Grasas y Aceites 76 (2)
April-June 2025, 2320
ISSN-L: 0017-3495, eISSN: 1988-4214
https://doi.org/10.3989/gya.0435251.2320

Chemical profile, antibacterial activity and antibiotic-modifying effects of the fixed oil of *Annona squamosa* L. (Annonaceae)

A.C.C. Donelardy[a,✉], D.O.D. Leite[a], J.B. do Nascimento[a], L.L.L. Nascimento[a], F.F.G. Rodrigues[a], J.W.G. Castro[a], N.K.G. de Carvalho[a,b], J.W.S. Mendes[a], F.F.G-Rodrigues[a] and J.G.M. da Costa[a,b,✉]

[a]Department of Biological Chemistry, Natural Products Research Laboratory – LPPN, Regional University of Cariri, Rua Coronel Antônio Luiz, 1161 – Pimenta, Crato, Ceará 63105-010, Brazil
[b]Northeast Biotechnology Network – RENORBIO, State University of Ceará, Av. Silas Munguba, 1700, Campus do Itaperi, Fortaleza, Ceará 60714-903, Brazil2
✉Corresponding authors: cecilia.donelardy@urca.br; galberto.martins@urca.br

Submitted: 23 April 2025; Accepted: 01 August 2025; Published: 27 January 2026

SUMMARY: *Annona squamosa* Linn (Annonaceae) is a medicinal plant used to treat various ailments such as urinary infections, diarrhea, and fever. The aim of this study was to determine the chemical profile and evaluate the antibacterial and antibiotic-modifying activities of the fixed oil from *A. squamosa* seeds (OFSAs). The antibacterial activity was evaluated by determining the Minimum Inhibitory Concentration (MIC) and antibiotic modulation with aminoglycosides. The chemical analysis of the OFSAS identified 21 fatty acid esters, with elaidic acid being the major compound, comprising 38.06% of the oil. The MIC antibacterial assay showed inhibitory effects and the modulation with aminoglycoside antibiotics demonstrated enhanced antibacterial activity. Statistical analysis of the modulation assay was performed using two-way ANOVA followed by Tukey's post hoc test, with ****$p < 0.0001$. The use of OFSAs represents a promising perspective for application in antibacterial therapy, with further research needed, particularly regarding its mechanisms of action.

KEY-WORDS: *Annona squamosa*; *Antibacterial activity; CG-MS; Elaidic acid.*

RESUMEN: ***Perfil químico, actividad antibacteriana y efectos modificadores de los antibióticos del aceite* de annona squamosa *L. (annonaceae).*** *Annona squamosa* Linn (Annonaceae) es una planta medicinal utilizada para tratar diversas dolencias, como infecciones urinarias, diarrea y fiebre. El objetivo de este estudio fue determinar el perfil químico y evaluar las actividades antibacterianas y de modificación antibiótica del aceite de semillas de *A. squamosa* (OFSAs). La actividad antibacteriana fue evaluada mediante la determinación de la concentración mínima inhibitoria (CMI) y la modulación antibiótica con aminoglucósidos. El análisis químico de los OFSAs identificó 21 ésteres de ácidos grasos, siendo el ácido elaídico el compuesto principal, representando el 38,06% del aceite. El ensayo antibacteriano CMI mostró efectos inhibitorios y la modulación con antibióticos aminoglucósidos demostró una mayor actividad antibacteriana. El análisis estadístico del ensayo de modulación se realizó utilizando ANOVA de dos vías seguido de la prueba post hoc de Tukey, con ****$p < 0,0001$. El uso de los OFSAs representa una perspectiva prometedora para su aplicación en la terapia antibacteriana, aunque se necesitan más investigaciones, especialmente en cuanto a sus mecanismos de acción.

PALABRAS CLAVE: *Ácido elaidico; Actividad antibacteriana; Annona squamosa; CG-MS.*

Citation/Cómo citar este artículo: Donelardy ACC, Leite DOD, Nascimento JB do, Nascimento LLL, Rodrigues FFG, Castro JWG, Carvalho NKG de, Mendes JWS, Rodrigues FFG-, Costa JGM da. 2025. Chemical profile, antibacterial activity and antibiotic-modifying effects of the fixed oil of *annona squamosa* L. (Annonaceae). *Grasas Aceites* **76** (2), 2320. https://doi.org/10.3989/gya.0435251.2320

1. INTRODUCTION

Bacterial resistance to antibiotics is a growing global health problem which threatens the effectiveness of medicine. With the lack of antibiotics capable of treating diseases, the risk of infections and the number of affected individuals continue to rise (Neto *et al*., 2023). In this context, the use of medicinal plants has been improving therapeutic techniques due to the presence of secondary metabolites that provide various properties. Thus, the search for plants that can be used to combat bacterial infections becomes increasingly relevant (Arora *et al*., 2024).

The Annonaceae family includes 122 genera and approximately 2,440 species found in tropical and subtropical countries. The biological activities of plants from this family are mainly attributed to the common chemical composition among the species, which includes secondary metabolites such as acetogenins, alkaloids, and terpenes (Pinheiro, 2022). The genus *Annona* belongs to this family, comprising species known for their therapeutic and nutritional uses, such as *A. muricata*, *A. squamosa*, *A. cherimola*, *A. glabra*, and *A. reticulata* (Rangel *et al*., 2024).

Species of the *Annona* genus are used in traditional medicine as anti-infectious and anticancer agents, acting in the treatment of ulcers, dysentery, and boils. Therefore, the scientific interest in research that confirms the cited activities of these species, as well as their chemical characterizations, is necessary (Nugraha *et al*., 2019). The species *Annona squamosa* L. is widely used in folk medicine and is applied in the treatment of various ailments such as ulcers, prolapses, boils, nausea, and vomiting. In addition, it is used to reduce blood uric acid levels and as a muscle tonic (Ma *et al*., 2017; Moshi and Matoju, 2017; Santos *et al*., 2023).

A. squamosa has therapeutic properties, including anti-rheumatic, antidiabetic, antitumor, insecticidal, antiepidemic, antibacterial, and antioxidant effects (Ren *et al*., 2017; Maulana *et al*., 2023; Harahap *et al*., 2022; Sawant *et al*., 2023). Commonly known as "pinha," "sugar apple," or "ata," *A. squamosa* is a species native to the West Indies. Although native to tropical and subtropical countries, this species can be found in various regions, including Africa, India, Indonesia, Mexico, the United States, and Brazil (Sundaramahalingam *et al*., 2021).

Fixed oils (FO), also known as vegetable oils, have a basic chemical composition of triglycerides, unsaponifiable compounds, and free fatty acids. Triglycerides are identified as triesters of glycerol attached to long-chain fatty acid molecules, which are long-chain carboxylic acids. In industry, FOs are used as ingredients in cosmetics, such as moisturizers and bases (Bruno and Almeida, 2021). FOs can also be applied in the control of microorganisms, such as fungi and bacteria (Bezerra, 2023).

Recognizing the vast therapeutic potential of *A. squamosa*, studies on its chemical composition and biological activities are needed. Therefore, this study aimed to determine the chemical profile and evaluate the antibacterial and antibiotic-modifying activities of the fixed oil from *A. squamosa* seeds.

2. MATERIALS AND METHODS

2.1. Plant material

Fruits of *A. squamosa* were commercially purchased at the Juazeiro do Norte market (Ceará, Brazil). The seeds were manually separated from the pulp, sanitized with sodium hypochlorite (5 %), and then washed with distilled water. After cleaning, the *A. squamosa* seeds were dried in an oven at 60 °C and ground to obtain powder.

2.2. Extraction of fixed oil and transesterification

The extraction of the fixed oil was carried out using a Soxhlet apparatus with hexane for 4 hours. The solvent was then distilled in a rotary evaporator under reduced pressure, obtaining an extraction yield of 47.2 %.

For the transesterification process, 1 g of oil was mixed with methanol in an alkaline medium with potassium hydroxide and maintained under reflux for 2 hours. After the reaction was completed, the product was treated by column chromatography, and the collected fractions were analyzed by thin-layer chromatography for the determination of chemical composition.

2.3. GC-MS analysis

The methyl esters in the fixed oil from *A. squamosa* were analyzed using Shimadzu GC-MS QP2010 equipment, provided by Shimadzu Scientific Instruments Inc. (Columbia, MD, USA). The analysis was performed on a SH-Rtx-5 fused silica apolar capillary column (30 m × 0.25 mm ID; 0.25 µm film thickness), with helium gas as the carrier at a flow rate of 1.5 mL/min, with a split mode (1:100) and the injection port set to 220 ºC. A 1-µL sample of a 500-ppm solution prepared in dichloromethane was injected. The column was programmed to heat from 80 °C to 180 °C at 4 °C/min, then from 180 °C to 246 °C at 6.6 °C/min, and finally held at 280 °C for 10 minutes at 3.4 °C/min, with a total analysis time of 30 minutes. Spectra were obtained in the 40-350 m/z range with a sampling rate of 1.0 scan/s, an interface temperature of 280 °C, ion source temperature at 200 °C, and electron impact ionization at 70 eV. Individual segments were identified by computational searches using mass spectral databases and digital libraries (NIST 08), as well as by comparing the standard fragments with those already reported in the literature.

2.4. Antibacterial assays

2.4.1. Determination of minimum inhibitory concentration (MIC)

Antibacterial activity was evaluated using the CLSI (2015) microdilution method. The assay was carried out using standard Gram-negative strains: *Escherichia coli* ATCC 25226, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 27853, and multidrug-resistant strains: *Escherichia coli* 06, *Klebsiella pneumoniae Carbapenemase,* and *Pseudomonas aeruginosa* 027.

A stock solution was prepared by mixing 0.1 g of OFSAS, 1 mL of DMSO, and 9 mL of distilled water, giving a concentration of 1024 µL/mL The bacterial strains were activated in BHI medium (3.8 %) and incubated for 24 hours. After the initial culture, the inoculum was standardized to 10 % by adding 100 µL of the 3.8 % suspension. Serial dilutions of the oil were then performed in a 96-well plate by adding 100 µL of OFSAs (1024 µL/mL) to 100 µL of the bacterial inoculum at 10 %. Concentrations ranging from 512 to 8 µL/mL were tested and incubated at 35±2 °C for 24 hours.

The entire test was performed in triplicate, with the last row of the microdilution plate containing only the bacterial inoculums as a positive control. The reading was done colorimetrically by adding 25 µL of resazurin solution (0.01 %) to each well after incubation, where a color change from blue to pink indicates bacterial growth. The MIC was defined as the lowest concentration in the oil capable of inhibiting microorganism growth.

2.4.2. Antibiotic modifying activity

To evaluate the antibiotic-modifying activity, the effect of the oil as an enhancer of aminoglycoside antibiotics (amikacin and gentamicin) was analyzed using the methodology proposed by Coutinho *et al*. (2008). The test was performed in the presence and absence (positive control) of the natural compound by microdilution in triplicate. The subinhibitory concentration (MIC/8) of the oil was used with bacterial inoculums at 10 % BHI.

In the microdilution plate, 100 µL of antibiotic solutions at a concentration of 1024 µL/mL were distributed along with the inoculums containing the MIC/8 of the oil. Serial dilutions obtained antibiotic concentrations ranging from 512 to 0.5 µL/mL, as well as the inhibition control, which contained only the drugs and microorganisms. The 96-well plates were incubated at 35±2 °C for 24 hours, followed by reading with resazurin (0.01 %) as described previously.

2.5. Statistical analysis

The analyses for all assay data were performed three times, and the data were expressed as the mean (n=3) ± standard deviation (SD), using Analysis of Variance (ANOVA) followed by Tukey's multiple comparison test for data with a normal distribution and significantly similar standard deviations, using GraphPad Prism 6 software. Statistical values considered significant were with p-values of less than 0.05 ($p < 0.05$).

3. RESULTS AND DISCUSSION

3.1. Chromatographic analysis

The analysis of the OFSAS by GC-MS detected 21 methyl esters, with emphasis on the major ones: elaidic acid (38.06 %), arachidic acid (27.40 %), and palmitic acid (7.86 %). Table 1 lists the 21 identified compounds, along with the molecular formula of each compound, their percentage area, retention times, and their respective linear retention indices obtained. Figure 1 shows the chromatogram of the GC-MS analysis of OFSAS, where the compounds are identified with their respective retention times.

TABLE 1. Methyl esters of OFSAs detected by GC-MS

	Compounds	FM	%	RT	IR[1]
1	Octanal	$C_8H_{16}O$	0.30	4.536	1.222
2	Nonanal	$C_9H_{18}O$	0.66	5.658	1.200
3	Octanoic acid	$C_8H_{16}O_2$	0.54	7.481	1.294
4	Azelaaldehydic acid, methyl ester	$C_{10}H_{18}O_3$	0.50	8.330	1.356
5	Suberic acid monomethyl ester	$C_9H_{16}O_4$	0.22	8.799	1.391
6	Azelaic acid, monomethyl ester	$C_{10}H_{18}O_4$	0.23	9.835	1.507
7	2-pentadecanone	$C_{15}H_{30}O$	0.13	11.793	1.658
8	Methyl myristate	$C_{15}H_{30}O_2$	0.20	12.285	1.689
9	Methyl pentadecanoate	$C_{16}H_{32}O_2$	0.20	14.048	1.797
10	2-nonadecanone	$C_{19}H_{38}O$	0.15	15.255	1.877
11	Palmitic acid methyl ester	$C_{17}H_{34}O_2$	7.86	15.629	1.902
12	Hexadecanoic acid	$C_{16}H_{32}O_2$	0.30	16.094	1.936
13	Margaric acid methyl ester	$C_{18}H_{36}O_2$	2.64	17.029	2.005
14	Elaidic acid methyl ester	$C_{19}H_{36}O_2$	38.06	17.968	2.082
15	Stearic acid methyl ester	$C_{19}H_{38}O_2$	6.84	18.279	2.107
16	Methyl nonadecanoate	$C_{20}H_{40}O_2$	0.79	19.474	2.208
17	Methyl cis-9,10-epoxystearate	$C_{19}H_{36}O_3$	6.98	20.017	2.250
18	Methyl (6E,9E)-6,9-octadecadienoate	$C_{19}H_{34}O_2$	3.68	20.264	1.545
19	Arachidic acid methyl ester	$C_{21}H_{42}O_2$	27.40	20.834	2.299
20	Docosanoic acid methyl ester	$C_{23}H_{46}O_2$	1.26	24.226	2.511
21	Tetracosanoic acid	$C_{24}H_{48}O_2$	1.05	27.219	2.685
	TOTAL		100	30.000	

Some compounds found in the OFSAs have biological activities. Elaidic acid, which accounts for 38.06 % of the oil (1, RT 17.968 min), is mentioned in several publications for its properties such as antibiotic (Cabral *et al*., 2013) and anti-inflammatory (Xia *et al*., 2020). Elaidic acid is a stereoisomer (*trans*) of oleic acid, the main trans fatty acid found in vegetable oils and margarines. It was investigated as a cause of oxidative stress in mice due to its reduction in vitamin E levels (Ohomori *et al*., 2016).

Furthermore, the ingestion of vegetable oils rich in elaidic acid has been studied by Shao and Ford (2014) and Liu *et al*. (2022), who associate this acid with inflammation and oxidative stress in animals and humans, correlating this fatty acid with the release of reactive oxygen species (ROS) in organisms.

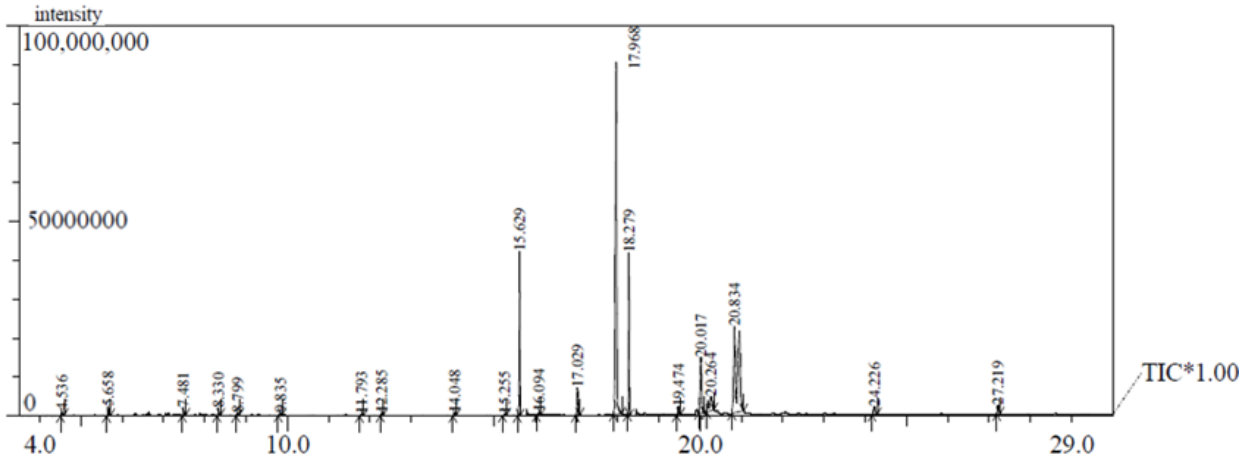

FIGURE 1. Chromatogram CG-MS of *OFSAs* Methyl Esters. Source: Author's own, (2024).

Recent research suggests that elaidic acid, combined with acrylamide, can act synergistically to cause cell damage and oxidation (Yuanyuan *et al*., 2024). Lai *et al*. (2024) determined that elaidic acid supplementation can suppress tumor growth, having a beneficial effect on humans. However, this fatty acid may be associated with coronary diseases and arteriosclerosis, promoting systemic inflammation (Debbabi *et al*., 2017).

Palmitic acid (2, RT 15.629 min) is a saturated fatty acid, the main constituent of palm oil, also present in OFSAS at 7.86 %. A high content of palmitic acid in food can have harmful health effects. However, although this acid is considered harmful to health, it is an essential component for cells, lipids, proteins, and other molecules due to its ability to promote better absorption of fats and calcium in organisms. In general, vegetable oils contain between 5 and 20 % palmitic acid in the sn-2 position (González *et al*., 2012; Mancini *et al*., 2015). Figure 2 shows the structures of the constituents identified in OFSAs.

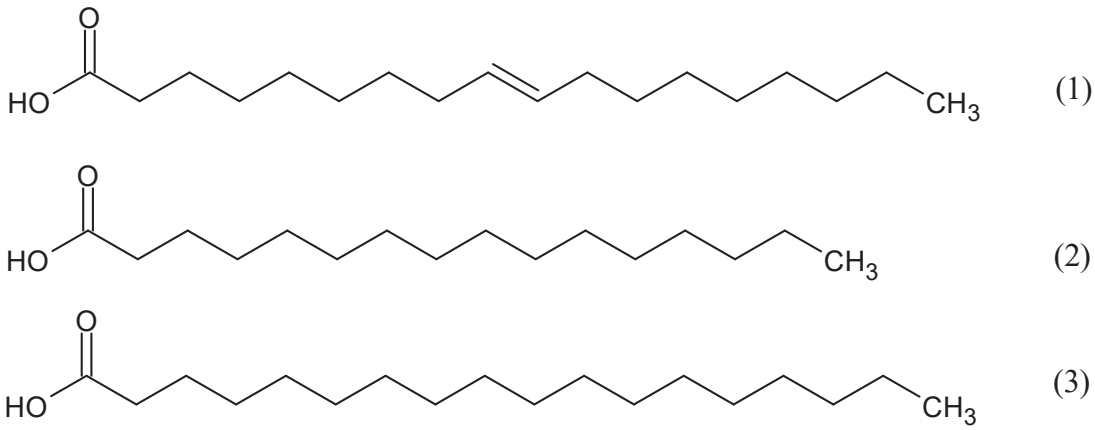

FIGURE 2. Structures of the major constituents identified in OFSAs (1) elaidic acid; (2) palmitic acid; (3) stearic acid. Source: Author's own, (2024).

3.2. Minimum inhibitory concentration (MIC)

The MIC results against the standard Gram-negative strains showed that OFSAs has an inhibitory effect, with MIC results of 512 µg/mL. For the multidrug-resistant bacterial strains, MIC values varied between 512 and ≥1024 µg/mL, depending on the bacterial species studied (Table 2).

TABLE 2. Minimum inhibitory concentration of OFSAs against standard gram-negative and multidrug-resistant strains

OFSAs	
BACTERIA	**MIC (µg/mL)**
E. coli ATCC 25226	512
E. coli 06	≥ 1024
P. aerugenosa ATCC 27853	512
P. aerugenosa 027	≥ 1024
K. pneumoniae ATCC 4352	512
KPC	512

Assays were conducted in triplicate (n=3). Two-way ANOVA followed by Tukey's post test, using GraphPad Prism 6.0 software. **** $p < 0.0001$. Source: Author's own, (2024).

Studies such as those by Albuquerque *et al.* (2024) report the correlation between the presence of acids such as linoleic, oleic, and palmitic acids and biological properties, including microbiological, neuroprotective, nutritional, and antibacterial activity. Furthermore, in a study evaluating the antibacterial activity of extracts of endophytic fungal metabolites from the Pantanal against multidrug-resistant bacteria, Borba (2023) observed the presence of oleic, linoleic, stearic, and palmitic acids in the extract of *Acremonium sp.* (NF14), correlating these compounds with the antibacterial therapeutic potential found.

The study by Pinto *et al.* (2017) showed that the methanolic extract of *A. squamosa* seeds did not yield significant MIC results against *K. pneumoniae*, *E. coli*, or *P. aeruginosa*. On the other hand, the oil from the seeds of the same species, studied by Holanda *et al*. (2023), demonstrated activity against *P. aeruginosa*, *K. pneumoniae*, *E. faecalis*, and *S. aureus*. The difference between these results may be related to the type of extraction and solvents used in each, contributing to different chemical compositions.

The chemical characterization of the same seed oil studied by Holanda *et al.* (2023) was also determined. Some major compounds found in that study were also detected in the OFSAs, such as palmitic acid, stearic acid, oleic acid, and linoleic acid. Therefore, the moderate activity found in the MIC of OFSAs is consistent with this study, as the MIC results and chemical composition are correlated.

3.3. Modulatory activity

For the modulatory action, the OFSAs exhibited both synergistic and antagonistic effects against the standard bacterial strains. The synergistic action of OFSAs was predominant against *P. aeruginosa*, both in combination with amikacin and gentamicin, with a reduction in the MIC from 64 to 16 µg/mL and from 256 µg/mL to 16 µg/mL, respectively.

For *E. coli* ATCC 25226 with amikacin and *K. pneumoniae* ATCC 4352 with gentamicin, the oil only stabilized bacterial growth, showing no modulatory action, with the MIC remaining at 256 µg/mL in both cases. Antagonistic results were observed when evaluating OFSAs with gentamicin against *E. coli* ATCC 25226, but when tested against *K. pneumoniae* ATCC 4352, the oil was able to enhance the action of the drug, reducing the MIC from 128 to 64 µg/mL (Figure 3).

As shown in Figure 4, synergism between OFSAs and antibiotics was observed for all the tested multidrug-resistant strains, with the exception of gentamicin against KPC, where no statistically significant difference was found. Against *P. aeruginosa* 027, there was a reduction in the MIC of amikacin from 128 µg/mL to 64 µg/mL and of gentamicin from 512 µg/mL to 64 µg/mL. Against *E. coli* 06, the oil reduced the MIC of amikacin from 256 µg/mL to 64 µg/mL, and gentamicin from 128 µg/mL to 8 µg/mL. Against KPC, there was potentiation of amikacin's antibacterial activity, reducing the MIC from 64 µg/mL to 8 µg/mL, which was the lowest MIC found in this study.

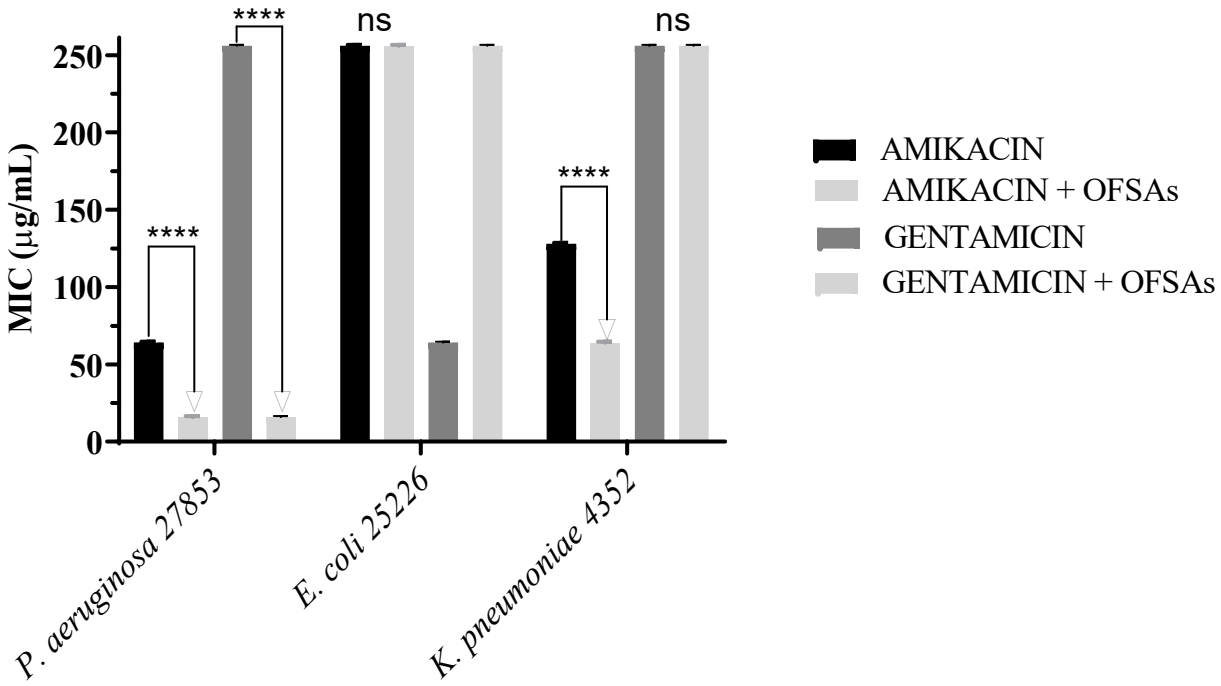

FIGURE 3. Modifying activity of the antibiotics amikacin and gentamicin combined with OFSAs against standard strains *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25226, and *K. pneumoniae* ATCC 4352. Two-way ANOVA followed by Tukey's post test, using GraphPad Prism 6.0 software. **** $p < 0.0001$; n=3. Source: Author's own, (2024).

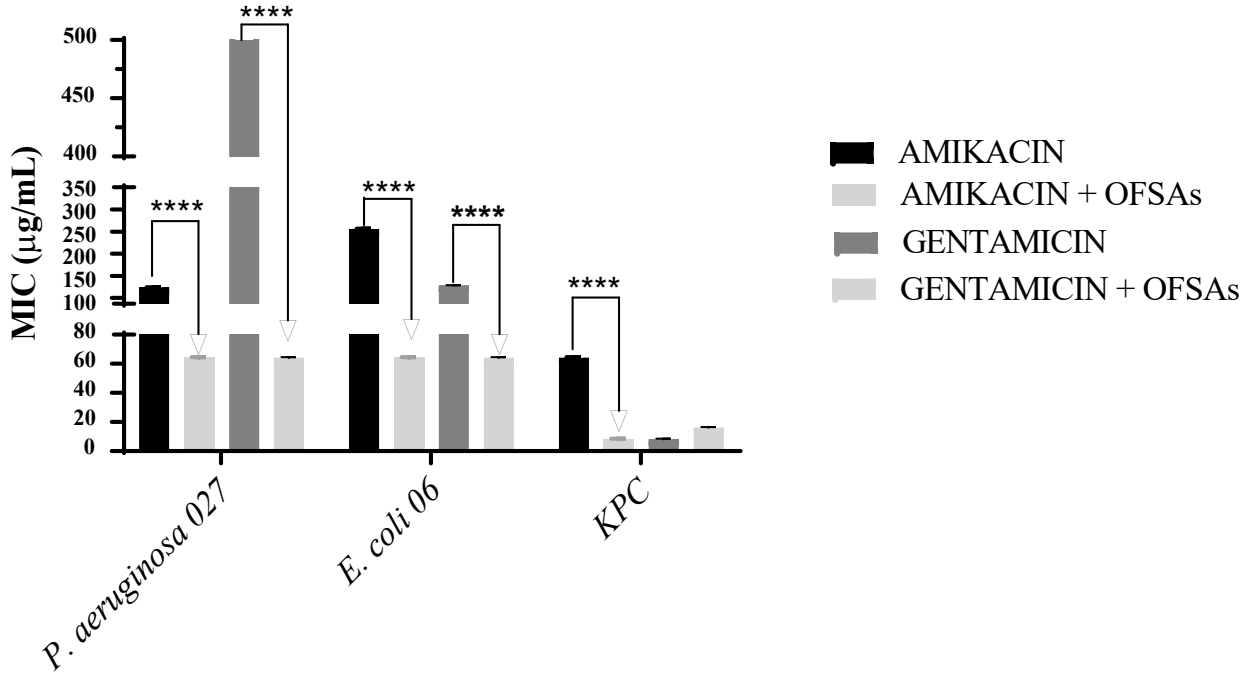

FIGURE 4. Modifying activity of the antibiotics amikacin and gentamicin combined with OFSAs against the multidrug-resistant strains *P. aeruginosa* 027, *E. coli* 06, and KPC**.** Two-way ANOVA followed by Tukey post test, using GraphPad Prism 6.0 software. **** $p < 0.0001$; n=3. Source: Author's own, (2024).

Antibiotic resistance in KPC has been reported by authors such as Souza, Ramalho, and Camargo (2020), who state that this strain is resistant to about 95 % of antimicrobial drugs. Bacterial resistance to

aminoglycoside drugs is associated not only with low permeability of the outer membrane but also with enzymatic modification or inactivation of the antibiotic (Urban-Chmiel *et al.*, 2022). Several studies show that natural products have therapeutic action against bacteria by enhancing the activity of antibiotics, making them potential alternatives for treating infections caused by multidrug-resistant strains (Tintino *et al*., 2015; Araújo *et al*., 2020).

According to Nonato (2020), the combination of antibiotics with natural products can reduce the amount needed for effective treatment due to the decrease in the minimum inhibitory concentration (MIC), as observed in the modulation. This occurs due to the synergistic effect of the combination, which promotes the penetration of the drug into the cell, overcoming the membrane permeability challenges present in Gram-negative bacteria.

4. CONCLUSIONS

The results obtained demonstrate that the fixed oil of *A. squamosa* seeds exhibits antibacterial activity with a moderate effect when tested alone against the strains used in this study. However, its ability to promote modulating action with aminoglycoside antibiotics such as gentamicin and amikacin suggests its potential as an adjunct in antibacterial therapy. The results of this biological activity are related to the chemical composition of OFSAs, which contains fatty acids with pro-oxidant and antimicrobial activities, as previously discussed. However, the potential risks associated with high doses of *A. squamosa* seeds, as observed in other studies, highlight the need for further investigation to better understand the therapeutic potential and possible limitations of this species.

ACKNOWLEDGMENTS

The authors thank the Natural Products Research Laboratory of the Department of Biological Chemistry, the Regional University of Cariri (URCA), and RENORBIO/UFC for institutional and technical support, as well as the Cearense Foundation for Scientific and Technological Development Support (FUNCAP), the Coordination for the Improvement of Higher Education Personnel (CAPES), and the National Council for Scientific and Technological Development (CNPq) for their support in the development of this work.

DECLARATION OF COMPETING INTEREST

The authors of this article declare that they have no financial, professional or personal conflicts of interest that could have inappropriately influenced this work.

AUTHORSHIP CONTRIBUTION STATEMENT

A.C.C. Donelardy: research, writing, formatting, and editing. D.O.D. Leite: idea conception and revision J.B. do Nascimento: research, formatting, and editing. L.L.L. Nascimento: research, formatting, and editing. F.F.G. Rodrigues: research, formatting, and editing. J.W.G. Castro: research, formatting, and editing. N.KG. de Carvalho: research, formatting, and editing. J.W.S. Mendes: research, formatting, and editing. F.F.G-Rodrigues: idea conception and revision. J.G.M. da Costa: idea conception and revision.

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