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Original Research

Antibiotic potentiating activity of *Casearia javitensis* Kunth (Salicaceae)

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Abstract

Antimicrobial resistance is a global concern, affecting public health and generating economic and social impacts, which requires global strategies to contain its spread and reduce associated deaths. Medicinal plants demonstrate efficacy against pathogenic microorganisms, offering alternatives in the fight against microbial resistance. As a highlight, *Casearia javitensis* has antimicrobial and antiparasitic properties of therapeutic relevance to cope with these microorganisms. This research aimed to evaluate the antibacterial activity of ethanolic extract of *C. javitensis* leaves (EECJ), as well as its antibiotic potentiating activity. Leaves of the species were collected, dried, crushed and subjected to extraction using ethanol. For the antimicrobial assays, conventional and multidrug-resistant bacterial (MDR) strains were used. The inhibition capacity was analyzed by means of the Minimum Inhibitory Concentration (MIC), at concentrations from 0.5 to 512 µg/mL. The potentiating activity was evaluated using subinhibitory concentrations of EECJ (MIC/8) in association with the antibiotic's gentamicin, ampicillin and norfloxacin. The data obtained was submitted to statistical analysis. The results indicated that EECJ did not present isolated antibacterial activity (MIC > 512 µg/mL); however, it has been shown to be effective as an antibiotic enhancer, reducing the MIC of gentamicin, ampicillin, and norfloxacin against the MDR strains of *E. coli*, *S. aureus,* and *P. aeruginosa*. These findings suggest that ethanolic extract of *C. javitensis* may be a promising alternative in combination therapies.

Keywords: *Ethanolic Extract; Antibacterial; Medicinal Plants; Antimicrobial Resistance.*

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1. Introduction

Antimicrobial resistance is a global concern that affects both developed and developing countries, with significant impacts on public health, as well as economic and social repercussions [1,2]. Projections by the Centers for Disease Control and Prevention (CDC) indicate that if the unchecked advance of antimicrobial resistance is not adequately addressed, the number of deaths attributed to infections caused by multidrug-resistant bacteria could exceed 10 million by 2050, surpassing the mortality rates associated with cancer and cardiovascular disease [3,4].

The progression of microbial resistance has been attributed to multiple factors, including the lack of innovation in the development of new antimicrobials, which do not keep pace with the speed at which resistance emerges. Other critical elements include inappropriate and uncontrolled use of antibiotics [5,6], the irrational prescription of these drugs [7] and the genetic mutations intrinsic to microorganisms, such as bacteria [8]. In this context, it is imperative to implement coordinated global strategies, aimed at both the development of new drugs and the mitigation of the emergence and spread of antimicrobial resistance, with the aim of reducing the mortality associated with this problem [2].

Medicinal plants have stood out as promising sources of antimicrobial agents due to their wide range of biological activities. Studies have demonstrated its effectiveness in combating pathogenic microorganisms, including bacteria and fungi, suggesting its potential as a therapeutic alternative to deal with multidrug-resistant microorganisms [9 - 11]. These plants can be used in different ways, employing various extraction techniques to produce extracts or essential oils rich in bioactive compounds. Such compounds have direct antibacterial activity or can act synergistically, increasing the efficacy of conventional drugs [12 - 14].

The Salicaceae family, composed of approximately 90 genera and 1,000 species, stands out for the genus *Casearia*, which includes several species recognized for their pharmacological and biological potential. From plants of this genus, plant extracts and essential oils with therapeutic properties can be obtained, including antiparasitic, antibacterial, antifungal, anti-inflammatory and hepatoprotective activities, as well as hypotriglyceridemiating effects. Its medicinal applications include the treatment of ulcers, dropsy, fissures, abdominal cramps, malaria fever, tonsillitis, wounds, severe bone fractures, and snakebites [15 - 20].

The species *Casearia javitensis* Kunth, belonging to the genus *Casearia*, is characterized as a shrub with a thin trunk, with a height ranging between 2 and 8 meters, as described by Sacramento, Zickel and Almeida-Jr [21]. Native to Brazil, it has a wide geographical distribution and is popularly known by names such as "capança", "mata-calado" or " mutamba-brava" [22]. Previous studies have confirmed relevant biological activities, including antiparasitic properties, with emphasis on its leishmanicidal action [23, 24], in addition to antimicrobial activities, such as antibacterial and antifungal action [25].

The investigation of natural products with proven antimicrobial activity supports the hypothesis that the ethanolic extract of *Casearia javitensis* has promising potential for the development of new therapeutic agents, based on its previously reported biological properties. In this context, the present study aims to evaluate the antibacterial activity of ethanolic extract of *C. javitensis* against conventional and multidrug-resistant (MDR) bacterial strains, as well as to investigate its ability to potentiate the action of antibiotics, with a view to application in future pharmacological approaches.

2. Materials and Methods

Obtaining a license and collecting the botanical material

To collect the plant material, the study was previously registered in the SISGEN (Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado) with code A64BA01 and in the SISBIO (Sistema de Autorização e Informação em Biodiversidade) number 77450-1. After obtaining the licenses, the leaves of *Casearia javitensis* (Fig. 1) were collected in the municipality of Crato, Ceará, Brazil, in January 2023. The material was identified in the field by botanist Dr. José Weverton Almeida-Bezerra.

Preparation of ethanolic extract (EE)

After collection, the leaves were selected, dried at room temperature and crushed to increase the contact surface, and were used in the preparation of the ethanolic extract of *Casearia javitensis* (EECJ). The crushed material was subjected to extraction by submersion in ethanol P.A. for 72 h. Then, the mixture was filtered, and the solvent removed by distillation in a rotary evaporator under reduced pressure, with temperature control between 30 - 40 °C in a rotary evaporator [26].

Fig 1. *Representative images of Casearia javitensis Kunth, collected in the municipality of Crato, in the state of Ceará, Brazil.*

2.3 Evaluation of antibacterial activity

2.3.1 Strains, culture media, and drugs

The antibacterial activity was evaluated using conventional bacterial strains and MDR. The reference strains used were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 25853 and *Staphylococcus aureus* ATCC 25923, while the MDR strains included *E. coli* 06, *P. aeruginosa* 24 and *S. aureus* 10. The culture medium used was Brain Heart Infusion (BHI; Merck KGaA, Darmstadt, Germany), following the manufacturer's specifications. The bacterial strains were diluted in 3 mL of sterile saline solution (0.9% NaCl), and the turbidity was adjusted to the McFarland 0.5 standard (1.5×10^8 CFU/mL). The reference drugs used were gentamicin, ampicillin, and norfloxacin as controls for commercial antibiotics.

2.3.2 Minimum Inhibitory Concentration (MIC)

To evaluate the ability of EECJ to inhibit bacterial growth, 100 µL of inoculum solution and 900 µL of culture medium (BHI) were added to microtiter plates (96-well microplates). Then, different concentrations of EECJ (0.5–512 µg/mL) were applied. The microplates were incubated in a bacteriological incubator at 37 °C for 24 h [27]. After incubation, liquid resazurin was used as an indicator, whose oxidation-reduction reaction signals bacterial growth. After one hour of reaction, the color was evaluated: violet indicated absence of growth, while light pink suggested an increase in the presence of bacteria. The tests were carried out in triplicates.

2.3.3 Antibiotic potentiating activity

The combination therapy capacity of EECJ with predefined antibiotics was assessed using subinhibitory concentrations of EECJ (MIC/8) in combination with the commercial antibiotic's gentamicin, ampicillin and norfloxacin. The assays were performed by microdilution in wells containing concentrations of 0.5–512 µg/mL of antibiotics, with 100 µL per well. The microplates were incubated in a bacteriological incubator at 37 °C for 24 h, and the experiments were conducted in triplicate [28].

2.4 Statistical analysis

The data means and their respective mean standard errors (SEM) were calculated and submitted to a unidirectional analysis of variance (ANOVA). Next, the reliability of the results was evaluated by Tukey's test, with a confidence level of 95%. The analysis was performed using the GraphPad Prism software, version 6 (GraphPad Software Inc., San Diego, CA, USA).

3. Result

The data from the evaluation of the antibacterial activity of EECJ indicated that the extract did not show significant activity against ATCC and MDR bacterial strains, with MIC greater than 512 µg/mL. However, when analyzing its ability to potentiate antibiotics, it was found that EECJ increases the efficacy of different drugs, such as gentamicin, ampicillin, and norfloxacin, against MDR strains of *E. coli* 06, *S. aureus* 10, and *P. aeruginosa* 24. As shown in Fig. 2, it was possible to observe a reduction in the MIC of gentamicin (from 20.15 µg/mL to 2.51 µg/mL) and norfloxacin (from 161.26 µg/mL to 64 µg/mL) against the *E. coli* 06 strain.

In addition, it was found that EECJ has potential for use in combination therapies, since its association with the antibiotics tested demonstrated a reduction in MIC in tests carried out with bacterial strains of *P. aeruginosa* (Gram-negative, Fig. 3) and *S. aureus* (Gram-positive, Fig. 4). The combination of norfloxacin and EECJ showed particularly relevant MIC values of 4 µg/mL and 6.34 µg/mL, respectively for *P. aeruginosa* and *S. aureus*.

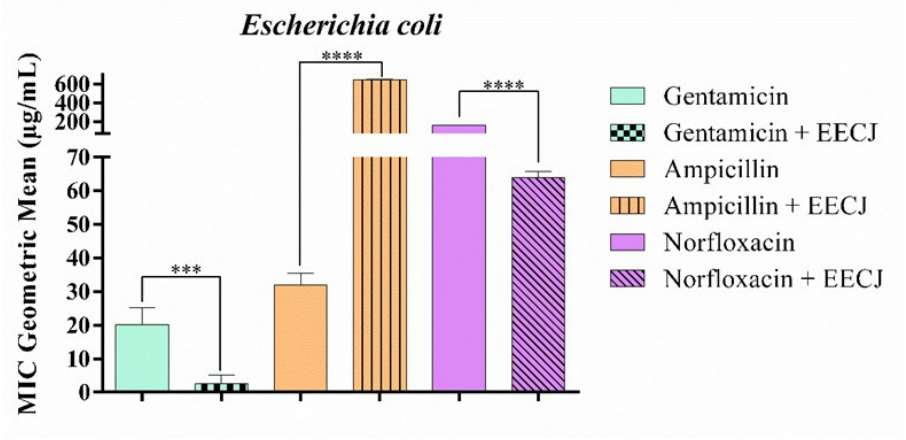

***Fig 2**. Minimum inhibitory concentration (MIC) of the ethanolic extract of Casearia javitensis (EECJ) associated with conventional antibiotics (gentamicin, ampicillin and norfloxacin) against multidrug-resistant strains of Escherichia coli 06. = p < 0.001; **** = p < 0.0001.*

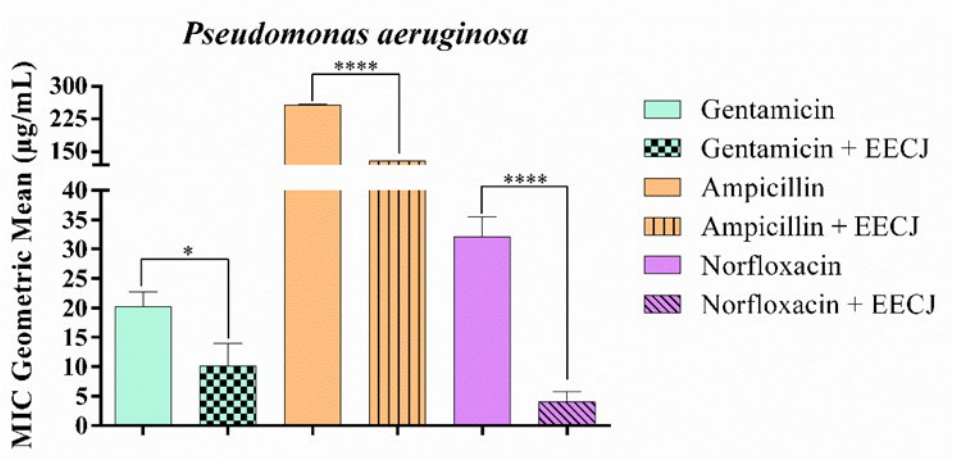

***Fig 3**. Minimum inhibitory concentration (MIC) of the ethanolic extract of Casearia javitensis (EECJ) associated with conventional antibiotics (gentamicin, ampicillin, and norfloxacin) against multidrug-resistant strains of Pseudomonas aeruginosa 24. * = p < 0.05; **** = p < 0.0001.*

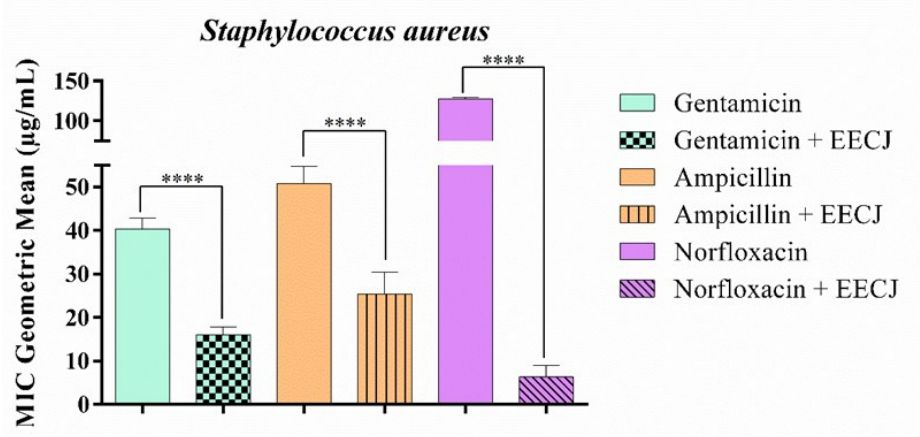

***Fig 4**. Minimum inhibitory concentration (MIC) of the ethanolic extract of Casearia javitensis (EECJ) associated with conventional antibiotics (gentamicin, ampicillin, and norfloxacin) against multidrug-resistant strains of Staphylococcus aureus 10. = p < 0.0001.*

4. Discussion

Growing antimicrobial resistance has become one of the world's greatest public health challenges, jeopardizing the effectiveness of many conventional antibiotics and increasing the severity of previously treatable infections. In this context, the search for new antimicrobial agents, especially those derived from natural sources, has gained prominence.

The genus *Casearia* has been widely associated with clinically relevant antimicrobial activities, especially the species *Casearia sylvestris*, whose antibacterial properties have been widely documented in the literature. Studies report its promising action against a variety of pathogenic bacteria. Among the Gram-positive microorganisms, *Streptococcus mutans*, *Enterococcus faecium,* and *Staphylococcus aureus* were particularly sensitive, with a minimum inhibitory concentration (MIC) of 250 µg/mL, while among the Gram-negative bacteria, *Escherichia coli,* and *Salmonella setubal* showed similar MIC [17, 29, 30]. In addition, *C. sylvestris* demonstrated antibiofilm activity, a relevant mechanism in the context of antimicrobial resistance, standing out as a potential alternative in combating persistent bacterial infections [31,32]. These findings corroborate the therapeutic value of the plant and suggest its potential for the development of new approaches to confront antimicrobial resistance.

Similarly, *Casearia tomentosa* Roxb. demonstrates antibacterial activity, with its bark extract inhibiting the growth of *Bacillus subtilis* (10.33 ± 3.05 mm inhibition) [33] and *E. coli* [16]. However, there are still limitations in the knowledge about the antibacterial activities and mechanisms of action associated with natural products of *C. javitensis*. EECJ has relevant antimicrobial potential for the control of pathogenic bacteria, in addition to antifungal activity, with no evidence of toxicity, according to evaluation in *an Artemia salina* model [25].

The antibacterial effect of *C. javitensis* extract can be attributed to the phytochemicals present, such as phenolic acids (chlorogenic acid), flavonols (isoquercitrin, quercetin-3-O-dipentoside, and kaempferol-3-O-robinobioside), and xanthones (xanthorramnin), identified by liquid chromatography coupled to mass spectrometry [24, 34]. These compounds, especially phenolics [35] and flavonoids [30], are indicated to be responsible for the observed antibacterial activity, making it a therapeutic possibility.

The ethanolic extract of *C. javitensis* (EECJ) has demonstrated a relevant clinical potential as a drug potentiating agent, however, its association with ampicillin has revealed an antagonistic effect against *Escherichia coli*. This antagonism can be explained by the competition between EECJ and ampicillin for the same sites of action. The scramble for microbial targets, along with complex molecular interactions, is an important factor in the manifestation of antagonistic effects, as discussed by Goñi et al. [36].

In addition, another possible explanation for this phenomenon may be related to the emergence of bacterial resistance through genetic mutations. These mutations can lead to the coding of proteins that alter penicillin-binding sites, decreasing ampicillin's affinity for its targets and compromising its efficacy. Changes in penicillin-binding proteins are well documented as a mechanism of resistance to β-lactam drugs, including ampicillin [8, 37].

The results of this study reinforce the potential of EECJ as a promising therapeutic alternative, due to its drug-enhancing activity. However, the observed antagonistic effect between EECJ and ampicillin against *E. coli* underscores the complexity of the interactions between plant compounds and antibiotics. These findings corroborate the literature on the interaction of medicinal plants with antibiotics, where, in some cases, the potentiating effect is observed, while in others, such as ours, antagonism may occur [9, 24].

The literature suggests that combining medicinal plants with antibiotics, while promising, requires detailed study to avoid unwanted antagonisms and optimize therapeutic outcomes [13, 31]. Therefore, the potential of EECJ should be carefully explored, considering its specific interactions with different classes of antibiotics, for the development of more effective combination therapies in combating antimicrobial resistance.

5. Conclusion

The ethanolic extract of *C. javitensis* did not demonstrate antibacterial activity of significant relevance against pathogenic bacterial strains. However, it showed potential as a potentiating agent when associated with antibiotics such as gentamicin and ampicillin, especially the combination with norfloxacin. Despite the promising results, the study has limitations related to the phytochemical characterization of the extract and the detailed analysis of the interactions between the extract and antibiotics. Future research is needed to clarify the mechanisms of action of these combinations, including molecular Docking analyses, as well as investigations into possible toxic effects through *in vivo tests*.

Conflict of Interest

The authors declare no conflict of interest.

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