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Review

Streptomyces, Greek Habitats and Novel Pharmaceuticals: A Promising Challenge

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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 strepomycetes, 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

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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, antihelminth, 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-pyrone 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 depolarizarion, 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 strepthonium 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. fimbriatus*, *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 antihelminthics, 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, staurosporine, 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, strepthonium A, petrocidin A and SKC3, are novel compounds with no other known producers. Greek environments, such as rhizosplere 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	soil	streptazolin streptenol A SS20846A	antibiotic antitumor antibiotic	[29] [36] [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]
S. sp. SBT345	sponge	ageloline A	antibiotic	[24]
		phencomycin	antibiotic	[22]
		strepoxazine A	antitumor	[22]
		strepthonium A	toxin production inhibitor	[25]
		tubermycin B	antibiotic	[22]
S. sp. SBT348	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. SBT349	sponge	unidentified	antioxidant	[51]

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