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Research Article

Phytochemical Profile and Modifying Potential of *Erythroxylum rosuliferum* O.E. Schulz (Erythroxylaceae) Extract on Antibiotic Activity

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Abstract

The growing bacterial resistance represents a global challenge, making it necessary to search for new therapeutic approaches, such as the use of medicinal plant extracts, to combat resistant microorganisms. Among these species, *Erythroxylum rosuliferum* O.E. Schulz has stood out due to the promising potential of the *Erythroxylum* genus, known for its diverse bioactivity. In this context, this study aimed to qualitatively analyze the phytochemistry of the extract, as well as investigate the antibacterial activity and the synergistic effect of the ethanolic extract of *Erythroxylum rosuliferum* leaves (EEER) in combination with antibiotics. For this purpose, the collected leaves were dehydrated, ground, and subjected to ethanolic extraction to obtain the extract, followed by phytochemical analysis of the classes present in the extract. The antibacterial activity of EEER was evaluated using standard and multidrug-resistant bacterial strains through the broth microdilution test to determine the Minimum Inhibitory Concentration (MIC). Additionally, antibiotic modulation was analyzed by combining the extract with gentamicin, ampicillin, and norfloxacin at subinhibitory concentrations (MIC/8), and the results were subjected to statistical analysis. The findings indicated the presence of active compounds such as flavabenoid tannins, flavonoids, xanthones, and chalcones in EEER. The antibacterial evaluation did not show significant effects (MIC > 512 µg/mL) against the tested strains. However, when combined with antibiotics, a potentiating effect was observed, significantly reducing the MIC of drugs like gentamicin, ampicillin, and norfloxacin against multidrug-resistant strains of *Escherichia coli*, *Staphylococcus aureus*, and Pseudomonas aeruginosa. These results suggest that the ethanolic extract of *E. rosuliferum* may contribute to combined therapeutic strategies, representing a promising alternative in combating bacterial resistance.

Keywords: *Combination therapy, Antibacterial, Bandeirinha.*

1. Introduction

Antimicrobial resistance represents a significant challenge today, a process that results in the reduced efficacy of antibiotics. This phenomenon occurs when microorganisms, such as bacteria and fungi, develop resistance mechanisms to drugs, causing severe impacts on a global scale. It is estimated that by 2050, it could be related to approximately 10 million deaths [1-3]. Various factors contribute to the uncontrolled spread of these mechanisms, including inadequate medical prescriptions, self-medication, indiscriminate use of antibiotics by the population, and failures in the regulation of their commercialization [4].

Given this scenario, it becomes evident that advanced measures are needed to prevent or reverse antimicrobial resistance. Among these strategies, the use of medicinal plants as a therapeutic alternative has gained attention, especially in the development of new drugs, particularly with antibacterial potential demonstrated in plant extracts and essential oils [5-7]. Plant-derived compounds can act through different mechanisms and modulate the susceptibility of resistant microorganisms to antibiotics [8].

Among medicinal plant species with pharmacological and therapeutic potential, the *Erythroxylum* genus has stood out due to its wide range of biologically active properties, including antioxidant, anti-inflammatory, and antimicrobial activities against bacteria and fungi, as well as antidiarrheal and antiparasitic effects. These activities are observed through the use of extracts obtained from different species, and it is suggested that such properties result from the presence of specific phytochemicals, such as tropane alkaloids [9-12].

Among the species of this genus, *Erythroxylum rosuliferum* O.E. Schulz, an endemic species of Brazil, popularly known as "bandeirinha," has received special attention due to its potential for various applications. Research conducted is associated with its phytochemical composition rich in bioactive compounds [13,14].

Considering the available knowledge in the literature and the growing need to identify natural compounds with antibacterial potential, this study aims to evaluate the antibacterial activity and antibiotic-modulating potential, as well as to perform a qualitative analysis of the ethanolic extract of *E. rosuliferum* leaves.

2. Materials and Methods

2.1 Collection of plant material

The leaves of the species *Erythroxylum rosuliferum* O.E.Schulz (Fig. 1) were collected in Chapada do Araripe, in the municipality of Crato, Ceará, Brazil, at geographic coordinates -7.272119S and -39.460795W, at 9:00 a.m. in January 2023. The material was identified by botanist Dr. José Weverton Almeida-Bezerra. The collection occurred after registration in the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SisGen), under the code A64BA01, and in the Biodiversity Authorization and Information System (SisBio), under the number 77450-1.

***Fig 1**. Photographic record of the collected species, Erythroxylum rosuliferum O.E. Schulz.*

2.2 Extraction Method

Leaves were carefully selected, dried at room temperature, and then ground to prepare the ethanolic extract of *E. rosuliferum* (EEER). The ground material was subjected to cold extraction by immersion in ethanol P.A. for 72 hours. Subsequently, the resulting solution was filtered, and the ethanol was removed using a rotary evaporator operating under reduced pressure, maintaining the temperature between 30 and 40 °C to preserve the active compounds [15].

2.3 Phytochemical Screening of the Extract

A preliminary phytochemical screening of the extract was performed to identify the main classes of secondary metabolites present, using the methods of [16] and [17], with modifications, as summarized in Table 1. In this assay, colorimetric techniques were employed to detect the presence of various classes of metabolites, such as phenols, flavones, flavonoids, chalkones, xanthones, alkaloids, flavanones, aurones, and pyrogallol tannins.

Table 1. Qualitative phytochemical determination methods.

Classes	Method	Reference
Phenols	$FeCl_3$ reaction	[17,18]
Hydrolyzable tannins	$FeCl_3$ reaction	[17]
Flababene tannins	$FeCl_3$ reaction	[17]
Anthocyanins	Acid and alkaline reaction	[17]
Anthocyanidins	Acid and alkaline reaction	[17]
Flavones	Alkaline reaction	[17]
Flavonols	Alkaline reaction	[17]
Xanthones	Alkaline reaction	[17]
Chalcones	Acid and alkaline reaction	[17]
Auronas	Acid and alkaline reaction	[17]
Flavanonols	Alkaline reaction	[17]
Leucoanthocyanidins	Acid and alkaline reaction	[17]
Catechins	Acid and alkaline reaction	[17]
Flavonones	Acid and alkaline reaction	[17]
Saponins	Foam time	[19]

Source of tabulated research: [20].

2.4 Antibacterial Activity

2.4.1 Microorganisms, Culture Media, and Drugs

The evaluation of antibacterial activity was conducted using conventional bacterial strains (ATCC) and multidrug-resistant (MDR) strains. The reference strains included Escherichia coli (ATCC 25922 and MDR 06), *Pseudomonas aeruginosa* (ATCC 25853 and MDR 24), and *Staphylococcus aureus* (ATCC 25923 and MDR 10). Cultivation was carried out using Brain Heart Infusion (BHI; Merck KGaA, Darmstadt, Germany) medium, following the manufacturer's specifications. After incubation in a biological incubator (37 °C, 24 h), bacterial suspensions were prepared with 3 mL of sterile saline solution (0.9% NaCl), adjusting turbidity to match the McFarland standard 0.5 (1.5×10^8 CFU/mL). For comparative control purposes, the antibiotics gentamicin, ampicillin, and norfloxacin were used.

2.4.2 Minimum Inhibitory Concentration (MIC)

The antibacterial activity of the extract was determined by the Minimum Inhibitory Concentration (MIC). For this purpose, 100 µL of bacterial inoculum solution and 900 µL of BHI culture medium were distributed in 96-well microplates. The extract was tested at different concentrations, ranging from 0.5 to 512 µg/mL, and added to the wells using the microdilution technique. The microplates were incubated in a bacteriological incubator at 37 °C for 24 hours. After this period, liquid resazurin was used as an indicator to detect bacterial growth based on the oxidation-reduction reaction. The color observed after one hour of reaction indicated the absence of bacterial growth when the solution remained purple, while a light pink hue indicated bacterial growth. All tests were performed in triplicate (n = 3).

2.4.3 Antibiotic-Modifying Activity

After determining the MIC, the potential combined interaction of EEER and antibiotics was evaluated using subinhibitory concentrations of the extract (MIC/8) in association with gentamicin, ampicillin, and norfloxacin. The assays were performed using the microdilution technique, in wells containing different concentrations of antibiotics, ranging from 0.5 to 512 µg/mL, with a volume of 100 µL per well. The microplates were incubated in a bacteriological incubator at 37 °C for 24 hours. All experiments were conducted in triplicate (n = 3) [21].

2.5 Statistical Analysis

The collected data were statistically analyzed by calculating the means and their respective standard errors of the mean (± SEM). Subsequently, a one-way analysis of variance (ANOVA) was applied, followed by Tukey's test to determine statistical significance, considering a 95% confidence level. Statistical analyses were performed using GraphPad Prism software, version 6 (GraphPad Software Inc., San Diego, CA, USA).

3. Results and Discussion

3.1 Phytochemistry of the Extract

The qualitative analysis of the phytochemical screening of the ethanolic extract of *E. rosuliferum* (EEER) revealed the presence of various active compounds, including flababênic tannins, flavonoids, xanthones, and chalcones, as presented in Table 2. These findings are consistent with previous studies, such as [13], which also identified similar compounds like tannins in EEER, as well as phenols, flavonoids, and alkaloids. Similar results were observed in the analysis of the ethanolic extract of *Erythroxylum revolutum* Mart. leaves, where tannins, phenols, flavonoids, and alkaloids were identified, such as 6-(2'-methylbutyryloxy)-3-hydroxy tropane and/or 6-butyryloxy-3-hydroxytropane [22].

Table 2. Phytochemical prospecting of the ethanolic extract of the leaves of *Erythroxylum rosuliferum* (EEER).

Classes	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
EEER	-	-	+	-	-	+	+	+	-	-	-	-	-	-	-

1: Phenols; 2: Hydrolyzable tannins; 3: Flababenic tannins; 4: Anthocyanins; 5: Anthocyanidins;6: Flavones; 7: Flavonols; 8: Xanthones; 9: Chalcones; 10: Aurones; 11: Flavanonols; 12: Leucoanthocyanidins; 13: Catechins; 14; Flavonones; 15: Foamy saponins; (-) Chemical class absence; (+) Chemical class presence.

These compounds exhibit considerable antimicrobial activity, with the xanthone class standing out due to its recognized antibacterial potential. This effect may be related to the molecular structure of these substances and their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties [23,24]. Derivatives of this class have demonstrated broad-spectrum antibacterial activity against various pathogenic bacteria, including Gram-negative microorganisms such as *Escherichia coli* and *Pseudomonas aeruginosa*, and Gram-positive ones such as *Staphylococcus aureus*, including methicillin-resistant strains [25,26].

Furthermore, compounds such as polyphenols, alkaloids, and tannins of plant origin have shown importance in combating antimicrobial resistance, acting against bacterial microorganisms through different mechanisms, such as inhibition of cell wall synthesis, interference with bacterial physiology, and modulation of antibiotic susceptibility [8,27]. Specifically, alkaloids can compromise cell membrane functions and bacterial metabolism, an effect observed in resistant strains of *S. aureus* [28].

3.2 Antibacterial and Modifying Activity

The evaluation of EEER's antibacterial activity data indicated that the extract did not exhibit significant antibacterial action against the ATCC and MDR strains since the MIC showed no effect at the highest concentration tested (MIC > 512 µg/mL). However, when analyzing the combination of EEER with antibiotics, a synergistic effect was observed in the action of gentamicin, ampicillin, and norfloxacin (Fig. 2), significantly reducing the MIC. The combination of EEER with ampicillin reduced the MIC in *P. aeruginosa* strains (MIC from 1024 µg/mL to 406.3 ± 1.49 µg/mL, a reduction of 60%) and E. coli (MIC from 1024 µg/mL to 512 µg/mL, a reduction of 50%).

Regarding *Pseudomonas aeruginosa*, the combination of EEER with gentamicin and norfloxacin did not show significant results. However, the association with norfloxacin against *E. coli* and *S. aureus* resulted in substantial reductions in MIC, reaching values of 50.7 ± 2.26 µg/mL and 203.1 ± 2.88 µg/mL, respectively. Additionally, the combination with gentamicin demonstrated a potentiating effect in inhibiting *E. coli* (MIC of 50.7 ± 1.49 µg/mL) and *S. aureus* (MIC of 50.7 ± 1.49 µg/mL). The variations in the results may be associated with factors such as the bacterial cell morphology, the classes of action of the antibiotics and their respective mechanisms, as well as the influence of specific metabolites present in the extract [5,8].

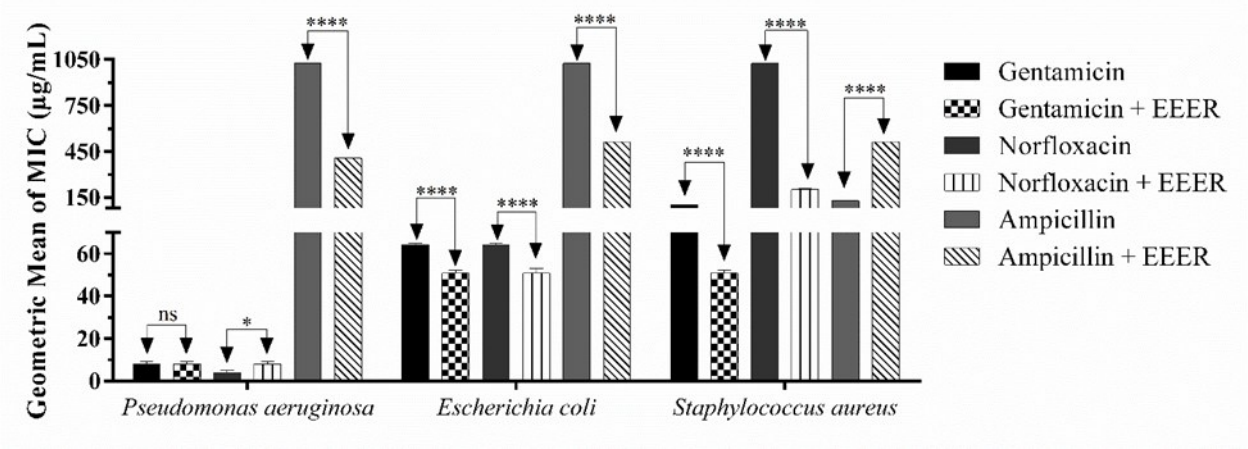

Fig 2. *Modified activity of conventional antibiotics from the ethanolic extract of Erythroxylum rosuliferum (EEER) against multidrug-resistant (MDR) bacterial strains; **** = p < 0.0001; * = p < 0.1; ns: not significant.*

The literature presents gaps regarding the antibacterial potential of EEER. However, different species of the *Erythroxylum* genus have demonstrated significant activity against pathogenic bacteria. Studies indicate that *Erythroxylum monogynum* Roxb. shows activity against *E. coli* strains [29], while the ethanolic extract of *Erythroxylum suberosum* St. Hil. exhibited an MIC of 250 µg/mL against *Staphylococcus aureus* ATCC 25923 [30]. Additionally, the ethanolic extract of *Erythroxylum coca* Lam. demonstrated antibacterial activity against *Streptococcus mutans* ATCC 25175 at concentrations of 50% and 75% [31].

The analysis of the synergy capacity of the ethanolic extract of *Erythroxylum rosuliferum* (EEER) with conventional antibiotics revealed an enhancement of these drugs' inhibitory potential. This potentiating effect was also observed in other species, such as *Erythroxylum revolutum*, whose combination with gentamicin resulted in a significant reduction in MIC against *Staphylococcus aureus* (68.8%), indicating the combined action of alkaloids [22]. This synergism may be related to the ability of these compounds to interfere with bacterial cell membrane integrity, promoting an increase in the therapeutic potential of antibiotics [6,32].

4. Conclusion

The qualitative analysis of the ethanolic extract of *Erythroxylum rosuliferum* (EEER) revealed the presence of bioactive compounds, such as flababenic tannins, flavonoids, xanthones, and chalcones. However, the antibacterial activity did not show a significant effect against standard and multidrug-resistant pathogenic bacterial strains. Nevertheless, the extract exhibited a potentiating effect when combined with antibiotics such as gentamicin, ampicillin, and norfloxacin, enhancing the efficacy of these drugs against Gram-positive and Gram-negative bacteria. Despite the promising results, the study presents some limitations, particularly concerning the more detailed characterization of the extract's phytochemical compounds and the understanding of the molecular interactions between EEER and the evaluated antibiotics.

Conflict of Interest

The authors declare no conflict of interest.

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