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Article

Friedelane Triterpenes with Cytotoxic Activity from the Leaves of *Maytenus quadrangulata* (Celastraceae)

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Three new triterpenes, 3,4-*seco*-3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**), friedelan-3α,11β-diol (**2**), 7β,26-epoxyfriedelan-3a,7a-diol (**3**), a mixture of two new triterpenes 3α-hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**) and eleven known compounds were obtained from the hexane extract of *Maytenus quadrangulata* leaves. The structures and the relative stereochemistry of the new triterpenes were established through 1D/2D nuclear magnetic resonance (NMR), high resolution mass spectrometry (HRMS), and Fourier transform infrared (FTIR) spectral data. The hexane extract and isolated compounds were submitted to the cytotoxicity assays against leukemia (THP-1 and K562), ovarian (TOV-21G) and breast cancer (MDA-MB-231) cell lines. Compounds **1**, **2** and 11β-hydroxyfriedelan-3-one (**15**) displayed high cytotoxicity and selectivity against leukemic cells when compared to positive control cytarabine (for THP-1) and imatinib (for K562). Furthermore, compound **2** showed similar cytotoxicity and an enhanced selectivity towards ovarian and breast cells in comparison to positive control etoposide.

Keywords: Celastraceae, *Maytenus*, pentacyclic triterpenes, cytotoxicity

Introduction

The Celastraceae family is composed of 1210 species distributed in 96 genera, which are found mainly in tropical and subtropical regions of South America, Asia and North Africa.[1,2] The genus *Maytenus* belongs to the Celastraceae family and displays different species commonly used in folk medicine to treat stomach problems and due to its anticancer, analgesic, anti-ulcerogenic, antiasthmatic, anti-inflammatory, anti-human immunodeficiency virus (HIV) and antimicrobial properties.[3,4] *Maytenus quadrangulata* (Schrad.) Loes, popularly known as "*espinho-de-deus*", is naturally found in the Atlantic Forest and Caatinga (savanna region) biome of Brazil in the states of Bahia, Espírito Santo and Minas Gerais.[5-7] Even though its great pharmacological potential, no phytochemical and biological evaluation involving *M. quadrangulata* was found in the literature.

Pentacyclic triterpenes are secondary metabolites commonly found in the genus *Maytenus*.[4,8] In recent years, such compounds have been increasingly studied due to their wide range of pharmacological activities, including antitumor, hepatoprotective, anti-inflammatory, hypoglycemic, antibacterial, antioxidant, anti-HIV, anti-trypanosome, leishmanicidal, antiarthritis and immunological adjuvant activities.[9] For example, friedelan-3-one exhibited gastric anti-ulcer, anti-inflammatory (*in vivo*), analgesic, antipyretic, and antioxidant activities.[10-12] Furthermore, friedelan-3-one and some of its derivatives, obtained from reactions involving the ketone

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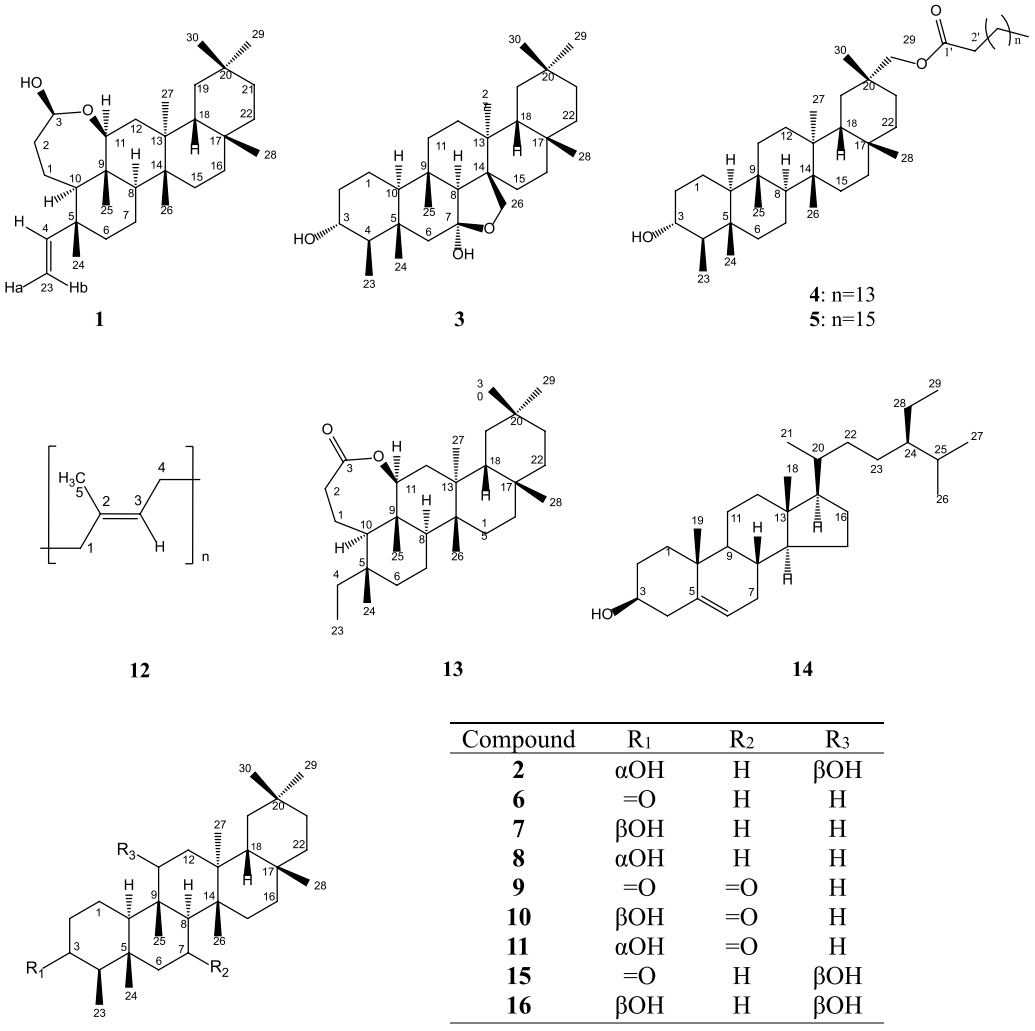
group at C-3, also demonstrated *in vitro* cytotoxic activity against THP-1 and K562 leukemia cell lines.[13]

In the present work, the phytochemical study of the *M. quadrangulata* hexane extract of the leaves led to the isolation of the three new triterpenes 3,4-*seco*-3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**), friedelan-3α,11β-diol (**2**), 7β,26-epoxyfriedelan-3a,7a-diol (**3**) and a mixture of the two new compounds 3α-hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**). Moreover, eleven known compounds were also obtained: friedelan-3-one (**6**), friedelan-3β-ol (**7**), friedelan-3α-ol (**8**), friedelan-3,7-dione (**9**), 3β-hydroxyfriedelan-7-one (**10**), 3α-hydroxyfriedelan-7-one (**11**), gutta-percha polymer (**12**), 3,4-*seco*-friedelan-3,11-olide (**13**), β-sitosterol (**14**), 11β-hydroxyfriedelan-3-one (**15**) and mixture of friedelan-3α,11β-diol (**2**) and friedelan-3β,11β-diol (**16**) (Figure 1). The structural elucidation of the new triterpenes **1**, **2**, **3**, **4** and **5** was accomplished by infrared (IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR), including two-dimensional experiments (heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), correlated spectroscopy (COSY) and nuclear overhauser effect spectroscopy (NOESY)), high-resolution atmospheric pressure chemical ionization mass spectrometry (HR-APCI-MS) and high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) analyses. The cytotoxicity of the compounds **1**, **2**, **6**-**11**, **13**, **15** and the hexane extract was evaluated against leukemia (THP-1 and K562), ovarian (TOV-21G) and breast cancer (MDA-MB-231) cell lines.

Experimental

Column chromatography (CC) was carried out with silica gel 60 (230-400 mesh or 70-230 mesh, Merck, Darmstadt, Germany). Medium pressure liquid chromatography (MPLC) was performed on a Biotage Isolera Spektra One system (Biotage, Uppsala, Sweden), using a Biotage Snap



Compound	R_1	R_2	R_3
2	αOH	H	βOH
6	=O	H	H
7	βOH	H	H
8	αOH	H	H
9	=O	=O	H
10	βOH	=O	H
11	αOH	=O	H
15	=O	H	βOH
16	βOH	H	βOH

Figure 1. Compounds **1**-**16** from *Maytenus quadrangulata* leaves.

cartridge of 50 g (Biotage, Uppsala, Sweden). The mobile phases were hexane, chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), ethyl acetate (AcOEt) and methanol, pure or in mixtures of increasing polarity. All solvents were Vetec (Duque de Caxias, Brazil) or Sigma-Aldrich (Saint Louis, USA), analytical grade. Pre-coated plates with silica gel 60 G (Vetec, Duque de Caxias, Brazil) were used in all thin layer chromatography (TLC) procedures. The melting temperatures of isolated compounds were determined on a Microchemical apparatus MQAPF-302 (Microchemical, Palhoça, Brazil), without correction for normal temperature and pressure conditions. The infrared spectra were obtained on a spectrometer Spectrum One PerkinElmer attenuated total reflection (ATR) (PerkinElmer, Massachusetts, USA) or Shimadzu IR-408 (Shimadzu, Singapore) (sample in KBr disk). 1D/2D NMR spectra were recorded on Bruker Avance DRX-400 and DRX-200 spectrometers (Bruker Avance, Billerica, USA), using $CDCl_3$ or $CDCl_3$ with some drops of pyridine (Py-d_5), as solvent. The chemical shifts (δ) were recorded in ppm using tetramethylsilane (TMS) as internal standard and the coupling constants (J) are given in Hz. The mass spectra were acquired in a high-resolution mass spectrometer of the Thermo Scientific Q-Exactive Orbitrap type (Thermo Fisher Scientific, Bremen, Germany), in positive or negative mode. The operating parameters of APCI ionization source were: spray voltage 5000 V, flow of 20 μL min^{-1}, sheath gas 10, capillary temperature 320 °C, auxiliary gas temperature 37 °C, s-lens 50. The operating parameters of HR-ESI ionization source were: spray voltage 5200 V, flow of 20 μL min^{-1}, sheath gas 12, capillary temperature 300 °C, auxiliary gas temperature 37 °C, s-lens 50. The compounds were detected and confirmed by the exact mass and isotopic parameters obtained in MS^1 and MS^2 spectra.

Plant material

Leaves of *Maytenus quadrangulata* were collected in the district of Brejo do Amparo, municipality of Januária (44º24'17.48'' W and 15º25'10.85'' S), Minas Gerais, Brazil, in February 2017. A voucher specimen (HMC, No. 405) was deposited in the Herbarium of the Departamento de Botânica, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais. The botanical material was registered at Conselho de Gestão do Patrimônio Genético (CGEN/SisGen), Brazil, under the number AAECF38.

Extraction and isolation

Leaves of *M. quadrangulata* were dried at room temperature and ground then, the powder (1743.0 g) was subjected to exhaustive extraction by maceration with hexane. A solid was formed during the partial removal of the hexane using a rotary evaporator (solid of the hexane extract (SHE), 465.0 mg, 1.3% of the hexane extract (HE)) and was filtered under reduced pressure. After filtration, the rest of the hexane has been completely removed to afford the hexane extract (HE: 36.3 g).

SHE (450.0 mg,) was subjected to CC using silica gel (50.8 g, 70-230 mesh) yielding 113 fractions, which were gathered in 8 groups (A1-A8), according to the TLC profiles. From these groups were obtained: friedelan-3-one (**6**) (A1-16.1 mg, hexane-CH_2Cl_2 7:3 v/v, 3.6% of SHE), mixture of compounds **6** and friedelan-3β-ol (**7**) (A2-82.2 mg, hexane-CH_2Cl_2 7:3 v/v, 18.3% of SHE), mixture of compounds **6**, **7** and friedelan-3α-ol (**8**) (A3-30.9 mg, hexane-CH_2Cl_2 6:4 v/v, 6.9% of SHE), friedelan-3α-ol (**8**) (A4-87.4 mg, hexane-CH_2Cl_2 6:4 v/v, 19.4% of SHE), friedelan-3,7-dione (**9**) (A5-6.9 mg, hexane-CH_2Cl_2 1:1 v/v, 1.5% of SHE), mixture of 3α-hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**) (A6-5.0 mg, hexane-CH_2Cl_2 3:7 v/v, 1.1% of SHE) and 3β-hydroxyfriedelan-7-one (**10**) (A7-11.0 mg, CH_2Cl_2-AcOEt 1:1 v/v, 2.4% of SHE). The group A8 was chromatographed (silica gel 230-400 mesh) to give 3α-hydroxyfriedelan-7-one (**11**) (14.0 mg, CH_2Cl_2-AcOEt 95:05 v/v, 3.1% of SHE).

The hexane extract (HE, 35.3 g) was subjected to CC using silica gel (765.7 g, 70-230 mesh) obtaining 190 fractions, which were gathered in 16 groups (B1-B16). From the groups B5 and B6 were obtained the gutta-percha polymer (**12**) (218.3 mg, hexane-CH_2Cl_2 7:3 v/v, 0.6% of HE) and mixture of compounds **6** and **7** (286.8 mg, hexane-CH_2Cl_2 7:3 v/v, 0.8% of HE), respectively. The other groups were submitted to successive CC (230-400 mesh), providing the constituents: compound **7** (B7-90.7 mg, hexane-CH_2Cl_2 6:4 v/v, 0.3% of HE), 3,4-*seco*-friedelan-3,11-olide (**13**) (B7-444.3 mg, hexane-CH_2Cl_2 1:9 v/v and B8-658.5 mg, hexane-CH_2Cl_2 1:1 v/v, 3.1% of HE), compound **8** (B9-14.5 mg, hexane-CH_2Cl_2 1:1 v/v, 0.04% of HE), 3,4-*seco*-3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**) (B9-39.6 mg, hexane-CH_2Cl_2 1:1 v/v, 0.1% of HE), β-sitosterol (**14**) (B10-158.5 mg, hexane-CH_2Cl_2 4:6 v/v, 0.4% of HE), mixture of compounds **4** and **5** (B11-37.2 mg, hexane-CH_2Cl_2 4:6 v/v, 0.1% of HE), compound **10** (B12-14.9 mg, hexane-CH_2Cl_2 4:6 v/v, 0.04% of HE), 11β-hydroxyfriedelan-3-one (**15**) (B13-23.3 mg, CH_2Cl_2-AcOEt 9:1 v/v and B14-57.2 mg, CH_2Cl_2-AcOEt 9:1 v/v, 0.2% of HE), the mixture of friedelan-3α,11β-diol (**2**) and friedelan-3β,11β-diol (**16**) (B15-19.0 mg, CH_2Cl_2-AcOEt 8:2 v/v, 0.05% of HE),

friedelan-3α,11β-diol (**2**) (B15-198.7 mg, CH_2Cl_2-AcOEt 8:2 v/v, 0.6% of HE), and 7β,26-epoxyfriedelan-3a,7a-diol (**3**) (B16-29.7 mg, CH_2Cl_2-AcOEt 6:4 v/v, 0.08% of HE).

3,4-*Seco*-3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**)

White solid; mp 121-123 °C; IR (ATR) ν / cm^{-1} 3436, 3224, 3006, 2943, 2931, 1637, 1453, 1384, 1115, 1035, 1026, 994, 907; ^1H and ^{13}C NMR data see Table 1; HRMS (APCI) (positive-ion mode) *m/z*, calcd. for $C_{30}H_{51}O_2^+$ $[M + H]^+$: 443.3884, found: 443.3886.

Friedelan-3α,11β-diol (**2**)

White solid; mp 248-250 °C; IR (KBr) ν / cm^{-1} 3492, 2974, 2934, 2866, 1462, 1386, 1004; ^1H and ^{13}C NMR data see Table 1; HRMS (ESI) (positive-ion mode) *m/z*, calcd. for $C_{30}H_{52}NaO_2^+$ $[M + Na]^+$: 467.3859, found: 467.3856.

7β,26-Epoxyfriedelan-3a,7a-diol (**3**)

White solid; mp 145-147 °C; ^1H and ^{13}C NMR data see Table 1; HRMS (ESI) (positive-ion mode) *m/z*, calcd. for $C_{30}H_{50}NaO_3^+$ $[M + Na]^+$: 481.3652, found: 481.3648.

3α-Hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**)

White solid; mp 126-130 °C; IR (KBr) ν / cm^{-1} 3488, 2928, 2856, 1736, 1708, 1462, 1386, 1170, 408; ^1H and ^{13}C NMR data see Table 1; HRMS (APCI) (positive-ion mode) *m/z*, calcd. for $C_{30}H_{51}O_2^+$ ($[M - 239]^+$ for **4** and $[M - 267]^+$ for **5**) 443.3884, found: 443.3886, *m/z*, calcd. for $C_{16}H_{31}O^+$ 239.2369, found: 239.2368, *m/z*, calcd. $C_{18}H_{35}O^+$ 267.2682, found: 267.2681; HRMS (APCI) (negative-ion mode): *m/z*, calcd. for $C_{16}H_{31}O_2^-$ $[M - terpenoid]^-$: 255.2330, found: 255.2328 (compound **4**); calcd. for $C_{18}H_{31}O_2^-$ $[M - terpenoid]^-$: 283.2643, found: 283.2643 (compound **5**).

3α-Hydroxyfriedelan-7-one (**11**)

White solid; mp 305-307 °C; IR (KBr) ν / cm^{-1} 3482, 2942, 2868, 1704, 1456, 1388, 1036, 1006; ^1H and ^{13}C NMR data see Table 1; HRMS (ESI) (positive-ion mode) *m/z*, calcd. for $C_{30}H_{51}O_2^+$ $[M + H]^+$: 443.3884; found: 443.3878.

Cytotoxicity evaluation

The cytotoxicity of the samples was evaluated against the human tumor cell lines THP-1 (human acute monocytic leukemia, ATCC-TIB-202), K562 (chronic myeloid leukemia, ATCC-CRL-3344), MDA-MB-231 (human cancer breast, ATCC-HTB-26) and TOV-21G (human cancer ovary, ATCC-HTB-26). The cytotoxicity of the samples against Wi-26VA4 cells (human lung embryonic fibroblast cells, ATCC- CCL-75) allowed to establish the selectivity index (SI). The cell viability was determined by colorimetric assay using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma-Aldrich, Saint Louis, USA). For the evaluation of cytotoxic activity, cells were placed in 96-well plates (1×10^6 cells *per* well) containing Roswell Park Memorial Institute 1640 (RPMI-1640) medium plus 10% fetal bovine serum (FBS). After the cell plating, the plates were incubated for 24 h at 37 ºC, in a 5% CO_2 atmosphere, in a humid environment, for consecutive addition of the samples to be tested. The cytotoxicity assays were performed in four serial dilutions on the decimal scale from the stock solution (compounds and positive control in dimethyl sulfoxide-DMSO), using RPMI-1640 with 1% FBS supplementation. Each concentration was tested in triplicate and each test was also repeated in triplicate. Cytarabine (Blausiegel, Fortaleza, Brazil) (for THP-1), imatinib (Eurofarma, São Paulo, Brazil) (for K562) and etoposide (Sigma-Aldrich, Saint Louis, USA) (for MDA-MB-231 and TOV-21G) were used as positive controls. After 48 h of incubation, the MTT reagent (100 µL, 5 mg mL^{-1}) was added to each well. After 3 h at 37 °C, 50 µL DMSO was added to each well to dissolve the formazan crystals. The colorimetric reading was measured at 550 nm using a SpectraMax Plus 384® microplate reader (Molecular Devices, San Jose, USA). The cytotoxicity was expressed by the sample concentration values that inhibit 50% of cell growth (IC_{50}) in comparison to the cells cultivated in the absence of the sample (negative control). The selectivity index (SI) was calculated by the ratio of the IC_{50} obtained for normal cells (Wi-26VA4) to that obtained for the cancer cell lines.

Results and Discussion

Compound **1** was obtained as a white amorphous powder with molecular formula $C_{30}H_{50}O_2$ as established by HR-APCI-MS (*m/z*: 443.3886 $[M + H]^+$, calcd. 443.3884). The IR spectrum displayed hydroxyl absorption at 3436 cm^{-1}, C–O stretch at 1026 cm^{-1}, C=C stretch at 1637 cm^{-1}, and out-of-plane bending vibrations of =C–H at 994 and 907 cm^{-1}. The ^1H NMR spectrum showed seven singlets of methyl groups (δ_H 0.93; 0.94; 0.95; 0.99; 1.02; 1.11 and 1.18), three signals characteristic of a monosubstituted alkene at δ_H 5.60 (dd, 1H, *J* 17.4 and 10.8 Hz), δ_H 4.95 (d, 1H, *J* 10.8 Hz) and δ_H 4.89 (d, 1H *J* 17.4 Hz), and two signals at δ_H 5.09 (ddd, 1H, *J* 8.7, 6.1, 2.5 Hz) and δ_H 3.84 (dd, 1H, *J* 11.0, 5.3 Hz) (Table 1). The ^{13}C spectral data were closely related to compound **13** (3,4-*seco*-friedelan-3,11β-olide),[8] suggesting a *seco*-friedelan with a possible hemiacetal ring involving

Table 1. [1]H (400 MHz) and [13]C NMR (100 MHz) data of compounds **1**, **2**, **3**, **4**, **5** and **11** isolated from hexane extract of *Maytenus quadrangulata* leaves

Atom	**1**[a]		**2**[a]		**3**[a]		**4** and **5**[a]		**11**[b]	
	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]
1	20.2	1.36	22.6	2.36 (α) 1.47 (β)	19.3	1.43 (β) 1.57 (α)	19.5	1.34	19.7	1.74
2	36.4	1.52 (β) 2.08 (α)	37.0	2.07 (β) 1.28 (α)	37.6	1.28 (α) 2.21 (β)	36.7	1.25 (α) 2.07(β)	36.2	2.20 (α) 1.49 (β)
3	95.8	5.09 (α); ddd; *J* 8.7, 6.1, 2.5	71.9	3.33 (β); td; *J* 10.7, 4.6	74.6	3.56 (β); td, *J* 11.0; 6.6	72.2	3.35 (β) td, *J* 10.4; 4.8	70.8	3.41; dt, *J* 10.3; 4.9
4	152.1	5.60 (α); dd; *J* 17.4, 10.8	53.4	1.05 (α)	53.3	1.55 (α)	53.3	1.05	53.1	1.42
5	42.0	–	39.0	–	42.1	–	38.1	–	44.2	–
6	42.0	1.42 (β) 1.38 (α)	41.5	1.78 (β) 1.03 (α)	47.0	1.74 2.01	41.4	1.04 (α) 1.77 (β)	57.8	2.21 (β) 2.30 (α); d, *J* 11.9
7	18.2	1.44	17.8	1.47	77.4	–	18.0	1.41	212.1	–
8	52.9	1.35 (α)	52.8	1.28 (α)	64.7	1.64 (α)	53.3	1.27	63.4	2.79; s
9	42.3	–	43.9	–	38.2	–	37.0	–	42.7	–
10	62.3	1.0 (α)	60.9	1.12 (α)	58.1	1.42 (α)	60.2	0.94	59.8	1.61
11	73.9	3.84 (α); dd; *J* 11.0, 5.3	76.9	3.60 (α); dt; *J* 11.3, 5.7	30.4	1.23 1.31	35.6	1.14 1.40	36.3	1.49
12	39.4	1.41 (β) 1.50 (α)	42.2	1.54 (α) 1.27 (β)	37.6	1.53 1.70	30.7	1.29	29.9	1.35
13	37.9	–	38.4	–	39.8	–	39.9	–	39.3	–
14	41.5	–	41.2	–	42.7	–	38.3	–	37.4	–
15	32.2	1.25 1.47	32.5	1.46 1.23	36.6	1.89 (α) 2.68 (β); ddd; *J* 13.6, 10.9, 5.9	32.5	1.50 (α) 1.28 (β)	31.9	1.14 (α) 1.99 (β)
16	36.0	1.34 1.55	36.1	1.53 1.34	35.8	1.48 (α) 1.68 (β)	36.0	1.32 1.57	35.5	1.39 (β) 1.50 (α)
17	30.1	–	30.2		32.0		30.4	–	30.1	–
18	42.7	1.57	42.7	1.55 (β)	45.5	1.23 (β)	41.9	1.60	41.8	1.64
19	35.5	1.20 1.38	35.5	1.38 1.20	32.9	1.21 1.32	29.7	1.27	34.9	1.24 1.39
20	28.2	–	28.3	–	28.6	–	31.8	–	28.0	–
21	32.8	1.27 1.45	32.9	1.45 1.26	35.8	1.02 1.27	28.2	1.34 1.44	32.8	1.28 1.51
22	39.4	0.92 (β) 1.44 (α)	39.3	1.47 0.93	38.1	1.33	39.3	1.42 (α) 0.97 (β)	38.6	0.95 1.53
23	111.1	4.95 (a); d; *J* 10.8 4.89 (b); d; *J* 17.4	10.0	0.90; d *J* 6.6	12.5	1.02; d; *J* 6.5	10.1	0.89	10.1	0.97; d; *J* 6.6
24	17.9	0.93; s	14.9	0.79; s	20.9	0.91; s	14.2	0.77; s	14.7	0.85; s
25	14.9	0.94; s	13.3	0.87; s	24.7	1.17; s	18.2	0.81; s	19.3	0.89; s
26	20.3	1.02; s	20.1	0.99; s	56.9	2.25 2.94; d; *J* 11.6	20.5	1.00; s	19.5	1.44; s
27	19.6	1.11; s	19.6	1.07; s	23.8	1.04; s	18.5	0.99; s	18.2	1.06; s
28	32.2	1.18; s	32.1	1.18; s	31.9	0.99; s	32.2	1.20; s	31.6	1.20; s
29	35.0	0.95; s	35.1	0.95; s	34.0	0.92; s	74.9	3.74; m	34.5	0.99; s
30	31.7	0.99; s	31.8	0.99; s	30.5	0.94; s	26.4	1.04; s	32.1	1.03; s

Table 1. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) data of compounds **1**, **2**, **3**, **4**, **5** and **11** isolated from hexane extract of *Maytenus quadrangulata* leaves (cont.)

Atom	**1**[a]		**2**[a]		**3**[a]		**4** and **5**[a]		**11**[b]	
	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]	δ_C	δ_H[c]
1'	–	2.32; d; *J* 2.5 (C_3-OH)	–	1.01 (C_{11}-OH)			174.3	–		
2'							34.7	2.33		
3'							25.3	1.64		
n							30.0-29.2	1.22-1.32		
14' (4) or 16' (5)							32.0	1.28		
15' (4) or 17'(5)							22.7	1.29		
16' (4) or 18' (5)							14.6	0.89		

[a]$CDCl_3$; [b]$CDCl_3$, with drops of pyridine-d_5; [c]signals without multiplicity are overlapped. δ ppm, *J* in Hz.

C-3 (δ_C 95.8) and C-11 (δ_C 73.9). The HMBC spectrum demonstrated correlations of C-3 (δ_C 95.8) with the signals at δ_H 3.84 (H-11), δ_H 1.36 (H-1) and δ_H 1.52 (H-2), and of H-11 with the signals of C-10 (δ_C 62.3), C-12 (δ_C 39.4) and C-25 (δ_C 14.9), confirming the presence of both C-3 and C-11 in the same ring (Figure 2). The NOESY spectrum established the alpha position for H-3 and H-11 through the correlations of H-11 with H-8 (δ_H 1.35), H-10 (δ_H 1.0), H-12α (δ_H 1.50) and H-27 (δ_H 1.11), and of H-3 with H-2α (δ_H 2.08) and H-1 (δ_H 1.36), also implying in the beta position of the hydroxyl group linked to C-3. Furthermore, the ^{13}C spectral data were also relatable to putranjivic acid,[14] especially regarding C-4 and C-23, implying a possible unsaturation between them. In the HSQC spectrum, H-23 (δ_H 4.95 and δ_H 4.89) correlated with C-23 (δ_C 111.1) and, in the COSY spectrum, with H-4 (δ_H 5.60). In the HMBC spectrum, the correlations of H-4 with C-5 (δ_C 42.0), C-10 and C-24 (δ_C 17.9) confirmed the presence of a double bond between C-4 and C-23 (Figures S1 to S10, Supplementary Information section). The dataset allowed us to indicate compound **1** as the new friedelane triterpene of 3,4-*seco*-3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**).

Compound **2** was isolated as a white amorphous powder with molecular formula $C_{30}H_{52}O_2$ as established by HR-ESI-MS (*m/z*: 467.3856 $[M + Na]^+$, calcd. 467.3859). The IR spectrum showed hydroxyl absorption at 3492 cm^{-1} and C–O stretch at 1004 cm^{-1}. The ^{1}H NMR spectrum displayed six singlets corresponding to seven methyl groups (δ_H 0.79, 3H; 0.87, 3H; 0.95, 3H; 0.99, 6H; 1.07, 3H; and 1.18, 3H), one doublet characteristic of a friedelane skeleton (H-23, δ_H 0.90, 3H, *J* 6.6 Hz), and signals attributed to carbinolic protons at δ_H 3.60 (dt, 3H, *J* 11.3 and 5.7 Hz) and δ_H 3.33 (td, H, *J* 10.7 and 4.6 Hz) (Table 1). The ^{13}C NMR spectral data were related to friedelan-3β,11β-diol (**16**),[15]

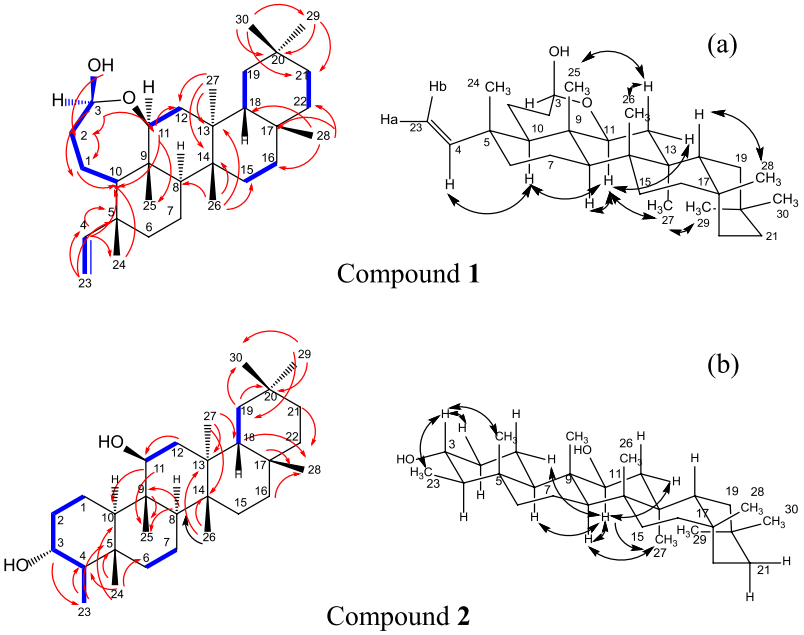


Figure 2. Correlations observed in COSY (▬), HMBC (➔) and NOESY (⟷): (a) for compound **1**, (b) for compound **2**.

with two signals at δ_C 71.9 and 76.9 from carbons bonded to hydroxyl groups. In the HMBC spectrum, the signal at δ_C 71.9 was attributed to C-3 according to the correlation with the doublet at δ_H 0.90 (H-23), which correlated with δ_C 53.4 (C-4) (Figure 2). The beta position of H-3 (δ_H 3.33) was confirmed by the NOESY spectrum correlations of this proton with the signals of H-24 (δ_H 0.79), H-23 (δ_H 0.90) and H-2β (δ_H 2.07). Thus, the hydroxyl group linked to C-3 was assigned at an alpha position, differently from the known compound **16**. Moreover, the signal at δ_C 76.9 was attributed to C-11 due to the correlations of the signal at δ_H 3.60 (H-11) with δ_C 60.9 (C-10) and δ_C 13.3 (C-25) in the HMBC. In the NOESY spectrum, the alpha position of H-11 was confirmed with the with H-1α (δ_H 2.36), H-8 (δ_H 1.28), H-10 (δ_H 1.12), H-12α (δ_H 1.54), and H-27 (δ_H 1.07), implying the beta position of the C-11 hydroxyl group (Figures S11 to S23, Supplementary Information section). The dataset allowed us to indicate compound **2** as the new friedelane triterpene friedelan-3α,11β-diol.

Compound **3** was isolated as a white solid with the molecular formula $C_{30}H_{50}O_3$ established by HR-ESI-MS (*m/z*: 481.3648 [M + Na]$^+$, calcd. 481.3652). The ^{1}H NMR spectrum showed six singlets (Table 1) attributed to six methyl groups (δ_H 1.17, 1.04, 0.99, 0.94, 0.92 and 0.91), one doublet characteristic of H-23 of a friedelane skeleton (δ_H 1.02, 3H, *J* 6.5 Hz) and a signal attributed to a carbinolic proton at δ_H 3.56 (td, 1H, *J* 11.0, 6.6 Hz). The ^{13}C NMR spectral data displayed three unshielded signals at δ_C 56.9, 74.6 and 77.4. As expected for friedelane compounds, the signal at δ_H 1.02 (H-23) correlated with C-3 (δ_C 74.6), C-4 (δ_C 53.3) and C-5 (δ_C 42.1) in the HMBC spectrum (Figure 3). Also, C-4 and C-5 correlated with H-6 (δ_H 1.74 and δ_H 2.01), and this proton further correlated with C-7 (δ_C 77.4), C-8 (δ_C 64.7) and C-10 (δ_C 58.1). Subsequent C-7 correlations with H-26 (δ_H 2.25 and δ_H 2.94) suggested a tetrahydropyran ring involving C-26 (δ_C 56.9) and C-7, further confirmed by the correlations of H-26 with C-8, C-14 (δ_C 42.7) and C-15 (δ_C 36.6). A similar ring was also observed in 24-hydroxy-3-oxohemiacetalfriedelane (rinol), isolated by Munvera *et al.*[16] who also suggested this phenomenon as a probable result of a reaction between a ketone group at C-3 and a primary alcohol at C-24. The NOESY correlations of H-26 with H-25 (δ_H 1.17) and H-28 (δ_H 0.99) allowed to certify the beta position of the CH_2O group, implying in the alpha position of the hydroxyl group at C-7 (Figures S24-S31, Supplementary Information section). The dataset allowed us to indicate compound **3** as the new friedelane triterpene7β,26-epoxyfriedelan-3a,7a-diol.

The mixture of compounds **4** and **5** was obtained as a white amorphous solid. The IR spectrum showed an alcohol O–H stretch band at 3488 cm^{-1} and an ester C=O stretch band at 1736 cm^{-1}. The ^{1}H NMR spectrum presented six singlets (δ_H 0.77, 0.81, 0.99, 1.00, 1.04 and 1.20) corresponding to six methyl groups and a characteristic methyl doublet signal related to H-23 of a friedelane skeleton at δ_H 0.89 (Table 1). This spectrum also showed two unshielded signals at δ_H 3.35 (td, 1H, *J* 10.4 and 4.8 Hz) and δ_H 3.74 (2H, m), probably belonging to protons bonded to an oxygenated carbon. The ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT-135) spectra presented one signal of an ester

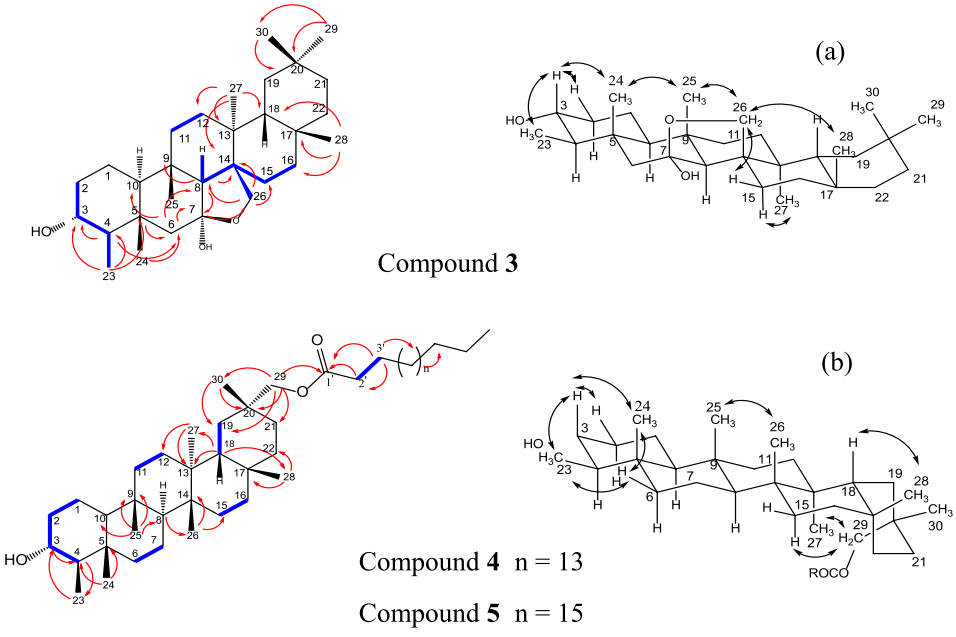


Figure 3. Correlations observed in COSY (▬), HMBC (➔) and NOESY (⟷): (a) for compound **3**, (b) for compounds **4** and **5**.

carbonyl at δ_c 174.3 and signals of methylene carbons between δ_c 29.2 and δ_c 30.0, possibly from a long chain ester. The ^{13}C NMR data of the mixture were closely related to 3β,29-dihydroxyfriedelane.[17] The HMBC correlations of the unshielded carbon at δ_C 72.2 with H-4 (δ_H1.05) and H-23 (δ_H 0.89), confirmed the hydroxyl group at C-3 (Figure 3). Additionally, H-3 (δ_H 3.35) showed correlations with H-2 (δ_H 1.25 and δ_H 2.07) and H-4 (δ_H 1.05) in the COSY spectrum. Furthermore, H-3 correlated with the signals of H-1 (δ_H 1.34), H-2β (δ_H 2.07), H-23 and H-24 (δ_H 0.77) in the NOESY spectrum, certifying the alpha position of the hydroxyl group linked to C-3 and the beta position of H-3. The ester group in C-29 was confirmed by correlations of the signal at δ_H 3.74 (H-29) with C-19 (δ_c 29.7), C-20 (δ_c 31.8), C-21 (δ_c 28.2), C-30 (δ_c 26.4), and C-1' (δ_c 174.3) in the HMBC spectrum. The chemical shift assignments of the mixture of **4** and **5** were completely established through detailed analysis of HSQC, HMBC, COSY and NOESY spectra (Figures S32 to S42, Supplementary Information section). In the positive mode, HR-APCI-MS spectrum of the mixture of **4** and **5** showed the fragment ion peak $C_{30}H_{51}O_2^+$ ([M-239]$^+$ for **4** and [M – 267]$^+$ for **5**) resulting from the $C_{29}O–C_{1'}$ bond breaking. Also, this spectrum presented peaks referring to the acylium ions at *m/z* 239.2368 $[C_{16}H_{31}O]^+$ (calcd. 239.2369) and at *m/z* 267.2681 $[C_{18}H_{35}O]^+$ (calcd. 267.2682). In the negative mode, the HR-APCI-MS analysis displayed two ion peaks [M-triterpenoid]$^-$ at *m/z* 255.2328 and 283.2643, referring to palmitate and stearate ions, respectively. Therefore, the mixture was identified as 3α-hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**).

Compound **11** was identified by 1D/2D NMR spectra and HR-ESI-MS as 3α-hydroxyfriedelan-7-one (Figures S63 to S72, Supplementary Information section). Even though the ^1H NMR data for this compound is found in the literature,[18-20] this is the first report for its ^{13}C NMR spectra data (Table 1). The other known compounds were identified as friedelan-3-one (**6**),[21] friedelan-3β-ol (**7**),[22] friedelan-3α-ol (**8**),[22] friedelan-3,7-dione (**9**),[23] 3β-hydroxyfriedelan-7-one (**10**),[23] gutta-percha (**12**),[24] 3,4-*seco*-friedelan-3,11-olide (**13**),[8] β-sitosterol (**14**),[25] 11β-hydroxyfriedelan-3-one (**15**)[26] and a mixture of friedelan-3α,11β-diol (**2**) and friedelan-3β,11β-diol (**16**)[15] by comparison of their ^1H and ^{13}C NMR data with those reported in the literature. Compounds **9** and **10** were reported for the first time as metabolites of a Celastraceae species.

Cytotoxicity assay

The cytotoxic activity of the hexane extract (HE), the solid obtained during the hexane extraction (SHE) and compounds **1**, **2**, **6**-**11**, **13**, **15** were assessed against human leukemia (THP-1 and K562), ovarian and breast cancer cell lines (TOV-21G and MDA-MB-231, respectively). Compound **3** was not evaluated due to its small amount, and the cytotoxic activities of compounds **12** and **14** were previously reported in the literature.[24,25] Lung embryonic fibroblast cells (Wi-26VA4, ATCC-CCL-75) were adopted to establish the selectivity index (SI) of the analyzed compounds. Furthermore, etoposide was employed as the control with a further assessment using cytarabine for THP-1 and imatinib for K562 (Table 2). HE showed moderate cytotoxicity (IC_{50} < 43 ± 5 μg mL^{-1}) against all tested cell lines, and SHE presented the best result against the THP-1 cell line (IC_{50} = 19 ± 1 μg mL^{-1}, SI = 3).

The results obtained for the leukemia cell lines (THP-1 and K562) demonstrated that all tested compounds showed IC_{50} values lower than 80 μg mL^{-1}. Compounds **1**, **2** and **15** displayed the best results (IC_{50} = 13 ± 1, 10.0 ± 0.9 and 14 ± 1 μg mL^{-1} and SI = 6, 5 and 4, respectively) against the THP-1 cell line. Also, compounds **2** and **15** presented good results against the K562 cell line (IC_{50} = 11 ± 1 and 16 ± 2 μg mL^{-1} and SI = 4 and 3, respectively). Concerning the ovarian and breast cancer cell lines, compound **2** was the most active and selective against TOV-21G and MDA-MB-23 cell lines (IC_{50} = 33 ± 3 and 13 ± 2 μg mL^{-1}, and SI = 2 and 4, respectively).

Indeed, observing the structures of compounds **2** and **15**, which displayed the best results against both THP-1 and K562, suggested that a hydroxyl group in C-11 may be relevant to the antileukemic activity. On the other hand, only compound **2**, which displayed a hydroxyl group at C-3, demonstrated good results against the ovarian and breast cancer cell lines. The results corroborated with the literature on triterpenes inhibiting cancer cell proliferation.[27-29] Pereira *et al.*[30] evaluated a series of pentacyclic triterpenes against leukemic cell lines (THP-1 and K562) and the best results were found for friedelan-3β-ol (**7**) and α-amyrin. Employing chemometric analysis, the authors observed that the activity could be related to the presence of a hydroxyl group at C-3 and its stereoelectronic interactions with molecular targets.[30] Thus, further structure-activity relationships studies should be conducted for a deeper understanding.

Conclusions

The phytochemical study of the hexane extract from *Maytenus quadrangulata* leaves led to the isolation of 14 triterpenes, one steroid and the polymer gutta-percha. The 1D/2D NMR spectral data of 3,4-*seco*-

Table 2. Cytotoxicity and selectivity of the hexane extract (HE), the solid obtained during the hexane extraction (SHE), and compounds **1**, **2**, **6**-**11**, **13** and **15** against leukemia, ovarian and breast cancer cell lines

Sample	Tested cell lines								
	THP-1[a]		K562[b]		TOV-21G[c]		MDA-MB-231[d]		Wi-26VA4[e]
	IC_{50} / (μg mL^{-1})	SI	IC_{50} / (μg mL^{-1})	SI	IC_{50} / (μg mL^{-1})	SI	IC_{50} / (μg mL^{-1})	SI	IC_{50} / (μg mL^{-1})
HE	31 ± 2	2	37 ± 3	2	43 ± 5	2	39 ± 3	2	66 ± 4
SHE	19 ± 1	3	43 ± 2	1	55 ± 5	1	49 ± 4	1	60 ± 3
1	13 ± 1	6	51 ± 4	2	> 100	ND	> 100	ND	83 ± 6
2	10.0 ± 0.9	5	11 ± 1	4	33 ± 3	2	13 ± 2	4	48 ± 2
6	–	ND	–	ND	> 100	ND	> 100	ND	68 ± 3
7	–	ND	–	ND	> 100	ND	> 100	ND	73 ± 4
8	46 ± 2	2	71 ± 6	1	66 ± 5	1	71 ± 6	1	84 ± 7
9	40 ± 3	2	69 ± 5	1	> 100	ND	> 100	ND	76 ± 5
10	38 ± 3	2	80 ± 6	1	>100	ND	> 100	ND	90 ± 7
11	50 ± 5	2	75 ± 7	1	81 ± 6	1	> 100	ND	89 ± 6
13	33 ± 4	2	63 ± 4	1	85 ± 6	0.9	> 100	ND	79 ± 4
15	14 ± 1	4	16 ± 2	3	> 100	ND	> 100	ND	52 ± 3
Etoposide	12 ± 2	0.7	9 ± 1	1	19 ± 2	0.5	12.0 ± 0.6	0.7	8.6 ± 0.1
Cytarabine	13 ± 1	5	ND	ND	–	ND	–	ND	76 ± 4
Imatinib	ND	ND	11 ± 1	7	–	ND	–	ND	79 ± 4
P value	< 0.05[a] > 0.05[b]	–	< 0.05[c] > 0.05[d]	–	< 0.05[e]	–	< 0.05[f] > 0.05[g]	–	< 0.05[h]

Values presented as average ± standard deviation. [a]THP-1, cytarabine and etoposide *vs.* all tested compounds; [b]THP-1, cytarabine and etoposide *vs.* **1**, **2** and **15**; [c]K562, imatinib and etoposide *vs.* all tested compounds; [d]K562, imatinib and etoposide *vs.* **1**; [e]TOV-21G, etoposide *vs.* all tested compounds; [f]MDA-MB-231, etoposide *vs.* all tested compounds; [g]MDA-MB-231, etoposide *vs.* **1**; [h]Wi-26VA4, cytarabine and imatinib *vs.* all tested compounds. THP-1: human acute monocytic leukemia; K562: chronic myeloid leukemia; MDA-MB-231: human cancer breast; TOV-21G: human cancer ovary; ND: not determined.

3,11β-epoxyfriedel-4(23)-en-3β-ol (**1**), friedelan-3α,11β-diol (**2**), 7β,26-epoxyfriedelan-3a,7a-diol (**3**) and a mixture of 3α-hydroxyfriedelan-29-yl palmitate (**4**) and 3α-hydroxyfriedelan-29-yl stearate (**5**) are herein described for the first time. Compound **2** demonstrated the best results among all tested samples, showing promising cytotoxicity and selectivity against THP-1, K562, TOV-21G and MDA-MB-231 cell lines.

Supplementary Information

Supplementary information (IR, NMR spectra of compounds **1**-**16** and HR-ESI-MS/HR-APCI-MS analyses of compounds **1**-**5** and **11**) (Figures S1-S89, Table S1) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

Mariana G. Aguilar performed the conceptualization, chemical experiments and methodology, data analysis, manuscript writing and critical review; Grasiely F. Sousa and Lucienir P. Duarte were responsible for the project management, chemical experiments and methodology supervision, data analysis, manuscript writing and critical review; Adriano P. Sabino and Fernanda C. G. Evangelista performed biological experiments and methodology supervision, data analysis and manuscript writing; Karen C. Camargo contributed to the chemical experiments and data analysis; Sidney A. V. Filho collaborated with the project management, manuscript writing and critical review; Yule R. F. Nunes performed the plant material gathering and identification.

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