

Bioactivity of Endophytes from the Brazilian Tropical Savannah

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Abstract

The Brazilian tropical savannah is a mosaic biome, the second largest in the Brazilian territory and the most biodiverse tropical savannah in the world. Endophytes and host plants have a symbiotic relationship, in which both are beneficial. The host plant provides protection to the endophytes, which, in turn, increase the fitness of the plant by inducing resistance to pathogens due to niche competition and/or synthesizing antibiotics, lytic enzymes and siderophores. Although initial studies on endophytes were directed to those living in symbiosis with temperate plants, in recent years, many reports describing the isolation of endophytic bacteria and fungi from tropical plants have been published. Secondary metabolites produced by endophytes are a promising source of bioactivity. The biochemical versatility and diversity of these microorganisms suggest that there are many unknown active compounds. Another important goal is the agronomic potential of endophytic fungi from tropical savannah. Bioprospecting studies have reported the potential of endophytes against a large number of phytopathogens responsible for large losses in economically important tropical crops. Thus far, the main method for controlling plant diseases is the application of chemicals. Nevertheless, chemicals cause toxic effects to humans, animals and the environment. Therefore, endophytic microorganisms have been considered an alternative for the control of phytopathogens and consequent augmented crop production. The lack of studies related to endophytes isolated from tropical environments enhances their importance. This review focuses on the potential activities produced by endophytes isolated from medicinal plants and their industrial, pharmaceutical and agronomic applications.

Keywords: Endophytic Microorganisms; Cerrado; Bioactive Compounds; Antimicrobial; Biocontrol; Plant Growth Promotion

The Brazilian tropical savannah, known as the Cerrado, is one of the richest habitats of the world with regard to diversity in fauna and flora [1]. The number of endemic plants is high, and it is estimated that more than 4400 species of higher plants can be found in this savannah [2-4]. The Cerrado ecosystem is characterized

by seasonal weather with an annual precipitation that varies between 1200 and 1800 mm and a dry season that occurs during 5 - 6 months a year and comprises a rich and characteristic flora [5], which makes it one of the 25 most important terrestrial biodiversity hotspots on the planet [4].

Endophytes are microorganisms that inhabit the interior of plant tissues without harming their hosts. This definition includes internal colonists with apparently neutral behavior, symbionts and bacteria that migrate between the surface and the inside of the plant during their endophytic phase [6]. The term endophyte is applied to microorganisms, frequently bacteria and fungi, that colonize living plant tissues for all or part of their life cycle but cause no apparent infection or symptoms of disease [7].

Significant attention has been given to the exploration of new bioactive compounds that can be synthesized by endophytic microorganisms [8]. It provides an alternative to the exploitation of plants, helping in the flora diversity preservation, which is becoming increasingly scarce in the world [9] as well as reducing the market value of these biomolecules [10]. The broad spectrum of biological activity of endophytes isolates allow, among other things, the exploration of substances with potential antimicrobial, and production of enzymes, which can be obtained on a large scale through fermentation and present a great potential for industrial applications [11,12].

Plants native to the Brazilian savannah are commonly used to treat skin diseases, ulcers, anemia, diabetes, malaria, inflammatory reactions, and hepatic diseases, and this medicinal flora has been used as folk medicine by different people as an alternative to high-priced pharmaceutical drugs [13,14]. Several endophytes from the Brazilian savannah have been reported for their microbial activities, such as antibiotic capability against gram-positive and gram-negative bacteria, antifungal activity, antibiotic resistance properties, enzyme production, antitumor activity, and anti-*Leishmania* activity [15-18].

This review comprises the concept and applications of endophytic microorganism and their relationship with medicinal plants. The medicinal utilization of these bioactive compounds produced by bacteria and fungi as well as agronomic potential for crop improvement have been explored.

Tropical savannah trees

The Brazilian Cerrado is a biome composed of savannah and forest ecosystems that cover approximately 2 million km², representing ca. 22% of the land surface of Brazil, plus small areas in eastern Bolivia and northwestern Paraguay [19].

Some research has shown that the Cerrado ecosystems can harbor a large and diverse population of plant-associated fungi with many new fungal taxa [20]. Although interest in microbial biodiversity in the Brazilian Cerrado has increased, the diversity, taxonomic composition, host affinity and biotechnological potential of fungi from this ecosystem remain unclear.

The Brazilian tropical savannah (Cerrado) is the second largest biome in Brazilian territory, with approximately 2,036,448 km², an area that is equivalent to almost a quarter (23,52%) of the national territory [21], and more than 6,000 vascular plant species [22]. This diversity results from the adverse environmental conditions caused by fire, leading to specific adaptations and different phyto-physiognomies that characterize the biome [23,24].

Bioactive molecules from tropical savannah endophytes

The Brazilian tropical savannah occupies a large area in Brazil and includes a high variety of plant species [1]. This diversity is an important source of endophytic microorganisms consisting mainly of bacteria and fungi that inhabit the interior of plants [25]. Endophytes represent an extensive source of promising natural products because large-scale cultivation may be able to produce an enormous amount of secondary metabolites while keeping costs reasonable [26,27]. Evidence suggests a close microbial-plant relationship that functions symbiotically [28,29].

Drug-resistant microorganisms have also generated attention in recent decades, and studies estimate that over 700,000 million deaths worldwide are caused by these microorganisms [30]. Considering studies developed by Allen, *et al.* [31], microorganisms can carry genes encoding resistance to the antibiotics they produce. Many important antibiotics in the pharmaceutical industry have been derived from microbial metabolites [32,33]. The biochemical versatility and diversity of these microorganisms suggest that there are many still unknown active compounds [26]. In this way, several studies have reported the potential of endophytic microorganisms obtained from the Brazilian tropical savannah in the production of metabolites with the potential to control human pathogens [16-18,25].

Assis [34] described endophytes associated with *Caryocar brasiliense*, a plant species native to the Brazilian tropical savannah [35]. Although *C. brasiliense* is commonly used in folk medicine

[36], there are only a few studies about its endophytic community and the production of secondary metabolites from this host plant [25,34]. According with Assis [34], forty-two endophytic microorganisms were isolated from *C. brasiliense* and one was identified as an actinobacteria belonging to the genus *Streptomyces*. In preliminary tests evaluating antimicrobial activity, six isolates showed activity against *Staphylococcus aureus* and one isolate, Actinobacteria, showed activity against *Candida albicans* and was selected for subsequent tests. Analysis of the growth kinetics of *Streptomyces* spp. demonstrated that the production of bioactive substances against *C. albicans* started at 40 hours. The bioactivity evaluation of the crude extract produced during coculture with potentially pathogenic microorganisms demonstrated a 50% increase in inhibition of *C. albicans* and promoted inhibition of *S. aureus*, which had not been reported in axenic culture. The microdilution assay evaluated the bioactivity of lyophilized crude extract against *C. albicans*, which demonstrated an inhibition rate higher than 90% at a concentration of 10 mg.mL⁻¹ and 56% at 2 mg.mL⁻¹.

Ruela [37] examined the biotechnological potential of *Bacillus pumilus*, isolated from *Tabebuia rosea alba*, a Brazilian tropical savannah tree in São Paulo state, Brazil, and its metabolites. Based on this, the author reported that the *B. pumilus* strain demonstrated inhibitory activity against *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Candida albicans*. The evaluation of the enzymatic activity showed positive results for lipase and esterase production. Satisfactory results were also observed for the performance of *B. pumilus* as a biological agent, which was able to inhibit the growth of 7 of the 16 phytopathogenic fungi tested. Interesting and promising results were observed regarding the antileishmanicidal and antitumor action of the extract from the *B. pumilus* strain.

Neris., et al. [18] worked with a total lyophilized extract (TLE) of *Paenibacillus polymyxa* RNC-D, which was isolated from *Prunus* spp. leaves that were collected from the Brazilian tropical savannah in São Carlos, SP, Brazil [25]. *P. polymyxa* strains are known for their capacity to segregate a large number of extracellular enzymes and bioactive substances [38,39]. The TLE of *P. polymyxa* RNC-D was tested in cell viability assays for cytotoxicity and cytokine production in fibroblast (BALB/3T3) and macrophage (J774A.1) cell lineages. A 50% mortality rate of fibroblasts (BALB/3T3) was observed in the 1.171 - 0.161 mg/mL and 0.956 - 0.112 mg/mL doses

after 48 and 72 hours, respectively, as well as a 50% mortality rate of macrophage cells (J774A.1) in the 0.994 - 0.170 mg/mL and 0.945 - 0.280 mg/mL doses after 48 and 72 hours, respectively. At \approx 1 mg/mL, the TLE significantly affected the growth kinetics at all the measured periods. At \approx 1 mg/mL, the extract induced apoptosis and necrosis in both tested lineages in 24 hours. Treatment with \approx 1 mg/mL led to the production of TNF- α and IFN- γ cytokines in 24 hours. IL-12 and IL-10 began to be detected after treatment with 0.1 mg/mL. However, with the 0.5 mg/mL dose, a significant reduction in IL-10 was observed in 24 hours. These data suggest that the TLE of *P. polymyxa* RNC-D modulated the production of cytokines with different patterns of immune response in a dose-dependent manner.

Piza., et al. [17] isolated endophytic actinomycetes from the endemic medicinal plant *Miconia albicans* (Sw.) Triana (Melastomataceae) collected in the Brazilian tropical savannah and evaluated the action of secondary metabolites on human pathogens. One isolate identified as *Amycolatopsis orientalis* inhibited the growth of *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Candida albicans* (ATCC 10231) and *Shigella sonnei* (ATCC 1578). The authors suggested that these findings can contribute to the discovery and characterization of new antimicrobial compounds with possible medical and/or industrial applications.

Serrano., et al. [16] reported the optimization of culture conditions for the production of antimicrobial metabolites by the endophytic bacterium *Paenibacillus polymyxa* RNC-D, isolated from leaves of *Prunus* spp., a Brazilian tropical savannah plant [25], against *Escherichia coli* ATCC 25922. This study demonstrated an important step in the development of strategies to elevate the production of antimicrobial molecules by this endophytic bacteria to control human pathogens.

Vaz., et al. [19] characterized the endophytic fungal community associated with three plants from Brazilian tropical savannah and determined the ability of these fungi to produce antimicrobial metabolites. Fungal endophyte communities associated with leaves of *Myrciaria floribunda*, *Alchornea castaneifolia*, and *Eugenia* aff. *bimarginata* were examined, collected from Brazilian savannah ecosystems, and studied for their ability to produce antimicrobial activity. A total of 93 isolates of endophytic fungi were obtained and identified by sequencing of internal transcribed spacer (ITS)

regions of the rRNA gene, which revealed the presence of 20 Ascomycota and three Basidiomycota taxa. The genus *Colletotrichum* is the most frequent endophyte associated with *M. floribunda* and *A. castaneifolia*. *Mycosphaerella* is the most frequent genus associated with *E. aff. bimarginata*. All fungal endophytic isolates were cultured, and the crude extracts were screened to examine the antimicrobial activities against pathogenic microorganisms. Thirty-eight fungal extracts presented antimicrobial activity against at least one of the different target microorganisms tested. *E. donezkii* and *C. gloesporioides* showed the best minimum inhibitory concentration (MIC) values, which were lower or similar to the MICs of known antibacterial and antifungal drugs. The results suggest that the plants of the Brazilian tropical savannah shelter a diverse endophytic fungal community, which includes bioactive taxa capable of producing promising antimicrobial metabolites.

According to Favoretto [15], twenty-six endophytic microorganisms were isolated from *Butia capitata* var *capitata* (Coquinho-do-cerrado), *Solanum lycocarpum* (Lobeira), *Stryphnodendron polyphyllu* (Barbatimão), *Miconia albicans* (Quaresmeira-white) and *Aegiphila lhotzliana* (Tamanqueira), which were collected on Brazilian tropical savannah at São Carlos, SP, Brazil. The isolates were characterized through macroscopic, physiological, biochemical and morph-dying characteristics, and these endophytic isolates were identified as *Streptomyces*. The antagonistic potential of the endophytic isolates was tested against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Serratia marcescens* ITB 1475, *Enterococcus faecalis* ATCC 29212, *Shigella sonnei* ATCC 10231 and *Candida albicans* ATCC 10231. The endophytes isolated from *B. capitata* var *capitata* inhibited the growth of *S. aureus* (13 mm) and *E. faecalis* (11 mm), and the endophytes isolated from *M. albicans* did not show bioactivity against the pathogens tested.

Working with endophytic actinomycetes, Ratti, et al. [25] demonstrated that the microorganisms isolated from *Cassia leptophylla*, a Brazilian tropical savannah tree in São Paulo state, Brazil, had no ability to inhibit a *Staphylococcus* coagulase-positive strain, while microorganisms isolated from *Prunus* spp. presented antibacterial activity when cultivated in peptone agar (PA) as well as in yeast extract agar (YA).

Among the diversity of trees in the Brazilian savannah, our research group has considered two species: *Stryphnodendron adstringens* (Mart.) Coville (Fabaceae) and *Solanum lycocarpum*

Saint-Hill (Solanaceae). *S. adstringens* (Mart.) is a small tree, with a height ranging from 2 to 8 meters, a tortuous trunk and rigid and rough bark popularly known in Brazil as Bartimão [40]. Similar to *S. lycocarpum*, *S. adstringens* trees have potential for medicinal applications. Its bark and fruit contain anti-inflammatory [41], antiviral [42] and antimicrobial properties [43]. *S. lycocarpum* is a hairy shrub or small much-branched tree approximately 4 meters tall and popularly known in Brazil as Lobeira because it is part of the diet of wolves [44,45]. It is a plant adapted to the savannah and can resist a low water input [46]. Furthermore, *S. lycocarpum* produces secondary metabolites that exhibit antioxidant, antibacterial, cytotoxic and inflammatory properties [47,48].

Torres [49] reported the study of 66 endophytic fungi obtained from *S. adstringens* and *S. lycocarpum* St. Hill collected in Brazilian Tropical Savannah Reserve from the Federal University of São Carlos, SP, Brazil. The endophytic strains were evaluated *in vitro* for their antagonistic potential against the phytopathogens *Colletotrichum* sp., *Fusarium oxysporum* and *Lasiodiplodia subglobosa* and for their ability to solubilize inorganic phosphate (Figure 1 and 2). The results showed that endophytic strains exhibited antagonistic activity against the phytopathogens tested. Additionally, we observed a potential to solubilize inorganic phosphate with a mean phosphate solubilization index, ranging from 1.46 to 1.93 and 1.19 to 2.61 by endophytic strains.

In similar work, Noriler, et al. [50] assessed the fungal community associated with *Stryphnodendron adstringens* leaves and petioles collected in the savannah area of Miranda, Mato Grosso do Sul State, Brazil. The authors verified the antimicrobial activity of crude extracts produced by the endophytes and suggested that *Diaporthe cf. heveae* LGMF 1631 may represent an alternative to be used in the biocontrol of the plant pathogens *Phyllosticta citricarpa* and *Colletotrichum abscissum*.

Faria, et al. [51] studied the endophytic fungal community associated with the roots of *Anacardium othonianum* Rizzini, popularly known as “caju-de-árvore-do-cerrado” (cashew tree of the Cerrado), collected in Goiás State, Brazil. A total of 67 fungal strains were obtained and identified by sequencing the internal transcribed spacer (ITS), which revealed the presence of twelve species. Clustering by similarity between the morphotypes of endophytic fungal species showed their division in *Basidiomycota* and *Ascomycota*

Figure 1: Dual culture plate assay between endophytic fungal isolates from *Stryphnodendron adstringens* (Mart.) Coville against the phytopathogen *Colletotrichum* sp., *Fusarium oxysporum* and *Lasiodiplodia subglobosa* grown in PDA. A) Interaction type CA1 for *Pseudofusicoccum* sp. BRA3 and *Colletotrichum* sp. B) Control *Colletotrichum* sp. C) Interaction type A for *Neofusicoccum* sp. BRA1 and *Fusarium oxysporum*. D) Control *Fusarium oxysporum*. E) Interaction type A for *Pseudofusicoccum* sp. BRA4 and *Lasiodiplodia subglobosa*. F) Control *Lasiodiplodia subglobosa*.

phyla. In this same study, seven endophytic strains isolated from *A. othonianum* Rizzini showed potential for phosphate solubilization and indole acetic acid (IAA) synthesis, which are important mechanisms for plant growth promotion.

Conclusion

The data exhibited here suggest that Brazilian tropical savannah plants are a good source for endophytic microorganisms and

Figure 2: Pectate lyase (A) and poligalacturonasis (B) production by endophytes *Neopestalotiopsis* sp. BFO4 and *Schizophyllum* sp. BFO12, respectively, obtained from *Stryphnodendron adstringens* (Mart.) Coville.

emphasize the potential of natural compounds that can be used in the pharmaceutical industry and agricultural fields.

Conflict of Interest

All the authors declared that there are no conflicts of interest associated with this publication.

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