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IN VITRO EVALUATION OF THE ANTIMICROBIAL POTENTIAL OF EXTRACTS OF *Hymenaea courbaril* L. (FABACEAE)

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ABSTRACT

Objective: The purpose of this study was to investigate the phytochemistry and antimicrobial potential of the methanol extracts of the sapwood (EMEHc) and leaves (EMFHc) of *Hymenaea courbaril* against pathogenic bacteria.

Method: For the development, plant products were collected and methanolic extracts of the sapwood and leaves of *H. courbaril* were prepared, allowing the chemical characterization. In the microbiological tests, the Minimum Inhibitory Concentration (MIC) and the modifying effect of antibiotics against the standard and multidrug-resistant strains of *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were determined.

Results and Discussion: Chemical characterization revealed the presence of classes of flavonoids, including flavones, flavonols, flanonols, catechins, and xanthones, recognized in both extracts. cEMF and cEHEM demonstrated a synergistic effect in most combinations with antibiotics tested against the bacteria analyzed, suggesting application as a combination therapy. These biological activities were shown to be related to the phytochemical composition identified, since they involve metabolites with proven biological activity.

Keywords: Natural Product, Multidrug-resistant Bacteria, Antimicrobial, Phytochemistry.

AVALIAÇÃO I*N VITRO* DO POTENCIAL ANTIMICROBIANO DOS EXTRATOS DE *Hymenaea courbaril* L. (FABACEAE)

RESUMO

Objetivo: Este estudo teve como propósito investigar a fitoquímica e o potencial antimicrobiano dos extratos metanólicos da entrecasca (EMEHc) e das folhas (EMFHc) da *Hymenaea courbaril* frente a bactérias patogênicas.

Método: Para a desenvolvimento, foram coletados produtos vegetais e preparados os extratos metanólicos da entrecasca e das folhas da *H. courbaril*, permitindo a caracterização química. Nos testes microbiológicos, foram determinados a Concentração Inibitória Mínima (CIM) e o efeito modificador de antibiótico frente às cepas padrões e multirresistentes de *Escherichia coli*, *Staphylococcus aureus* e *Pseudomonas aeruginosa*.

Resultados e Discussão: A caracterização química revelou a presença de classes de flavonoides, incluindo flavonas, flavonóis, flanonóis, catequinas e xantonas, reconhecidas em ambos os extratos. Os EMFHc e o EMEHc demonstraram efeito sinérgico na maioria das combinações com antibióticos testados contra as bactérias analisadas, sugerindo aplicação como terapia combinada. Essas atividades biológicas mostraram estar relacionadas à composição fitoquímica identificada, uma vez que envolvem metabólitos com atividade biológica comprovada.

Palavras-chave: Produto Natural, Bactérias Multirresistentes, Antimicrobiano, Fitoquímica.

EVALUACIÓN IN VITRO DEL POTENCIAL ANTIMICROBIANO DE EXTRACTOS DE *Hymenaea courbaril* L. (FABACEAE)

RESUMEN

Objetivo: El propósito de este estudio fue investigar el potencial fitoquímico y antimicrobiano de los extractos metanólicos de la albura (EMEHc) y las hojas (EMFHc) de *Hymenaea courbaril* contra bacterias patógenas.

Método: Para el desarrollo se recolectaron productos vegetales y se prepararon extractos metanólicos de la albura y hojas de *H. courbaril*, permitiendo la caracterización química. En las pruebas microbiológicas se determinó la Concentración Mínima Inhibitoria (CMI) y el efecto modificador de los antibióticos frente a las cepas estándar y multirresistentes de *Escherichia coli*, *Staphylococcus aureus* y *Pseudomonas aeruginosa*.

Resultados y Discusión: La caracterización química reveló la presencia de clases de flavonoides, incluyendo flavonas, flavonoles, flanonoles, catequinas y xantonas, reconocidas en ambos extractos. cEMF y cEHEM demostraron un efecto sinérgico en la mayoría de las combinaciones con antibióticos probados contra las bacterias analizadas, lo que sugiere su aplicación como terapia combinada. Se demostró que estas actividades biológicas

están relacionadas con la composición fitoquímica identificada, ya que involucran metabolitos con actividad biológica comprobada.

Palabras clave: Producto Natural, Bacterias Multirresistentes, Antimicrobiano, Fitoquímica.

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1 INTRODUCTION

Bacterial infections are responsible for the majority of hospital illnesses, and are mostly caused by multidrug-resistant (MDR) bacteria, rendering the therapeutic action of current antibiotics ineffective (Church & McKillip, 2021; Chiș *et al* ., 2022). This resistance may be associated with several factors that lead to the development of a survival strategy by these pathogenic microorganisms, factors such as indiscriminate and inappropriate use of antibiotics (Moreira *et al* ., 2024; Dhingra *et al* ., 2020) or intrinsic genetic mutations (Lima *et al* ., 2021).

Among the relevant bacterial microorganisms: *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* , are among the bacteria that have evasion mechanisms that prevent some medications from having an effective action, thus making it difficult to treat bacterial infections, making them targets of control for scientific research. Microorganisms can develop protection mechanisms to increase their lifespan in the environment they are in as a form of adaptation (Jian *et al* ., 2021; Avershina *et al* ., 2021; Christaki *et al* ., 2020).

New approaches have been developed to enhance the effect of antibiotics, with emphasis on the association with natural products. This strategy seeks to inactivate bacterial resistance mechanisms. In this context, the use of medicinal plants has gained relevance due to their broad biological activity and the potential to intensify therapeutic effects (Silva *et al*., 2024; Kebede *et al*., 2021). In Brazil, there is a large biodiversity of plants with promising pharmacological potential in research, possibly used in the future as therapeutic agents (Ferreira *et al*., 2023).

The Chapada do Araripe is recognized for its vast territorial extension and the rich biological diversity of medicinal plants, with applications in both pharmacological use and traditional medicine (Sá-Filho *et al*., 2021). Among the prominent species, *Hymenaea courbaril* L., popularly known as "jatobá", stands out for its antioxidant and antimicrobial properties (Scaramussa *et al*., 2024). In addition, this plant has potential for use in the food, pharmaceutical, agricultural defense and food preservation industries, due to its wide

applicability, which ranges from the treatment of human diseases to the control of agricultural pathogens (Schwartz, 2018).

The need for alternative measures to combat diseases caused by multidrug-resistant bacteria highlights the role of medicinal plants, due to their therapeutic properties. Among these, *H. courbaril*. shows promising potential as an antibacterial agent against multidrug-resistant (MDR) strains. Therefore, the present study aimed to analyze the phytochemistry of the methanolic extract of the inner bark and leaves of *Hymenaea courbaril*, as well as to evaluate the antimicrobial activity of the extracts against MDR bacteria.

2 MATERIALS AND METHODS

2.1 COLLECTION OF PLANT MATERIAL

For the study, the bark and leaves of *Hymenaea courbaril*, collected at Sítio Belém, located in the municipality of Abaiara, Ceará, Brazil, were selected.

2.2 PREPARATION OF METHANOLIC EXTRACT

To obtain the methanolic extracts from the inner bark of *Hymenaea courbaril* (EMEHc), the plant material was subjected to natural drying for 72 h, while to prepare the methanolic extract from the leaves of *H. courbaril* (EMFHc), fresh materials were used. After this step, both materials were weighed and crushed to increase the contact area, facilitating the extraction of the components. Then, the materials were subjected to extraction with methanolic solvent for a period of 72 h.

After extraction, the material was initially filtered with a large mesh cloth to remove larger solids, followed by a second filtration with cotton to eliminate visible residues. The solvent was then condensed by vacuum distillation in a rotary evaporator and, subsequently, the extracts were placed in a water bath at 60ºC for 120 h to ensure complete evaporation of the methanol, resulting in the crude extracts. The final yield of the crude extracts obtained was 7.58% EMFHc and 6.33% for EMEHc.

2.3 PHYTOCHEMICAL PROSPECTING

The presence of secondary metabolites in EMEHc and EMFHc were analyzed based on

color changes and precipitate formation (Matos, 2009). To identify chemical compounds, tests were performed targeting phenols, pyrogallic tannins, flababene tannins, anthocyanins, anthocyanidins, flavones, flavonols, xanthones, chalcones, aurones, flavonoids, leucoanthocyanidins, catechins, flavanones and alkaloids. The methods employed used the observation of color changes or precipitate formation after the addition of specific reagents.

2.4 ANTIBACTERIAL ACTIVITY

2.4.1 Strains, culture media and inocula

The microorganisms used in the tests were obtained from the bacterial bank of the Leão Sampaio University Center. Standard (ATCC) and multidrug-resistant (MDR) strains of *Escherichia coli* (ATCC 25922 and MDR 27), *Staphylococcus aureus* (ATCC 25923 and MDR 358), and *Pseudomonas aeruginosa* (ATCC 27853 and MDR 31) were used. Brain Heart Infusion (BHI) medium was used at the concentration recommended by the manufacturer, including the version diluted to 10%, prepared and sterilized in advance, according to the standards established by the manufacturer. To prepare the bacterial inocula, a bacterial loop was diluted in 10% BHI and incubated at 35 °C for 24 h, following the CLSI guidelines (2015).

2.4.2 Solution and drugs

For the initial solutions, 10 mg of EMFHc was dissolved in 1 mL of dimethyl sulfoxide (DMSO), while 10 mg of EMCHc was solubilized in 1 mL of distilled water, resulting in an initial concentration of 10 mg/mL. The solutions were then diluted in distilled water to reach a concentration of 1024 µg/mL. In the case of EMFHc, the DMSO ratio was adjusted to 10%. These solutions were used to prepare 1:1 serial dilutions in the microdilution test, obtaining concentrations of 512 to 8 µg/mL, with the final DMSO concentration in EMFHc reduced to 5% or less. The reference drugs used in the tests were the antibiotics amikacin and gentamicin.

2.4.3 Minimum Inhibitory Concentration (MIC)

To evaluate the antibacterial activity, the Minimum Inhibitory Concentration (MIC) was used to determine the inhibition potential, using the microdilution methodology in microtiter plates. For this, the test solutions were prepared at a doubled concentration (1024 µg/mL) in

relation to the initial concentration, using a volume of 100 µL, and subjected to serial dilutions of 1:1 in 10% BHI broth. In each well containing 100 µL of culture medium, a sample of the bacterial inoculum diluted in a proportion of 1:10 was added (Silva *et al* ., 2024).

The assays included negative controls (culture medium), positive controls (medium with inoculum), and inhibition controls with solutions at concentrations of 512 to 8 µg/mL. The plates were incubated at 35 °C for 24 h. Resazurin sodium prepared in sterile distilled water at a concentration of 0.01% was used for reading. After the incubation period (35 °C for 24 h), 20 µL of the solution was added to each well, followed by an additional incubation of 1 h (60 min) at room temperature. The color change from blue to pink indicated bacterial growth in the wells (Almeida-Bezerra *et al* ., 2023).

2.4.4 Antibiotic potentiating activity

The combined potential of each extract was evaluated using the aminoglycoside antibiotics amikacin and gentamicin, at concentrations ranging from 2500 to 2.5 µg/mL, distributed in microplates. The extracts were diluted in 10% BHI broth, using the previously determined MIC, being used in subinhibitory concentrations (MIC/8). The antibiotic solutions were dissolved in distilled water, reaching initial concentrations of 5000 µg/mL, which were subjected to serial dilutions of 1:1 in BHI broth (10%), with volumes of 100 µL. BHI (100 µL) was added to the plate wells, and bacterial inoculum diluted in a proportion of 1:10. The plates were incubated at 35 °C for 24 h, and the reading was performed with the addition of liquid resazurin, following the same procedure adopted in the determination of the MIC. The color change indicated the presence of bacterial growth (Matias *et al* ., 2013).

2.5 STATISTICAL ANALYSIS

The test results were performed in triplicate (n = 3), and presented with the geometric mean by calculating the standard error of the mean and standard deviation. The statistical analysis of the data obtained was applied in the two-way ANOVA test, Bonferroni post-test with the GraphPad Prism 6.0 program, considering $p < 0.05$ as significant.

3 RESULTS AND DISCUSSION

The increase in antimicrobial resistance over the decades has been recognized as a

global problem, resulting in a significant number of deaths (Church & McKillip, 2021; Chiș *et al* ., 2022; Christaki *et al* ., 2020). As a result, there has been a significant increase in research focused on natural products, with the aim of identifying substances with therapeutic potential. Such investigations are often based on ethnobotanical knowledge previously used in certain regions of interest (Silva *et al* ., 2024; Sá-Filho *et al* ., 2021).

The activity observed in natural products is associated with secondary compounds present in plants, whose classification can be determined through screening tests, such as phytochemical characterization (Dubale *et al* ., 2023). In the present study, the classes of secondary metabolites identified in EMFHc and EMEHc extracts are described in Table 1. Phytochemical analysis revealed the presence of xanthones, compounds known for their ability to reduce free radical activity, giving them antioxidant potential (Masters & Bräse, 2012; Soares *et al* ., 2022).

The analysis of secondary metabolites present in methanolic extracts revealed the identification of substances belonging to the classes of flavonoids, flavones, flanonoids, xanthones and catechins, for both extracts. These compounds have broad efficacy against several microorganisms, attributed to the formation of soluble protein complexes capable of interacting with the bacterial cell wall. In addition, some lipophilic flavonoids can cause partial destruction of the membrane of certain microorganisms (Dubale *et al* ., 2023; Tsuchiya *et al* ., 1996). The antimicrobial properties have been shown to be effective against bacteria such as *Staphylococcus aureus* (Thebti *et al*., 2023).

Table 1

Phytochemical constituents present in methanolic extracts of leaves (EMFHc) and inner bark (EMEHc) of Hymenaea courbaril.

Extracts	Constituents										
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
EMEHc	-	-	+	+	+	+	-	-	-	+	-
EMFHc	-	-	+	+	+	+	-	-	-	+	-

C1 = Anthocyanins; C2 = Anthocyanidins; C3 = Flavones; C4 = Flavonols; C5 = Flanonols; C6 = Xanthones; C7 = Chalcones; C8 = Avrones; C9 = Leocoanticianidins; C10 = Catechins; C11 = Flavonones; (+) = Presence; (-) = Absence.

The antimicrobial action of EMFHc was observed against strains of *S. aureus* and *P. aeruginosa*, with MIC values of 16 µg/mL, while EMEHc presented a reduced antimicrobial spectrum against all strains analyzed, with MIC equal to or greater than 1024 µg/mL. In the combined action tests, both compounds exhibited synergism with amikacin ($p < 0.001$). In the case of gentamicin, statistical significance was detected only in strains of *S. aureus* and *P.*

aeruginosa ($p < 0.05$). Previous studies indicate the antimicrobial activity of *H. courbaril* against bacteria such as *S. aureus*, *P. aeruginosa* and *Salmonella enteritidis*, especially with the use of ethanolic extracts that present antibacterial potential (Scaramussa *et al*., 2024).

Several mechanisms can interfere with microbial growth, some of which are validated by the interaction between substances that favor the penetration of antibiotics and/or intensify the interaction with the bacterial lipid bilayer, impacting the respiratory chain and energy production (Berube & Parish, 2018; Taheri-Araghi *et al*., 2024).

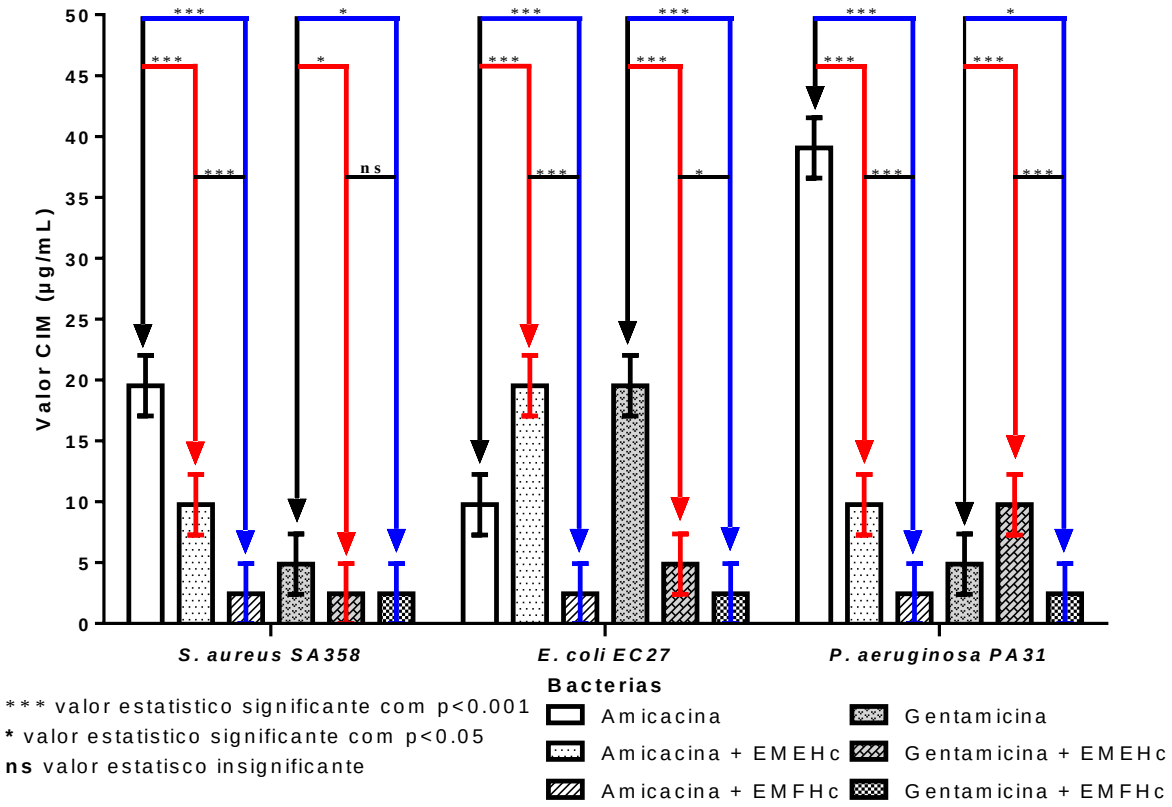
In the present study, the combined activity test revealed that EMEHc demonstrated synergism with the antibiotics tested in most of the bacteria analyzed, with the exception of *E. coli* with amikacin and *P. aeruginosa* with gentamicin, where antagonism was observed. EMFHc showed a synergistic effect with both antibiotics for all bacteria tested. These results highlight the potential of *H. courbaril* as a promising alternative in the treatment of infections caused by pathogenic bacteria (Sá *et al*., 2011).

The antimicrobial properties of *H. courbaril* have shown promising results, including the activity present in its fruits, suggesting a possible alternative use (Correa *et al*., 2020). The evaluation of the hydroalcoholic extract of the trunk bark of this species revealed antimicrobial activity against strains of enteropathogenic *Escherichia coli (Gonçalves et al* ., 2011), while the crude hydroalcoholic extracts of the inner bark showed 54.0% inhibition against *Staphylococcus* sp. at a concentration of 2.5 mg/mL (Fernandes *et al* ., 2005). Furthermore, the species has demonstrated potential as an antioxidant and antibiofilm agent, attributed to the high content of phenolic compounds (Cruz *et al*., 2023).

The investigation conducted by Martins *et al*. (2010) analyzed crude ethanolic extract obtained from the bark and floury pulp of *H. courbaril*. The results indicated that the extract presented antimicrobial activity against Gram-positive bacteria, while the bark extract did not demonstrate any activity against the pathogens tested. In our findings, it was observed that of the methanolic extracts of the species, it was verified that EMFHc presented superior performance to EMEHc, although the results of the latter cannot be considered irrelevant.

Figure 1

Graphic evaluation of the combined antibacterial activity of methanolic extracts of leaves (EMFHc) and inner bark (EMEHc) of Hymenaea courbaril with antibiotics.



4 CONCLUSION

Extracts of *H. courbaril* have shown to be promising options in the search for substances capable of inhibiting bacterial growth and enhancing the effect of antimicrobial drugs, as evidenced by synergism with antibiotics. It was observed that both EMEHc and EMFHc demonstrate similarity in phytochemical analysis, with the presence of compounds such as flavones, flavonols, flanonols, xanthones and catechins. It is important to highlight the need to invest in research related to the medicinal use of medicinal plants, such as *H. courbaril* , widely used by traditional communities, with the aim of identifying and validating the presence of effective compounds for the therapeutic purposes for which they are intended.

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