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INTERFACES CIENTÍFICAS

ANTIMICROBIAL ACTIVITY OF ACTINOBACTERIA FROM COMPOSTING SOILS OF OIL PALM (*ELAEIS GUINEENSES*) AGAINST PATHOGENIC BACTERIA OF CLINICAL IMPORTANCE

ATIVIDADE ANTIMICROBIANA DE ACTINOBACTÉRIAS DE SOLOS DE COMPOSTAGEM DE ÓLEO DE PALMA (*ELAEIS GUINEENSES*) CONTRA BACTÉRIAS PATOGÊNICAS DE IMPORTÂNCIA CLÍNICA

ACTIVIDAD ANTIMICROBIANA DE ACTINOBACTERIAS DE SUELOS DE COMPOSTAJE DE PALMA ACEITERA (*ELAEIS GUINEENSES*) FRENTE A BACTERIAS PATÓGENAS DE IMPORTANCIA CLÍNICA

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ABSTRACT

Actinobacteria are Gram-positive bacteria known for forming filamentous structures named mycelium and hyphae. They stand out from other bacteria by their high production of secondary metabolites with antimicrobial properties. Composting sites are favorable to produce these metabolites due to the competition patterns held by the presence of a large number of microorganisms. The importance of actinobacteria turns out in the multidrug-resistant bacteria scenario, a consequence of selective pressure on pathogenic bacteria, directly related to the wrong antibiotic administration. This research aimed to evaluate the antimicrobial potential of actinobacteria isolated from composting soil against five clinical importance pathogenic bacteria. The experiment used the direct sensibility test method, and the antimicrobial potential was verified by the presence of an inhibition halo around the actinobacterial colonies. Among the isolates, seven strains showed inhibitory effects on the growth of at least one of the pathogenic bacteria tested. The results of this research demonstrated that actinobacteria can be an important source of antimicrobial biomolecules which can be used to develop new drugs.

KEYWORDS

Actinobacteria; Composting; Antimicrobial Potential; Oil Palm, Antibiotic resistance.

RESUMO

As actinobactérias são bactérias Gram-positivas conhecidas por formarem estruturas filamentosas, denominadas micélios e hifas. Elas se destacam em relação a outras bactérias pela sua alta capacidade de produzir metabólitos secundários com propriedades antimicrobianas. Os locais de compostagem são favoráveis à produção destes metabólitos, devido aos padrões de competitividade decorrentes da presença de um grande número de micro-organismos. A importância das actinobactérias se revela no cenário da resistência bacteriana, uma consequência da pressão seletiva sobre bactérias patogênicas, diretamente relacionada à administração incorreta de antibióticos. O objetivo deste trabalho foi avaliar o potencial antimicrobiano de actinobactérias isoladas de solos de compostagem sobre cinco bactérias patogênicas de importância clínica. O experimento foi realizado por meio do teste de sensibilidade direto e o potencial antimicrobiano foi verificado pela presença de halos de inibição ao redor das colônias de actinobactérias. Entre os isolados, sete cepas demonstraram ação inibitória sobre pelo menos uma das bactérias patogênicas testadas. Os resultados deste trabalho demonstraram que as actinobactérias podem ser importantes fontes de biomoléculas antimicrobianas que podem ser utilizadas no desenvolvimento de novos fármacos.

PALAVRAS-CHAVE

Actinobactérias. Compostagem. Potencial Antimicrobiano. Óleo de Palma. Resistência a Antibióticos.

RESUMEN

Las actinobacterias son bacterias Gram positivas conocidas por formar estructuras filamentosas denominadas micelios e hifas. Se distinguen de otras bacterias por su gran capacidad para producir metabolitos secundarios con propiedades antimicrobianas. Los lugares de compostaje son favorables para la producción de estos metabolitos debido a los patrones competitivos resultantes de la presencia de un gran número de microorganismos. La importancia de las actinobacterias se pone de manifiesto en el escenario de la resistencia a los antimicrobianos, consecuencia de la presión selectiva sobre las bacterias patógenas, directamente relacionada con la administración incorrecta de antibióticos. El objetivo de este estudio fue evaluar el potencial antimicrobiano de actinobacterias aisladas de suelos compostados sobre cinco bacterias patógenas de importancia clínica. El experimento se llevó a cabo mediante una prueba de sensibilidad directa y el potencial antimicrobiano se verificó por la presencia de un halo de inhibición alrededor de las colonias de actinobacterias. Entre los aislados, siete cepas mostraron acción antimicrobiana contra al menos una de las bacterias patógenas ensayadas. Los resultados de este estudio demuestran que las actinobacterias pueden ser importantes fuentes de biomoléculas antimicrobianas que pueden utilizarse en el desarrollo de nuevos fármacos.

PALABRAS-CLAVE

Actinobacterias; Compostaje; Potencial antimicrobiano; Palma aceitera, Resistencia a los antibióticos.

1 INTRODUCTION

The name "actinobacteria" derives from the Greek "Aktis" (trace) and "Mykes" (fungi) and it is used to characterize Gram-positive bacteria constituted of mycelium, with thin filamentous and branched structures named hyphae (TRUJILLO, 2008 GEORJON *et al.*, 2023). A fundamental aspect find in this group is the variety of morphologies, such as cocci and rod-shaped bacteria, mycelium forming and color, hyphae distribution, sporulation and medium diffusible pigment production (FERNANDES *et al.*, 2022; MARTINS *et al.*, 2022). They also have important physiological and metabolic properties, such as the production of enzymes and several antimicrobial agents (AZMAN *et al.*, 2015; ZOTHANPUIA *et al.*, 2018; SELIM *et al.*, 2021).

In composting sites, the nutrient availability and the constant physicochemical changes establish competition patterns between the bacteria living in the soil, prevailing those that have the capacity to synthesize substances that can inhibit the growth of other microorganisms (PROCÓPIO *et al.*, 2012; VURUKONDA *et al.*, 2018; MITRA *et al.*, 2022). The presence of other bacteria stimulates the production of bioactive compounds and secondary metabolites antagonistic to the growth of plant pathogens, fungi and other root colonizers (STAMFORD *et al.*, 2005; RODRIGUES, 2006; AMARAL *et al.*, 2020).

Actinobacteria stand out from other soil microorganisms by synthesizing antibiotic substances (MOKNI-TLILI et al., 2013; CAVALCANTE et al., 2017; SANTOS-ABERTURAS; VIOR, 2022). These bacteria are responsible for producing approximately two thirds of all natural antimicrobials used in medicine, veterinary and agriculture, with the genus *Streptomyces* being the largest producer of these bioactive molecules (MAST; STEGMANN, 2019; ALAM et al., 2022; DONALD *et al.*, 2022). The relevance of these compounds turns out in the multidrug resistant bacteria scenario, which is a major challenge for society, because of its high mortality rate (YANG *et al.*, 2021).

The bacterial multidrug resistance is one of the most relevant health problems today since many bacteria before susceptible to commonly used antibiotics have stopped responding to these same drugs (MORAES *et al.*, 2016; EISENREICH, 2022). The development of antibiotics resistance is a natural phenomenon resulting from selective pressure on bacteria (SANTOS, 2004; MAESTRI *et al.*, 2020), but it has undergone a very accelerated expansion due to the inappropriate use of these drugs, with a clear relation between the increase of the consumption of antimicrobial drugs with higher levels of bacterial resistance (ANVISA, 2007; KHARE *et al.*, 2021).

The World Health Organization published the new list of bacterial priority pathogens, which includes *A. baumannii* resistant to carbapenems and *Enterobacteriaceae* resistant to 3rd generation cephalosporins and carbapenems as critical priority, *S. typhi* and *Shigella* spp. resistant to fluoroquinolones, *E. faecium* resistant to vancomycin, *P. aeruginosa* resistant to carbapenems, Non-typhoidal *Salmonella* resistant to fluoroquinolones, *N. gonorrhoeae* resistant to 3rd generation cephalosporins and fluoroquinolones and *S. aureus* resistant to methicillin as high priority, and Group A *Streptococci and S. pneumoniae* resistant to macrolides, *H. influenzae* ampicillin-resistant and Group B *Streptococci* penicillin-resistant as medium group (WHO, 2024).

The possibility of isolating bacteria that produce substances with potential industrial and pharmaceutical use in uncommon environments is still not much performed. Considered as a source of selective pressure on microbiota, composting soils can be an important supply of biodiversity between actinobacteria. Therefore, the aim of this research was to demonstrate the production of antimicrobial compounds by actinobacteria strains against pathogens of clinical importance.

2 MATERIAL AND METHODS:

2.1 BACTERIAL STRAINS

The 15 bacterial strains used in this work were previously isolated and identified in our work (UESUGI *et al.*, 2023) and maintained in the bacterial collection of the Laboratory of Applied Microbiology and Genetics of Microrganisms from University of the State of Pará, Pará, Brazil. The strains were preserved in skimmed milk at -10°C and were reactivated on Reasoner 2 Agar and incubated at 35°C for 48 hours.

2.2 ANTIBACTERIAL POTENTIAL

To determine the antimicrobial compound production by the isolated bacteria, the direct sensibility test methodology was performed, from which the ability to inhibit the growth of pathogenic bacteria by the isolated actinobacteria was evaluated. The selected actinobacteria were tested against strains of pathogenic bacteria with clinical relevance that are among the priority pathogens of the World Health Organization (WHO) for research and development of new antimicrobials (WHO, 2024), represented in Table 1.

Table 1 – Pathogenic bacteria strains chosen for the Direct Sensibility Test and their sensibility profile

STRAIN	ATCC®	DESCRIPTION
Escherichia coli	25922	Does not produce verotoxin and it is a CLSI control strain for susceptibility testing.
Enterococcus faecalis	29212	Vancomycin susceptible.
Klebsiella pneumoniae carbapenemase	-	Producer of carbapenem resistance enzymes.
Pseudomonas aeruginosa	-	Sensitive only to polymyxin.
Staphylococcus aureus	25923	Susceptible to wide range penicillin.

aATCC: American Type Culture Collection; CLSI: Clinical Laboratory Standarts Institute.
Source: Prepared by the authors

All pathogenic bacteria strains tested were obtained from the bacterial collection from the Laboratory of Applied Microbiology and Genetics of Microorganisms, from University of the State of Pará, Brazil.

2.3 DIRECT SENSIBILITY TEST

The pathogenic bacteria strains were seeded in TSA and performed by disposable loops using the streak method. Then, the agar plates were incubated at 36°C for 24h. After the growth, it was made a bacterial suspension of 0.5 on McFarland scale in saline solution 0.9% and this inoculum was seeded in Mueller Hinton Agar (MHA) plates performed by mat spreading technique according to the method of Martins *et al*. (2022).

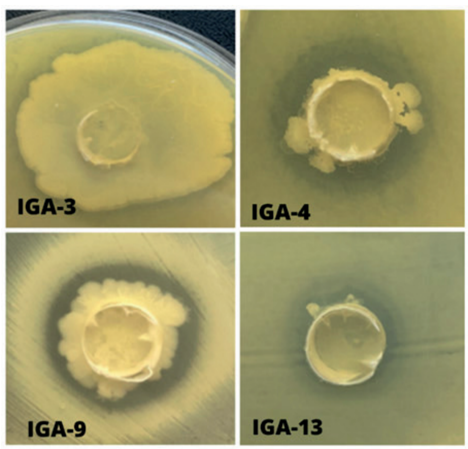
Then, using sterile test tubes, wells about 1 cm in diameter were made in the agar plates about 3 cm apart. These wells were filled with fragments of the same size taken from the actinobacteria growth media containing the bacterial colonies.

The technique was performed with all test strains, which were properly identified and incubated at 30°C for 48h. After the incubation period, the antibacterial potential of the tested actinobacteria was evaluated through the measurement, in millimeters, of the inhibition halos formed around the actinobacteria colonies.

3 RESULTS

The interpretation of the Direct Sensibility Test was performed after 48h of incubation, in which we sought to analyze the presence of inhibition halos of the pathogenic bacteria around the regions where the agar fragments containing the actinobacteria were placed (Figure 1).

Figure 1 – Inhibition halos of the actinobacteria against the pathogenic strains, indicated by the clearer zones around the colonies (arrow)



Source: Research data

It was observed that seven strains (46.6%) presented inhibitory potential against at least one of the pathogenic bacteria tested, whereas eight strains (53.3%) did not inhibit the growth of any bacteria. The best inhibition spectrum was against *Escherichia coli,* showed by five strains (33.3%) and the lowest was on *Enterococcus faecalis* with only one strain (6%), as illustrated in Table 2.

Table 2 – Inhibition halos in millimeters of actinobacteria strains against pathogenic bacteria.

STRAIN	Escherichia coli	Enterococcus faecalis	Klebsiella sp.	Pseudomonas aeruginosa	Staphylococcus aureus
IGA-1	-	-	-	-	-
IGA-2	-	-	-	-	-
IGA-3	43 mm	-	-	16 mm	-
IGA-4	20 mm	-	-	19 mm	-
IGA-5	-	-	-	-	-
IGA-6	15 mm	18 mm	17 mm	-	15 mm
IGA-7	-	-	-	-	-
IGA-8	-	-	-	-	-
IGA-9	-	-	-	-	23 mm
IGA-10	-	-	-	-	-
IGA-11	-	-	-	-	16 mm
IGA-12	-	-	-	-	-
IGA-13	16 mm	-	17 mm	-	-
IGA-14	-	-	-	-	-
IGA-15	13 mm	-	16 mm	-	-

amm: Diameter in millimeters; (-) Halo absence. Source: Research data

4 DISCUSSION

According to Zaheera *et al*. (2020), *Enterococcus spp.* is intrinsically resistant to cephalosporins and trimethoprim-sulfamethoxazole and shows low resistance to β-lactams and aminoglycosides. In the research by Daquioag and Penuliar (2021) with soil actinobacteria, the inhibition spectrum against *E. faecalis* was the lowest among all tested bacteria, with a 17,5 mm halo, similar to what was obtained in this work. Compared to the existing literature, our results indicate that enterococci may be more resistant to the antimicrobials in general, including those produced by actinobacteria.

In Alhumaid *et al*. (2021) and Gebremariam *et al*. (2022) experiments, different drugs were tested on *Staphylococcus aureus* and *Enterococcus sp.* Among them, vancomycin showed an inhibition zone of 12 mm and 15 mm on *Enterococcus sp.* and on *S. aureus* respectively, and linezolid with an inhibition zone of 20 mm to *Enterococcus sp.* and a halo equal or larger than 21 mm to *S. aureus* (CLSI, 2005; EUCAST, 2023). All actinobacteria strains tested had shown an inhibition halo superior to 12 mm, similar to vancomycin, on the other hand only one of them presented an inhibition halo superior to 20 mm, similar to linezolid.

Chavarría-Pizarro *et al*. (2024) tested the antibacterial effect of different actinobacterial strains from wasps against *E. coli.* In their work, the inhibition halos of positive strains ranged from 12.5 mm to 28.3 mm. The antibacterial spectra observed in this work were similar, with larger halos ranging from 13 mm to 43 mm. The halos produced by the tested bacteria were also close to the standard expected from drugs traditionally used against *E. coli.* Our results show that antibacterial compounds produced by actinobacteria are potential candidates for the development of new antibiotics (BrCAST, 2024).

An important finding was the inhibition of multidrug-resistant *Pseudomonas aeruginosa* by two actinobacteria strains. This bacterium is an opportunistic pathogen that affects cystic fibrosis and immunocompromised patients and it has a high resistance pattern to a variety of antibiotics, such as aminoglycosides, quinolones and beta-lactams (DIGGLE; WHITELEY, 2020; ASAMENEW *et al*., 2023). One of the drugs of choice to treat the infection is Polymyxin B, considered effective in the formation of halos ranging from 14 to 18 mm (PANG *et al*., 2019; EUCAST, 2023). Both actinobacteria that inhibited the growth of *P. aeruginosa* in this work formed inhibition halos greater than 14 mm, which indicates that they have a similar antibacterial effect to the drug.

Studies indicate that actinobacteria have greater activity against Gram-positive pathogens compared to Gram-negative (OUCHARI *et al*., 2019; AIT ASSOU, 2023). This contrast is related to the structural differences between the cells, as Gram-positive bacteria have a thick cell wall constituted by peptidoglycan, while Gram-negative bacteria have a lipopolysaccharide rich external membrane, which makes them impermeable (BUDHATHOKI; SHRESTHA; 2020; SAPKOTA *et al*., 2020). Nevertheless, actinobacteria isolated in this work presented a better inhibition spectrum against Gram-negative, such as *E. coli* and *Klebsiella sp.*, different from what was found in the literature.

Production of secondary metabolites by actinobacteria is related to morphological and physiological variations, which include nutrient concentration, such as carbon and nitrogen, presence of competitors and cell density (VAN DER MEIJ *et al*. 2017; SIMEIS; SERRA, 2021). Their capacity of adaptation to these conditions is due to the production of antimicrobial molecules, which is reflected in the production of different antibiotics, such as cyclopolylactones, aminoglycosides, streptotricins, actinomycins and quinoxaline peptides, which have different spectra of action (CHINNATHAMBI *et al*., 2023).

The genus *Streptomyces* is known for being the greater producer of bioactive compounds and secondary metabolites among actinobacteria (EBRAHIMI-ZARANDI *et al*., 2023). They can be found in different habitats, including fresh water, rhizosphere and compost, as well as in exotic environments, such as hot springs and bird feathers (GOPALAKRISHNAN *et al*., 2020; KORTAM *et al*., 2023; SARMIENTO-VIZCAÍNO *et al*., 2023). The high production of antibacterial compounds by actinobacteria from composting may be related to the presence of this genus between the isolates (UESUGI *et al*., 2023).

The synthesis of antibiotics by Streptomyces strains occurs through several enzymatic complexes, such as polyketide synthases, non-ribosomal peptide synthases, or both (QUINN *et al.*, 2020). The biosynthesis of polyketides and non-ribosomal peptides involves the enzymes PKS and NRPS, respectively, which have similar biosynthetic pathways, but different chemical structures, that allow them to interact with different sites on the same target, enhancing their spectra (ROBERTSEN; MUSIOL--KROLL, 2019). Polyketides are important natural products, since they have wide applicability to microorganisms, such as bacteria, fungi and parasites (SELIM *et al*., 2021).

The study by Montiel-Riquelme *et al*. (2020), the authors considered that the best diameter to assess the susceptibility of *K. pneumoniae* carbapenemase (KPC) to cephalosporins and carbapenems must be equal or superior to 16 mm. In our work, the strains that inhibited the growth of KPC produced halos between 16 and 17 mm, similar to the expected antibiotics. Thus, the isolated bacteria produced an effective number of antimicrobial substances that could possibly be applied in the elaboration of drugs for multi-resistant bacteria.

The inhibitory action of the actinobacteria on pathogenic strains can be classified into three types: good, moderate and low/absent (ARANGO *et al*., 2018). It is considered good when the inhibition halo formed is larger than 20 mm, between 10 and 20 mm it is considered moderate and less than 10 mm it is low or absent. In general, it was observed that all actinobacteria strains that showed an inhibition potential against other bacteria produced moderate to good activity, with all zones of inhibition bigger than 10 mm.

The emergency of microbial resistance to multiple drugs is a great challenge to global public health (WISE *et al*., 2024). According to Anderson *et al*. (2023) developing drugs with structures that inhibit specific cellular targets could be a promising strategy. Although the exploration of new environments increases the repository of actinobacteria that potentially produce secondary metabolites, it is through the combination of metabolomics and genetic engineering techniques that new biomolecules with antimicrobial properties can be discovered (JOSE *et al*., 2021).

Antimicrobial production by actinobacteria is controlled by transcriptional regulators in response to physiological and environmental signals (WU *et al*., 2021). The high adaptability of actinomycetes in hostile environments makes them promising for the production of antimicrobial compounds (VERMA *et al*., 2018; HUI *et al*., 2021). Therefore, Al-Shaibani *et al*. (2021) emphasize the need to look for potentially antibiotic-producing strains in less explored locations, such as thermophilic, alkalophilic and halophilic, where growth conditions are more extreme.

According to Hu *et al*. (2020), rare actinomycetes or non-*Streptomyces* are also potential producers of antimicrobial molecules that have not been well studied. Among the drugs produced by these group of actinobacteria there are macrolides, rifampicin and glycopeptides (PARRA *et al*., 2023). The possibility of isolating common and rare actinobacteria from unconventional environments could be an interesting proposal for future research on the development of new antimicrobial drugs, taking into account the promising results with the actinobacteria found in this work.

5 CONCLUSION

Microbial resistance to antibiotics continues to be a major challenge for public health worldwide. For this reason, the search for biomolecules with antimicrobial action is a very suitable alternative in this scenario. The results obtained in our work show that actinobacteria are promising sources of antibacterial compounds that can be used to develop new drugs. Therefore, it should be emphasized that research into new antibiotics produced from bacterial strains should be more encouraged and carried out in our country, given the great microbial diversity in our ecosystems and the possibility of finding new bacterial species with such unique properties.

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