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Coccoloba marginata Benth fruits: a rich source of bioactive compounds

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Abstract

The aim of the present study was to investigate the chemical profiles of the fruit extracts of *Coccoloba marginata* Benth and the cytotoxic activity of the ethanolic extract against two cell lines, HCT8 (human colon carcinoma) and A549 (lung adenocarcinoma). The ethanolic extract was found to contain gallic and protocatechuic acids, flavonoids derived from quercetin and myricetin, and anthocyanins. This extract inhibited the growth of cancer cells (GI_{50}: 123.2 µg GAE/mL for A549 and GI_{50}: 44.15 µg GAE/mL for HCT8, where GAE stands for Gallic Acid Equivalent) without cytotoxic effects on normal cells (GI_{50}: 145.9 µg GAE/mL for human umbilical vein endothelial cell). However, the selectivity index (< 1) indicated low specificity. Therefore, the results suggest that the phenolic compound-rich ethanolic extract exhibits promising antitumor effects. Nonetheless, further studies are needed to enhance its efficacy and selectivity, emphasizing the value of biodiversity for sustainable natural therapies.

Keywords: polygonaceae, Cipó-pau, phenolic acids; flavonoids; cytotoxic activity.

Practical Application: Ethanolic extract of *Coccoloba marginata* fruits shows a potential anticancer effect.

1 INTRODUCTION

The proper functioning of the body is one of the essential elements for people's quality of life. To achieve this, it is crucial that our diet includes fundamental nutrients, such as micronutrients and phenolic compounds, which may vary according to the different stages of life (Kumar et al., 2024; Maggini et al., 2018; Michalak et al., 2021; Zgoła-Grześkowiak & Grześkowiak, 2021).

In this context, the World Health Organization (WHO) provides guidelines on the types of foods required for each age group. Over the years, it has been observed that many individuals tend to have an inadequate diet, either due to a lack of time to prepare nutritious and complete meals or because of the convenience of products available on supermarket shelves (Imtiyaz et al., 2023). Thus, it is common for micronutrients and phenolic compounds to be consumed in insufficient quantities in the contemporary diet. Therefore, it is often necessary to rely on supplements to address deficiencies in these vital nutrients, as an individual's health and well-being are optimized when nutrients are present at adequate levels (Gonçalves et al., 2022; Kodentsova & Risnik, 2020a, 2020b; Kumar et al., 2021).

From this perspective, it is crucial to understand that the formulation of nutritional supplements requires the careful selection of appropriate raw materials for the extraction and development of bioactive compounds. In this context, the Amazon emerges as a promising region for such investigations. Analyzing the bioactive compounds present in Amazonian fruits is essential to exploring their nutritional and therapeutic potential, creating innovative products, valuing local biodiversity, and promoting sustainable development. By doing so, we can unveil nature's secrets and contribute to society's health and well-being while respecting and protecting the invaluable Brazilian Amazon (Lima et al., 2023; Sánchez-Capa et al., 2023; Sousa et al., 2021).

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Investigation of the chemical constituents of plants has contributed to the identification of bioactive compounds with significant therapeutic potential, playing a crucial role in the development of new drugs and dietary supplements (Dar et al., 2023; Dincheva et al., 2023; Krishnaprabu, 2020; Shrinet et al., 2021; Tiwari & Shukla, 2020).

Among the various fruits of the Amazon region, *Coccoloba marginata* Benth (Figure 1), commonly known as "cipó-pau" or "ocaimã," is a polymorphic species of the Polygonaceae family. This plant exhibits variations in habits, leaves, and inflorescences, taking the form of a climbing shrub, vine, or small tree. In the Cerrado biome, it bears fruit between July and October, with seeds dispersed by birds and pollination carried out by bees, dipterans, and beetles. The species is utilized in ornamentation and environmental restoration, thriving in rocky Cerrado areas, riparian forests, and gallery forests within the Cerrado, Amazon, and Atlantic Forest biomes. Its distribution spans across Brazil, except for the southern region (Melo, 2020).

In the *Coccoloba* genus, several species have been studied for their pharmacological properties, including antioxidant, antimicrobial, and cytotoxic activities. Research conducted on species such as *C. peltata* Schott, for instance, has identified chemical compounds with moderate cytotoxic activity against cancer cell lines. Similarly, studies on *C. mollis* Casaretto have highlighted triterpenes as bioactive compounds of the plant, underscoring its pharmacological potential (Hamed et al., 2024; Oliveira et al., 2008).

Thus, the characterization of bioactive compounds in fruits of *Coccoloba* species is of great importance to human health. Phenolic compounds, such as flavonoids and phenolic acids found in fruits, are widely recognized for their antioxidant properties, which neutralize free radicals and reduce oxidative stress, a factor associated with the development of chronic diseases (Cosme et al., 2020; Rudrapal et al., 2022; Silva et al., 2022). Moreover, the cytotoxic activity of certain phytochemicals present in this genus has garnered interest in the field of oncology, being considered promising for the development of anticancer agents.

In this context, the study of the chemical constituents of *C. marginata* fruit and its potential cytotoxic activities is essential to expand scientific knowledge about the benefits of this species. The identification and characterization of its bioactive compounds from its extract can provide a basis for the development of new therapeutic agents while contributing to the valorization of native natural resources with economic and medicinal potential.

Figure 1. Fruits of *C. marginata* Benth.

1.1 Relevance of the work

This study is a pioneering effort in the chemical characterization and cytotoxic activity evaluation of the fruits of *Coccoloba marginata*. In the ethanolic extract, two phenolic acids, eight flavonoids derived from quercetin and myricetin, and five anthocyanins were identified. This extract demonstrated a promising antitumor effect. The results highlight the therapeutic potential of the species, although its low selectivity calls for further investigation. The research underscores the importance of prospecting bioactive compounds in underexplored native species, with potential for the development of pharmacological and biotechnological applications based on Brazilian biodiversity.

2 MATERIAL AND METHODS

2.1 Material

HPLC-grade methanol, acetonitrile and formic acid were acquired from Merck (Darmstadt, Germany). Distilled water was purified using a Milli-Q water purification apparatus (Millipore, Bedford, MA, USA). Leucine enkephalin reference solution was purchased from Waters Co (Manchester, UK). Other reagents and solvents were of analytical grade and commercially available.

2.2 Sample collection

The fruit was collected at Poço Encantado Waterfall (-13.873795993310823, -47.260703013005354), located in the municipality of Alto Paraíso, in the state of Goiás, Brazil. After collection, the fruit was transported to the Amazon Science and Technology Studies Center at the Federal Institute of Education, Science, and Technology of Amazonas, where it underwent sanitation, freezing, and lyophilization at the Núcleo de Estudos em Ciência e Tecnologia da Amazônia (NECTAM).

2.3 Extract preparation

The whole fruit, including seed, peel, and pulp, was lyophilized and ground into a fine and homogeneous powder using a blender (Li1.5 Skymsen). Initially, 50 grams of the pulverized sample were placed in a hermetically sealed glass container with hexane (Êxodo Científica) in a 1:10 (weight/volume) ratio and subjected to ultrasonic bath extraction (SSBu10L, Prolab) at room temperature (approximately 25 °C). After this step, the solvent was separated by filtration using filter paper for subsequent treatment and fatty acid analysis, while the solid residue was dried and then subjected to ethanolic extraction.

The ethanol extraction (Êxodo Científica) was carried out in a glass container, using the same 1:10 (weight/volume) ratio, and macerated in an ultrasonic bath for 30 minutes, three times. After separation, the solution was filtered through qualitative filter paper.

2.3.1 Preparation of extract for analysis by solid phase extraction

The solid-phase extraction (SPE) process involves four primary operational steps: column activation (balance and conditioning), sample loading, washing, and elution. These parameters were employed to extract sugar residues from the samples to facilitate the identification of phenolic compounds present in the extract. Figure 2 illustrates the complete SPE procedure.

2.4 Ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry analyses

The extract from solid-phase extraction treatment were dissolved in methanol and filtered through a polyvinylidene fluoride (PVDF) membrane (13 mm × 0.22 µm, WHATMAN) to a chromatographic vial (1.5 mL). Filtered samples were sonicated to remove air bubbles for analysis by high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC-QToF/MS) analyses. The analyses were performed on a Waters Xevo® G2-XS QT of mass spectrometer (Waters Co. Manchester, UK) coupled to an Acquity HClass UPLC and monitored with MassLynx® software (v. 4.1). Separation of the metabolites was achieved on an Acquity UPLC BEH C18 with reverse phase column (100 mm × 2.1 mm i.d, 1.7 µm particle size) at 40°C (± 2 °C) and eluted with a gradient system of 0.1% formic acid aqueous solution (A) and 0.1% formic acid in acetonitrile (B) at a flow rate of 0.3 mL/min, using the following linear gradient elution program (A:B, in %: 0–15 min [98:2], 15–20 min [80:20], 20–25 min [60:40], 25–27 min [2:98] 27–27.10 min [98:2], 27.10–30 [98:2]). The injection volume was 10 µL. The nebulization process operated in negative mode, with the mass range between 100 and 1,500 amu, and a scan time of 0.2 s. The ESI source parameters were: capillary voltage of 3.0 kV, desolvation temperature of 250 °C; source temperature of 100 °C; cone voltage 30 V; cone gas flow of 50 L h^{-1}. The desolvation gas flow for negative polarity was 700 L/h. Both low (MS^1, 6 eV) and high (MS^2, ramped from 20 to 35 eV) collision energy data were recorded by employing MS^E continuum mode, acquisition time 0 to 30 minutes and mass correction during acquisition by an external reference (LockSprayTM), Leucine enkephalin (m/z 554.2615 $[M-H]^-$ and 556.2771 $[M+H]^+$) was used as the lock mass calibrant.

2.5 Nuclear magnetic resonance analysis

The ethanolic extract (10.0 mg) was dissolved in CD_3OD (530.0 µL) containing tetramethylsilane (TMS) as the internal reference (0.0 ppm, ≥ 99.0% purity). This solution was transferred to a 5 mm nuclear magnetic resonance (NMR) tube. NMR analyses (^1H, ^1H–^1H COSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC) were performed on a 11.75 T spectrometer Bruker® Avance III HD BBFO Plus SmartProbeTM (New York, NY, USA) observing ^1H and ^{13}C at 500.13 MHz and 125.8 MHz at 298.0 K, respectively (Mar et al., 2021).

2.6 Gas chromatography coupled to mass spectrometry analysis

After drying the hexane extract, 10 mg of the lipid fraction were mixed with 0.25 mL of chloroform/methanol (2:1; v/v) and 500 µL of 0.1 M NaOH in methanol. This mixture was heated at 60 °C for 30 minutes. Subsequently, the reaction was halted by adding 0.2 mL of distilled water. The formed fatty acid methyl esters (FAMEs) were extracted by adding 1 mL of hexane, followed by vortex agitation for one minute. After agitation, the upper phase was isolated and collected according to the established methodology of Vasquez et al. (2021), with modifications.

The procedure was repeated with the lower phase to recover the remaining FAMEs. The mixture was agitated and left to stand for 30 min, after which 1 mg/mL of hexane was collected and analyzed using a gas chromatography-mass spectrometry (GC-MS) system (Nexis GC2030, GCMS-QP2020 NX,

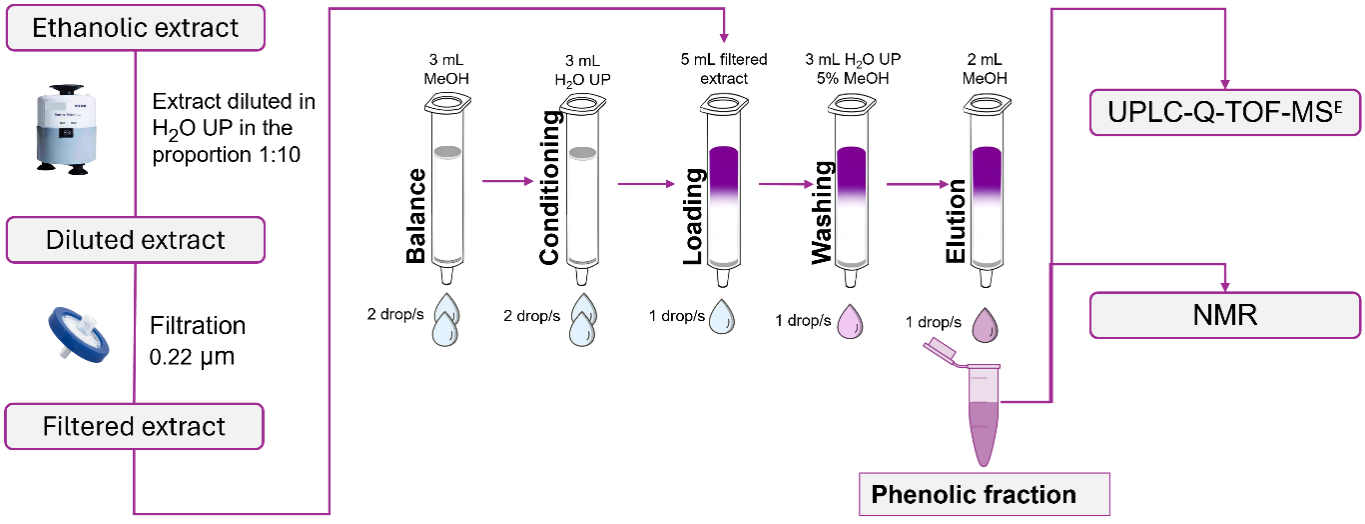

Figure 2. Preparation of extract for analysis by solid phase extraction.
UPLC-Q-TOF-MS^E: Ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; NMR: nuclear magnetic resonance.

Shimadzu) installed at the Analytical Center of the Federal Institute of Amazonas, Manaus Centro campus (IFAM-CMC). The system was equipped with a split-splitless injector and an automatic sampler. The FAMEs were separated using a SHRTx-5Sil-MS fused silica capillary column (30 m, 0.25 mm id, and 0.25 µm). Helium was used as the carrier gas at a flow rate of 2 mL/min. The injection temperature was set to 260 °C in split mode, with an injection volume of 1 µL. The mass spectrometer's ion source and interface temperatures were maintained at 230 and 280 °C, respectively.

The injection temperature was set at 220 °C in split mode, with an injection volume of 1 µL. The ion source and interface temperatures of the mass spectrometer were maintained at 220 and 220 °C, respectively. Chromatographic analysis began at 40 °C, with a ramp rate of 3 °C/min up to 210 °C, where it was held for 5 min. The total runtime of the program was 61.67 minutes. Mass spectra were obtained by electron impact ionization at 70 eV. The scan rate was 1.6 scans/s over a mass range of 30–700 amu. Fatty acid identification was carried out using the WILEY 275 and National Institute of Standards and Technology (NIST 3.0) libraries. Analytical determinations were performed in duplicate, and results were expressed as grams of fatty acid per 100 g of FAMEs (Vasquez et al., 2021).

2.7 Assays of cytotoxicity and proliferation

Ethanolic extract was suspended in ultrapure water before use in the biological assays. Human colorectal ileocecal adenocarcinoma (HCT8), human lung epithelial cell adenocarcinoma (A549), and normal human umbilical vein endothelial cell (HUVEC) were used for the *in vitro* assays. All cells were cultured in DMEM/Ham-F12 medium, supplemented with 10% fetal bovine serum, and 100 µg/mL penicillin. For the cytotoxicity test, cells were seeded into 96-well plates at 5×10^3 cells/well (A549), 6×10^3 cells/well (HUVEC), and 1×10^4 cells/well (HCT8) density and incubated for 24 hours. Based on the quantification of free phenolic compounds, the tested concentrations of *C. marginata* fruit extract were established (10 to 250 µg GAE/mL) and cells were treated. After 48 hours of incubation, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.5 mg/mL) was added to each well and incubated for 4 hours at 37 °C. This reagent is reduced to blue formazan crystals by metabolically active cells. In a sequence, the formazan crystals formed were dissolved in DMSO and the absorbance was measured at 570 nm (Paes et al., 2024). The IC_{50} (50% cell viability inhibition), GI_{50} (50% growth inhibition), and LC_{50} (50% cell death) parameters were performed. Additionally, the selectivity index (SI) was calculated by the ratio of IC_{50} (normal cell line) / IC_{50} (cancer cell line) (Carmo et al., 2019).

3 RESULTS AND DISCUSSION

3.1 Chemical characterization

In recent years, UPLC-Q-TOF-MS^E has been used as an effective analytical tool for chemical characterization and metabolite identification because of its high resolution, sensitivity and accuracy. TOF-MS^E technology uses two interleaved scan functions with different collision energies, allowing for the simultaneous acquisition of precursor ions with low collision energy and fragment ions with high collision energy (Xu et al., 2020). Both MS full scan and MS^E high-energy fragment information can be obtained from a single LC injection, which has increased the credibility of results when identifying unknown compounds (Xu et al., 2016).

The application of UPLC-qTOF-MS is widely carried out for the structural elucidation of polyphenols due to the nature of these compounds present in the extracts (Sanches et al., 2022; Wei et al., 2024; Xu et al., 2016, 2020). Thus, both negative and positive ionization modes are employed for identification. Despite being detectable by both ionization modes, most phenolic subclasses are detected in negative mode because the sensitivity is better and they mainly produce the ion $[M-H]^-$. In contrast, the positive mode is used for anthocyanins subclass since $[M]^+$ ion is the predominant specie generated due to its structure (Díaz-de-Cerio et al., 2023).

Analyses by UPLC-MS/MS and 1D and 2D NMR of the ethanolic extract of *C. marginata* fruits allowed the identification of 15 compounds (Table 1). The analysis of the constituents was performed comparatively between the extract and spectral data described in the literature. The constituents presented in the sample examined in this study are, mainly, phenolic acids and flavonoids. Figure 3 shows the base peak intensity chromatogram of peaks 3 to 10 corresponding to Table 1 in negative ionization mode. Based on the peak intensity in the chromatogram (UV, Figure 3), it can be concluded that compound **7** (RT 13.21 min) is the major compound, followed by compounds 8 (RT 13.71 min), 5 (RT 11.36 min), 6 (RT 11.60 min), and 4 (RT 10.59 min).

Peak 1 was identified as gallic acid (**1**, RT at 1.8 min), and exhibited an $[M-H]^-$ ion at *m/z* 169.0137 and, upon fragmentation (MS^2), an intense ion at *m/z* 125 due to the loss of a carbon dioxide molecule $[M-H-CO_2]^-$ (44 Da). Confirmation of the compound was achieved through the observation of a singlet at δ 7.07 ppm (s, H-2, H-6) in the ^1H NMR spectrum. This signal showed a direct correlation with the carbon at 109.0 ppm (C-2, C-6) and long-range correlations with carbons at δ 138.1 (C-4), δ 144.7 (C-3, C-5), and δ 169.0 (C-7). Gallic acid had been previously identified in *C. cowellii* (Méndez et al., 2021).

Peak 2 (RT at 3.59 min) showed a mass of $[M-H]^-$ ion at *m/z* 153.0186 (error –1.1 ppm) and, in the secondary mass spectra, *m/z* 109 and 153. This result was compared with the retention time of the analyte and the standard used, and peak 2 was identified as protocatechuic acid (**2**). In the ^1H NMR spectrum, a signal at δ 7.44 (dd, J = 8.1, 2.1 Hz, H-6) was observed, consistent with the literature (Chen et al., 2018).

Peaks 3 and 5 showed fragments at *m/z* 316 $[M-H]^-$ in the second-order spectrum, confirming the loss of sugar through heterolytic cleavage, suggesting the presence of the aglycone myricetin (Méndez et al., 2021). Peak 3 (RT at 9.69 min) presented an *m/z* 479.0825 $[M-H]^-$ and fragments at *m/z* 316 (missing of hexoside), which correspond to myricetin aglycones, *m/z* 271 (losses of CO and OH from *m/z* 316), and *m/z* 179, corresponding to the characteristic fragment ions of aglycone (Jiang

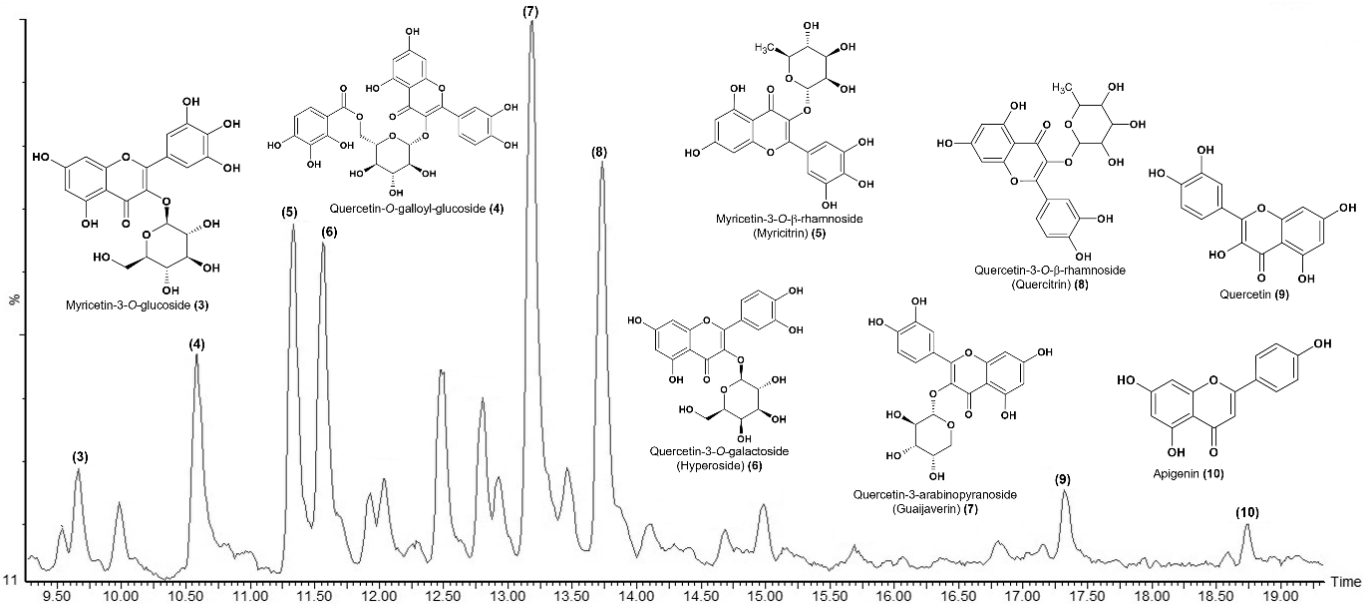

Figure 3. Base peak intensity chromatogram in negative ion mode of the methanolic extract of *C. marginata* fruits.

et al., 2021). The aromatic region in the ^{1}H NMR spectrum (δ 5.5 to 10.0) revealed the presence of flavonoids previously reported in the *Coccoloba genus* (Figure 4) (Méndez et al., 2021; Wafa et al., 2023). The data obtained from MS and 1D and 2D NMR confirmed the substance myricetin-3-*O*-glucoside (**3**) (Oliveira et al., 2021). Compound **5** (RT 11.36 min) exhibited an unprotonated ion at *m/z* 463.0853 $[M-H]^-$ (-4.9 ppm), and fragmentation ions at *m/z* 316 due to the aglycone characteristic of myricetin, a loss of rhamnose residue loss (146 Da) and fragment at *m/z* 271, due to the losses of 46 Da (C_2H_2O) from myricetin group. The compound corresponding to peak 5 was confirmed by ^{1}H NMR signals at δ 6.20 (m, H-6), δ 6.36 (d, *J* = 2.0 Hz, H-8), and δ 6.97 (s, H-2', 6'). Additionally, a signal at δ 5.30 (d, *J* = 1.5 Hz, H-1") was observed, attributed to the anomeric hydrogen of a rhamnose unit, and a doublet at δ 0.94 (d, *J* = 6.2 Hz, H-6") indicating the presence of a methyl group. Therefore, the constituent myricitrin (**5**) was confirmed based on spectral data from the literature (Oliveira et al., 2021).

Compounds **4** (RT 10.59 min), **6** (RT 11.60 min), **7** (RT 13.21 min) and **8** (RT 13.71 min) showed a fragmentation ion at *m/z* 301 $[M-H]^-$, assigned to quercetin aglycone. Thus, compound **4** exhibited an ion at *m/z* 615.1005 $[M-H]^-$ (error 3.1 ppm). Based on the MS/MS daughter ions corresponding to the loss of a galloyl moiety and a hexose moiety at *m/z* 463 $[M - 152 - H]^-$ and *m/z* 301 $[M - 152 - 162 - H]^-$, the existence of a quercetin moiety is indicated. Thus, compound **4** was further tentatively identified as quercetin-*O*-galloyl-glucoside by its high intensity radical aglycone ion at *m/z* 300 in MS/MS spectra, a similar fragmentation profile described in literature (Ain et al., 2024). The flavonoid quercetin-*O*-galloyl-glucoside (**4**) was confirmed by signals corresponding to the meta coupling of system A at δ 6.17 (d, *J* = 2.1 Hz, H-6) and δ 6.39 (d, *J* = 2.1 Hz, H-8). Additionally, signals were observed at δ 7.76 (d, *J* = 2.1 Hz, H-2'), δ 6.82 (d, *J* = 8.1 Hz, H-5'), and a doublet of doublets at δ 7.61 (dd, *J* = 8.1, 2.1 Hz), consistent with the B system 3', 4'-dioxigenated. The anomeric hydrogen in (**4**) was confirmed by a doublet at δ 5.18 (d, *J* = 7.8 Hz, H-1") that showed a ^{1}H–^{13}C HSQC correlation map with the carbon at δ 103.4 (C-1"). The presence of the galloyl group was confirmed by the signal at δ 6.80 (s, H-2, H-6), which exhibited a direct correlation with the carbon at 109.0 ppm (C-2, C-6) (Oliveira et al., 2024).

Compound **6** (RT 11.60 min) displayed $[M-H]^-$ ion at *m/z* 463.0853 (error -4.9 ppm) and MS^2 fragments at *m/z* 300 (loss of 162 Da) and *m/z* 271 and *m/z* 255, due to the fragmentation of quercetin aglycone (Jiang et al., 2024). The flavonoid hyperoside (**6**) was characterized by resonances at δ 6.20 (d, *J* = 2.0 Hz, H-6), δ 6.40 (d, *J* = 2.0 Hz, H-8), and two doublets at δ 7.85 (d, *J* = 2.2 Hz, H-2') and δ 6.84 (d, *J* = 8.3 Hz, H-5') (Oliveira et al., 2021). This substance exhibits a diverse range of biological activities, including anti-tumor, anti-inflammatory, anti-oxidative, antifungal and anti-viral properties. Due to these characteristics, hyperoside is considered as a candidate for the treatment of various diseases, such as sepsis, arthritis, colitis, diabetic nephropathy, myocardial ischemia-reperfusion, pulmonary fibrosis, and cancers (Gao et al., 2019; Peng et al., 2022; Wang et al., 2022).

Compound **7** (RT 13.21 min) showed an unprotonated molecular ion at *m/z* 433.0769 $[M-H]^-$ (error –0.4 ppm) in the primary mass spectrum with the fragment peaks at *m/z* 300 and 271 in the secondary mass spectrum. In addition, the major compound in the extract is the flavonoid guaijaverin (**7**), which revealed in its ^{1}H NMR profile the presence of the B system through spin-spin coupling at δ 6.90 (d, *J* = 2.1 Hz, H-5') and δ 7.51 (dd, *J* = 8.3, 2.1 Hz, H-6'). These signals showed a direct correlation with the carbons at δ 114.8 (C-5') and δ 121.7 (C-6'), respectively. Moreover, they exhibited a long-range ^{1}H–^{13}C HMBC correlation map with the carbons at δ 121.5 (C-1'), δ 144.9 (C-3'), δ 148.5 (C-4'), and δ 121.7 (C-6') (Oliveira et al., 2021). The potential bioactivity of this polyphenol was demonstrated in several studies that had established an *in vitro*

Table 1. Compounds identified in the *Coccoloba marginata* fruits by ultra-performance liquid chromatography couple with quadrupole time-of-flight mass spectrometry (UPLC-qTOF-MS) and nuclear magnetic resonance.

Nº	RT (min)	Compound	$[M-H]^-$ Calculated	$[M-H]^-$ Observed (ion formula, error in ppm)	Fragment (%Intensity)	d ^{1}H in ppm (J, Hz)	d ^{13}C in ppm	References
Phenolic acids								
1	1.81	Gallic acid	169.0137	169.0128 ($C_7H_6O_5$, -5.1)	169 (100), 125 (80)	7.07 (s, H-2, H-6).	109.0 (C-2, C-6), 138.1 (C-4), 144.7 (C-3, C-5), 169.0 (C-7).	(Oliveira et al., 2024)
2	3.59	Protocatechuic acid	153.0188	153.0186 ($C_7H_6O_4$, -1.1)	109 (100), 153 (50)	7.44 (dd, *J* = 8.1, 2.1 Hz, H-6)	116.2 (C-6).	(Chen et al., 2018)
Quercetin and Myricetin derivatives								
3	9.69	Myricetin-3-*O*-glucoside	479.0825	479.0836 ($C_{21}H_{20}O_{13}$, 2.3)	316 (100), 271 (10), 179 (5)	7.40 (s, H-2', H-6'), 5.20 (d, *J* = 7.3 Hz, H-1").	108.6 (C-2', C-6'), 103.5 (C-1").	(Oliveira et al., 2021)
4	10.59	Quercetin-*O*-galloyl-glucoside	615.0986	615.1005 ($C_{28}H_{24}O_{16}$, 3.1)	615 (100) 463 (80), 300 (20), 301 (18)	6.17 (d, *J* = 2.1 Hz, H-6), 6.39 (d, *J* = 2.1 Hz, H-8), 7.76 (d, *J* = 2.1 Hz, H-2'), 6.82 (d, *J* = 8.1 Hz, H-5'), 7.61 (dd, *J* = 8.1; 2.1 Hz), 5.18 (d, *J* = 7.8 Hz, H-1") Galloyl: 6.80 (s, H-2, H-6).	98.5 (C-6), 93.2 (C-8), 116.1 (C-2'), 114.3 (C-5'), 121.7 (C-6'), 103.4 (C-1"). Galloyl: 109.0 (C-2, C-6)	(Oliveira et al., 2024)
5	11.36	Myricitrin-3-*O*-b-rhamnoside (Myricitrin)	463.0876	463.0853 ($C_{21}H_{20}O_{12}$, -4.9)	463 (100), 316 (80), 271 (12), 289 (5)	6.20 (m, H-6), 6.36 (d; *J* = 2.0 Hz; H-8), 6.97 (s; H-2', 6'), 5.30 (d, *J* = 1.5 Hz, H-1"), 0.96 (d, *J* = 6.2 Hz, H-6").	161.9 (C-5), 98.6 (C-6), 93.4 (C-8), 108.3 (C-2', C-6'), 102.1 (C-1"), 70.7 (C-2"), 70.8 (C-3"), 71.8 (C-4"), 16.8 (C-6")	(Oliveira et al., 2021)
6	11.60	Quercetin-3-*O*-galactoside (Hyperoside)	463.0876	463.0853 ($C_{21}H_{20}O_{12}$, -4.9)	300 (100), 463 (70), 271 (15), 255 (10)	6.20 (d, *J* = 2.0 Hz, H-6), 6.40 (d; *J* = 2.0 Hz; H-8), 7.85 (d, *J* = 2.2 Hz, H-2'), 6.84 (d, *J* = 8.3 Hz, H-5').	98.4 (C-6), 93.4 (C-8), 116.4 (C-2'), 114.6 (C-2').	(Oliveira et al., 2021)
7	13.21	Quercetin-3-arabinopyranoside (Guaijaverin)	433.0771	433.0769 ($C_{20}H_{18}O_{11}$, -0,4)	300 (100), 271 (50), 255 (15)	6.90 (d, *J* = 2.1 Hz, H-5'), 7.51 (dd, *J* = 8.3, 2.1 Hz, H-6'), 5.18 (d, *J* = 7.8 Hz, H-1").	121.5 (C-1'), 144.9 (C-3'), 148.5 (C-4'), 114.8 (C-5'), 121.7 (C-6'), 103.4 (C-1").	(Oliveira et al., 2021)
8	13.71	Quercetin-3-*O*-b-rhamnoside (Quercitrin)	447.0927	447.0940 ($C_{21}H_{20}O_{11}$, 2,9)	301 (100), 447 (90), 271 (10), 151 (5)	6.20 (m, H-6), 6.42 (d; *J* = 2.0 Hz; H-8), 7.36 (d, *J* = 2.1 Hz, H-2'), 6.93 (d, *J* = 8.3 Hz, H-5'), 7.30 (dd, *J* = 8.3, 2.1 Hz, H-6'), 5.33 (m, H-1"), 0.98 (d, *J* = 6.2 Hz, H-6").	98.5 (C-6), 93.4 (C-8), 121.8 (C-1'), 115.5 (C-2'), 145.1 (C-3'), 148.6 (C-4'), 115.0 (C-5'), 121.6 (C-6'), 102.1 (C-1"), 70.7 (C-2"), 16.3 (C-6").	(Oliveira et al., 2021)
9	17.35	Quercetin	301.0349	301.0340 ($C_{15}H_{10}O_7$, -2,9)	301 (100), 151 (60), 179 (20)	7.80 (d, *J* = 2.1 Hz, H-2'), 6.93 (d, *J* = 8.3 Hz, H-5'), 7.51 (dd, *J* = 8.3, 2.1 Hz, H-6').	121.8 (C-1'), 116.3 (C-2'), 145.1 (C-3'), 115.0 (C-5'), 121.6 (C-6').	(Colacicco et al., 2023)
10	18.75	Apigenin	269.0450	269.0431 ($C_{15}H_{10}O_5$, -6,9)	269 (100), 117 (40), 151 (25)	7.98 (d, *J* = 8.9, H-2', H-6')	-	(Tavakoli et al., 2022)
Anthocyanins								
11	5.23	Delphinidin-3-*O*-glucoside	465.1033	465.1049 ($C_{21}H_{21}O_{12}^+$, 3.4)	303 (100)	-	-	(Schnitker et al., 2024)
12	6.33	Cyanidin-3-*O*-glucoside	449.1084	449.1085 ($C_{21}H_{21}O_{11}^+$, 0.2)	287 (100)	-	-	(Schnitker et al., 2024)
13	6.77	Delphinidin-3-O-rhamnoside	449.1084	449.1095 ($C_{21}H_{21}O_{11}^+$, 2.9)	303 (100)	-	-	(Yin et al., 2024)
14	7.32	Cyanidin-3-*O*-arabinoside	419.0978	419.0991 ($C_{20}H_{19}O_{10}^+$, 3.1)	287 (100)	-	-	(Schnitker et al., 2024)
15	8.33	Cyanidin-3-*O*-rhamnoside	433.1135	433.1140 ($C_{21}H_{21}O_{10}^+$, 1.1)	287 (100)	-	-	(Viel et al., 2022)

RT: retention time; ppm: parts per million.

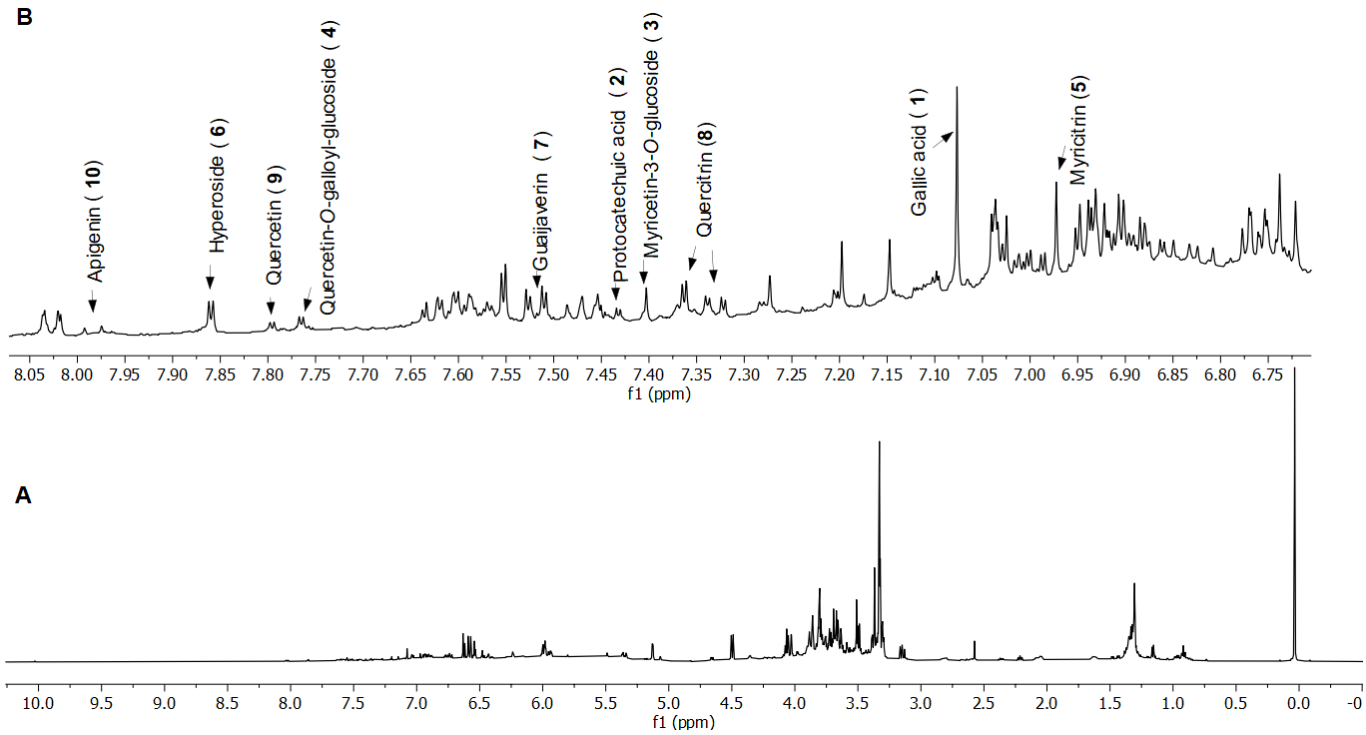

Figure 4. **(A)** Hydrogen (^{1}H) nuclear magnetic resonance spectra of the ethanolic extract of *C. marginata* fruits (500.13 MHz, CD_3OD). **(B)** Amplification of the ^{1}H nuclear magnetic resonance spectra (6.7-8.0 ppm) for the signals of the constituents (1 to 10) identified in the ethanolic extract of *C. marginata* fruits (500.13 MHz, CD_3OD).

glucose-uptake promoting a bioassay model to investigate the hypoglycemic activity of guaijaverin and avicularin, which exhibited the major hypoglycemic ingredients among the 14 compounds isolated from guava leaf (Houël et al., 2016; Zhu et al., 2020).

Another compound that showed a peak of higher intensity in the chromatogram (UV) and in the ^{1}H NMR spectrum is the glycosylated flavonoid quercitrin (quercetin-3-*O*-rhamnoside) (**8**). This constituent displayed a peak at *m/z* 447.0940 $[M-H]^-$ and a secondary fragment at *m/z* 301, corresponding to the loss of a rhamnose unit (146 Da). The flavonol (**8**) was characterized by resonances at δ 6.20 (m, H-6) and δ 6.42 (d, *J* = 2.0 Hz, H-8). Additionally, characteristic signals of the typical B-ring system of 3', 4'-disubstituted flavonoids were observed at δ 7.36 (d, *J* = 2.1 Hz, H-2'), δ 6.93 (d, *J* = 8.3 Hz, H-5'), and δ 7.30 (dd, *J* = 8.3, 2.1 Hz, H-6'). The anomeric hydrogen was confirmed by a doublet at δ 5.33 (m, H-1") that showed a direct correlation with the carbon at δ 102.1 (C-1") (Oliveira et al., 2021). Nowadays, quercitrin has become one of the research hotspots of natural active ingredients because of its protective effects in bone, stomach, heart, brain, liver, and other important organs. Additionally, quercitrin, known for its potent antioxidant activity, has been reported to participate in the therapy of various diseases, including osteoporosis, osteoarthritis, gastric ulcer, inflammatory bowel disease, atherosclerosis, stroke, diabetes mellitus, neuropathies, immune diseases, cancer, and liver injury. Its action occurs through the modulation of oxidative stress, inflammation, and specific molecular pathways associated with the progression of these conditions (Chen et al., 2022; Mar et al., 2020).

Quercetin (**9**) was confirmed by signals at δ 7.80 (d, *J* = 2.1 Hz, H-2'), δ 6.93 (d, *J* = 8.3 Hz, H-5'), and δ 7.51 (dd, *J* = 8.3, 2.1 Hz, H-6'), which displayed a ^{1}H–^{13}C HSQC correlation map with the carbons at δ 116.3 (C-2'), δ 115.0 (C-5'), and δ 121.6 (C-6'), respectively (Colacicco et al., 2023). Peak 10 (RT 18.75 min) with *m/z* 269 $[M-H]^-$ was confirmed as apigenin (**10**) through the ^{1}H signal at δ 7.98 (d, *J* = 8.9 Hz, H-2', H-6') (Tavakoli et al., 2022). In addition to these compounds the detection of **10** was evaluated, due to the ion at *m/z* 269.0431 $[M-H]^-$ (error -6.9 ppm), that was confirmed by standard RT comparison at 18.75 min.

In this study, the anthocyanins identified through UPLC-QTOF/MS analysis in positive mode were derivatives of delphinidins and cyanidins. Peak 11 (RT 5.23 min) showed a protonated ion at *m/z* 465.1049 $[M+H]^+$ (error 3.4 ppm), corresponding to the molecular formula $C_{21}H_{21}O_{12}^+$. The MS^2 spectrum presented fragmentation at *m/z* 303 $[M+H]^+$, suggesting the loss of a hexose unit (162 Da). Based on the literature, the data are consistent with the anthocyanin delphinidin-3-*O*-glucoside (**11**). Another derivative of delphinidin, identified at a retention time of 6.77 min due to *m/z* 449.1095 $[M+H]^+$ (molecular formula $C_{21}H_{21}O_{11}^+$, error 2.9 ppm) and MS^2 fragment at *m/z* 303 (loss of 146 Da), is delphinidin-3-*O*-rhamnoside (**13**).

The cyanidins were identified by searching for the aglycone ion *m/z* 287 $[M+H]^+$, resulting in three substances: cyanidin-3-*O*-glucoside (**12**, *m/z* 449.1085 $[M+H]^+$, error 0.2 ppm), cyanidin-3-*O*-arabinoside (**14**, *m/z* 419.0991 $[M+H]^+$, error 3.1 ppm), and cyanidin-3-*O*-rhamnoside (**15**, *m/z* 433.1140

$[M+H]^+$, error 1.1 ppm), due to the loss of sugar fractions of 162, 132, and 146 Da, respectively.

As mentioned above, the other class of polyphenols determined in this study was that of anthocyanins, which are responsible for flowers' colors, from pink to blue, but they are also present in leaves, fruits, and roots. Anthocyanins are also recognized for their biological properties, which, together with their bright color, make them interesting additives for food preparations (Zeng et al., 2018). From a chemical point of view, and as mentioned above, anthocyanins are the anthocyanidins *O*-glycosides. Anthocyanidins highly oxidized 2-aryl-3-hydroxychromenylium are also colored pigments, although less stable, and consequently few examples are found in nature, the most widespread derivatives being cyanidin, responsible for red to magenta colors, and delphinidin, responsible for purple to blue colors. This color differentiation may be associated with one of the main rules of these flavonoids in plants, which is to attract animals for pollination, and different colors attract different animals. In addition, the presence of a sugar moiety promotes some changes in color brightness. The most common sugar is glucose with a β-linkage, but galactose, rhamnose, and xylose are also found. Moreover, these sugar moieties can have acyl substituents, highlighting cinnamic acyl derivatives, such as caffeic, ferulic, and *p*-coumaric acids, due to these phenolic acids' rules in plants' antioxidant activity (Dias et al., 2021; Dong et al., 2024; Kumazawa et al., 2024; Mesquita et al., 2023).

Among the flavonoids, quercetin stands out for its potent antioxidant and anti-inflammatory activity, with significant impacts on cardiovascular health, as reported by Nazari-Khanamiri and Ghasemnejad-Berenji (2023). It also exhibits anticancer effects, inhibiting the proliferation of tumor cells. Derivatives such as quercetin-3-*O*-galactoside (hyperoside) have demonstrated efficacy in protecting against neurodegenerative and hepatic diseases (Gao et al., 2019; Huang et al., 2021). Quercetin-3-*O*-β-rhamnoside (quercitrin) exhibits anti-inflammatory and hepatoprotective properties, according to Wagner et al. (2006). Another relevant compound, quercetin-*O*-galloyl-glucoside, possesses antioxidant and antimicrobial properties (Samini, 2019).

Myricitrin (myricetin-3-*O*-β-rhamnoside) is widely recognized for its neuroprotective effects and is being investigated for the treatment of neurodegenerative diseases, such as Alzheimer's, according to Zhang et al. (2020). Myricetin derivatives are also potent antioxidants, with protective effects against type 2 diabetes (Niisato & Marunaka, 2023). Apigenin, another flavonoid, exhibits anxiolytic and anticancer properties, as reported by Imran et al. (2020) and Xu et al. (2021). It acts as a modulator of metabolic pathways associated with oxidative stress, contributing to the prevention of various chronic conditions.

Phenolic compounds, including phenolic acids, flavonoids, and anthocyanins, have received significant scientific attention due to their bioactive properties and health benefits. Gallic acid, for instance, exhibits a strong antioxidant activity, as demonstrated by Sani and Hokmabadi (2023), protecting cells against oxidative stress and reducing DNA damage. Furthermore, it shows anticancer and anti-inflammatory potential, as indicated by Tuli et al. (2022). Similarly, protocatechuic acid exhibits antioxidant and cardioprotective effects (Li et al. 2023), which also highlights its efficacy in reducing inflammatory processes. Among the anthocyanins, delphinidin-3-*O*-glucoside stands out for its antioxidant properties and its potential to reduce the risk of cardiovascular diseases (Chen et al., 2019). Cyanidin-3-*O*-glucoside exhibits protective effects on eye health and improves vascular health (Kamaruddin et al., 2022; Peng et al., 2022). Additionally, compounds such as cyanidin-3-*O*-arabinoside and cyanidin-3-*O*-rhamnoside have demonstrated antioxidant and anti-inflammatory properties, as well as protective effects against obesity and diabetes (Deepa et al., 2023; Khutami et al., 2022).

3.2 Fatty acid profile

The main fatty acids (FA) extracted from the hexane fraction of the *Coccoloba marginata* fruit extract were identified. Myristic acid was detected with a retention time of 42.895 minutes, presenting *m/z* values of 228 (literature data for FA) and 242 (experimental values for FAMEs), with a relative percentage of 4.0%. Palmitic acid, the most abundant compound, had a retention time of 49.883 minutes, with *m/z* values of 256 (FA) and 270 (FAME), representing 54.7% of the composition. Stearic acid was identified with a retention time of 56.172 minutes and *m/z* values of 284 (FA) and 298 (FAME), accounting for 16.3%. The total sum of the identified FAs was 75.0%. The *m/z* values for FAs are based on literature data, while the values for FAME are experimental.

The fatty acids tetradecanoic (myristic acid), palmitic, and stearic are saturated compounds widely distributed in nature, playing important roles in living organisms and industrial applications (Thammasut et al., 2023).

Tetradecanoic acid, also known as myristic acid, has a 14-carbon chain. It is primarily found in vegetable oils, such as coconut oil, and in animal fats. This FA acts as a precursor in the synthesis of complex lipids, serving as an essential structural component of cell membranes. Additionally, it has significant use in the cosmetics industry and in lubricants due to its low volatility. Despite being a saturated FA, its impact on cardiovascular diseases is considered lower compared to long-chain FA (Dinh et al., 2021; Perna & Hewlings, 2023; Shramko et al., 2020).

Palmitic acid, composed of 16 carbon atoms, is the most abundant saturated FA in living organisms. It plays a crucial role in the synthesis of energy-storing lipids and in cellular signaling. Industrially, it is widely used in the production of soaps, detergents, and cosmetics due to its chemical stability (Costa et al., 2023; Vesga-Jiménez et al., 2022). However, from a health perspective, excessive consumption of palmitic acid is associated with a higher risk of developing metabolic diseases, such as type 2 diabetes and atherosclerosis (Annevelink et al., 2023)

Stearic acid, on the other hand, is composed of 18 carbon atoms and is predominantly found in animal fats and, to a lesser extent, in vegetable oils such as cocoa and shea butter. It serves as an important energy source and can be converted into oleic acid by the body, contributing to healthy metabolic functions. Unlike other saturated FA, stearic acid has a neutral impact on blood cholesterol levels, making it less harmful to

cardiovascular health (Nascimento & Scalabrini, 2020; Santos et al., 2022; Sellem et al., 2022). Additionally, its high thermal stability makes it ideal for industrial applications, such as the production of candles, cosmetics, and lubricants (Valenzuela et al., 2011).

3.3 Cytotoxic activity

The cytotoxicity analysis of the whole fruit extract of *C. marginata* on A549 (human lung carcinoma cells), HCT8 (human colorectal carcinoma cells), and HUVEC (human endothelial cells) cell lines revealed promising bioactive properties. The parameters evaluated included IC_{50}, GI_{50}, and LC_{50}, which allow inferences about the extract's ability to inhibit cell growth and induce cell death.

For IC_{50}, which represents the concentration required to inhibit 50% of cell growth, the A549 cell line demonstrated greater sensitivity, with a value of 206 µg GAE/mL, while the HCT8 and HUVEC cell lines showed values above 250 µg GAE/mL, indicating lower sensitivity to the extract. Regarding GI_{50}, which evaluates the reduction in cell growth compared to untreated cells, the HCT8 cell line presented the lowest value (44.15 µg GAE/mL), suggesting greater efficacy of the extract in inhibiting cell growth in this specific line. Meanwhile, LC_{50}, which measures the concentration required to cause a net 50% reduction in the number of cells compared to the initial count, was above 250 µg GAE/mL for all cell lines, indicating low direct lethality (Figure 5).

The results suggest that the fruit extract of *C. marginata* exhibits moderate cytotoxic properties, with greater selectivity for tumor cells (A549 and HCT8) compared to normal cells (HUVEC). This selectivity is a desirable characteristic in therapeutic compounds, as it indicates lower toxicity to normal cells. The greater sensitivity observed in tumor cells may be associated with the presence of bioactive compounds in the extract, such as flavonoids (quercetin, myricetin) and phenolic acids, which are known for their antitumor and antioxidant properties (Afroze et al., 2020; Girardelo et al., 2020; Hossain et al., 2022). This difference in sensitivity may be related to metabolic variations between the cell lines or greater vulnerability of A549 cells to the bioactive compounds present in the extract. However, the overall low selectivity limits the therapeutic potential of the extract in its crude form (Campoccia et al., 2021).

On the other hand, the high LC_{50} values (> 250 µg GAE/mL) indicate low direct lethality of the extract, which may limit its effectiveness in isolated therapeutic applications. However, this also highlights the need for additional studies to identify and isolate specific compounds with higher cytotoxic activity. The analysis of metabolic pathways modulated by the extract, as well as testing in *in vivo* models, would be important to confirm its efficacy and safety.

The IC_{50}, which represents the concentration required to inhibit 50% of cell growth, revealed that HUVEC cells had a value of 183.3 µg GAE/mL, indicating low cytotoxicity for normal cells. For A549 cells, the value was 206.9 µg GAE/mL, demonstrating moderate cytotoxicity for lung carcinoma cells. In contrast, HCT-8 cells showed IC_{50} values greater than 250 µg GAE/mL, suggesting a low activity of the extract on this cell line. The SI, calculated as the ratio between the IC_{50} of normal cells (HUVEC) and the IC_{50} of tumor cells, indicated values of 0.89 for the HUVEC/A549 comparison and 0.73 for HUVEC/HCT-8. These values, which are less than 1, indicate low selectivity of the extract for tumor cells compared to normal cells. This means the extract exhibits similar cytotoxic activity in both normal and tumor cells, which is a limitation for its use as a therapeutic compound since selectivity is a desirable feature to avoid toxic effects on healthy cells (Campoccia et al., 2021; Shifa et al., 2024).

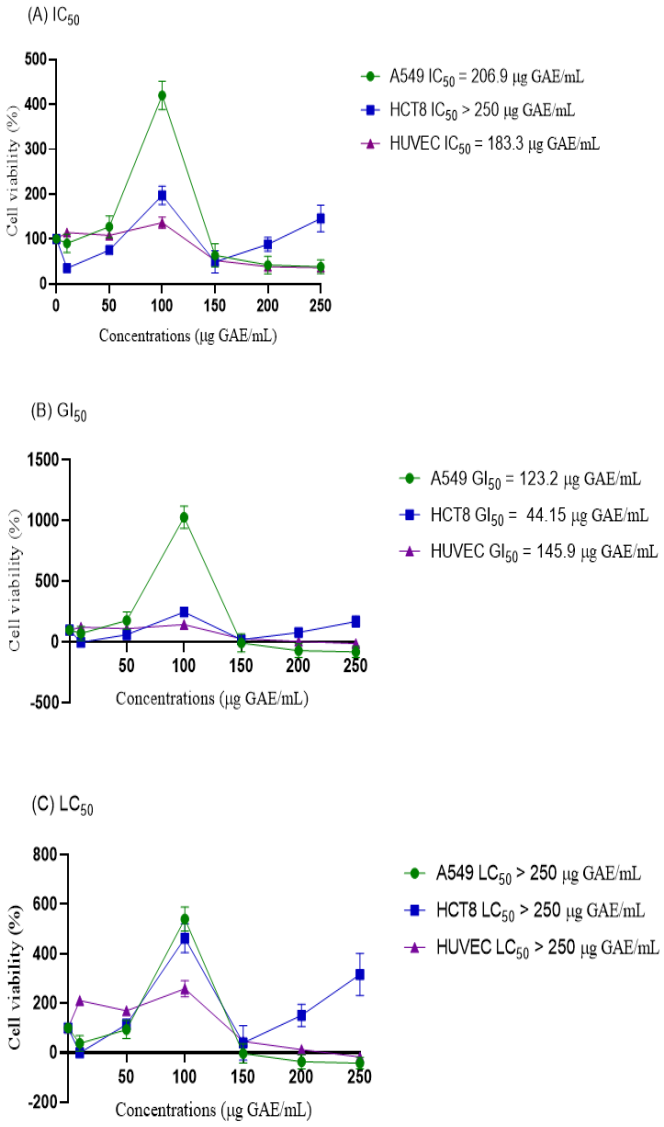

Figure 5. Cytotoxicity of whole *Coccoloba marginata* fruit in A549, HCT8, and HUVEC cell lines. **(A)** IC_{50}: the concentration of the agent that inhibits cell growth by 50%. **(B)** GI_{50}: the concentration of the agent that inhibits growth by 50% relative to untreated cells. **(C)** LC_{50}: the concentration of the agent that results in a net loss of 50% of cells compared to the initial number at the start of treatment.

The SI, calculated as the ratio between the IC_{50} of normal cells (HUVEC) and the IC_{50} of tumor cells, indicated values of 0.89 for the HUVEC/A549 comparison and 0.73 for HUVEC/

HCT-8. These values, which are less than 1, indicate low selectivity of the extract for tumor cells compared to normal cells. This means the extract exhibits similar cytotoxic activity in both normal and tumor cells, which is a limitation for its use as a therapeutic compound since selectivity is a desirable feature to avoid toxic effects on healthy cells (Campoccia et al., 2021; Shifa et al., 2024).

To improve its applicability, the isolation of specific active compounds would be necessary, as this could enhance the selectivity and efficacy of the extract. Furthermore, future studies could focus on chemical modifications of the isolated compounds to improve their affinity for tumor cells and reduce toxicity for normal cells. *In vivo* testing would also be essential to evaluate the extract's safety and efficacy in more complex biological systems.

4 CONCLUSIONS

Phenolic acids and flavonoids are crucial to human health due to their antioxidant, anti-inflammatory and anti-cancer properties, as well as their role in supporting cardiovascular and neurological health. Likewise, FA have significant biological and industrial relevance, with their impact on human health highlighting the need for balanced consumption and sustainable research. This pioneering study on *C. marginata* fruits reveals a rich source of bioactive compounds, demonstrating promising therapeutic potential, particularly in their cytotoxic sensitivity to tumor cells. However, the limited selectivity of the extract poses a challenge to its immediate application. Future research should focus on the quantification and detailed characterization of its bioactive compounds to identify those with the greatest therapeutic potential. Furthermore, efforts to increase the cytotoxic activity and selectivity of the extract are essential to advance its use in pharmacological applications. These discoveries pave the way for further exploration of the therapeutic and industrial applications of *C. marginata* fruits, emphasizing their potential as a valuable resource for biotechnological innovation.

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