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Systematic Review Article

The Antibacterial Activities of Secondary Metabolites Derived from *Streptomyces* sp.

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Abstract: The spreading of infectious diseases caused by the emergence of Multidrug-Resistant (MDR) pathogens is a global threat that has led to numerous deaths annually. In view of this, there is an overwhelming need to discover new bioactive compounds with effective antimicrobial properties. Concurrently, the genus *Streptomyces* has a growing reputation as a potential biological source of various antibiotics and other bioactive metabolites. *Streptomyces* sp. has been isolated from different sources, including terrestrial and marine habitats with a myriad of promising compounds that could be used to treat MDR pathogens. Therefore, this study presents a systematic review of the antibacterial activities of *Streptomyces*-derived secondary metabolites. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist were employed in this study to collect relevant articles from two research databases, namely PubMed and Science Direct. The selection process includes identification, screening, eligibility, and inclusion of articles. Several keywords and criteria were established for the screening and selection process. Based on the results, a total of 26 articles were selected from 70 potential articles. The articles were published between 2015 and 2020 with most studies being published in 2020, indicating an increased interest in *Streptomyces* and its derived compounds. Approximately 51 different *Streptomyces*-derived compounds have been identified, ranging from crude extracts, pure

compounds, and partially purified compounds. Various parameters were also used to assess their antibacterial activities, particularly the Minimum Inhibitory Concentration (MIC) (69%) and the zone of inhibition (11%). Moreover, the antibacterial activities of these compounds were effective on numerous gram-positive and gram-negative bacteria. Furthermore, 46% and 54% of the selected studies were focused on inhibiting MDR and non-MDR pathogens, respectively. In conclusion, both crude and purified compounds from *Streptomyces* sp. exhibited strong antibacterial effects. It is expected that extensive future research would develop a standard method to compare the antibacterial strength of each extracted compound from *Streptomyces* sp. and determine the most effective bioactive compounds to treat diseases caused by MDR pathogens.

Keywords: *Streptomyces*; Secondary Metabolites; Bioactive Compounds; Multidrug-Resistant Pathogens; Antibacterial Activity; *in vitro*

1. Introduction

The re-emergence and transmission of Multidrug-Resistant (MDR) pathogens have become an alarming global health crisis, particularly in developing countries with a high prevalence in hospitals, convalescent homes, and community settings [1]. These human pathogens lead to severe infections of the skin and soft tissues as well as systemic chronic diseases, which are responsible for significant mortalities [2]. The increased bacterial resistance is associated with several factors, such as misuse of antibiotics to treat infections and accelerated transmission of vertical and horizontal genes between bacterial species [3]. Nevertheless, the growing concern over the spreading of MDR pathogens is related to the limited novel antimicrobial agents to substitute those made ineffective by MDR strains [4]. Hence, the discovery, design, and development of new antibacterial drugs have become a more relevant topic in the scientific community to combat emerging MDR pathogens [5].

Streptomyces, which belongs to the phylum Actinobacteria and is a member of the order of Actinomycetales, is a prolific source of antibiotics and other bioactive secondary metabolites [6] . The aerobic gram-positive *Streptomyces* is rich in guanine-cytosine content (GC-content) and possesses both aerial and substrate mycelium [7]. *Streptomyces* have been isolated from numerous sources, including terrestrial (soil, insects, animals, and plants) as well as marine (sediment, fish, corals, sponge) habitats [8]. To date, over 800 species have been discovered with valid names [9,10].

It is understood that members of the *Streptomyces* generate a plethora of secondary metabolites with unique structures and exhibit antimicrobial activities [11]. Almost 75% of the commercially available antibacterial drugs in the market have been developed by this genus alone [12]. These bioactive compounds are primarily extracellular, produced during the growth phase, and are not necessary for growth and reproduction, providing them with a competitive advantage over other microorganisms [13,14]. They also produce numerous secondary with

unique structures belonging to alkaloids, flavonoids, terpenoids, amino acids, and steroids, which have potentially useful medical benefits to humans [15].

In view of the remarkable properties of *Streptomyces* sp. and the essential need to seek alternative bioactive compounds to suppress the emergence of MDR pathogens, this review was carried out to provide the latest insight on the available secondary metabolites derived from *Streptomyces* sp. and their antibacterial activities. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was implemented to gather relevant literature studies from several research databases. Following the selection of articles, a thorough review of each article was conducted to obtain important information regarding the outlined topic.

2. Materials and Methods

2.1. Literature Search Strategies

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist [16]. An electronic literature search was conducted using two databases, namely PubMed and Science Direct. The search was performed using the following search string: '*Streptomyces*' AND 'Secondary metabolites' OR 'Bioactive compounds' AND 'pathogens' AND 'antibacterial activity' AND '*in vitro*'.

2.2. Eligibility Criteria and Study Selection

The criteria for the review process included *in vitro* studies on the antibacterial activities of *Streptomyces*-derived secondary metabolites against pathogens. In addition, articles that were (1) only available in abstract form; (2) not written in English; and (3) books and books chapters, reviews, meta-analyses, conference/proceeding papers, letters to the editor, commentaries, and thesis, were excluded from the search process. The bibliographies of relevant articles were also examined to identify potential articles that were overlooked during the database search. Figure 1 depicts the selection process, from identification to screening, eligibility, and inclusion of articles.

2.3. Study Exclusion

Three independent reviewers (RME, YWK, and MM) screened and extracted the search results by referring to the titles and abstracts, followed by a full-text screening process. Articles that failed to meet the selection criteria were excluded. In case of a disagreement regarding the selection of an article, a group discussion was held with three more reviewers (KYC, NMZ, and NM).

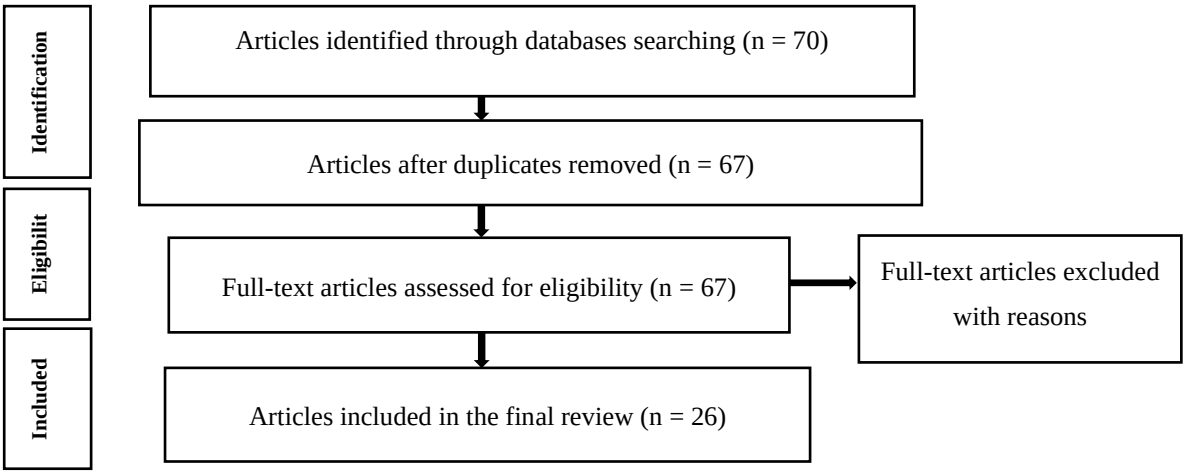


Figure 1. PRISMA flowchart of the systematic literature search.

3. Results

3.1. Extraction of Articles

The preliminary literature search found 70 possible articles, which only include *in vitro* studies and excluded those related to animal or human studies. Three redundant articles were found and immediately removed. The remaining 67 articles were then screened by reviewing the titles and abstracts. Eventually, 41 articles were removed since they did not meet the review criteria. Therefore, 26 articles were selected for the final full-text review process. Figure 2A depicts the number of articles that were published between 2015 and 2020, while Figure 2B shows the number of articles based on the country of origin with the highest number of published articles in India, followed by China.

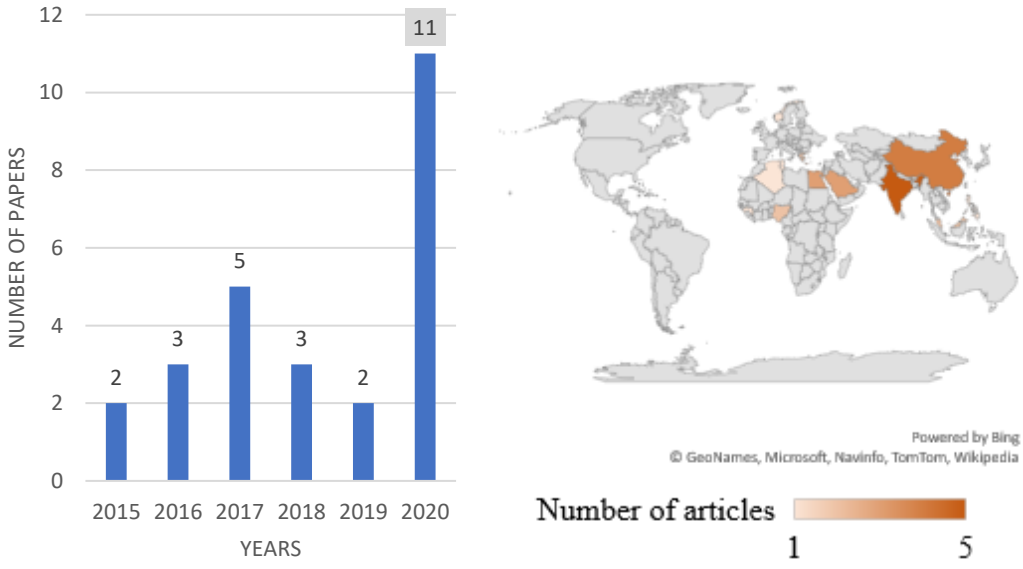


Figure 2. Number of published articles based on (A) year throughout 2015–2020 and (B) publication distribution according to the country of origin.

3.2. General Findings

The systematic review focused only on the antibacterial properties of *Streptomyces* species. The extracted data include the author's name, year of publication, *Streptomyces* species, source/ location of isolation, extracted secondary metabolites, pathogens, type of substance, and strength of the antibacterial activity, as presented in Table 1. Approximately 51 extracted compounds were utilised in the 26 reviewed articles. The chemical structures of each extracted secondary metabolite in the selected articles are shown in Figure 3. The compound of interest was used in the form of crude extracts (8 studies), both crude and pure compounds (3 studies), and partially purified compounds (2 studies). The remaining 13 studies used different pure compounds, as depicted in Figure 4. Moreover, 50% of the *Streptomyces* studies were related to terrestrial sources, while the rest were marine-based sources. Of the terrestrial species, 61% of them were found in soil, followed by 31% in plants and 8% in insects (Figure 5).

Table 1. Extracted secondary metabolites from *Streptomyces* sp. and their strength of antibacterial activity.

***Streptomyces* species**	**Source/ location**	**Extracted secondary metabolites**	**Type of bacteria**	**Type of substance**	**Strength of antibacterial activity**	**Ref.**
Streptomyces sp. strain SBT343	Marine sponge, Greece	**1.** Azalomycin **2.** Streptocytosine **3.** Streptocytosine C **4.** Daryamide A **5.** Azmerone **6.** Antimycin B1 **7.** Usabamycin A **8.** Actinoramide D	**Gram-positive bacteria:** *Staphylococcus aureus* and *Staphylococcus epidermidis*	Crude extract	• BIC: BIC50 (62.5 µg/mL), BIC71.35 (250 µg/mL) • MIC: NM • Inhibition zone: NM	[17]
Streptomyces sp. strain SBT348	Marine sponge, Greece	**9.** Compound SKC3	**Gram-positive bacteria:** *S. aureus* and *S. epidermidis.* SKC3 is more effective against MSRA, MSSA, and VRSA but not against **Gram-negative bacteria:** *Pseudomonas aeruginosa*	Crude extract and pure compound	• MIC of pure compound (31.25 µg/mL) • BIC90 (3.95 µg/mL) • BIC90 of crude extract (62.5 µg/mL) on *S. epidermidis* • Inhibition zone: NM	[18]
Streptomyces griseorubens strain DSD069	Marine sediment, The Philippines	**<u>Anthracycline shunt metabolites:</u>** **10.** Bisanhydroaklavinone **11.** Hydroxy bisanhydroaklavinone	**Gram-positive bacteria:** MRSA	Crude extract and pure compounds	• MIC of crude extract (2.44 µg/mL) • MIC of both compounds (6.25 µg/mL and 50.00 µg/mL, respectively) • Inhibition zone of crude extract (15 mm)	[13]
Streptomyces sp. strain Al-Dhabi-100 (Novel strain)	Marine soil sediment, Saudi Arabia	**12.** Benzenebutanoic acid **13.** Benzestrol **14.** 1-(2,6-dimethyl-4-propoxyphenyl) propan-1-one **15.** Phenol, 4-(1,1-dimethylpropyl) **16.** 1-(2,6-dimethyl-4-pro poxyphenyl) propan-1-one **17.** Ethyl 2-propylphenyl ester	**Gram-positive bacteria:** *Enterococcus faecalis*, *Bacillus subtilis*, *S. aureus*, and *S. epidermidis* **Gram-negative bacteria:** *Klebsiella pneumoniae* **Acid-fast bacteria:** *Mycobacterium tuberculosis*	Partially purified compounds	• MIC of the fractions (62.5, 31.25, 125, and 250, 125 µg/mL, respectively) • MBC of the fractions (62.5 to 500 µg/mL) • MIC against *M. tuberculosis* was not stated • Inhibition zone: NM	[19]

		18. Phenol, 2-methyl-4-(1,1,3,3-tetramethyl butyl) **19.** Androst-5,16-diene-3.beta.-ol **20.** Beta.-carotene-3,30-diol, (3R, 30 R)-all-trans-				
Streptomyces zhazhouensis strain CA-185989	Marine sediment, Equatorial Guinea	**21.** Isoikarugamycin **22.** 28-N-methylikarugamycin **23.** 30-oxo-28-N-methylikarugamycin	**Gram-positive bacteria** MRSA	Pure compounds	• MIC of the pure compounds (2–4, 1–2, and 2–4 µg/mL, respectively) • MBC: NM • Inhibition zone: NM	[20]
Streptomyces sp. strain EG1	Marine wet sediment, Egypt	New tetracene derivatives: **24.** Mersaquinone **25.** Tetracenomycin D **26.** Resistoflavin **27.** Resistomycin	**Gram-positive bacteria** MRSA	Pure compounds	• MIC of the pure mersaquinone (3.36 µg/mL) • BIC: NM • Inhibition zone: NM	[21]
Streptomyces xinghaiensis strain OY62 and *Streptomyces rimosus* strain OG95	Marine sediment, Nigeria	**28.** Phenol,2,4-bis (1,1-dimethyl ethyl)- **29.** 1,2-benzene dicarboxylic acid, bis(2-methyl propyl ester **30.** Phthalic acid, isobutyl 2-pentyl ester **31.** 1,2-benzene dicarboxylic acid, butyl octyl ester **32.** 9-octadecenoic acid, methyl ester **33.** 9-octadecenamide **34.** Dibutyl phthalate **35.** Bis(2-ethylhexyl) phthalate	**Gram-positive bacteria:** *E. faecalis* and *B. subtilis* **Gram-negative bacteria**: *Campylobacter jejuni, P. aeruginosa,* and *Salmonella typhimurium*	Partially purified compounds	• MIC of partially purified extract of co-cultured (3.12–6.25) • MBC: (12.5–25.0 µg/mL)	[22]
Streptomyces sp. strain Al-Dhabi-97	Marine sediment, Saudi Arabia	**36.** 1-phenanthrenemethanol **37.** Phthalic acid, di(2-propylpentyl) ester **38.** Benzenebutanoic acid **39.** Podocarp-7-en-3-one **40.** Indole-3-carboxaldehyde	**Gram-positive bacteria:** *B. subtilis, E. faecalis, S. epidermidis,* and *S. aureus* **Gram-negative bacteria:**	Crude extract	• MIC value of the crude extract against gram-positive bacteria (500, 250, 125, and 62.5 µg/mL, respectively) and gram-negative bacteria	[23]

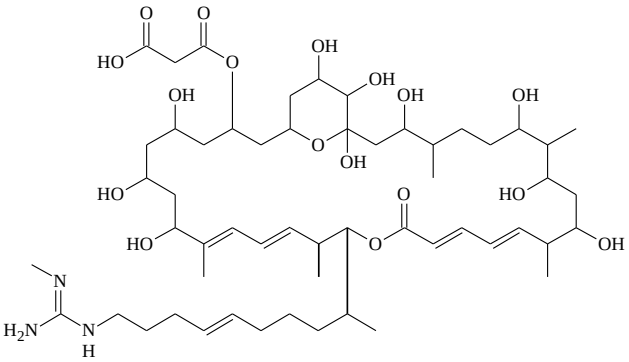
			P. aeruginosa, *K. pneumoniae*, *Escherichia coli*, and *Salmonella paratyphi*		(500, 500, 250, and > 250 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	
Streptomyces sp. strain Al-Dhabi-90	Marine sediment, Saudi Arabia	**41.** 3-methylpyridazine **42.** n-hexadecenoic acid **43.** Indazol-4-one **44.** Octadecanoic acid **45.** 3a-methyl-6-(4-methyl phenyl) sul	**Gram-positive bacteria:** *S. aureus* **Gram-negative bacteria:** *K. pneumoniae* and ESBL (*E. coli*, *P. aeruginosa*, and *Proteus mirabilis*) **Gram-positive bacteria:** Vancomycin-resistant *Enterococcus faecium*	Crude extract	• MIC of the crude extract (12.5, 50, 12.5, 25, and 50 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	[24]
Streptomyces sp. strain KCB132	Marine sediment, China	Five angucyclinones: **46.** (±)-pratensilin D **47.** Pratensilin A **48.** Kiamycin E **49.** Two angucyclinones tetrangulol **50.** 8-O-methylteterangulol	**Gram-positive bacteria:** *S. aureus* and *Bacillus cereus*	Pure compounds	• MIC of (-) pratensilin D (4 µg/mL). In contrast, its (+) enantiomer showed no MIC value • BIC: NM • Inhibition zone: NM	[25]
Streptomyces sp. strain ADI95-16	Marine sponge, Tautra	**51.** Echinomycin **52.** Linearmycin	**Gram-positive bacteria:** *B. cereus*	Pure compounds	• MIC: NM • BIC: NM • Inhibition zone: NM	[9]
Streptomyces sp. strain ASK2	Rhizosphere soil, India	**53.** ASK2	**Gram-negative bacteria:** MDR *K. pneumoniae*	Pure compound	• MBEC of the pure compound (240 µg/mL) • MIC: NM • Inhibition zone: NM	[26]
Streptomyces sp. strain HNM0039 (Novel strain)	Marine sponge, China	**54.** Tirandamycins A **55.** Tirandamycins B	**Gram-positive bacteria:** *Streptococcus agalactiae*	Pure compounds	• MIC of purified compounds A and B (2.52 and 2.55 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	[27]
Streptomyces sp. strain SCSIO11594	Deep sea sediment, South China	**56.** Marangucycline A **57.** Marangucycline B **58.** Dehydroxyaquayamycin **59.** Undecyloprodigiosin **60.** Metacycloprodigiosin	**Gram-positive bacteria:** *E. faecalis* and methicillin-resistant *S. epidermidis* strain shhs-E1	Pure compounds	• MIC of compounds 1–3 (64.0 µg/mL) and *E. faecalis* (16.0 µg/mL) against S. *epidermidis* • BIC: NM • Inhibition zone: NM	[28]

Streptomyces levis	Agricultural soil, north India	**61.** 2,6-disubstituted chromone derivative	**Gram-positive bacteria:** *S. aureus* **Gram-negative bacteria:** *P. aeruginosa* and *K. pneumoniae*	Pure compounds	• MIC of active compounds (6.25, 12.5, and 6.25 µg/mL, respectively) • BIC: NM • Zone of inhibition of the pure compounds (24, 20, and 23 mm, respectively)	[29]
Streptomyces sp. strain ERI-15	Soil, India	**62.** Dibutyl phthalate **63.** 8-hydroxyquinoline **64.** 2-amino-3-chlorobenzoic acid	**Gram-positive bacteria:** S. *aureus*, *B. subtilis*, and MRSA **Gram-negative bacteria:** *E. coli*	Crude extract	• MIC: NM • BIC: NM • Zone inhibition of fractions (12–16 mm)	[30]
Streptomyces misionensis strain V16R3Y1	Soil, Tunisian oasis	**65.** Cyclo-(L-prolyl-L-leucine), cyclo-(L-leu-L-pro) **66.** Phenylacetamide	**Gram-positive bacteria:** *S. aureus*, *E. faecalis*, and *B. cereus* **Gram-negative bacteria:** *P. aeruginosa*, *Escherichia ferusonii*, and *Salmonella enterica*	Pure compounds	• MIC of pure compounds (30, 12, 16, 34, 230, and 11 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	[31]
Streptomyces sp. strain S17	Soil, Egypt	**67.** Behenic acid (docosanoic acid) **68.** Borrelidin **69.** 1H-pyrrole-2-carboxylic acid	**Gram-negative bacteria:** *P. aeruginosa*	Pure compounds	• MIC: NM • BIC: NM • Inhibition zone: NM • Quorum sensing inhibitory concentration (1 mg/mL)	[32]
Streptomyces sp. strain AT37-1 (Novel strain)	Soil, Algeria	**70.** Furanone derivative	**Gram-positive bacteria:** MRSA	Pure compound	• MIC of pure compound (15–30 µg/mL) • MBIC: 10–15 µg/mL • Inhibition zone: NM	[3]
Streptomyces sp. strain MUSC125	Mangrove soil, Malaysia	**71.** Thiophene,2-butyl-5-ethyl **72.** 8-IN-aziridylethylaminol-2-6, dimethyloctene-2 **73.** Pyrroli1,2-alpyrazine-1,4-dion, hexahydro	**Gram-positive bacteria:** MRSA and biofilm	Crude extract	• MIC of crude extract (12.5–25 mg/mL) • MIBC: 1.5625 mg/mL • Inhibition zone: NM	[33]

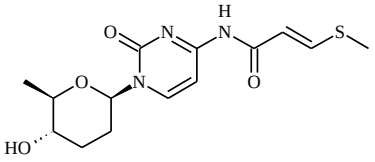
		74. 9,9-dimethyl-3,7-diazabicyclo [3.3.1] nonane				
Streptomyces cuspidosporus strain SA4	Agriculture soil, Egypt	**75.** 1,2-benzene dicarboxylic acid **76.** Bis(2-methylpropyl) ester	**Gram-positive bacteria:** S. *aureus* and *B. subtilis* **Gram-negative bacteria:** *E. coli*, *K. pneumoniae*, *Salmonella typhi*, *Proteus vulgaris*, *Shigella flexneri*, and *P. aeroginosa*	Crude extract and pure compound	• MIC: NM • BIC: NM • Zone of inhibition of partially purified and crude extract at 75 µg (16, 20, 22, 19, 20,17, 18, and 7 mm, respectively)	[34]
Endophytic *Streptomyces coelicolor* strain AZRA37	Medicinal plant, *Azadirachta indica*, India	**77.** Cryptic metabolites	**Gram-negative bacteria:** *Aeromonas hydrophilia*, *S. typhi*, and *S. flexneri* **Gram-positive bacteria:** *E. faecalis* and *S. aureus*	Crude extract	• MIC of crude compounds (40 µg/mL) against gram-negative bacteria and (60 µg/mL) against gram-positive bacteria • BIC: NM • Inhibition zone: NM	[35]
Streptomyces sp. strain SUK25	Beehive ginger plant (*Zingiber spectabile*), Malaysia	**78.** Cyclo-(tryptophanyl-prolyl) **79.** Chloramphenicol	**Gram-positive bacteria:** MRSA	Pure compounds	• MIC of pure compounds (8 and 16 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	[36]
S. ceolicolor strain AOBKF977550	Sawdust, Lagos Lagoon, Nigeria	16 secondary metabolites: **80.** Mutamicin **81.** Hyberimycin **82.** Kanamycin **83.** Daunorubicin **84.** Indolyl-3-carboxylic acid **85.** Mitomycin **86.** 2-phenylacetamide **87.** Streptomycin **88.** Mithramycin **89.** Pilacamycin **90.** Gentamicin **91.** Etamycin **92.** Chloromycetin **93.** Hydroxygentamycin **94.** Tetracycline **95.** Pimprinine	**Gram-positive bacteria:** MRSA and *Bacillus coagulans* **Gram-negative bacteria:** *E. coli* and *K. pneumoniae*	Crude extract	• MIC: NM • BIC: NM • Inhibition zone range from 16 to 21 mm	[37]

Streptomyces olivaceus strain LEP7	Lichen, tree bark, Nilgiris, Tamilnadu	**96.** Cyclopentene	**Gram-negative bacteria:** *E. coli*, *P. aeruginosa*, *Klebsiella sp*, and *Acinetobacter sp* **Gram-positive bacteria:** *S. aureus*	Crude extract	• MIC of partially purified compound (7.81 µg/mL against *E. coli* and *P. aeruginosa*) • BIC: NM • Inhibition zone range between 6 and 12 mm, while no zone of inhibition against *Acinetobacter* sp.	[38]
Streptomyces globisporus strain WA5-2-37	Intestinal tract of American cockroach (*Periplaneta americana*), China	**97.** Actinomycin X2 **98.** Collismycin A	**Gram-positive bacteria:** MRSA	Pure compounds	• MIC of both compounds (0.25 and 8 µg/mL, respectively) • BIC: NM • Inhibition zone: NM	[39]

Note: MIC = Minimum Inhibitory Concentration; BIC = Biofilm Inhibitory Concentration; MBIC50 = Minimal Biofilm Inhibition Concentration at 50%; NM = Not measured, MRSA = Methicillin-Resistant *Staphylococcus aureus*



1. Azalomycin



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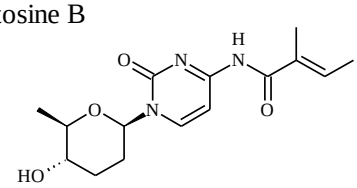
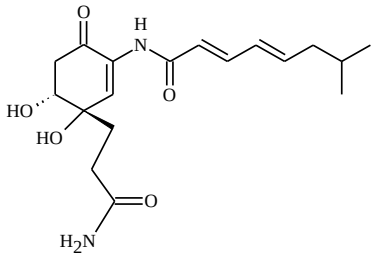
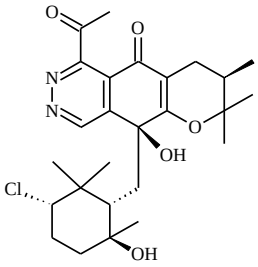


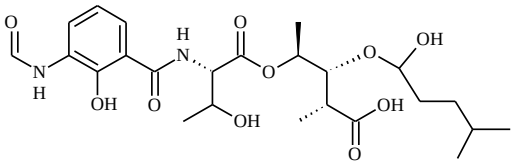
3. Streptocytosine C



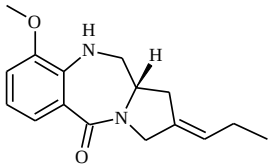
4. Daryamide A



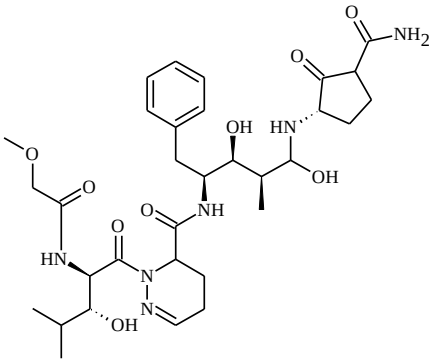
5. Azamerone



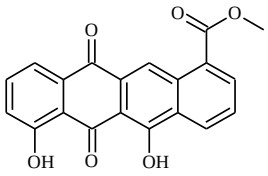
6. Antimycin B1



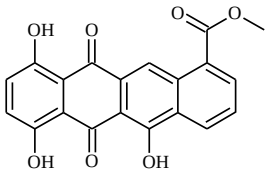
7. Usabamycin A



8. Actinoramide D



9. Bisanhydroaklavinone



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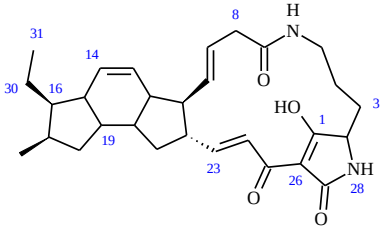
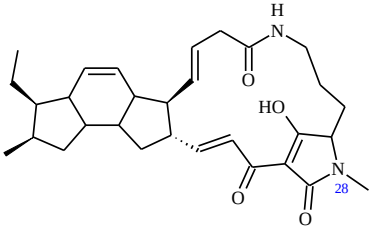
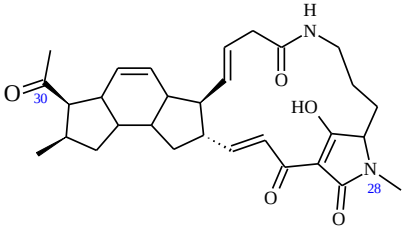


11. Isoikarugamycin

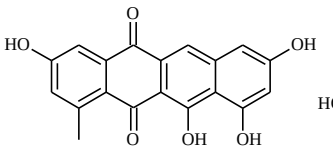


12. 28-*N*-methylikarugamycin

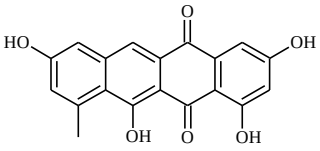


13. 30-oxo-28-*N*-methylikarugamycin

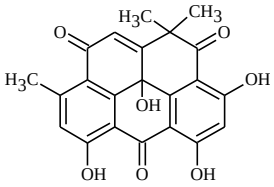
Figure 3. Chemical structures of extracted secondary metabolites that included in the selected articles.



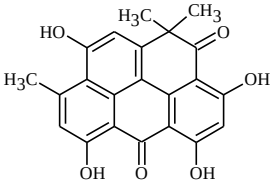
14. Mersaquinone



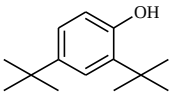
15. Tetracenomycin



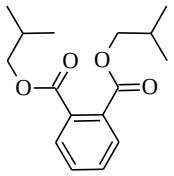
16. Resistoflavin



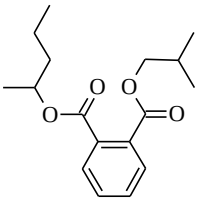
17. Resistomycin



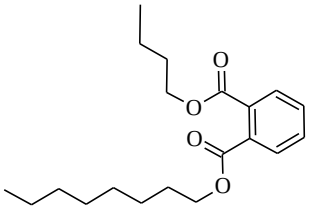
18. Phenol, 2,4-bis (1,1-dimethyethyl)



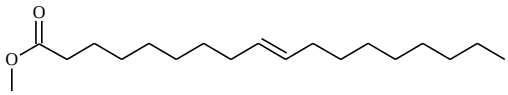
19. 1,2-Benzene dicarboxylic acid bis (2-methyl propyl ester)



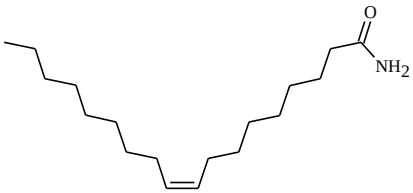
20. Phthalic acid isobutyl 2-pentyl ester



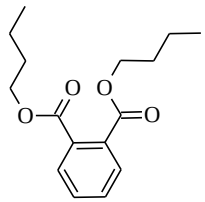
21. 1,2-Benzene dicarboxylic acid, butyl octyl ester



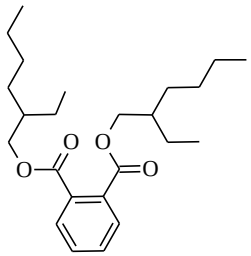
22. 9-Octadecenoic acid, methyl ester



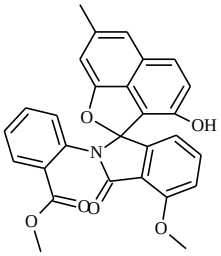
23. 9-Octadecenamide



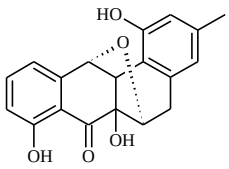
24. Dibutyl phthalate



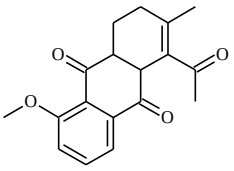
25. Bis (2-ethylhexyl) phthalate



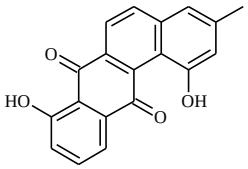
26. (*R*,*S*)-Pratensilin D



27. Pratensilin A

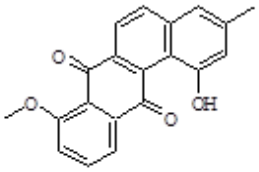


28. Kiamycin E

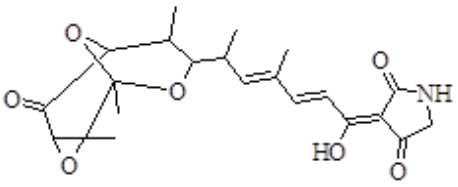


29. Tetrangulol

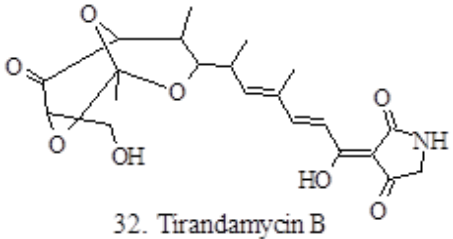
Figure 3. Cont.



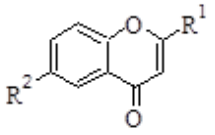
30. *8-O*-methyltetrangulol



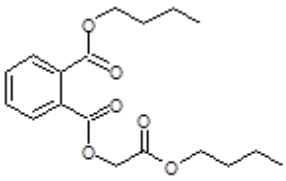
31. Tirandamycin A



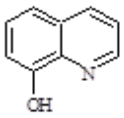
32. Tirandamycin B



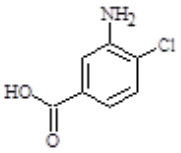
33. 2,6-Disubstituted chromone derivative



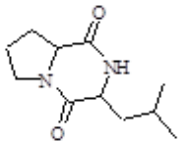
34. Dibutyl phthalate



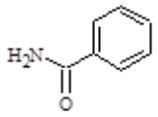
35. *8*-Hydroxyquinoline



36. *2*-amino-*3*-chloro benzoic acid

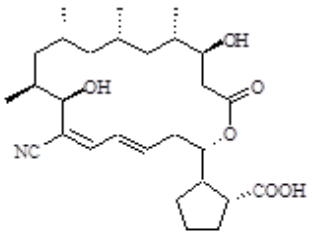


37. *cyclo*-(*L*-prolyl-*L*-leucine); *cyclo*-(*L*-leu-*L*-pro)

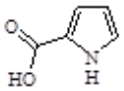


38. Phenylacetamide

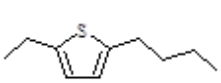
39. Behenic acid (docosanoic acid)



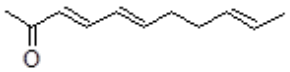
40. Borrelidin



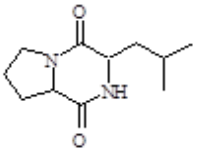
41. 1H-pyrrole-2-carboxylic acid



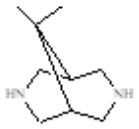
42. Thiphene, 2-butyl-5-ethyl



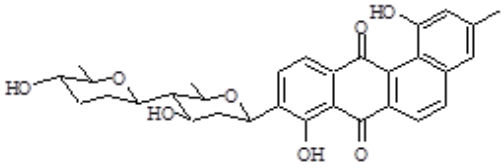
43. 8-[*N*-aziridylethylamino]-2,6-dimethyloctene-2



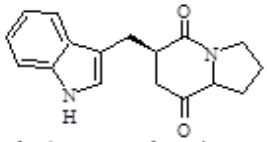
44. Pyrrolo[1,2-a]pyrazine-1,,4-dion-hexahydro



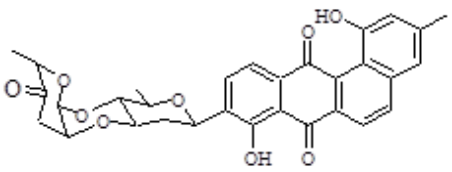
45. 9,9-Dimethyl-3,7-diaza bicyclo[3,3,1]nonane



47. marangucycline A

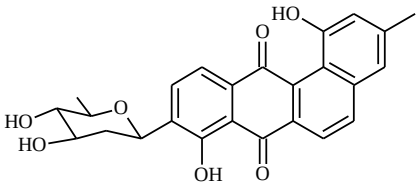


46. *cyclo*-(*L-tryptophanyl-L-propyl*)

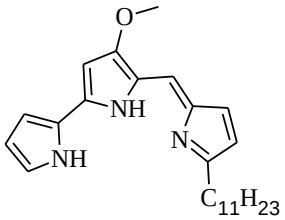


48. marangucycline B

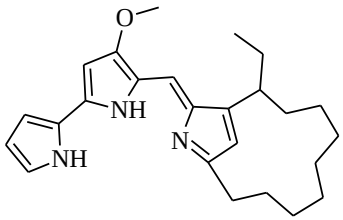
Figure 3. Cont.



49. Dehydroxyaquayamycin



50. Undecycloprodigiosin



51. Metacycloprodigiosin

Figure 3. Cont.

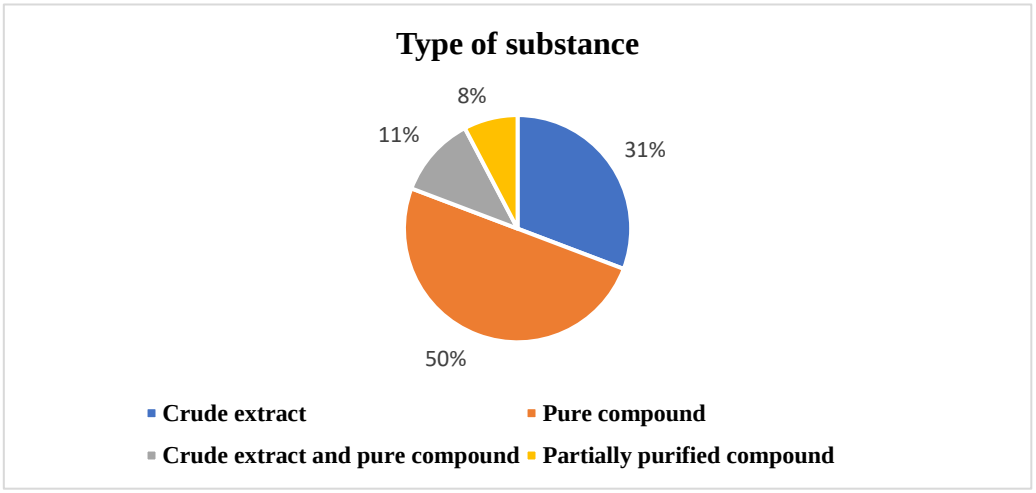


Figure 4. Percentage of reviewed articles that utilised crude extracts, pure compounds, both (crude extract and pure compounds), and partially purified compounds.

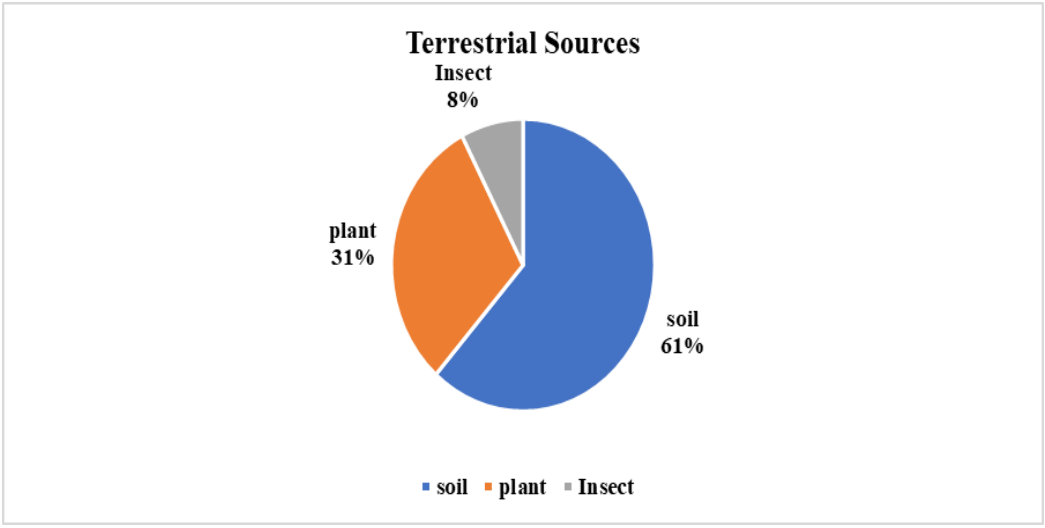


Figure 5. Percentage of terrestrial sources of different *Streptomyces* species, including soil, plant, and insect.

3.3. *Streptomyces* as a Biological Source of Secondary Metabolites

The comprehensive analysis of the selected articles revealed the implementation of various analytical methods to assess the antibacterial properties of *Streptomyces*-derived compounds. The Minimum Inhibitory Concentration (MIC) is the most commonly employed analysis (69%), followed by the zone of inhibition (11%). Interestingly, several studies applied multiple analyses to determine the bacteriostatic or bactericidal properties of the tested compounds. Furthermore, both gram-positive and gram-negative bacteria were involved in these studies, where 46% and 54% of the selected studies emphasised the inhibition of MDR and non-MDR pathogens, respectively. Figure 6 portrays the numerous analytical methods used to measure the antibacterial properties of *Streptomyces*-derived compounds based on the 26 selected articles.

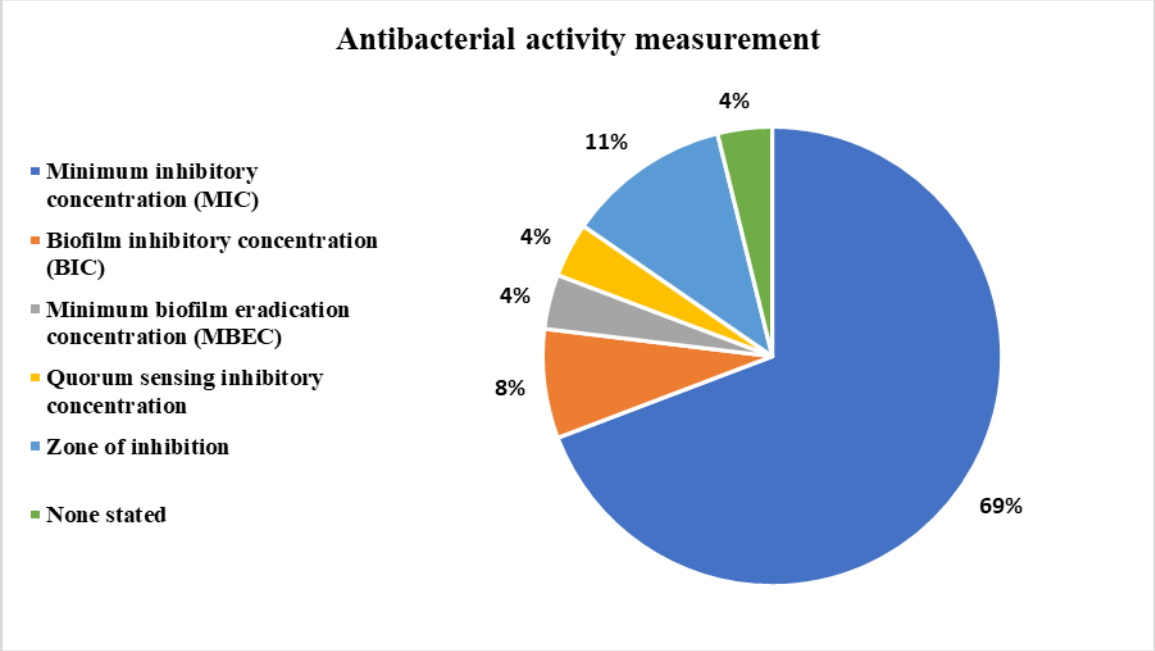


Figure 6. Numerous analytical methods used to measure the antibacterial properties of *Streptomyces*-derived compounds.

4. Discussion

Despite the breakthrough in the development of novel antibiotics and their successful commercialisation, infectious diseases are still considered the leading cause of death worldwide [18]. One of the main factors is the emergence of MDR pathogens among pathogenic microorganisms. Consequently, this has triggered the urgent need to continuously seek new potential bioactive compounds. Ironically, various microbial strains were found to

produce bioactive compounds with significant antimicrobial properties. In fact, about 75% of the available antibiotics were isolated from the genus *Streptomyces* [40].

4.1. Isolation and Source of Streptomyces Species

A plethora of *Streptomyces* sp. has been isolated from different habitats, including marine, soil, plant debris, dung, and house dust. Usually, *Streptomyces* sp. can adapt to various environmental conditions, such as different temperature ranges, varying nutrient availability, and diverse dissolved oxygen levels and pressure, which allows them to produce a wide range of metabolites that are beneficial to human health [41,42]. For example, Balasubramanian *et al*. [17] isolated demonstrated the anti-biofilm efficacy of an organic extract from *Streptomyces* sp. strain SBT343, which was isolated from marine sponge *Petrosia ficiformis.* In a separate study, Balasubramanian *et al*. [18] described the anti-staphylococcal activity of an organic extract from *Streptomyces* sp. strain SBT348, which was isolated from the same sponge. Furthermore, Rahman *et al*. [43] revealed the antibacterial activity of an organic extract from *Streptomyces* sp. strain MARS-17 isolated from *Streptomyces parvulus.* It was noted that environmental factors had somehow minor effects that lead to some differences in the antibacterial activities observed between different *Streptomyces species.* For example, *Streptomyces* isolated from marine sources showed better antibacterial activity as compared to *Streptomyces* derived from other sources such as plants.

Concurrently, research efforts have focused on the exploration of bioactive substances from other sources of *Streptomyces*, such as insects, soils, and plants. For instance, Chen *et al*. [39] investigated the anti-MRSA efficacy of purified extracts from *S. globisporus* strain WA5-2-37 from the intestinal tract of American cockroaches (*P. americana*). Similarly, Alshaibani *et al*. [36] examined the anti-MRSA efficacy of endophytic *Streptomyces* sp. strain SUK25 isolated from the root of the Beehive ginger plant (*Z. spectabile*). Meanwhile, *Streptomyces* sp. strain MUSC135T was isolated from a soil sample collected from a mangrove forest on the east coast of Peninsular Malaysia and exhibited a broad spectrum of bacitracin against MRSA ATCC BAA-44.40.

4.2. Antibacterial Activity of Streptomyces-derived Crude Extracts

In general, the present review was unable to suggest a solid finding regarding the antibacterial activities of *Streptomyces*-derived compounds due to various factors, such as follows: (1) Each literature study utilised different types and strains of pathogens; (2) Various

positive controls (antibiotics) were used for comparison in each article; (3) The inconsistent use of analytical method to assess the antibacterial activity. In fact, even similar parameters were measured differently according to each article; and (4) The addition of external substances to the growth medium that may induce or inhibit the antibacterial activities of *Streptomyces*-derived extracts. For example, Abdullah Al-Dhabi *et al.* [23] used a micro-broth dilution assay for the MIC analysis, while Adeyemo *et al.* [22] used a macro-broth dilution method for the MIC testing to assess the antibacterial activity of *Streptomyces*-derived compounds.

Furthermore, 5 out of 8 studies (62.5%) that used crude extracts showed significant antibacterial activities compared to the positive controls used in each study. As reported by Paderog *et al.* [12], the crude extract of *S. griseorubens* strain DSD069 recorded the highest antibacterial activity against MRSA with an MIC value of 2.44 µg/mL compared to tetracycline (positive control). However, the result could be misleading as the considerably high antibacterial activity could be attributed to the weak effect of tetracycline against MRSA. Another article used a different strain of MRSA to examine the antibacterial activity of a crude extract of *Streptomyces* sp. strain MUSC125. The result showed a lower antibacterial activity with an MIC range of 12.5–25 mg/mL, which was weaker compared to vancomycin [33]. Thus, it would be more practical to use MIC with a standard positive control to measure and compare the antibacterial strength of *Streptomyces*-derived extracted secondary metabolites.

Apart from that, Al-Dhabi *et al.* [24] studied the antibacterial activity of crude extract from *Streptomyces* sp. strain Al-Dhabi-90 towards different drug-resistant Extended-Spectrum Beta-Lactamase (ESBL) pathogens. The recorded antibacterial activity with MIC values varying from 12.5 to 50 µg/mL could be attributed to the effect of crude extracts that altered the membrane integrity and blocked the cellular constituents of the pathogens. As a result, the growth of pathogens was effectively inhibited. A more recent study by Al-Dhabi *et al.* [23] demonstrated a greater antibacterial activity of a crude extract from *Streptomyces* sp. strain Al-Dhabi-97 against gram-positive pathogens compared to gram-negative pathogens with MIC values of 62.5–500 µg/mL but weaker than streptomycin (positive control). Despite the thicker cell wall of gram-positive bacteria compared to that of gram-negative bacteria, the extremely complex structure of the cell wall in gram-negative bacteria that contains various viscous components, such as lipids, lipoproteins, and lipopolysaccharides, makes it more difficult for the active compounds to penetrate the cells, thus, reducing the antibacterial activity against gram-negative bacteria.

Regarding the addition of inducers to the growth media, Kumar *et al*. [35] supplemented 25 µm 5-azacytidine in the crude extract of *S. coelicolor* strain AZRA37. The extract showed high antibacterial activity against both gram-positive and gram-negative bacteria with MIC values of 40 µg/mL compared to that of untreated control with an MIC value of 60 µg/mL. Nevertheless, the enhanced activity might be due to the presence of 5-azacytidine in the growth medium that stimulated the production of additional compounds, which in turn contributed to the favourable outcome [35].

In one study, Balasubramanian *et al*. [17] employed the Biofilm Inhibitory Concentration (BIC) as an alternative method to evaluate the antibacterial activity of marine *Streptomyces* sp. strain SBT343 extract. The bacterial extract showed a significant reduction in staphylococcal biofilm formation after 24 hours of growth. Although the anti-biofilm effect exhibited by *Streptomyces* sp. strain SBT343 was at a much lower concentration (62.5–250 µg/mL) compared to sodium metaperiodate at a concentration of 40 mM (positive control), the anti-biofilm activity of the extract was dose-dependent and not due to growth effect [17]. Balasubramanian *et al*. [18] also proved the anti-biofilm activity of *Streptomyces* sp. strain SBT348 isolated from the same marine sponge against *Staphylococcal epidermidis* at a concentration of 62.5 µg/mL. The biofilm formation was reduced by ~90% and was designated as the BIC90 [18].

4.3. Antibacterial Activity of Purified Streptomyces-derived Secondary Metabolites

Past studies have also screened the antibacterial activities of pure compounds isolated from *Streptomyces* sp. through various methods, particularly the micro- or macro-dilution method. Out of the 26 selected articles, 12 of them (46.15%) showed the antibacterial activity of pure compounds at different concentrations, incubation times, and types of bacterial pathogens.

As shown in Figure 2, approximately 51 extracted secondary metabolites have been identified and reported in past studies. In one study, Chen and colleagues reported that actinomycin X_2 was more potent against MRSA after 12 hours of incubation at a lower MIC value of 0.25 µg/mL compared to collismycin A (MIC value of 8 µg/mL) with vancomycin as the positive control. The result could be due to the destruction of the MRSA cell membrane after treatment with these two compounds [35]. This study was also the first to derive actinomycin X_2 and collismycin A produced by *S. globisporus* strain WA5-2-37, which was isolated from the intestinal tract of American cockroaches (*P. americana*).

In another study, Wang *et al*. [44] evaluated the antibacterial activity of actinomycins D, X_2, and two new natural neoactinomycins A and B against various strains of *E. coli, K. pneumoniae*, MRSA, and Vancomycin-Resistant *Enterococcus* (VRE). Comparatively, actinomycins D and X_2 were very effective against MRSA and VRE with MIC values of 0.125–0.25 μg/mL, while neoactinomycins A and B showed moderate to weak antibacterial activities against MRSA and VRE with MIC values of 16–64 μg/mL and 128 μg/mL, respectively. Nevertheless, all actinomycins recorded weak activity against the different strains of *E. coli* and *K. pneumoniae* with MIC values of greater than 128 μg/mL [44].

A study by Lacret *et al.* [20] reported the first findings on the chemical composition of marine strain extracts closely related to the recently published terrestrial species *S. zhaozhouensis* [20]. It was found that the isoikarugamycin, 28-N-methyllikaguramycin, and ikarugamycin extracts exhibited high growth inhibition of MRSA after 24 hours of incubation with MIC values of 2–4, 1–2, and 2–4 μg/mL, respectively. The strong antibacterial activity was attributed to the presence of ethyl group in the molecules of these compounds.

Furthermore, Paderog *et al*. [12] reported that the strong activity of *S. griseorubens* strain DSD069 crude extract against MRSA was associated with one of the identified compounds, namely bisanhydroaklavinone (**9**), which strongly inhibited MRSA with an MIC value of 6.25 μg/mL compared to 1-Hydroxybisanhydroaklavinone (**10**) and tetracycline (positive control) that displayed a relatively weak antibacterial activity of 50 μg/mL each. The occurrence may be due to the degradation effects of *Streptomyces* compounds on the cell membrane of MRSA, as demonstrated by the protein and DNA leakage and loss of essential cell components, abnormal cell shrinkage, and increased membrane permeability [12].

Recently, Kim *et al.* [21] isolated Mersaquinone (**14**) from marine-derived *Streptomyces* sp. strain EG1. The extracted compound showed moderate antibacterial activity against MRSA compared to ciprofloxacin hydrochloride hydrate with MIC values of 3.36 μg/mL and 0.93 μM, respectively. This phenomenon was probably due to the carbon skeleton of tetracenomycin derivatives, which have been reported to exhibit considerable anti-MRSA activities [21]. Meanwhile, Alshaibani and his colleagues extracted two compounds from endophytic *Streptomyces* SUK25 comprising cyclo-(tryptophanyl-prolyl) (**46**) and chloramphenicol. Both extracts showed good antibacterial activity against MRSA with MIC values of 16 μg/mL and 8 μg/mL, respectively. The strong antibacterial activity could destroy the cell membrane of MRSA, subsequently inhibiting its growth [36].

Besides that, Driche *et al*. [3] reported the isolation of a furanone derivative from a Saharan soil-derived *Streptomyces* sp. strain AT37. The compound was considered to belong to the furanone heterocyclic family group of antibiotics E-975, which comprised numerous natural products and medicines with various biological activities [3]. Based on the results, the compound exhibited strong antibacterial activity against several MRSA and Vancomycin-Resistant *S. aureus* (VRSA) strains. The extracted compound also recorded a significant decrease in the formation of biofilm by MRSA and Methicillin-Sensitive *Staphylococcus aureus* (MSSA) with an $MBIC_{50}$ of 15 µg/mL and 10 µg/mL, respectively. Interestingly, Song and colleagues discovered that dehydroxyaquayamycin (**49**) extracted from deep-sea *Streptomyces* sp. strain SCSIO 11594 exhibited a selective antibacterial activity against methicillin-resistant *S. epidermidis*-strain shhs-E1 with an MIC of 16 µg/mL. The result could be due to the presence of cyclic peptides [28].

Guo and colleagues reported the characteristics of two new cleavage angucyclinones that were isolated from a Chinese marine *Streptomyces* sp. The (-) pratensilin D (**26**) was effective against *B. cereus* with an MIC value of 4 µg/mL [25]. In contrast, its enantiomer (+) structure showed no effect against all tested bacteria with an MIC of up to 64 µg/mL. Previously, angucyclinones have been proven to be a prolific source of antibiotics for the production of 45% of all reported active metabolites [25]. Huang and colleagues also identified two active compounds derived by *Streptomyces* sp., which consist of tirandamycins A and B (**31,31**), isolated from a novel marine sponge. Both bioactive compounds displayed potent inhibitory activities against *S. agalactiae* with MIC values of 2.52 and 2.55 µg/mL, respectively, compared to tobramycin (positive control). The antibacterial activity of tirandamycins A and B against gram-positive bacteria has been highlighted in past studies, which showed their role in inhibiting bacterial RNA polymerase [27]. In addition, Saadouli *et al*. reported the isolation and antibacterial evaluation of cyclo-(L-leu-L-pro) (**37**) derived from S. *misionensis* V16R3Y1, which was isolated from soil in the Tunisian oasis. The cyclo dipeptide compound was most susceptible to *S. enterica,* followed by *E. faecalis*, *B. cereus*, and *S. aureus* with MIC values of 11,12, 16, and 30 µg/mL, respectively. The pyrrolo pyrazine was recognised as the main contributing component to the strong antibacterial activity of the cyclo dipeptide compound [31].

5. Conclusion and Future Perspectives

Based on the 26 selected articles, this systematic review highlighted the significant antibacterial activities of approximately 51 *Streptomyces*-derived crude extract and pure compounds against gram-positive and gram-negative pathogens. Various *Streptomyces* sp.

have been isolated from a diverse range of habitats and showed promising organic extracts with strong antibacterial activities. Nevertheless, the efforts of most antibiotic screening programs were not fully utilised as most research persistently focused only on the already known secondary metabolites. Therefore, further research is required to compare the antibacterial activity of both crude extract and pure compounds. With the rapid emergence of MDR pathogens, it is essentially vital to put more effort into isolating novel classes of antimicrobial compounds. For this reason, investigative studies should be intensified to induce novel secondary metabolite production from *Streptomyces* biosynthetic silent gene cluster. In addition, the nature and chemical structure of the purified compounds should be thoroughly studied to determine the compound with the highest antibacterial activities. Their ability to react with extracellular and soluble proteins as well as the complex bacterial cell wall should also be explored so that the mechanism of action can be improved to achieve effective medical treatment against MDR-related infectious diseases.

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