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ANTIMICROBIAL ACTIVITY OF GLANDULAR SUBSTANCES FROM *ATTA SEXDENS* (HYMENOPTERA: FORMICIDAE)

ATIVIDADE ANTIMICROBIANA DE SUBSTÂNCIAS GLANDULARES DE *ATTA SEXDENS* (HYMENOPTERA: FORMICIDAE)

ACTIVIDAD ANTIMICROBIANA DE SUSTANCIAS GLANDULARES DE *ATTA SEXDENS* (HYMENOPTERA: FORMICIDAE)

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ABSTRACT

As a defense strategy, *Atta* ants evolved with the production of glandular secretions that act as antibiotics. In this context, the aim of this study was to evaluate the antimicrobial activity of glandular secretions from *Atta sexdens* specie. The glandular secretions were extracted from the mandibular and metapleural glands, tested for antimicrobial activity by the diffusion method. Inhibition tests were performed against two pathogenic bacteria, *Staphylococcus aureus* and *Escherichia coli*. The mandibular gland secretion showed activity against *Staphylococcus aureus* and *Escherichia coli* (with inhibition halos of 11.1 and 18.8 mm, respectively). The secretion metapleural gland secretions showed activity against *Staphylococcus aureus* with inhibition halos of 11.1mm. *Atta sexdens* ants represent an alternative source for the prospection of compounds with antibacterial potential. The substances identified in the metapleural and mandibular glands secretions are predominantly acidic and expressed in the form of sterile fatty acids (carboxylic and phenolic). The tested glandular secretions showed antimicrobial activity against *S. aureus* and *E. coli*. It is noteworthy that this research is a pioneer in addressing the antibiotics potential bioprospection for an ant specie that occurs in southern Brazil.

KEYWORDS

Antibiotics; Biodiversity; Bioprospection; Ants.

RESUMO

Como estratégia de defesa, as formigas *Atta* evoluíram com a produção de secreções glandulares que atuam como antibióticos. Nesse contexto, o objetivo deste estudo foi avaliar a atividade antimicrobiana das secreções glandulares da espécie *Atta sexdens*. As secreções glandulares foram extraídas das glândulas mandibular e metapleural e testadas quanto à atividade antimicrobiana pelo método de difusão. Os testes de inibição foram realizados contra duas bactérias patogênicas, *Staphylococcus aureus* e *Escherichia coli*. A secreção da glândula mandibular mostrou atividade contra *Staphylococcus aureus* e *Escherichia coli* (com halos de inibição de 11,1 e 18,8 mm, respectivamente). As secreções da glândula metapleural mostraram atividade contra *Staphylococcus aureus* com halos de inibição de 11,1 mm. As formigas *Atta sexdens* representam uma fonte alternativa para a prospecção de compostos com potencial antibacteriano. As substâncias identificadas nas secreções das glândulas metapleural e mandibular são predominantemente ácidas e expressas na forma de ácidos graxos estéreis (carboxílicos e fenólicos). As secreções glandulares testadas apresentaram atividade antimicrobiana contra *S. aureus* e *E. coli*. Vale ressaltar que esta pesquisa é pioneira na abordagem do potencial de bioprospecção de antibióticos para uma espécie de formiga que ocorre no sul do Brasil.

PALAVRAS-CHAVE

Antibióticos; Biodiversidade; Bioprospecção; Formigas.

RESUMEN

Como estrategia de defensa, las hormigas *Atta* evolucionaron con la producción de secreciones glandulares que actúan como antibióticos. En este contexto, el objetivo de este estudio fue evaluar la actividad antimicrobiana de las secreciones glandulares de la especie *Atta sexdens*. Las secreciones glandulares se extrajeron de las glándulas mandibulares y metapleurales, y se analizó su actividad antimicrobiana por el método de difusión. Se realizaron pruebas de inhibición contra dos bacterias patógenas, *Staphylococcus aureus* y *Escherichia coli*. La secreción de la glándula mandibular mostró actividad contra *Staphylococcus aureus* y *Escherichia coli* (con halos de inhibición de 11,1 mm y 18,8 mm, respectivamente). La secreción de la glándula metapleural mostró actividad contra *Staphylococcus aureus* con halos de inhibición de 11,1 mm. Las hormigas *Atta sexdens* representan una fuente alternativa para la prospección de compuestos con potencial antibacteriano. Las sustancias identificadas en las secreciones de las glándulas metapleurales y mandibulares son predominantemente ácidas y se expresan en forma de ácidos grasos estériles (carboxílicos y fenólicos). Las secreciones glandulares analizadas mostraron actividad antimicrobiana contra *S. aureus* y *E. coli*. Es importante

destacar que esta investigación es pionera en abordar la bioprospección del potencial antibiótico de una especie de hormiga presente en el sur de Brasil.

PALABRAS CLAVE

Antibióticos; Biodiversidad; Bioprospección; Hormigas.

1 INTRODUCTION

Bioprospecting refers to the idea of searching for substances in plants, animals or microorganisms that are potentially useful to humanity (ASTOLFI FILHO *et al.*, 2014; MILLER *et al.*, 2017; HUG *et al.*, 2018). The relationship between organisms and the environment produce secondary metabolites. These can originate active principles with potential for bioprospecting and biotechnological application (MILLER *et al.*, 2017).

Most bioprospecting research of new drugs focuses on analysis of botanical biodiversity (SITTENFELD *et al.*, 1999; TAVARES, 2014). However, there is the possibility of diversifying the natural sources of secondary metabolites. Little is known about these compounds in insects, other invertebrates and vertebrates, as well as microorganisms (ZIEMERT *et al.*, 2014; PENESYAN *et al.*, 2015). Species of eusocial organisms such as ants have evolved antimicrobial compounds by natural selection (STOW *et al.*, 2007) and represent an opportune group for conducting bioprospecting research (STOW; BEATTIE, 2008).

Ants have about 85 exocrine glands that secrete chemical substances (ADAMS *et al.*, 2012; BILLEN; SOBOTNÍK, 2015; BILLEN, 2019). The evolutionary origin suggests that most of these glands are used for defense against pathogens (YEK; MUELLER, 2011; VANDER MEER, 2012; BILLEN, 2019). The ecological niche and selective pressure can act as a regulator and influence the composition and quantity of gland secretions (YEK; MUELLER, 2011; BILLEN, 2017). The same compound can be produced by different glands and have different functions. Ants are able to use compounds and varying concentrations to alter the function of their gland secretions (ADAMS *et al.*, 2012).

The growing resistance to antimicrobials justifies the search for new products with antibiotic properties (LIMA *et al.*, 2015; BROWN; WRIGHT, 2016). In the hospital environment, the strains resistant to multiple antibiotics increase the morbidity and costs inherent in healthcare, as well as mortality rates from infections (ALMEIDA; FARIAS, 2014; ANVISA, 2017). However, resistance to conventional antibiotics goes beyond the hospital setting and is characterized as a global public health problem (DIAS *et al.*, 2010; ALMEIDA; FARIAS, 2014; ANVISA, 2017), making necessary research at finding new alternatives to improve antibiotic therapy a constant necessity (PEREIRA; OLIVEIRA, 2016; LIMA *et al.*, 2017).

The *Atta* ants belong to the tribe Attini, which is part of the subfamily Myrmicinae. All Attini species are obligate symbionts of mutualistic Basidiomycota fungi (Agaricales) (HÖLLDOBLER; WILSON 1990; VANDER MEER, 2012; SILVESTRE *et al.*, 2015). The society formed by leaf-cutting ants is one of

the most complex and elaborate (HÖLLDOBLER; WILSON 1990). The mutualistic association between leaf-cutting ants and fungi has evolved to such a complex level that the two can no longer survive separately (MOREIRA *et al*., 2011; TRAGUST, 2016).

The genus *Atta* comprises 19 species, of which, nine occur in Brazil (BACCARO *et al*., 2015; SILVESTRE *et al*., 2015). Morphologically, *Atta* ants are characterized by having three pairs of spines on the mesosoma and the first tergite of the gastrula smooth, without tubercles (FERNÁNDEZ, 2003; BACCARO *et al*., 2015). These ants are popularly known as "saúvas", "içás" or "tanajuras" (BACCARO *et al*., 2015; SILVESTRE *et al*., 2015).

In Brazil, the species *Atta sexdens* (Linnaues, 1758) is widely distributed (MARICONI, 1970; SILVESTRE *et al*., 2015). An *A. sexdens* colony can contain up to one million individuals (FOWLER *et al*., 1986). In inventories carried out in southern Brazil, this specie was found in environments such as green areas, forest fragments, squares, parks and gardens (LUTINSKI *et al*., 2017).

Attini ant colonies constitute ideal microenvironments for the development of symbiotic microorganisms or that expose the colony to potentially lethal diseases (HÖLLDOBLER; WILSON 1990; TRANTER *et al*., 2015; PENICK *et al*., 2018). This suggests that *Atta* ants evolved greater or more efficient protection to ensure the development of individuals and maintain the colony health. The way to achieve this may have been by increasing the size of the matapleural gland with a more potent and efficient antimicrobial (VANDER MEER, 2012; TRAGUST, 2016). The mandibular glands of *Atta* ants also have a wide range of toxic chemical compounds with repellent and antimicrobial effects (MENDONÇA *et al*., 2009; QUINET *et al*., 2012; TRAGUST, 2016). For these reasons, these ants have motivated research aimed at identifying antimicrobial substances from their gland secretions. In this context, this study evaluated the antimicrobial activity of mandibular and metapleural glands secretions from *A. sexdens* specie.

2 METHODS

The ants were sampled by actively searching previously mapped colonies in the municipalities of Guatambu (27° 5'27.36" S; 52° 38'24.76" O) and Palmitos (27° 4'37.61" S; 53° 9'19'.10.76" O), Santa Catarina, from 9am to 5pm, from October 2021 to January 2022. Individuals (workers) were collected while foraging near the colonies (MENDONÇA *et al*., 2009; VIEIRA *et al*., 2012). The ants were stored in glass vials with lids, duly labeled (date, collector, place of collection) and confirmed at the specific level according to the keys proposed by Della Lucia (1993) and Antweb (2019). The material was frozen to kill the ants and facilitate sorting and separation of the body parts where the glands were found.

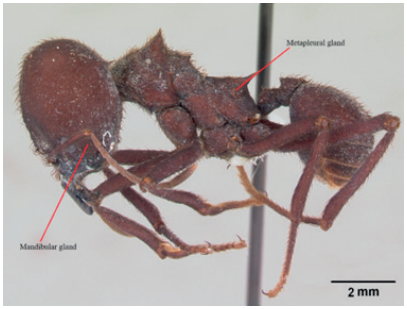
The sampling did not have an impact on local diversity because it´s a species with colonies with numerous individuals (FERNÁNDEZ, 2003; BACCARO *et al*., 2015), abundant colonies, frequently found in studies carried out in the western region of Santa Catarina (CALDART *et al*., 2012; LUTINSKI *et al*., 2017).

2.1 PROCEDURE FOR REMOVING BODY PARTS

To remove the region of the body where the gland is located, the ants were manipulated using fine-tipped tweezers in a glass Petri dish. The cephalic capsule and the mesosoma were removed. The separated body parts were placed in a glass vial and stored in a freezer for later extraction of the gland secretions with solvent.

The Mandibular glands are located in the frontal region of the cephalic capsule and the Metapleural glands in the postolateral region of the thorax called the metathorax, as shown in Figure 1.

Figure 1 - *Atta sexdens*: Gland location in lateral view of body.



2.2 GLAND SECRETIONS EXTRACTION

Fifteen grams of each body part containing the glands were macerated and immersed in 250 ml of dichloromethane (CH2Cl2) during 72 hours to remove the gland secretions. The solution was filtered under vacuum to remove the solvent and concentrate the sample. To eliminate possible solvent residues, the glandular secretion were left in an oven at 35°C during two hours. The glandular secretions were sealed and stored at - 80 °C (SONG *et al.*, 2012).

2.3 CHEMICAL CHARACTERIZATION

The chemical characterization of the gland secretions was carried out using 20 µg of the crude extract and 1 mL of methanol (MeOH), conditioned in glass vials suitable for analysis using gas chromatography (GC) coupled with electrospray ionization mass spectrometry (EM/ESI). The samples were subjected to an ultrasound bath during two minutes to homogenize and then analyzed using GC-MS. This method makes it possible to separate a multicomponent mixture from a natural extract. The separation is related to the physicochemical characteristics of each substance. The fragments generated in CG-ESI provide characteristic information about the substance that is useful in identifying most volatiles (HOENIGSBERGER *et al.*, 2018; CHEVRETTE *et al.*, 2019). The GC-ESI analyses were carried out in the Environmental Ecology Laboratory of Unochapecó.

2.4 MICROBIAL INHIBITION TESTS

The inhibition tests were carried out with *Staphylococcus aureus* (F. J. Rosenbach) (ATCC: 25923) and *Escherichia coli* (T. Escherich) (ATCC:25922) of commercial origin. Gram-positive bacteria (*S.*

aureus) have a cell wall with several peptidoglycan layers, which makes them rigid and thick. Gram-negative bacteria (*E. coli*) have only a thin layer of peptidoglycan (SILVA; NEUFELD, 2006), which interferes with the degree of toxicity of glands secretions (LIMA *et al.*, 2017).

In order to assess the antimicrobial activity of the extracts, diffusion tests were carried out on solid media, according to National Committee for Clinical Laboratory Standards (CLSI, 2012) recommendations. *Escherichia coli* and *S. aureus* bacteria were grown in Brain Heart Infusion (BHI) broth and placed in a bacteriological oven for 24 hours at 37±1 ºC.

After this period, some bacterial colonies were isolated to adjust the concentration of the bacterial suspension for reading on the spectrophotometer. For this, the colonies were grown on Mueller Hinton (MH) agar plates. After solidifying the agar, a small sample of the bacterial suspension was removed using a loop and placed on the culture medium. Using a Drigalski loop, this sample was spread over the culture medium to isolate the colonies. The plates were incubated in bacteriological oven during 24 hours at a temperature of 37±1 ºC (CLSI, 2012).

To adjust the bacterial suspension to 104 CFU mL-1 (Colony Forming Units per mL), the colonies were removed from the plates using a disposable loop and diluted in test tubes with sterile saline water (0.85%). To obtain this concentration, the absorbance was read on a spectrophotometer at a wavelength of 619 nm, with values between 0.04 and 0.049 (CLSI, 2012).

After adjusting, the bacteria were seeded on Mueller Hinton (MH) agar plates and, using a swab, the suspension was spread over the culture medium, sowing in three directions to ensure total coverage of the microorganism on the plate. Three equidistant holes with an average diameter of 9 mm were made in each plate, where the extracts were placed (CLSI, 2012).

Filter paper was placed over the top of the plates to prevent water droplets from coming into contact with the agar and disturbing the reading of the inhibition halos. The plates were incubated for 24 hours at 37±1 ºC. The tests were carried out in triplicate and the inhibition halos were measured using a caliper (CLSI, 2012). As a control, was used only the agar and the solvent used to extract the substances, to observe the presence of possible solvent traces and its effect on the development of the microorganisms.

2.5 DATA ANALYSIS

The data was analyzed and presented descriptively using tables built in Excel For Windows® (Microsoft Inc.). In the diffusion test, the average surface growth inhibition around the well was evaluated (CLSI, 2012), followed by the standard deviation ($p \leq 0.05$).

2.6 ETHICAL ISSUES

The sampling was authorized by ICMBio (Chico Mendes Institute for Biodiversity Conservation, "Authorization for activities for scientific purposes" n° 73721 of 16/12/2019. The research is registered in SISGEN (National System for the Management of Genetic Heritage and Associated Traditional Knowledge), n° A3B3F91.

3 RESULTS

The main substance identified in the mandibular and metapleural glands secretion of *A. sexdens* ants was mellein (Figure 2 and Figure 3).

Figure 2 - Main substances (%) in samples of *Atta sexdens* mandibular gland secretion extracted with dichloromethane, March 2022.

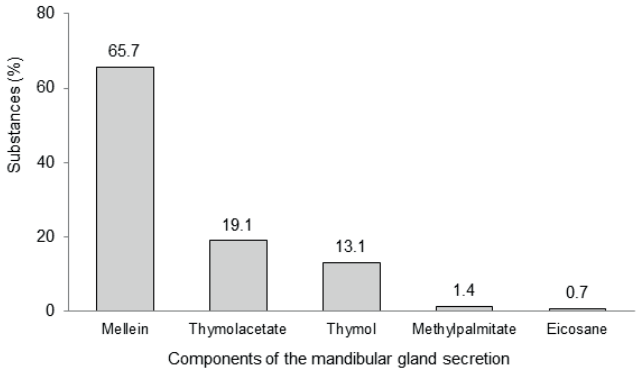
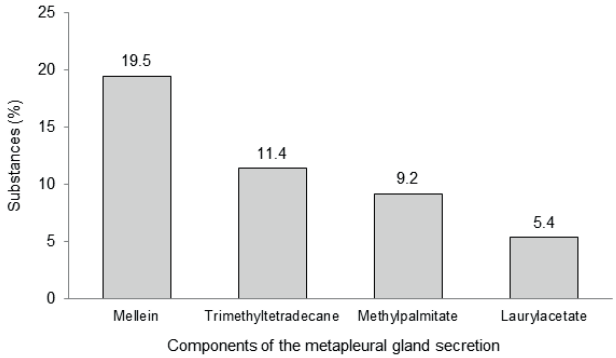


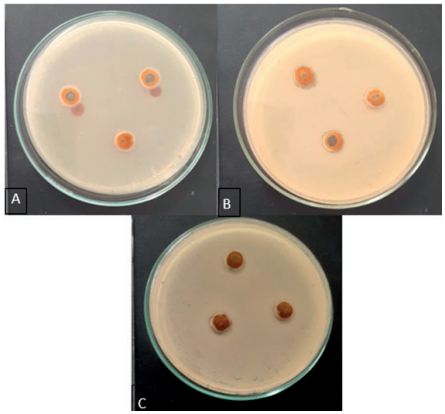
Figure 3 - Main substances (%) in samples of *Atta sexdens* metapleural gland secretion extracted with dichloromethane, March 2022.



The mandibular gland secretion inhibited the two strains tested, *S. aureus* (11.1mm ±0.01mm) and *E. coli* (10.8mm ±0.3mm). The metapleural secretion showed activity with the formation of a narrow halo for *S. aureus* (11.1mm ±0.4mm). In the control treatment, no inhibitory effect on micro-organisms was observed in this condition.

On the plate with the mandibular gland secretions, a more defined and visible inhibition halo of was formed (Figure 4A and Figure 4B). The plate with the metapleural gland secretion showed activity with the formation of a translucent and less noticeable halo around each well (Figure 4C).

Figure 4 - *Atta sexdens* mandibular and metapleural gland secretions glands activities on *Staphylococcus aureus* and *Escherichia coli*. A) Inhibition halo of the mandibular gland secretion on *Escherichia coli*. B) Inhibition halo of mandibular gland secretion on *Staphylococcus aureus*. C) Inhibition halo of metapleural gland secretion on *Staphylococcus aureus*.



4 DISCUSSION

The secretion of the *A. sexdens* mandibular gland showed antimicrobial activity on *S. aureus* and *E. coli* with the formation of an inhibition halo. The secretion from the metapleural gland showed evidence of antimicrobial activity on *S. aureus* with the formation of a narrower inhibition halo.

Atta species (Attini tribe) occur in Neotropical region and live in colonies formed by large individual's number, related to each other and in obligatory mutualism with fungal culture. These factors within the colony constitute ideal microenvironments for symbiotic microorganisms development or those that expose the colony to disease (HÖLLDOBLER; WILSON, 1990; TRANTER *et al.*, 2015; PENICK *et al.*, 2018). As an adaptation and survival strategy, the evidences indicate the evolution of a more elaborate individual immune defenses in these species (VANDER MEER, 2012; TRAGUST, 2016). We identified predominantly substances acidic and expressed in the form of fatty acids and carboxylic and phenolic sterols in the metapleural and mandibular glands secretion of *A. sexdens* ants. These correspond to the substances normally found in metapleural and mandibular glands secretions of fungus-growing ants that live in large, complex societies (MENDONÇA *et al.*, 2009; PENICK *et al.*, 2018).

The metapleural gland secretion of ant species of Attini tribe is known mainly for the production of antibiotics capable of inhibiting fungi and bacteria that develop inside the colonies (YEK *et al.*, 2012; TRANTER *et al.*, 2015). The antimicrobial action of Attini metapleural gland secretion has already been confirmed in bacteria and fungi that cause pathogenic diseases in humans (NASCIMENTO *et al.*, 1996; ORTIUS-LECHNER *et al.*, 2000). Nascimento *et al.* (1996) confirmed the antimicrobial activity of the main constituents of *Atta cephalotes* (Linnaeus, 1758) and *Acromyrmex octospinosus* (Reich,

1793) metapleural gland secretions on *S. aureus* and *Candida albicans*. In this way, our results corroborated these authors about antimicrobial activity on *S. aureus*.

The *Atta* spp. mandibular gland secretion also has a wide range of compounds with antimicrobial action (MARSARO-JUNIOR *et al.*, 2001; MENDONÇA *et al.*, 2009; QUINET *et al.*, 2012; TRAGUST, 2016), including resistant strains to conventional antibiotics (MENDONÇA *et al.*, 2009). The mandibular glands these ants also have a proven toxic, repellent effect (MENDONÇA *et al.*, 2009; QUINET *et al.*, 2012; TRAGUST, 2016). We verified that the *A. sexdens* mandibular gland secretion showed antimicrobial activity on *S. aureus* and *E. coli*, supporting the substances action spectrum.

The antimicrobial action of Attini ants gland secretions is attributed to the main constituents, acidic nature of these secretions (MARSARO-JUNIOR *et al.*, 2001; MENDONÇA *et al.*, 2009; TRAGUST, 2016). The way in which ants use the antibiotics produced by the mandibular and metapleural glands is still not well understood (MENDONÇA *et al.*, 2009; PENICK *et al.*, 2018). Studies on identifying the antimicrobial action of *A. sexdens* gland secretions are scarce in the scientific literature.

The scientific literature states that the function of the mandibular and metapleural glands secretions of Attini tribe ants is to preserve the mutualistic relationship between ants and fungi and to protect the colony against the invasion of pathogenic microorganisms (MENDONÇA *et al.*, 2009; TRANTER *et al.*, 2015). To this goal, they have evolved glandular secretions production that can act as antibiotics (MENDONÇA *et al.*, 2009; PENICK *et al.*, 2018). The antimicrobial action identified in *A. sexdens* mandibular and metapleural glands secretions can be attributed to the presence of substances such as mellein, identified as the main constituent. Mellein, when present in insects such as wasps and termites, is known to exhibit a broad antimicrobial spectrum (WEISS *et al.*, 2014; MITAKA *et al.*, 2018). However, its action of ant's gland secretions is little known and may represent an alternative source for bioprospecting substances with antibiotic action.

Compounds such as thymol, thymol acetate and methyl hexadecanoate were also identified in the gland secretions of *A. sexdens*. These substances are characterized as natural phenols with proven antimicrobial activity (SANTOS *et al.*, 2014; ESCOBAR *et al.*, 2020) and may contribute to the antimicrobial activity verified in this study. These compounds also have antioxidant, anti-inflammatory and healing activity when extracted from plant sources (SANTOS *et al.*, 2014; ESCOBAR *et al.*, 2020). However, there is a lack in the scientific literature identifying these compounds in insects, with ants being an option to diversify their origin.

Regarding the method used to extract the gland secretions in this study, even though it´s recommended for extracting larger volumes, it may have contributed to extract less pure compounds (LIU *et al.*, 2017). This may have contributed to the less effective results found in this study, evidenced by the formation of a small inhibition halo on microorganisms tested, suggesting the need for additional purification steps of the extracted substances.

The lower antimicrobial activity for the metapleural gland secretion may be related to the fact that the metapleural gland does not block the release of secretions, which flow freely from the ant's movements (YEK; MUELLER, 2011). This may have contributed to the loss of volumes from this gland secretion during the collecting procedure, sorting and removing the ants' metathorax. It was necessary to macerate a greater number of body parts in order to achieve the amount of secretion needed for the

experiment, increasing the presence of other substances in the constitution of the gland secretion and reducing the effectiveness of the antimicrobial action.

5 CONCLUSION

The *A. sexdens* gland compounds correspond to substances already identified in other species belonging to the same tribe.

The mandibular gland secretion showed antimicrobial action for two microorganisms tested. The metapleural gland secretion showed antimicrobial activity on *S. aureus*.

Atta sexdens ants represent an alternative source for bioprospecting substances with antibiotic potential. In this context, we highlight the richness of ant fauna that occur in the southern region of Brazil and the fact that this research is a pioneer in addressing the potential for bioprospecting antibiotics found in these insects in this region.

The results open up possibilities for further studies aimed at isolating and testing active molecules from *A. sexdens* glands secretions, as well as testing the action spectrum of these substances.

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