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Lebbeckoside C, a new triterpenoid saponin from the stem barks of *Albizia lebbeck* inhibits the growth of human glioblastoma cells

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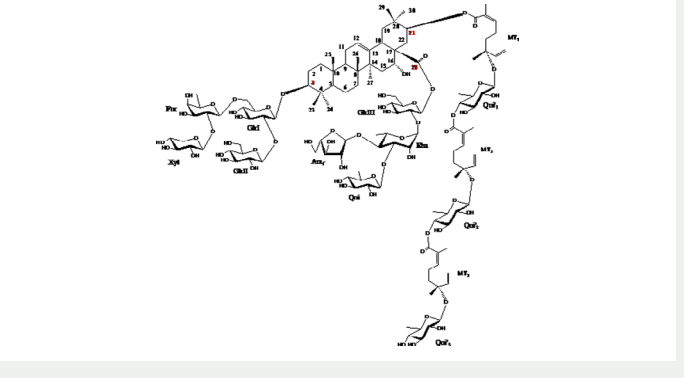
ABSTRACT

One new acacic acid-type saponin, named lebbeckoside C (**1**), was isolated from the stem barks of *Albizia lebbeck*. Its structure was established on the basis of extensive analysis of 1D and 2D NMR (^{1}H, ^{13}C NMR, DEPT, COSY, TOCSY, ROESY, HSQC and HMBC) experiments, HRESIMS studies, and by chemical evidence as 3-*O*-[*β*-D-xylopyranosyl-(I→2)-*β*-D-fucopyranosyl-(1→6)-[*β*-D-glucopyranosyl(1→2)]-*β*-D-glucopyranosyl]-21-*O*-{(2*E*,6*S*)-6-*O*-{4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl) octa-2,7-dienoyl]-4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl) octa-2,7-dienoyl]-*β*-D-quinovopyranosyl}-2,6-dimethylocta-2,7-dienoyl} acacic acid 28 *O*-[*β*-D-quinovopyranosyl-(I→3)-[*α*-L-arabinofuranosyl-(I→4)]-*α*-L-rhamnopyranosyl-(I→2)-*β*-D-glucopyranosyl] ester. The isolated saponin (**1**) displayed significant cytotoxic activity against the human glioblastoma cell line U-87 MG and TG1 stem-like glioma cells isolated from a patient tumor with IC_{50} values of 1.69 and 1.44 µM, respectively.



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1. Introduction

Albizia lebbeck (L.) Benth is a pantropical species distributed in Africa, Asia, America, and Australia. In West Africa, it is traditionally used against diarrhea, dysentery, hemorrhoids, bronchitis, asthma, eczema, and leprosy (Arbonier 2009). Antiproliferative, nootropic, anxiolytic, haemolytic, anti-diarrhoeal, antioxidant, anti-arthritic and antifungal activities have been reported (Faisal et al. 2012), and the oral administration of saponin fraction isolated from its bark to male rats has been reported to significantly reduce fertility through reduction of sperm mobility and density (Gupta et al. 2005). Recently, the *in vitro* antimalarial activity of this plant against *Plasmodium falciparum* chloroquine (CQ) sensitive (MRC2) and CQ resistant (RKL9) strains were reported (Kalia et al. 2015). Previous investigation of its stem barks revealed the presence of glycosides of acacic acid lactones (Pal et al. 1995), and our last investigation on the saponin content of its roots unveiled the presence of two new acacic acid-type saponins, lebbeckosides A–B, molecules cytotoxic at a micromolar concentration towards high-grade glioma cancer cells including those with stem-like cell properties, known to be resistant to standard treatments (Noté et al. 2015).

In the present study, we describe the isolation, structural determination, and cytotoxic evaluation of one new additional triterpenoid saponin isolated from its stem barks, named lebbeckoside C (**1**).

2. Results and discussion

The air-dried finely powdered of the stem barks of *A. lebbeck* were extracted with EtOH 70% in a Soxhlet apparatus. After evaporation of the solvent, the resulting dark residue was suspended in water and partitioned against *n*-BuOH saturated with water. The *n*-BuOH phase was then evaporated to dryness affording a brown gum which was submitted to column chromatography (CC) using Diaion HP-20 resin yielding enriched saponins fractions which were submitted to VLC using silica gel to give three main subfractions. Purification of the eluated subfractions by Semprep-HPLC afforded one new triterpenoid saponin, named lebbeckoside C (**1**) (Figure 1).

Lebbeckoside C (**1**) was obtained as a white amorphous powder. Its positive HR-ESI-MS gave a pseudo-molecular ion peak at *m/z* 2632.2616 $[M + NH_4]^+$ with its isotopic peaks at *m/z* 2631.2572, 2633.2635 and the corresponding doubly charged ion peaks at *m/z* 1244.6112, 1245.1120, and 1246.1142 $[M + 2\ (NH_4)]^{2+}$. Consequently, lebbeckoside C was assigned a $C_{124}H_{196}O_{58}$ molecular formula. Upon acid hydrolysis with 2.0 M HCl, **1** gave an acacic acid lactone unit, which was identified with an authentic sample, together with glucose (Glc), xylose (Xyl), fucose (Fuc), quinovose (Qui), arabinofuranose (Ara_f), and rhamnose (Rha), which were identified by co-TLC with authentic samples. The absolute configuration of these sugar residues was determined to be D for Glc, Xyl, Fuc, Qui, and L for Rha and Ara_f based on GC analysis of their trimethylsilyl thiazolidine derivatives (See Experimental Section) (Chaabi et al. 2010). ^{1}H NMR spectrum of **1** showed seven angular methyl groups as singlets at δ_H 0.99, 1.03, 1.07, 1.15, 1.18, 1.32, and 1.90 (each 3H, s), one olefinic proton at δ_H 5.68 (H-12), one oxygen-bearing methine proton at δ_H 3.52 (H-3), and sugar proton signals between δ_H 3.74–6.30. Its ^{13}C NMR spectrum showed two olefinic carbon signals at δ_C 123.3 and 143.2, suggesting that **1** was an oleanane type triterpenoid saponin. 1D (^{1}H and ^{13}C NMR, DEPT) and 2D (COSY, HSQC and HMBC) NMR techniques permitted the unambiguous assignment

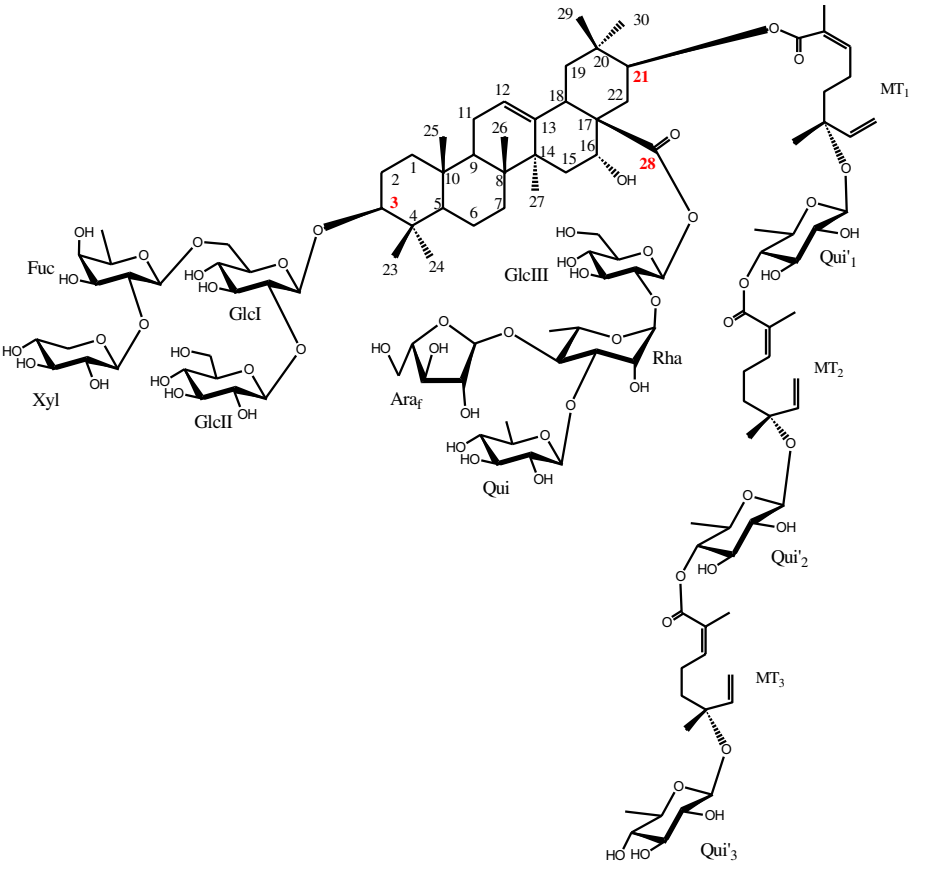

Figure 1. Chemical structure of lebbeckoside C (**1**).

of all ^{1}H and ^{13}C NMR signals of the aglycon of **1** which was identified as acacic acid (3β, 16α, 21β-trihydroxyolean-12-ene-28-oic acid) by comparison of its ^{1}H and ^{13}C NMR signals with those reported in the literature (Table S1) (Noté et al. 2015, 2016).

Substitutions at C-3 and C-28 of acacic acid were evidenced by the observed glycosylation-induced shifts of C-3 at δ_C 88.9 (deshielded signal for C-3 of the aglycon) and of C-28 at δ_C 174.9 (shielded signal for C-28 of the aglycon). Substitution at C-21 was ascertained from the acylation-induced shift observed for C-21 at δ_C 77.5 (deshielded signal for C-21 of the aglycon). All of these data established that **1** was a 21-acyl 3, 28-bidesmosidic acacic acid derivative, sugar chains being linked to C-3 and C-28 through an ether and ester bond, respectively.

Concerning the sugar units, the ^{1}H NMR spectrum of **1** showed eleven anomeric protons at δ_H 4.89 (1H, d, J = 7.7 Hz), 4.90 (1H, d, J = 7.3 Hz), 4.91 (1H, d, J = 7.7 Hz), 4.97 (1H, d, J = 7.9 Hz), 4.99 (1H, d, J = 7.9 Hz), 5.09 (1H, d, J = 6.6 Hz), 5.29 (1H, d, J = 8.0 Hz), 5.43 (1H, d, J = 7.7 Hz), 6.16 (1H, d, J = 7.6 Hz), 6.29 (1H, brs), and 6.30 (1H, brs) which gave correlations in the HSQC spectrum with carbon atom resonances at δ_C 105.2, 99.6, 99.6, 97.2, 103.7, 107.3, 105.9, 106.2, 95.8, 111.5 and 101.6, respectively (Tables S2 and S3). The ^{1}H and ^{13}C NMR data (Tables S2–S3) of the monosaccharide residues were assigned starting, either from the readily identifiable anomeric proton of each hexosyl or pentosyl unit, or from the CH_3-proton

doublet of each 6-deoxyhexosyl unit, by means of COSY, TOCSY, NOESY, HSQC, and HMBC spectra obtained for this compound. Based on the coupling constants of the anomeric protons and the chemical shifts of the anomeric carbons, the anomeric configuration of the sugar moieties were determined as *β* for the glucose, xylose, fucose, and quinovose moieties and *α* for rhamnose and arabinofuranose moieties. In addition, the ^{1}H NMR spectrum of compound **1** exhibited three olefinic proton signals at δ_H 6.89 (t, J = 7.3 Hz), 7.00 (t, J = 7.4 Hz), and 7.08 (t, J = 7.4 Hz), and three groups of one-substituted olefinic proton signals, one group at δ_H 6.24 (dd, J = 10.3; 17.5 Hz), 5.30 (d, J = 10.3 Hz) and 5.40 (d, J = 17.5 Hz), another group at δ_H 6.28 (dd, J = 10.6; 17.0 Hz), 5.29 (d, J = 10.6 Hz) and 5.48 (d, J = 17.0 Hz), and the last group at δ_H 5.98 (dd, J = 10.6; 17.0 Hz), 5.25 (d, J = 10.6 Hz) and 5.47 (d, J = 17.0 Hz), indicating that compound **1** had three monoterpenoid units (Liu et al. 2010).

Extensive analysis of 1D and 2D NMR spectra of **1**, revealed that the sugar moiety at C-3 was identical to that of prosapogenin 2 (Haddad et al. 2002), julibroside J_{31} and prosapogenin-8 (Zheng et al. 2006), gummiferaoside A (Cao et al. 2007), and gummiferaoside D (Simo et al. 2017), and that the monoterpene-quinovosyl moiety at C-21 was identical to that of coriarioside A (Noté et al. 2009), coriariosides C and D (Noté et al. 2010), gummiferaoside C (Cao et al. 2007), lebbeckoside A (Noté et al. 2015), and zygiaoside A (Noté et al. 2016). Hence, the units attached at C-3 and C-21 of the aglycon of **1** were established as 3-*O*-[*β*-D-xylopyranosyl-(l→2)-*β*-D-fucopyranosyl-(1→6)-[*β*-D-glucopyranosyl(1→2)]-*β*-D-glucopyranosyl], and {(2*E*,6*S*)-6-*O*-{4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl)octa-2,7-dienoyl]-4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl)octa-2,7-dienoyl]-*β*-D-quinovopyranosyl}-2,6-dimethylocta-2,7-dienoyl}, respectively.

In the same way, extensive analysis of 1D and 2D NMR spectra of **1**, revealed that the sugar moiety at C-28 was identical to that of pithelucoside A (Ma et al. 2008). Hence, the unit attached at C-28 of the aglycone was established as *β*-D-quinovopyranosyl -(l→3)-[*α*-L-arabinofuranosyl-(l→4)]-*α*-L-rhamnopyranosyl-(l→2)-*β*-D-glucopyranoside. Consequently, the structure of lebbeckoside C (**1**) was established as 3-*O*-[*β*-D-xylopyranosyl-(l→2)-*β*-D-fucopyranosyl-(1→6)-[*β*-D-glucopyranosyl(1→2)]-*β*-D-glucopyranosyl]-21-*O*-{(2*E*,6*S*)-6-*O*-{4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl)octa-2,7-dienoyl]-4-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-*O*-(*β*-D-quinovopyranosyl)octa-2,7-dienoyl]-*β*-D-quinovopyranosyl}-2,6-dimethylocta-2,7-dienoyl}acacic acid 28 *O*-[*β*-D-quinovopyranosyl-(l→3)-[*α*-L-arabinofuranosyl-(l→4)]-*α*-L-rhamnopyranosyl-(l→2)-*β*-D-glucopyranosyl] ester, a new acacic acid-type saponin.

Since lebbeckosides A and B isolated from the roots of the same species were reported to be active on U87 glioblastoma cells, and on highly aggressive, drug resistant stem-like glioblastoma propagating TG 1 cells isolated from a patient tumor (Noté et al. 2015), lebbeckoside C (**1**), isolated from the stem barks of *A. lebbeck*, was also tested for cytotoxicity against the human glioblastoma cell line U-87 MG and TG1 stem-like glioma cells, using Tamoxifen® (31 µM for U-87 MG, and 14 µM for TG 1, respectively) as a positive control. The isolated lebbeckoside C (**1**) inhibits U-87 MG and TG1 stem-like glioma cells survival, assessed by ATP level measurements, with IC_{50} values of 1.69 and 1.44 µM, respectively. The only difference between lebbeckoside C (**1**) and lebbeckoside A (Noté et al. 2015) lies in the substitution pattern of the tetrasaccharide moiety at C-28, and in the oligosaccharide moiety at C-3 of the acacic acid aglycone, with a tetrasaccharide moiety at C-3 in lebbeckoside C (**1**), instead of a trisaccharide moiety described in lebbeckoside A, and differing from lebbeckoside A by the nature of sugars composing the tetrasaccharide moiety at C-2.

3. Experimental

3.1. General experimental procedure

Optical rotations were measured on a Jasco P-200 polarimeter. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded at room temperature in pyridine-d_5 using a Bruker AVANCE III 500 spectrometer and chemical shifts are given in δ (ppm) value relative to TMS as internal standard. HRESIMS spectra were recorded on a microTOF ESI-TOF mass spectrometer (Agilent) operating in positive mode. Analytical HPLC was performed on Varian 920-LC apparatus equipped with an autosampler, a pump, a diode array detector, and Galaxie software. Semipreparative HPLC was performed on Gilson apparatus equipped with Trilution LC software using a Nucleodur 100-5 C18 ec (21 × 250 mm, 5 µm) column purchased from Machery-Nagel (Germany). Thin layer chromatography (TLC) were performed on precoated silica gel plates (60 F_{254}, Merck) (*n*-BuOH-AcOH-H_2O, 65:15:25), and the spots were observed after spray with Komarowsky reagent, a (5:1) mixture of *p*-hydroxybenzaldehyde (2% in MeOH) and (50% H_2O in EtOH). Vacuum-liquid chromatography (VLC) was carried out using silica gel 60 (15–40 and 40–63 µm).

3.2. Plant material

The stem barks of *A. lebbeck* were harvested at Nkolbisson, Yaoundé peripheral quarter, in Cameroon in October 2016 under the guidance of Dr Paul Nana, botanist of the National Herbarium of Cameroon (NHC), where one specimen (47206/HNC) was deposited.

3.3. Extraction and isolation

Air-dried finely powdered stem barks of *A. lebbeck* (100 g) were extracted with EtOH 70% in a Soxhlet apparatus. This hydroalcoholic solution was then evaporated to dryness under reduced pressure to give a dark residue (15.0 g) which was suspended in 100 mL of water and partitioned against *n*-BuOH (3 × 300 mL) satured with H_20. The *n*-BuOH phase was evaporated to dryness affording 6.15 g of a brown gum which was taken in a minimum amount of water (10 mL) and then submitted to column chromatography (CC) using Diaion HP-20 resin, eluting with H_2O, 50% MeOH, 70% MeOH, 80% MeOH, 90% MeOH, and 100% MeOH, successively giving four main fractions (LR1—LR4) after TLC monitoring. The 80% MeOH fraction (LR3) was evaporated to dryness yielding a crude saponin mixture (2.03 g) that was then submitted to VLC using silica gel 60 (15–40 µm), eluted with CH_2Cl_2–MeOH (80:20) and CH_2Cl_2-MeOH-H_2O (70:30:5, 60:32:6.5) to give three main subfractions (LR31—LR33). Subfraction LR33 (135.6 mg) was purified by semipreparative HPLC using gradient system of CH_3CN-H_2O (20 mL/min) to yield compound **1** (t_R, 26.41 min, 5.6 mg), while the subfractions LR31 and LR32 yielded the previous isolated lebbeckosides A and B.

3.4. Acid hydrolysis and GC analysis

Each saponin (2 mg) was hydrolyzed with 2 mL of 2 M HCl at 85 °C during 2 h. After cooling, the solvent was removed under reduced pressure. The sugar mixture was extracted from the aqueous phase (10 mL) and washed with CH_2Cl_2 (3 × 5 mL). Combined CH_2Cl_2 extracts were washed with water to give after evaporation the aglycon moiety, which was compared

with authentic standard sample by co-TLC. The sugars were first analyzed by TLC over silica gel ($CHCl_3$–MeOH–H_2O, 8:5:1) by comparison with standard samples. The absolute configuration of each monosaccharide was determined from GC–MS analysis of their trimethylsilylated derivatives by comparison with authentic samples using the method previously described (Chaabi et al. 2010). The following sugars were detected: D-glucose, D-fucose, D-xylose, D-quinovose, L-arabinofuranose, and L-rhamnose.

3.5. Inhibitory effect of lebbeckoside C (1)

Glioblastoma U87-MG cells were purchased from ATCC and expanded according to the supplier's instructions. Stem-like glioblastoma (WHO grade IV glioma) propagating cells (TG1) were obtained from Dr H. Chneiweiss (Sainte Anne Hospital, Paris, France) and grown as previously described (Patru et al. 2010). Neurospheres were mechanically dissociated before treatment. All cultures were maintained at 37 °C in a humidified atmosphere with 5% CO_2. The cytotoxicity of lebbeckoside C (**1**) was assessed as described previously (Noté et al. 2015).

3.6. Lebbeckoside C (1)

Amorphous white powder; $[\alpha]_D^{25}$ − 31 (c = 0.15, MeOH); HRESIMS (positive ion mode) *m/z* 2632.2616 ($[M + NH_4]^+$ Calcd for $C_{124}H_{200}O_{58}N$ 2632.2765); ^1H/ ^{13}C NMR (The ^1H NMR data of **1** was measured at 500 MHz and the ^{13}C NMR spectra at 125 MHz in pyridine-d_5. Ordered in the No. of **1**): ***Aglycon***: δ 1.66, 1.18/39.2; 2.30, 1.94/27.1; 3.52/88.9; —/40.3; 0.94/56.4; 1.59, 1.63/18.9; 1.78/34.1; —/40.4; 1.93/47.4; —/37.4; 2.47, 2.25/23.8; 5.68 (1H, br s)/123.3; —/143.2; —/42.4; 2.31, 2.12/36.2; 5.32/74.0; —/51.9; 3.47/41.4; 1.42, 2.95/48.3; —/35.5; 5.40/77.5; 2.21, 2.87/36.7; 1.32 (3H, s)/28.5; 1.18 (3H, s)/17.2; 1.03 (3H, s)/16.3; 1.15 (3H, s)/17.5; 1.90 (3H, s)/27.6; —/174.9; 0.99 (3H, s)/29.4; 1.07 (3H, s)/19.4. ***MT*$_1$**: δ —/168.1; —/128.8; 6.89 (1H, t, 7.3)/142.8; 2.44/24.0; 1.75/41.0; —/79.9; 6.24 (1H, dd, 10.3, 17.5)/144.5; 5.30 (1H, d, 10.3), 5.40 (1H, d, 17.5)/115.7; 1.84 (3H, s)/13.1; 1.51 (3H, s)/24.1. ***MT*$_2$**: δ —/167.7; —/125.5; 7.00 (1H, t, 7.4)/143.3; 2.48, 2.26/23.7; 1.79/40.8; —/80.0; 6.28 (1H, dd, 10.6, 17.0)/144.4; 5.29 (1H, d, 10.6), 5.48 (1H, d, 17.0)/115.4; 1.96 (3H, s)/13.1; 1.56 (3H, s)/24.2. ***MT*$_3$**: δ —/167.9; —/128.5; 7.09 (1H, t, 7.2)/143.3; 2.46, 2.26/23.8; 1.79/40.8; —/79.9; 5.98 (1H, dd, 10.6, 17.0)/144.3; 5.25 (1H, d, 10.6), 5.47 (1H, d, 17.0)/115.1; 1.94 (3H, s)/13.1; 1.58 (3H, s)/24.3. ***Qui'*$_1$**: δ 4.91 (1H, d, 7.7)/99.6; 4.03/75.8; 4.22/76.3; 5.38/77.7; 3.73/73.1; 1.53 (3H, d, 6.3)/18.8. ***Qui'*$_2$**: δ 4.90 (1H, d, 7.3)/99.6; 4.04/75.9; 4.22/76.2; 5.65/75.9; 3.76/73.0; 1.60 (3H, d, 6.4)/18.9. ***Qui'*$_3$**: δ 4.97 (1H, d, 7.9)/97.2; 4.07/76.1; 4.23/76.3; 3.73/77.2; 3.71/72.9; 1.63 (3H, d, 6.4)/19.0. ***Glc I***: δ 4.89 (1H, d, 7.7)/105.2; 4.30/83.2; 4.27/78.4; 4.23/71.5; 4.05/76.8; 4.40, 4.77/70.0. ***Glc II***: δ 5.43 (1H, d, 7.7)/106.2; 4.16/75.6; 4.15/78.8; 4.17/72.4; 3.96/78.5; 4.30, 4.49/63.1. ***Fuc***: δ 4.99 (1H, d, 7.9)/103.7; 4.47/82.6; 4.14/75.5; 4.06/72.2; 3.80/71.6, 1.37 (3H, d, 6.4)/18.5. ***Xyl***: δ 5.09 (1H, d, 6.6)/107.3; 4.10/75.9; 4.05/77.8; 4.14/71.2; 3.63, 4.48/67.5. ***Glc III***: δ 6.16 (1H, d, 7.6)/95.8; 4.31/76.3; 4.12/78.7; 4.17/71.4; 4.02/79.3; 4.27, 4.39/62.3. ***Rha:*** δ 6.30 (1H, brs)/101.6; 5.03/71.4; 4.82/82.2; 4.53/79.5; 4.67/68.9; 1.82 (3H, d, 6.4)/18.9. ***Qui:*** δ 5.29 (1H, d, 8.0)/105.9; 3.98/75.8; 3.92/78.5; 4.08/76.2; 3.83/73.3; 1.52 (3H, d, 6.0)/18.7. ***Araf:*** δ 6.29 (1H, br s)/111.5; 5.04/84.7; 4.86/78.7; 4.83/86.1; 4.20, 4.27/62.8.

(Overlapped proton NMR signals are reported without designated multiplicity).

4. Conclusions

This study unveiled the presence of one new triterpenoid saponin from the stem barks of *A. lebbeck*. In comparison with the previous isolated triterpenoid saponins from the roots of the same plant, they share the same structural features: they all have acacic acid as aglycon unit, oligosaccharide moieties at C-3 and C-28, and an acyl group at C-21, differing from lebbeckoside A (Noté et al. 2015) only by the nature, number, and the substitution pattern of the oligosaccharide moieties attached at C-3 and C-28. Since lebbeckoside C (**1**) (1.44 µM) and lebbeckoside A (1.36 µM) (Noté et al. 2015) showed a similar cytotoxicity against TG1 stem-like glioma cells, these substitution patterns seem to have no influence in mediating cytotoxicity against TG1 stem-like glioma cells. Nevertheless, further studies are necessary to support this conclusion.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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