

Antiviral Activity and Chemical Characterization of *Ficus citrifolia* Mill. (Moraceae) Leaf Extract Against Emerging Arboviruses

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Abstract

Arboviral diseases pose a serious public health problem, particularly in tropical regions, where environmental conditions favor the proliferation of mosquito vectors, facilitating viral transmission and leading to debilitating clinical manifestations ranging from fever and joint pain to severe neurological complications. This study evaluated the *in vitro* antiviral activity and phytochemical profile of the ethanolic extract of *Ficus citrifolia* Mill. leaves (Moraceae). Using high-resolution LC-MS/MS analysis, 21 compounds were identified, including phenolic acids, flavonoids, lignans, terpenes, and steroids - many of which are known for their antiviral and anti-inflammatory properties. The extract exhibited significant antiviral activity against Mayaro virus (EC₅₀: 61.24 µg/mL, SI: 12.96), Chikungunya virus (EC₅₀: 117.92 µg/mL, SI: 6.73), and Zika virus (EC₅₀: 117.29 µg/mL, SI: 6.77), with no observed activity against Oropouche virus. The findings highlight the potential of *F. citrifolia* as a source of antiviral agents and support its traditional use in treating inflammatory and infectious diseases. Further studies, including bioassay-guided fractionation and mechanistic evaluations, are recommended to identify the active constituents and assess clinical applicability.

Introduction

Arboviruses stand out as infectious agents transmitted to humans by the bite of infected blood-feeding arthropods. Tropical and subtropical climates greatly facilitate the reproduction of these vectors, especially in countries such as Brazil, where climatic conditions favor the spread of arboviruses such as dengue, yellow fever, chikungunya, Zika, Mayaro, and Oropouche. Although these diseases are endemic, they continue to be neglected, with 1,645,678 cases reported in the Americas in 2020 based on PAHO and WHO (2020).

In developing countries such as Brazil, unorganized urbanization and poor sanitation infrastructure increase the vulnerability of the population. In addition, the lack of effective vaccines and antivirals aggravates the situation, overburdening health systems and favoring outbreaks in the words Girard et al. (2020). The resurgence of Zika (ZIKV), Oropouche (OROV), Mayaro (MAYV), and Chikungunya (CHIKV) in urban centers has intensified these challenges. These viruses produce similar symptoms, such as fever, rashes, and severe joint pain, sometimes progressing to chronic arthritis. ZIKV is known to cause congenital malformations and vertical transmission, as noted by Pielnaa et al. (2020), and OROV has recently been linked to similar physical changes and vertical transmission as described by Schwartz, Dashraath & Baud (2024). MAYV can cause complications such as myocarditis, hemorrhagic syndromes, and neurological manifestations.

Faced with these clinical challenges, the search for new therapeutic sources has increasingly turned to the ancestral knowledge of traditional communities about medicinal plants. The biodiversity of the Amazon offers several species with therapeutic potential, supporting traditional healing practices and providing an accessible alternative.

Among these species, those of the genus *Ficus* are widely used in traditional medicine for their anti-inflammatory, analgesic, and healing properties, as stated by Lansky et al. (2008). These plants are known for their rich chemiodiversity, including organic acids, phenolic compounds, and terpenes reported in Cruz et al. (2022). Previous studies have demonstrated the therapeutic effects of species such as *F. iteophylla*, which reduced pain and inflammation in rodents, as discussed in Abdulmalik et al. (2011) and *amplissima*, which exhibited anti-inflammatory, antioxidant, and wound-healing properties *in vivo* based on Arunachalam & Parimelazhagan (2012).

Although these effects are not directly antiviral, viral pathogens induce inflammatory responses in the host as part of the infection process, in accordance with Pinggen et al. (2016). Ethnopharmacological applications may therefore be linked to antiviral potential, as evidenced by *F. sur* and *F. rubiginosa* inhibiting herpes simplex virus type 1 (HSV-1), as described by Sieniawska et al. (2022) and Dell'Annunziata et al. (2022), *F. deltoidea* showing antiviral activity against dengue virus type 2, according to Wu et al. (2024) and *carica* inhibiting SARS-CoV-2 replication, based on Hamed et al. (2023).

Although several *Ficus* species have been studied, no research has evaluated the antiviral potential of *F. citrifolia*, commonly known as "fig tree" or "black gameleira." Previous studies have highlighted the antimicrobial effects of its ethanolic leaf extract against *Mycobacterium tuberculosis*, as well as the antiproliferative effect of three lignans isolated from the leaf extract with dichloromethane, as reported by Antoun et al. (2001) and Baetas et al. (2018). Furthermore, the isolated lignans show promising antiviral potential, in the words of Carvalho et al. (2023).

Based on these findings and the ongoing search for new antiviral agents, we conducted a study to evaluate the *in vitro* antiviral properties of the ethanolic extract of *F. citrifolia* leaves against the MAYV, CHIKV, ZIKV, and OROV strains. In addition, we performed chemical profiling using high-resolution mass spectrometry (HR-LCMS) to support future phytopharmacological investigations of this species.

Material and Methods

Plant collection, identification and extraction

Leaves of *F. citrifolia* (Moraceae) were collected in Belém, (Pará, Brazil) under the coordinates 01°02'28" latitude and 048°27'00" longitude, in the reserve of the Brazilian Agricultural Research Corporation (EMBRAPA-PA) and cataloged under voucher No. IAN202214. Access to genetic heritage was legalized before the National System for the Management of Genetic Heritage and Associated Traditional Knowledge (SISGEN) under the registration AF01766 (available at <https://sisgen.gov.br>).

The botanical material was washed, oven-dried at $45 \pm 1^\circ\text{C}$. The dried material was ground in a knife mill and sieved through in mesh screens with an average nominal opening of $180\ \mu\text{m}$.

Extraction was performed with ethanol (99.5%, w/w, TEDIA®; 1:10, m/v), using 300 g of dried and crushed material in two cycles of 24 hours each, at room temperature. The extract was vacuum filtered and dried in an oven ($45 \pm 1^\circ\text{C}$) until constant weight. The crude extract yielded (EEFC) 14 g.

The sample (crude extract) was cleaned by solid phase extraction (SPE) using a 50 mg C18 cartridge (Phenomenex, Torrance, CA, USA). The cartridge was preconditioned according to the manufacturer. 10 mg of sample was dissolved in 1.0 mL of $\text{H}_2\text{O}:\text{ACN}$ (2:8, v/v) and eluted through the cartridge. The volume was collected, and a second volume was passed through the cartridge. The volumes were pooled and dried, yielding 2.3 mg, which was stored away from light until analysis.

LC-MS analysis

LC-MS analyses were performed on a Xevo G2-S QToF HRMS (Waters Corp., Milford, MA, USA) with an Electrospray source, using leucine enkephalin for accurate mass calibration. MassLynx 4.1 controlled the system and data acquisition. The extract (2 mg/mL) was injected (2 μL) into a BEH C18 column ($50 \times 2.1\ \text{mm}$, $1.7\ \mu\text{m}$) at 40°C , with Ultrapure water (A) and acetonitrile (B) as mobile phases at a $300\ \mu\text{L}/\text{min}$ flow rate. The gradient was: 0–18 min (10–100% B), 18–20 min (100% B), 20–21 min (100–10% B), and 21–24 min (10% B). Positive and negative ionization modes were used across the m/z range 50–1200. Data Dependent Acquisition (Top 5) was applied, with collision energy from 15 to 65 eV and scan time of 0.1 s. Tolerances for charge states, peak extraction, and deisotoping were set at $\pm 0.2\ \text{Da}$, $2\ \text{Da}$, $\pm 3\ \text{Da}$, and $6\ \text{Da}$, respectively. Source/desolvation temperatures were $150^\circ\text{C}/300^\circ\text{C}$, with gas flow rates of $20\ \text{L}/\text{h}$ and $600\ \text{L}/\text{h}$, respectively.

Data processing and annotation of chemical compounds

The .raw data were converted to mzML format using MSConvert 3.0.2 (Chambers et al. 2012) (ProteoWizard, Palo Alto, CA, USA). Data processing was performed with MZmine 4.2.0 (Schmid et al. 2023). Ion detection thresholds were set at 1.0×10^3 for MS^1 and 8.0×10^1 for MS^2 . Deconvolution was done using Local Minimum Resolver with a chromatographic threshold of 80%. Retention time and mobility intervals were set at 0.050, with a minimum absolute height of 1000 and peak-to-peak ratio of 1.7. Isotope detection had a 10 ppm error and 0.2 min retention time tolerance, for charges + 1 to + 2. Peak alignment used 3:1 m/z tolerance and 0.2 min retention time margin. Data were filtered to exclude features without MS^2 spectra and blank features, resulting in 256 features in negative and 353 in positive mode. Identification was performed via Global Natural Products Social Molecular Networking (GNPS), which is a MS/MS spectral library devised by Wang et al. (2016). The detailed analyses can be accessed via the IDs: for the negative mode, ID = 57c3e0b4cedf4f698ee422b761de598d, and for the positive mode, ID = 7f6942fd82484d0d9f2fd0ab8af95450.

Antiviral activity of the extract

Cell lines

In the *in vitro* assays, Vero continuous lineage cells (CCL-81), which are fibroblast-like cells derived from the kidney of the African green monkey (*Cercopithecus aethiops*) obtained from the American Type Culture Collection (ATCC; USA) were used. The cells were cultured in Dulbecco's Modified Eagle's Minimal Essential Medium (DMEM; Sigma-Aldrich, USA), which was supplemented with 5% fetal bovine serum (FBS; Gibco, USA), penicillin/streptomycin (200U/mL) and amphotericin B (2.5g/mL) from Sigma-Aldrich (USA). Cell culture was conducted according to the guidelines established by the ATCC (2022), and the environment was maintained at 37°C with 5% CO_2 and humidity.

The arboviruses Mayaro (*Alphavirus*), Chikungunya (*Alphavirus*), Zika (*Orthoflavivirus*) and Oropouche (*Orthobunyavirus*) were used in the antiviral trials. The Mayaro virus (MAYV), strain Acre27 (GenBank KM400591), was initially isolated during an epidemiological survey from a blood sample of a febrile, malaria-negative patient collected in Acrelândia, in the Amazon Basin, Acre, Brazil by Terzian et al. (2015). The Chikungunya virus (CHIKV) strain S27-African (GenBank AF369024) was initially isolated from a febrile patient and serves as a prototype for the African genotype authored by Khan et al. (2002). Zika virus (ZIKV) strain PE243/2015 (GenBank KX197192.1) was initially recovered from a patient in the state of Pernambuco, Brazil, who presented with the classic symptoms of Zika fever, but did not have any neurological complications during the 2015 outbreak reported by Donald et al. (2016). The Oropouche virus (OROV), strain BeAn19991 (GenBank KP052850-KP052852), which represents the prototype of the Brazilian genotype, was initially isolated from a "sloth" (*Bradypus tridactylus*) in Pará (Brazil) in 1960 made by Saeed et al. (2000).

Cytotoxicity assays

Vero cells were seeded in 96-well microplates at a density of 5×10^4 cells/well and incubated at 37°C overnight. After this period, the culture medium was replaced with various concentrations of *F. citrifolia* samples, serially diluted 1:2 in DMEM medium with 1% FBS. The experiment was carried out in triplicate. DMSO was used to solubilize the extracts, maintaining the same proportion as the vehicle control. Untreated cells were also kept as a control. The plates were incubated at 37°C for 48 hours. Cell viability was assessed using the MTT (methylthiazolyl diphenyl tetrazolium bromide) colorimetric assay, and absorbance was measured at $490\ \text{nm}$ using a spectrophotometer. Using a regression analysis, the cytotoxic

concentration for 50% of the cells (CC_{50}) of each extract was determined by comparing the viability of the treated cells with that of the untreated cells.

Antiviral activity assays

Vero cells were seeded in 96-well plates at a density of 5×10^4 cells/well and infected with MAYV, CHIKV, ZIKV or OROV at a multiplicity of infection (MOI) of 1. They were then treated with different concentrations of *F. citrifolia* extract (EEFC), starting with non-cytotoxic concentrations. The control groups, which include uninfected and untreated cells, received only the culture medium. In contrast, the virus control groups were infected without any treatment. All tests were carried out in triplicate and incubated for 48 hours at 37°C for MAYV, CHIKV and OROV, and 72 hours for ZIKV. Cell viability was then determined using the MTT colorimetric assay after the incubation period. The effective concentration for 50% of the cells (EC_{50}) was determined using regression analysis and represented the concentration that protected 50% of the infected cells compared to the virus control. The antiviral selectivity of the extract was assessed using the selectivity index (SI), which is defined as the ratio of CC_{50} to EC_{50} .

Results and Discussion

Identification of Compounds

LC-MS analysis in the negative $[M-H]^-$ and positive $[M+H]^+$ modes enabled the annotation of 21 chemical compounds belonging to different classes, such as: phenolic acids, flavonoids (flavones, flavanones, flavonols, isoflavones), lignans, fatty acids and terpenes. Of these, 10 were identified through an integrated approach, which combined high-precision experimental data in comparison with the fragments found in the literature and 11 through analysis carried out using the GNPS platform. The results obtained so far provide a solid basis for understanding the chemical composition of the species.

Table 1 shows the compounds annotated with their respective experimental m/z values compared to the theoretical values calculated from the molecular formulas. The experimental error remained below 5 ppm for all the compounds, indicating high precision in the identification. Compounds such as caffeic acid (**1**), identified on the basis of its characteristic fragment m/z 135 by Sineiawska et al. (2022). Pinoresinol (**13**) with fragments m/z 342, 327, 311, 151 and 136 as done by Patyra, Dudek and Kiss (2022). Naringenin (**14**), with m/z 151, 119, 107 explained by Zeng et al. (2018). (Iso)orientin (**5**) with m/z 327, 297, 285 and (iso)vitexin (**8**) m/z 311, 283, 269, 134 by Amaral et al. (2019)., proved to be consistent with data previously reported in the literature, giving greater reliability to the annotation carried out.

Table 1
Chemical compounds annotated for the ethanolic extract of *F. citrifolia* leaves.

Compound	RT (min)	Molecular formula	Experimental <i>m/z</i>	Teorical <i>m/z</i>	Error (ppm)	Fragments (MS/MS)	Putative name	Chemical class	Ionization mode
1	0.51	C ₉ H ₈ O ₄	179.0346	179.0344	1.1	135	caffeic acid*	Phenolic acid	[M-H] ⁻
2	2.43	C ₂₁ H ₂₀ O ₁₁	447.0920	447.0927	1.5	357, 327, 297, 285	orientin	Flavone	[M-H] ⁻
3	2.76	C ₂₁ H ₂₀ O ₁₀	431.0973	431.0978	1.1	311, 284, 283, 269, 239, 161, 135	vitexin	Flavone	[M-H] ⁻
4	2.89	C ₁₁ H ₁₆ O ₃	197.1172	197.1178	3.0	197, 179, 161, 135, 107	(epi)loliolide	Monoterpene	[M + H] ⁺
5	3.01	C ₂₁ H ₂₀ O ₁₁	447.0920	447.0927	1.5	327, 297, 285	(iso)orientin*	Flavone	[M-H] ⁻
6	3.29	C ₁₁ H ₁₆ O ₃	197.1178	197.1178	0	197, 179, 161, 135, 107	loliolide	Monoterpene	[M + H] ⁺
7	3.55	C ₂₁ H ₂₂ O ₁₀	433.1122	433.1135	3.0	433, 313, 295, 272, 271	naringenin-7-O-glucoside	Flavanone	[M-H] ⁻
8	3.56	C ₂₁ H ₂₀ O ₁₀	431.0968	431.0978	2.3	311, 283, 269, 134	(iso)vitexin*	Flavone	[M-H] ⁻
9	4.59	C ₁₅ H ₁₂ O ₆	287.0552	287.0556	1.3	287, 151, 135, 125, 107	eriodictyol	Flavanone	[M-H] ⁻
10	4.78	C ₁₅ H ₁₀ O ₆	285.0398	285.0399	0.3	285, 151, 133, 107	luteolin	Flavone	[M-H] ⁻
11	4.88	C ₁₅ H ₁₀ O ₇	301.0345	301.0348	0.9	178, 159, 151, 139, 121, 107	quercetin	Flavonol	[M-H] ⁻
12	5.05	C ₁₁ H ₁₂ O ₄	207.0654	207.0657	1.4	207, 179, 161, 135, 134	ethyl caffeate	Phenolic acid	[M-H] ⁻
13	5.09	C ₂₀ H ₂₂ O ₆	357.1335	357.1338	0.8	342, 327, 311, 151, 136	pinoresinol*	Lignan	[M-H] ⁻
14	5.50	C ₁₅ H ₁₂ O ₅	271.0607	271.0606	0.3	151, 119, 107	naringenin*	Flavanone	[M-H] ⁻
15	5.60	C ₁₅ H ₁₀ O ₅	269.0453	269.0450	1.1	159, 151, 117, 107	apigenin	Flavone	[M-H] ⁻
16	7.71	C ₁₅ H ₁₂ O ₄	255.0656	255.0657	0.3	255, 213, 187, 151, 125, 107	pinocembrin	Flavanone	[M-H] ⁻
17	9.41	C ₂₀ H ₁₈ O ₅	339.1222	339.1232	2.9	283, 271, 255, 153	isowighteone*	Isoflavone	[M + H] ⁺
18	10.29	C ₂₀ H ₁₆ O ₅	337.1070	337.1076	1.7	319, 295, 283, 271, 247	alpinumisoflavone*	Isoflavone	[M + H] ⁺
19	10.71	C ₂₀ H ₁₆ O ₅	337.1071	337.1076	1.4	319, 295, 283, 271, 247	(iso)alpinumisoflavone*	Isoflavone	[M + H] ⁺
20	17.94	C ₃₀ H ₄₈ O	425.3763	425.3783	4.7	407, 231, 191, 177, 109	lupenone*	Triterpene	[M + H] ⁺
*Notes made based on chemical prospecting of previous studies reported for the genus and comparative analysis of spectra available in the literature.									

Compound	RT (min)	Molecular formula	Experimental <i>m/z</i>	Teorical <i>m/z</i>	Error (ppm)	Fragments (MS/MS)	Putative name	Chemical class	Ionization mode
21	19.04	C ₂₉ H ₄₈ O	413.3764	413.3783	4.5	311, 297, 283, 255	stigmasterol*	Steroid	[M + H] ⁺
*Notes made based on chemical prospecting of previous studies reported for the genus and comparative analysis of spectra available in the literature.									

Among the flavonoids, the isoflavones isowighteone (**17**), alpinumisoflavone (**18**) and (iso)alpinumisoflavone (**19**) were observed. Their characteristic fragmentations corroborate the proposed structures, including the loss of the prenyl group, resulting in the ion of *m/z* 283 and 271, common to all of them. Isowighteone (**17**) showed fragments at *m/z* 283, 271, 255 and 153 (Hostettmann; Marston and Wolfender 2005), and alpinumisoflavone (**18**) and (iso)alpinumisoflavone (**19**) showed fragments at *m/z* 319, 295, 283, 271 and 247 showed by Chen et al. (2024). The triterpene lupenone (**20**) with ions at *m/z* 407, 231, 191, 177 and 109 as described by Wang et al. (2020) and the steroid stigmasterol (**21**) with *m/z* at 311, 297, 283, 255 were also identified, reinforcing the chemical complexity of the species by Rozenberg et al. (2003). The compounds orientin (**2**), vitexin (**3**), (epi)loliolide (**4**), loliolide (**6**), narigerin-7-O-glucoside (**7**), eriodictiol (**9**), luteolin (**10**), quercetin (**11**), ethyl caffeate (**12**), apigenin (**15**) and pinocembrin (**16**) were identified using the GNPS platform. This tool made it possible to correlate the experimental mass spectra with data libraries of previously described compounds.

Cytotoxicity and antiviral activity of the extract

Table 2 presents the cytotoxicity (CC₅₀) and antiviral activity results for the ethanolic extract of *F. citrifolia* leaves. The extract showed a CC₅₀ of 793.92 µg/mL. The effective concentrations (EC₅₀) and selectivity indices (SI) were 61.24 µg/mL (SI 12.96) for MAYV, 117.92 µg/mL (SI 6.73) for CHIKV, and 117.29 µg/mL (SI 6.77) for ZIKV. No antiviral activity was observed against OROV. The lack of effect may be attributed to OROV’s segmented negative-sense RNA genome, which presents replication mechanisms distinct from unsegmented arboviruses like MAYV, CHIKV, and ZIKV (Files et al., 2022; Emmanuel et al., 2021).

Table 2
– Antiviral activity and cytotoxicity threshold for the ethanolic extract of *Ficus citrifolia* leaves.

Cytotoxic concentration (CC ₅₀ , µg/mL)	793.92	
Arbovirus	Effective concentration (EC ₅₀ , µg/mL)	Selectivity index (SI)
MAYV	61.24 ± 5.56	12.96
OROV	nd	nd
CHIKV	117.92 ± 2.52	6.73
ZIKV	117.29 ± 37.16	6.77
Note: MAYV (Mayaro virus); OROV (Oropouche virus); CHIKV (Chikungunya virus); ZIKV (Zika virus); nd (not detected).		
(Brito, 2025; European Centre for Disease Prevention and Control, 2025).		

Ficus species are rich in diverse secondary metabolites such as flavonoids, terpenes, phenols, sterols, and lignans (Chandra et al., 2023), which may underlie the observed biological effects. The high SI values, particularly against MAYV (12.96), suggest a therapeutic potential with low cytotoxicity, reinforcing the extract’s promise against Orthoflavivirus and Alphavirus.

LC-MS/MS analysis enabled the identification of compounds potentially linked to this antiviral activity. Caffeic acid (**1**) has shown activity against ILHV and ZIKV by binding to the viral envelope protein (Saivish et al., 2023). Its derivative, ethyl caffeate (**12**), also exhibited antiviral effects by inhibiting HIV protease (Wang et al., 2019).

Among flavonoids, orientin (**2**) blocks SARS-CoV-2 entry into host cells (Bhowmik et al., 2021), while isoorientin (**5**) inhibits the spike-ACE2 interaction (Chen et al., 2023). Luteolin (**10**) is known for broad-spectrum antiviral action against influenza, herpesvirus, and coronaviruses (Lu et al., 2023). Vitexin (**3**) and isovitexin (**8**) inhibit H1N1 and offer protection against COVID-19 (Sadati et al., 2019; Ferdausi et al., 2022). Apigenin (**15**) interferes with replication of DNA and RNA viruses, including HSV, HCV, DENV, and SARS-CoV (Lee et al., 2023).

Flavanones identified include eriodictyol (**9**), which modulates inflammatory cytokines relevant in CHIKV and MAYV infections (Deng et al., 2020). Naringenin (**14**) and its glycoside naringenin-7-O-glucoside (**7**), along with pinocembrin (**16**), reduce ZIKV RNA synthesis and affect viral proteins (Cataneo et al., 2021; Lee et al., 2019). Quercetin (**11**) disrupts MAYV entry and RNA replication (Santos et al., 2014), supporting the strong activity observed against this virus (EC₅₀ 61.24 µg/mL; SI 12.96).

Pinoresinol (**13**), a lignan reported in *F. citrifolia*, has demonstrated anti-HBV effects (Wang et al., 2013). Prenylated isoflavones such as isowighteone (**17**), alpinumisoflavone (**18**), and its isomer, known from the genus (Bankeu et al., 2011), may also contribute due to increased

lipophilicity and membrane interaction potential (Ateba et al., 2019).

Monoterpenes like loliolide (**6**), identified in the genus (Zhang et al., 2024), inhibit HCV entry (Chung et al., 2016). Its epimer, (epi)loliolide (**4**), although not linked to antiviral activity, shows anti-hepatocellular carcinoma properties (Gangadhar et al., 2020). The triterpene lupenone (**20**) has activity against CHIKV, while stigmasterol (**21**) inhibits HSV replication (Bhakat & Soliman, 2015; Petrera, Níttolo & Alché, 2014).

These results suggest that the antiviral effect may arise from synergistic interactions among metabolites rather than isolated actions (Caesar & Cech, 2019). The chemical complexity of *F. citrifolia* supports its antiviral activity and points to its potential for therapeutic development. Further studies, including bioguided fractionation and molecular docking, are essential to elucidate specific mechanisms and identify active constituents.

Declarations

Authors' contributions

Horrana Acácio Mardegan designed the studies. Horrana Acácio Mardegan, Allana Martins dos Santos Ataíde, Loueny Celine Ribeiro Andrade and Johan Carlos Costa Santiago conducted LC-MS experiments. Cíntia Lopes de Brito Guimarães designed antiviral assays. Horrana Acácio Mardegan, Allana Martins dos Santos Ataíde and Johan Carlos Costa Santiago conducted MS/MS data processing. Horrana Acácio Mardegan and Johan Carlos Costa Santiago performed metabolite characterization. Horrana Acácio Mardegan, Allana Martins dos Santos Ataíde, Loueny Celine Ribeiro Andrade and Abraão de Jesus Barbosa Muribeca searched the pharmacological properties of the annotated metabolites. Ariane Coelho Ferraz, Marília Bueno da Silva Menegatto and Cíntia Lopes de Brito Magalhães performed and discussed *in vitro* antiviral assays with the extracts. Horrana Acácio Mardegan, Allana Martins dos Santos Ataíde, Johan Carlos Costa Santiago, Abraão de Jesus Barbosa Muribeca wrote the manuscript. Sônia das Graças Santa Rosa Pamplona, Cíntia Lopes de Brito Magalhães, Abraão de Jesus Barbosa Muribeca, Consuelo Yumiko Yoshioka e Silva and Milton Nascimento da Silva reviewed the whole manuscript and provided comments. All authors have read and agreed to the published version of the manuscript.

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Supplementary Information

Not applicable.

Ethics approval

Not applicable. This study did not involve human participants or animal experiments.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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