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Actinobacteria: Versatile Microorganisms with Medical and Pharmaceutical Application

Rosilma de O. Araujo-Melo[1], Igor F. A. C. Souza[2], Maria C. V. Vicalvi-Costa[1], Janete M. de Araújo[1], Kêsia X. R. F. de Sena[1] and Luana C. B. B. Coelho[3*]

[1]Departamento de Antibióticos, Centro de Biociências, Universidade Federal de Pernambuco (UFPE), Avenida dos Economistas, S/N, Cidade Universitária, Recife-PE, CEP 52171-011, Brazil.
[2]Faculdade Integrada de Pernambuco, Avenida Caxangá, nº 4477, Várzea, Recife-PE, CEP 50740-000, Brazil.
[3]Departamento de Bioquímica, Centro de Biociências, UFPE, Avenida Moraes Rego, S/N, Cidade Universitária, Recife-PE, CEP 50670-420, Brazil.

Authors' contributions

This work was collaboration among all authors. Authors ROAM, IFACS and LCBBC managed the literature search and wrote the manuscript. Authors KXRFS and JMA participated in revision of this article. Author MCVVC contributed with comments and English translation. Authors ROAM, JMA and LCBBC designed, supervised and managed the study performed. All authors read and approved the final manuscript.

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ABSTRACT

The Actinobacteria receive much attention, since they produce a variety of metabolites, including antibiotics and enzyme inhibitors. These bacteria are distributed in various habitats, including soil, ocean, extreme environments, lichen, plants, and animals. The classification of Actinobacteria based upon the morphological observation, physiological and biochemical characteristics were not adequate to differentiate the genera of this phylum. Following, another identification was available based in the distribution of specific constituents from the cellular wall, such as diaminopimelic acid and carbohydrates. With the advent of molecular biology, the identification of genera and species was more reliable. The screening of microbial natural products has become an important route to

**Corresponding author: E-mail: lcbbcoelho@gmail.com;*

discover new bioactive compounds in order to develop new therapeutic agents. Actinobacteria remains one of the leading producers of biopharmaceuticals; endophytic Actinobacteria also yield secondary metabolites with wide range of biological activity. This review focus on gathering relevant information on identification, classification, chemical diversity of Actinobacteria, as well as reveals some biotechnological applications of these bacteria.

Keywords: Actinobacteria; microorganisms; biotechnology potential.

1. INTRODUCTION

Previously, the Actinobacteria were called actinomycetes, name of greek origin, where aktis means "lightning" and mykes, fungus, or "radial growth as fungus" that were initially classified as an intermediate group between fungi and bacteria. Investigations with electron microscopy and cytological studies showed that filamentous bacteria are prokaryotic [1].

The phylum Actinobacteria contains unicellular, Gram-positive, aerobic, facultative anaerobic or anaerobic microorganisms [2]. There is predominant filamentous morphology with the ability to form filiform aggregates due to the formation of hyphae with a diameter between 0.5 to 1.0 µm resembling the filaments of fungi (Fig. 1). The diameter of Actinobacteria cells varies between 0.5 and 2.0 µm, generally less than 1.0 µm, being most of free life or saprophytic [3].

Actinobacteria can be autotrophic, heterotrophic, chemotrophic or phototrophic, however, for the most part, they are chemoorganotrophic, which grow at neutral pH; But there are some acidophilic, alkalophilic or halophilic [3]. The majority of Actinobacteria are mesophilic and the optimum temperature for growth is between 25ºC and 30ºC. At temperatures below 5ºC growth is virtually null, and above 55ºC, there are some thermophilic species, belonging to the genus *Streptomyces*, *Thermonospora* and *Thermoactinomyces*. However, high temperatures can be lethal if the microorganism is not in a humid environment [4].

The less evolved Actinobacteria have an incomplete mycelial development, which occurs only during active growth. However, most developed ones have two types of mycelium, in the substrate, the rhizoids; and outside substrate, the aerial mycelium. The Actinobacteria, which produce mycelium using this structure for attachment and penetration, can release enzymes that degrade essential compounds in order to obtain nutritional supplements [5].

Actinobacteria produce spores that allow survival in extreme habitats conferring protection, normally correlated to their morphological diversity, leading to the formation of a wide variety of spore structures. There are the arthrospores in *Streptomyces*, endospores in *Thermoactinomyces*, aleuriospores in the genus *Micromonospora* and mobile zoospores in *Oerskovia*, *Geodermatophilus* and *Kitasatoa* [6,7].

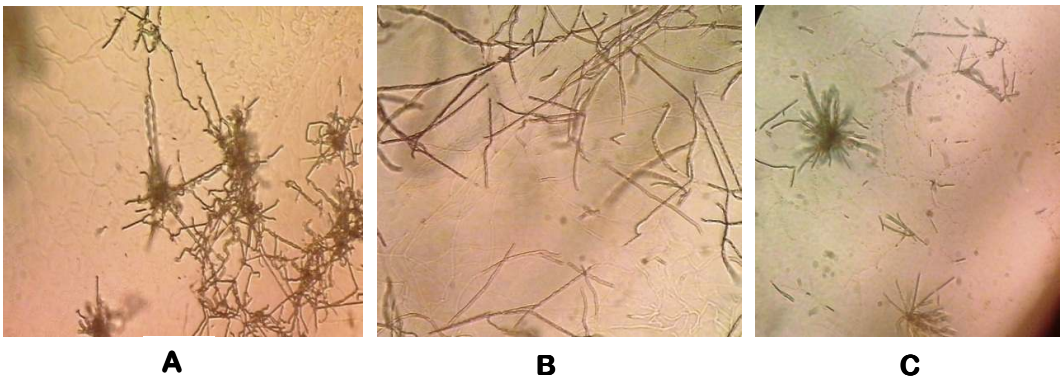

Fig. 1. Optical microscopy of Actinobacteria: A, *Streptomyces* sp. (spiral spore chains); B, *Nocardiopsis sp.* (long chains of spores in abundance); C, *Streptomyces* sp. (straight verticillate chains)

The growth cycle of some Actinobacteria is primarily designed for sporulation phase. After germination of the spores, vegetative mycelium substrata grows at the surface and inside of the solid culture medium, until it differentiates into reproductive aerial mycelium on which spore formation occurs [8]. At the stage of formation of these spores, pigments and antimicrobial substances are produced occurring activation of secondary metabolism [9].

The cell wall is composed of peptidoglycans, lipoproteins, lipopolysaccharides, teichoic acids, among others. The presence of guanine-cytosine (GC) from 63 to 75% constitutes a group of bacteria with a higher percentage of that pair of nitrogenous base with genomes ranging from 2.5 Mb to 9.7 MB [3,4,10]. On solid culture media, they have colonies dry or coriaceous, which may be smooth to wrinkled appearance with strong adhesion to the culture medium, which can be coated by air or reproductive mycelium, and this is a peculiar feature. This aerial mycelium can have different colors in different culture media for the same species, such as white and gray (Fig. 2).

The Actinobacteria have a characteristic odor of "wet earth", which is related to volatile compounds produced by its secondary metabolism, such as geosmin. Besides that, feature intense metabolic activity, producing terpenoids, pigments and extracellular enzymes with which degrade organic matter of plant and animal origin producing secondary metabolites of economic importance [11]. These microorganisms have a worldwide distribution and occur in plants, isolated from leaves and roots [12]. The soil is the most common habitat of Actinobacteria, being abundant in rhizosphere soil region influenced by the roots of the plant [13,14]; The bacteria can occur in the desert [15]; Mangrove [16]; Pasture [17]; Insects [18]; And marine organisms [19].

Filamentous bacteria are found in extreme habitats such as marine sediments [20], glaciers [21] and hyper-arid desert [22]. In addition, are included pathogens (particularly from the genus *Corynebacterium*, *Mycobacterium*, *Nocardia*, *Propionibacterium* and *Tropheryma*), inhabitants of soil (for example, *Micromonospora* and *Streptomyces*), plant commensal (e.g., *Frankia* spp.), and gastrointestinal commensal (*Bifidobacterium* spp.) [23,24].

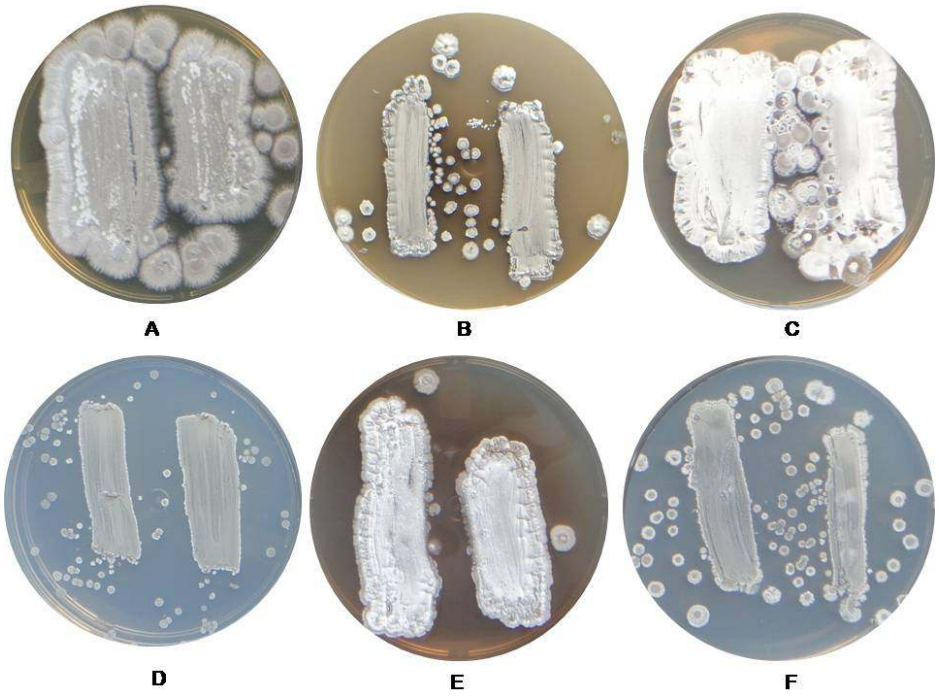

Fig. 2. Macroscopic characteristics of *Streptomyces* spp. in different media of solid culture. A, agar malt yeast [ISP2]; B, international *Streptomyces* project medium 4 [ISP4]; C, casein starch agar [CAA]; D, glycerol starch agar [GAA]; E, Czapek [CZ] and F, medium complete [MC]

2. TAXONOMY

The molecular, biochemical or physiological characteristics to distinguish between species belonging to the phylum Actinobacteria from other bacteria were not known initially. However, after the advent of genomic analysis, specific proteins identified from the Actinobacteria helped to distinguish Actinobacteria and subgroups [25].

Waksman & Henrici [26] proposed the classification system of Actinobacteria based on micro-morphology and variable cellular wall chemotype; there are four main types of cellular wall (Table 1). The most common approach used to classify genres within the group of Actinobacteria includes phylogeny based upon 16S rRNA [27].

This characterization followed the composition and structure of peptidoglycan by the amino acid located in position 3 of the side chain from the tetrapeptides, the presence of glycine in interpeptide bridges and carbohydrate contained in peptidoglycans. In addition to the above mentioned groups of Actinobacteria there are *Actinomyces* (V- lysine; Ornithine), *Rothia* (VI-lysine and aspartic acid), *Oerskovia* (VI + Gal-lysine; Galactose; Aspartic acid), *Agromyces* (2,4-D acid diaminobutyric acid and glycine) and *Mycoplana* (meso-DAP numerous amino acids) [28].

Mingma et al. [32] isolated from 317 Actinobacteria, 77 from roots of leguminous plants and 240 from rhizosphere soil. Analysis of the cellular wall showed that 289 strains were of type L, L-isomer of 2-6- diaminopimelic acid, whereas 28 strains had the meso isomer. Isolates were identified by sequence analysis of 16S rRNA, whose L-DAP were identified as *Streptomyces* sp.; however, isolates which contained meso-DAP belonged to the genera *Amycolatopsis, Isoptericola, Micromonospora, Microbispora, Nocardia, Nonomuraea, Promicromonospora and Pseudonocardia.*

Table 1. Major constituents of the cellular wall from actinobacteria and its relation to the taxonomy

Group	Cellular wall type	DAP: 2-6-diaminopimelic acid	Detected major constituents
Streptomyces (Streptoverticillium, Chainia, Actinopycnidium, Actinosporangium, Elytrosporangium); Microellobosporia; Sprorichthya Nocardiopsis Intrasporangium	I	L,L	Glycine
Micromonospora Actinoplanes; Amorphosporangium; Ampullariella; Dactylosporangium	II	Meso	Xylose, arabinose
Actinomadura Dermatophilus Microbiospora, Pilimelia Actinoplanes Frankia Streptosporangium; Spirillospora; Planomonospora Dermatophilus	III	Meso	Madurose, without arabinose and xylose
Nocardia Rhodococcus Corynebacterium Mycobacterium Saccharomonospora Micropolyspora Pseudonocardia Thermomonospora	IV	Meso	Galactose, arabinose and without xylose

Data obtained from [28,29,30,31].

The Actinobacteria is considered one of the largest phylum in the domain Bacteria; This is inferred from the standard phylogenetic branch 16S rRNA of belonging microorganisms. The separation of the phylum from other taxa of Bacteria concerns insertions/deletions in some proteins, the presence of a large insertion in the 23S rRNA gene and different arrangements of genes [33].

The order Actinomycetales consists of 63 genera [34], generally divided into two groups. The nocardioforme actinomycetes feature with crude mycelium followed by fragmentation; the group esporoactinomicetes displays an aerial mycelium network well developed with spores. In the latter group are the *Streptomyces* genus, *Actinoplanes* and *Microbispora*, among others [35].

The most recent data about the taxonomic classification of the phylum Actinobacteria, present in Bergey's Manual of Systematic Bacteriology 2012, include five classes, 19 orders, 50 families and 221 genera; Also Acidimicrobiia, Actinobacteria, Coriobacteriia, Rubrobacteria and Thermoleophilia, the constituent classes [4].

3. LIFE CYCLE

The life cycle of Actinobacteria varies with the nutritional status, that is, under good growing conditions exhibit septated mycelia similar to multicellular fungi; While in limiting conditions, only the vegetative mycelia is developed [36]. The microorganisms have a complex life cycle which begins by germinating the spores, causing the vegetative mycelia with branching hyphae which penetrate the substrate being responsible for support and adsorption of nutrients, metabolizing organic sources (polysaccharides, proteins, lipids and aromatic compounds), by extracellular enzymes. The vegetative mycelium or primary hyphae originates the secondary hyphae or aerial mycelium, which protrude on the substrate surface constituting the reproductive mycelium undergoing morphological differentiation, which include septation and spore formation. These are formed as a result of nutrient reduction, most of which are thermosensitive, but well support desiccation that are important in adaptation, promoting survival of the species during dry season [8,37].

Most genres reproduced by the formation of spores may vary from mobile zoospores to specialized propagules [38]. Within this Actinobacteria group are the sporoactinomycetes forming spores in specific regions of the aerial mycelium, produced in large quantities, where each one has germination potential. *Streptomyces* are characteristic arthrospores; in *Thermoactinomyces*, endospores; in *Micromonospora*, aleuriospores; in *Actinoplanaceae*, *Geodermatophilus*, *Kitasatoa* and *Oerskovia*, mobile zoospores [7,39]. However, *Micrococcus*, *Arthrobacter* and *Corynebacterium* genera reproduce by binary fission, whereas the genera *Mycobacterium*, *Nocardia* and *Rhodococcus*, known as nocardioforme Actinobacteria, have rudimentary mycelium which fragments into coccoid elements, yielding a new mycelium [40].

The pigments and secondary metabolites are produced at the stage of spore formation due to activation of secondary metabolism [8,41], which accumulates *in vitro* during the fermentative process. This methodology consists of the cultivation of microorganism in special conditions, necessary for maximum production of the desired metabolite, which may occur, in liquid or solid media, but the liquid assets are the most used by industry [42].

The temperature control and pH, in which there is a great productivity of metabolite, are important factors to be established. It is interesting to note that the variation in production of the compounds depends upon both environmental factors and genetic of the microorganism. This variation is apparently caused by the low specificity of the enzymes involved in secondary metabolism, since errors in the processing of these substances would not be lethal to the microorganism [42].

4. ISOLATION AND IDENTIFICATION OF ACTINOBACTERIA

The phylum Actinobacteria is isolated from different sources, such as, soils, plants, animals and humans (pathogens, like *Mycobacterium tuberculosis* and *Corynebacterium diphtheriae*) [42]. The diversity of the phylum is influenced by environmental factors such as temperature, pH and nutrient availability, promoting the development and proliferation of Actinobacteria [12].

The plate cultivation method, used for the study of microorganisms is used as being effective to analyze the morphological characteristics of Actinobacteria. The presence, shape and color of

the mycelia and spores, as well as the characteristic of the colonies can allow classifying as family and gender, being very important the choice of suitable culture media, aiming to promote differences in development due to nutritional and population dynamics involved in the environment [43].

Most Actinobacteria grow in culture media, such as Agar Triplicase Soy, Blood Agar, Brain Heart Infusion, for not producing mucopolysaccharides, such as other bacteria, exhibit dry and not creamy colonies. For the differentiation and development of spores and / or pigments, it is necessary a culture media supplemented with colloidal chitin, oat, starch with inorganic salts, and water with certain polysaccharides such as carbon source, yeast extract or peptone. For example, some colonies of *Streptomyces* species which grow as hard bright and pale colonies in Nutrient Agar. In a medium with oat, or medium starch with inorganic salts, bright yellow colonies can grow with powdery aerial mycelium of various colors [44].

The growth of Actinobacteria colonies on solid medium can be visualized after 3 to 4 days of incubation, but the development of mature aerial mycelium with spores range from 7 to 14 days; In some slow growing strains, the development of colony can take up to a month in culture [45]. However, growth in stationary liquid media is restricted to the formation of a surface film or particulate sediment leaving the liquid medium transparent, facilitating differentiation. Medium contaminated by bacteria becomes turbid, as can be seen in Fig. 3. Agitation at a speed between 200 and 220 rpm allows a better aeration. Unlike non-filamentous bacteria, Actinobacteria may grow forming pellets or filament groups in liquid medium.

The microscopic examination reveals the micro-morphology of Actinobacteria varying depending on the genus; For example, *Arthrobacter* and *Rhodococcus* result in coccobacillus shape, *Nocardia* shows fragmentation of hyphae, and *Streptomyces* is highly differentiated with branched aerial mycelium. Regarding the spores, there are types, number and arrangements of the chain, in *Microbispora* in longitudinal pairs; *Streptomyces*, spiral spore chains, straight or verticillate, while in *Actinoplanes* and *Streptosporangio*, the spores are within the sporangium. The use of electron microscopy has some additional information about the surface of the spores, such as smooth, wrinkled, prickly or downy [46, 47, 48].

A B C

Fig. 3. Actinobacteria growth in liquid medium. A, agar yeast malt (ISP-2) sterile and clear; B, pure Actinobacteria (particulate sediment) and C, contaminated Actinobacteria

A biochemical nutritional and physiological characterization occurs along the cultivation in order to assist in the classification. Some assays may be performed as the use of different sources of carbon and nitrogen, antibiotic resistance, substrate degradation tests, growth test on different conditions and biochemical tests, such as the catalase and proteolysis [31,48].

The macro and micromorphologic analysis combined with other biochemical tests and physiological nutrition, are usually not sufficient for distinguishing Actinobacteria from other groups of Gram-positive bacteria. Thus, the analysis of genotypic characteristics, by molecular biology techniques, presents itself as a highly effective alternative to classify, identify and determine the phylogenetic relationships within the group of Actinobacteria [49].

A widely used method is the analysis by PCR (Polymerase Chain Reaction) [50]. The subunits 16S and 23S rRNA molecules are fairly large and therefore contain sufficient information to allow meaningful comparisons. The 16S rRNA gene is more manageable than the 23S in

experiments; Therefore, it is widely used in phylogenetic studies [10].

The guanine and cytosine content (GC) in the Actinobacteria DNA can vary from 51% to *Corynebacterium* genus, more than 70% in species of *Streptomyces* and *Frankia*, but less than 50% was observed in *Tropheryma whipplei* [7].

The sequence of nucleotides from 16S rRNA is highly conserved in some regions, containing also variable regions; Mutation rates are relatively low. A large number of sequences are available in databases, facilitating the identification of regions with unique sequences by alignments, with consequent determination of species. In addition to the highly conserved sequences, the 16S rRNA gene has very variable regions, which enable the measurement of both near and far phylogenetic relationships, allowing determine the Domain, Division, Family, Class, Order, genus and species of the analyzed microorganisms [51].

5. ENDOPHYTIC ACTINOBACTERIA

Some associations between Actinobacteria and plants are well characterized within the *Actinomycetales* order, where there are examples of phytopathogenic, symbiotic and endophytic species. Regarding endophytic Actinobacteria, higher plant tissues constitute an important niche. Biodiversity of endophytic Actinobacteria is huge and have been isolated from different internal tissues of a variety of vegetables such as wheat, rice, potatoes, carrots, tomatoes and citrus fruits [52,53], different species of woody trees, ferns and mosses [12].

Endophytic microorganisms enter the plant primarily through the roots; however, aerial parts, such as flowers, stems and cotyledons can be used as input ports (Fig. 4). The penetration may occur through active forms in tissues of plants by the use of hydrolytic enzymes such as cellulases and pectinases, or passively promoted by natural openings or caused by injury [54].

The first Actinobacteria isolated from plants of internal tissues belong to the genus *Frankia*, a nitrogen fixer microorganism from legumes [55]. However, the Actinobacteria genera reported in the literature as more frequent in plant tissues are *Streptomyces*, *Microbispora*, *Micromonospora* and *Nocardioides* [56,57].

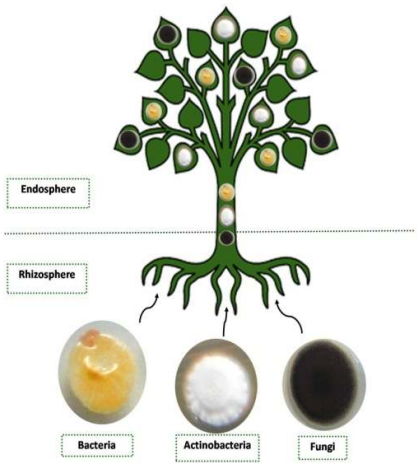

Fig. 4. Schematic representation of a vegetable colonization by bacteria and fungi

In the work carried by Rao et al. [58], endophytic Actinobacteria were isolated in 117 strains from *Combretum latifolium* (*Combretaceae*), representing 9 different genera of Actinobacteria among them *Streptomyces* (35%), *Nocardiopsis* (17%) and *Micromonospora* (13%). The preliminary evaluation of antibacterial activity showed that all strains of *Streptomyces* spp. exhibited significant activity against the tested pathogens; CLA-66 and CLA-68 strains, Nocardiopsis sp., also showed satisfactory results.

The work carried out by Tanvir et al. [59] allowed the isolation of endophytic Actinobacteria of *Parthenium hysterophoru: Ageratum conyzoides, Sonchus oleraceus* and *Hieracium canadense*. Most of the isolates were obtained from roots (69.7%) being the predominant genus *Streptomyces* while *Amycolatopsis*, *Pseudonocardia*, *Nocardia*, and *Micromonospora* were also isolated in lower frequency. From total isolates, 47.2% showed antimicrobial activity, while 52.1% and 66.6% showed potent cytotoxicity and antioxidant activity, respectively.

Numerous Actinobacteria genera have been isolated from marine environments such as marine sediments and several species of sponges. Vincent et al. [60] identified and isolated 180 Actinobacteria from 16 different species of sponges. Phylogenetic analysis revealed the presence of Actinobacteria belonging to the genera *Micromonospora, Verrucosispora, Streptomyces, Salinispora, Solwaraspora, Mycobacterium* and *Cellulosimicrobium.*

Janso et al. [61] performed isolation of 123 endophytic Actinobacteria from roots and leaves of tropical plants, which were more prevalent in roots and the following genera were identified: *Sphaerisporangium*, *Planotetraspora*, *Thermomonosporae*, *Micromonosporacea*. In addition to performing bioactivity tests and mass spectrometry liquid-chromatography (LC-MS) to profiles of crude extracts of fermentation in 91 strains. About 60% of the extracts exhibit bioactivity and LC-MS spectra profiles indicative of secondary metabolites.

Other bioactive compounds were obtained from endophytic Actinobacteria, as anguciclines with antimicrobial activity against *Bacillus cereus* and *Listeria monocytogeneses* [62]; Irumamicine, 14952b and X-17-hydroxy-venturicidina A the active compounds, which are all taken from the same strain of *Streptomyces* sp. [63]; 8-hydroxyquinoline with activity against pathogenic Gram-positive and Gram-negative bacteria [64].

The kakadumicine, a broad-spectrum antibiotic with action on *Plasmodium falciparum*, the causative agent of malaria, was produced by strain *Streptomyces* sp. (NRRL 30566), endophytic of *Grevillea pteridifolia* [65]. The munumbicines, peptidic antibiotic produced by *Streptomyces* sp. (NRRL 30562), obtained from medicinal plant *Kennedia nigriscans*, has a broad spectrum of action on Gram-positive bacteria such as *Bacillus anthracis* and multiresistant *Mycobacterium tuberculosis*. The munumbicine B proved to be active also against methicillin-resistant *Staphylococcus aureus* (MRSA) but the best activity was against *Plasmodium falciparium* [66].

6. ACTINOBACTERIA BIOTECHNO-LOGICAL IMPORTANCE

The first antibiotic was isolated from the genus *Streptomyces*, in the 1940s; From that moment, the Actinobacteria highlighted in the production of active compounds [67,68]. These microorganisms hold an extremely rich and diverse metabolism, producing secondary metabolites of extraordinary chemical variety, which attracted the attention of biotechnology branch [60], with applications in human medicine, animal and agriculture [58,69,70,71]. The most studied and representative genera with this potential are *Microbispora*, *Micromonospora*, *Nocardia* and *Streptomyces* [72].

Products from Actinobacteria include antibiotics, antifungals, extracellular enzymes (chitinases, peroxidases, glucanases), enzyme inhibitors, neurotransmitters, terpenoids, pigments, anti-tumor, plant growth promoters, pesticides, etc. [73]. From 45% of composites with biological activities derived from filamentous Actinobacteria, approximately 80% of 7,600 compounds are produced by *Streptomyces* sp. characterizing this genus as one of the most important in producing bioactive compounds [74]. Even with this metabolic diversity, only about 10% of the total number of natural products synthesized by these organisms were discovered [75].

Silva Lacerda et al. [76] assessed the antimicrobial potential of Actinobacteria isolated from *Caesalpinia pyramidalis* rhizosphere of the Caatinga Biome, evaluating 78 Actinobacteria for antimicrobial activity. The isolates of 52.9% (obtained at 37ºC) and 47.05% (produced at 45ºC) had activity against *Bacillus subtilis*, *Staphylococcus aureus* methicillin-resistant (MRSA), *Fusarium moniliforme* and *Candida albicans*. Highlighting the isolated C1.129 identified by 16S rDNA analysis as *Streptomyces parvulus*, fermented in liquid medium, a crude ethanolic extract showed a MIC of 0.97 µg / mL for MRSA and *B. subtilis*; An ethyl acetate extract showed MIC of 3.9 .µg / ml for *S. aureus* and MRSA, showing the great potential of metabolites produced.

There are several bioactive compounds industrially produced by Actinobacteria. The antibacterials, such as penicillins, cephalosporins, and many macrolides; antifungal agents, such as amphotericin B and nystatin; immunosuppressants, such as FK-506, ascomycin and rapamycin; Chemotherapeutic agents such as bleomycin, dactinomycin, doxorubicin, staurosporine; Herbicides, such as phosphinothricin; In the treatment of diabetes, such as acarbose; And anthelmintic agents such as avermectin and milbemycin [77].

Another source of promising uses of metabolites originating from Actinobacteria is from endophytic microorganisms, since they may act to improve crop yields by its host protection against pathogens. Therefore, the presence of endophytic Actinobacteria may represent an important agent in the development and maintenance of plant health and act on plant growth, through assimilation of nutrients and production of secondary metabolites.

Endophytic Actinobacteria, are considered as bio-inoculants to improve crop performance

through organic agriculture. The association of endophytes with plants allows the discovery of new taxons and its metabolites with new chemical structures of biotechnological importance [78].

The work of Soares et al. [79] demonstrated the effect of soil inoculation with six isolates of Actinobacteria, on tomato seedlings as compared with uninoculated soil control. After 30 days, the seedlings were collected to determine the height, stem diameter, dry weight of shoots and roots as well as accumulation of nutrients. The Actinobacteria isolated promoted significant increases in growth and accumulation of nutrients in tomato seedlings.

Thirty-four endophytic Actinobacteria were isolated from plant roots, of which twenty-nine isolates belonging to the *Streptomyces* genus and five belonging to other genus. All isolates were screened for antifungal activity against *Rhizoctonia solani*; six strains were selected for biocontrol of *R. solani* in sterile and non-sterile soil to promote the growth of tomato seedlings. In both soils, tomato seeds coated with endophytics significantly reduced the severity of tipping tomatoes [80].

The study by Conti et al. [81] using an endophytic Actinobacteria of *Lychnophora ericoides* evaluated the biotechnological potential of extracts from filamentous bacteria using antimicrobial and cytotoxic assays, as well as investigation of chemical profile. A percentage of 92% of the extracts showed high or moderate activity against at least one type of cancer cell or pathogenic microbial agents. Sixteen compounds, of which 2,3-dihydro-2,2-dimethyl-4 (1H)-quinazolinone, showed potent cytotoxic activity against all cancer cell lines tested.

Endophytics are equipped with degradation pathways, producing metabolites, which could promote cleaning of pesticides through bio-emulsifiers. Recently the use of endophytic Actinobacteria has been proposed for bioremediation. Fuentes et al. [82] performed assays using pure and Actinobacteria culture associations with the purpose to achieve bioremediation of chlordane (insecticide), using six *Streptomyces* sp., which showed no growth inhibition, and were assayed for removing chlordane. In pure cultures, all strains showed dechlorination activity and removal of chlordane.

7. CONCLUSIONS

Actinobacteria, microorganisms widely distributed in nature, inhabit mainly the soil. These prokaryotes are broadly responsible for the production of various metabolites commercially available, such as antibiotics. Endophytic Actinobacteria also produce active substances, and have important functions in the development of plants with agro industrial interest. This review provides data with a focus on spreading the importance of these microorganisms, as well as turn the attention to the fact that more studies are necessary for application of these Actinobacteria as innovative biotechnological tools.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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