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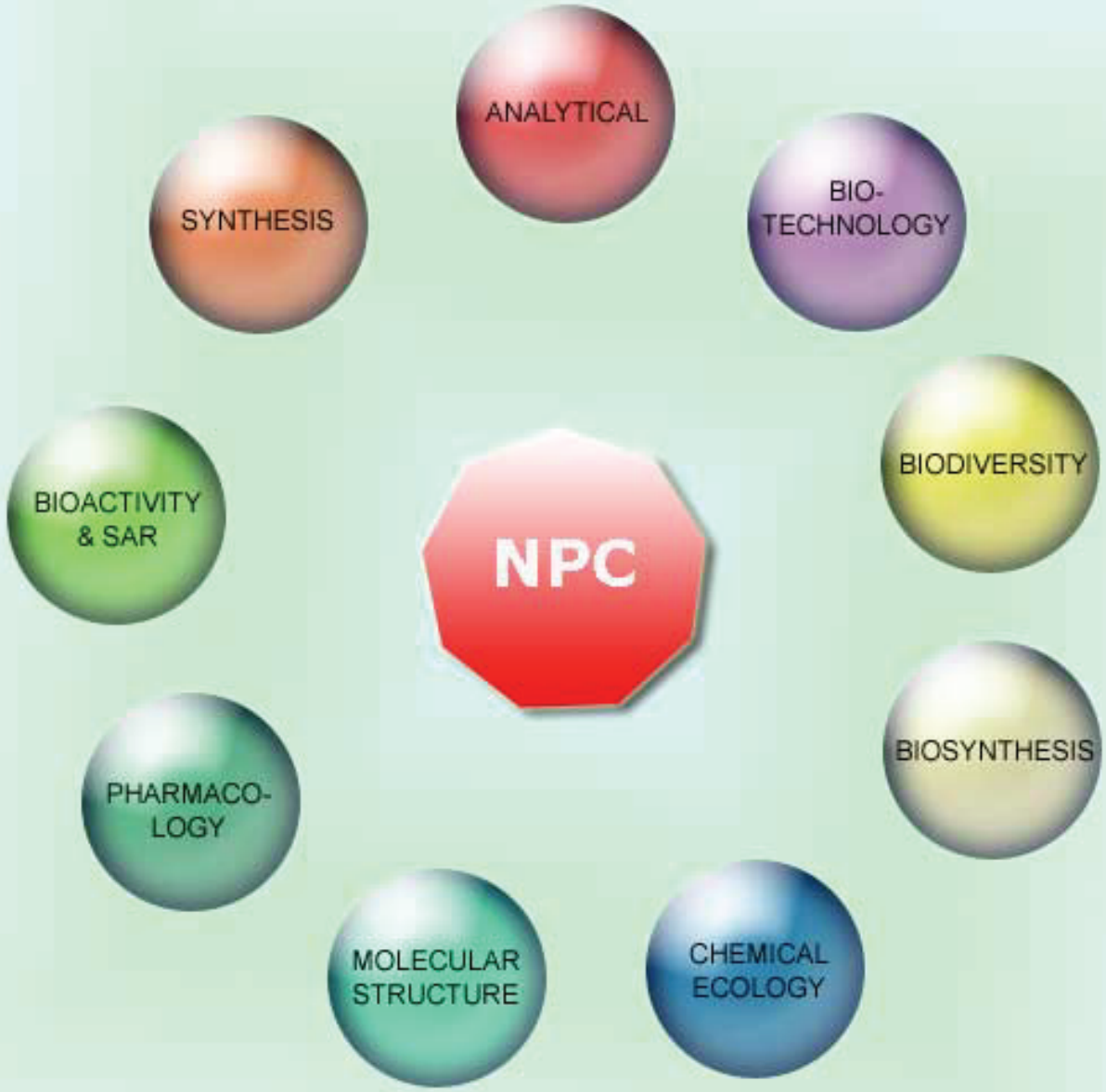

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New Acetylated Saponins from the Leaves of *Trevesia palmata*

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Two new acetylated saponins, acetyltrevesiasaponins A (**1**) and B (**2**), were isolated from the leaves of *Trevesia palmata*. Their chemical structures were determined by analysis of HR-ESI-MS and NMR spectra. Compound **2** was also confirmed by alkaline hydrolysis and identification its prosapogenin **2a**. Compounds **1**, **2**, and **2a** were evaluated inhibitory effect on NO production in LPS stimulated BV2 cells. Compound **2** showed weak activity (IC_{50} 40.7 μM).

Keywords: *Trevesia palmata*, Acetyltrevesiasaponin A, Acetyltrevesiasaponin B, Nitric oxide inhibition.

Saponins are important secondary metabolites which abundantly produce by plants. They are divided in two types: triterpene and steroid glycosides. Both of them had wide range of biological activities either in beneficial or detrimental effects on human health, pesticidal activity, and industrial applications [1]. Biological properties of saponins have been reviewed mainly in cytotoxic and anti-inflammatory activities. They are believed responsible for pharmacological effects of many plants in oriental medicines [2]. For example, *Panax ginseng* and numerous plants belonging Araliaceae family were found rich of saponins and known as famous traditional medicines in many countries. Accumulation of different types of saponins in the plants caused different pharmacological effects and made them become unique ingredient in folk remedies [3]. *Trevesia palmata* (Araliaceae family) is a Vietnamese traditional plant which has been used for reducing heat, treatment of inflammation, and health promoting effects. It was reported rich in oleanane-type saponins [4]. In our course to investigate saponins from medicinal plants belonging Araliaceae family, the leaves of *Trevesia palmata* were extracted in methanol and purified using various chromatographic techniques to obtain new acetylated saponins (**1** and **2**, Figure 1). Inflammatory activity of obtained compounds were also evaluated by nitric oxide assay.

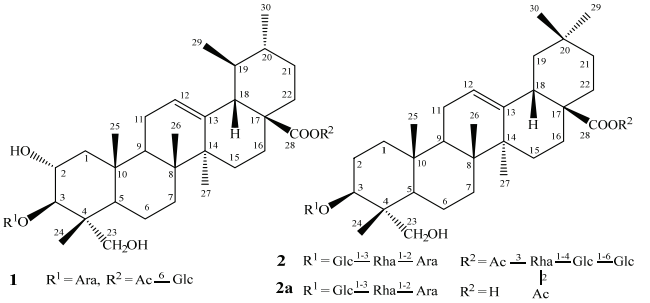

Figure 1: Chemical structure of compounds **1** and **2**.

Compound **1** was isolated as a white amorphous powder. Its molecular was deduced to be $C_{43}H_{68}O_{15}$ by HR-ESI-MS analysis, showing a quasi-molecular ion peak at *m/z* 859.4233 $[M+Cl]^-$ (calcd. for $C_{43}H_{68}O_{15}Cl$, 859.4247). The ^{1}H-NMR of **1** appeared a lot of shielded proton signals at δ_H 0.77 ~ 2.05, suggesting a triterpenoid substance. Besides, three proton signals at downfield region δ_H 5.28 (1H, br s), 5.36 (1H, d, J = 8.0 Hz), and 4.30 (1H, d, J = 8.0 Hz) were assigned for an olefinic and two anomeric protons. Seven methyl signals were observed including five singlet (δ_H 0.77, 0.84, 1.05, 1.15, 2.07) and two doublet (δ_H 0.91 and 0.99, each J = 6.0 Hz) splitting patterns. The presence of two un-equivalent secondary methyl groups and large J coupling constant of H-18 (δ_H 2.29, d, J = 11.0 Hz) could suggest compound **1** to be an ursane-type saponin. Analysis of ^{13}C-NMR and DEPT spectra of **1** revealed the signals of 43 carbons and classified into eight non-protonated carbons, 17 methines, 11 methylenes, and 7 methyls. Of these, an ursane-type triterpene backbone contains 30 carbons. A carbonyl carbon δ_C 172.7 and a methyl group (δ_C 20.8 / δ_H 2.07) were characterized for an acetyl group. Remaining 11 carbons suggested the presence of a hexose and a pentose in sugar moieties of **1**. In addition, two olefinic carbons δ_C 127.0 (CH) and 139.2 (C) indicated a trisubstituted double bond in the ursane skeleton; and HMBC correlation between methyl protons (δ_H 1.15, H-27) and quaternary olefinic carbon δ_C 139.2 confirmed location of double bond at C-12/C-13. The downfield chemical shifts of C-3 (δ_C 88.3), C-23 (δ_C 64.0) and HMBC correlations from H-24 (δ_H 0.77) and H-23 (δ_H 3.28 and 3.71) to C-3, C-4 (δ_C 45.2), C-5 (δ_C 47.7) indicated an oxygenated carbon C-3 and a free hydroxy group at C-23 (Figure 2). COSY cross peak between H-3 (δ_H 3.46) and H-2 (δ_H 3.81) and chemical shift of C-2 (δ_C 68.0) indicated an additional free hydroxy group at C-2. Next, a HMBC correlation from anomeric proton δ_H 4.30 to C-3 (δ_C 88.3) and a set of COSY cross peaks Ara H-1 (δ_H 4.30)/ Ara H-2 (δ_H 3.60)/ Ara H-3 (δ_H 3.53)/ Ara H-4 (δ_H 3.84)/ Ara H-5 (δ_H 3.64 and 3.93) indicating a pentose linked to aglycone at C-3. On the other hand, corresponding carbon chemical shift of pentose Ara C-1 (δ_C 106.3), Ara C-2 (δ_C 72.9), Ara C-3 (δ_C 74.6), Ara C-4 (δ_C 70.1), Ara C-5 (δ_C 67.8) and broad singlet signal of Ara H-4 (δ_H 3.84) were demonstrated for an arabinopyranosyl unit [5]. Other anomeric proton at δ_H 5.36 and H-18 (δ_H 2.29) had HMBC correlations with carbonyl carbon C-28 (δ_C 177.8) which was indicated a carbonyl carbon at C-28 and hexose unit binding with aglycone at C-28 by a glycoside ester linkage. Similarly, COSY

Table 1: NMR spectroscopic data of aglycone moiety for compounds **1** and **2**.

Pos.	1		2	
	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)
1	47.4	0.88 (m)/ 2.05 (m)	39.7	0.99 (m)/ 1.63 (m)
2	68.0	3.81 (m)	26.6	1.77 (m)/ 1.89 (m)
3	88.3	3.46 (d, 9.5)	82.5	3.64 (m)
4	45.2	-	44.0	-
5	47.7	1.34 (m)	48.1	1.28 (m)
6	18.8	1.33 (m)/ 1.49 (m)	18.8	1.38 (m)/ 1.50 (m)
7	33.6	1.31 (m)/ 1.63 (m)	33.3	1.29 (m)/ 1.64 (m)
8	41.0	-	40.7	-
9	48.8	1.63 (m)	49.0	1.65 (m)
10	38.5	-	37.7	-
11	24.5	1.97 (m)	24.6	1.93 (m)
12	127.0	5.28 (br s)	123.8	5.29 (br s)
13	139.2	-	144.9	-
14	43.4	-	43.0	-
15	29.0	1.11 (m)/ 1.97 (m)	29.0	1.11 (m)/ 1.79 (m)
16	25.2	1.75 (m)/ 2.09 (m)	24.1	1.73 (m)/ 2.07 (m)
17	49.4	-	48.1	-
18	54.2	2.29 (d, 11.0)	42.5	2.89 (dd, 3.5, 13.5)
19	40.4	1.41 (m)	47.2	1.18 (m)/ 1.72 (m)
20	40.2	0.99 (m)	31.5	-
21	31.7	1.38 (m)/ 1.53 (m)	34.9	1.24 (m)/ 1.41 (m)
22	37.5	1.70 (m)/ 1.72 (m)	33.3	1.61 (m)/ 1.74 (m)
23	64.0	3.28 (d, 11.0)/ 3.71 (d, 11.0)	64.6	3.36 (d, 11.5)/ 3.57 (d, 11.5)
24	14.5	0.77 (s)	13.7	0.72 (s)
25	18.0	1.05 (s)	16.5	1.00 (s)
26	17.6	0.84 (s)	17.9	0.82 (s)
27	24.1	1.15 (s)	26.4	1.19 (s)
28	177.8	-	178.2	-
29	17.7	0.91 (d, 6.0)	33.5	0.93 (s)
30	21.5	0.99 (d, 6.0)	24.1	0.97 (s)

cross peaks of Glc H-1 (δ_H 5.36)/ Glc H-2 (δ_H 3.35)/ Glc H-3 (δ_H 3.40)/ Glc H-4 (δ_H 3.35)/ Glc H-5 (δ_H 3.53)/ Glc H-6 (δ_H 4.20 and 4.29) and corresponding carbons Glc C-1 (δ_C 95.4)/ Glc C-2 (δ_C 73.8)/Glc C-3 (δ_C 78.1)/Glc C-4 (δ_C 71.2)/Glc C-5 (δ_C 75.8)/Glc C-6 (δ_C 64.6) suggested hexose to be glucopyranose. The presence of D-glucose and L-arabinose were also confirmed by acid hydrolysis following by GC analysis their TMS products in comparison with authentic sugars (Supplementary data). Acetyl group attached to Glc C-6 which was confirmed by HMBC correlations between Glc H-6 (δ_H 4.20 and 4.29) and acetyl carbonyl carbon (δ_C 172.7). Finally, the configurations at C-2, C-3, and C-4 were established by ROESY analysis (Figure 2) and by specific observed splitting pattern in the ^{1}H-NMR. The large *J* coupling constant of H-2/H-3 (9.5 Hz) indicated that both protons located at *trans-axial* positions. Therefore, ROESY correlations from H-2 (δ_H 3.81) to H-24 (δ_H 0.77) and H-25 (δ_H 1.05) were proved all *axial-β* orientations of C-25, C-24, and H-2 (Figure 2) and hence hydroxy group at C-2 and hydroxymethylene group at C-4 were *equatorial*-α orientations. Aslo, ROESY correlations between H-3 (δ_H 3.46) and H-5 (δ_H 1.34) was proved *axial-α* orientations of H-3 and H-5, indicating *equatorial-β* orientation of oxygenated group at C-3. Consequently, chemical structure of **1** was established. It was a new acetylated derivative of ilekudinoside C saponin [5] and named as acetyltrevesiasaponin A.

Compound **2** showed a quasi-molecular ion peak at *m/z* 1465.6851 $[M-H]^-$, indicating a molecular formula of $C_{69}H_{110}O_{33}$ (calcd. for $C_{69}H_{109}O_{33}$, 1465.6851.) which was well consisted with ^{13}C-NMR analysis. Like compound **1**, a lot of proton signals in upfield region suggested compound **2** also to be a triterpenoid. However, the appreance of six sheilded tertiery methyl signals (δ_H 0.72, 0.82, 0.93, 0.97, 1.00, 1.19) and double doublet signal of H-18 (δ_H 2.89, dd, *J* = 3.5 and 13.5 Hz) suggested compound **2** belonging an oleanane-type triterpene. Six anomeric protons (δ_H 5.34, 5.19, 4.53, 4.52, 4.91, 4.44) corresponded with six sugar units in **2**. The presence of two acetyl groups was easily recognized by resonant signals including two carbonyl carbons δ_C 171.9, 172.2 and two de-shielded methyl groups δ_C 20.7/ δ_H 2.11, δ_C 20.8/ δ_H 2.04. Next,

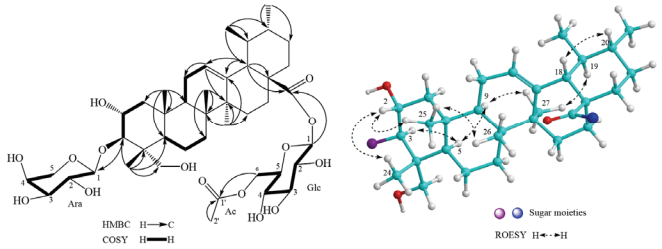

Figure 2: Important HMBC, COSY, and ROESY correlations for compound **1**.

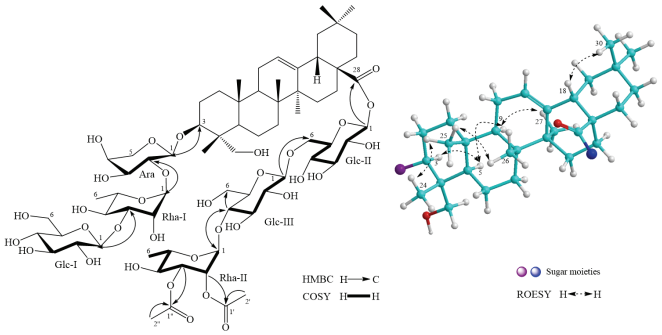

Figure 3: Important HMBC, COSY, and ROESY correlations for compound **2**.

Table 2: NMR spectroscopic data for sugar moieties of compounds **1** and **2**.

Pos.	1		2		2	
	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)
	3-*O*Ara		3-*O*Ara		28-*O*GlcII	
1	106.3	4.30 (d, 8.0)	105.0	4.52 (d, 5.5)	95.8	5.34 (d, 8.0)
2	72.9	3.60 (dd, 8.0, 9.0)	76.9	3.67 (m)	73.8	3.35 (m)
3	74.6	3.53 (m)	74.0	3.67 (m)	78.2	3.42 (m)
4	70.1	3.84 (m)	69.7	3.79 (m)	71.0	3.42 (m)
5	67.8	3.64 (br d, 12.0)	65.6	3.86*	78.2	3.54 (m)
		3.93 (dd, 2.0, 2.0)		3.53 (br d, 11.5)		
6					69.4	4.09 (dd, 2.5, 10.5)
						3.82 (dd, 5.0, 10.5)
	28-*O*Glc		RhaI		GlcIII	
1	95.4	5.36 (d, 8.0)	101.8	5.19 (br s)	104.3	4.44 (d, 7.5)
2	73.8	3.35 (m)	71.1	4.26 (br s)	75.6	3.24 (dd, 7.5, 9.0)
3	78.1	3.40 (m)	82.8	3.90 (m)	76.5	3.52 (dd, 9.0, 9.0)
4	71.2	3.35 (m)	72.6	3.59 (m)	78.3	3.63 (dd, 9.0, 9.0)
5	75.8	3.53 (m)	70.1	3.93 (m)	77.8	3.34 (m)
6	64.6	4.20 (dd, 5.0, 12.0)	18.1	1.28 (d, 6.5)	61.6	3.85*
		4.29 (dd, 2.5, 12.0)				3.68*
			GlcI		RhaII	
1			105.8	4.53 (d, 8.0)	99.4	4.91 (d, 1.5)
2			75.4	3.32 (dd, 8.0, 9.5)	71.6	5.20 (dd, 1.5, 3.0)
3			77.8	3.42 (m)	73.0	5.07 (dd, 3.0, 10.0)
4			71.3	3.34 (m)	71.3	3.54 (m)
5			77.8	3.34 (m)	70.3	4.23 (m)
6			62.5	3.88 (dd, 2.5,11.5)	17.8	1.31 (d, 6.5)
				3.71 (dd, 5.0, 11.5)		
	Acetyl				Acetyl	
1′	172.7	-			171.9	-
2′	20.8	2.07 (s)			20.7	2.11 (s)
1″					172.2	-
2″					20.8	2.04 (s)

*)Overlapped signals.

attachments of substituted groups into aglycone moiety were determined with the help of 2D-NMR analysis. Similar with compound **1**, the downfield chemical shifts of C-3 (δ_C 82.5), C-23 (δ_C 64.6) and HMBC correlations from H-24 (δ_H 0.72) and H-23 (δ_H 3.36 and 3.57) to C-3, C-4 (δ_C 44.0), C-5 (δ_C 48.1) indicated an oxygenated carbon C-3 and a free hydroxy group at C-23. ROESY correlations of H-3 (δ_H 3.64)/H-5 (δ_H 1.28) and H-24 (δ_H 0.72)/H-25 (δ_H 1.00) demonstrated relative *β* configuration of oxygenated group at C-3 and *α* configuration of hydroxymethyl group at C-4, respectively (Figure 3). A pair of olefinic carbons (δ_C 123.8/ δ_H 5.29 and δ_C 144.9) and HMBC correlation from methyl protons (δ_H 1.19, H-27) to quaternary olefinic carbon (δ_C 144.9) confirmed the location of double bond at C-12/C-13. A downfield carbon signal δ_C

178.2 was assigned for a carbonyl carbon C-28. Thus, aglycone moiety of **2** was determined to be 3*β*,23-dihydroxyolean-12-en-28-oic acid. On the other hand, HMBC correlations from anomeric protons δ_H 4.52 to C-3, δ_H 5.34 to C-28 (δ_C 178.2) indicated that sugar moieties were attached to aglycone at both C-3 and C-28 by *O*-glycoside and *O*-glycoside ester linkages, respectively. Because of containing two saccharide chains in the molecular, chemical structure of **2** was then elucidated by partial hydrolysis. Fortunately, alkaline hydrolysis of **2** obtained hederagenin 3-*O*-*β*-D-glucopyranosyl-(1→3)-*α*-L-rhamnopyranosyl (1→2)-*α*-L- arabinopyranoside (**2a**) a known saponin previously reported from *T. palmata* [4] and also isolated by the authors from this plant. 1D- and 2D-NMR spectra of **2a** were taken (Supplementary data) and well agreed with those reported in the literature [6]. Therefore, a saccharide chain at C-3 was determined to be *β*-D-glucopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*α*-L- arabinopyranosyl group. The ^{13}C-NMR data of remaining sugar chain at C-28 suggested it to be another trisaccharide comprising two glucose units and one rhamnose unit (Table 2). Of these, HMBC correlation between anomeric proton GlcIII H-1 (δ_H 4.44) and methylene carbon GlcII C-6 (δ_C 69.4) indicated *O*-(1→6) glycosidic linkage between GlcIII and GlcII. Downfield shifted of GlcIII C-4 (δ_C 78.3) and HMBC correlations from GlcIII H-4 (δ_H 3.63) to RhaII-C1 (δ_C 99.4), GlcIII C-6 (δ_H 61.6) confirming RhaII unit attached to GlcIII C-4 to form *α*-L-rhamnopyranosyl-(1→4)-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl group. The presence of monosaccharide including D-glucose, L-rhamnose, and L-arabinose in **2** were also reconfirmed by acid hydrolysis followed by conversion into TMS selective stereoisomer derivatives and GC analysis in comparison with authentic monosaccharides (Supplementary data). Finally, positions of acetyl groups were to be attaching at RhaII C-2 and RhaII C-3. Particularly, related proton signals of terminal rhamnopyranosyl group (RhaII) were clearly recognized by COSY cross peaks RhaII H-1 (δ_H 4.91)/ RhaII H-2 (δ_H 5.20)/ RhaII H-3 (δ_H 5.07). Later, the HMBC correlations from RhaII H-2 (δ_H 5.20) to acetyl carbonyl carbon δ_C 171.9, RhaII H-2 (δ_H 5.07) to second acetyl carbonyl carbon δ_C 172.2 which were confirmed positions of acetyl groups at RhaII C-2 and RhaII C-3. Consequently, chemical structure of compound **2** was established to be a new acetylated saponin and named as acetyltrevensiasaponin B.

Compounds **1**, **2**, and **2a** were evaluated their effect on NO production in LPS-activated BV2 cells. As the results, compound **2** exhibited weak inhibitory activity (IC_{50} 40.7 μM). However, its prosapogenin **2a** showed cytotoxicity towards BV2 cells. At a concentration as low as 20 μM, compound **2a** induced 81.7% dead cells. Compound **1** did not effect on NO production (IC_{50} > 100 μM).

Experimental

General: Optical rotations, Jasco DIP-370 automatic polarimeter; NMR, Bruker AM500 FT-NMR spectrometer; HR-ESI-MS, Agilent 6530 Accurate Mass Q-TOF LC/MS system.

Plant material: The leaves of *T. palmata* (Roxb. ex Lindl.) Vis., collected at Vi Xuyen, Ha Giang province, Vietnam, in May, 2015, were identified by MSc. Nghiem Duc Trong, Ha Noi University of Pharmacy. A voucher specimen (HNIP/18247/16) was deposited at the Ha Noi University of Pharmacy.

Extraction and isolation: The dried and powdered leaves of *T. palmata* (5.0 kg) were extracted with methanol at 50°C in ultrasonic bath (three times, each 8 L of methanol in 60 minutes). After removal of solvent, 530 g crude extract was suspended with 3 L of water and separated in turn with *n*-hexane, dichloromethane, ethyl acetate to give corresponding extracts and water layer. Ethyl acetate extract (60 g) was chromatographed on a silica gel column and eluted with dichloromethane/methanol (0-100% volume of methanol) to give eight fractions TPE1-TPE8. The TPE4 fraction was repeatedly chromatographed on a silica gel column, eluting with dichloromethane/acetone/water (1/2/0.1, v/v/v) to give nine fractions TPE4A-TPE4I. Purification of fraction TPE4G obtained compound **1** (15 mg) using reverse phase C-18 resin column chromatography (CC) with acetone/water (1/1, v/v) as eluent. Water layer (370 g) was loaded on a diaion HP-20 resin column, washed with water, and then eluted stepwise with methanol/water (25, 50, 75, and 100% volume of methanol) to give four fractions TPW1-TPW4. Fraction TPW3 was roughly separated by silica gel CC eluting with dichloromethane/methanol (0-50% volume of methanol) to give six fractions TPW3A-TPW3F. Fraction TPW3D was continuously chromatographed on a silica gel column, eluting with dichloromethane/acetone/water (1/4/0.4, v/v/v) to give twelve fractions TPW3D1-TPW3D12. Fraction TPW3D7 was first subjected to a silica gel CC, eluting with dichloromethane/methanol/water (1/4/0.4, v/v/v) and then purified by a reverse phase C-18 resin CC, eluting with acetone/water (1/1.2, v/v) to obtain compound **2** (110 mg).

Acetyltrevesiasaponin A (1)

White amorphous powder.
$[\alpha]_D^{25}$: +17.2 (*c* 0.23, MeOH).
^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD) are given in the Table 1 and 2.
HR-ESI-MS: *m/z* 859.4233 $[M+Cl]^-$ calcd for $C_{43}H_{68}O_{15}Cl$, 859.4252.

Acetyltrevesiasaponin B (2)

White amorphous powder.
$[\alpha]_D^{25}$: -22.8 (*c* 0.14, MeOH).
^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD) are given in the Table 1 and 2.
HR-ESI-MS: *m/z* 1465.6851 $[M-H]^-$ calcd for $C_{69}H_{109}O_{33}$, 1465.6851.

Alkaline analysis: Compound **2** (30 mg) was dissolved in 10 mL solution of KOH 1.0 M in 1,4-dioxane/water (1/1, v/v) and refluxed at 80 °C for 30 minutes. Reaction solution was cooled down, neutralized with HCl 1M and separated with *n*-butanol (twice, each 10 mL). Organic layer was evaporated and purified on a reverse phase C-18 column chromatography, eluting with acetone/water (2/3, v/v) to give prosapogenin **2a** (12 mg).

Compound 2a

White amorphous powder.
$[\alpha]_D^{25}$: -14.7 (*c* 0.11, MeOH).
HR-ESI-MS: *m/z* 911.5011 $[M-H]^-$ calcd for $C_{47}H_{75}O_{17}$, 911.5004.
^{1}H-NMR (500 MHz, CD_3OD) δ_H ppm: 5.26 (br s, H-12), 2.86 (br d, 10.5, H-18), 0.72 (s, H-24), 0.99 (s, H-25), 0.83 (s, H-26), 1.19 (s, H-27), 0.93 (s, H-29), 0.96 (s, H-30), 4.52 (d, *J* = 5.5 Hz, Ara-H1) 5.18 (br s, Rha H-1), 4.54 (d, *J* = 7.5 Hz, Glc H-1); ^{13}C-NMR (500 MHz, CD_3OD) δ_H ppm: 39.6 (C-1), 26.5 (C-2), 82.4 (C-3), 43.9 (C-4), 48.0 (C-5), 18.8 (C-6), 33.4 (C-7), 40.4 (C-8), 48.9 (C-9), 37.6 (C-10), 24.5 (C-11), 123.5 (C-12), 145.2 (C-13), 42.9 (C-14), 28.8 (C-15), 24.0 (C-16), 47.6 (C-17), 42.7 (C-18), 47.2 (C-19), 31.6 (C-20), 34.9 (C-21), 33.8 (C-22), 64.5 (C-23), 13.7 (C-24), 16.4 (C-25), 17.8 (C-26), 26.5 (C-27), 181.9 (C-28), 33.6 (C-29), 24.0 (C-30), 104.9 (Ara C-1), 76.9 (Ara C-2), 73.9 (Ara C-3), 69.6 (Ara C-4), 65.6 (Ara C-5), 101.7 (Rha C-1), 71.0 (Rha C-2), 82.7 (Rha C-3), 72.5 (Rha C-4), 70.1 (Rha C-5), 18.1 (Rha C-6), 105.7 (Glc C-1), 75.3 (Glc C-2), 77.7 (Glc C-3), 71.2 (Glc C-4), 77.7 (Glc C-5), and 62.4 (Glc C-6).

Nitric oxide assay: The nitric oxide production in BV2 cells was measured by Griess reaction via an indicator, nitrite concentration, as previously described [7].

Supplementary data: HR-ESI-MS and NMR spectra compounds **1**, **2**, and **2a** can be found in the online version.

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