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Study on chemical constituents from *Ixeris dentata*

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Abstract. *Ixeris dentata* (Thunb. ex Thunb.) Nakai (family Asteraceae) a plant widely distributed in Viet Nam, is a perennial herb that grows to a height of 0.5 m. It has been used as a medicinal herb medicine since ancient times for the treatment of calculi, dyspepsia, indigestion, pneumonia, hepatitis, contusion, and tumors in Northeast Asia. The biological activities of this plant have been shown to be neuroprotective, anti-mutagenic, anti-hyperlipidemic, anti-inflammatory, anti-allergic, and anti-proliferative activities. It is also composed of aliphatics, triterpenoids, sesquiterpene, and glycosides. However, research on the phytochemistry of this plant has yet to be conducted in Viet Nam. In this study, five phenolics including chlorogenic acid (**1**), 3,5-di-*O*-caffeoylquinic acid (**2**), 4,5-di-*O*-caffeoylquinic acid (**3**), citrusin C (**4**), 4-allyl-2,6-dimethoxyphenol *O*-*β*-D-glupyranoside (**5**), and two sesquiterpene lactones, 8-epidesacylcynaropicrin glucoside (**6**) and ixerisoside A (**7**) were isolated from the methanol extract of the leaves of *Ixeris dentata* using combined chromatographic methods. Their chemical structures were determined by analysis of MS, NMR spectra data as well as comparison with those reported in the literature.

Keywords: Ixeris dentata, Asteraceae, phenolic, sesquiterpene lactone

Classification numbers: 1.1.1, 1.1.6.

1. INTRODUCTION

Ixeris dentata (Thunb. ex Thunb.) Nakai (family Asteraceae), a plant widely distributed in Viet Nam, is a perennial plant that grows to a height of 0.5 m [1]. It has been used as a medicinal herb since ancient times for the treatment of indigestion, pneumonia, hepatitis, contusion, and tumors in Northeast Asia. The major classes of organic compounds have been isolated, including aliphatics, triterpenoids, phenolics, and sesquiterpene glycosides [2 - 5]. Previous studies showed that it had various physiological functions, including neuroprotective [6], anti-mutagenic [7], anti-hyperlipidemic [8], anti-inflammatory [9], anti-allergic [10], and anti-proliferative activities [11]. These biological activities have been attributed to the presence of various bioactive compounds in their composition. However, research on the phytochemistry of this plant has yet to be conducted in Viet Nam. In this study, we reported the isolation and structure

elucidation of five phenolics and two sesquiterpene lactones from the methanol extract of the leaves of *I. dentata*.

2. MATERIALS AND METHODS

2.1. Plant materials

The aerial parts of *Ixeris dentata* (Thunb. ex Thunb.) Nakai were collected in Hoa Binh, Viet Nam, in August 2021, and identified by Dr. Ninh Khac Ban, Institute of Marine Biochemistry (Vietnam Academy of Science and Technology). A voucher specimen (ID2108) was deposited at the Hanoi University of Science (Vietnam National University).

2.2. General experimental procedures

All NMR spectra were recorded on a Varian AM400 spectrometer (400 MHz for ^{1}H-NMR and 100MHz for ^{13}C-NMR). Column chromatography was performed using silica gel (Kieselgel 60, 70 - 230 mesh, and 230 - 400 mesh, Merck) or RP-18 resins (150 µm, Fuji Silysia Chemical Ltd.). Thin layer chromatography (TLC) was carried out using pre-coated silica gel 60 F_{254} (0.25 mm, Merck) and RP-18 F_{254S} plates (0.25 mm, Merck).

2.3. Extraction and isolation

The dried powder of the *I. dentata* aerial parts (1.0 kg) was sonicated with hot methanol to give the methanol extract (150 g) after concentrating under reduced pressure. The extract was suspended in water and successively partitioned with dichloromethane, and ethyl acetate, giving dichloromethane (ID1, 45.0 g), ethyl acetate extracts (ID2, 26.0 g), and water layer (ID4). ID4 was loaded on a Diaion HP-20 column, followed by eluting with water and increasing MeOH concentration in water to obtain four fractions, ID4A - ID4D. The ID4C fraction was chromatographed on a silica gel column eluted with gradient solvents of dichloromethane/MeOH (50/1, 25/1, 10/1, and 5/1, etc.) to obtain four fractions, ID4C1 - ID4C4. ID4C1 was chromatographed on a silica gel column eluted with dichloromethane/acetone (1/1, etc.) to give three fractions, ID4C1A - ID4C1C. The ID4C1A fraction was chromatographed on an RP-18 column eluted with acetone/water (1/1.5, etc.) to give compounds **2** (15.0 mg) and **3** (10.0 mg). The ID4C1B fraction was further chromatographed on an HPLC using J′sphere ODS H-80 column (250 mm length × 20 mm I.D) eluted with ACN in H_2O (30 %, etc.) yielding compound **1** (8.0 mg). The ID4D fraction was chromatographed on a silica gel column eluted with gradient solvents of dichloromethane/MeOH (50/1, 25/1, 10/1, and 5/1, etc.) to obtain three fractions, ID4D1 - ID4D3. The ID4D1 fraction was run on a silica gel column eluted with dichloromethane/acetone (2/1, etc.) to give three fractions, ID4D1A - ID4D1C. The ID4C1A fraction was chromatographed on an RP-18 column eluted with acetone/water (1/1, etc.) to give compounds **4** (6.0 mg) and **5** (8.0 mg). The ID4D1C fraction was further applied on an RP-18 column eluted with methanol/water (2/1, v/v) to give compounds **6** (9.0 mg) and **7** (7.0 mg).

Chlorogenic acid (**1**)**:** White amorphous powder; ESI-MS *m/z* 355 $[M+H]^+$, $C_{16}H_{18}O_9$; ^{1}H- and ^{13}C-NMR (D_2O): see Table 1.

3,5-Di-*O*-caffeoylquinic acid (**2**)**:** White amorphous powder; ESI-MS *m/z* 517 $[M+H]^+$, $C_{25}H_{24}O_{12}$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 1.

4,5-Di-*O*-caffeoylquinic acid (**3**)**:** White amorphous powder; ESI-MS *m/z* 517 $[M+H]^+$, $C_{25}H_{24}O_{12}$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 1.

Citrusin C (**4**)**:** White amorphous powder; ESI-MS *m/z* 327 $[M+H]^+$, $C_{16}H_{22}O_7$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 2.

4-allyl-2,6-dimethoxyphenol *O-β*-D-glucopyranoside (**5**)**:** White amorphous powder; ESI-MS *m/z* 357 $[M+H]^+$, $C_{17}H_{24}O_8$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 2.

8-epidesacylcynaropicrin glucoside (**6**)**:** White amorphous powder; ESI-MS *m/z* 447 $[M+Na]^+$, $C_{21}H_{28}O_9$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 2.

Ixerisoside A (**7**)**:** White amorphous powder; ESI-MS *m/z* 559 $[M+H]^+$, $C_{29}H_{34}O_{11}$; ^{1}H- and ^{13}C-NMR (CD_3OD): see Table 2.

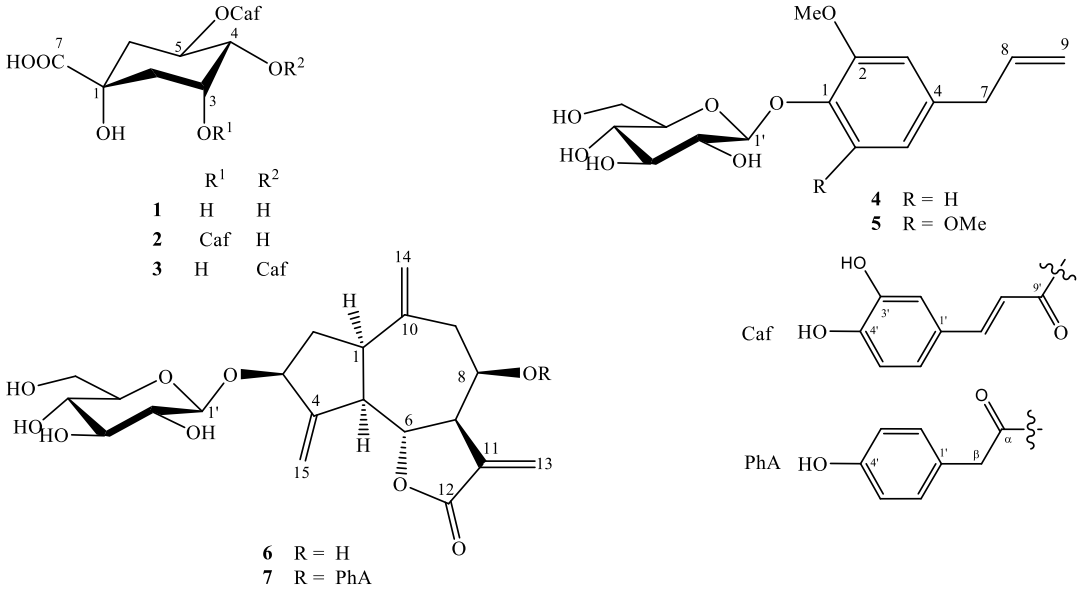

Figure 1. Chemical structures of compounds **1**-**7** from *I. dentata*.

3. RESULTS AND DISCUSSION

Compound **1** was obtained as a white amorphous powder. The ^{1}H-NMR spectra showed the proton signals of three aromatic protons of an ABX aromatic spin system at δ_H 6.56 (d, J = 8.0 Hz), 6.60 (d, J = 8.0 Hz), and 6.70 (s), two *trans* olefinic protons at δ_H 5.85 (d, J = 16.0 Hz) and 7.13 (d, J = 16.0 Hz), three oxygenated methines at δ_H 3.61 (m), 4.02 (m), and 5.06 (m), and two methylene groups at δ_H 1.82 (2H, m), 1.79 (1H, m), and 1.96 (1H, m). The ^{13}C-NMR spectrum confirmed the presence of 16 carbon atoms, including two carbonyl carbons at δ_C168.9 and 180.8, six aromatic carbons at δ_C114.8, 115.8, 122.5, 126.6, 143.9, and 146.8, two olefinic carbons at δ_C 113.9 and 145.8, four oxygenated methines at δ_C 70.6, 70.9, 72.8, and 76.7, and two methylenes at δ_C 37.1 and 38.3 (Table 1). The analysis of the ^{1}H and ^{13}C-NMR brought three spin systems relative to the C_2–C_6 segment, the C_7–C_8 *trans*, disubstituted ethylene moiety defined a tri-substituted aromatic ring type ABX spin system (Fig. 1). The HMBC correlations between H-2 (δ_H 1.82) and C-1 (δ_C 76.7)/C-7 (δ_C 180.8) and between H-6 (δ_H 1.79 and 1.96) and C-7 suggested the carboxyl and hydroxyl groups at C-1. The *trans* configuration of the double bond and carbonyl group were indicated at C-7′/C-8′ and C-9′, respectively, confirmed by the HMBC correlations from H-7′ (δ_H 7.13) to C-2′ (δ_C 114.8)/C-6′ (δ_C 122.5)/C-8′ (δ_C 113.9)/C-9′ (δ_C 168.9); from H-8′ (δ_H 5.85) to C-9′ and C-1′ (δ_C 126.6). The HMBC correlations between H-2′ (δ_H 6.70) and C-1′/C-3′ (δ_C 143.9)/C-4′ (δ_C 146.8); H-5′ (δ_H 6.56) and C-3′/C-4′ indicated two

hydroxy groups located at C-3′ and C-4′. In addition, the caffeoyl moiety linked to quinic acid at C-5 by the HMBC correlations between H-5 and C-9′ (Fig. 2). Furthermore, the ESI-MS of **1** exhibited an ion at *m/z* 355 $[M+H]^+$, corresponding to the molecular formula of $C_{16}H_{18}O_9$. Thus, compound **1** was elucidated to be 5-*O*-caffeoyl quinic acid or chlorogenic acid, a compound that was previously isolated from *I. dentata* [12]. Its NMR data were also found to match well with previous data [12].

Table 1. NMR data for compounds **1**-**3**.

C		**1**	**C**		**2**		**3**
	δ_C	δ_H (**mult., *J* in Hz**)		δ_C	δ_H (**mult., *J* = Hz**)	δ_C	δ_H (**mult., *J* = Hz**)
1	76.7	-	1	76.4		75.6	-
2	37.1	1.82 (m)	2	37.7	2.26 (d, 14.0) 2.20 (d, 14.0)	38.1	2.05 (m)
3	70.6	4.02 (m)	3	74.5	5.37 (br s)	67.7	4.11 (m)
4	72.8	3.61 (m)	4	72.5	3.89 (d, 7.0)	74.6	5.17 (m)
5	70.9	5.06 (m)	5	73.3	5.53 (m)	69.9	5.61 (m)
6	38.3	1.79 (m) 1.96 (m)	6	41.0	2.09 (m)	39.7	2.05 (m) 2.18 (m)
7	180.8	-	7	181.7	-	181.9	-
1′	126.6	-	1′, 1″	127.7 128.0	- -	127.5 127.6	- -
2′	114.8	6.70 (s)	2′, 2″	116.4 116.5	6.78 (d, 2.0) 6.78 (d, 2.0)	114.9 115.1	6.99 (s) 7.03 (s)
3′	143.9	-	3′, 3″	149.5	-	146.8 146.9	- -
4′	146.8	-	4′, 4″	149.7	-	149.8 150.0	- -
5′	115.8	6.56 (d, 8.0)	5′, 5″	115.0 115.1	7.05 (d, 8.0) 7.05 (d, 8.0)	116.4 116.5	6.71 (d, 8.0) 6.73 (d, 8.0)
6′	122.5	6.60 (d, 8.0)	6′, 6″	122.9 123.0	6.95 (dd, 2.0, 8.0) 6.95 (dd, 2.0, 8.0)	123.2 123.3	6.85 (d, 8.0) 6.90 (d, 8.0)
7′	145.8	7.13 (d, 16.0)	7′, 7″	146.8 146.9	7.58 (d, 16.0) 7.58 (d, 16.0)	147.2 147.4	7.49 (d, 16.0) 7.56 (d, 16.0)
8′	113.9	5.85 (d, 16.0)	8′, 8″	116.0 115.4	6.40 (d, 16.0) 6.28 (d, 16.0)	114.8 114.9	6.22 (d, 16.0) 6.28 (d, 16.0)
9′	168.9	-	9′, 9″	169.0 169.4	- -	168.4	-

Compound **2** was isolated as a white amorphous powder. Compound **2** possessed a molecular formula of $C_{25}H_{24}O_{12}$, deduced from ESI-MS at *m/z* 517 $[M+H]^+$. The ^{1}H-NMR spectrum of **2** showed six aromatic protons belonging to two ABX aromatic spin systems, four olefinic protons of two *trans* double bonds due to the large coupling constants (J = 16.0 Hz), three oxygenated methines, and two methylenes. The ^{13}C-NMR spectrum of **2** showed signals of 25 carbons, including three carbonyl carbons, four olefinics, twelve aromatics, three oxygenated methines, two methylenes, and one quaternary carbon. The analysis of ^{1}H- and ^{13}C-NMR data indicated that the structure of **2** was similar to that of **1** except for an addition of one caffeoyl

moiety. Thus, the structure of **2** was proposed as 3,5-di-*O*-caffeoylquinic acid. Furthermore, the NMR and ESI-MS data of **2** were compared and well agreed with those of 3,5-di-*O*-caffeoylquinic acid in the literature. Thus, compound **2** was established to be 3,5-di-*O*-caffeoylquinic acid, a compound previously isolated from *Chrysanthemum coronarium* [13].

Compound **3** was obtained as a white amorphous powder. The molecular formula of **3** was determined as $C_{25}H_{24}O_{12}$, the same as that of **2** because they had the same *pseudo* ion pick at *m/z* 517 $[M+H]^+$ in the ESI-MS. In addition, the NMR spectra of **3** were almost similar to the corresponding spectra of **2**. These suggested that they were constitutional isomers. Thus, the structure of **3** was proposed as 4,5-di-*O*-caffeoylquinic acid, an isomer of **2** in which the location of the additional caffeoyl moiety was at C-4 of quinic acid. Moreover, the NMR data of **3** were compared to the corresponding data of 4,5-di-*O*-caffeoylquinic acid, a compound previously isolated from *Chrysanthemum coronarium* [13] and found to match well. Thus, the structure of **3** was determined.

Compound **4** was obtained as a white amorphous powder. The ^{1}H-NMR spectrum showed three aromatic proton signals at δ_H 7.06 (1 H, d, J = 8.0 Hz, H-6), 6.80 (1H, s, H-3), 6.70 (1H, d, J = 8.0 Hz, H-5); three olefinic protons at δ_H 5.92 (1H, m, H-8) and 5.01 (2H, dd, J = 9.6, 15.8 Hz, H-9); two methylene protons at δ_H 3.31 (2H, m, H-7); and a methoxy group at δ_H 3.81 (3H, s). Moreover, typical signals due to a glucosyl moiety were observed at δ_H 4.82 (1H, d, J = 7.5 Hz, H-1′), 3.82 (1H, d, J = 11.6 Hz, H_{glc}-6′a), and 3.66 (1H, dd, J = 5.4, 11.6 Hz, H_{glc}-6′b), of which the coupling constant of anomeric proton indicated the *β*-linkage with the aglycone. The ^{13}C-NMR spectrum showed signals due to D-glucopyranoside, trisubstituted aromatic carbons at δ_C 150.8 (C-2), 146.3 (C-1), and 136.4 (C-4), aromatic carbons at δ_C 122.1 (C-5), 114.1 (C-3), and 118.2 (C-6); two olefinic carbons at δ_C 139.0 (C-8) and 115.9 (C-9); and one methoxy carbon at δ_C 56.7. The location of the double bond at C-8/C-9 was indicated by the HMBC correlations between H-8 (δ_H 5.92) and C-4 (δ_C 136.4)/C-7 (δ_C 40.8)/C-9 (δ_C 115.9) and between H-9 (δ_H 5.01) and C-7, C-8 (δ_C 139.0). The methoxy group was located at C-2, confirmed by HMBC correlations between the methoxy group at δ_H 3.81 and C-2 (δ_C 150.8). The HMBC correlation from H-1′ (δ_H 4.82) to C-1 (δ_C 146.3) confirmed the *β*-D-glucopyranoside linked to the aromatic ring at C-1 (Fig. 2). Consequently, compound **4** was determined to be citrusin C. Its ^{1}H and ^{13}C NMR data were identical with those reported in the literature [14].

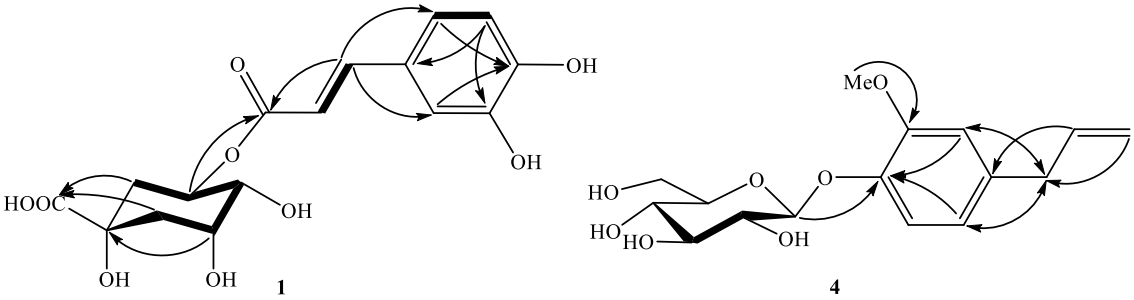

Figure 2. Key HMBC correlations of compounds **1** and **4**.

Compound **5** was isolated as a white amorphous powder. It showed identical NMR signals with those of compound **4** except for adding a methoxy group at δ_H 3.80 and δ_C 57.0. Comparing the NMR data of **5** with those reported in the literature, **5** was identified as 4-allyl-2,6-dimethoxyphenol *O*-*β*-D-glucopyranoside [15].

Compound **6** was obtained as a white amorphous powder. The molecular formula of **6** was established as $C_{21}H_{28}O_9$ at *m/z* 447 $[M+Na]^+$ by ESI-MS. The ^1H NMR spectrum showed three exocyclic methylene resonances at δ_H 5.63 (d, J = 3.5 Hz) and 6.26 (d, J = 3.5 Hz); 4.91 (s) and 5.06 (s); 5.35 (d, J = 2.0 Hz) and 5.41 (d, J = 2.0 Hz) and the β-linkage of the glucopyranosyl moiety was deduced from the coupling constant J = 7.8 Hz of the anomeric proton signal at δ_H 4.44 as listed in Table 2.

Table 2. NMR data for compounds **4**-**7**.

C		**4**		**5**			**6**		**7**
	δ_C	**δ_H (mult., *J*, Hz)**	**δ_C**	**δ_H (mult., *J*, Hz)**		**δ_C**	**δ_H (mult., *J*, Hz)**	**δ_C**	**δ_H (mult., *J*, Hz)**
1	146.3	-	138.4	-	1	46.5	2.97 (m)	45.3	2.93 (m)
2	150.8	-	154.2	-	2	38.8	1.94 (m) 2.32 (m)	38.6	1.92 (m) 2.33 (m)
3	114.1	6.80 (s)	107.4	6.51 (s)	3	81.4	4.62 (m)	81.5	4.60 (m)
4	136.4	-	134.6	-	4	150.9	-	150.8	-
5	122.1	6.70 (d, 8.0)	107.4	6.51 (s)	5	52.3	2.73 (t, 9.6)	51.0	2.77 (m)
6	118.2	7.06 (d, 8.0)	154.2	-	6	79.7	4.58 (m)	80.2	4.45 (m)
7	40.8	3.31 (m)	41.4	3.18 (m)	7	50.6	3.05 (m)	49.0	3.20 (m)
8	139.0	5.92 (m)	138.7	5.94 (ddt, 6.5, 10.0, 17.0)	8	67.1	4.30 (m)	69.3	5.46
9	115.9	5.01 (dd, 9.6, 15.8)	116.2	5.03 (d, 10.0) 5.08 (d, 17.0)	9	42.7	2.37 (dd, 6.6, 14.0) 2.54 (dd, 6.0, 14.0)	41.4	2.48 (m)
2-OMe	56.7	3.81 (s)	57.0	3.80 (s)	10	145.4	-	144.4	-
6-OMe			57.0	3.80 (s)	11	137.8	-	136.7	-
1-*O*-Glc					12	172.2	-	171.3	-
1′	103.1	4.82 (d, 7.5)	105.5	4.79 (d, 7.5)	13	122.4	5.63 (d, 3.5) 6.26 (d, 3.5)	122.3	5.41 (s) 6.01 (s)
2′	74.9	3.44	75.7	3.44	14	117.0	4.91 (s) 5.06 (s)	117.7	5.03 (s) 4.75 (s)
3′	78.2	3.44	78.3	3.44	15	113.4	5.35 (d, 2.0) 5.41 (d, 2.0)	112.5	5.31 (s) 5.46 (s)
4′	71.4	3.36	71.3	3.38	1′	103.4	4.44 (d, 7.8)	103.9	4.38 (d, 7.2)
5′	77.8	3.18	77.8	3.18	2′	75.3	3.21	75.3	3.23
6′	62.5	3.66 (dd, 5.4, 11.6) 3.82 (d, 11.6)	62.6	3.64 (dd, 5.1, 12.0) 3.76 (dd, 3.2, 12.0)	3′	78.1	3.31	78.2	3.33
					4′	71.7	3.25	71.7	3.26
					5′	77.9	3.23	77.9	3.24
					6′	62.8	3.64 (dd, 5.6, 11.4) 3.85 (d, 11.4)	62.8	3.64 (dd, 4.6, 11.6) 3.85 (d, 11.6)
					α			172.9	-
					β			41.2	3.45 (s)
					1″			126.1	-
					2″, 6″			131.4	6.97 (d, 8.0)
					3″, 5″			116.3	6.67 (d, 8.0)
					4″			157.6	-

The characteristic coupling pattern of the oxymethine proton at δ_H 4.58 (1H, m), assignable to the lactonic proton at C6, indicated the *trans*-diaxial disposition of the protons at C-5 (α), C-6 (β), and C-7 (α), which strongly suggested the skeleton of a guaiane-type sesquiterpene lactone.

The ^{13}CNMR and DEPT spectra of **6** revealed signals of 21 carbons, including one carbonyl carbon at δ_C 172.2, two quaternary carbons at δ_C 137.8, 145.4, eleven methines (δ_C 46.5, 50.6, 52.3, 67.1, 71.7, 75.3, 77.9, 78.1, 79.7, 81.4, and 103.4), and six methylenes (δ_C 38.8, 42.7, 62.8, 113.4, 117.0 and 122.4). Among them, ^{13}C-NMR chemical shifts of C-1′ (δ_C 103.4), C-2′ (δ_C 75.3), C-3′ (δ_C 78.1), C-4′ (δ_C 71.7), C-5′ (δ_C 77.9), and C-6′ (δ_C 62.8) suggested the presence of glucopyranosyl sugar moiety. The NMR data of **6** were similar to those of 8-epidesacylcynaropicrin glucoside [16]. Thus, compound **6** was established as an 8-epidesacylcynaropicrin glucoside, a compound previously isolated from this species [17].

Compound **7** was obtained as a white amorphous powder. Its ESI-MS showed a pseudo-molecular ion peak *m/z*517 $[M+H]^+$, corresponding to the molecular formula of $C_{29}H_{34}O_{11}$. The NMR data of **7** were closely comparable to those of **6**, except for adding a *p*-hydroxy phenylacetyl group in the molecule. These signals clearly showed that the *para* coupling protons pattern at [(δ_H 6.97 (d, J = 8 Hz), H-2″, H-6″); and (δ_H 6.67 (d, J = 8 Hz), H-3″, H-5″)] and acetylphenyl signals at δ_C 172.9 and 41.2 in the NMR spectrum of **7**. The comparison of the NMR data of compound **7** with the reference [18] suggested that **7** was ixerisoside A.

4. CONCLUSION

Five phenolics, chlorogenic acid (**1**), 3,5-Di-*O*-caffeoylquinic acid (**2**), 4,5-Di-*O*-caffeoylquinic acid (**3**), citrusin C (**4**), 4-allyl-2,6-dimethoxyphenol *O*-*β*-D-glupyranoside (**5**)**,** and two sesquiterpene lactones 8-epidesacylcynaropicrin glucoside (**6**), ixerisoside A (**7**) were isolated from the leaves of *Ixeris dentata* using combined chromatographic methods.

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CRediT authorship contribution statement: Nguyen Tien Dung: research idea, isolation, Le Thi Huyen: research idea, structure elucidation, writing.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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