Abstract: Bacteria of the genus *Streptomyces* produce a very large number of secondary metabolites, many of which are of vital importance to modern medicine. There is great interest in the discovery of novel pharmaceutical compounds derived from streptomycetes, since novel antibiotics, anticancer and compounds for treating other conditions are urgently needed. Greece, as proven by recent research, possesses microbial reservoirs with a high diversity of *Streptomyces* populations, which provide a rich pool of strains with potential pharmaceutical value. This review examines the compounds of pharmaceutical interest that have been derived from Greek *Streptomyces* isolates. The compounds reported in the literature include antibiotics, antitumor compounds, biofilm inhibitors, antiparasitics, bacterial toxin production inhibitors and antioxidants. The streptomycete biodiversity of Greek environments remains relatively unexamined and is therefore a very promising resource for potential novel pharmaceuticals.

Keywords: *Streptomyces*; actinobacteria; natural products; microbial products; antibiotics; anticancer

1. Introduction

Bacteria belonging to the genus *Streptomyces* are major producers of natural products; it has been estimated that 45% of metabolites from microbial sources [1] or about 17% of all known active secondary metabolites [2] originate from this genus, which contains over 800 species [3]. It is estimated that each strain has the potential to produce on average more than 30 secondary metabolites [4]. These natural products are very important in medicine, and they have a very wide variety of applications; streptomycetes are known to produce antitumor, immunosuppressive, anti-inflammatory, antiparasitic, antihelminthic, antiviral, antibacterial, antifungal and antidiabetic compounds [5].

The large number of *Streptomyces* secondary metabolites are likely produced due to the complexity of soil environments and the interactions of *Streptomyces* with other organisms [6] during long evolutionary periods; it is estimated that this genus originated 400 million years ago [7]. *Streptomyces* are non-motile actinobacteria that produce hyphal filaments to form a fungus-like mycelium, which expands in search of nutrients. They spread by generating aerial hyphae that produce spores, which are easily dispersed to new environments [8]. Ecologically, streptomycetes are abundant in soil, where they play a key role in recycling cell walls of fungi and plants [7] but are also found in other environments such as oceanic sediments and in symbiosis with plants, fungi and animals [6].

The geomorphological and climate conditions prevailing in Greece, including its geographical position and its dry Mediterranean climate, result in soil reservoirs that have a high taxonomic and functional diversity of *Streptomyces* populations, providing a rich pool of strains with potential pharmaceutical value [9]. In addition to medicine, Greek strains have potential applications in the field of agriculture as biocontrol agents and growth promoters [9–11]. Each of these streptomycetes produces multiple secondary metabolites; for example, *Streptomyces ambofaciens* BI0048, an endophyte isolated from the red alga *Laurencia glandulifera* from Attiki, produced 10 different α-pyrones polyketides as well as benzoic acid,
hydrocinnamic acid and (E)-cinnamic acid [12]. Other examples include Streptomyces sp. Acta 1383, which produces five different fluostatins in addition to other compounds [13], and Streptomyces sp. Acta 1362, which produces multiple angucyclines [14,15].

This review first provides a brief overview of the pharmaceutical uses of streptomycete secondary metabolites and examine the natural products with potential pharmaceutical applications isolated from Greek indigenous strains belonging to this genus.

2. Antibiotics

Antibiotics derived from Streptomyces are very important medically; 50% of clinically relevant antibiotics originate from this genus [16], and it is estimated that the genus as a whole is able to produce approximately 100,000 antibiotic compounds, of which only 1–3% have been discovered so far [17]. The primary drug classes for clinical antibiotics are aminoglycosides, β-lactams, glycopeptides, macrolides and tetracyclines [18,19]. Some of the most notable and widely used antibiotics include chloramphenicol, which interferes with protein synthesis by binding to the 50S ribosomal subunit blocking peptidyl transferase, kanamycin, neomycin, streptomycin and tetracyclines, which prevent protein synthesis by binding to the 30S ribosomal subunit and interfering with the assembly of the initiation complex, daptomycin, which inserts into cell membranes and causes depolarization, and platensimycin, which disrupts cell membranes by inhibiting fatty acid synthesis [20]. It is therefore unsurprising that a number of compounds with antibacterial activity have been isolated from Greek streptomycetes.

Streptomyces sp. strain SBT345, isolated from a sponge originating from the marine environment of Milos, produces the phenazine compound phencomycin, which displays antibiotic activity against Gram-positive bacteria. This compound has also been isolated from S. sp. HIL Y-9031725 [21]. S. sp. SBT345 also produces tubermycin B, which is used as an antibacterial for the biocontrol of plant diseases [22] and was also found in S. antibioticus Tü 2706 [23]. In addition, it produces ageloline A, a compound that has demonstrated antioxidant activity and growth inhibition of Chlamydia trachomatis [24]. Finally, S. sp. SBT345 is able to produce strephonium A, a chlorinated quaternary ammonium compound that inhibits Shiga toxin production in enterohemorrhagic Escherichia coli [25]. This compound could therefore potentially help treat enterohemorrhagic E. coli infections.

The strains Streptomyces sp. strain SBT343 and S. sp. strain SBT348, also isolated from a sponge in Milos, are able to produce compounds such as SKC3 that significantly inhibit staphylococcal biofilm formation on polystyrene, glass and contact lens surfaces without affecting bacterial growth [26,27]. Pathogens in biofilms cause persistent infections, including urinary tract infections, cystic fibrosis, chronic obstructive pulmonary disease and chronic wounds [16] that are very hard to treat, which is why compounds that can inhibit biofilm formation are of great medical interest [28].

Streptomyces luteogriseus strain FH-S 1307, isolated from a soil sample collected in Kyparissia, produces streptazolin, an antibiotic and antifungal compound also isolated from S. viridochromogenes [29] and S. sp. FH-S 2184 [30], as well as the alkaloid SS20846A, which has antibacterial, anticonvulsant and DNA binding properties and which was also isolated from S. sp. S20846A [31].

The oxytetracycline resistance genes otrA and otrB, were originally discovered in the oxytetracycline-producing Streptomyces rimosus [32]. A screening discovered the otrA and otrB genes in Streptomyces rochei strain ER2, which was isolated from seawater from Evia [33]. The presence of both resistance genes indicates that this strain either contains the entire oxytetracycline biosynthetic cluster or had recently acquired these genes from an environmental Streptomyces strain possessing it, suggesting the presence of oxytetracycline producers in the Greek environment.

3. Antitumor Compounds

Streptomycetes are not important solely for the antibiotics they produce; more than 50% of cytotoxic compounds of microbial origin approved in cancer therapy are derived
from actinobacteria [34]. Bleomycin, which binds to GC-rich DNA regions and causes single-strand breaks; dactinomycin, which binds to DNA and prevents RNA synthesis; anthracyclines, which inhibit topoisomerase II and prevent replication; mithramycin, an RNA synthesis inhibitor; the mitomycins and azynomycin B, which crosslink the complementary DNA strands and prevent replication; enendiyne, which binds to DNA and causes oxidative damage; and pentostatin, which inhibits adenosine deaminase, which is required for the synthesis of DNA precursors, are all important antitumor compounds that have been isolated from *Streptomyces* [20,35]. A relatively large number of natural products with potential antitumor activity have been isolated from Greek streptomycetes. *Streptomyces luteogriseus* strain FH-S 1307, isolated from a soil sample collected in Kyparissia, when grown in mannitol soya flour medium was found to produce a variety of bioactive secondary metabolites [36]. These include streptenol A, a potent cholesterol biosynthesis inhibitor, and shows antitumor and immuno-stimulating activity [37], which has also been isolated from *S. fimбриatus*, *S. cirratus*, and *S. sp. HS-HY-045* [38].

*Streptomyces* sp. strain ACTA 1383, which was isolated from the rhizosphere of *Ebenus sibthorpii* in Kaisariani, was found to produce multiple novel fluostatin compounds. One of those compounds, fluostatin C, which has also been isolated from *Micromonospora rosaria* SCSIO N160 [39], was discovered to have moderate inhibitory activity on three tumor cell lines [13]. Since fluostatin C has been successfully synthesized using the Diels-Alder reaction [40,41] as well as having its biosynthetic cluster heterologously expressed in *S. coelicolor* [42], it is a promising anticancer drug candidate.

*Streptomyces* sp. strain ACTA 1362 was isolated from the rhizosphere of *Pinus brutia* in Crete and was found to produce two novel angucyclines termed grecocyclines [14]. Grecocycline A exhibited cytotoxic activity against the human cancer cell lines HepG2 and HT-29 while grecocycline B inhibited protein tyrosin phosphatase B1, which is a promising target for cancer treatment [15]. The grecocycline biosynthetic gene cluster has been successfully cloned and heterologously expressed in *S. albus* J1074 [43].

The strain *Streptomyces* sp. SBT345, isolated from a sponge from the marine environment of Milos, was found to produce strepoxazine A, a novel phenoxanin analogue that demonstrated cytotoxic activity against leukaemia HL-60 cells. [22]. In addition, the strain *S. sp. SBT348*, also isolated from the same habitat, produces new cyclic dipeptide, petrocidin A, which exhibited significant cytotoxicity towards the human promyelocytic HL-60 and the human colon adenocarcinoma HT-29 cell lines [44].

### 4. Antiparasitic Compounds

Antiparasitics are compounds used to treat protozoan and helminth infections, including malaria, trypanosomiasis, leishmaniasis and toxoplasmosis [45]. There is not a large number of antiparasitic drugs, and only a total of 20 novel drugs have been approved over the past 40 years [46]. However, there are antiparasitics derived from streptomycetes in widespread use including ivermectin, used to treat worm infections; avermectin, used against arthropod parasites; and the milbemycins, used as anthelminthics, insecticidals and acaricidals [47].

Two strains, *Streptomyces* sp. SBT344 and S. sp. SBT348, isolated from sponges from the marine environment of Milos, were found to produce antitrypanosomal compounds that inhibited the growth of *Trypanosoma brucei* [48]. There are other secondary metabolites isolated from streptomycetes, including tetromycin B, staurorosporine, valinomycin and sinefungin VA, which have demonstrated antitrypanosomal activity, indicating that this genus is a promising source of novel drugs for the treatment of trypanosomiasis [47].

### 5. Antioxidants

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues. Oxidative stress can result in cancer, cardiovascular disease, neurological disease, rheumatoid arthritis and kidney disease [49]. There is considerable research interest in antioxidants as potential
treatments for these diseases and Streptomyces isolates appear to be a promising source of novel antioxidants [50].

Antioxidants have also been discovered in Greek strains. The Streptomyces sp. strain SBT349, isolated from Milos sponges, produced compounds with antioxidant activities [51]. Two compounds, 2,3-dihydroxybenzoic acid and 2,3-dihydroxybenzamide, isolated from S. sp. stain SBT348 were also found to have antioxidant activity [44]. 2,3-dihydroxybenzoic acid has also been isolated from the plants Phyllanthus acidus [52] and Salvinia molesta [53], while 2,3-dihydroxybenzamide has also been isolated from the actinomycete strain USF-TC31 [54]. These compounds merit further investigation as potential treatments.

6. Conclusions

The rise in antibiotic-resistant pathogens across the world [19] and the fact that cancer is one of the most serious human health problems [55] resulted in the necessity to discover novel antibiotic and anticancer natural metabolites. The genus Streptomyces remains an ideal source for them, as two thirds of novel bioactive compounds discovered from Actinobacteria between 2015 and 2019 were isolated from streptomycetes [20]. A wide variety of secondary metabolites with potential medical applications have been found in Greek Streptomyces isolates; they include antibiotic, antiparasitic, antitumor and antioxidant compounds (Table 1). Some of these compounds, including streptazolin, streptenol A, SS20846A, fluostatin C, tubermycin B, 2,3-dihydroxybenzoic acid and 2,3-dihydroxybenzamide have also been discovered in other organisms. However, the majority of compounds, including grecocycline A, grecocycline B, ageloline A, phencomycin, strepoxazine A, streptonium A, petrocidin A and SKC3, are novel compounds with no other known producers. Greek environments, such as rhizospere soils, are both rich in streptomycetes and relatively unexplored, making them of great research interest [11]. Actinobacteria, which include Streptomyces, are dominant in arid environments [56], which explains why they are easily isolated from Greek soils. In addition, Greece contains deep seas, hot springs, volcanic environments, caves and salt lakes, all of which may host rare, important or extremophile streptomycetes, which are of particular interest [2,57].

A single isolation of streptomycetes from sponges originating in the island of Milos has led to the isolation and characterization of more than 10 compounds with promising therapeutic properties from Streptomyces isolates [58]. A thorough search of other unique Greek environments is likely to lead to the discovery of numerous novel natural products that may be clinically useful.

Table 1. Greek Streptomyces isolates, compounds they produce and their activities. The strain S. sp. SBT349 has had its genome sequenced [51] and is available via DSMZ under the number DSM 100667 [59]; the other strains have not had their genomes sequenced and are available via the research organizations that worked on them.

| Strain          | Source                  | Compound      | Activity    | Reference |
|-----------------|-------------------------|---------------|-------------|-----------|
| *Streptomyces*  | **luteogriseus FH-S 1307** | streptazolin | antibiotic  | [29]      |
|                 |                         | streptenol A  | antitumor   | [36]      |
|                 |                         | SS20846A      | antibiotic  | [31]      |
| *S. sp. ACTA 1383* | *Ebenus sibthorpii* rhizosphere | fluostatin C | antitumor   | [13]      |
| *S. sp. ACTA 1362* | *Pinus brutia* rhizosphere | grecocycline A | antitumor   | [15]      |
|                 |                         | grecocycline B | antitumor   | [15]      |
| *S. sp. SBT343* | sponge                  | unidentified  | biofilm inhibitor | [26] |
Table 1. Cont.

| Strain    | Source  | Compound                  | Activity                | Reference |
|-----------|---------|---------------------------|-------------------------|-----------|
| S. sp. SBT344 sponge | unidentified | antiparasitic | [48] |
|           |         | ageloline A               | antibiotic              | [24] |
|           |         | phencomycin               | antibiotic              | [22] |
|           |         | strepoxazine A            | antitumor               | [22] |
|           |         | streptophonium A          | toxin production inhibitor | [25] |
|           |         | tubermycin B              | antibiotic              | [22] |
| S. sp. SBT345 sponge | 2,3-dihydroxybenzoic acid | antioxidant             | [44] |
|           |         | 2,3-dihydroxybenzamide    | antioxidant             | [44] |
|           |         | petrocidin A              | antitumor               | [44] |
|           |         | SKC3                      | biofilm inhibitor       | [27] |
|           |         | unidentified              | antiparasitic           | [48] |
| S. sp. SBT348 sponge | 2,3-dihydroxybenzoic acid | antioxidant             | [44] |
|           |         | petrocidin A              | antitumor               | [44] |
|           |         | SKC3                      | biofilm inhibitor       | [27] |
|           |         | unidentified              | antioxidant           | [51] |

Author Contributions: Conceptualization, P.L. and A.D.K.; writing—original draft preparation, P.L.; writing—review and editing, A.D.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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

References
1. Chassagne, F.; Cabanac, G.; Hubert, G.; David, B.; Marti, G. The landscape of natural product diversity and their pharmacological relevance from a focus on the Dictionary of Natural Products (R). Phytochem. Rev. 2019, 18, 601–622. [CrossRef]
2. Hui, M.L.; Tan, L.T.; Letchumanan, V.; He, Y.W.; Fang, C.M.; Chan, K.G.; Law, J.W.; Lee, L.H. The extremophilic actinobacteria: From microbes to medicine. Antibiotics 2021, 10, 682. [CrossRef] [PubMed]
3. Al-Shaibani, M.M.; Radin Mohamed, R.M.S.; Sidik, N.M.; El Enshasy, H.A.; Al-Gheethi, A.; Noman, E.; Al-Mekhlafi, N.A.; Zin, N.M. Biodiversity of secondary metabolites compounds isolated from phylum actinobacteria and its therapeutic applications. Molecules 2021, 26, 4504. [CrossRef]
4. Lee, N.; Kim, W.; Hwang, S.; Lee, Y.; Cho, S.; Palsson, B.; Cho, B.K. Thirty complete Streptomyces genome sequences for mining novel secondary metabolite biosynthetic gene clusters. Sci. Data 2020, 7, 55. [CrossRef]
5. Ul Hassan, S.S.; Shaikh, A.L. Marine actinobacteria as a drug treasure house. Biomed. Pharmacother. 2017, 87, 46–57. [CrossRef]
6. Seipke, R.F.; Kaltenpoth, M.; Hutchings, M.I. Streptomyces as symbionts: An emerging and widespread theme? FEMS Microbiol. Rev. 2012, 36, 862–876. [CrossRef] [PubMed]
7. Chater, K.F. Recent advances in understanding Streptomyces. F1000Research 2016, 5, 2795. [CrossRef] [PubMed]
8. Quinn, G.A.; Banat, A.M.; Abdelhameed, A.M.; Banat, I.M. Streptomyces from traditional medicine: Sources of new innovations in antibiotic discovery. J. Med. Microbiol. 2020, 69, 1040–1048. [CrossRef]
9. Kanini, G.S.; Katsifas, E.A.; Savvides, A.L.; Hatzinikolaou, D.G.; Karagouni, A.D. Greek indigenous streptomycetes as biocontrol agents against the soil-borne fungal plant pathogen Rhizoctonia solani. J. Appl. Microbiol. 2013, 114, 1468–1479. [CrossRef] [PubMed]
10. Kanini, G.S.; Katsifas, E.A.; Savvides, A.L.; Karagouni, A.D. Streptomyces rochei ACTA1551, an indigenous Greek isolate studied as a potential biocontrol agent against Fusarium oxysporum f. sp. Ipomeoeicisi. Biomed. Res. Int. 2013, 2013, 387230. [CrossRef]
11. Meidani, C.; Savvidis, A.; Lampropoulou, E.; Sagia, A.; Katsifas, E.; Monokrousos, N.; Hatzinikolaou, D.G.; Karagouni, A.D.; Giannoutsou, E.; Adamakis, I.S.; et al. The nematcidal potential of bioactive Streptomyces strains isolated from Greek rhizosphere soils tested on Arabidopsis plants of varying susceptibility to Meloidogyne spp. Plants 2020, 9, 699. [CrossRef]
12. Rab, E.; Kekos, D.; Roussis, V.; Ioannou, E. α-Pyrone Polyketides from Streptomyces ambifaciens BI0048, an Endophytic Actinobacterial Strain Isolated from the Red Alga Laurencia glandulifera. Mar. Drugs 2017, 15, 389. [CrossRef]
13. Baur, S.; Niehaus, J.; Karagouni, A.D.; Katsifas, E.A.; Chalikou, K.; Meintanis, C.; Jones, A.L.; Goodfellow, M.; Ward, A.C.; Beil, W.; et al. Fluostatins C–E, novel members of the fluostatin family produced by Streptomyces strain Acta 1383. J. Antibiot. 2006, 59, 293–297. [CrossRef]
14. Paululat, T.; Katsifas, E.A.; Karagouni, A.D.; Fiedler, H.P. Grecoketides A and B: New naphthoquinones from *Streptomyces* sp. acta 1362. *Eur. J. Org. Chem.* 2008, 2008, 9283–9288. [CrossRef]

15. Paululat, T.; Kulik, A.; Hausmann, H.; Karagouni, A.D.; Zinecker, H.; Imhoff, J.F.; Fiedler, H.P. Grecocyclines: New angucyclines from *Streptomyces* sp. acta 1362. *Eur. J. Org. Chem.* 2010, 2344–2350. [CrossRef]

16. Jagannathan, S.V.; Manemann, E.M.; Rowe, S.E.; Callender, M.C.; Soto, W. Marine actinomycetes, new sources of biotechnological products. *Mar. Drugs* 2021, 19, 365. [CrossRef]

17. Waite, M.G.; Tickoo, R.; Jog, M.M.; Bhole, B.D. How many antibiotics are produced by the genus *Streptomyces?* *Arch. Microbiol.* 2001, 176, 386–390. [CrossRef] [PubMed]

18. Mast, Y.; Stegmann, E. *Actinomycetes*: The antibiotics producers. *Antibiotics* 2019, 8, 105. [CrossRef]

19. De Simeis, D.; Serra, S. *Actinomycetes*: A never-ending source of bioactive compounds—An overview on antibiotics production. *Antibiotics* 2021, 10, 483. [CrossRef] [PubMed]

20. Jose, P.A.; Maharsi, A.; Jha, B. Actinobacteria in natural products research: Progress and prospects. *Microb. Res.* 2021, 246, 126708. [CrossRef] [PubMed]

21. Chatterjee, S.; Vijayakumar, E.K.; Franco, C.M.; Maurya, R.; Blumbach, J.; Ganguli, B.N. Phencomycin, a new antibiotic from a *Streptomyces* sp. *J. Antibiot.* 1990, 43, 1542–1551. [CrossRef]

22. Cheng, C.; Othman, E.M.; Fekete, A.; Kriskiche, M.; Stopper, H.; Edrada-Ebel, R.; Mueller, M.J.; Hentschel, U.; Abdelmohsen, U.R. *Streptomyces* sp. BSB512 inhibits staphylococcal biofilm formation. *Infect. Drug Resist.* 2018, 11, 3021–3026. [CrossRef] [PubMed]

23. Geiger, A.; Keller-Schierlein, W.; Brandl, M.; Zahner, H. Metabolites of microorganisms. 247. Phenazines from *Streptomyces antibioticus*, strain Tu 2706. *J. Antibiot.* 1988, 41, 1901–1904. [CrossRef]

24. Cheng, C.; Othman, E.M.; Reimer, A.; Grune, M.; Kozjak-Pavlovic, V.; Stopper, H.; Hentschel, U.; Abdelmohsen, U.R. New anthocyanidin and anthocyanidin quinolone from *Streptomyces* sp. *Tetrahedron Lett.* 2016, 57, 4196–4199. [CrossRef]

25. Mishra, R.; Panda, A.K.; De Mandal, S.; Shakeel, M.; Bisht, S.S.; Khan, J. Natural anti-biofilm agents: Strategies to control *biofilm-forming* pathogens. *Front. Microbiol.* 2015, 6, 774–789. [CrossRef]

26. Balasubramanian, S.; Othman, E.M.; Kampik, D.; Stopper, H.; Edrada-Ebel, R.; Mueller, M.J.; Hentschel, U.; Abdelmohsen, U.R. Inhibitory potential of strepthonium A against Shiga toxin production in enterohemorrhagic *Escherichia coli* (EHEC) strain EDL933. *Nat. Prod. Res.* 2017, 31, 2818–2823. [CrossRef]

27. Balasubramanian, S.; Othman, E.M.; Kampik, D.; Stopper, H.; Abdelmohsen, U.R. Marine sponge-derived *Streptomyces* sp. SBT343 extract inhibits staphylococcal biofilm formation. *Front. Microbiol.* 2017, 8, 236. [CrossRef]

28. Balasubramanian, S.; Skaf, J.; Holzgrabe, U.; Bharti, R.; Forstner, K.U.; Ziebuhr, W.; Humeida, U.H.; Abdelmohsen, U.R.; Oelschlaeger, T.A. A new bioactive compound from the marine sponge-derived *Streptomyces* sp. SBT348 inhibits staphylococcal growth and biofilm formation. *Front. Microbiol.* 2018, 9, 1473. [CrossRef] [PubMed]

29. Mishra, R.; Panda, A.K.; De Mandal, S.; Shakeel, M.; Bisht, S.S.; Khan, J. Natural anti-biofilm agents: Strategies to control biofilm-forming pathogens. *Front. Microbiol.* 2020, 11, 566325. [CrossRef]

30. Perry, J.A.; Koteva, K.; Verschoor, C.P.; Wang, W.; Bowdish, D.M.; Wright, G.D. A macrophage-stimulating compound from a screen of microbial natural products. *J. Med. Chem.* 2015, 58, 40–46. [CrossRef]

31. Yamada, H.; Aoyagi, S.; Kimbashi, S. Stereoselective total synthesis of natural (+)-streptazolin via a palladium-catalyzed enyne bicyclization approach. *J. Am. Chem. Soc.* 1996, 118, 1054–1059. [CrossRef]

32. Chattopadhyay, A.K.; Hanessian, S. Cyclic enamiones. Part II: Applications as versatile intermediates in alkaloid synthesis. *Chem. Commun.* 2015, 51, 16450–16457. [CrossRef] [PubMed]

33. Yin, S.; Wang, X.; Shi, M.; Yuan, F.; Wang, H.; Jia, X.; Sun, J.; Liu, T.; Yang, K.; Zhang, Y.; et al. Improvement of oxytetracycline production mediated via cooperation of resistance genes in *Streptomyces rimosus*. *Sci. China Life Sci.* 2017, 60, 992–999. [CrossRef]

34. Nikolakopoulou, T.L.; Egan, S.; van Overbeek, L.S.; Guillaume, G.; Heuer, H.; Wellington, E.M.; van Elsas, J.D.; Collard, J.M.; Smalla, K.; Karagouni, A.D. PCR detection of oxytetracycline resistance genes otr(A) and otr(B) in *Streptomyces* sp. *Tetrahedron Lett.* 2017, 58, 236–239. [CrossRef]

35. Djinni, I.; Defant, A.; Kecha, M.; Mancini, I. Actinobacteria derived from Algerian ecosystems as a prominent source of antimicrobial molecules. *Antibiotics* 2019, 8, 172. [CrossRef] [PubMed]

36. Busi, S.; Pattnaik, S.S. *Current Status and Applications of Actinobacteria in the Production of Anticancerous Compounds*; Elsevier Science Bv: Amsterdam, The Netherlands, 2018; pp. 137–153.

37. Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kröne, P.; Zeeck, A. Secondary metabolites by chemical screening. 4. Detection, isolation and biological activities of chiral synthons from *Streptomyces*. *J. Antibiot.* 1991, 44, 797–800. [CrossRef] [PubMed]

38. Enders, D.; Hundertmark, T. Asymmetric synthesis of (+)- and (-)-strepтоленол A. *Eur. J. Org. Chem.* 1999, 1999, 751–756. [CrossRef]

39. Groenhagen, U.; Maczka, M.; Dickshat, J.S.; Schulz, S. Streptopyridines, volatile pyridine alkaloids produced by *Streptomyces* sp. *FORMS. Beilstein J. Org. Chem.* 2014, 10, 1421–1432. [CrossRef]

40. Zhang, W.; Liu, Z.; Li, S.; Lu, Y.; Chen, Y.; Zhang, H.; Zhang, G.; Zhu, Y.; Liu, J.; Zhang, C. Fluostatins I-K from the South China Sea-derived *Micromonaspora rosaria* SCSIO 1160. *J. Nat. Prod.* 2012, 75, 1937–1943. [CrossRef]

41. Yu, M.; Danishefsky, S.J. A direct route to fluostatin C by a fascinating Diels-Alder reaction. *J. Am. Chem. Soc.* 2008, 130, 2783–2785. [CrossRef] [PubMed]
Microbiol. Res. 2021, 12

41. Mehta, G.; Kumar, Y.C.S.; Das, M. A de novo Diels-Alder strategy toward the novel pentacyclic natural product fluostatin C: A concise synthesis of 6-deoxyfluostatin C. *Tetrahedron Lett.* 2011, 52, 3505–3508. [CrossRef]

42. Yang, C.; Huang, C.; Zhang, W.; Zhu, Y.; Zhang, C. Heterologous expression of fluostatin gene cluster leads to a bioactive heterodimer. *Org. Lett.* 2015, 17, 5324–5327. [CrossRef]

43. Bilyk, O.; Sekurova, O.N.; Zotchev, S.B.; Luzhetskyy, A. Cloning and heterologous expression of the greccyclone biosynthetic gene cluster. *PLoS ONE* 2016, 11, e0158682. [CrossRef] [PubMed]

44. Cheng, C.; Othman, E.M.; Stopper, H.; Edrada-Ebel, R.; Hentschel, U.; Abdelmohsen, U.R. Isolation of petrocidin A, a new cytotoxic cyclic dipeptide from the marine sponge-derived bacterium *Streptomyces* sp. SBT348. *Mar. Drugs* 2017, 15, 383. [CrossRef] [PubMed]

45. Kappagoda, S.; Singh, U.; Blackburn, B.G. Antiparasitic therapy. *Mayo Clin. Proc.* 2011, 86, 561–583. [CrossRef]

46. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J. Nat. Prod.* 2020, 83, 770–803. [CrossRef]

47. Solecka, J.; Zajko, J.; Postek, M.; Rajnisz, A. Biologically active secondary metabolites from *Actinomycetes*. *Cent. Eur. J. Biol.* 2012, 7, 373–390. [CrossRef]

48. Cheng, C.; MacIntyre, L.; Abdelmohsen, U.R.; Horn, H.; Polymenakou, P.N.; Edrada-Ebel, R.; Hentschel, U. Biodiversity, anti-trypanosomal activity screening, and metabolomic profiling of actinomycites isolated from Mediterranean sponges. *PLoS ONE* 2015, 10, e0138528. [CrossRef]

49. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative stress: Harms and benefits for human health. *Oxid. Med. Cell. Longev.* 2017, 2017, 8416763. [CrossRef]

50. Tan, L.T.; Mahendra, C.K.; Yow, Y.Y.; Chan, K.G.; Khan, T.M.; Lee, L.H.; Goh, B.H. *Streptomyces* sp. MUM273b: A mangrove-derived potential source for antioxidant and UVB radiation protectants. *MicrobiologyOpen* 2017, 8, e0859. [CrossRef]

51. Horn, H.; Cheng, C.; Edrada-Ebel, R.; Hentschel, U.; Abdelmohsen, U.R. Draft genome sequences of three chemically rich actinomycetes isolated from Mediterranean sponges. *Mar. Genom.* 2015, 24 Pt 3, 285–287. [CrossRef]

52. Sousa, M.; Ousingsawat, J.; Seitz, R.; Puntheeranurak, S.; Regalado, A.; Schmidt, A.; Grego, T.; Jansakul, C.; Am-aral, M.D.; Schreiber, R.; et al. An extract from the medicinal plant *Phyllanthus acidus* and its isolated com-pounds induce airway chloride secretion: A potential treatment for cystic fibrosis. *Mol. Pharmacol.* 2007, 71, 366–376. [CrossRef] [PubMed]

53. Choudhary, M.I.; Naheed, N.; Abbaskhan, A.; Musharraf, S.G.; Siddiqui, H.; Atta Ur, R. Phenolic and other con-stituents of fresh water fern *Salvinia molesta*. *Phytochemistry* 2008, 69, 1018–1023. [CrossRef] [PubMed]

54. Sugiyama, Y.; Hirota, A. New potent DPPH radical scavengers from a marine-derived actinomycete strain USF-TC31. *Biosci. Biotechnol. Biochem.* 2009, 73, 2731–2734. [CrossRef]

55. Ravikumar, S.; Fredimoses, M.; Gnanadesigan, M. Anticancer property of sediment actinomycetes against MCF-7 and MDA-MB-231 cell lines. *Asian Pac. J. Trop. Biomed.* 2012, 2, 92–96. [CrossRef]

56. Mohammadipanah, F.; Wink, J. Actinobacteria from arid and desert habitats: Diversity and biological activity. *Front. Microbiol.* 2016, 6, 1541. [CrossRef]

57. Sivalingam, P.; Hong, K.; Pote, J.; Prabakar, K. Extreme environment *Streptomyces*: Potential sources for new antibacterial and anticancer drug leads? *Int. J. Microbiol.* 2019, 2019, 5283948. [CrossRef] [PubMed]

58. Edrada-Ebel, R.; AEvarsson, A.; Polymenakou, P.; Hentschel, U.; Carettoni, D.; Day, J.; Green, D.; Hreggvidsson, G.O.; Harvey, L.; McNeil, B. SeaBioTech: From seabed to test-bed: Harvesting the potential of marine biodiversity for industrial biotechnology. In *Grand Challenges in Marine Biotechnology*; Rampelotto, P.H., Trincone, A., Eds.; Grand Challenges in Biology and Biotechnology; Springer International Publishing Ag: Cham, Switzerland, 2018; pp. 451–504.

59. German Collection of Microorganisms and Cell Cultures. Available online: https://www.dsmz.de/collection/catalogue/details/culture/DSM-100667 (accessed on 30 October 2021).