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Abstract

This brief review aims to draw attention to the biotechnological potential of actinomycetes. Their main uses as sources of antibiotics and in agriculture would be enough not to neglect them; however, as we will see, their biotechnological application is much broader. Far from intending to exhaust this issue, we present a short survey of the research involving actinomycetes and their applications published in the last 23 years. We highlight a perspective for the discovery of new active ingredients or new applications for the known metabolites of these microorganisms that, for approximately 80 years, since the discovery of streptomycin, have been the main source of antibiotics. Based on the collected data, we organize the text to show how the cosmopolitanism of actinomycetes and the evolutionary biotic and abiotic ecological relationships of actinomycetes translate into the expression of metabolites in the environment and the richness of biosynthetic gene clusters, many of which remain silenced in traditional laboratory cultures. We also present the main strategies used in the twenty-first century to promote the expression of these silenced genes and obtain new secondary metabolites from known or new strains. Many of these metabolites have biological activities relevant to medicine, agriculture, and biotechnology industries, including candidates for new drugs or drug models against infectious and non-infectious diseases. Below, we present significant examples of the antimicrobial spectrum of actinomycetes, which is the most commonly investigated and best known, as well as their non-antimicrobial spectrum, which is becoming better known and increasingly explored.

Keywords (separated by '-') Actinomycetes - Biotechnological perspective - Bioactive metabolites - New applications

Footnote Information



Biotechnological potential of actinomycetes in the 21st century: a brief review

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Keywords Actinomycetes · Biotechnological perspective · Bioactive metabolites · New applications

Introduction

In the last century, the production of antibiotics provided exponential human and socioeconomic growth that had never been seen before (Okeke et al. 1999). However, the side effects of the misuse of antimicrobials have become a big concern in the twenty-first century in the form of difficult-to-treat infectious diseases in humans and animals, as well as biocide-resistant plant pathogens (Murray et al. 2022; Raymaekers et al. 2020). Resistance, the main side effect, has become a reality that significantly affects people's lives with regard to health and food, and resistant pathogens have caused the death of millions of people around the world, in addition to harming the production of huge amounts of animal and plant food sources every year (World Health Organization 2016; World Health Organization 2022a). In view of this, in order to mitigate antimicrobial resistance, many researchers have looked into chemical synthesis and semisynthesis as alternatives for the biosynthesis of new antimicrobials, whether inspired by nature or not. However, these alternatives have been unable to meet the increased demand for new medical and agro-industrial antimicrobials (Wright et al. 2014), which has been aggravated by the emergence of multidrug-resistant microorganisms. This has increased the search for microorganisms that can produce new bioactive substances (Hoque et al. 2022; Van Der Meij et al. 2017). Besides this, together with the resistance of pathogenic microorganisms, the growth in the incidence of diseases such as cancer and diabetes, among others, as well as the need to promote more sustainable technological alternatives (Oliveira et al. 2022), challenges us to explore to a greater extent the biotechnological potential of the actinomycetes that are present in the most varied ecosystems and which have a broad biotechnological spectrum (Fig. 1) (Azman et al. 2015; Mahajan and Balachandran 2012; Pereira et al. 2020).

In fact, the biotechnological potential of actinomycetes is far from being completely known; however, as we will see in this brief review, this potential is not only limited to antibiotics and use in agriculture,

there could be many other biotechnological applications. In contrast to the rich potential indicated by the data of this review, there are very few biotechnological investigations and applications related to these bacteria, which belong to the phylum *Actinobacteria*. This phylum has approximately 374 genera and thousands of described species (Donald et al. 2022). The genus *Streptomyces* can be highlighted for having the greatest number of species and considerable reports of microbial natural products (MNPs). In addition, from the 1940s, this genus caused the rise in research involving actinomycetes, which began with a triumphant entry into the group of genetic resources that produce MNPs. The person responsible for this feat was Dr. Selman Waksman, who, while studying soil microorganisms, found *Streptomyces griseus*, from which he isolated streptomycin, which is an efficient bactericide against one of the greatest executioners of humanity: *Mycobacterium tuberculosis*. This feat earned his group the Nobel Prize for Medicine in 1952 (Schatz et al. 1944; Waksman and Woodruff 1940; Woodruff 2014).

From the discovery of streptomycin up until 2010, actinomycetes were responsible for 42% of the more than 23,000 MNPs discovered, most of these being antimicrobial, thus equaling the proportion of MNPs produced by fungi (Kekuda et al. 2010), a much larger group in terms of species. Recently, more than 15,000 MNPs originating from strains of the phylum *Actinobacteria* have been estimated, many of which showed activities outside the antimicrobial spectrum (Table 1) (Lacey and Rutledge 2022; Quinn et al. 2020; Wang et al. 2022; Yan et al. 2022). This extraordinary ability of actinomycetes to produce MNPs is consistent with their cosmopolitan nature, and the fact that, through evolution, they have adapted to the most diverse environments, from the mildest to the most extreme. This originates, among other causes, in the ecological relationships that actinomycetes have with other organisms, notably the plants, colonizing them in practically all tissues in a harmonious or pathogenic way, as well as in competitive relationships in soils and aquatic environments, fighting battles with other microbes armed with the most diverse metabolites (Al-Ansari et al. 2020; Janardhan et al. 2014; Kokkini et al. 2022; Nalini and Prakash 2017; Van Bergeijk et al. 2020).

In the exploitation of this wealth of metabolites, in general, within the universe of actinomycetes, new

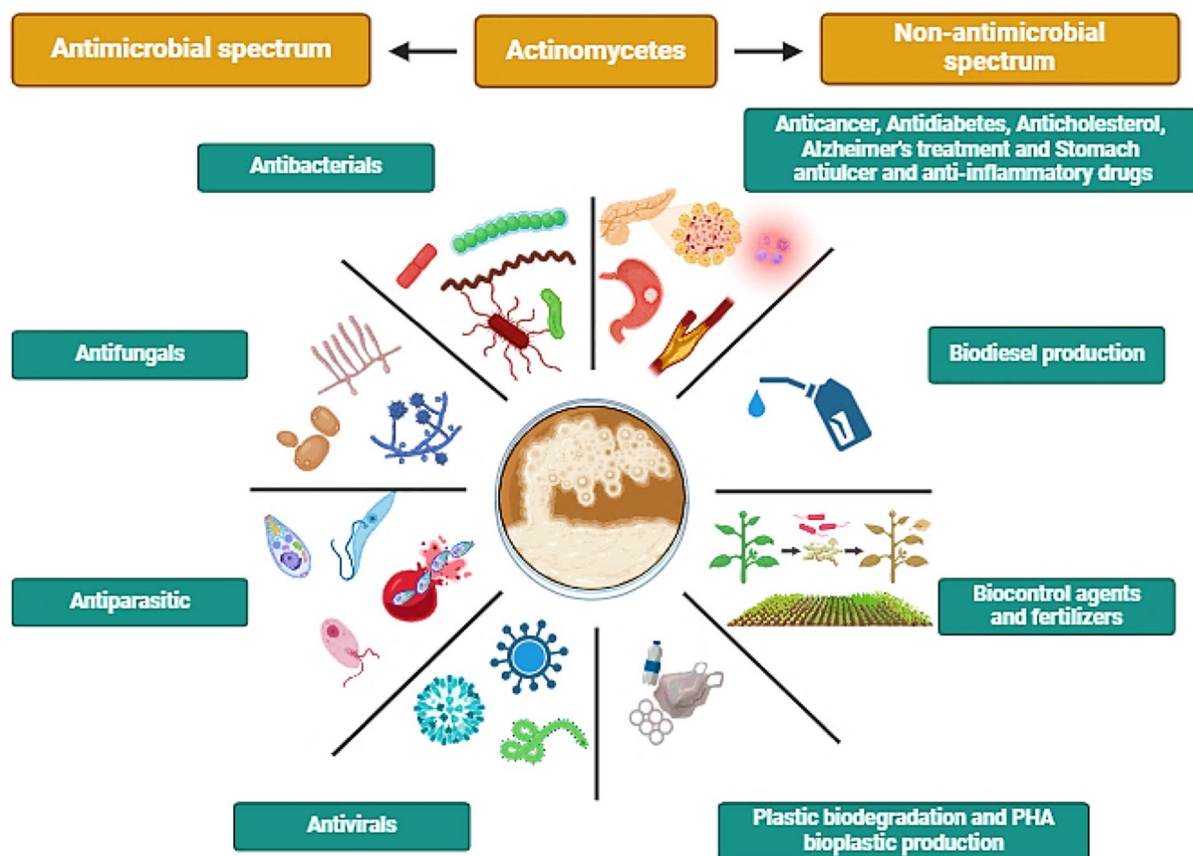


Fig. 1 Biotechnological spectrum of actinomycetes. Best known for their antimicrobial spectrum, on the left, the actinomycetes have gained notoriety for their potential application in several other fields, shown in the examples on the right

isolates stand out for presenting new activities in *in vitro* and *in situ* bioassays (Akshatha et al. 2014; Martinet et al. 2019). In parallel, several genomic and metabolomic studies have revealed a wealth of MNPs hidden in the genomes of several well-known isolates, as well as in newly discovered isolates, thus leading to the emergence in the twenty-first century of a new generation of bioactive substances (Challis 2008, 2014). Among the examples of successful metabolomic approaches, one of the most used for putatively targeting those new metabolites is the Global Natural Products Social Molecular Networking (GNPS), with its numerous tools and public spectrometric databases (Atanasov et al. 2021; Baskiyar et al. 2022; Xu et al. 2019; Wang et al. 2016).

Widely portrayed as sources of bioactive metabolites for various medical and agro-industrial applications, actinomycetes are still chemically very little known. Most related works only report the activity

of the actinobacterial extracts but are inconclusive whether their bioactive compounds would be known, similar to known, or new. Furthermore, for medicines, it is not enough to identify the substances. Several studies are still needed to confirm its therapeutic viability as a new drug, including preclinical and clinical tests with animals and humans. Among the trials, it is critical to determine the patterns of absorption, distribution, metabolism, excretion, and chemical toxicity (ADMET) of a potential new drug. Unfortunately, about 50% of bioactive natural metabolites do not achieve good results in ADMET, which makes them unfeasible as chemotherapies and generates considerable wear (Cai et al. 2023; Guan et al. 2019; Ouyang et al. 2021).

In this context, our main objective in this brief review is to provide the reader with a survey of the research that has been published in the last 23 years involving actinomycetes and their applications,

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Table 1 Examples of recently reported data on metabolites from actinomycetes and their activities

Organisms (origins)	Metabolites	Molecular formulas	Activities	References
<i>Streptomyces</i> sp. OID44 (marine)	Epoxinnamide	$C_{62}H_{79}N_{11}O_{20}$	Anticancer	Kang et al. (2022)*
<i>Streptomyces</i> sp. JB5 (bog)	Dentigerumycin E	$C_{39}H_{63}N_9O_{16}$	Anticancer	Shin et al. (2018)*
<i>Streptomyces</i> sp. AMD43 (bog)	Taenamide A	$C_{51}H_{85}N_{11}O_{16}$	Anti-tuberculosis	Cui et al. (2022)*
<i>Streptomyces</i> sp. JMS132 (marine)	Cystargamides C and D	(C) $C_{51}H_{63}N_7O_{13}$, (D) $C_{47}H_{55}N_7O_{13}$	Antioxidant activity	Seo et al. (2022)*
<i>S. fungicidicus</i> SYH3 (soil)	6-(5-Hydroxy-6-methylheptyl)-5,6-dihydro-2 H-pyran-2-one	$C_{13}H_{22}O_3$	Antifungal	Liu et al. (2022a)
<i>Streptomyces</i> sp. 211726 (man-grove rhizosphere of <i>Heritiera globosa</i>)	Azalomycin F analogues 1–7	$C_{57}H_{98}N_3O_{17}$, $C_{59}H_{105}N_4O_{15}$, $C_{60}H_{106}N_3O_{15}$, $C_{61}H_{108}N_3O_{15}$, $C_{62}H_{110}N_3O_{15}$, $C_{64}H_{114}N_3O_{15}$, $C_{65}H_{116}N_3O_{15}$	Antifungal and Anticancer	Yuan et al. (2013)
<i>Streptomyces</i> sp. KP6107 (soil)	Niphimycin	$C_{59}H_{103}N_3O_{18}$	Antifungal	Kim et al. (2013)
<i>S. antibioticus</i> H12-15 (marine)	Neoantimycin A and B	(A) $C_{27}H_{39}NO_7$, (B) $C_{26}H_{37}NO_7$	Antifungal and Anticancer	Hu et al. (2017)
<i>Streptomyces</i> sp. CT37 (rhizosphere of a <i>Caesalpinioideae</i>)	1H-indole-3-carboxaldehyde	C_9H_7NO	Antifungal	Fang et al. (2020)
<i>Streptomyces</i> sp. neu-D50 (root endophyte)	Borrelidin	$C_{28}H_{43}NO_6$	Antifungal	Liu et al. (2012a)
<i>Streptomyces</i> canus BYB02 (termite)	Resistomycin (1) and Tetracenomycin D (2)	(1) $C_{22}H_{16}O_6$, (2) $C_{19}H_{12}O_6$	Antifungal	Zhang et al. (2013)
<i>Streptomyces</i> strain YIM PH20095 (rhizosphere of <i>Panax notoginseng</i>)	Strephenazine A1, B2, and C3	(A1) $C_{14}H_{19}N_2O_4$, (B2) $C_{20}H_{17}N_4O_2$, (C3) $C_{19}H_{14}N_3O_3$	Antifungal	Chen et al. (2019)
<i>Streptomyces</i> sp. NBU3104 (sea sponge)	Antimycins I, J, K, M, and P	(I) $C_{26}H_{36}N_2O_9$, (J) $C_{30}H_{36}N_2O_9$, (K) $C_{27}H_{38}N_2O_9$, (M) $C_{30}H_{44}N_2O_9$, (P) $C_{31}H_{46}N_2O_9$	Antifungal	Li et al. (2022)*
<i>Streptomyces</i> sp. SN194 (soil)	Chloroxaloterpin A and B	(A) $C_{28}H_{37}ClN_2O_3$, (B) $C_{28}H_{36}ClNO_3$	Antifungal	Bi and Yu (2016)
<i>S. yongxingensis</i> sp. nov. (<i>Menella woodin</i>)	Niphimycin C	$C_{59}H_{103}N_3O_{18}$	Antifungal	Chen et al. (2022)*
<i>S. antibioticus</i> OUCT16-23 (marine)	Filipin analogues 1- 8, 11, and 12	(1) $C_{28}H_{44}O_9$, (2) $C_{29}H_{46}O_9$, (3) $C_{29}H_{46}O_{10}$, (5) $C_{34}H_{56}O_{10}$, (6) $C_{33}H_{54}O_{10}$, (7) $C_{34}H_{56}O_{10}$, (8) $C_{35}H_{58}O_{10}$, (11) $C_{27}H_{42}O_8$, (12) $C_{37}H_{62}O_{11}$	Antifungal	Bao et al. (2022)*

Table 1 (continued)

Organisms (origins)	Metabolites	Molecular formulas	Activities	References
<i>S. distallicus</i> (NRRL WC3846) (soil)	Aureothin (1), Allo-aureothin (2), Deoxyaureothin (3), 4',7-Dihydroxyisoflavone (4), 2-Methyl-5-(3-indolyl) oxazole (5), and 2-Ethyl-5-(3-indolyl) oxazole (6)	(1) $C_{22}H_{23}NO_6$, (2) $C_{22}H_{23}NO_6$, (3) $C_{22}H_{25}NO_5$, (4) $C_{15}H_{10}O_4$, (5) $C_{12}H_{10}N_2O$, (6) $C_{13}H_{12}N_2O$	Larvicidal	Kim et al. (2022)*
<i>Streptomyces</i> sp. CNQ343 (marine sediments)	Bahamaolides A and B	(A) $C_{39}H_{64}O_{11}$, (B) $C_{39}H_{64}O_{11}$	Antifungal	Kim et al. (2012)
<i>Streptomyces</i> strain N11-34 (marine)	Nyuzenamide A and B	(A) $C_{66}H_{81}N_{11}O_{20}$, (B) $C_{67}H_{83}N_{11}O_{20}$	Antifungal and Anticancer	Karim et al. (2021)
<i>Streptomyces</i> sp. Lt 005 (marine)	Anhydroxofoliamycin	$C_{22}H_{24}O_8$	Anti-inflammatory, regenerative, and protective of nerve cells	Leiros et al. (2014)
<i>Streptomyces</i> strain KRA17-580 (soil)	Cinnoline-4- carboxamide (1) and Cinnoline-4-carboxylic acid (2)	(1) $C_9H_7N_3O_2$, (2) $C_9H_6N_2O_2$	Herbicide	Kim et al. (2020)
<i>Streptomyces</i> sp. RB110-1 (termite)	Terimidomycin A	$C_{70}H_{119}NO_{20}$	Antifungal	Um et al. (2021)
<i>S. avermitilis</i> TM24 (genetically modified)	macrolides 1—10	(1) $C_{46}H_{70}O_{15}$, (2) $C_{46}H_{66}O_{12}$, (3) $C_{46}H_{72}O_{14}$, (4) $C_{46}H_{72}O_{14}$, (5) $C_{46}H_{66}O_{13}$, (6) $C_{46}H_{66}O_{12}$, (7) $C_{38}H_{52}O_9$, (8) $C_{39}H_{60}O_{10}$, (9) $C_{40}H_{62}O_{10}$, (10) $C_{39}H_{61}NO_{10}$	Antifungal and Anticancer	Feng et al. (2019)*
<i>S. solisilvae</i> HNM30702 (rhizosphere of <i>Cephalotaxus hainanensis</i>)	Soliseptide A	$C_{31}H_{54}N_8O_9$	Antibacterial and Antifungal	Wang et al. (2018)
<i>Streptomyces</i> sp. RM-4-15 (soil)	Ruthmycin	$C_{21}H_{22}O_7$	Antifungal	Wang et al. (2014)
<i>S. albolongus</i> (<i>Elephas maximus</i>)	19-Methoxybaflomycin C1 amide (1), 21-Deoxybaflomycin A1 (2) and A2 (3), (1 β ,4 β ,4a β ,8 α)-4,8a-Dimethyloctahydronaphthalene-1,4a(2H)-diol (4), (1 β ,4 β ,4a β ,7 α ,8 α)-4,8a-Dimethyloctahydronaphthalene-1,4a,7(2H)-triol (5)	(1) $C_{40}H_{63}NO_{11}$, (2) $C_{35}H_{58}O_8$, (3) $C_{36}H_{60}O_8$, (4) $C_{12}H_{22}O_2$, (5) $C_{12}H_{22}O_3$	Antibacterial, antifungal, and anticancer	Ding et al. (2016)
<i>Streptomyces</i> Species MBT28 (soil)	7-prenylisatin	$C_{13}H_{13}NO_2$	Antibacterial	Wu et al. (2015a)

Table 1 (continued)

Organisms (origins)	Metabolites	Molecular formulas	Activities	References
<i>S. caniferus</i> CA-271066 (marine)	Caniferolide A	$C_{77}H_{122}O_{31}S$	Neuro-inflammation attenuative, decreasing of oxidative stress and beta-amyloid, and Tau anti-pathology agent	Alvarino et al. (2019)
<i>Streptomyces</i> sp. AD-3-6 (soil)	Nybmomycin B, C, and nybmomycin D	(B) $C_{16}H_{12}N_2O_5$, (C) $C_{15}H_{14}N_2O_4$, (D) $C_{16}H_{16}N_2O_3$	Antibacterial, antifungal, and anticancer	Wang et al. (2019a)
<i>Streptomyces</i> sp. KY11784 (líquen <i>Pseudocyphellaria dissimilis</i>)	Skylamycin D and E	(D) $C_{75}H_{66}N_{12}O_{21}$, (E) $C_{75}H_{66}N_{12}O_{20}$	Antibacterial and Antifungal	Bracegirdle et al. (2021)*
<i>S. lomondensis</i> S015 (soil)	1-carboxyl-6-formyl-4,7,9-trihydroxy-phenazin	$C_{14}H_9N_2O_6$	Antifungal	Deng et al. (2021)
<i>S. eurocidicus</i> CGMCC 4.1086	Naphthocyclinone 1—6	(1) $C_{34}H_{33}O_{13}$, (2) $C_{36}H_{35}O_{14}$, (3) $C_{33}H_{31}O_{13}$, (4) $C_{35}H_{33}O_{14}$, (5) $C_{35}H_{31}O_{14}$, (6) $C_{35}H_{33}O_{14}$	Antifungal	Li et al. (2023a)*
<i>S. griseus</i> ATCC 12475	Grisenomycin A and B	(A) $C_{65}H_{93}N_{15}O_{18}$, (B) $C_{65}H_{90}N_{14}O_{18}$	Antiviral	Li et al. (2023b)*
<i>Streptomyces</i> sp. PKU-EA00015 (<i>Salvia miltiorrhiza</i>)	Streptimidazoles A—G	(A) $C_{11}H_{19}N_3O_3$, (B) $C_{11}H_{19}N_3O_4$, (C) $C_{12}H_{21}N_3O_4$, (D) $C_{12}H_{21}N_3O_5$, (E) $C_{10}H_{17}N_3O_5$, (F) $C_{12}H_{21}N_3O_2$, (G) $C_{12}H_{21}N_3O_2$	Antifungal	Sun et al. (2020)
<i>Streptomyces</i> sp. ZQ4BG (man-grove)	Polyene-polyol macrolides 1—9	(1) $C_{36}H_{58}O_{10}$, (2) $C_{37}H_{60}O_{10}$, (3) $C_{36}H_{60}O_{12}$, (4) $C_{36}H_{58}O_{11}$, (5) $C_{37}H_{60}O_{11}$, (6) $C_{36}H_{58}O_{11}$, (7) $C_{36}H_{58}O_{11}$, (8) $C_{35}H_{56}O_{11}$, (9) $C_{36}H_{58}O_{11}$	Antifungal and anticancer	Wang et al. (2017)
<i>S. argenteolus</i>	Argenteolide A	$C_{35}H_{55}NO_{14}$	Antibacterial and anticancer	Liu et al. (2022b)*
<i>Streptomyces</i> sp. XMA39	Streptoxepinomycin C and D	(C) $C_{23}H_{33}NO_{10}$, (D) $C_{23}H_{29}NO_9$	Antibacterial, antifungal, and anticancer	Jiang et al. (2018)
<i>S. atrovirens</i> LQ13 (soil)	Atrovimycin	$C_{65}H_{90}O_{20}N_{10}$	Antibacterial and Antifungal	Liu et al. (2019a)*
<i>Streptomyces</i> sp. PU-MM59 (Himalayan)	Himalaquinones A—G	(1) $C_{19}H_{14}O_7$, (2) $C_{20}H_{16}O_7$, (3) $C_{20}H_{16}O_7$, (4) $C_{20}H_{16}O_6$, (5) $C_{20}H_{16}O_6$, (6) $C_{21}H_{16}O_6$, (7) $C_{20}H_{16}O_6$	Antibacterial, antifungal, and anticancer	Zhang et al. (2021)
<i>Streptomyces</i> sp. HTL16 (feces of <i>Dama dama</i>)	Bafilomycin M	$C_{35}H_{54}O_7$	Antiviral	Xie et al. (2021)

Table 1 (continued)

Organisms (origins)	Metabolites	Molecular formulas	Activities	References
<i>Streptomyces</i> sp. strain P8-A2 (soil)	Azodyrecin B	$C_{19}H_{36}N_2O_3$	Anticancer	Wibowo et al. (2020)
<i>Streptomyces</i> sp. ICBG1318 (<i>Melipona scutellaris</i>)	Meliponomycins A and B	(A) $C_{36}H_{61}N_7O_{12}$, (B) $C_{37}H_{63}N_7O_{12}$	Larvicidal, antibacterials, and antiparasitic	Menegatti et al. (2020)
<i>Streptomyces</i> sp. DM28 (Riverine sediment)	Dumulmycin	$C_{33}H_{48}O_8$	Antibacterial	An et al. (2021)*
<i>Streptomyces</i> sp. Q22 (mangrove)	Bagremycin C	$C_{20}H_{20}N_2O_6S$	Antifungal and anticancer	Chen et al. (2017)
<i>Streptomyces</i> sp. GKU 257-1 (marine)	Sattahipmycin	$C_{26}H_{19}NO_8$	Antibacterial and antiparasitic	Leetanasaksakul et al. (2022)
<i>S. canescens</i>	Candidicidins A3, A2D, A1	(A3) $C_{59}H_{86}O_{18}N_2$, (A2D) $C_{59}H_{84}O_{18}N_2$, (A1) $C_{59}H_{84}O_{17}N_2$	Antifungal	Szczepblewski et al. (2017)
<i>S. xiamenensis</i> 318 (mangrove)	Capsimycins 2, B, C, D, E, F, G	(2) $C_{30}H_{40}N_2O_6$, (B) $C_{29}H_{38}N_2O_5$, (C) $C_{29}H_{40}N_2O_6$, (D) $C_{30}H_{39}N_2O_5Cl$, (E) $C_{31}H_{44}N_2O_7$, (F) $C_{30}H_{42}N_2O_6$, (G) $C_{29}H_{38}N_2O_6$	Anticancer	Yu et al. (2017)
<i>Streptomyces</i> sp. CMAA 1527 and <i>Streptomyces</i> sp. CMAA 1653 (<i>Deschampsia antarctica</i>)	Cinerubin B, actinomycin V	(B) $C_{42}H_{51}NO_{16}$, (V) $C_{62}H_{84}N_{12}O_{17}$	Anticancer	Silva et al. (2020)
<i>Streptomyces</i> sp. NRRL S-4 (ARS culture collection)	Venturicidin E	$C_{41}H_{69}NO_{11}$	Anticancer	Li et al. (2020a, b)
<i>Streptomyces</i> sp. ZZ741 (marine)	Streptoglutarinides A—J	(A) $C_{15}H_{21}NO_5$, (B) $C_{15}H_{21}NO_5$, (C) $C_{15}H_{19}NO_5$, (D) $C_{15}H_{21}NO_5$, (E) $C_{15}H_{21}NO_6$, (F) $C_{15}H_{21}NO_6$, (G) $C_{15}H_{21}NO_5$, (H) $C_{15}H_{23}NO_5$, (I) $C_{15}H_{23}NO_5$, (J) $C_{15}H_{21}NO_4$	Antibacterial, antifungal, and anticancer	Zhang et al. (2019)
<i>Micromonospora</i> sp. AKA109 (marine)	Akazaoxime	$C_{11}H_{20}N_2O_5$	Antibacterial	Komaki et al. (2023)*
<i>Micromonospora</i> sp. M71-A77 (marine)	Levantilide A and B	(A) $C_{30}H_{52}O_6$, (B) $C_{30}H_{50}O_6$	Anticancer	Gärtner et al. (2011)
<i>Micromonospora</i> sp. SCSIO 07395 (marine)	Microechmycin A–E	(A) $C_{15}H_{12}N_2O_4$, (B) $C_{18}H_{18}N_2O_6$, (C) $C_{23}H_{20}N_2O_4$, (D) $C_{33}H_{28}N_4O_9$, (E) $C_{33}H_{28}N_4O_9$	Antibacterial	Cheng et al. (2023)
<i>Micromonospora</i> sp. WH06 (soil)	N-acetyltryptamine	$C_{12}H_{14}N_2O$	Antiparasitic	Ran et al. (2022)

Table 1 (continued)

Organisms (origins)	Metabolites	Molecular formulas	Activities	References
<i>M. matsumotoense</i> M-412 (marine)	Paulomycin G	$C_{20}H_{22}N_2O_{11}S$	Anticancer	Sarmiento-Vizcaino et al. (2017)
<i>Micromonospora</i> sp. G039 (marine)	Isopimar-2-one-3 α -ol-8,15-diene (1), Lagumycin B (2)	(1) $C_{20}H_{30}O_2$, (2) $C_{18}H_{12}O_5$	Antibacterial	Mulowney et al. (2015)
<i>Micromonospora</i> sp. CNJ-878 (marine)	Juvenimycin C	$C_{29}H_{48}O_{10}$	Anticancer	Carlson et al. (2013)
<i>Micromonospora</i> sp. RV115 (sea sponge)	Diazepinomicin	$C_{28}H_{34}N_2O_4$	Anticancer, antiparasitic, and antioxidant	Abdelmohsen et al. (2012)
<i>Micromonospora</i> sp. GMKU326	Maklamicin	$C_{32}H_{44}O_6$	Antibacterial	Igarashi et al. (2011)
<i>Micromonospora</i> sp. B006 (freshwater)	Diazepinomicin	$C_{28}H_{34}N_2O_4$	Syndrome Phelan-McDermid and epilepsy	Braesel et al. (2018)
<i>Micromonospora</i> sp. AKA109 (marine)	Akazaoxime	$C_{11}H_{20}N_2O_5$	Antibacterial	Igarashi et al. (2021)
<i>M. yangpuensis</i> DSM 45577	YPM F and G	(F) $C_{26}H_{17}NO_8$, (G) $C_{26}H_{17}NO_7$	Anticancer	Wang et al. (2019c)
<i>Nocardia</i> sp. Acta 3026 (man-grove)	Nocardichelin A and B	(A) $C_{40}H_{63}N_5O_8$, (B) $C_{38}H_{61}N_5O_8$	Anticancer	Schneider et al. (2007)
<i>Nocardia</i> sp. WMMB215 (<i>Trididemnum orbiculatum</i>)	Peptidolipin B and E	(B) $C_{59}H_{107}N_7O_{11}$, (E) $C_{61}H_{109}N_7O_{11}$	Antibacterial	Wyche et al. (2012)
<i>Kitasatospora</i> sp. CPCC 204717 (<i>Huperzia serrata</i>)	Zelkovamycin and Zelkovamycin E	$C_{36}H_{45}O_9N_9S$, (E) $C_{35}H_{44}N_9O_9S$	Antiviral	Hao et al. (2020), Hao et al. (2022)
<i>K. griseola</i> MF730-N6	Satosporin B and C	(B) $C_{28}H_{46}O_9$, (C) $C_{22}H_{36}O_4$	Anticancer and Antibacterial	Arens et al. (2013)
<i>Kitasatospora</i> sp. HKI 714 (soil)	Endophenazines 2, A1, G	(2) $C_{15}H_{10}N_2O_4$, (A1) $C_{18}H_{16}O_3N_2$, (G) $C_{18}H_{16}O_3N_2$	Antibacterial	Heine et al. (2014)
<i>K. cystarginea</i> NRRL-B16505 (soil)	Cystargolide A and B	(A) $C_{18}H_{30}N_2O_6$, (B) $C_{17}H_{28}N_2O_6$	Anticancer	Gill et al. (2015)
<i>Kitasatospora</i> sp. (Alaska soil)	Cyclodepsipeptide 1 and 2, and kitastatin 1 (3)	(1) $C_{37}H_{53}N_3O_{13}$, (2) $C_{36}H_{51}N_3O_{13}$, (3) $C_{36}H_{53}N_3O_{12}$	Antibacterial, antifungal, and anticancer	Pettit et al. (2007)
<i>Kitasatospora</i> sp. MBT66. (soil)	Endophenazines (A—E)	(1) $C_{20}H_{21}N_3O_6$, (2) $C_{15}H_{12}N_2O_4$, (3) $C_{18}H_{16}N_2O_3$, (4) $C_{18}H_{16}N_2O_3$, (5) $C_{18}H_{16}N_2O_3$	Antibacterial	Wu et al. (2015b)

This Table highlights data between 2012 and 2023. *Genomic and metabolomic mining studies

highlighting a perspective for the discovery of new active ingredients or new applications for the known metabolites of these microorganisms. As criteria for the bibliographic survey, priority was given to scientific publications from the last 23 years reporting biological activities and isolation of substances from actinomycetes. The databases consulted were Web of Science, Springer Nature, Elsevier, PubMed, and Google Scholar. Keywords selected were actinomycetes and antibiotics; anti-bacterial; antifungal; antiparasitic; antimalarial; anti-inflammatories; diabetes; Alzheimers; antileishmaniasis; antitrypanosomal; antiviral; biocontrol; fertilizers; antiacetylcholinesterase; biofuel. Each keyword was individually combined with the word actinomycetes in all the databases accessed. Based on the data collected, we considered: the cosmopolitanism of actinomycetes in relation to the expression of metabolites in the environment and the limitations and alternatives for the synthesis of MNPs in the laboratory; the most commonly targeted antimicrobial spectrum; and the increasingly explored non-antimicrobial spectrum. In the conclusion, we point out some practical issues with the aim of drawing the attention of people and interested entities to the great biotechnological potential of actinomycetes in various fields and the need to explore and preserve the environments that are still little explored.

Cosmopolitanism and environmental expressions vs. laboratory expressions of MNPs from actinomycetes

Actinomycetes are mostly free-living and polynutritional (Djebaili et al. 2021; Van Bergeijk et al. 2020). Their cosmopolitanism shows their ability to establish complex ecological relationships in different environments and with other living beings, a presumable consequence of their evolution that gives them an extraordinary capacity to produce primary and secondary metabolites. This capacity seems more evident when one considers the genomes of these microorganisms since they code approximately 800 proteins involved in various ecological functions. Most are hydrolytic enzymes, cellulases, chitinases, and proteases, which give them an incomparable arsenal to exploit any ecosystem (Bentley et al. 2002; Van Bergeijk et al. 2020). The influence of the ecological

relationships of actinomycetes on their metabolism can be understood through chemical and genetic studies, which allow us to interpret their interactive signals via expressions of primary and secondary metabolites and discover the groups of genes (or biosynthetic gene clusters – BGCs) involved in the synthesis of MNPs (Fig. 2) (Rutledge and Challis 2015; Van Bergeijk et al. 2020; Javed et al. 2021). Below are some examples of the adaptability of actinomycetes to different environments and their complex ecological relationships that cause the expression of MNPs that can be used for various purposes. There are also examples of successful laboratory cases of the use of silenced genes of actinomycetes for the expression of new metabolites.

Examples of the production potential of natural products by actinomycetes in different ecological relationships

As with our own organism, through evolution, microorganisms have adapted to different environmental and food conditions by utilizing their genetic arsenal to produce appropriate enzymes and MNPs. Presumably, coevolution with other living beings under the most diverse and often adverse conditions has enhanced this arsenal and its metabolic expression. The known specificity of this metabolic expression to different environmental stimuli suggests the need to collect actinomycetes from different habitats. As we will see in the examples below, this potentiates the discovery of different strains with different productions of MNPs.

Rhizosphere – In a given area of soil, the rhizosphere is the most nutritious and most biodiverse region, as it is filled with a nutritious exudate, which is disputed by actinomycetes, fungi, protozoa, and eubacteria (Lugtenberg 2015). In this chemical warfare environment, when fed by exudate, actinomycetes compensate vegetables with protection through the secretion of antimicrobials, nitrogen fixation, production of growth hormones and enzymes capable of metabolizing complex carbohydrates (Djebaili et al. 2021; Ujváry 2010). Protection against phytopathogens (biocontrol) and stringency conditions may have induced evolution to the point that there is communication between actinomycetes and plants, which occurs through inorganic and organic signaling (Djebaili et al. 2021; Javed et al. 2021; Ujváry 2010; Van

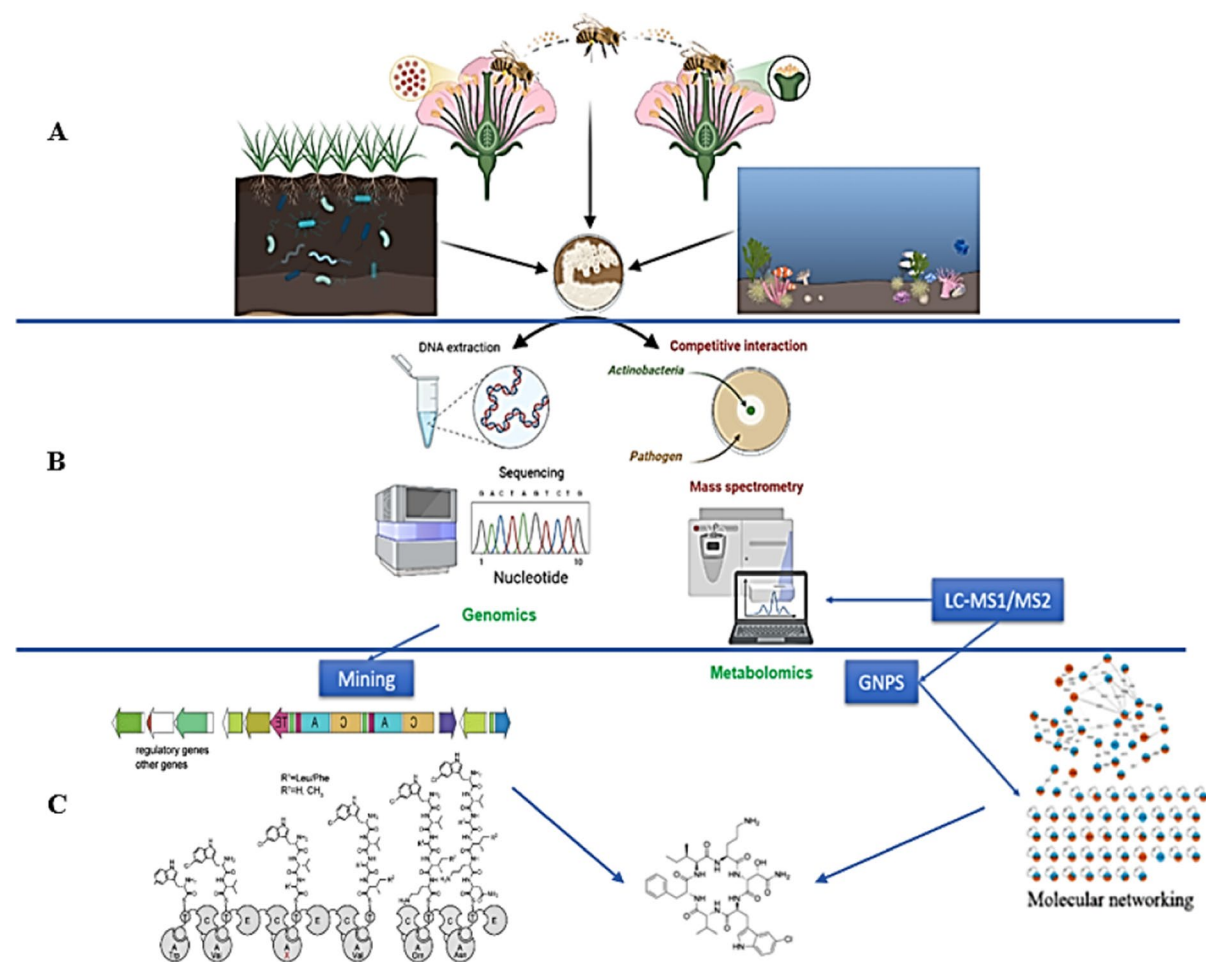


Fig. 2 Methodological strategies for prospecting MNPs. **A** The microorganism is isolated from any nature environment; **B** Its DNA sequences and metabolites are obtained under appro-

priate conditions; **C** Metabolites are prospected by genomic mining and confronting the mass spectra with databases (for example, GNPS). For more details see the main text

Der Meij et al. 2017; Van Bergeijk et al. 2020; Van der Ent et al. 2009). Thus, in the rhizospheric exudate, many chemical distress signals can be emitted, such as the plant-stress hormones jasmonic acid and salicylic acid, which stimulate the secretion of antibiotics by actinomycetes (Van Der Meij et al. 2018; Van Bergeijk et al. 2020).

Insects – The class Insecta Linnaeus, 1758, a rich source of biodiversity, may harbor an even greater richness in actinomycetes and their metabolites. This is what can be deduced from studies such as that of Matarrita-Carranza et al. (2017), who evaluated the influence of these bacteria within the order *Hymenoptera*, which has more than 150,000 species of insects (Aguir et al. 2013). From the 29 tropical species

studied, including those of the families *Apidae* (bees), *Vespidae* (wasps), and *Formicidae* (ants), 197 cultivable actinomycetes were isolated, whose bioassays indicated the potential antimicrobial activities of their metabolites. There is an apparent mutualistic association in which bacteria, being fed, establish a defense mechanism against microbial pathogens in favor of the host insects (Hanshew et al. 2015; Huang et al. 2020).

Marine sponges – Equally exciting are the studies in search of knowledge regarding actinomycetes that interact with organisms in marine environments. These studies have resulted in the discovery of new candidates for producers of MNPs of biotechnological interest. This is the case of the actinomycetes from

sponges, which are organisms that filter and decompose particles, and are of extreme relevance to our planet. They are also natural hosts of various groups of recycling microorganisms (Balskus 2014). This relationship of high complexity and adversity should certainly stimulate the production of a varied range of bioactive compounds. An important example in this sense is given by Cheng et al. (2015), who studied the diversity of 12 species of sponges from the Mediterranean Sea and isolated 64 actinomycetes, eight of which showed antiprotozoal activity for *Trypanosoma brucei* (TC221). In other studies, with actinomycetes isolated from marine sponges, Nagarajan et al. (2015) and Santos et al. (2015) detected antibacterial, antifungal, and anticancer activities for the metabolites produced by the studied strains.

The previous examples reveal that actinomycetes in different origins can present varied biotechnological potential—antibiotics for plant defense, antipathogens for insect protection, and antibacterial, antifungal, and anticancer metabolites associated with marine organisms. In perspective, the most diverse environment on the planet can host the most different actinomycetes with inestimable wealth in bioactive metabolites. However, many metabolites with potent medicinal and agroindustrial properties are not produced in laboratory conditions because these do not provide the physical and chemical stimuli of the original accessed ecosystems. Thus, as we will briefly discuss in the following sections, several studies have sought to understand the molecular systems involved in the activation of synthesis pathways and have revealed the limiting factors for the discovery of new MNPs.

Limiting factors for the synthesis of MNPs via cultivation in the laboratory

Recent reviews highlight the limitations of the current culture media and isolation methods that are available for actinomycetes (Donald et al. 2022; Hemmerling and Piel 2022). In laboratories, culture media lack complexity and are devoid of the environmental biological, chemical and physical stimuli necessary to activate biosynthetic gene clusters (BGCs) and thus promote the synthesis of microbial natural products (MNPs). For example, in the laboratory, how can one reproduce the environmental conditions of the diversity of marine actinomycetes, which are subject

to great nutritional variations, of symbionts (animals and algae) and of temperature and pressure, without counting their diverse origins, as in the reported case of spores of *Streptomyces* strains transported from soils via river runoff to the bottom of the oceans, where they are subject to evolutionary pressure distinct from terrestrial pressure (Moran et al. 1995). Equally difficult to reproduce are the conditions to which microbial strains from nutrient-poor sites such as hot springs and oligotrophic Antarctic and desert soils are subjected to, as well as endophytic strains that lose their original phyto-communication and interaction with the host plant microbiome. All these factors are evolutionary agents that regulate the secondary metabolism and chemodiversity of actinomycetes and, although laboratory conditions are very different from environmental ones, strategies have been developed to increase the amount of MNPs produced by these bacteria. Strategies such as thermal and electric shocks, nutritional adaptations of culture media with the addition of environmental substances that have a stimulating effect and the heterologous expression of BGCs from genomes of non-cultivable strains, among others, have favored discoveries of new MNPs (Donald et al. 2022; Hemmerling and Piel 2022), mainly in marine prospections (Tenebro et al. (2021).

Actinomycetes and MNPs eliciting agents

The proposal of nutritional, physical, chemical, and biological agents for stimulation has become a promising strategy for the synthesis and discovery of MNPs, especially when combined with the knowledge of the genomic diversity of the biosynthetic gene clusters (BGCs) of a strain, as will be seen in the next section. An excellent example of the influence of nutritional stimulation on the synthesis of MNPs occurred via the limitation of carbon and nitrogen in cultures of *Saccharopolyspora erythraea* and *Sc. hygroscopicus* (Wilson and Bushell 1995), which resulted in increased production of the macrolide Erythromycin and coincided with the accumulation of tRNA and amino acids and the attenuation of protein synthesis. These results seem to reveal a typical situation of competition for nutrients, with a consequent need for territory protection that must occur in natural conditions.

An interesting stimulation strategy consists in disrupting the metabolism of strains with sub-inhibitory

concentrations (SICs) of antibiotics, which leads to the stimulation of higher concentrations of other antibiotics and awakens cryptic BGCs involved with MNPs syntheses. For example, the SIC (of 5 µg/mL) of chloramphenicol – inhibitor of protein synthesis in prokaryotes – increased the synthesis of the antibiotic actinomycin (calcium-dependent synthesis) and piperidamycin in *S. albus*, while the SIC of the synthetic ARC2 (an analogue of triclosan) – which partially inhibits the synthesis of fatty acids – also increased the synthesis of polyketide antibiotics in *S. albus* (Tanaka et al. 2017). In another example, the marine strain *Streptomyces* sp. HB202 (*Halichondria panicea*), under the effects of SICs of tetracycline or bacitracin, produced several compounds from the group of phenazines named *streptophenazines* A-H. *Streptophenazines* C and H showed activities against *Bacillus subtilis*, while C was also active against *Staphylococcus lentus* (Mitova et al. 2008).

In another approach using exposure to natural or synthetic chemical compounds, the strain *Micromonospora kermanensis* DSM 45485 was subjected to alkaline pH and the individual influence of valproic acid, dimethyl sulfoxide (DMSO), lanthanum chloride, triclosan, and of the culture supernatant of *Pseudomonas aeruginosa* UTMC 1404, and showed gram-negative biological activity (Mohammadipanah et al. 2020). Considering that in these tests the culture medium (ISP2) was the same in the presence and absence of stimulants and that, in the absence of these, biological activity was not observed, this example reveals possible space defense behavior in response to chemical attacks, which in the environment may mean the presence of hostile organisms. In another case, when trying to stimulate *S. hygroscopicus* to increase the production of the macrolide ascomycin (FK520), a potent antifungal and immunosuppressant, various chemicals at low concentration levels were used as stimulants. Among them, the chemical compound DMSO, used as a carbon source, stood out for doubling the production of ascomycin (FK520) (Wang et al. 2019b).

As actinomycetes are ubiquitous, they carry in their genomes the evolutionary marks of their experiences in communities and diverse environments of the Earth recorded in their DNA, especially in clusters of active or cryptic biosynthetic genes (BGCs). A good biological mechanism for stimulating cryptic BGCs is co-cultivation of two strains from the same

environment. This was demonstrated in experiments of co-culture of *S. luteireticuli* NIIST-D31 with *S. luteovorticillatus* NIIST-D47 and resulted in the synthesis of new stereochemical variants of streptophenazine (S1 and S2) and 1-N-methylalbonoursin, and with *S. thioluteus* NIIST-D63, resulting in new streptophenazines and again in 1-N-methylalbonoursin (Induja et al. 2023). Moreover, in co-cultivation of *Streptomyces venezuelae* and *Saccharomyces cerevisiae* with an abundance of glucose, *S. venezuelae* produced the volatile trimethylamine (Jones et al. 2017).

Finally, there are also examples of metallic chemical elements, including rare earths and heavy metals, as stimulants of the synthesis of MNPs by actinomycetes. Thus, the syntheses of dactinomycin, actinomycin and streptomycin by *S. antibioticus*, *S. parvulus* and *S. griseus* were increased when the culture media were supplemented with scandium (Sc³⁺) (Zong et al. 2022). In another case, when supplemented with nickel, a marine strain of *Streptomyces* produced angucycline (Zong et al. 2022). All of the examples above seem to reveal that, in their evolution, the strains of actinomycetes were storing a powerful arsenal of chemical weapons in the form of genes or BGCs. This arsenal has made them uniquely prepared to survive numerous environmental adversities, including competition for space and food, attacks by other organisms, exposure to toxic chemical substances or elements, and abiotic environmental changes. This same arsenal could be the solution to numerous problems involving human health and agriculture, among other biotechnological possibilities. In this perspective, we will see below that the uses of stimulants have been improving and more robust techniques are being used in approaches that aim to improve the discovery of MNPs.

Genomic and metabolic mining for production of MNPs

Despite understanding some of the mechanisms of activation of BGCs, it is still a challenge to overcome their complexities, since many pathways share several enzymes (Craney et al. 2013). As we have seen, when isolating a microorganism from a given ecosystem, we limit them to laboratory conditions, and these do not provide the same extracellular signals of its former environment with all the abiotic and biotic challenges it had to overcome to survive,

possibly causing it to lose its genuine production of active ingredients. However, through genomic studies, it is possible to quantify the BGCs in the DNA of a microorganism and estimate its potential ability to produce known and unknown MNPs. Let's look at three examples: in the first, in a study that analyzed 1,110 genomes of *Streptomyces*, 34 main classes of BGCs were found among the strains, which presented a variety of 8 to 83 BGCs, with the predominance of NRPS (1,062 genomes), PKS1 (981 genomes), terpenes (697 genomes), lantipeptides (540 genomes), butyrolactone (503 genomes), pks2 (499 genomes), bacteriocin (419 genomes), and Pks3 (366 genomes) (Belknap et al. 2020). According to the authors, assessing whether the quantities of important copies of BGCs (e.g., NRPS and PKS) and their distributions in genomes are associated with variations in the syntheses and biological activities of MNPs is fundamental. In the second example, the distributions of BGCs linked to the metabolic pathways PKS and NRPS were investigated in the genomes of 75 strains of *Salinispora arenicola* (37), *Salinispora tropica* (7), and *Salinispora pacifica* (31), in which 1,924 KS domains and 1,693 C domains were found that represent enzymes related to these pathways (PKS and NRPS) in this exclusively marine genus (Ziemert et al. 2014). The authors estimated that this high diversity was acquired through horizontal gene transfer and noted that it focuses on strains in what they called genomic islands of BGCs that can change position. This dynamic of position change is still poorly understood but it has a great influence on the synthesis of MNPs. Finally, in the third example, in strains of *Amycolatopsis* spp. from different geographical regions, it is observed that they carry between 14 and 45 BGCs, with a predominance of PKS, NRPS, hybrid, RiPP and terpene (Adamek et al. 2018).

All of the above examples reveal only part of the operation of an approach aimed at rationally combining genomic mining with metabolomics. Figure 2 shows the main steps of these two fruitful combined methodologies utilized in recent years to prospect MNPs. After isolating the microorganism from nature (Fig. 2A), its DNA sequences and metabolic extracts are obtained. The production of bioactive metabolites can be induced, for example, by exposition to antimicrobial substances or by competitive cultivation with target pathogens (Fig. 2B). Finally, the MNPs are prospected by genomic mining and comparison

of the mass spectra of components of the microorganism extracts with databases (for example, GNPS) (Fig. 2C).

Gene mining is widely used and fundamental for genetic engineering, which has numerous ways of encoding the products of silenced pathways. In a recent study, Cheng et al. (2023) identified a gene cluster (mich BGC) relative to benzoxazole alkaloids in the strain of *Micromonospora* sp. SCSIO 07395. The heterologous expression of the mich BGC gene in *S. albus* Del14 resulted in five new alkaloids, the microecmycins A–E, among which the microecmycin A demonstrated moderate antibacterial activity. On the other hand, the analysis of data obtained via LC-MS1/MS2, using the GNPS platform, has also been a powerful tool for the dereplication of extracts and the discovery of new metabolites. (Atanasov et al. 2021; Baskiyar et al. 2022; Xu et al. 2019; Wang et al. 2016). Although the chemical study of an extract by conventional metabolite identification and purification techniques can result in bioactive metabolites, the genomic quantification of BGCs, combined with the bio-guided and rapid characterization of metabolomic profiles, allows us to evaluate and optimize the acquisition of active ingredients and other promising substances from microorganisms (Gohain et al. 2015; Moon et al. 2019), as can be seen in the following examples.

Gohain et al. (2015) studied the microbial diversity of six Indian medicinal plants and obtained 76 actinomycetes, with a prevalence of the genus *Streptomyces*. According to the authors, 21 of the isolates presented activities in biological assays against fungal and bacterial pathogens. In addition, 85% were detected producing bands for the BGCs polyketide synthase (PKS) type-II and 14% for PKS-I. The characterization and quantification of silenced BGCs allows them to be cloned and expressed in model organisms. For example, Qian et al. (2019) sequenced the genome of *Streptomyces* sp. (Tü 6314) and found a cryptic BGC PKS type II (skt), then cloned it using the *Streptomyces* pSET152 vector. Via heterologous expression in *S. coelicolor*, they managed to produce six polyketides, of which four showed activities against the HIV1 virus.

With the same purpose of taking advantage of the potential of silenced genes, among the other methodologies used to activate these genes, the methodology called HiTES (high performance eliciting screens)

has been used. In summary, it combines the use of a reporter gene that is integrated in the vicinity of the silenced BGCs and analyzes the effect of hundreds of substances, which are candidates for eliciting the metabolites associated with these cryptic genes. Any substance added individually to the culture in wells of 96-well plates that has the desired effect, signaled by the significantly increased response of the reporter gene in the modified actinomycetes, relative to the control (a well without any testing substance added), is then used as an inducer in a larger scale culture. This methodology ideally leads to the production of new metabolites from the genes that were silenced and were awakened by it (Xu et al. 2017). Using this methodology, these authors achieved the expression of 14 new products from *S. albus* (J1074), which included a novel antifungal and a cancer cell multiplication inhibitor.

The same group led by Professor Mohammad R. Seyedsayamdost, using the modified HiTES methodology they called “Bioactivity-HiTES” (Moon et al. 2019), detected cryptic antibiotics in three lineages of actinomycetes. The bioactivity-HiTES methodology was described as similar to the previous one, in that actinomycetes are grown in 96-well plates in the presence of a library of tens or hundreds of natural substances. Subsequently, the media cultured by each bacterium in the individual presence of each candidate elicitor substance were tested for bioactivity. In this case, they were tested for the inhibition of Gram-negative bacteria. As a result, the authors discovered two cryptic antibiotics against *Escherichia coli* and *Acinetobacter baumannii*, as well as a new naphthoquinone epoxy. The advantage of this new approach is that it dispenses any genetic manipulation of the strains of actinomycetes, thus saving resources and time.

Since the first decade of the twenty-first century, ever-increasing genome mining approaches seem to have overcome the most optimistic previsions that could be made about the incalculable natural products to be discovered from actinomycetes. In such approaches, the analyses of gene sequences frequently result in the discovery of many “orphan” biosynthetic pathways (Challis 2008). In addition to the aforementioned papers, in recent years, there have been a number of reviews on innovations and studies regarding the biosynthesis of new MNPs, among which those of Craney et al. (2013), De Simeis and Serra (2021),

Gomez-Escribano et al. (2021), Gong et al. (2021), Jiang et al. (2018), Li et al. (2021), Wu et al. (2021) and Zhang et al. (2022) stand out. In general, all the above reports reveal the gene mining approaches as the most promising and powerful tools to address the continuous challenge of finding new bioactive metabolites, especially antimicrobials. Table 1 portrays some of the most recent studies and discoveries of new groups of bioactive natural products. Many of these discoveries were made using metabolomics via the GNPS platform, genomic mining of BGCs, or both approaches together (Le Loarer et al. 2023).

Antimicrobial spectrum

Cultivable and non-cultivable actinomycete strains can be found in soils or other environments ranging from oligotrophic ones to copiotrophic ones, from acidic to basic pH, from dry to flooded locations, and from high to low temperatures, among other factors. In their genomes, these strains carry BGCs and the epigenetic marks of ecological pressures that permeate their primary and secondary metabolic activities. Many of these ecological pressures come from forced coexistence with other microorganisms, often in hostile situations. This is not without reason since, historically, the main application of actinomycete metabolites has been within the antimicrobial spectrum, where it still has its greatest biotechnological importance. Below, we will see several examples from the last decades that consolidate the potential of actinomycetes and project them as fundamental sources of metabolites for the continuous need to combat human pathogens and agriculture, especially drug-resistant or multidrug-resistant strains.

Antibacterials

Microbial resistance to antibiotics (MRA) has claimed the lives of thousands of people in recent decades (Stephens et al. 2017; Alvarez-Uria et al. 2018). According to annual surveys by the World Health Organization that began in 2015, such a public health problem is a major threat to humanity because of the emergence of multi-drug resistant (MDR) strains (Exner et al. 2017; World Health Organization 2016; World Health Organization 2021). As examples, there are reports of multidrug-resistant strains of

E. coli, the main causes of infant deaths from diarrhea and septicemia (Stephens et al. 2017). There are also records of multidrug-resistant strains of *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Enterobacter* sp., which are the most frequently responsible for infections in people in intensive care units (ICU), and these may progress to septicemia (World Health Organization 2022a). In summary, resistance to antibacterials can be represented by the three most successful and understood mechanisms: (I) uses of efflux pumps, plasma membrane structures that expel them into the extracellular environment; (II) by the actions of cytosolic enzymes that metabolize them; (III) and through target alterations, which is another way to circumvent the actions of these drugs (Fisher et al. 2022).

The appeal is an urgent one since the global scenario resembles a pandemic condition because of the rapid spread of MDR strains. There have been several studies that have sought to explore the biotechnological potential of actinomycetes and present new candidate isolates for bioactive producers of MNPs via screening using the method of co-cultures with MDR strains. In one of these studies, isolates from Egyptian soils (identified as *S. griseus*, *S. flaveolus*, and other actinomycetes) showed themselves to have the potential to be effective against MDR bacterial and fungal pathogens (Elbendary et al. 2018). In another study, among 100 strains of endophytic actinomycetes from seaweed (*Caulerpa racemosa*) that were tested, five showed antagonist activities for gram-negative MDR bacteria, which are considered to be among the most virulent pathogens because they have a thicker cell wall (Rajivgandhi et al. 2018). While many examples like these remain to be confirmed or have had the active ingredients identified, they signalize substances capable of circumventing the resistance mechanisms of MDR microorganisms and reveal that new classes of antibiotics with different mechanisms of action may be possible.

As an example of the potential of the marine environment to be a source of new antibiotics, a new antibiotic, namely desertomycin G, was produced by *S. althioticus* MSM3 isolated from the macroalgae *Ulva* sp. (Braña et al. 2019). This substance stands out for its spectrum that is extended beyond bactericidal activity against *M. tuberculosis*, and presents activity against gram-positive and negative pathogens, and acts on cancer cells of the human breast

adenocarcinoma (MCF-7) and colon carcinoma (DLD-1) lineages. Active ingredients that present these characteristics are of great relevance, since people who perform cancer treatments are more prone to infections and such substances can help prevent infections.

The studies above are just some of the examples of screenings carried out and published in several papers in recent years and emphasize the antibacterial and biotechnological potential of actinomycetes isolated from marine sponges (Almaary et al. 2021), soils (Rajivgandhi et al. 2018), vegetables (Tanvir et al. 2016), and mangroves (Dasgupta et al. 2015). Although reports like these reveal only a small fraction of an entire universe that is still little explored, it is exciting to find isolates that are so promising and capable of knocking out numerous pathogens with MDR strains and MRA, which give us hope that it will be possible to minimize the numerous deaths in hospital settings (Ahmad et al. 2017; Elsayed et al. 2020). On the other hand, the urgency and continued need for new drugs to face resistant-to-drug microorganisms seem to require more and improved research on the promising Phylum of actinomycetes, among other potential solutions.

Antifungals

As with pathogenic bacteria, in recent decades, fungal resistance and the emergence of MDR strains has been increasing alarmingly worldwide (Benedict et al. 2022). Pathogenic fungi are opportunists and the deadly enemies of immunosuppressed people; every year since 2012, at least 1.4 million deaths of people who are victims of fungal infections have been recorded (Benedict et al. 2022; Brown et al. 2012). Undoubtedly, *Candida albicans*, *C. auris*, *C. glabrata*, and *C. tropicalis* are the main culprits for these infections, a fact aggravated by the emergence of strains that resist at least two or more antifungals of the azole and polyene classes, and one of the echinocandins (Benedict et al. 2022; Chowdhary et al. 2017; Pristov and Ghannoum 2019). It is not without reason that one of the main disease control bodies, CDC (Centers for Disease Control and Prevention), emphasizes the urgent need for new antifungals in its recent warning to the scientific community about the increased lethality of fungal infections due to the rapid emergence of MDR strains (Zhang et al. 2022).

This global scenario has driven the prospection of new genetic resources that produce MNPs that can increase the arsenal of available antifungals (Pristov and Ghannoum 2019). In one of the first prospections at the beginning of the twenty-first century, in a screening of 320 actinomycetes from Moroccan soils for antifungal activities, 23 showed strong activities against *C. tropicalis* R2 and *Pythium irregulare* (the latter resistant to amphotericin B and nystatin) without interference in ergosterol synthesis, i.e., with non-polyenic and azoe mechanisms of action (Ouhdouch et al. 2001). Resistance to polyenes and azoes occurs when drugs of these classes do not inhibit the synthesis of ergosterol or do not have affinities for it in the cell membrane after modification (Pristov and Ghannoum 2019). Furthermore, ergosterol is very similar to human cell cholesterol and this is a limiting factor for these classes (Bhattacharya et al. 2020). As an alternative to ergosterol synthesis inhibitors, synthetic substances have been used, such as echinocandins, a class of antifungals that inhibit the synthesis of the fungal cell wall, a structure that is not seen in human cells. Another lesser-known class that does not inhibit ergosterol synthesis is that of flucytosines, among them 5-flucytosine (5FC), which acts by inhibiting nucleic acid synthesis in fungi (Bhattacharya et al. 2020; Pristov and Ghannoum 2019).

Despite the relative efficacy of echinocandins and flucytosines, there are several other studies that have sought natural antifungals, preferably not inhibitors of ergosterol synthesis, as in the screening of actinomycetes by the Moroccan researchers mentioned in the previous paragraph. Another important finding was the discovery of turbinmycin, produced by the actinomycete strain *Micromonospora* sp. (WMMC-415), which was isolated from the sea sponge *Ecteinascidia turbinata* and is a promising active ingredient that suppresses one of the most resistant fungal pathogens, namely *C. auris*, as well as *Aspergillus fumigatus* (Zhang et al. 2020). In a differentiated mechanism of action, turbinmycin targets a cytosolic protein, Sec14, which is indispensable for fungi and is involved in the intracellular transport of substances produced in the endoplasmic reticulum.

In comparison to screening that seeks new antibacterials, the amount of prospection carried out for new antifungals is much lower; however, several studies and reviews have speculated on many candidate actinomycetes as potential producers of new fungicides

against the MDR strains of *C. albicans*, *C. auris*, *C. glabrata* and *C. Tropicalis*, for example (Alkhalifah 2021; Liu et al. 2019b). The severity of fungal diseases, the continuous emergence of drug-resistant strains, the difficulty arising from fungal cells being eukaryotic, like ours, and the antifungal potential of actinomycetes, make them natural targets in the search for new antifungal models, ideally capable of attacking only fungal cells and not human ones.

Antivirals

Recently, for about three years, the world experienced a new pandemic triggered by the severe acute respiratory syndrome—Coronavirus 2 (SARS-CoV-2), which, up until 2022, claimed more than 6 million lives (Bharati et al. 2022). It is an exception, but respiratory syndromes and influenza are serious public health problems and are caused by the most prevalent viruses (World Health Organization 2022b)). One of these viral diseases, syncytial virus syndrome, affected about 33.8 million children under 5 years of age, with approximately 3.4 million severe cases and 199,000 deaths in 2005 (Nair et al. 2010). According to data from the World Health Organization, millions of people live with viral hepatitis (types: A, B and C), which causes millions of deaths every year. The development of recidivism of pathogenic viruses and the increase of emerging viruses due to lack of basic sanitation, malnutrition and climate change are expected (World Health Organization 2022b).

The development of antivirals is much slower compared to that of antibacterials and antifungals because immunization or vaccination is the preferred method for preventing or containing these types of pathologies. However, the pandemic caused by SARS-CoV-2 showed us the need for emergency drugs, and computational methods were very important in these circumstances since they enabled in silico assays using known substances. In one case using this method, 50 bioactive compounds isolated from mangrove actinomycetes were tested against the NSP10-methyltransferase of the etiological agent of SARS-CoV-2 (Muhammad et al. 2022). Among those substances, sespenine, xiamycin-C, xiamycin-D, xiamycin-E, xiamycin-methyl-ester, and xiamycin-A showed the greatest neutralization capabilities of this major enzyme for the replication cycle of this virus. In fact, the need for antivirals

for widespread diseases predates COVID-19. In a recent example, in 2013, the American continent experienced the Zika virus (ZIKV) epidemic that affected millions of people, some of whom developed Guillain-Barré syndrome and microcephaly (Saiz and Martín-Acebes 2017). On this occasion, numerous bioactive isolates of actinomycetes were tested in silico and some, such as daptomycin and nanchangmycin, showed strong activities against the causative agent, though previously these had not been described for the treatment of this virus (Barrows et al. 2016; Rausch et al. 2017).

In this challenging context for the development of new antivirals, there are findings that have brought hope to people affected by HIV-1 viruses. Studies of the isolate *S. albosporus* resulted in the isolation of *N,N,N*-(trimethylated)-Tyr-L-Leu-L-Val-L-Leu-(dehydrated)-His, which is able to inhibit the protease-HIV-1 that is essential for the cycle of this pathogen (Liu et al. 2012b). Similarly, ahmpatinin-iBu from *Streptomyces* sp. (CPCC202950) was found to be a potent inhibitor of the same HIV-1 protease (Chen et al. 2018). On the other hand, 3-acetyl-5-methyl-2'-deoxyuridine, derived from *S. microflavus*, was active in bioassays against hepatitis B virus, herpes simplex type 1 and 2 (HSV-1 and HSV-2) and varicella zoster virus (VZV) (Li et al. 2011).

In the studies mentioned above, we see examples of the still little explored potential of actinomycetes for the production of antivirals, and in silico assays for the screening of substances with this potential. However, in silico assays allow us to only preliminarily observe the affinity of a substance for a target and this is not enough for emergency uses – since other experiments, including those involving the pharmacokinetics and pharmacodynamics of an active ingredient, are necessary in order to establish its real efficacy as well as the correct dosage, among other factors. As an example, while having been indicated by in silico assays for SARS-CoV-2, hydroxychloroquine and azithromycin were not effective against the COVID-19 disease (Braz et al. 2020). Viral diseases have already killed an incalculable number of people, and the most efficient weapon is vaccines; however, seeking new drugs that help in the treatment of viruses is essential in order to reduce mortality, and actinomycetes have already demonstrated their ability to provide MNPs that can help in the treatment of numerous viruses.

Antiparasitic

Of the parasitic diseases, malaria is one of the most devastating and deadly. The African continent is the most affected by this disease and approximately 96% or 627,000 deaths from the disease occurred here in 2020 (Chan et al. 2022). Around the world, the vectors of malaria are the mosquitoes from the genus *Anopheles*, including *An. gambiae*, *An. coluzzii*, and *An. arabiensis*, which transmit the protozoa *Plasmodium vivax*, *P. falciparum*, *P. malariae*, *P. ovale*, and *P. knowlesi* (Barney et al. 2022).

P. falciparum is the one that causes the greatest concern, since it is the most incident and responsible for the most aggressive form of this parasitosis, in addition to presenting strains that are resistant to current antiparasitic drugs (Sissoko et al. 2017; World Health Organization et al. 2022b). In addition to malaria, which is an endemic parasitosis in tropical and subtropical regions, other protozoan-transmitted diseases, such as leishmaniasis and trypanosomiasis (Chagas disease), are public health problems in most of these regions because of antimonial resistance. When not treated correctly, they can progress to more serious conditions and lead to death (Davies-Bolorunduro et al. 2021). Similarly, and also very serious, *Entamoeba histolytica* infections affected approximately 50 million people in 2012 alone, of which 100,000 died. In a recent review, amoebiasis is already considered the third most deadly parasitosis worldwide, especially in underdeveloped countries in Central/South America, Africa, and Asia due to poor basic sanitation. With an average of 70,000 deaths in recent years, this parasitosis can affect several organs in our body, which can lead to a more serious condition (Jasni et al. 2022).

Tests of the crude extract of *S. canus* (N25) showed the best antiprotozoal activities for *P. falciparum*, in addition to also inhibiting the protozoan *Toxoplasma gondii*, the causative agent of toxoplasmosis. Phenazine-1-carboxylic acid, which is capable of inhibiting these pathogens, was identified in the fractions (Pagmadulam et al. 2020). Staurosporine (STS) and 7-oxostaurosporine (7OSTS), isolated from *S. Sanyensis*, showed excellent antiparasitic activities against *Leishmania amazonensis*, *L. donovani*, as well as *T. cruzi* and *T. brucei* (Cartuche et al. 2020), which are the causative agents of Chagas disease and sleeping sickness. In another study, these

protozoa were neutralized in vitro by actinoallolide-
A from *Actinoallomurus fulvus* (MK10-036) (Ina-
hashi et al. 2015). Regarding infections caused by *E.*
histolytica, noting the resistance and toxic effects of
drugs, a study of extracts of marine actinomycetes
yielded echinomycin-A and tyrandamycin-A, which
showed strong antiamebiasis activities and reduced
the growth of *E. histolytica* (HM1:IMSS) and *E.*
histolytica (Col) by 84.2% and 64.8%, respectively
(Espinosa et al. 2012). To date, several studies have
highlighted numerous MNPs with the capacity to
suppress numerous protozoa and their resistances,
among which several isolates from actinomycetes, as
shown in the review by Estrella-Parra et al. (2022).
Since the beginning of the twenty-first century, many
studies have been published reporting screening with
isolates from actinomycetes, which, among other
activities, showed antimicrobial activities. Although
actinomycetes are natural targets in the search for new
antimicrobial models, there is an urgent need for an
investigation of the biological activities of recently
isolated promising strains, since most studies end in
preliminary stages without the substances responsible
for the activities becoming known.

Non-antimicrobial spectrum

Anticancer

The field of medicine faces difficulties in treating
various types of cancers. This disease has claimed
millions of lives worldwide and is character-
ized by the emergence and proliferation of abnor-
mal, aggressive, and invasive cells (Pimentel et al.
2011; Sung et al. 2021). Data from the beginning
of the twenty-first century show that the global can-
cer burden in 2000 reached 10 million new cases
and 6 million deaths, with 22 million people liv-
ing with cancer in this period (Parkin 2001). Sev-
eral projections of the time predicted that these
numbers would increase or even double, with the
need for more studies in search of new producers
of anticancer drugs (Rahib et al. 2014; Sung et al.
2021). Recently, these projections were confirmed;
for example, in a survey of data from 2018, a sig-
nificant increase in annual incidence was observed,
with general estimates of 18.1 million new cases
and the occurrence of 9.6 million deaths that year

(Ferlay et al. 2019). By 2020, these figures reached
19.3 million new cases, with female breast cancer
(11.7%) surpassing lung cancer (11.4%), followed
by colorectal cancer (10.0%), prostate (7.3%), and
stomach (5.6%) cancer (Sung et al. 2021; World
Health Organization 2022b).

Many isolates from actinomycetes are promising
in producing active ingredients with antimicrobial
and anticancer capabilities. As an example, among
41 endophytic isolates from *Streptomyces* spp., 31.7%
showed cytotoxic activities against the cancer cells
A549 (lung), 29.3% for HL-60 (blood), 85.4% for
BEL-7404 (liver), and 90.2% for P388D1 (blood),
with seven standing out as the most promising line-
ages (Li et al. 2008). It should be noted that lung and
liver cancers are among the most common and the
deadliest (Sung et al. 2021). In a more recent study,
three isolates of *Streptomyces* spp. from soils and
marine sediments showed antimicrobial and antican-
cer activities in their crude extracts (Abdel-Aziz et al.
2019). In its extract, the most notable isolate, *Strep-*
tomycetes sp. D-EGY, presented an IC_{50} of 0.85 μ g/mL
for the HepG2 lineage (human hepatocellular carci-
noma). The authors reported forty isolated and identi-
fied compounds from this extract, whose correlations
with anticancer activity should be investigated.

In two other studies carried out in recent years,
expectations seem more favorable. Firstly, as reported
above, the bactericidal desertomycin G against *M.*
tuberculosis is also active against cancer cells of the
human breast adenocarcinoma (MCF-7) and colon
carcinoma (DLD-1) lineages (Braña et al. 2019).
Next, caerulomycin A isolated from *Actinoalloteichus*
cyanogriseus (DSM 43889) showed broad spectrum
cytotoxic activities against cancer cell lines A375
(melanoma), A549 (lung), H1299 (lung), HepG2
(liver), HT29 (human colon), HL-60 (blood), and
M624 (muscle) (Tong et al. 2022). The study of its
mechanism of action indicated its ability to interfere
in the formation of microtubes and DNA replication,
acting specifically on the enzymes responsible for the
polymerization of microtubes and on topoisomer-
ase I, which is responsible for the relaxation of the
DNA molecule during its replication. According to
the authors, this is the second active ingredient iso-
lated from microorganisms with anticancer activ-
ity that acts on two targets, unlike Taxol® (isolated
from plants), which acts only on the synthesis of
microtubes.

In comparison with the anticancer drugs available on the market, mostly derived from plants, these aspirants can be considered superior and have lower cost, thus revealing that screening for metabolites from actinomycetes can be very attractive. However, although numerous reviews and studies have consolidated the broad spectrum of action of the bioactive compounds of these bacteria (Aamir et al. 2020; Ek-Ramos et al. 2019; Law et al. 2020; Salam et al. 2017; Tanvir et al. 2019; Taechowisan et al. 2017), there is much more to discover regarding the anticancer potential of actinobacterial metabolites. Some of the anticancer metabolites are possibly the same ones that actinomycetes utilize against fungi in nature, since fungi are eukaryotic beings like us, substances that can fight fungi can also fight cancers that are made up of our own modified cells. While this hypothesis also signs a risk of toxicity for healthy human cells, it might be a good idea to look for both anticancer substances among antifungal compounds and antifungals among anticancer metabolites.

Antidiabetes

In the twenty-first century, among the chronic diseases, diabetes stands out, especially type 2 diabetes (on average 95% of cases), which is the deadliest. This is a metabolic dysfunction that results from low insulin availability or inadequate reception of target cells to insulin (Alharbi 2016; Cousin et al. 2022; Roper et al. 2002). According to one of the latest reports of the World Health Organization (2022b), this disease was one of the main factors that predisposes affected people to a more serious state of SARS-CoV-2 (World Health Organization 2022b). In the United States alone, one of the most obese populations in the world, it is estimated that 10% of the population has one of the types of diabetes (Hulett et al. 2022).

The endophytic isolate *S. longisporoflavus* stands out for producing an extract with inhibitory activity for the enzyme alpha-amylase (Akshatha et al. 2014)); this enzyme hinders the absorption of glucose in patients with type 2 diabetes mellitus. In fact, to treat type 2 diabetes, some bioactive isolates of actinomycetes, such as voglibose (Mahmud 2003) and acarbose (De Melo et al. 2006), obtained from *S. hygroscopicus-limoneus* and *S. calvus*, respectively, are already being used. Voglibose works by inhibiting

alpha-glucosidase, thus lowering blood glucose levels in people with diabetes mellitus (De Melo et al. 2006), and acarbose is an inhibitor of alpha-glucosidase and alpha-amylase in the treatment of type 2 diabetes mellitus (Xu et al. 2009). Furthermore, more recently, in the study by Kawahara et al. (2023), a new candidate for the treatment of diabetes mellitus 2, the alkaloid amamine (1), isolated from *Kitasatospora* sp. HGTA304, was able to inhibit α -glucosidase with an IC_{50} value (56 μ M) approximately ten times lower than acarbose (549 μ M). Results such as these give us hope that we can find more promising isolates from actinomycetes that can be used to treat chronic diseases such as diabetes.

Anticholesterol

Cholesterol is an essential component of human cells, but its excess in the bloodstream can cause harm to human health, especially heart problems (Seenak et al. 2021). In an investigation of a BGC of *S. lunae-lactis* MM109, which synthesizes distinct MNPs, it was observed that the availability of iron in mineral form is essential for the synthesis of p-vinylphenyl-3-nitroso-4-hydroxybenzoate, which is a precursor of trimeric ferroverdins that have anticholesterol activity (Martinet et al. 2019). The discovery of new ferroverdins may aid in the treatment of cardiac sarcoidosis, which is a heart inflammation related to high levels of cholesterol in the blood.

Alzheimer's treatment

Alzheimer's is a neurodegenerative disease that causes dementia and affects thousands of people every year (Almasi et al. 2018). Its physiological mechanisms are still being investigated; however, the accumulations of β -amyloid and acetylcholinesterase within the neocortex are determining factors. Indeed, acetylcholinesterase inhibitors help improve the availability of acetylcholine, a neurotransmitter that is indispensable for cognitive activities and memory. This activity helps to decrease the negative effects of β -amyloid accumulation in the neocortex (Barage and Sonawane 2015). It is estimated that by 2050 every 33 s a person will be affected by this disease (Alzheimer's Association 2017; Almasi et al. 2018; Bush 2003; Calderon-Garcidueñas and Duyckaerts 2018). There are still no drugs made from actinomycetes that

can be used in the treatment of this neurodegenerative disease, but some studies already report the possibility of actinomycetes being sources of active ingredients capable of assisting in its treatment. We can cite, as an example, a study of the endophytic community of *Gynura cusimbua*, a Chinese medicinal plant that, according to the traditional knowledge of this region, is used in the prevention of hypertension, coronary heart disease, Alzheimer's and atherosclerosis. This study showed that this plant has a rich diversity of actinomycetes. The study also hypothesizes that some of the metabolites found in the plant related to biological activities may originate from actinomycetes (Zhang et al. 2016). Another study strengthens this hypothesis since, among more than 200 actinomycetes from sponges of the Caspian Sea and Persian Gulf, 50% presented extracts with anti-acetylcholinesterase activity (Almasi et al. 2018). The authors emphasize that the various compounds isolated and characterized with activities can assist in the treatment of neurodegenerative diseases that affect cognition and memory.

1176 Stomach antiulcer and anti-inflammatory drugs

In studies of the microbiota of an endemic sponge in the Red Sea (*Spheciospongia mastoidea*), an actinomycete (RA2) was identified that is capable of producing two compounds, butylcycloheptylprodigiosin and undecylprodigiosin. These substances showed antiulcer and anti-inflammatory activities in experiments with rats that suffered stomach injuries induced by hydrochloric acid/ethanol. When these RA2 compounds were administered orally, decreased rates of lesions in areas of ulceration, histopathological abnormalities, and neutrophil infiltration were observed. These results are similar to those of omeprazole, the standard antiulcer drug (Abdelfattah et al. 2019). On the other hand, *S. gramineus*, associated with the lichen *Leptogium trichophorum*, together with three known actinofuranones produced six promising new actinofuranones (D to I) (Ma et al. 2018). Among them, two known and two new actinofuranones stood out as potential candidates for anti-inflammatory drugs due to their results in tests of attenuation of nitric oxide (NO) production and evasions of pro-inflammatory cytokines (IL-6) and tumor necrosis factor- α (TNF- α).

Protection, fertilization and improvement of plant production 1200
1201

High food yields in agricultural production depend on fertilizers, pesticides, and biocontrol agents. On this question, much remains to be explored within the fascinating actinomycetes group, as can be inferred from many studies. For example, a significant increase was observed in the fertility of the date palm (*Phoenix dactylifera* L.) when actinomycetes were inoculated into its rhizosphere, thus improving the life cycle of this vegetable of economic importance for Egypt. Improvements noted in the appearance of the fruits, which had higher levels of sugars, organic acids, essential amino acids, unsaturated fatty acids, phenolic acids, flavonoids, vitamins and minerals. In addition, improvements were observed in antitumor, antioxidant, antiprotozoal, and antimicrobial activities (fungi and bacteria) of fruits of date palms treated with actinomycetes (Abdelgawad et al. 2019). In another case, 11 isolates of the genera *Norcadia*, *Streptomyces*, and *Janibacter* from turmeric (*Curcuma longa* L.) and ginger (*Zingiber officinale*) presented activities against the phytopathogens *Alternaria pimpriana* and *Colletotrichum coccodes* (Osaro-Matthew et al. 2020).

The protection of plants and the improvement in the quality of their fruits exemplified above seem closely associated and this improvement is a possible consequence of the elimination of phytopathogens, rather than a direct advantage to the plant. This is also observed in the following two examples, in which, together with the biocontrol of phytopathogens, significant improvements in fruit quality were reported. In the first case, an endophytic community of actinomycetes from healthy cucumber plants stood out due to the biocontrol of the phytopathogen *Fusarium oxysporum* f. sp. cucumerinum, which is the cause of wilting. The strain *Streptomyces* sp. NBRC 100767 showed the strongest activity and azalomycin B was responsible (Cao et al. 2020). In the other study, the strain *Streptomyces* sp. JKTJ-3 presented a broad spectrum of biocontrol and was capable of inhibiting 12 phytopathogens, including *Pythium aphanidermatum*, which is responsible for wilting in watermelon seedlings (Ge et al. 2023).

In addition to isolates from soils or endophytes, strains of actinomycetes from other ecosystems may show activity against phytopathogens. Recently, a

consortium of actinomycetes isolated from insect intestines was reported as being promising strains for the biocontrol of *Bipolaris maydis*, which causes rust on wheat leaves (Wang et al. 2023). *Streptomyces* sp. SN5431 was the most successful in biological tests with extracts, and the substance tiuslactone B, from its fermented broth, was responsible for the fungicidal activity.

The fight against nematodes that affect vegetables can also be aided by actinomycetes. The strain *Micromonospora* sp. WH06 is reported as a potential biocontrol agent of the nematode *Meloidogyne incognita*, which causes lesions in the roots of *Meloidogyne* spp. Benzenepropanoic acid, isolated from the fermented broth of *Micromonospora* sp. WH06, causes 99% mortality with a dose of 200 µg/mL after 72 h and inhibition of egg hatching in *M. incognita* (Ran et al. 2022).

Volatile compounds (VOCs) from actinomycetes have also shown antimicrobial activities. The volatile 2-methyl-1-butanol, 3-methyl-1-butanol, pyridine and phenylethyl alcohol of *Streptomyces* sp. SPS-33 strain showed strong in vivo and in vitro activities against the phytopathogen *Ceratocystis fimbriata*, which causes charcoal rot in sweet potato plants (Li et al. 2020a, b). Decreased water loss and increased anti-oxidant activity were also observed.

The applicability of promising strains of actinomycetes in agriculture is becoming a more sustainable and economically viable strategy. In the harmonious relationship with plants, actinomycetes benefit from a nutritious and attractive phyto-exudate and produce several secondary metabolites with phyto-propagating and phyto-protective activities (Van der Meij et al. 2017; Olanrewaju and Babalola 2019; Trivedi et al. 2020). Hormones secreted by actinomycetes, or induced by them in plants, stimulate several important activities in plants. For example, the secretion of the phytohormone auxin (indole-acetic acid) promotes the elongation of the roots – which allows them to reach more nutrients – and also the activation of plant immunity against fungal phytopathogens. Cytokinin helps to delay plant deterioration and aging; gibberellin helps in root enlargement, resistance to salt stress and endosymbiotic interactions; ethylene stimulates root colonization and immune responses against microbial pathogens; and, finally, polyamines are involved in senescence, fruit maturation, flowering, organogenesis, morphogenesis and embryogenesis.

These hormones, which are secreted by actinomycetes, act in all the physiological processes of plants, from seed germination to resilience to abiotic and biotic stresses and are synthesized mainly by strains of the genus *Streptomyces* and other rare genera (*Nocardiopsis*, *Micromonospora* and *Amycolatopsis*, among others) (Ebrahimi-Zarandi et al. 2023; Oyedoh et al. 2023a). Among the enzymes, nitrogenases are quite well known. They have the ability to convert N₂ (not usable by plants) into NH₃ (usable by plants) for the synthesis of proteins, secondary metabolites, DNA and RNA (AbdElgawad et al. 2020; Al-Rashdi et al. 2022; Rosenblueth et al. 2018).

As in these few examples, due to their ability to fix nitrogen in the rhizosphere and their potential to inhibit phytopathogens, actinomycetes are strong candidates that can be explored for improvements in the production of many plants. The ecological activities of actinomycetes in favor of plants are a model for more sustainable agriculture, with emphasis on the genus *Streptomyces* and some strains of rare genera of actinomycetes that have been gaining recognition (Oyedoh et al. 2023a, 2023b).

Remediation, promotion of bioavailability and solubilization of minerals

The advantages of using actinomycetes as bioremediators consists in the fact that they do not present risks to the health of animals, humans, plants, or the soil and aquatic environments. Their biological activities are stimulated when the nutritional and ecological conditions of their niches are made available. Enzymes (chitinase, cellulase, glucanase, protease, lipases, and phospholipase, among others) secreted by actinomycetes exert important biological activities for the environment and plants. For example, chitinase, glucanase, lipases, and phospholipase degrade cell walls and plasma membranes of microbial phytopathogens, which are competing and neutral microbes (Selim et al. 2021). In fact, there are several examples of actinomycetes being environmental purifiers, among which we can highlight the genus *Rhodococcus*, which presents itself as a diverse mediator. Thus, strains of this genus are capable of producing 3-chlorobenzoate 1,2-dioxygenase (3CBDO), an enzyme capable of degrading the herbicide 3-chlorobenzoate (3CBA) (Emelyanova et al. 2023). Other strains, isolated from Arctic soils,

are capable of oxidizing hydrocarbons (Semenova et al. 2022), and others are capable of degrading non-steroid anti-inflammatory pharmaceutical products, such as ibuprofen, meloxicam and naproxen (Ivshina et al. 2022). This genus is also promising in the promotion of mineral bioavailability, as in the case of a strain of *Rhodococcus* sp. that, through non-ribosomal peptide synthetases enzymes, synthesizes several siderophores (rhodochelin, rhequichelin, requibactin, rhodobactin and heterobactin A), which demonstrates that the strain can be used as an agricultural aid for iron bioavailability (Sarkar and Suthindhiran 2022). There are also reports of strains of *Streptomyces* and *Promicromonospora* isolated from Moroccan soils that are capable of solubilizing phosphate (Boussellham et al 2022). In fact, actinomycetes harbor a consortium of underexploited enzymes in their genomes, and are able to act in the decomposition of plant and animal organic matter, and solubilization of inorganic substances (manganese (Mn), cobalt (Co), lithium (Li), copper (Cu), zinc (Zn), cadmium (Cd), nickel (Ni), aluminum (Al), and magnesium (Mg)) in simpler states for biological uses (Imade and Babalola 2021; Schwabe et al. 2018).

Other biotechnological applications focused not only on medicine and agriculture

There is certainly still much to be revealed about the potential biotechnological application of actinomycetes, both in targeting products and processes, not only in medicine and agriculture. Two of these applications are related to the search for more sustainable alternatives for the production of fuels and biodegradable plastics. Recently, an innovative method for biodiesel production was created using the actinomycetes *Piscicoccus intestinalis* (WA3) and the microalgae *Tetrademus obliquus* (AARLG022) in co-culture for biomass enrichment using the biogas digestate effluent (BDE) method (Kumsiri et al. 2021). The authors observed the increase of long-chain lipids, indole-3-acetic acid, and siderophores by *T. obliquus* in co-culture with *P. intestinalis*-WA3 (fertilizer agent) when they compared the results with those of *T. obliquus* monoculture. It is an encouraging result that opens up a promising horizon to be explored, in this case, to improve biodiesel production using algae. In another relevant study, strains from three genera of actinomycetes: *S. gougerotti*, *M. matsumotoense*,

and *N. prasina* demonstrated the ability to degrade low-density polyethylene (LDPE), polystyrene (PS), and polylactic acid (PLA) under varied conditions (Oliveira et al. 2022). Furthermore, mainly the *S. gougerotti* and *M. matsumotoense* strains were able to use those plastics as carbon sources to produce polyhydroxyalkanoate (PHA) bioplastics. In this sustainable context, actinomycetes gain yet another important applicability within their fascinating biotechnological spectrum.

Conclusion

The studies presented in this review are a small sample of the enormous biotechnological potential of actinomycetes, regarding which our knowledge and exploitation are rapidly expanding. As such, considering the data described here and the literature, the metabolites of actinomycetes can meet numerous medical, agricultural and industrial demands far beyond what is currently known and used. Using gene mining technologies further enhances the discovery of the immense metabolic wealth hidden in the genomes of known species and new isolates, as highlighted by several studies. Thus, with the help of genomics and metabolomics, a new generation of antibiotics and substances of biotechnological interest is being revealed. Considering the advances of the last century, since the discovery of streptomycin in 1944, the first 23 years of the twenty-first century represent a considerable leap forward in research into the potential of actinomycetes. Therefore, for the forthcoming decades, one can imagine the development of innovative products using actinomycetes as a source of metabolites that are capable of treating numerous pathologies and assisting in various therapies, among other biotechnological applications. However, it is necessary to improve many research approaches to go beyond preliminary results. It is required to face this question in its deep causes, among which we highlight the isolation of many research teams, low level of funding, and lack of strategic and effective planning. Everyone's effort is essential: governments, funding bodies, research institutions, and the researchers themselves. We must also highlight the need to investigate the many little-known environments with a high potential for exploring the metabolic richness of actinomycetes and other microorganisms, among

which we highlight the aquatic environments of fresh or saltwater and tropical forest environments, especially the Amazon. Unfortunately, many of these environments suffer constant degradation and much of their microbiota is being extinguished without us being able to discover and take advantage of their biotechnological potential.

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Declarations

Competing interests The authors declare no competing interests.

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