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# New oleanane-type saponins from the leaves of *Derris trifoliata*

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Phytochemical investigation of the polar fraction of the leaves of *Derris trifoliata* led to the isolation of five new oleanane-type saponins, named derristrifosides A–E (1–5). Their chemical structures were elucidated through comprehensive analyses of HR-ESI-MS and one-dimensional and two-dimensional NMR spectra. These new saponins possess a cantoniensistriol-type sapogenin framework, which is rarely found in vascular plants. Compounds 1–5 exhibited weak inhibitory activity against nitric oxide (NO) production in LPS-stimulated RAW 264.7 cells and weak antiproliferative activity against SK-LU-1 and Hep-G2 human cancer cell lines.

## Introduction

Plants of the genus *Derris*, such as *D. elliptica*, *D. montana*, and *D. trifoliata*, have long been used as natural piscicides and insecticides.<sup>1</sup> Previous phytochemical studies on these species have indicated that the *Derris* genus is a rich source of rotenoids and prenylated flavonoids, including flavanones, flavones, isoflavones, pterocarpanes, and chalcones.<sup>2–5</sup> To date, hundreds of such compounds have been isolated from *Derris* species.<sup>6</sup> Rotenone and its derivatives are known for their piscicidal and insecticidal properties.<sup>7</sup> In addition, rotenoids and prenylated flavonoids have been reported to exhibit various biological activities, such as cytotoxic, anti-inflammatory, antimicrobial, and  $\alpha$ -glucosidase inhibitory effects.<sup>2,8–10</sup>

*Derris trifoliata*, a climbing plant, is widely distributed in tropical mangrove forests. Its fresh roots are traditionally pounded and mixed with water for use in fishing and as an insect repellent.<sup>11,12</sup> In folk medicine, *D. trifoliata* has been used to enhance the immune system and to treat inflammation, coughs, and diarrhea.<sup>13</sup> Our previous phytochemical studies revealed several rotenoids and prenylated flavonoids from the ethyl acetate fraction of *D. trifoliata* leaves. Some isolated compounds, such as 6 $\alpha$ ,12 $\alpha$ -12hydroxyelliptone, (2*S*-

lonchocarpol D, lonchocarpol C<sub>1</sub>, and lonchocarpol C<sub>2</sub>, exhibited cytotoxic effects against SK-LU-1 and Hep-G2 human cancer cell lines, with IC<sub>50</sub> values ranging from 7.11 to 34.85  $\mu$ M.<sup>13</sup> As rotenoids are relatively non-polar substances, most previous studies have focused on less polar fractions for compound isolation and purification.<sup>11–15</sup> However, traditional medicinal preparations are usually made as decoctions, which preferentially extract polar constituents. Therefore, we selected the polar fraction of *D. trifoliata* for further phytochemical investigation. Herein, we report the identification of five new oleanane-type saponins from the leaves of *D. trifoliata* and their antiproliferative and nitric oxide production inhibitory activities.

## Experimental

### General experimental procedures

The optical rotations were measured using a Jasco P2000 polarimeter. The 1D and 2D NMR spectra were recorded on a Bruker Avance NEO 600 MHz spectrometer. HR-ESI-MS data were acquired using an Agilent 6530 Accurate-Mass QTOF LC/MS system. Thin-layer chromatography (TLC) was performed on pre-coated silica gel or reversed-phase C18 (RP18) plates. Column chromatography was carried out using silica gel (40–63  $\mu$ m) or RP18 (150  $\mu$ m) as adsorbents. Semi-preparative HPLC was performed on an Agilent 1260 Infinity II system equipped with a binary pump, autosampler, and DAD detector, using a YMC J'sphere ODS-H80 (20  $\times$  250 mm, 4  $\mu$ m) column. The mobile phases consisted of isocratic systems of methanol/water or acetonitrile/water at a flow rate of 3 mL min<sup>-1</sup>.

### Plant material

The leaves of *Derris trifoliata* Lour. (Fabaceae family) were collected at Xuan Thuy National Park, Nam Dinh province, Vietnam, in May 2024 and taxonomically identified by botanist

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Table 1 <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectral data for 1–3 in CD<sub>3</sub>OD

No.	1		2		3	
	$\delta_C$	$\delta_H$ (mult., <i>J</i> in Hz)	$\delta_C$	$\delta_H$ (mult., <i>J</i> in Hz)	$\delta_C$	$\delta_H$ (mult., <i>J</i> in Hz)
1	40.0	1.05 (m)/1.64 (m)	40.0	1.04 (m)/1.64 (m)	40.0	1.01 (m)/1.64 (m)
2	27.1	1.04 (m)/1.92 (m)	27.1	1.04 (m)/1.92 (m)	27.1	1.04 (m)/1.95 (m)
3	91.1	3.24 (dd, 11.4, 4.2)	91.3	3.26 (dd, 11.4, 4.2)	92.0	3.20 (dd, 11.4, 4.2)
4	40.5	—	40.5	—	40.5	—
5	57.0	0.80 (br d, 11.4)	57.0	0.81 (br d, 11.4)	57.1	0.79 (br d, 11.4)
6	19.3	1.47 (br d, 11.4)/1.60 (m)	19.3	1.47 (br d, 11.4)/1.60 (m)	19.3	1.44 (br d, 11.4)/1.58 (m)
7	33.7	1.38 (m)/1.60 (m)	33.7	1.38 (m)/1.59 (m)	33.8	1.37 (m)/1.58 (m)
8	41.2	—	41.3	—	41.3	—
9	49.0	1.63 (m)	49.0	1.62 (m)	48.9	1.61 (m)
10	37.7	—	37.8	—	37.8	—
11	24.7	1.92 (m)/1.94 (m)	24.7	1.90 (m)/1.95 (m)	24.6	1.90 (m)/1.95 (m)
12	123.9	5.26 (t, 3.0)	123.8	5.26 (t, 3.0)	123.9	5.26 (t, 3.0)
13	145.0	—	145.0	—	145.0	—
14	43.0	—	43.0	—	43.0	—
15	27.0	1.70 (m)/2.05 (br d, 13.2)	27.0	1.71 (m)/2.04 (br d, 13.2)	27.0	1.76 (m)/2.00 (br d, 13.2)
16	28.2	1.03 (m)/1.92 (m)	28.2	1.05 (m)/1.95 (m)	28.2	1.05 (m)/1.95 (m)
17	40.0	—	40.0	—	39.9	—
18	44.4	2.27 (dd, 13.2, 3.6)	44.5	2.27 (dd, 13.2, 3.6)	44.5	2.27 (dd, 13.2, 3.6)
19	47.9	1.18 (dd, 13.2, 4.2)/1.97 (m)	47.9	1.17 (dd, 13.2, 3.6)/1.96 (m)	47.9	1.17 (br d, 13.2)/1.96 (m)
20	37.3	—	37.3	—	37.3	—
21	85.6	3.53 (d, 3.0)	85.5	3.53 (d, 3.0)	85.8	3.54 (d, 3.0)
22	79.8	3.44 (d, 3.0)	79.7	3.44 (d, 3.0)	79.7	3.46 (d, 3.0)
23	28.5	1.09 (s)	28.4	1.09 (s)	28.8	1.13 (s)
24	17.0	0.90 (s)	16.9	0.91 (s)	16.9	0.91 (s)
25	16.1	1.00 (s)	16.1	1.00 (s)	16.0	1.00 (s)
26	17.5	1.04 (s)	17.5	1.04 (s)	17.5	1.04 (s)
27	26.9	1.20 (s)	26.9	1.20 (s)	26.9	1.20 (s)
28	22.0	0.98 (s)	22.1	0.98 (s)	22.0	0.98 (s)
29	31.3	0.96 (s)	31.3	0.96 (s)	31.3	0.96 (s)
30	21.8	1.08 (s)	21.8	1.08 (s)	21.7	1.08 (s)
21-O-Rha			21-O-Rha		21-O-Rha	
1'	104.7	4.80 (d, 1.8)	104.7	4.80 (br s)	104.4	4.83 (d, 1.2)
2'	72.3	3.94 (dd, 4.8, 1.8)	72.3	3.93 (br s)	72.2	3.97 (br s)
3'	72.3	3.80 (m)	72.3	3.79 (m)	72.3	3.80 (m)
4'	74.0	3.41 (m)	74.0	3.41 (m)	74.2	3.41 (m)
5'	70.4	3.76 (m)	70.4	3.76 (m)	70.4	3.78 (m)
6'	18.0	1.27 (d, 7.0)	18.0	1.27 (d, 7.0)	17.9	1.27 (d, 7.2)
3-O-Glu			3-O-Glu		3-O-Glu	
1''	105.2	4.48 (d, 7.8)	105.3	4.49 (d, 7.8)	105.4	4.45 (d, 7.8)
2''	83.7	3.51 (m)	82.0	3.57 (m)	79.1	3.72 (m)
3''	78.0	3.75 (m)	78.0	3.73 (m)	78.9	3.68 (m)
4''	72.9	3.52 (m)	73.1	3.52 (m)	73.9	3.48 (m)
5''	76.6	3.58 (d, 9.6)	76.6	3.58 (d, 9.0)	76.7	3.57 (d, 9.0)
6''	176.8	—	177.0	—	176.7	—
2''-O-Gal			2''-O-Glc		2''-O-Gal	
1'''	104.4	4.74 (d, 7.8)	103.3	4.87 (d, 7.8)	102.8	4.85 (d, 7.8)
2'''	83.5	3.79 (m)	85.4	3.42 (dd, 7.8, 9.6)	77.3	3.70 (m)
3'''	74.8	3.71 (m)	76.7	3.58 (m)	76.0	3.65 (m)
4'''	69.7	3.89 (br s)	72.0	3.22 (m)	71.0	3.80 (br s)
5'''	76.5	3.48 (m)	77.5	3.58 (m)	76.7	3.48 (m)
6'''	62.1	3.69 <sup>a</sup> /3.75 <sup>a</sup>	63.3	3.61 <sup>a</sup> /3.84 (dd, 12.0, 2.4)	62.8	3.67 <sup>a</sup> /3.81 <sup>a</sup>
2'''-O-Glc			2'''-O-Rha		2'''-O-Rha	
1''''	106.2	4.64 (d, 7.8)	106.1	4.61 (d, 7.8)	101.9	5.22 (d, 1.2)
2''''	76.4	3.30 (d, 9.0)	76.4	3.30 (m)	72.2	3.96 (m)
3''''	78.9	3.38 (m)	78.9	3.38 (m)	72.4	3.80 (m)
4''''	71.0	3.39 (m)	71.0	3.38 (m)	74.0	3.45 (m)
5''''	77.5	3.42 (m)	77.5	3.41 (m)	69.8	4.16 (m)
6''''	62.3	3.77 <sup>a</sup> /3.95 (br d, 10.8)	62.3	3.77 <sup>a</sup> /3.95 (br d, 10.8)	18.2	1.26 (d, 7.2)

<sup>a</sup> Overlapped signal.

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### Extraction and isolation

The dried powdered leaves of *Derris trifoliata* (7.2 kg) were macerated with methanol (MeOH) in an ultrasonic bath (three times: 20 L MeOH at room temperature for 1 h each) to afford a methanolic residue (289 g). The methanol extract was suspended in water (4.0 L) and successively partitioned with dichloromethane and ethyl acetate to yield the corresponding dichloromethane-soluble, ethyl acetate-soluble, and aqueous fractions. The aqueous layer was applied to a Diaion HP-20 column, washed with water, and eluted with methanol to give the polar fraction, designated DFW (44 g). The DFW fraction was loaded on a silica gel column chromatography and eluted with dichloromethane/methanol/water (3/1/0.1, v/v/v) to give three fractions, DFW1–DFW3. Fraction DFW2 was separated on an RP18 column using methanol/water (1/4, v/v) as the eluent to give five fractions, DFW2A–DFW2E. Fraction DFW2C was

purified by semi-preparative HPLC using 20% acetonitrile in water as the mobile phase to give compounds **1** (15.8 mg,  $t_R$  34.1 min) and **2** (20.7 mg,  $t_R$  36.0 min). Fraction DFW2D was separated on a silica gel column, eluting with dichloromethane/methanol/water (5/1/0.1, v/v/v) to give three fractions, DFW2D1–DFW2D3. Fraction DFW2D1 was purified by semi-preparative HPLC using 20% acetonitrile in water to give compound **3** (22.4 mg,  $t_R$  32.9 min). Fraction DFW2D2 was purified by semi-preparative HPLC using 20% acetonitrile in water to give compounds **4** (20.8 mg,  $t_R$  37.6 min) and **5** (18.5 mg,  $t_R$  41.1 min).

**Derristrifoside A (1).** White amorphous powder;  $[\alpha]_D^{28}$ : –30.3 ( $c$  0.1, MeOH); UV: none significant maxima absorption in the range of 200–400 nm; HR-ESI-MS  $m/z$ : 1103.5641  $[M-H]^-$ , (calcd. for  $[C_{54}H_{87}O_{23}]^-$ , 1103.5644,  $\Delta = -0.3$  ppm);  $^1H$ - and  $^{13}C$ -NMR data are shown in the Table 1.

**Derristrifoside B (2).** White amorphous powder;  $[\alpha]_D^{28}$ : –23.9 ( $c$  0.1, MeOH); UV: none significant maxima absorption in the range of 200–400 nm; HR-ESI-MS  $m/z$ : 1103.5624  $[M-H]^-$ , (calcd. for  $[C_{54}H_{87}O_{23}]^-$ , 1103.5644,  $\Delta = -1.3$  ppm);  $^1H$ - and  $^{13}C$ -NMR data are shown in the Table 1.

Table 2  $^1H$ -NMR and  $^{13}C$ -NMR spectral data for 4–5 in DMSO- $d_6$

4 (aglycon)			5 (aglycon)		4 (sugar moieties)			5 (sugar moieties)	
No.	$\delta_C$	$\delta_H$ (mult., $J$ in Hz)	$\delta_C$	$\delta_H$ (mult., $J$ in Hz)	No.	$\delta_C$	$\delta_H$ (mult., $J$ in Hz)	$\delta_C$	$\delta_H$ (mult., $J$ in Hz)
1	38.2	0.87 (m)/1.50 (m)	38.2	0.87 (m)/1.50 (m)					
2	25.5	0.90 (m)/1.65 (m)	25.6	0.90 (m)/1.65 (m)	1'	102.8	4.61 (br s)	102.8	4.61 (br s)
3	89.4	3.24 (m)	89.0	3.17 (m)	2'	70.6	3.68 (m)	70.5	3.68 (m)
4	43.0	—	43.2	—	3'	70.6	3.59 (m)	70.5	3.59 (m)
5	55.3	0.85 (m)	55.4	0.83 (m)	4'	72.2	3.16 (m)	72.1	3.16 (m)
6	18.1	1.35 (m)/1.53 (m)	18.2	1.33 (m)/1.55 (m)	5'	68.7	3.62 (m)	68.7	3.62 (m)
7	32.3	1.25 (m)/1.45 (m)	32.3	1.25 (m)/1.45 (m)	6'	17.8	1.10 (m)	17.8	1.09 (m)
8	40.4	—	40.4	—					
9	46.9	1.50 (m)	46.9	1.49 (m)	1''	103.1	4.34 (d, 7.8)	103.1	4.31 (d, 7.8)
10	35.9	—	35.9	—	2''	78.4	3.37 (m)	79.0	3.26 (m)
11	23.3	1.80 (m)	23.3	1.80 (m)	3''	82.1	3.50 (m)	83.8	3.17 (m)
12	121.7	5.16 (brs)	121.7	5.16 (brs)	4''	71.8	3.20 (m)	71.8	3.17 (m)
13	143.7	—	143.7	—	5''	76.5	3.55 <sup>a</sup>	76.5	3.54 <sup>a</sup>
14	41.4	—	41.3	—	6''	173.4	—	173.4	—
15	25.6	1.63 (m)/1.97 (m)	25.4	1.63 (m)/1.97 (m)					
16	26.6	0.93 (m)/1.73 (m)	26.6	0.93 (m)/1.73 (m)	1'''	100.7	4.81 (d, 7.8)	101.2	4.78 (d, 7.8)
17	38.4	—	38.3	—	2'''	72.6	3.50 (m)	72.1	3.18 (m)
18	42.7	2.13 (br d, 11.4)	42.7	2.12 (br d, 11.4)	3'''	74.3	3.34 (m)	75.4	3.28 (m)
19	46.2	1.02 (m)/1.84 (m)	46.2	1.03 (m)/1.84 (m)	4'''	68.3	3.65 (br s)	69.2	3.27 (m)
20	35.9	—	35.9	—	5'''	74.8	3.37 (m)	65.2	2.97 (dd, 10.2, 11.4)
21	82.5	3.40 (br s)	82.5	3.40 (br s)	6'''	60.2	3.52 <sup>a</sup> /3.48 <sup>a</sup>		3.63 <sup>a</sup>
22	77.3	3.25 (br s)	77.3	3.25 (br s)					
23	22.2	1.08 (s)	22.1	1.08 (s)	1''''	104.6	4.38 (d, 7.8)	104.7	4.36 (d, 7.8)
24	62.4	3.14 (m)	61.7	3.12 (m)	2''''	74.8	3.03 (m)	75.0	3.03 (m)
		3.88 (d, 9.0)		3.89 (d, 9.0)	3''''	76.2	3.17 (m)	76.0	3.17 (m)
25	15.3	0.81 (s)	15.1	0.81 (s)	4''''	69.9	3.10 (m)	69.7	3.10 (m)
26	16.4	0.90 (s)	16.4	0.91 (s)	5''''	77.2	3.12 (m)	77.3	3.13 (m)
27	26.1	1.11 (s)	26.1	1.11 (s)	6''''	61.0	3.73 (dd, 10.2, 4.2)	60.9	3.72 <sup>a</sup>
28	21.4	0.85 (s)	21.3	0.85 (s)			3.50 <sup>a</sup>		3.49 <sup>a</sup>
29	30.4	0.85 (s)	30.4	0.85 (s)					
30	21.5	0.97 (s)	21.5	0.97 (s)					

<sup>a</sup> Overlapped signal.



**Derristrifoside C (3).** White amorphous powder;  $[\alpha]_D^{28}$ :  $-18.6$  ( $c$  0.1, MeOH); UV: none significant maxima absorption in the range of 200–400 nm; HR-ESI-MS  $m/z$ : 1087.5692  $[M-H]^-$ , (calcd. for  $[C_{54}H_{87}O_{22}]^-$ , 1087.5694,  $\Delta = -0.2$  ppm);  $^1H$ - and  $^{13}C$ -NMR data are shown in the Table 1.

**Derristrifoside D (4).** White amorphous powder;  $[\alpha]_D^{28}$ :  $-35.5$  ( $c$  0.1, MeOH); UV: none significant maxima absorption in the range of 200–400 nm; HR-ESI-MS  $m/z$ : 1119.5570  $[M-H]^-$ , (calcd. for  $[C_{54}H_{87}O_{24}]^-$ , 1119.5593,  $\Delta = -2.1$  ppm);  $^1H$ - and  $^{13}C$ -NMR data are shown in the Table 2.

**Derristrifoside E (5).** White amorphous powder;  $[\alpha]_D^{28}$ :  $-39.4$  ( $c$  0.1, MeOH); UV: none significant maxima absorption in the range of 200–400 nm; HR-ESI-MS  $m/z$ : 1089.5485  $[M-H]^-$ , (calcd. for  $[C_{53}H_{85}O_{23}]^-$ , 1089.5487,  $\Delta = -0.2$  ppm);  $^1H$ - and  $^{13}C$ -NMR data are shown in the Table 2.

### Cytotoxic assay

Cytotoxic effects against SK-LU-1 and Hep-G2 cell lines were determined using Sulforhodamine B (SRB) assay as previously described and referred to SI.<sup>13,16</sup>

### Nitric oxide assay

Nitric oxide assay was performed as previously described and referred to SI.<sup>17</sup>

## Results and discussion

The methanol extract from the leaves of *D. trifoliata* was thus successively fractionated with dichloromethane and ethyl acetate, followed by purification of the aqueous fraction through flash column chromatography and HPLC, to yield five oleanane-type saponins (1–5).

Compound **1** (Fig. 1) was isolated as a white amorphous powder. The negative-ion HR-ESI-MS spectrum of **1** showed a deprotonated molecular ion corresponding to the molecular

formula  $C_{54}H_{88}O_{23}$  ( $m/z$  1103.5641  $[M-H]^-$ ; calcd. for  $[C_{54}H_{87}O_{23}]^-$ , 1103.5638), indicating 11 indices of hydrogen deficiency. The  $^1H$ -NMR and HSQC spectra of **1** exhibited signals corresponding to eight methyl group [ $\delta_H$  1.20, 1.09, 1.08, 1.04, 1.00, 0.98, 0.96, and 0.90 (each 3H, s)], one olefinic proton [ $\delta_H$  5.26 (1H, t,  $J = 3.0$  Hz)], and four anomeric protons [ $\delta_H$  4.80 (1H, d,  $J = 1.8$  Hz), 4.74 (1H, d,  $J = 7.8$  Hz), 4.64 (1H, d,  $J = 7.8$  Hz), and 4.48 (1H, d,  $J = 7.8$  Hz)]. The  $^{13}C$ -NMR spectrum of **1** revealed signals of 54 carbons. Of these, 30 carbons were assigned to a triterpene skeleton and the remaining 24 carbons to four hexose-type monosaccharide units. The presence of eight singlet methyl groups, a C=C double bond ( $\delta_C$  145.0 and 123.9), and splitting pattern of the H-18 signal [ $\delta_H$  2.27 (dd,  $J = 13.2$  and 3.6 Hz)] indicated that compound **1** was a derivative of an olean-12-ene triterpene. The COSY cross peaks between H-18 ( $\delta_H$  2.27) and H<sub>2</sub>-19 ( $\delta_H$  1.18 and 1.97), the HMBC correlations between H<sub>3</sub>-29 ( $\delta_H$  0.96)/H<sub>3</sub>-30 ( $\delta_H$  1.08) and C-19 ( $\delta_C$  47.9)/C-20 ( $\delta_C$  37.3)/C-21 ( $\delta_C$  85.6), and the HMBC correlation between an anomeric proton ( $\delta_H$  4.80) and C-21 ( $\delta_C$  85.6) suggested *O*-glycosylation at C-21. Moreover, the small coupling constant of this anomeric proton ( $\delta_H$  4.80,  $J = 1.8$  Hz), the consecutive COSY correlations among H-1' ( $\delta_H$  4.80)/H-2' ( $\delta_H$  3.94)/H-3' ( $\delta_H$  3.80)/H-4' ( $\delta_H$  3.41)/H-5' ( $\delta_H$  3.76)/H<sub>3</sub>-6' ( $\delta_H$  1.27), and the corresponding carbon signals [C-1' ( $\delta_C$  104.7)/C-2' ( $\delta_C$  72.3)/C-3' ( $\delta_C$  72.3)/C-4' ( $\delta_C$  74.0)/C-5' ( $\delta_C$  70.4)/C-6' ( $\delta_C$  18.0)] illustrated an *O*- $\alpha$ -rhamnopyranosyl group attached at C-21. A COSY correlation between H-21 ( $\delta_H$  3.53) and H-22 ( $\delta_H$  3.44), together with the chemical shift of C-22 ( $\delta_C$  79.8), suggested the presence of a hydroxyl group at C-22. In addition, HMBC correlations between H<sub>3</sub>-23 ( $\delta_H$  1.09)/H<sub>3</sub>-24 ( $\delta_H$  0.90) and C-3 ( $\delta_C$  91.1)/C-4 ( $\delta_C$  40.5)/C-5 ( $\delta_C$  57.0), along with an HMBC correlation between an anomeric proton ( $\delta_H$  4.48) and C-3 ( $\delta_C$  91.1), indicated another *O*-glycosylation at C-3. A large coupling constant of this anomeric proton ( $\delta_H$  4.48,  $J = 7.8$  Hz), the COSY correlations among H-1'' ( $\delta_H$  4.48)/H-2'' ( $\delta_H$  3.51)/H-3'' ( $\delta_H$  3.75)/H-4'' ( $\delta_H$

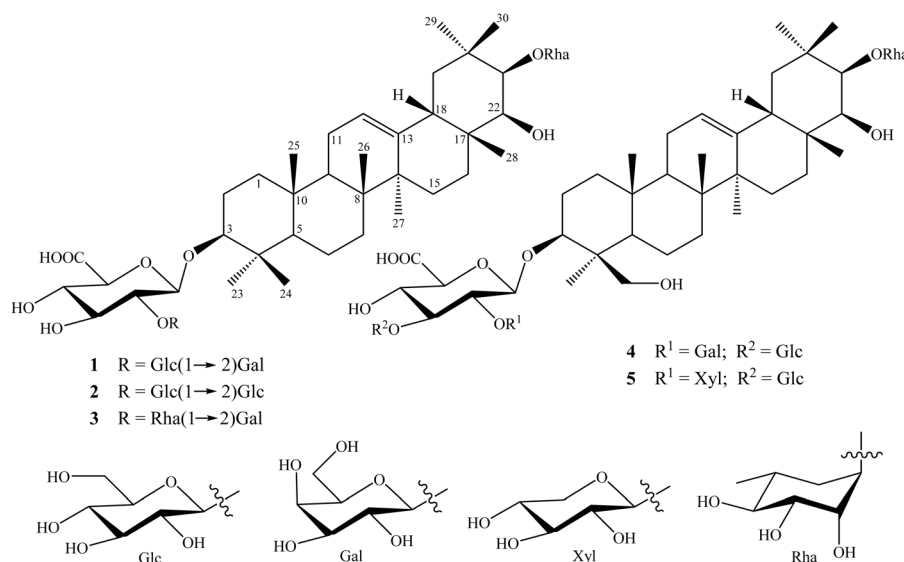


Fig. 1 New oleanane-type saponins 1–5 isolated from the leaves of *D. trifoliata*.



3.52)/H-5'' ( $\delta_{\text{H}}$  3.58), and the HMBC correlation between H-5'' ( $\delta_{\text{H}}$  3.58) and C-6'' ( $\delta_{\text{C}}$  176.8) suggested an *O*- $\beta$ -glucuronopyranosyl group attached at C-3. Subsequently, an HMBC correlation between an anomeric proton ( $\delta_{\text{H}}$  4.74) and C-2'' ( $\delta_{\text{C}}$  83.7), COSY correlations among H-1''' ( $\delta_{\text{H}}$  4.74)/H-2''' ( $\delta_{\text{H}}$  3.79)/H-3''' ( $\delta_{\text{H}}$  3.71)/H-4''' ( $\delta_{\text{H}}$  3.89)/H-5''' ( $\delta_{\text{H}}$  3.48)/H-2-6''' ( $\delta_{\text{H}}$  3.69 and 3.75), and the broad singlet of H-4''' ( $\delta_{\text{H}}$  3.89) demonstrated the presence of an *O*- $\beta$ -galactopyranosyl group linked to the glucuronic acid moiety at C-2''. The final sugar unit was identified as a  $\beta$ -glucopyranosyl group, based on the chemical shift of the carbinol carbons ( $\delta_{\text{C}}$  106.2, 76.4, 78.9, 71.0, 77.5, 62.3) and the coupling constant of its anomeric proton ( $\delta_{\text{H}}$  4.64,  $J = 7.8$  Hz). The HMBC correlation between Glc H-1'''' ( $\delta_{\text{H}}$  4.64) and C-2''' ( $\delta_{\text{C}}$  83.5) indicated that the *O*- $\beta$ -glucopyranosyl group was linked to C-2''' of the galactopyranosyl unit (Fig. 2). The presence of D-glucuronic acid, D-galactose, D-glucose, and L-rhamnose was confirmed by acid hydrolysis of **1**, followed by TLC comparison with authentic standards and verification of optical rotation signs (SI).<sup>18,19</sup> The stereochemistry of the aglycone moiety was established through analysis of the NOESY spectrum and the coupling constants between  $H_{\text{axial}}-H_{\text{axial}}$  ( $J_{\text{ax/ax}}$ ) and  $H_{\text{axial}}-H_{\text{equatorial}}$  ( $J_{\text{ax/eq}}$ ) protons (Fig. 3). The NOESY correlation between H-5 ( $\delta_{\text{H}}$  0.80) and H-3 ( $\delta_{\text{H}}$  3.24), together with  $J_{\text{ax/ax}} = 11.4$  Hz for H-3 ( $\delta_{\text{H}}$  3.24), indicated axial- $\alpha$  orientation for both H-3 and H-5. Similarly, the NOESY correlation between H-18 ( $\delta_{\text{H}}$  2.27) and H<sub>3</sub>-30 ( $\delta_{\text{H}}$  1.08), and  $J_{\text{ax/ax}} = 13.2$  Hz for H-18 ( $\delta_{\text{H}}$  2.27) indicated *axial-beta* orientation for H-18 and methyl group C-30. The NOESY correlation of H<sub>3</sub>-29 ( $\delta_{\text{H}}$  0.96)/H-21 ( $\delta_{\text{H}}$  3.53), along with  $J_{\text{ax/eq}} = 3.0$  Hz for H-21/H-22, suggested axial- $\alpha$

orientation for H-21 and equatorial- $\alpha$  orientation for H-22. The  $\alpha$  orientation of H-22 was further validated by NOESY correlation between H-22 ( $\delta_{\text{H}}$  3.44) and  $H_{\text{equatorial-16}}$  ( $\delta_{\text{H}}$  1.03) as well as the identical chemical shifts of C-21 ( $\delta_{\text{C}}$  85.6) and C-22 ( $\delta_{\text{C-21}}$  85.5 and  $\delta_{\text{C-22}}$  79.7).<sup>20</sup> Thus, aglycone of **1** was identified as cantoniensistriol, an uncommon sapogenin found in vascular plants.<sup>21,22</sup> Consequently, compound **1** was elucidated as 3-*O*- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-galactopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-glucuronopyranosyl cantoniensistriol 21-*O*- $\alpha$ -L-rhamnopyranoside, a new compound named as derristrifoside **A**.

Compound **2** (Fig. 1) was isolated as a white amorphous powder. The molecular formula of **2** was determined to be identical with that of **1**, C<sub>54</sub>H<sub>88</sub>O<sub>23</sub>, as indicated by a deprotonated molecular ion in the HR-ESI-MS spectrum ( $m/z$  1103.5624 [M-H]<sup>-</sup>; calcd. for [C<sub>54</sub>H<sub>87</sub>O<sub>23</sub>]<sup>-</sup>, 1103.5638). Moreover, the 1D and 2D NMR spectral data (Table 1 and Fig. 2) of **2** were similar to those of **1**, except that the signals corresponding to a  $\beta$ -galactopyranosyl group ( $\delta_{\text{C}}$  104.4, 83.5, 74.8, 69.7, 76.5, and 62.1 in **1**) were replaced by those of an additional  $\beta$ -glucopyranosyl group ( $\delta_{\text{C}}$  103.3, 85.4, 76.7, 72.0, 77.5, and 63.3 in **2**). The structural difference in sugar moiety of **2** was elucidated through analysis of the HSQC, HMBC, and COSY spectra. The COSY cross-peak between Glu H-1'' ( $\delta_{\text{H}}$  4.49) and Glu H-2'' ( $\delta_{\text{H}}$  3.57), the HSQC correlation between Glu H-2'' ( $\delta_{\text{H}}$  3.57) and Glu C-2'' ( $\delta_{\text{C}}$  82.0), and the HBMC correlation between Glc H-1''' ( $\delta_{\text{H}}$  4.87) and Glu C-2'' ( $\delta_{\text{C}}$  82.0) established a structural fragment of a glucopyranosyl-(1  $\rightarrow$  2)-glucuronopyranosyl unit. Similarly, the

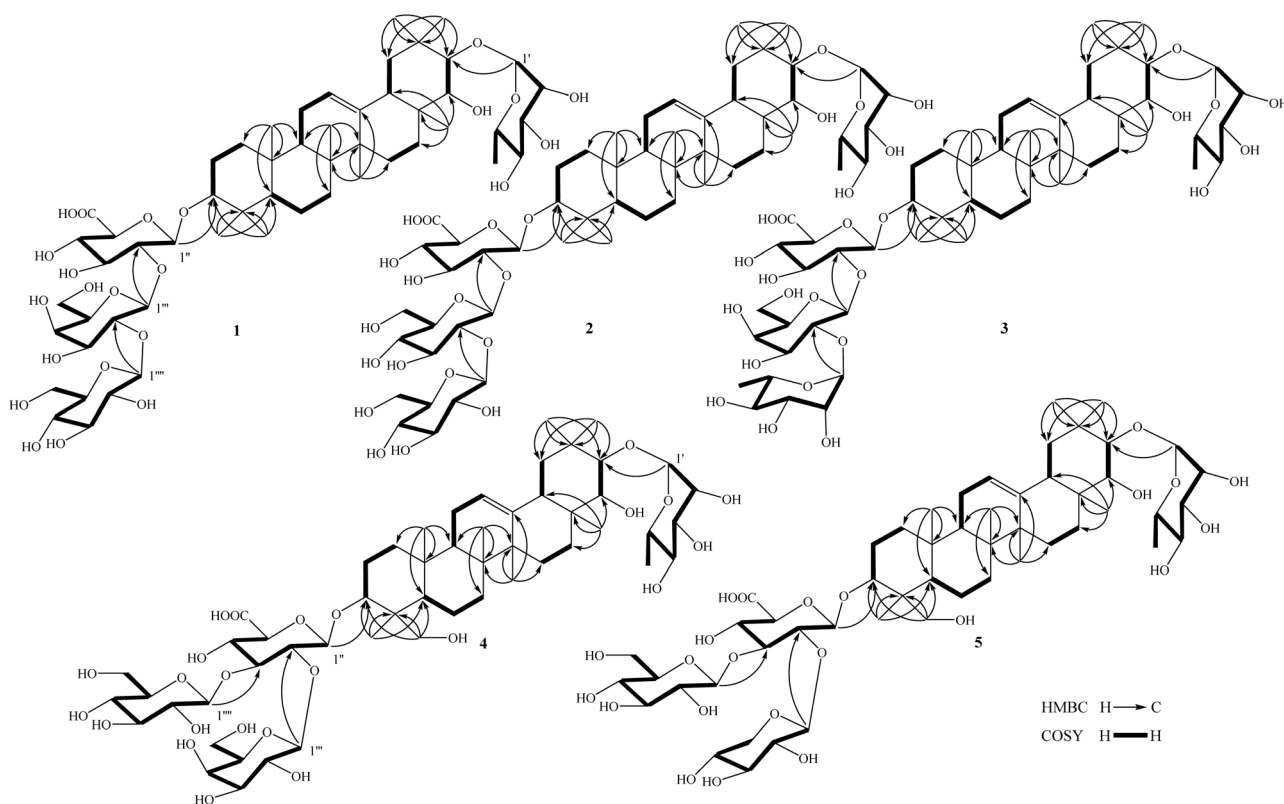


Fig. 2 Key HMBC and COSY correlations of compounds 1–5.



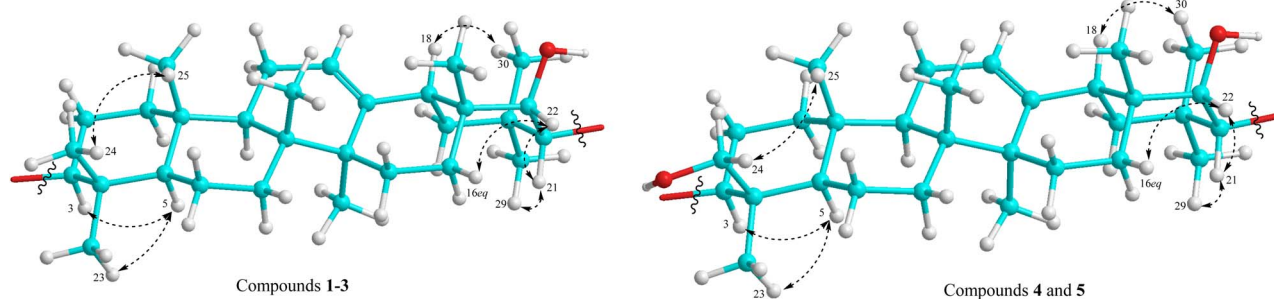


Fig. 3 Important NOESY correlations at aglycone moiety of compounds 1–5.

COSY cross-peak between Glc H-1''' ( $\delta_{\text{H}}$  4.87) and Glc H-2''' ( $\delta_{\text{H}}$  3.42), the HSQC correlation between Glc H-2''' ( $\delta_{\text{H}}$  3.42) and Glc C-2''' ( $\delta_{\text{C}}$  85.4), the HBMC correlation between Glc H-1'''' ( $\delta_{\text{H}}$  4.61) and Glc C-2''' ( $\delta_{\text{C}}$  85.4) demonstrated that a second glucopyranosyl group was attached at C-2''' of the first glucopyranosyl unit, forming a trisaccharide moiety: glucopyranosyl-(1  $\rightarrow$  2)-glucopyranosyl-(1  $\rightarrow$  2)-glucopyranose. This trisaccharide moiety was linked to C-3 of the aglycone, as confirmed by an HMBC correlation between Glu H-1'' ( $\delta_{\text{H}}$  4.49) and C-3 (91.3). Acid hydrolysis of 2 yielded D-glucuronic acid, D-glucose, and L-rhamnose, which were identified by comparison with standard monosaccharides using TLC and confirmed by the positive signs of optical rotations (SI).<sup>18,19</sup> Consequently, compound 2 was identified as 3-*O*- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-glucuronopyranosyl cantoniensistriol 21-*O*- $\alpha$ -L-rhamnopyranoside, a new compound named derristrifoside B (Fig. 3).

Compound 3 (Fig. 1) was isolated as a white amorphous powder. The molecular formula of 3 was determined to be  $\text{C}_{54}\text{H}_{88}\text{O}_{22}$  based on its deprotonated molecular ion in the HR-ESI-MS spectrum ( $m/z$  1087.5692 [ $\text{M-H}$ ]<sup>-</sup>; calcd. for [ $\text{C}_{54}\text{H}_{87}\text{O}_{22}$ ]<sup>-</sup>, 1087.5694). The NMR data indicated that compound 3 differed from both 1 and 2 by the sugar moiety attached at C-3 of the aglycone. The <sup>1</sup>H-NMR spectrum of 3 displayed a broad singlet carbinol proton ( $\delta_{\text{H}}$  3.80, Gal H-4'''), suggesting the presence of galactopyranosyl group similar to that in 1 ( $\delta_{\text{H}}$  3.89, Gal H-4'''). In contrast to 1 and 2, the appearance of an anomeric proton [ $\delta_{\text{H}}$  5.22 (d,  $J$  = 1.2 Hz)] and additional doublet methyl signals [ $\delta_{\text{H}}$  1.26 (d,  $J$  = 7.2 Hz)] in the <sup>1</sup>H-NMR spectrum suggested replacement of a  $\beta$ -glucopyranosyl group (in 1 and 2) by an  $\alpha$ -rhamnopyranosyl group (in 3). The COSY cross-peak between Glu H-1'' ( $\delta_{\text{H}}$  4.45) and Glu H-2'' ( $\delta_{\text{H}}$  3.72), the HSQC correlation between Glu H-2'' ( $\delta_{\text{H}}$  3.72) and Glu C-2'' ( $\delta_{\text{C}}$  79.1), and the HBMC correlation between Gal H-1'''' ( $\delta_{\text{H}}$  4.85) and Glu C-2'' ( $\delta_{\text{C}}$  79.1) established a structural fragment of a galactopyranosyl-(1  $\rightarrow$  2)-glucuronopyranosyl group. Similarly, the COSY cross-peak between Gal H-1'''' ( $\delta_{\text{H}}$  4.85) and Gal H-2''' ( $\delta_{\text{H}}$  3.70), the HSQC correlation between Gal H-2''' ( $\delta_{\text{H}}$  3.70) and Gal C-2''' ( $\delta_{\text{C}}$  77.3), and the HBMC correlation of Rha H-1'''' ( $\delta_{\text{H}}$  5.22) and Gal C-2''' ( $\delta_{\text{C}}$  77.3) demonstrated that an  $\alpha$ -rhamnopyranosyl group was attached at C-2''' of the galactopyranosyl to form a trisaccharide: rhamnopyranosyl-(1  $\rightarrow$  2)-galactopyranosyl-(1  $\rightarrow$  2)-glucopyranose. This trisaccharide moiety was linked to C-3 of the aglycone, confirmed by an HMBC

correlation between Glu H-1'' ( $\delta_{\text{H}}$  4.45) and C-3 ( $\delta_{\text{C}}$  92.0). Acid hydrolysis of 3 yielded D-glucuronic acid, D-galactose, and L-rhamnose, identified by TLC comparison with authentic standards and optical rotation data. (SI).<sup>18,19</sup> Consequently, compound 3 was characterized as 3-*O*- $\alpha$ -L-rhamnopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-galactopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-glucuronopyranosyl cantoniensistriol 21-*O*- $\alpha$ -L-rhamnopyranoside, a new compound named derristrifoside C.

Compound 4 (Fig. 1) was isolated as a white amorphous powder. The negative-ion HR-ESI-MS spectrum of 4 showed a deprotonated molecular ion corresponding to  $\text{C}_{54}\text{H}_{88}\text{O}_{24}$  ( $m/z$  1119.5570 [ $\text{M-H}$ ]<sup>-</sup>; calcd. for [ $\text{C}_{54}\text{H}_{87}\text{O}_{24}$ ]<sup>-</sup>, 1119.5593), indicating 11 indices of hydrogen deficiency. Comparison of the <sup>1</sup>H- and <sup>13</sup>C-NMR data of 4 with those of 1–3 suggested that 4 was also an olean-12-ene type glycoside. The NMR data showed seven singlet methyl groups [ $\delta_{\text{H}}$  1.11 (3H), 1.08 (3H), 0.97 (3H), 0.90 (3H), 0.85 (6H), and 0.81 (3H)] and one oxygenated methylene group ( $\delta_{\text{C}}$  62.4/ $\delta_{\text{H}}$  3.88 and 3.14), suggesting hydroxylation of one of the eight tertiary methyl groups in the olean-12-ene backbone. The HMBC correlations between H<sub>3</sub>-23 ( $\delta_{\text{H}}$  1.08) and C-3 ( $\delta_{\text{C}}$  89.4)/C-4 ( $\delta_{\text{C}}$  43.0)/C-5 ( $\delta_{\text{C}}$  55.3)/C-24 ( $\delta_{\text{C}}$  62.4) confirmed hydroxylation at C-24. Two other oxygenated groups in the aglycone, an *O*- $\alpha$ -rhamnopyranosyl group at C-21 and a hydroxy group at C-22, were identified similarly to those in 1–3 by COSY, HMBC, and analysis of  $J$ -coupling patterns. A NOESY correlation between H-5 ( $\delta_{\text{H}}$  0.85) and H-3 ( $\delta_{\text{H}}$  3.24) indicated axial- $\alpha$  orientation of both protons. NOESY correlations between H-3 ( $\delta_{\text{H}}$  3.24)/H-5 ( $\delta_{\text{H}}$  0.85) and H<sub>3</sub>-23 ( $\delta_{\text{H}}$  1.08), and between H<sub>2</sub>-24 ( $\delta_{\text{H}}$  3.88) and H<sub>3</sub>-25 ( $\delta_{\text{H}}$  0.81) confirmed axial- $\beta$  orientation of hydroxymethylene group (C-24). The NOESY correlation between H-18 ( $\delta_{\text{H}}$  2.13) and H<sub>3</sub>-30 ( $\delta_{\text{H}}$  0.97), along with  $J_{\text{ax/ax}}$  = 11.4 Hz for H-18 ( $\delta_{\text{H}}$  2.13) indicated axial- $\beta$  orientation for both H-18 and methyl group C-30. The NOESY correlation between H<sub>3</sub>-29 ( $\delta_{\text{H}}$  0.85) and H-21 ( $\delta_{\text{H}}$  3.40), together with broad singlets for both H-21 and H-22 ( $J_{\text{ax/eq}}$  coupling), suggested  $\alpha$ -axial and  $\alpha$ -equatorial orientations for H-21 and H-22, respectively. Therefore, aglycone of 4 was established as 24-hydroxycantoniensistriol. Besides the *O*- $\alpha$ -rhamnopyranosyl group at C-21, the presence of three anomeric protons [ $\delta_{\text{H}}$  4.81 (d,  $J$  = 7.8 Hz), 4.38 (d,  $J$  = 7.8 Hz), and 4.34 (d,  $J$  = 7.8 Hz)], a carboxylic carbon ( $\delta_{\text{C}}$  173.4), and a broad singlet carbinol proton ( $\delta_{\text{H}}$  3.65) indicated that the second sugar moiety was a trisaccharide composed of  $\beta$ -glucopyranose,  $\beta$ -galactopyranosyl, and  $\beta$ -glucopyranosyl units. The COSY cross-



peak between Glu H-1'' ( $\delta_{\text{H}}$  4.34) and Glu H-2'' ( $\delta_{\text{H}}$  3.37), the HSQC correlation between Glu H-2'' ( $\delta_{\text{H}}$  3.37) and Glu C-2'' ( $\delta_{\text{C}}$  78.4), and the HBMC correlation between Gal H-1''' ( $\delta_{\text{H}}$  4.81) and Glu C-2'' ( $\delta_{\text{C}}$  78.4) established a  $\beta$ -galactopyranosyl-(1 $\rightarrow$ 2)- $\beta$ -glucuronopyranosyl fragment. Additionally, COSY cross-peak between Glu H-2'' ( $\delta_{\text{H}}$  3.37) and Glu H-3'' ( $\delta_{\text{H}}$  3.50), the HSQC correlation between Glu H-3'' ( $\delta_{\text{H}}$  3.50) and Glu C-3'' ( $\delta_{\text{C}}$  82.1), and the HBMC correlation between Glc H-1'''' ( $\delta_{\text{H}}$  4.38) and Glu C-3'' ( $\delta_{\text{C}}$  82.1) demonstrated that a  $\beta$ -glucopyranosyl group was attached at C-3'' of the glucopyranose units, forming a trisaccharide:  $\beta$ -glucopyranosyl-(1 $\rightarrow$ 3)-[ $\beta$ -galactopyranosyl-(1 $\rightarrow$ 2)]- $\beta$ -glucopyranose. This trisaccharide was linked to C-3 of aglycone, as confirmed by an HMBC correlation between Glu H-1'' ( $\delta_{\text{H}}$  4.34) and C-3 ( $\delta_{\text{C}}$  89.4). Acid hydrolysis of **4** yielded D-glucuronic acid, D-galactose, D-glucose, and L-rhamnose, identified by TLC comparison with standards and optical rotation data (SI).<sup>18,19</sup> Consequently, compound **4** was elucidated as 3-O- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)-[ $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 2)]- $\beta$ -D-glucuronopyranosyl-24-hydroxycantoniensistriol 21-O- $\alpha$ -L-rhamnopyranoside, a new compound named derristrifoside D.

Compound **5** (Fig. 1) was isolated as a white amorphous powder. The molecular formula of **5** was determined as C<sub>53</sub>H<sub>86</sub>O<sub>23</sub> based on its deprotonated molecular ion in the HR-ESI-MS spectrum ( $m/z$  1089.5485 [M-H]<sup>-</sup>; calcd. for [C<sub>53</sub>H<sub>85</sub>O<sub>23</sub>]<sup>-</sup>, 1089.5487). Comparison of the NMR data between **4** and **5** indicated that **5** differed from **4** in the trisaccharide moiety attached at C-3 of the aglycone. Specifically, the  $\beta$ -galactopyranosyl group (a hexose) in **4** was replaced by a  $\beta$ -xylopyranosyl group (a pentose) in **5**. The presence of the  $\beta$ -xylopyranosyl group in **5** was supported by the signals of an anomeric carbon/proton [ $\delta_{\text{C}}$  101.2/ $\delta_{\text{H}}$  4.78 (d,  $J$  = 7.8 Hz)], three carbinol carbons ( $\delta_{\text{C}}$  72.1, 75.4, and 69.2), and one oxygenated methylene group [ $\delta_{\text{C}}$  65.2/ $\delta_{\text{H}}$  3.63 and 2.97 (dd,  $J$  = 10.2 and 11.4 Hz)]. The COSY cross-peak between Glu H-1'' ( $\delta_{\text{H}}$  4.31) and Glu H-2'' ( $\delta_{\text{H}}$  3.26), the HSQC correlation between Glu H-2'' ( $\delta_{\text{H}}$  3.26) and Glu C-2'' ( $\delta_{\text{C}}$  79.0), and the HBMC correlation between Xyl H-1''' ( $\delta_{\text{H}}$  4.78) and Glu C-2'' ( $\delta_{\text{C}}$  79.0) established a  $\beta$ -xylopyranosyl-(1 $\rightarrow$ 2)- $\beta$ -glucuronopyranosyl fragment. The COSY cross-peak between Glu H-2'' ( $\delta_{\text{H}}$  3.26) and Glu H-3'' ( $\delta_{\text{H}}$  3.17), the

HSQC correlation between Glu H-3'' ( $\delta_{\text{H}}$  3.17) and Glu C-3'' ( $\delta_{\text{C}}$  83.8), and the HBMC correlation between Glc H-1'''' ( $\delta_{\text{H}}$  4.36) and Glu C-3'' ( $\delta_{\text{C}}$  83.8) demonstrated that a  $\beta$ -glucopyranosyl group was attached at C-3'' of the glucopyranose units, forming a trisaccharide:  $\beta$ -glucopyranosyl-(1 $\rightarrow$ 3)-[ $\beta$ -xylopyranosyl-(1 $\rightarrow$ 2)]- $\beta$ -glucopyranose. This trisaccharide was linked to C-3 of the aglycone, as confirmed by an HMBC correlation between Glu H-1'' ( $\delta_{\text{H}}$  4.31) and C-3 ( $\delta_{\text{C}}$  89.0). Acid hydrolysis of **5** yielded D-glucuronic acid, D-glucose, D-xylose, and L-rhamnose, which were identified by TLC comparison with authentic standards and confirmed by optical rotations (SI).<sup>18,19</sup> Thus, compound **5** was identified as 3-O- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)-[ $\beta$ -D-xylopyranosyl-(1 $\rightarrow$ 2)]- $\beta$ -D-glucuronopyranosyl-24-hydroxycantoniensistriol 21-O- $\alpha$ -L-rhamnopyranoside, a new compound named derristrifoside E.

Compounds **1–5** were evaluated for their effects on nitric oxide (NO) production in LPS-activated RAW 264.7 cells and for cytotoxic activity against SK-LU-1 and Hep-G2 human cancer cell lines (Table 3, SI). Unfortunately, at a concentration of 20  $\mu\text{M}$ , all tested compounds exhibited only weak inhibitory activities toward NO production (inhibitory rates in ranging from 12.17  $\pm$  1.22% to 17.09  $\pm$  1.16%) and weak cytotoxic effects (cytotoxic rates in ranging from 8.02  $\pm$  0.84% to 23.31  $\pm$  0.56%). Although these compounds showed weak activity in both cytotoxicity and NO inhibition, saponins possessing a cantoniensistriol-type sapogenin framework are rarely found in vascular plants. Therefore, this study represents the first report of the cytotoxic and NO inhibitory activities of cantoniensistriol-type saponins.

## Conclusions

In conclusion, phytochemical investigation of the leaves of *Derris trifoliata* led to the isolation of five new oleanane-type saponins possessing a cantoniensistriol framework. Their structures were determined based on HR-ESI-MS and extensive NMR analyses. Five isolated compounds exhibited weak inhibitory effects on NO production in LPS-activated RAW 264.7 cells and weak antiproliferative activity against SK-LU-1 and Hep-G2 human cancer cell lines. Our results highlight that the leaves of *Derris trifoliata* contain unusual cantoniensistriol-type saponins. This is also the first report of the cytotoxic and NO production inhibitory activities of these saponins.

## Author contributions

BTN Trang, BTM Anh, NT Mai, TT Nga contributed to research idea, isolation and prepare samples for bioassay; PV Kiem, BH Tai, BTT Trang contributed to structure elucidation; BTT Trang, NT Mai, BH Tai, PV Kiem contributed to writing and editing.

## Conflicts of interest

The authors declare no conflicts of interest.

Table 3 NO inhibition and cytotoxic effects of compounds **1–5** at a concentration of 20  $\mu\text{M}$

Comp.	NO inhibition (%)	Cytotoxicity (%)	
		SK-LU-1	Hep-G2
<b>1</b>	12.17 $\pm$ 1.22	21.23 $\pm$ 1.91	15.15 $\pm$ 1.05
<b>2</b>	15.07 $\pm$ 0.84	14.68 $\pm$ 1.07	8.02 $\pm$ 0.84
<b>3</b>	16.67 $\pm$ 0.92	23.31 $\pm$ 0.56	17.77 $\pm$ 1.15
<b>4</b>	16.33 $\pm$ 1.03	12.22 $\pm$ 1.02	13.40 $\pm$ 1.11
<b>5</b>	17.09 $\pm$ 1.16	17.59 $\pm$ 0.96	12.17 $\pm$ 1.07
Dex <sup>a</sup>	54.23 $\pm$ 1.17	—	—
Ell <sup>b</sup>	—	78.62 $\pm$ 1.25	79.85 $\pm$ 1.78

<sup>a</sup> Dexamethasone (20  $\mu\text{M}$ ) and. <sup>b</sup> Ellipticine (2.0  $\mu\text{g mL}^{-1}$ ) were used as positive control. Data are expressed as mean  $\pm$  SD of triplicate experiments ( $n$  = 3). Statistical significances ( $P$  < 0.05) are determined by one-way ANOVA compare to vehicle group.



## Data availability

Supplementary information (SI): HR-ESI-MS and NMR spectra of all new compounds would be found along with manuscript at the Journal home page. See DOI: <https://doi.org/10.1039/d5ra08300a>.

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