert soil	[233]
Gordonic acid	polyketide glycoside	G+	Acid mine drainage soil	[234]
Ulleungmycin A and B	Non-ribosmal peptide	G+	Volcanic soil	[235]
Quinomycin A–C	Pyranonapthaquinone	G+	Mountain Soil	[236]
Actinomycin Y_6–Y_9	Bi-cyclic chromopeptide lactone	G+	Soil	[237]
2-amino-*N*-(2-amino-3-phenylpropanoyl)-*N*-hydroxy-3-phenylpropanamide	Hydroxamic acid	G+ & G-	Desert soil	[238]
Angucyclines and angucyclinones	Benz[*a*]anthracene polyketide	G+	Soil	[239]
Streptanoate	Amide ester	G+	Soil	[240]
Xiakemycin A	Pyranonaphthoquinone	G+	Soil	[241]
Methyl ealaiophylins	Macrodiolide	G+	Soil	[242]
7-Prenylisatin	Isatin	G+	Mountain soils	[243]
Marine Source				
Mersaquinone 1	Tetracene	MRSA	Marine sediment	[244]
Dionemycin 1	Chlorinated bis-indole alkaloid	MRSA & G+	Marine sediment	[245]
Streptoglutarimide A–J	Glutarimide	MRSA	Marine mud	[246]
Maculosin-*O*-*α*-L-rhamnopyranoside	Diketopiperazine glycoside	MRSA, G+ & G-	Coastal soil	[247]
Strepoxepinmycin A−D	Naphthoquinone	MRSA, G+ & G-	Marine-derived	[248]
Niphimycin C−E	Macrolide	G+, MRSA &VRE	Marine sediment	[249]
Rakicidin F	Cyclic depsipeptide	G+ & G-	Marine sponge	[250]
Ala-geninthiocin 1	Thiopeptide	G+	Marine sediment	[251]
Fradiamine A	Hydroxamic acid siderophore	G+	Deep-sea sediment	[252]
Lobophorin K	Spirotetronate glycoside	G+	Deep-sea coral	[253]
Pteridic acid C–G	Spiroketal polyketide	G+ & G-	coral	[254]
Neo-actinomycin A and B	Phenoxazine	MRSA & VRE	Marine sediment	[255]
Spiroindimicin E and F	Chlorinated bis-indole alkaloid	G+	Marine sediment	[256]
Ilamycin P	Non-ribosmal peptide	G+	Marine sediment	[257]
Ghanamycin A & B	*γ-Butyrolactone*	Phytopathogens (G+ & G-)	Saltcedar from intertidal zone	[258]
(2*E*, 6*E*)-3,7,11-trimethyldodeca-2,6-dienedioic acid (2)	Unsaturdated fatty Acid	G+	Marine sediment	[259]
Aldgamycin J−O	Macrolide	G+& G-	Marine sediment	[260]

G+–Gram-positive bacteria, G—Gram-negative bacteria, MRSA–Methicillin Resistant *Staphylococcus aureus*, VRE–Vancomycin Resistant *Enterococci*.

6.5. Anticancer Activity

Cancer is a major health crisis and is also a major cause of death globally [246]. Scientific fields devoted to treating cancer have developed rapidly and discoveries in therapeutic methods such as chemotherapy, immunotherapy, radiotherapy and surgery offer effective treatments for cancerous tumors [260]. Natural resources have a high potential in the production of anticancer compounds. A suitable source of anticancer compounds is from *Streptomyces* spp. [260]. During the study period of this review, a total of 82 new anticancer compounds were isolated from 38 *Streptomyces* spp. (Table 10). Figure 6 showed some examples of new compounds isolated from *Streptomyces* spp. with significant anticancer activity.

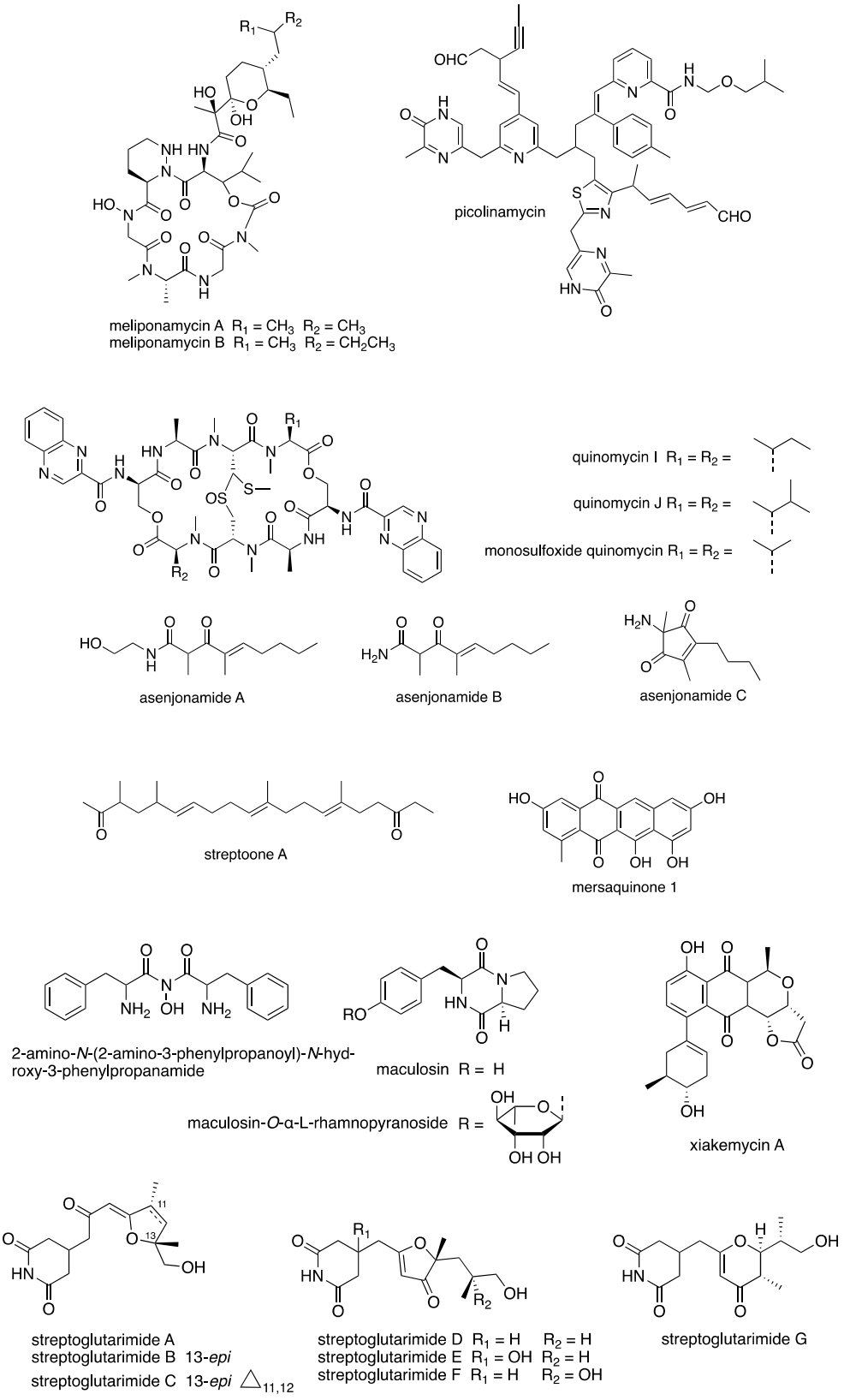

Figure 5. Examples of new compounds isolated from *Streptomyces* spp. between 2015 and 2020 with antibacterial activity.

Table 10. Novel/new anticancer bioactive compounds isolated from *Streptomyces* spp. between 2015 and 2020.

Novel/New Anticancer Compound	Chemical Class	Sample Environment	Ref.
Terrestrial Source			
Azodyrecin B	Azoxide fatty acid	Soil	[261]
Streptimidone 1 & 3	Glutarimide	Soil	[262]
Ilamycin G−R	Non-ribosmal peptide	Soil	[257]
9-Methylstreptimidone 2-α-D-glucopyranoside and hydroxyiso-9-methylstreptimidone	Glutarimide	Soil	[127]
Baraphenazine E	Phenazine	Soil	[263]
Naquihexcin C, E & I	Pyranonaphthoquinone glycoside	Soil	[264]
Nalidixic acid	Quinolone	Rhizospheric soil	[228]
Quinomycin 1 & 3	Cyclic depsipeptide	Mount soil	[229]
ε-Rhodomycinone 1, 4 & 8 and β-Rhodomycinone 2, 3, 5–7 & 9−12	Anthracycline	Soil	[265]
Ulleungdin	Lasso peptide	Soil	[266]
Tetracenoquinocin A	Anthracycline	Soil	[267]
Hisunic acid 1	*Cyclic polyketide*	Soil	[268]
Herbicidin L	Adenosine-nucleoside	Soil	[269]
Actinomycin 2−5	Bicyclic chromopeptide lactone	Soil	[237]
Spectinabilin 1	Linear polyene	Head of ant (*Camponotus japonicas* Mayr)	[270]
Angucycline	Benz[a]anthracene polyketide	Soil	[239]
Streptanoate	Amide ester	Soil	[240]
1,19-Seco-avermectin 3−5	Macrolide	Soil	[271]
Marine Source			
Piericidin F	Pyridine-containing linear polyketide	Mangrove soil	[272]
Salternamide A	Cyclohexenone-containing linear polyketide	Saltern soil	[273]
Donghaecyclinone A–C	Benz[a]anthracene polyketide	Volcanic island marine sediment	[274]
Tetrahydroanthracene derivative 4	Dimeric tetrahydroanthracene	Mairne sponge	[275]
Microeunicellol A	Terpene	Marine sediment	[276]
Dionemycin 1	Chlorinated bis-indole alkaloid	Marine sediment	[245]
2-*epi*-Anthracimycin 2	Macrolide	Marine sediment	[277]
Lactoquinomycin C & D	Napthaquinone	Marine sediment	[278]
10-*epi*-HSAF, 10-*epi*-deOH-HAS, d 10-*epi*-maltophilin, 10-*epi*-xanthobaccin C & 10-*epi*-hydroxymaltophilin	Polycyclic tetramate macrolactam	Mangrove sediment	[279]
Neothioviridamide	Polythioamide	Mangrove soil	[280]
1-hydroxymethyl-8-hydroxy-anthraquinone-3-carboxylic acid	Anthraquinone	Fresh sea anemone (H. lineata)	[281]
Bagremycin C	para-hydroxybenzoic acid ester	Mangrove soils	[282]
Strepoxepinmycin C & D	Naphthoquinone	Marine sediment	[248]
Cyclizidine C	Indolizidine alkaloid	Marine sediment	[283]
9-HydroxyK252c, 3-hydroxy-3′-Nacetylholyrine A, 3- hydroxyholyrine A, streptocarbazole E	Indolocarbazole	Marine sediment	[284]
Geninthiocin 1	Macrocyclic peptide	Subtidal marine sediment	[251]
Deformylated antimycin 6 & 7	Diester alkaloid	Mangrove sediment	[285]
Lobophorin K	Spirotetronate glycoside	Deep sea coral	[253]
Neo-actinomycin A	Bi-cyclic chromopeptide lactone	Marine sediment	[255]
Drimentine I	Hybrid isoprenoid-diketopiperazine	Marine sediment	[286]

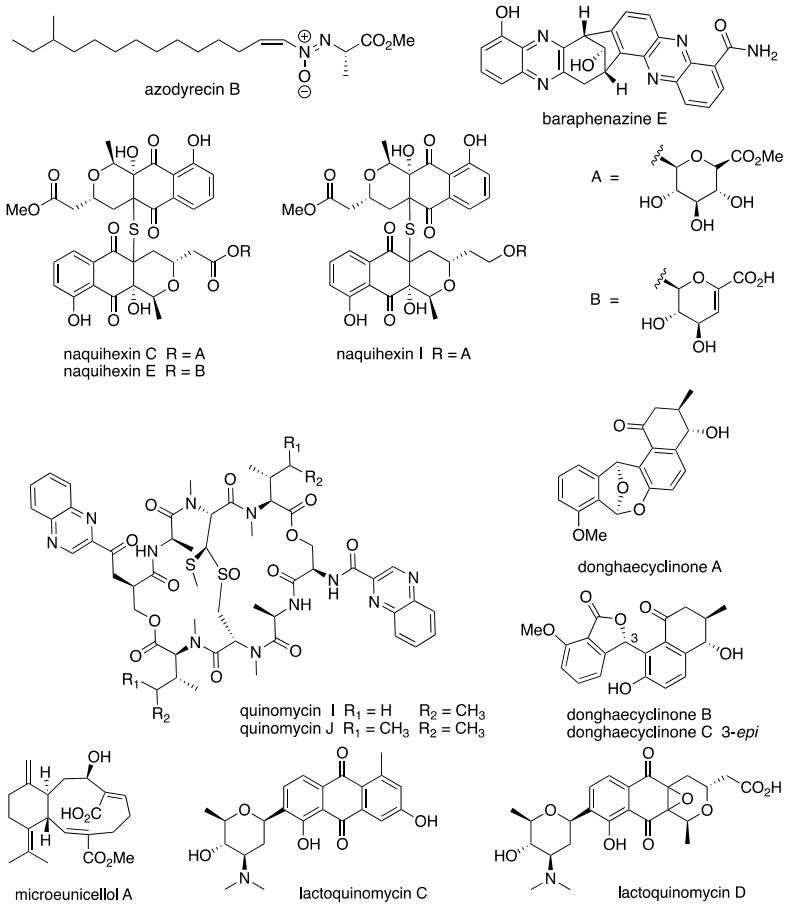

Figure 6. Examples of new compounds isolated from *Streptomyces* spp. between 2015 and 2020 with anticancer activity.

6.6. Enzyme Inhibitor/Inducer Activity

Streptomycetes also produce metabolites with enzyme modulatory activity. There were 27 new compounds derived from 11 *Streptomyces* spp. during the period of study and these compounds exhibit both enzymes inducing and/or inhibitory activity (Table 11).

Table 11. Novel/new compounds with enzyme modulatory activity isolated from *Streptomyces* spp. between 2015 and 2020.

Novel/New Antifungal Compound	Chemical Class	Enzyme Modulatory Activity	Sample Environment	Ref.
Terrestrial Source				
Ulleungamide C	Cyclic depsipeptide	Inhibitor and inducer	Soil	[287]
Formicolide A and B	Macrolide	Inducer	Ant gut (*Formica yessensis*)	[288]
Naphthacemycin B_5-B_{13}	Naphthacene	Inhibitor	Medicinal plant *Senecio scandens*	[289]
Strepantibin A−C	Terphenyl	Inhibitor	Larvae of mud dauber wasp (*Sceliphron madraspatanum*)	[290]
Dinghupeptin A & B	Cyclodepsipeptide	Inhibitor	Soil	[291]
Lorneic acid F & I	Trisubstituted aromatic acid	Inhibitor	Bark of *Betula mandshurica* Nakai	[280]
Marine Source				
Mohangic acid E	Linear polyene	Inducer	Marine mud flat	[292]
Salternamide A and D	Cyclohexenone-containing linear polyketide	Inhibitor	Saltern soil	[273]
Strepoxepinmycin D	Naphthoquinone	Inhibitor	Marine sediment	[248]
Cyclizidine C, F, H & I	Indolizidine alkaloid	Inhibitor	Marine sediment	[283]
3-hydroxy-K252c	Indolocarbazole	Inhibitor	Marine sediment	[284]

Figure 7 showed some examples of new compounds isolated from *Streptomyces* spp. with significant enzyme modulatory activity.

6.7. Antifungal

New antifungal drugs are urgently needed to alleviate infectious diseases caused by pathogenic fungi. At present, drug resistant fungi are evolving continuously, so the need to find new antifungal drugs is increasing. For example, the multi-drug resistant fungi *Candida albicans, Aspergillus fumigatus*, and *Candida glabrata* have all been shown to be resistant to azole drugs after their drug binding sites mutated, thereby reducing binding affinity. In addition, other therapeutic antifungal drugs were also ineffective against these multi-drug resistant species. [293–296]. Interestingly, several compounds obtained from *Streptomyces* spp. have antifungal properties that could be utilized in fighting against drug-resistant and fungal pathogens. 33 new antifungal compounds were reported from nine *Streptomyces* spp. between 2015 and 2020 (Table 12). Figure 8 showed some examples of new compounds isolated from *Streptomyces* spp. with significant antifungal activity.

6.8. Other Biological Activity

There were also new natural products from Streptomycetes, which show other biological activities as described in Table 13 below. A total of 18 different bioactivities were recorded from 23 *Streptomyces* spp., which produced 45 bioactive compounds in total between 2015 and 2020 (Table 13). Figure 9 showed some examples of new compounds isolated from *Streptomyces* spp. with other biological activity.

Table 12. Novel/new antifungal therapeutic compounds isolated from *Streptomyces* spp. between 2015 and 2020.

Novel/New Antifungal Compound	Chemical Class	Sample Environment	Ref.
Terrestrial Source			
Picolinamycin	Pyrimidine alkaloid	Soil	[225]
Baraphenazine E	Phenazine	Soil	[263]
2-amino-*N*-(2-amino-3-phenylpropanoyl)-*N*-hydroxy-3-phenylpropanamide	Hydroxamic acid	Desert soil	[238]
Rimocidin derivative BU16	Macrolide	Soil	[294]
Filipin III, 15-Glycidylfilipin III, 16α, 17α-Epoxyfilipin V &16β, 17β-Epoxyfilipin V	Macrolide	Soil	[297]
Streptoone B	Linear polyketide	Soil	[232]
Abyssomicin M−X	Spirotetronate polyketide	Creek soil	[231]
Marine Source			
Streptoglutarimide A−J	Glutarimide	Marine mud	[246]
Flavofungin I and II	Macrolide	Mangrove soil	[298]

Table 13. Other biological activity from novel/new compounds isolated from *Streptomyces* spp. between 2015 and 2020.

Novel/New Bioactive Compound	Chemical Class	Biological Activity	Sample Environment	Ref.
Naphthacemycin B_5-B_{13}	Naphthacene	Antidiabetic	Medicinal plant *Senecio scandens*	[289]
Benwamycin 2 & 6	Trialkyl-substituted polyketide	Antiproliferative	Soil	[299]
Suncheonoside A, B, and D	Benzothioate glycosides	Antidiabetic	Marine sediment	[300]
Strepantibin A and B	Terpenyl	Antiproliferative	Larvae of mud dauber wasp *Sceliphron madraspatanum*	[290]
Trienomycin J	Macrolide	Antiproliferative	Moss soil-derived	[301]
Streptovitacin A	Glutarimide	Antiproliferative	Marine mud	[246]
Nahuoic acid B−E	Polyol polyketide	Antibiofilm	Marine sediment	[302]
Napyradiomycin SF2415B3	Hybrid isoprenoid		Marine sediment	[303]
Camporidine A	Prenylated naphthoquinone	Anti-inflammatory	Gut of carpenter ant *Camponotus kiusiuensis*	[304]

Table 13. *Cont.*

Novel/New Bioactive Compound	Chemical Class	Biological Activity	Sample Environment	Ref.
Formicolide A and B	Macrolide	Antiangiogenic	Gut bacterial strain of the wood ant (*Formica yessensis*)	[288]
Meliponamycin A & B	Cyclic hexadepsipeptide	Entomopathogenic	*Melipona scutellaris* nurse bees	[211]
Isarubrolone 3 & 4	Polycyclic tropoloalkaloid	Autophagy inducer	Soil	[305]
Abyssomicin I	Spirotetronate polyketide	Inhibits tumor cell invasion	Rock soil	[50]
Naquihexcin C	Pyranonaphthoquinone glycoside	HIV-1 inhibitor	Rhizospheric soil	[264]
Camporidine A	Prenylated naphthoquinone	Antimetastatic	Gut of carpenter ant (*Camponotus kiusiuensis)*	[304]
Aturanoside A & B	Anthraquinone glycoside	Suppresses vascular endothelial growth factor (VEGF)	Soil	[306]
Trienomycin J−L	Macrolide	Inhibited nitric oxide production	Soil moss	[301]
Herbicidin L	Adenosine-nucleoside	Antiparasitic	Soil	[269]
Simamycin	Prenylated nucleoside	Induces differentiation of preadipocytes into matured adipocytes	Soil	[307]
Oxachelin CSpoxazomicin D	Oxazoline carboxamide, peptide	Potent neuroprotectives	Soil	[308]
Aotaphenazine	Phenazine	Overcome tumor necrosisFactor-related apoptosis-inducing ligand (TRAIL).	Soil	[309]
Aotaphenazine	Phenazine	Enhances the levels of apoptosis inducing proteins	Soil	[309]
Inubosin B	Acridine alkaloid	Ngn2 promoter activity and induces mRNA expression of genes related to neural stem cell differentiation.	Soil	[310]

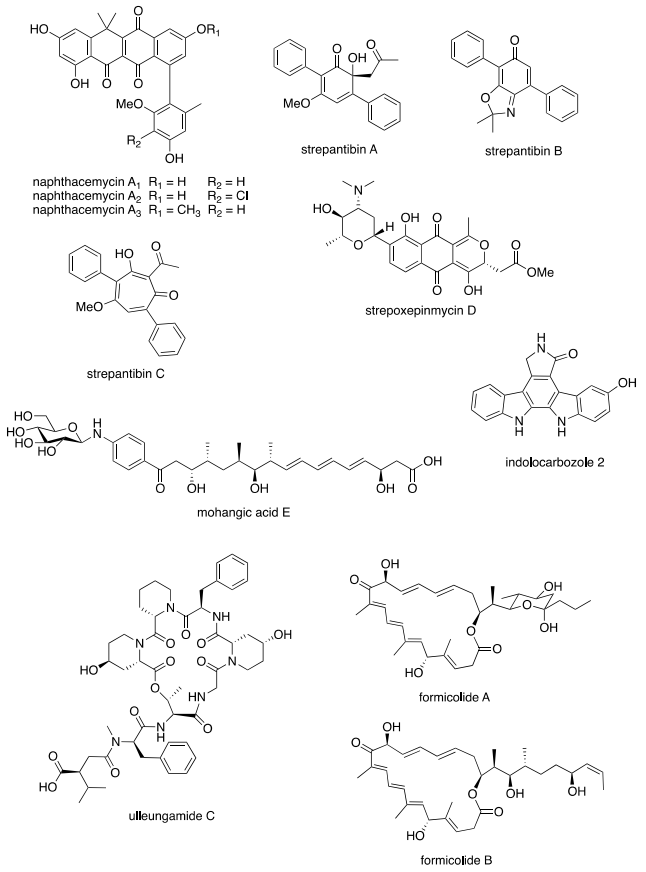

Figure 7. Examples of new compounds isolated from *Streptomyces* spp. between 2015 and 2020 with enzyme modulatory activity.

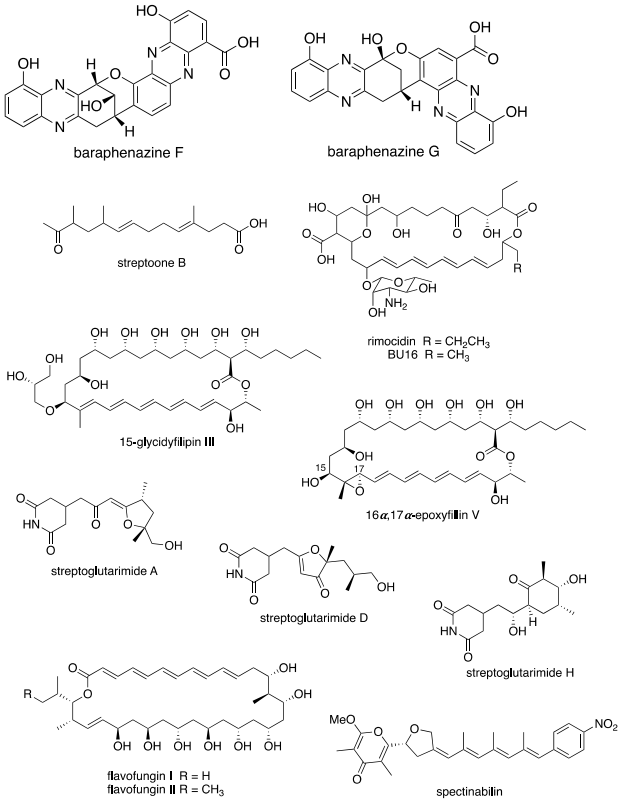

Figure 8. Examples of new compounds isolated from *Streptomyces* spp. between 2015 and 2020 with antifungal activity.

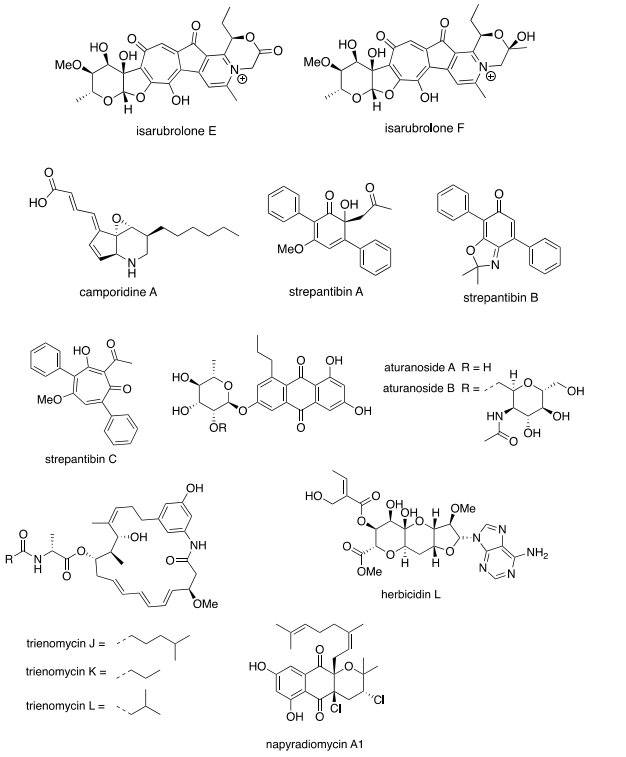

Figure 9. Examples of new compounds isolated from *Streptomyces* spp. between 2015 and 2020 with other biological activity.

Streptomyces spp. are still a potential source of new and interesting secondary metabolites with diverse bioactivities. The significant biological activity of new secondary metabo-

lites obtained from the genus *Streptomycetes* is dominated by antibacterial activity, followed by anticancer, antifungal and enzyme modulatory activities as shown in Figure 10.

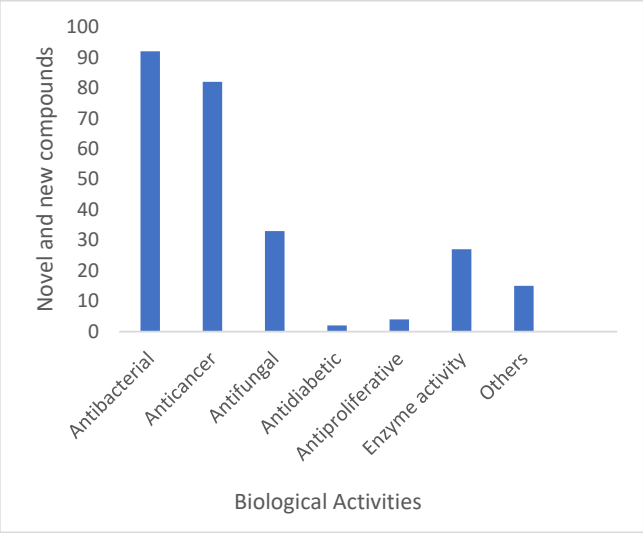

Figure 10. Biological activities exhibited by novel and new secondary metabolites reported from terrestrial and marine Streptomyces spp. between 2015 and 2020.

7. Conclusions and Future Perspectives

During the six years of study (January 2015 to December 2020), a high number of new *Streptomyces* spp. were isolated from terrestrial and marine environments using different isolation procedures. This includes different pre-treatment methods such as chemical, physical and thermal treatments that were used with various selective isolation media to promote the isolation of a total of 135 new Streptomycetes. From this total, 108 new *Streptomyces* spp. (80%) were sourced from terrestrial habitats and 27 (20%) from marine habitats. Additionally, a total of 279 new natural products have been isolated from 121 *Streptomyces* spp. with diverse biological activities. A high number (91) of the new natural products shows antibacterial activity followed by anticancer and antifungal effects.

Streptomyces species are undoubtedly a potential source of pharmaceutically important drugs. Despite the tireless efforts of Scientists to discover bioactive metabolites from other prokaryotic sources, including rare actinomycetes, and synthetic drug production, species of the genus *Streptomyces* are still recognized as a major producer of microbial metabolites. A thorough knowledge and understanding of microbial physiology and metabolism is essential for the successful isolation of novel *Streptomyces* spp. Culture independent studies have also shown that there are large numbers of *Streptomycetes* and new natural products that are remain undiscovered under typical laboratory conditions [14,157]. This should be a guide for the future selective isolation procedure to target these *Streptomyces* spp. and activate their silent biosynthetic gene clusters, which are not expressed under typical laboratory conditions, for new drug discovery. In addition, more effort should be invested in the marine environment for the discovery of new *Streptomyces* spp. and their associated bioactivities.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microbiolres13030031/s1, Table S1: Isolation media compositions.

Author Contributions: Conceptualization, L.D., A.P. and R.S.; Writing—original draft preparation, L.D., A.P. and R.S.; Writing—review and editing, L.D., A.P. and T.T.; Supervision, A.P. and T.T.; Critically evaluated and edited the manuscript, J.O. and R.A.K. Sadly R.S. tragically died in an accident in 2021. All authors have read and agreed to the published version of the manuscript.

Funding: Robert A. Keyzers has provided funding for open access publication fees.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The lead author L.D would like to thank the University of the South Pacific for funding her studies and Robert A. Keyzers for providing open access publication fees. All the authors would like to thank their respective departments for their support and cooperation.

Conflicts of Interest: The authors declare no conflict of interest.

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