Chapter

Plant-Associated Microorganisms as a Potent Bio-Factory of Active Molecules against Multiresistant Pathogens

Felipe de Paula Nogueira Cruz, Andréa Cristina Bogas and Cristina Paiva de Sousa

Abstract

Antibiotic-resistant pathogens are a public health threat that has rapidly spread over decades due to continuous and uncontrolled administration of antimicrobial medicines, becoming an ever-increasing worldwide concern. Since the past decade, no significant innovations have been made, so the search for new compounds that face multidrug-resistant pathogens is critically important. Plant-symbiont microorganisms are capable of producing a variety of bioactive natural products, making it possible to treat several infectious diseases. Biotechnological processes using microorganisms have been increasing in recent years since the discovery of Paclitaxel, an important antimitotic produced by the endophyte *Taxomyces andreanae*. It was isolated for the first time from the native tree of Pacific *Taxus brevifolia*. Several studies have demonstrated the isolation and characterization of promising and potent substances capable of inhibiting these pathogens. In addition, both rhizospheric and endophytic communities represent an unexplored reserve of unique chemical structures for drug development. This chapter focuses on the potential of plant-derived microorganisms as a source of bioactive substances and the perspectives for further studies and their application.

Keywords: antimicrobial resistance, endophytes, natural products, rhizosphere, superbugs, *Streptomyces* spp.

1. Introduction

The discovery of medicines in the treatment of infectious diseases represents one of the most significant accomplishments of humankind. The introduction of antibiotics made it possible to treat previously incurable diseases.

Major classes of antibiotics were discovered between the 1940s and 1960s, where soil-derived actinobacteria produced most of them. However, several decades passed without significant innovations until the discovery and development of oxazolidinones in 2010 (**Figure 1**). Moreover, the continuous uncontrolled use of these medicines favored the rapid spread of resistant pathogens, where new compounds were discovered, and their introduction into clinical practice was not fast enough [1–5].

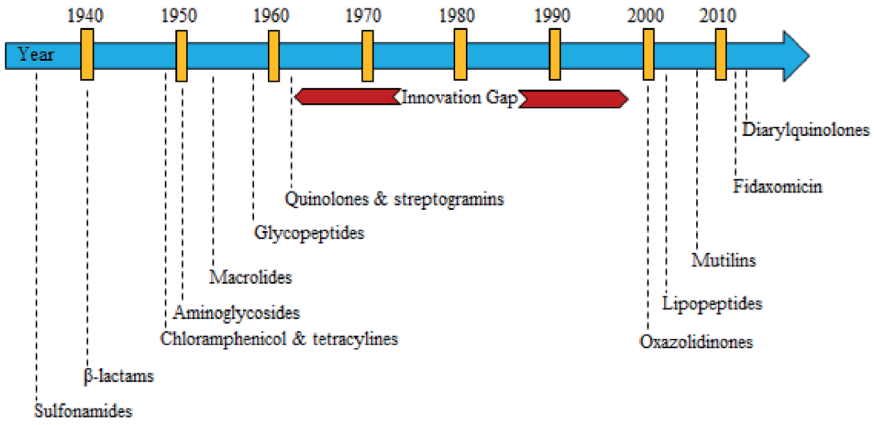


Figure 1.
Timeline of antibiotic discovery that shows no new classes of antibiotics between the years 1962 and 2000 adapted from: [6, 7].

The CDC (Centers for Disease Control and Prevention) has recognized the emerging antibiotic resistance as a significant threat to public health [8]. Superbugs, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), show antibiotic resistance rates that surpass 50% in 5 out of 6 world regions; in contrast, the multidrug-resistant *Acinetobacter baumannii*, described as a dangerous agent by the Society of Infectious Diseases of America (SIDA), is a notable threat in intensive care units (ICUs) due to the development of resistance to broad-spectrum antibiotics [5, 8–10].

Therefore, the search for compounds and the exploration of niches that harbor microorganisms that produce bioactive metabolites are critically important [11–13]. Several studies have shown that plant tissues represent a rich source of natural products for pharmaceutical and biotechnological interest. Most of these compounds are produced by microorganisms that live in intimate interaction with the host plant without causing damage; therefore, they are known as endophytes [11, 14, 15].

In the same context, the rhizosphere's microbiome can exert profound direct and indirect effects on plant growth, nutrition, and health in natural ecosystems. Its micro-community (bacteria, oomycetes, viruses, archeas, fungi and arbuscular mycorrhizae) is attracted and fed by nutrients, exudates, border cells and mucilage that are released by the root of the plant [16].

Relevant studies have reported potent antimicrobial compounds, such as teixobactin, isolated from the non-cultivable bacterium *Eleftheria terrae* [17]. According to the authors in [17], teixobactin inhibits cell wall synthesis by binding to the highly conserved region of lipid precursors of peptidoglycan and teichoic acid. In addition, *S. aureus* and *Mycobacterium tuberculosis* did not develop resistance to teixobactin.

In the study by [18], endophytic fungi were isolated from the medicinal plant *Orthosiphon stamineus*, where 92% of them exhibited significant inhibitory activity against different species of bacterial pathogens and filamentous fungi.

Paenibacillus polymyxa can be found in several habitats. Its characteristic metabolism and production of substances enhance biotechnological applications based on the production of bioactive molecules. It is also widely applied in commercial agriculture as a bio-fertilizer grow plant promoter, biological control, and environmental remediation. In [19], *P. polymyxa* was endophytically isolated from *Prunus* spp., and the author reported the isolation of molecules which potently inhibited *S. aureus* and *E. coli*.

Herein, we address a review topic concerning the potential of rhizospheric and endophytic microorganisms as producers of antimicrobial compounds.

2. Endophytes: an overview

In 1866, de Bary outlined the first distinction between endophytes and plant pathogens. These microorganisms (typically fungi or bacteria) colonize the plant's internal tissues and live part of its life or its entire life cycle without causing apparent damage, establishing a mutualistic interaction with the host plant. Moreover, endophytes are capable of producing beneficial substances, such as alkaloids, enzymes, antibiotics and other compounds that protect and help the plant under stress conditions in exchange for nutrients and protection provided by the host plant [14, 15, 20–22].

In this context, plants have served humanity for centuries and led to the discovery of novel bioactive compounds. However, concerns regarding biodiversity and conservation, as well as large quantities of plant tissue, are required to produce sufficient yields of compounds [23]. According to [24], paclitaxel isolation requires about 10,000 kg of *T. brevifolia* bark to yield 1 kg. On the other hand, several studies have shown that endophytes may produce similar or even the same bioactive compounds as their plant hosts [20, 23, 25].

Fungi are skilled producers of natural products, including antitumor agents, cholesterol-lowering agents, immunosuppressants and antibiotics [25, 26]. The study by [27] detected potent antimicrobial properties of the natural product extract (NPE) of endophytic fungi associated with *Myrciaria floribunda*, *Alchornea castaneifolia* and *Eugenia aff. Bimarginata* against several pathogens. The methanolic extracts presented MIC values ranging from 7.8 to 1000 μg/mL against *C. krusei*, *C. parapsilosis*, *C. neoformans*, *C. albicans*, and *C. glabrata*. The inhibition of *S. aureus* and *B. cereus* ranged from 7.8 to >1000 μg/mL. Also, endophytic fungi were isolated from *Cinnamomum mercadoi*, a medicinal tree endemic to the Philippines. The ethyl acetate extract of *Fusarium* sp. presented moderate inhibition against *E. coli*, *E. aerogenes*, *S. aureus*, and *B. cereus* with minimum inhibitory concentrations of 2.1, 4.2, 4.2, and 3.8 mg/mL, respectively [28].

Therefore, the emerging use of endophytes in the research and development of new drugs represents the most successful example of bioactive natural products in medicine, pharmaceutical and biotechnological applications. **Table 1** provides an idea of some secondary metabolites of endophytic fungi and bacteria tested against resistant and multidrug-resistant microorganisms.

3. Rhizospheric microorganisms: an overview

The term rhizosphere was first used in 1904 by agronomist and plant physiologist Lorenz Hiltner to describe the interface between plant roots and the soil inhabited by a unique microbial community, which is influenced by the chemical release from plant roots [49]. In recent years, based on the relative proximity and influence to the root, the rhizosphere definition has been refined to include three zones: (i) endorhizosphere, which includes portions of the cortex and endoderm, where microorganisms and mineral ions occupy free space between cells (apoplastic space); (ii) rhizoplane, a middle zone adjacent to the root's epidermal cells and mucilage; and (iii) ectorhizosphere, which extends from the rhizoplane out into the bulk soil and is colonized by the microorganisms that are either free-living or non-symbionts [50, 51].

Endophytic fungi				
Endophyte	**Host plant**	**Compound**	**Target strain**	**Reference**
Trichoderma ovalisporum	*Panax notoginseng*	Shikimic acid	*S. aureus*	[29]
			E. coli	
Fusarium oxysporum	*Cinnamomum kanehirae*	Beauvericin	MR *S. aureus*	[30]
			B. subtilis (ATCC66333)	
Diaporthe phaseolorum	*Laguncularia racemosa*	3-Hidroxypropionic acid	*S. aureus*	[31]
			S. typhi	
Pestalotiopsis mangiferae	*Mangifera indica*	4-(2,4,7-trioxa-bicyclo[4.1.0]heptan-3-yl) phenol (1)	*B. subtilis* (MTCC 441)	[32]
			E. coli (MTCC 443)	
			P. aeruginosa (MTCC 424)	
			K. pneumonia (MTCC 109)	
			C. albicans (MTCC 227)	
Xylaria sp.	*Anoectochilus setaceus*	Helvolic acid	*B. subtilis* (UBC 344)	[33]
			MR *S. aureus* ATCC 33591	
Aspergillus terreus	*Carthamus lanatus*	(22E,24R)-stigmasta-5,7,22-trien-3-β-ol; Aspernolide F	*S. aureus* MRSA (ATCC 33591)	[34]
			C. neoformans (ATCC 90113)	
Hypocrea virens	*Premna serratifolia* L.	Gliotoxin	*C. neoformans* (ATCC 90113)	[35]
			B. subtilis (UBC 344)	
			S. aureus (ATCC 43300)	
			S. aureus MRSA (ATCC 33591)	
			E. coli (UBC 8161)	
			P. aeruginosa (ATCC 27853)	
			C. albicans (ATCC 90028)	
Aspergillus sp. TJ23	*Hypericum perforatum*	Spiroaspertrione A	*S. aureus* MRSA	[36]
Aspergillus sp. TJ23	*Hypericum perforatum*	Aspermerodione	*S. aureus* MRSA (ATCC 43300)	[37]

Endophytic fungi				
Endophyte	**Host plant**	**Compound**	**Target strain**	**Reference**
Phomopsis asparagi	*Paris polyphylla*	Diphenyl ethers derivates	*S. aureus* MRSA (ZR11)	[38]
Athelia rolfsii	*Coleus amboinicus* Lour.	Hemiterpenoid compounds	*S. aureus* (ATCC 25923)	[39]
			E. coli (ATCC 11229)	
			P. aeruginosa (ATCC 27853)	
			B. subtilis (ATCC 6633)	
			S. typhi (clinical)	
			S. mutans (ATCC 25175)	
Endophytic bacteria				
Streptomyces sp.	*Kandelia candel*	Indolosesquiterpenes	*S. aureus* MRSA	[40]
			Enterococcus faecalis VRE	
Streptomyces sp.	*Kandelia candel*	Eudesmene-type sesquiterpenes (kandenols)	*B. subtilis* (ATCC 6633)	[41]
S. sundarbansensis	*Fucus* sp.	Polyketides (2-hydroxy-5-((6-hydroxy-4-oxo-4H-pyran-2-yl) methyl) -2- propylchroman-4 one)	*S. aureus* MRSA (ATCC 43300)	[42]
Streptomyces sp.	*Dysophylla stellata*	2-amino-3,4-dihydroxy-5-methoxybenzamide	*E. coli*	[43]
			C. albicans	
Streptomyces sp.	*Dracaena cochinchinensis*	(*Z*)-tridec-7-ene-1,2,13-tricarboxylic acid	*S. epidermis* MRSA (ATCC 35984)	[44]
			S. aureus MRSA (ATCC 25923)	
		Actinomycin-D	*E. coli* (ATCC 25922)	
			K. pneumoniae (ATCC 13883)	
Streptomyces sp.	*Zingiber spectabile*	Diketopiperazine *cyclo* (tryptophanyl-prolyl); chloramphenicol	*S. aureus* MRSA (ATCC 43300)	[45]
			S. aureus MRSA (ATCC 49476)	
			S.aureus MRSA (ATCC 33591)	
Microbispora sp.	*Vochysia divergens*	1-Acetyl-β-carboline	*S. aureus* MSSA	[46]
			S. aureus MRSA	

Endophytic fungi				
Endophyte	**Host plant**	**Compound**	**Target strain**	**Reference**
S. cavourensis	*Cinnamomum cassia*	1-Monolinolein, bafilomycin D; nonactic acid; daidzein	*S. aureus* MRSA (ATCC 33591)	[47]
		3′-Hydroxydaidzein	*S. epidermidis* MRSE (ATCC 35984)	
Luteibacter sp.	*Astrocaryum sciophilum*	(*R*)-2-hydroxy-13 methyltetradecanoic acid, (*R*)-3-hydroxy-14methylpentadecanoic acid, (*S*)-β-hydroxypalmitic acid; (*R*)-3-hydroxy-15 methylhexadecanoic acid, (*R*)-3-hydroxy-13-methyltetradecanoic acid, 13-methyltetradecanoic acid; 9Z-hexadecenoic acid, 15-methyl-9*Z*-hexadecenoic acid	*S. aureus* MRSA	[48]
Streptomyces sp.	*Epipremnum aureum*	Phenylalanine-arginine β-naphthylamide	*Mycobacterium tuberculosis*	[49]
			B. cereus (ATCC11778)	
			E. faecium (ATCC51559)	
			A. baumannii (ATCC19606)	

Table 1.
Secondary metabolites produced by endophytic fungi and bacteria with antimicrobial activity (2010–2020).

The rhizosphere is a complex and dynamic region, where bacteria (including Plant Growth-Promoting Rhizobacteria—PGPR), fungi (including Arbuscular Mycorrhizal Fungi – AMF), oomycetes, viruses and archaea are attracted by chemical compounds (sugars, proteins, fatty acids, organics acids, vitamins, and other cellular components) released in the vicinity of the plant roots [16, 52, 53]. These rhizodeposits are used as carbon sources by microorganisms and represent an essential source of carbon allocated to the roots and available to plants through photosynthesis [54].

Rhizodeposits also contain secondary metabolites (flavonoids, antimicrobials and others) involved in establishing symbiosis or repelling plant pathogens and pests [55, 56].

The establishment of the symbiotic plant-PGPR interaction in the rhizosphere can favor the plant growth through direct and indirect mechanisms. The first one includes the fixation of atmospheric nitrogen [57], phosphate solubilization [58] or any other process capable of supplying the plant with some of its previously unavailable nutrients. Many PGPRs also produce phytohormones, such as auxins (Indole-3-acetic acid) and cytokinin, which exert strong effects on root and shoot growth, respectively [59–61]. The indirect mechanisms of plant growth prevent the deleterious effects of pathogens and include competition for nutrients and niches, induction of systemic resistance (Jasmonic acid (JA), and ethylene), and lytic

enzymes (chitinase, pectinase, cellulase, glucanase, protease, xylanase), siderophore, bacteriocins and antibiotics production [62] (**Figure 2**).

The phyla of PGPR commonly found in the rhizosphere are Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes; among the main genera, *Burkholderia*, *Azotobacter, Pseudomonas*, *Bacillus, Methylobacterium*, *Serratia*, *Streptomyces*, *Azospirillum*, *Herbaspirillum* and *Rhizobium* can be mentioned [63, 64]. The latter can establish an effective symbiotic relationship with plant species of the Leguminosae

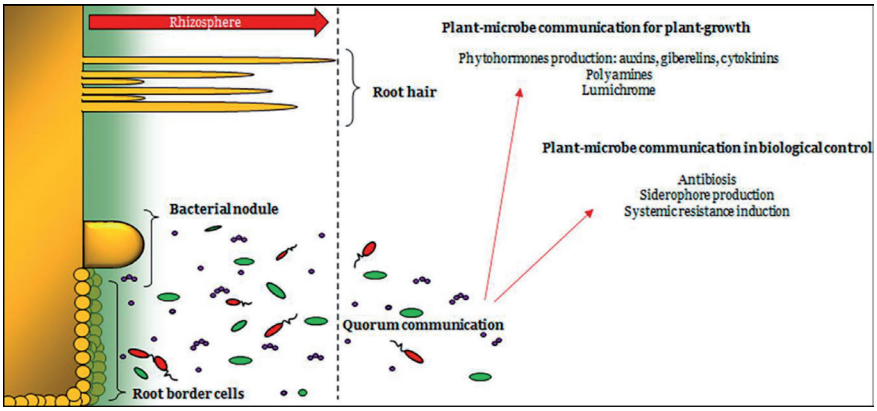


Figure 2.
Basic scheme of the rhizospheric space showing saprophytic and symbiotic bacteria and fungi, including arbuscular mycorrhizal fungi. Adapted from [16].

Rhizospheric microorganism	Compound/extracts	Target strains	Reference
Fungi			
Aspergillus awamori F12	Emodin	*S. aureus*	[75]
		B. subtilis	
Penicillium simplicissimum MA-332	Penicisimpins A–C	*E. coli*	[76]
		Micrococcus luteus	
		P. aeruginosa	
Aspergillus niger MTCC 12676	Ethanol and ethyl acetate extracts	*Streptococcus mutans* (MTCC497)	[77]
		S. aureus (MTCC7443)	
		E. coli (MTCC40)	
		C. albicans (MTCC227)	
		Candida glabrata (MTCC3814)	
Bacteria			
Bacillus pumilus	Bacteriocin-like inhibitory substance (BLIS)	*Listeria monocytogenes* (PTCC 1163)	[78]
		B. cereus (PTCC 1015)	
		S. aureus MRSA (ATCC 1912)	
		Enterococcus VRE	

Rhizospheric microorganism	Compound/extracts	Target strains	Reference
Streptomyces sp. SRDP-H03	Ethyl acetate extract	*S. aureus* (NCIM-2079)	[79]
		B. cereus (NCIM-2016)	
		B. subtilis (NCIM-2699)	
		E. coli (NCIM-2685)	
		K. pneumoniae (NCIM-2957)	
		Vibrio cholerae (MTCC-3905)	
Exiguobacterium mexicanum MSSRFS9	3,6,18-trione, 9,10-dihydro-12 -hydroxyl-2methyl-5-(phenyl methyl)(5-alpha, 10- alpha)-dihydroergotamine (C3) and dipropyl—S-propyl ester (C4)	*E. coli* (ATCC 25922)	[80]
		Shigella flexneri (ATCC 12022)	
		K. pneumonia (ATCC 700603)	
		Salmonella enterica (ATCC 14028)	
Streptomyces sp.	Crude extract	*B. subtilis* (UFPEDA-86)	[81]
	Ethanolic fraction	*S. aureus* (UFPEDA-02)	
	Ethyl acetate fraction	*S. aureus* (MRSA) (UFPEDA-700)	
		C. albicans (UFPEDA-1007)	
Micromonospora sp. A2	- Ethyl acetate extract; – FT-IR included aldehydes, alkynes, 2 aromatic rings, alkanes and alkynes	*S. aureus* MRSA	[82]
Pantoea agglomerans	1-Octadecane and 1-nonadecanol	*Klebsiella* sp. *S. aureus* *S. pneumonia*	[83]
Streptomyces strain M7	Actinomycins	*S. aureus* MRSA (MTCC 96)	[84]
		Enterococcus VRE	
Streptomyces sp. VITBKA3	Ethyl acetate extract	*S. aureus* MRSA (ATCC 43300)	[85]
	(1,1-Dichloropentane (DCP) (76%) - major compound in partial purification)	*S. aureus* MRSA (ATCC700699)	

Table 2.
Secondary metabolites produced by rhizosphere-derived microorganisms and antimicrobial activity against pathogenic microbes.

family and colonize the host plant's root system and form nodules, increasing biological nitrogen fixation, growth and yield of crops [65, 66]. AMF also plays a crucial role in plant health, increasing the efficiency of mineral uptake to promote growth and suppress pathogens [67, 68]. *Aspergillus*, *Fusarium*, *Penicillium*, *Verticillium*, and *Trichoderma* are among the most common fungi genera in the soil [69, 70].

Due to its fundamental function in suppressing pathogens, as well as endophytes, rhizospheric fungi and bacteria, these microorganisms have attracted the attention of researchers as a new source of valuable bioactive metabolites with antimicrobial activity [71–73]. Since antibiotic resistance is a serious global health concern [74], exploring the potential of these microorganisms to discover novel medicine is also of great urgency. In this way, in recent years, secondary metabolites partially or totally identified from microorganisms that inhabit the rhizosphere have been shown to possess antimicrobial activities against important pathogen agents. **Table 2** provides an overview of selected studies that represent significant advances in the search for secondary metabolites produced from rhizospheric fungi and bacteria tested against resistant and multidrug-resistant microorganisms.

Therefore, these and other studies emphasize the vital importance of continuing scientific research to find new antimicrobials and other compounds produced from rhizosphere microorganisms for other biotechnological purposes.

4. Actinobacteria and natural antimicrobial products

Actinobacteria phyla have a high G + C DNA content and share both the characteristics of bacteria and fungi. These Gram-positive filamentous bacteria belong to one of the largest taxonomic groups recognized in the Bacteria domain, widely distributed across ecosystems [86–88].

In terms of metabolite production, the *Streptomyces* genus (**Figure 3**) stands out from other microorganisms due to its variety of bioactive substances and secondary metabolites of economic interest, since more than 80% of the industrially produced antibiotics are processed by this group of microorganisms [89–91].

Streptomyces tubercidicus is known to produce tubercidin, a potent substance that can inhibit several metabolic processes, including pathogens, such as *Trypanosoma cruzi*, viruses, fungi, and present a cytotoxic activity. However, few studies have been done on the isolation of *S. tubercidicus* and only four have been published in the production of bioactive substances [92, 93]. Ratti [94] endophytically isolated the strain of *Streptomyces tubercidicus* (RND-C) from *Solanum lycocarpum* Saint Hill, a medicinal plant typically found in the Brazilian tropical savannah, known for its anti-inflammatory properties. The fractions of the Natural product extract showed high antibiotic activity against *E. coli* and *S. aureus*.

The development of biofilm inhibitors has become a priority in recent years. Bacterial biofilms can tolerate antibiotics and host defense systems, leading to the emergence of drug-resistant and totally drug-resistant infections. As previously mentioned, *Acinetobacter baumannii* leads the list of priority pathogens resistant to antibiotics; therefore, biofilm inhibitors can be applied to decrease antibiotic tolerance by bacteria [95–97]. In this context, [96] conducted a study involving a mutasynthetic approach. Wild-type of *Streptomyces gandocaensis*, isolated from the marine sediment of the island of Punta Mona, in Costa Rica, was ribosome-engineered based on a streptomycin-resistant phenotypes of *S. gandocaensis*, resulting in the activation and improvement of the production of active metabolites. The results showed a production of new substances called cahuitamycins, a peptidic metabolite that showed a potent inhibition in the formation of the biofilm produced by *Acinetobacter baumannii*.

Other studies report different strategies to successfully induce secondary metabolism and, subsequently, produce compounds that are not produced under usual growing conditions. Cryptic genes consist of silent sequences of DNA that are not expressed during the life cycle of a microorganism and can occur through mutations and recombination processes in a few members of a population [98–100].

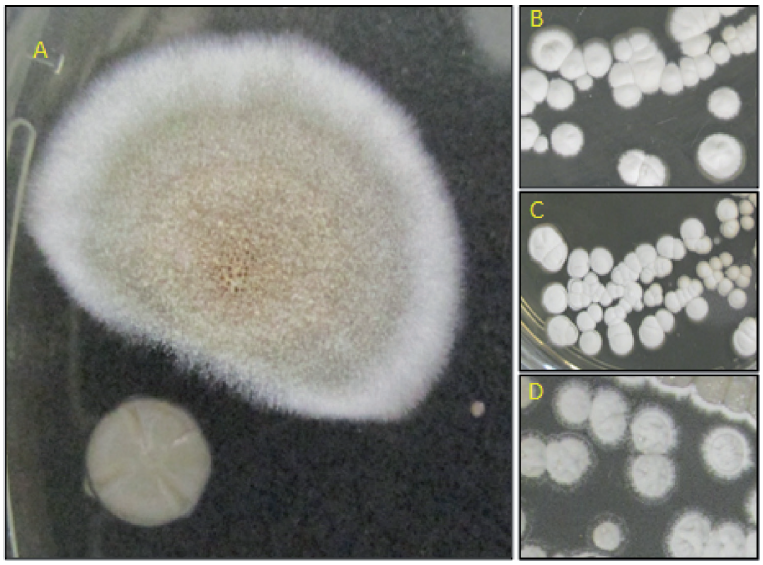


Figure 3.
(A) *Antifungal activity produced by the endophytic Streptomyces sp. during the isolation.* (B–D) *Diversity of rhizospheric streptomycete colonies.*

In this context, cultured actinobacteria combined with mycolic acid-containing bacteria (*Rhodococcus erythropolis*, *Dietzia* spp., *Nocardia* spp., *Williamsia* spp., *Gordonia* spp., *Mycobacterium* spp., and *Corynebacterium* spp.) has been a useful approach for the discovery of antimicrobial natural products [99, 101–103]. However, [102] suggests that mycolic acid is insufficient to activate these cryptic genes in *Streptomyces lividans* under monoculture conditions. According to the report, the direct attachment of *S. lividans* cells on the mycolic acid-containing bacteria is crucial for the successful activation of secondary metabolism.

Caraballo-Rodríguez [3] tested the endophytic actinobacteria *Streptomyces cattleya* RLe1, *S. mobaraensis* RLe3, *S. albospinus* RLe7, *Streptomyces* sp. RLe9 and *Kytasatospora cystarginea* RLe10 co-cultured with endophytic fungi *Coniochaeta* sp. FLe4 and *Colletotrichum boninense* isolated from the Brazilian medicinal plant *Lychnophora ericoides*. The authors identified the broad-spectrum angucycline derived from *S. mobaraensis* and two molecules produced by endophytic fungi.

As already mentioned, the process of antibiotic resistance is spreading rapidly in relation to the discovery of new compounds and their introduction into clinical practice. The CDC classifies pathogens such as *B. anthracis* as biohazard category A, whose infection is fatal, and the symptoms may be similar to a common cold [104]. The preliminary study by [105] involved the isolation of the endophytic and rhizospheric microbiome associated with the medicinal plant *Polygala* sp. Natural products extracts produced by rhizoplane-derived actinomycetes showed potent inhibition against *A. baumannii*, *B. anthracis*, *E. coli* CFT073, *L. monocytogenes*, MR *S. aureus*, *S. enterica*, and *S. flexneri*.

Caryocar brasiliense, known as Pequi, is a tree native to the Brazilian savannah and commonly used in folk medicine. Bioactive substances such as gallic acid, quinic acid, ellagic acid, glucogalin, and corilagin were found in its extracts. In addition, they show a growth inhibition rate of the phytopathogenic *Alternaria solani* [106]. A rhizospheric strain of *Streptomyces* sp. was isolated from *C. brasiliense*, whose crude extract obtained from the axenic cultivation was able to inhibit *C. albicans*; in contrast, the co-cultured *Streptomyces* sp. extract increased the growth of *C. albicans* in 50% and promoted the inhibition of *S. aureus* [107].

Biotechnologically, the *Streptomyces* genus is known to be a skilled producer of a wide range of bioactive substances and represents an unexplored reservoir of unique chemical structures.

5. Natural products and endophytic fungi

The scientific interest in fungal natural products gained notoriety after the paclitaxel discovery [108]. Endophytic fungi exhibit the ability to synthesize plant-derived compounds by mimicking the metabolic pathways of the host plant, which confers multifaceted applications in the fields of agriculture, medicine, and pharmaceuticals [109].

The medicinal plant barbatimão (*Stryphnodendron adstringens*) has healing properties, antimicrobial, antioxidant, and anti-inflammatory activities, and its bark has a rich tannin-content [107, 110]. The study by [111] investigated the antimicrobial and anticancer activities of several fungi isolated from *S. adstringens*. The extract of *Nigrospora oryzae* promoted antifungal activity and inhibited the growth of *C. albicans* and *C. sphaerospermum*, while the extracts of *Diaporthe phaseolorum* and *Xylaria* spp. presented anticancer activities.

Although toxic to humans and animals, mycotoxins are secondary metabolites known for their cytotoxic effect against malignant cells [112]. Several species of *Fusarium* and *Beauveria bassiana* are skilled producers of mycotoxins, such as Beauvericin, which promote apoptosis in mammalian cells and exhibit insecticidal properties [113, 114], while Ochratoxin A is produced by some species of fungi, such as *Aspergillus* spp. and *Penicillium* spp. [115, 116].

The superbug methicillin-resistant *Staphylococcus aureus* is responsible for higher mortality rates in the community and hospital-acquired infections [117] due to its ability to resist multiple classes of antibiotics [118, 119]. In this context, fungal alkaloids are known for their potent antibacterial, anticancer, antiparasitic, and insecticidal activities [120]. In [121], a novel alkaloid compound, GKK1032C, is reported, which is produced by *Penicillium* sp. endophytically associated with the mangrove plant, exhibiting potent activity against methicillin-resistant *S. aureus*.

Saponins exhibit a wide range of biological activities, such as antifungal, hemolytic, antiviral, and immunomodulatory. These compounds represent an alternative to overcome multidrug-resistant microorganisms since they can act synergistically with antibiotics. Moreover, medicines that were once considered ineffective due to resistance problems might be effective for resistant microbes [122, 123]. Nevertheless, as reported by [124], saponin from *Quillaja saponaria* bark did not present synergistic activity in combination with ampicillin, streptomycin, and ciprofloxacin against a clinical strain of *E. coli*. In a short communication from [125], the isolation of triterpenoid saponins produced by the endophytic fungi *Fusarium oxysporum* and *Aspergillus niger* isolated from *Panax notoginseng* was reported. According to the authors, saponin extracts exhibited moderate to high antimicrobial activity against the pathogens tested.

6. Concluding remarks

Antibiotic-resistant microbes represent a severe threat to the public health system worldwide. Furthermore, multidrug-resistant 'ESKAPE' organisms (*Enterococcus* spp., *Staphylococcus aureus*, *Klebsiella* spp., *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp) are strictly associated with high rates of morbidity and mortality, as well as an economic impact.

In this chapter, we highlighted the strategies of antimicrobial drug discovery produced by endophytes and rhizospheric microorganisms, since enormous untapped resources remain. The use of such microbes in biotechnological processes has increased in recent years, as they are skilled producers of natural bioactive products that can be used as pharmaceuticals to face this ever-increasing threat.

Conflict of interest

The authors declare no conflict of interest.

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