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].

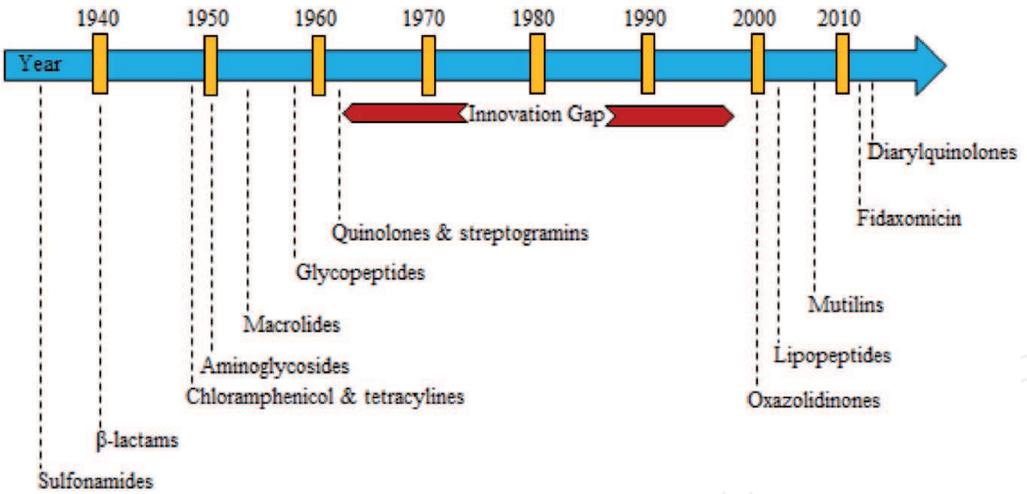

Figure 1.
Timeline of antibiotic discovery that shows no new classes of antibiotics between the years 1962 and 2000 adapted from: [6, 7].

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

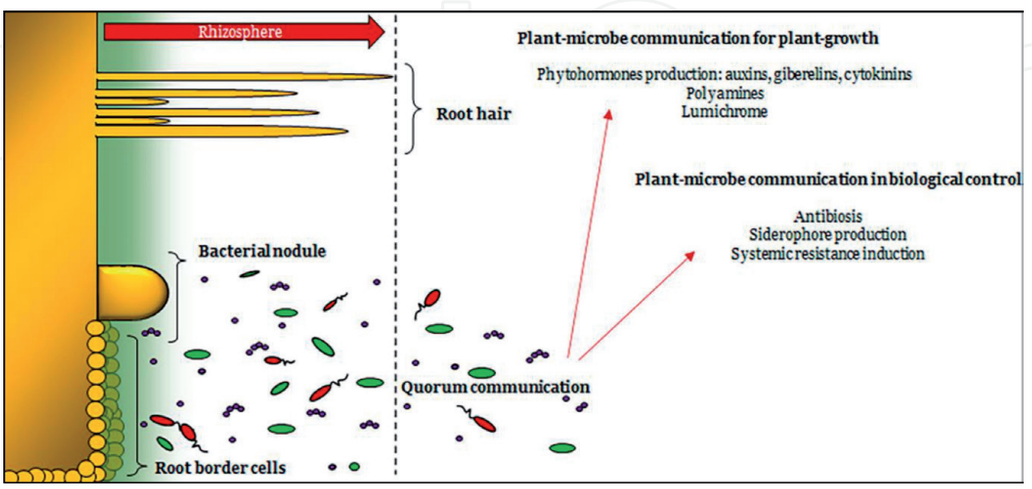

Figure 2.
Basic scheme of the rhizospheric space showing saprophytic and symbiotic bacteria and fungi, including arbuscular mycorrhizal fungi. Adapted from [16].

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].

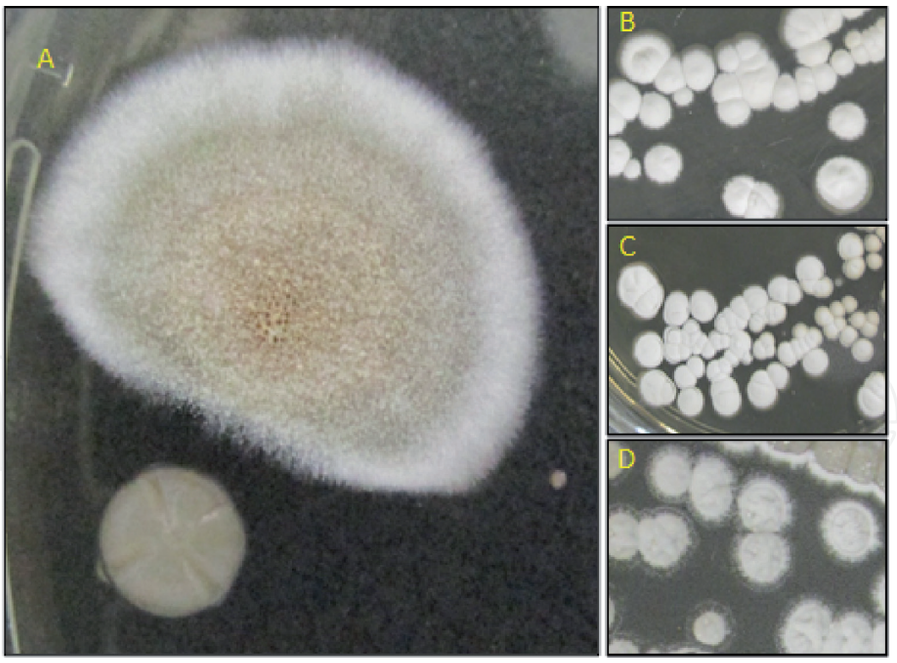

Figure 3.
(A) *Antifungal activity produced by the endophytic Streptomyces sp. during the isolation.* (B–D) *Diversity of rhizospheric streptomycete colonies.*

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.

Funding

This manuscript was financially supported by Sao Paulo State Research Support Foundation (FAPESP) through project number 2016/13423-5.

Author details

Felipe de Paula Nogueira Cruz[1,2], Andréa Cristina Bogas[1,2] and Cristina Paiva de Sousa[1,2]*

1 Laboratory of Microbiology and Biomolecules—LaMiB, Department of Morphology and Pathology, Federal University of São Carlos, Brazil

2 Biotechnology Graduate Program, Federal University of Sao Carlos, Brazil

*Address all correspondence to: prokarya@ufscar.br

References

[1] Lewis K, Epstein S, D'Onofrio A, Ling LL. Uncultured microorganisms as a source of secondary metabolites. Journal of Antibiotics (Tokyo). 2010;**63**(8):468-476. DOI: 10.1038/ja.2010.87

[2] Piza ACMT, Hokka C, Sousa C. Endophytic actinomycetes from *Miconia albicans* (Sw.) Triana (Melastomataceae) and evaluation of its antimicrobial activity. Journal of Science Research and Reports. 2015;**4**(4):281-291. DOI: 10.9734/JSRR/2015/13237

[3] Caraballo-Rodríguez AM, Dorrestein PC, Pupo MT. Molecular inter-kingdom interactions of endophytes isolated from *Lychnophora ericoides*. Scientific Reports. 2017;**7**(1):5373. Published: July 14, 2017. DOI: 10.1038/s41598-017-05532-5

[4] Nicolaou KC, Rigol S. A brief history of antibiotics and select advances in their synthesis. Journal of Antibiotics (Tokyo). 2018;**71**(2):153-184. DOI: 10.1038/ja.2017.62

[5] Chen CH, Kuo HY, Hsu PJ, et al. Clonal spread of carbapenem-resistant *Acinetobacter baumannii* across a community hospital and its affiliated long-term care facilities: A cross sectional study. Journal of Microbiology, Immunology, and Infection. 2018;**51**(3):377-384. DOI: 10.1016/j.jmii.2017.08.001

[6] Fischbach MA, Walsh CT. Antibiotics for emerging pathogens. Science. 2009;**325**(5944):1089-1093. DOI: 10.1126/science.1176667

[7] Walsh CT, Wencewicz TA. Prospects for new antibiotics: A molecule-centered perspective. Journal of Antibiotics (Tokyo). 2014;**67**(1):7-22. DOI: 10.1038/ja.2013.49

[8] Nair DR, Chen J, Monteiro JM, et al. A quinolinol-based small molecule with anti-MRSA activity that targets bacterial membrane and promotes fermentative metabolism. Journal of Antibiotics (Tokyo). 2017;**70**(10):1009-1019. DOI: 10.1038/ja.2017.79

[9] Huggins WM, Minrovic BM, Corey BW, et al. 1,2,4-Triazolidine-3-thiones as narrow spectrum antibiotics against multidrug-resistant *Acinetobacter baumannii*. ACS Medicinal Chemistry Letters. 2016;**8**(1):27-31. Published: November 12, 2016. DOI: 10.1021/acsmedchemlett.6b00296

[10] Sommer MOA, Munck C, Toft-Kehler RV, Andersson DI. Prediction of antibiotic resistance: Time for a new preclinical paradigm? Nature Reviews. Microbiology. 2017;**15**(11):689-696. DOI: 10.1038/nrmicro.2017.75

[11] Joseph B, Pryia MR. Bioactive compounds from endophytes and their potential in pharmaceutical effect: A review. American Journal of Biochemistry and Molecular Biology. 2011;**1**(3):291-309. DOI: 10.3923/ajbmb.2011.291.309

[12] Matsumoto A, Takahashi Y. Endophytic actinomycetes: Promising source of novel bioactive compounds. Journal of Antibiotics (Tokyo). 2017;**70**(5):514-519. DOI: 10.1038/ja.2017.20

[13] Vigliotta G, Giordano D, Verdino A, et al. New compounds for a good old class: Synthesis of two B-lactam bearing cephalosporins and their evaluation with a multidisciplinary approach. Bioorganic & Medicinal Chemistry. 2020;**28**(4):115302. DOI: 10.1016/j.bmc.2019.115302

[14] Azevedo JL, Maccheroni W Jr, Pereira JO, De Araújo WL. Endophytic microorganisms: A review on insect control and recent advances on tropical plants. Electronic Journal of

Biotechnology. 2000;**3**:15-16. DOI: 10.2225/vol3-issue1fulltext-4

[15] Pacifico D, Squartini A, Crucitti D, et al. The role of the Endophytic microbiome in the grapevine response to environmental triggers. Frontiers in Plant Science. 2019;**10**:1256. Published: October 9, 2019. DOI: 10.3389/fpls.2019.01256

[16] Philippot L, Raaijmakers JM, Lemanceau P, van der Putten WH. Going back to the roots: The microbial ecology of the rhizosphere. Nature Reviews. Microbiology. 2013;**11**(11):789-799. DOI: 10.1038/nrmicro3109

[17] Ling LL, Schneider T, Peoples AJ, et al. A new antibiotic kills pathogens without detectable resistance [published correction appears in Nature. 2015 Apr 16;520(7547):388]. Nature. 2015;**517**(7535):455-459. DOI: 10.1038/nature14098

[18] Tong WY, Darah I, Latiffah Z. Antimicrobial activities of endophytic fungal isolates from medicinal herb *Orthosiphon stamineus* Benth. Journal of Medicinal Plant Research: Planta Medica. 2011;**5**:831-836

[19] Serrano NFG. Purificação e caracterização bioquímica de substâncias bioativas produzidas por endofítico isolado de *Prunus* spp. Dissertation. Sao Carlos, Sao Paulo, Brazil: Federal University of São Carlos. 2009

[20] Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. Frontiers in Microbiology. 2016;**7**:1538. Published: September 2016, 29. DOI: 10.3389/fmicb.2016.01538

[21] Kandel SL, Joubert PM, Doty SL. Bacterial endophyte colonization and distribution within plants. Microorganisms. 2017;**5**(4):77. Published: November 25, 2017. DOI: 10.3390/microorganisms5040077

[22] White JF, Kingsley KL, Zhang Q, et al. Review: Endophytic microbes and their potential applications in crop management. Pest Management Science. 2019;**75**(10):2558-2565. DOI: 10.1002/ps.5527

[23] Alvin A, Miller KI, Neilan BA. Exploring the potential of endophytes from medicinal plants as sources of antimycobacterial compounds. Microbiological Research. 2014;**169**(7-8):483-495. DOI: 10.1016/j.micres.2013.12.009

[24] Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science. 1993;**260**(5105):214-216. DOI: 10.1126/science.8097061

[25] Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. Journal of Natural Products. 2004;**67**(2):257-268. DOI: 10.1021/np030397v

[26] Pan F, Su TJ, Cai SM, Wu W. Fungal endophyte-derived *Fritillaria unibracteata* var. *wabuensis*: diversity, antioxidant capacities in vitro and relations to phenolic, flavonoid or saponin compounds. Scientific Reports. 2017;**7**:42008. Published: February 6, 2017. DOI: 10.1038/srep42008

[27] Vaz ABM, Brandão LR, Vieira MLA, Pimenta RS, Morais PB, Sobral MEG, et al. Diversity and antimicrobial activity of fungal endophyte communities associated with plants of Brazilian savanna ecosystems. African Journal of Microbiology Research. 2012;**6**(13):3173-3185. DOI: 10.5897/AJMR11.1359

[28] Marcellano JP, Collanto AS, Fuentes RG. Antibacterial activity of endophytic fungi isolated from the bark of *Cinnamomum mercadoi*. The Pharmacogenomics Journal.

2017;**9**(3):405-409. DOI: 10.5530/pj.2017.3.69

[29] Dang L, Li G, Yang Z, et al. Chemical constituents from the endophytic fungus Trichoderma ovalisporum isolated from *Panax notoginseng*. Annales de Microbiologie. 2010;**60**:317-320 https://doi.org/10.1007/s13213-010-0043-2

[30] Wang QX, Li SF, Zhao F, et al. Chemical constituents from endophytic fungus *Fusarium oxysporum*. Fitoterapia. 2011;**82**(5):777-781. DOI: 10.1016/j.fitote.2011.04.002

[31] Sebastianes FL, Cabedo N, El Aouad N, et al. 3-hydroxypropionic acid as an antibacterial agent from endophytic fungi *Diaporthe phaseolorum*. Current Microbiology. 2012;**65**(5):622-632. DOI: 10.1007/s00284-012-0206-4

[32] Subban K, Subramani R, Johnpaul M. A novel antibacterial and antifungal phenolic compound from the endophytic fungus *Pestalotiopsis mangiferae*. Natural Product Research. 2013;**27**(16):1445-1449. DOI: 10.1080/14786419.2012.722091

[33] Ratnaweera PB, Williams DE, de Silva ED, Wijesundera RL, Dalisay DS, Andersen RJ. Helvolic acid, an antibacterial nortriterpenoid from a fungal endophyte, *Xylaria* sp. of orchid *Anoectochilus setaceus* endemic to Sri Lanka. Mycology. 2014;**5**(1):23-28. DOI: 10.1080/21501203.2014.892905

[34] Ibrahim SRM, Elkhayat ES, Mohamed GA, Khedr AIM, Fouad MA, Kotb MHR, et al. Aspernolides F and G, new butyrolactones from the endophytic fungus *Aspergillus terreus*. Phytochemistry Letters. 2015;**14**:84-90 http://doi.org/10.1016/j.phytol.2015.09.006

[35] Ratnaweera PB, de Silva ED, Wijesundera RLC, Andersen RJ. Antimicrobial constituents of *Hypocrea virens*, an endophyte of the mangrove-associate plant *Premna serratifolia* L. Journal of the National Science Foundation of Sri Lanka. 2016;**44**:43-51. DOI: 10.4038/jnsfsr.v44i1.7980

[36] He Y, Hu Z, Sun W, et al. Spiroaspertrione a, a bridged spirocyclic meroterpenoid, as a potent potentiator of oxacillin against methicillin-resistant *Staphylococcus aureus* from *Aspergillus* sp. TJ23. The Journal of Organic Chemistry. 2017;**82**(6):3125-3131. DOI: 10.1021/acs.joc.7b00056

[37] Qiao Y, Zhang X, He Y, et al. Aspermerodione, a novel fungal metabolite with an unusual 2,6-dioxabicyclo[2.2.1]heptane skeleton, as an inhibitor of penicillin-binding protein 2a. Scientific Reports. 2018;**8**(1):5454. Published: April 3, 2018. DOI: 10.1038/s41598-018-23817-1

[38] Hu S, Liang M, Mi Q, et al. Two new diphenyl ether derivatives from the fermentation products of the endophytic fungus *Phomopsis asparagi*. Chemistry of Natural Compounds. 2019;**55**:843-846. DOI: 10.1007/s10600-019-02828-y

[39] Astuti P, Rollando R, Wahyuono S, Nurrochmad A. Antimicrobial activities of isoprene compounds produced by an endophytic fungus isolated from the leaves of *Coleus amboinicus* Lour. Journal of Pharmacy and Pharmacognosy Research. 2020;**8**(4):280-289

[40] Ding L, Maier A, Fiebig HH, Lin WH, Hertweck C. A family of multicyclic indolosesquiterpenes from a bacterial endophyte. Organic & Biomolecular Chemistry. 2011;**9**(11):4029-4031. DOI: 10.1039/c1ob05283g

[41] Ding L, Maier A, Fiebig HH, Lin WH, Peschel G, Hertweck C, et al. Eudesmenes from an endophytic Streptomyces sp. of the mangrove tree

Kandelia candel. Journal of Natural Products. 2012;**75**(12):2223-2227. DOI: 10.1021/np300387n

[42] Djinni I, Defant A, Kecha M, Mancini I. Antibacterial polyketides from the marine alga-derived endophitic *Streptomyces sundarbansensis*: A study on hydroxypyrone tautomerism. Marine Drugs. 2013;**11**(1):124-135. Published: January 10, 2013. DOI: 10.3390/md11010124

[43] Yang X, Peng T, Yang Y, et al. Antimicrobial and antioxidant activities of a new benzamide from endophytic *Streptomyces* sp. YIM 67086. Natural Product Research. 2015;**29**(4):331-335. DOI: 10.1080/14786419.2014.945174

[44] Khieu TN, Liu MJ, Nimaichand S, et al. Characterization and evaluation of antimicrobial and cytotoxic effects of *Streptomyces* sp. HUST012 isolated from medicinal plant *Dracaena cochinchinensis* Lour. Frontiers in Microbiology. 2015;**6**:574. Published 2015 Jun 8. DOI: 10.3389/fmicb.2015.00574

[45] Alshaibani MM, Jalil J, Sidik NM, Edrada-Ebel R, Zin NM. Isolation and characterization of cyclo-(tryptophanyl-prolyl) and chloramphenicol from *Streptomyces* sp. SUK 25 with antimethicillin-resistant *Staphylococcus aureus* activity. Drug Design, Development and Therapy. 2016;**10**:1817-1827. Published: May 31, 2016. DOI: 10.2147/DDDT.S101212

[46] Gos FMWR, Savi DC, Shaaban KA, et al. Antibacterial activity of endophytic actinomycetes isolated from the medicinal plant *Vochysia divergens* (Pantanal, Brazil). Frontiers in Microbiology. 2017;**8**:1642. Published: September 6, 2017. DOI: 10.3389/fmicb.2017.01642

[47] Vu HT, Nguyen DT, Nguyen HQ, et al. Antimicrobial and cytotoxic properties of bioactive metabolites produced by *Streptomyces cavourensis* YBQ59 isolated from *Cinnamomum cassia* Prels in Yen Bai Province of Vietnam. Current Microbiology. 2018;**75**(10):1247-1255. DOI: 10.1007/s00284-018-1517-x

[48] Bunbamrung N, Intaraudom C, Dramae A, et al. Antibacterial, antitubercular, antimalarial and cytotoxic substances from the endophytic *Streptomyces* sp. TBRC7642. Phytochemistry. 2020;**172**:112275. DOI: 10.1016/j.phytochem.2020.112275

[49] Hartmann A, Rothballer M, Schmid M. Lorenz Hiltner, a pioneer in rhizosphere microbial ecology and soil bacteriology research. Plant and Soil. 2008;**312**:7-14. DOI: 10.1007/s11104-007-9514-z

[50] Parray JA, Mir MY, Shameen N. Rhizosphere engineering and agricultural productivity. In: Sustainable Agriculture: Biotechniques in Plant Biology. 2019. DOI: 10.1007/978-981-13-8840-8

[51] Sabale SN, Suryawanshi PP, Krishnaraj PU. Soil Metagenomics: Concepts and Applications, Metagenomics. In: Hozzein WN, editor. Basics, Methods and Applications. IntechOpen; 2019. DOI: 10.5772/intechopen.88958

[52] Brahmaprakash GP, Sahu PK, Lavanya G, Nair SS, Gangaraddi VK, Gupta A. Microbial Functions of the Rhizosphere. In: Singh D, Singh H, Prabha R, editors. Plant-Microbe Interactions in Agro-Ecological Perspectives; Singapore: Springer; 2019. DOI: 10.1007/978-981-10-5813-4_10

[53] Dini-Andreote F, Gumiere T, Durrer A. Exploring interactions of plant microbiomes. Science in Agriculture. 2014;**71**:528-539. DOI: 10.1590/0103-9016-2014-0195

[54] Jones D, Nguyen C, Finlay DR. Carbon flow in the rhizosphere: Carbon trading at the soil–root interface. Plant and Soil. 2009;**321**:5-33. DOI: 10.1007/s11104-009-9925-0

[55] Hassan MK, McInroy JA, Kloepper JW. The interactions of rhizodeposits with plant growth-promoting rhizobacteria in the rhizosphere: A review. Agriculture. 2019;**9**(7):142. DOI: 10.3390/agriculture9070142

[56] Venturi V, Keel C. Signaling in the rhizosphere. Trends in Plant Science. 2016;**21**(3):187-198. DOI: 10.1016/j.tplants.2016.01.005

[57] Kuan KB, Othman R, Abdul Rahim K, Shamsuddin ZH. Plant growth-promoting rhizobacteria inoculation to enhance vegetative growth, nitrogen fixation and nitrogen remobilisation of maize under greenhouse conditions. PLoS One. 2016;**11**(3):e0152478. DOI: 10.1371/journal.pone.0152478

[58] Mehta P, Walia A, Kulshrestha S, Chauhan A, Shirkot CK. Efficiency of plant growth-promoting P-solubilizing *Bacillus circulans* CB7 for enhancement of tomato growth under net house conditions. Journal of Basic Microbiology. 2015;**55**(1):33-44. DOI: 10.1002/jobm.201300562

[59] Gupta G, Parihar SS, Ahirwar NK, Snehi SK, Singh V. Plant growth promoting rhizobacteria (PGPR): Current and future prospects for development of sustainable agriculture. Journal of Microbial and Biochemical Technology. 2015;**7**:096-102. DOI: 10.4172/1948-5948.1000188

[60] Patel T, Saraf M. Biosynthesis of phytohormones from novel rhizobacterial isolates and their in vitro plant growth-promoting efficacy. Journal of Plant Interactions. 2017;**12**:480-487. DOI: 10.1080/17429145.2017.1392625

[61] Berendsen RL, Pieterse CM, Bakker PA. The rhizosphere microbiome and plant health. Trends in Plant Science. 2012;**17**(8):478-486. DOI: 10.1016/j.tplants.2012.04.001

[62] Yadav S, Singh K, Chandra R. Plant Growth–Promoting Rhizobacteria (PGPR) and Bioremediation of Industrial Waste. In: Chandra R, Sobti RC, editor. Microbes for Sustainable Development and Bioremediation. Boca Raton: CRC Press; 2019. DOI: 10.1201/9780429275876

[63] Kour D, Rana KL, Yadav N, Yadav AN, Kumar A, Meena VS, et al. Rhizosphere microbiomes: Biodiversity, mechanisms of plant growth promotion, and biotechnological applications for sustainable agriculture. In: Kumar A, Meena V, editors. Plant Growth Promoting Rhizobacteria for Agricultural Sustainability. Singapura: Springer; 2019. DOI: 10.1007/978-981-13-7553-8_2

[64] Shastri B, Kumar R. Microbial secondary metabolites and plant microbe communications in the rhizosphere. In: Singh, J.S. New and Future Developments in Microbial Biotechnology and Bioengineering. Microbes in Soil, Crop and Environmental Sustainability. B.V: Elsevier; 2019. pp. 93-111. DOI: 10.1016/B978-0-12-818258-1.00006-6

[65] Alam F, Bhuiyan MA, Alam SS, Waghmode TR, Kim PJ, Lee YB. Effect of rhizobium sp. BARIRGm901 inoculation on nodulation, nitrogen fixation and yield of soybean (*Glycine max*) genotypes in gray terrace soil. Bioscience, Biotechnology, and Biochemistry. 2015;**79**(10):1660-1668. DOI: 10.1080/09168451.2015.1044931

[66] Getahun A, Muleta D, Assefa F, Kiros S. Field application of Rhizobial inoculants in enhancing faba bean production in acidic soils: An innovative strategy to improve crop productivity. In: Akhtar M, editor. Salt Stress, Microbes, and Plant Interactions: Causes and Solution. Singapore: Springer; 2019. DOI: 10.1007/978-981-13-8801-9

[67] Amballa H, Bhumi NR. Significance of arbuscular mycorrhizal fungi and

rhizosphere microflora in plant growth and nutrition. In: Choudhary et al., editors. Plant-Microbe Interaction: An Approach to Sustainable Agriculture. Singapura: Springer; 2016. pp. 417-452. DOI: 10.1007/978-981-10-2854-0

[68] Singh I, Giri B. Arbuscular mycorrhiza mediated control of plant pathogens. In: Varma A, Prasad R, Tuteja N, editors. Mycorrhiza—Nutrient Uptake, Biocontrol, Ecorestoration. Cham: Springer; 2017. DOI: 10.1007/978-3-319-68867-1

[69] Brahmaprakash GP, Sahu PK, Nair GLSS, Gangaraddi VK, Gupta A. Microbial functions of the rhizosphere. In: Singh DP, Singh HB, Prabha R, editors. Plant-Microbe Interactions in Agro-Ecological Perspectives. Springer; 2017. DOI: 10.1007/978-981-10-5813-4

[70] Pattnaik SS, Busi S. Rhizosphere fungi: Diversity and potential biotechnological applications. In: Yadav A, Misha S, Singh S, Gupta A, editors. Recent Advancement in White Biotechnology Through Fungi. Fungal Biology. Cham: Springer; 2019. DOI: 10.1007/978-3-030-10480-1

[71] Iniyan AM, Kannan RR, Vincent SGP. Characterization of culturable actinomycetes associated with halophytic rhizosphere as potential source of antibiotics. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences. 2015;**87**:233-242. DOI: 10.1007/s40011-015-0601-2

[72] Muleta A, Assefa F. Isolation and screening of antibiotic producing actinomycetes from rhizosphere and agricultural soils. African Journal of Biotechnology. 2018;**17**:700-714. DOI: 10.5897/AJB2017.16080

[73] Zhang TY, Wu YY, Zhang MY, Cheng J, Dube B, et al. New antimicrobial compounds produced by *Seltsamia galinsogisoli* sp. nov., isolated from *Galinsoga parvifora* as potential inhibitors of FtsZ. Scientific Reports. 2019;**9**:8319. DOI: 10.1038/s41598-019-44810-2

[74] Ahmad M, Khan AU. Global economic impact of antibiotic resistance: A review. Journal of Global Antimicrobial Resistance. 2019;**19**: 313-316. DOI: 10.1016/j.jgar.2019.05.024

[75] Chang M, Wang J, Tian F, Zhang Q, Ye B. Antibacterial activity of secondary metabolites from Aspergillus awamori F12 isolated from rhizospheric soil of Rhizophora stylosa Griff. Chinese: Wei Sheng Wu Xue Bao; Oct 2010;**50**(10):1385-1391. PMID: 21141475

[76] Xu R, Li XM, Wang BG. Penicisimpins A–C, three new dihydroisocoumarins from Penicillium simplicissimum MA-332, a marine fungus derived from the rhizosphere of the mangrove plant *Bruguiera sexangula* var. *rhynchopetala*. Phytochemistry Letters. 2016;**17**:114-118. DOI: 10.1016/j.phytol.2016.07.003

[77] Singh A, Kumar M, Salar RK. Isolation of a novel antimicrobial compounds producing fungus *Aspergillus Niger* MTCC 12676 and evaluation of its antimicrobial activity against selected pathogenic microorganisms. Journal of Pure and Applied Microbiology. 2017;**11**(3): 1457-1464. DOI: 10.22207/JPAM.11.3.29

[78] Zaghian S, Shokri D, Emtiazi G. Co-production of a UV-stable bacteriocin-like inhibitory substance (BLIS) and indole-3-acetic acid hormone (IAA) and their optimization by Taguchi design in *Bacillus pumilus*. Annales de Microbiologie. 2011;**62**:1189-1197. DOI: 10.1007/s13213-011-0359-6

[79] Rakesh KN, Junaid S, Dileep N, Kekuda PTR. Antibacterial and antioxidant activities of *Streptomyces* species SRDP-H03 isolated

from soil of Hosudi, Karnataka, India. Journal of Drug Delivery Science and Technology. 2013;(4):47-53. DOI: 10.22270/jddt.v3i4.568

[80] Shanthakumar SP, Duraisamy P, Vishwanath G, Selvanesan BC, Ramaraj V, Vasantharaj David B. Broad spectrum antimicrobial compounds from the bacterium *Exiguobacterium mexicanum* MSSRFS9. Microbiological Research. 2015;**178**:59-65. DOI: 10.1016/j.micres.2015.06.007

[81] Silva-Lacerda GR, Santana RC, Vicalvi-Costa MC, et al. Antimicrobial potential of actinobacteria isolated from the rhizosphere of the Caatinga biome plant *Caesalpinia pyramidalis* Tul. Genetics and Molecular Research. 2016;**15**(1):15017488. Published: March 4, 2016. DOI: 10.4238/gmr.15017488

[82] Abdullahi U, Obidah JS, Jada SM. Characterization of antibiotics inhibitory to methicillin resistant *Staphylococcus aureus* (MRSA) from soil actinomycetes. Asian Journal of Research in Medical and Pharmaceutical Sciences. 2018;**4**(2):1-13. DOI: 10.9734/AJRIMPS/2018/39742

[83] Nair NM, Kanthasamy R, Mahesh R, Selvam SIK, Ramalakshmi S. Production and characterization of antimicrobials from isolate *Pantoea agglomerans* of Medicago sativa plant rhizosphere soil. Journal of Applied and Natural Sciences. 2019;**11**(2):267-272. DOI: 10.31018/ jans.v11i2.203

[84] Sharma M, Manhas RK. Purification and characterization of actinomycins from Streptomyces strain M7 active against methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus*. BMC Microbiology. 2019;**19**(1):44. Published: February 19, 2019. DOI: 10.1186/s12866-019-1405-y

[85] Bhakyashree K, Kannabiran K. Actinomycetes mediated targeting of drug resistant MRSA pathogens. Journal of King Saud University—Science. 2020;**32**:260-264. DOI: 10.1016/j.jksus.2018.04.034

[86] Barka EA, Vatsa P, Sanchez L, et al. Taxonomy, physiology, and natural products of actinobacteria [published correction appears in Microbiol Mol Biol Rev. 2016 Nov 9;80(4): iii]. Microbiology and Molecular Biology Reviews. 2015;**80**(1):1-43. Published: November 25, 2015. DOI: 10.1128/MMBR.00019-15

[87] Anandan R, Dharumadurai D, Manogaran GP. An Introduction to Actinobacteria. In: Dhanasekaran D, Jiang Y, editors. Actinobacteria - Basics and Biotechnological Applications. IntechOpen; 2016. DOI: 10.5772/62329

[88] Azman AS, Mawang CI, Khairat JE, AbuBakar S. Actinobacteria-a promising natural source of anti-biofilm agents. International Microbiology. 2019;**22**(4):403-409. DOI: 10.1007/s10123-019-00066-4

[89] Bérdy J. Bioactive Microbial Metabolites [published correction appears in J Antibiot (Tokyo). 2005 Apr;58(4):C-1]. Journal of Antibiotics (Tokyo). 2005;**58**(1):1-26. DOI: 10.1038/ja.2005.1

[90] Qin S, Xing K, Jiang JH, Xu LH, Li WJ. Biodiversity, bioactive natural products and biotechnological potential of plant-associated endophytic actinobacteria. Applied Microbiology and Biotechnology. 2011;**89**(3):457-473. DOI: 10.1007/s00253-010-2923-6

[91] Genilloud O. Actinomycetes: Still a source of novel antibiotics. Natural Product Reports. 2017;**34**(10):1203-1232. DOI: 10.1039/c7np00026j

[92] Smulson ME, Suhadolnik RJ. The biosynthesis of the 7-deazaadenine ribonucleoside, tubercidin, by *Streptomyces tubercidicus*. The

Journal of Biological Chemistry. 1967;**242**(12):2872-2876

[93] Kónya A, Szabó Z, Láng I, Barta I, Salát J. Production of FK520 by *Streptomyces tubercidicus*. Microbiological Research. 2008;**163**(6):624-632. DOI: 10.1016/j.micres.2006.10.002

[94] Ratti RP, Piza ACMT, Malpass AC, Hokka CO, Dubreuil JD, Sousa CP. Growing kinetics and antimicrobial activity of Streptomyces tubercidicus crude extracts. In: Microorganisms in Industry and Environment from Scientific and Industrial Research to Consumer Products. Vol. 1. Singapore: World Scientific Publishing Company Pvt Ltd. (Org.); 2010. pp. 589-592

[95] Böttcher T, Kolodkin-Gal I, Kolter R, Losick R, Clardy J. Synthesis and activity of biomimetic biofilm disruptors. Journal of the American Chemical Society. 2013;**135**(8):2927-2930. DOI: 10.1021/ja3120955

[96] Park SR, Tripathi A, Wu J, et al. Discovery of cahuitamycins as biofilm inhibitors derived from a convergent biosynthetic pathway. Nature Communications. 2016;**7**:10710. Published: February 16, 2016. DOI: 10.1038/ncomms10710

[97] Sharma D, Misba L, Khan AU. Antibiotics versus biofilm: An emerging battleground in microbial communities. Antimicrobial Resistance and Infection Control. 2019;**8**:76. Published: May 16, 2019. DOI: 10.1186/s13756-019-0533-3

[98] Tamburini E, Mastromei G. Do bacterial cryptic genes really exist? Research in Microbiology. 2000;**151**(3):179-182. DOI: 10.1016/s0923-2508(00)00137-6

[99] Onaka H. Novel antibiotic screening methods to awaken silent or cryptic secondary metabolic pathways in actinomycetes. Journal of Antibiotics (Tokyo). 2017;**70**(8):865-870. DOI: 10.1038/ja.2017.51

[100] Chagas FO, Pupo MT. Chemical interaction of endophytic fungi and actinobacteria from *Lychnophora ericoides* in co-cultures. Microbiological Research. 2018;**212-213**:10-16. DOI: 10.1016/j.micres.2018.04.005

[101] Onaka H, Mori Y, Igarashi Y, Furumai T. Mycolic acid-containing bacteria induce natural-product biosynthesis in *Streptomyces* species. Applied and Environmental Microbiology. 2011;**77**(2):400-406. DOI: 10.1128/AEM.01337-10

[102] Asamizu S, Ozaki T, Teramoto K, Satoh K, Onaka H. Killing of mycolic acid-containing bacteria aborted induction of antibiotic production by *Streptomyces* in combined-culture. PLoS One. 2015;**10**(11):e0142372. DOI: 10.1371/journal.pone.0142372

[103] Romano S, Jackson SA, Patry S, Dobson ADW. Extending the "one strain many compounds" (OSMAC) principle to marine microorganisms. Marine Drugs. 2018;**16**(7):244. Published: July 23, 2018. DOI: 10.3390/md16070244

[104] Falcinelli SD, Shi MC, Friedlander AM, Chua J. Green tea and epigallocatechin-3-gallate are bactericidal against *Bacillus anthracis*. FEMS Microbiology Letters. 2017;**364**(12). DOI: 10.1093/femsle/fnx127

[105] Nogueira Cruz FP. Isolation of the Endophytic and Rhizospheric Microbiome Associated with Polygala Spp.: Evaluation of the Biotechnological Potential and Antimicrobial Activity. Thesis, Federal University of Sao Carlos; 2018

[106] Breda CA, Gasperini AM, Garcia VL, et al. Phytochemical analysis and antifungal activity of extracts from leaves and fruit residues of Brazilian

savanna plants aiming its use as safe fungicides. Natural Products and Bioprospecting. 2016;**6**(4):195-204. DOI: 10.1007/s13659-016-0101-y

[107] Assis PC. Bactérias endofíticas isoladas de Caryocar brasiliense: atividade enzimática, antimicrobiana, leishimanicida e co-cultura com microrganismos patogênicos. Dissertation, Federal University of Sao Carlos; 2018

[108] Naik BS. Developments in taxol production through endophytic fungal biotechnology: A review. Oriental Pharmacy and Experimental Medicine. 2019;**19**:1-13. DOI: 10.1007/s13596-018-0352-8

[109] Paramanantham P, Pattnaik S, Siddhardha B. Natural products from endophytic fungi: Synthesis and applications. In: Singh BP, editor. Advances in Endophytic Fungal Research: Present Status and Future Challenges. Cham: Springer International Publishing; 2019. pp. 83-103. DOI: 10.1007/978-3-030-03589-1_5

[110] Torres FL. Isolamento, caracterização e potencial biotecnológico de fungos endofíticos associados à plantas do Cerrado. Dissertation, Federal University of Sao Carlos; 2018

[111] Carvalho CR, Gonçalves VN, Pereira CB, Johann S, Galliza IV, et al. The diversity, antimicrobial and anticancer activity of endophytic fungi associated with the medicinal plant *Stryphnodendron adstringens* (Mart.) Coville (Fabaceae) from the Brazilian savannah. Symbiosis. 2012;**57**:95-107

[112] Loi M, Leonardis S, Mulè G, Logrieco AF, PC. A novel and potentially multifaceted dehydroascorbate reductase increasing the antioxidant systems is induced by beauvericinin tomato. Antioxidants (Basel). 2020;**9**(5):E435. Published: May 16, 2020. DOI: 10.3390/antiox9050435

[113] Taevernier L, Veryser L, Roche N, et al. Human skin permeation of emerging mycotoxins (beauvericin and enniatins). Journal of Exposure Science & Environmental Epidemiology. 2016;**26**(3):277-287. DOI: 10.1038/jes.2015.10

[114] Mallebrera B, Prosperini A, Font G, Ruiz MJ. In vitro mechanisms of beauvericin toxicity: A review. Food and Chemical Toxicology. 2018;**111**:537-545. DOI: 10.1016/j.fct.2017.11.019

[115] Vega FE, Posada F, Peterson SW, Gianfagna TJ, Chaves F. Penicillium species endophytic in coffee plants and ochratoxin a production. Mycologia. 2006;**98**(1):31-42. DOI: 10.3852/mycologia.98.1.31

[116] Mondani L, Palumbo R, Tsitsigiannis D, Perdikis D, Mazzoni E, Battilani P. Pest management and ochratoxin a contamination in grapes: A review. Toxins (Basel). 2020;**12**(5):E303. Published: May 7, 2020. DOI: 10.3390/toxins12050303

[117] Pervaiz A, Khan R, Anwar F, Mushtaq G, Kamal MA, Khan H. Alkaloids: An emerging antibacterial modality against methicillin resistant *Staphylococcus aureus*. Current Pharmaceutical Design. 2016;**22**(28):4420-4429. DOI: 10.2174/1381612822999160629115627

[118] Lakhundi S, Zhang K. Methicillin-resistant *Staphylococcus aureus*: Molecular characterization, evolution, and epidemiology. Clinical Microbiology Reviews. 2018;**31**(4) e00020-18. Published: September 12, 2018. DOI: 10.1128/CMR.00020-18

[119] Turner NA, Sharma-Kuinkel BK, Maskarinec SA, et al. Methicillin-resistant Staphylococcus aureus: An overview of basic and clinical research.

Nature Reviews. Microbiology. 2019;**17**(4):203-218. DOI: 10.1038/s41579-018-0147-4

[120] Newmister SA, Gober CM, Romminger S, et al. OxaD: A versatile indolic nitrone synthase from the marine-derived fungus *Penicillium oxalicum* F30. Journal of the American Chemical Society. 2016;**138**(35):11176-11184. DOI: 10.1021/jacs.6b04915

[121] Qi X, Li X, Zhao J, et al. GKK1032C, a new alkaloid compound from the endophytic fungus *Penicillium* sp. CPCC 400817 with activity against methicillin-resistant *S. aureus*. Journal of Antibiotics (Tokyo). 2019;**72**(4):237-240. DOI: 10.1038/s41429-019-0144-5

[122] Liu J, Yang X, He J, Xia M, Xu L, Yang S. Structure analysis of triterpene saponins in *Polygala tenuifolia* by electrospray ionization ion trap multiple-stage mass spectrometry. Journal of Mass Spectrometry. 2007;**42**(7):861-873. DOI: 10.1002/jms.1210

[123] Tagousop CN, Tamokou JD, Kengne IC, Ngnokam D, Voutquenne-Nazabadioko L. Antimicrobial activities of saponins from Melanthera elliptica and their synergistic effects with antibiotics against pathogenic phenotypes. Chemistry Central Journal. 2018;**12**(1):97. Published: September 20, 2018. DOI: 10.1186/s13065-018-0466-6

[124] Arabski M, Węgierek-Ciuk A, Czerwonka G, Lankoff A, Kaca W. Effects of saponins against clinical *E. coli* strains and eukaryotic cell line. Journal of Biomedicine & Biotechnology. 2012;**2012**:286216. DOI: 10.1155/2012/286216

[125] Jin Z, Gao L, Zhang L, et al. Antimicrobial activity of saponins produced by two novel endophytic fungi from *Panax notoginseng*. Natural Product Research. 2017;**31**(22):2700-2703. DOI: 10.1080/14786419.2017.1292265