Saponins from Roots of *Kalopanax septemlobus* (THUNB.) KOIDZ., Ciqiu: Structures of Kalopanax-saponins C, D, E and F

Chun-Jie SHAO,[a] Ryoji KASAI,[b] Jing-Da XU[a] and Osamu TANAKA*,[b]

Department of Chemistry, Bethune University of Medical Sciences,[a] Xinmin Street 6, Changchun, China and Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine,[b] Kasumi, Minami-ku, Hiroshima 734, Japan. *Received August 10, 1988*

Four new triterpenoid saponins named kalopanax-saponins C (4), D (5), E (6) and F (7) were isolated from the roots of *Kalopanax septemlobus* (THUNB.) KOIDZ. together with three known saponins, kalopanax-saponins A (1) and B (2), and chikusetsusaponin IV (3). On the basis of chemical and spectral data, the structures of these new saponins were elucidated to be as follows: (4), 3-*O*-α-rhamnopyranosyl-(1→2)-[β-glucopyranosyl-(1→3)]-α-arabinopyranosyl hederagenin 28-*O*-α-rhamnopyranosyl-(1→4)-β-glucopyranosyl-(1→6)-β-glucopyranosyl ester; (5), 3-*O*-α-rhamnopyranosyl-(1→2)-[β-glucopyranosyl-(1→3)]-α-arabinopyranosyl oleanolic acid 28-*O*-α-rhamnopyranosyl-(1→4)-β-glucopyranosyl-(1→6)-β-glucopyranosyl ester; (6), 3-*O*-β-glucopyranosyl-(1→3)-β-glucuronopyranosyl oleanolic acid; (7), 3-*O*-α-arabinopyranosyl-(1→2)-[β-glucopyranosyl-(1→3)]-β-glucuronopyranosyl oleanolic acid 28-*O*-β-glucopyranosyl ester.

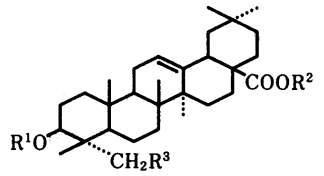
Keywords *Kalopanax septemlobus*; Araliaceae; saponin; kalopanax-saponin; oleanolic acid glycoside; hederagenin glycoside; Chinese folk medicine; ciqiu

The roots of *Kalopanax septemlobus* (THUNB.) KOIDZ. (Chinese name: 刺楸, ciqiu, Japanese name: harigiri) (Araliaceae) have been used as an anti-rheumatic, anti-inflammatory, expectorant and tranquilizer in China.[1] The isolation and structural determination of hederagenin saponins named kalopanax-saponins A (**1**) and B (**2**), have already been reported.[2] In our continuing studies on the chemical constituents of Araliaceous plants, we have re-investigated the triterpenoid saponins of roots of this plant collected in Jilin district, North-East China. This paper deals with the isolation and structural elucidation of four new saponins and the identification of three known saponins.

A suspension of the methanol extract of the roots in water was washed with ethyl acetate and then extracted with 1-butanol saturated with water. The butanol extract was chromatographed on silica gel and finally purified by recrystalization or high-performance liquid chromatography (HPLC) to give seven saponins, **1**—**7**, in yields of 0.02, 1.64, 0.01, 0.08, 0.03, 0.002 and 0.02%, respectively.

Based on analysis of the proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra and the results of acid and alkaline hydrolysis as well as comparison of the optical rotations, **1** and **2** were proved to be identical with kalopanax-saponins A and B, respectively.[2] Compound **3** was identified as chikusetsusaponin IV, which has already been isolated from rhizomes of *Panax japonicus*,[3] by direct comparison of the ^{13}C-NMR spectra and optical rotation with those of an authentic sample.

On acid hydrolysis, the new saponin **4** gave hederagenin (**8**), glucose, arabinose and rhamnose. In the ^{13}C-NMR spectrum of **4**, the signals due to the aglycone moiety were in good agreement with those of the 28-glycosyl ester of 3-*O*-glycosyl hederagenin (bisdesmoside of **8**)[4] and those due to the sugar moiety showed the presence of six monosaccharide units. On selective cleavage of the ester-glycoside linkage with anhydrous LiI and 2,6-lutidine in anhydrous methanol,[5] **4** afforded a prosapogenin (**9**) and a methyl trisaccharide (**10**) which was identified as methyl α-rhamnopyranosyl-(1→4)- β-glucopyranosyl-(1→6)- (α and β)-glucopyranoside by comparison of the ^{13}C-NMR spectrum with that of an authentic sample of **10**.[5] Acid hydrolysis of **9** gave **8**, glucose, arabinose and rhamnose. The sugar sequence analysis of permethylated **9** showed the presence of 2,3-linked arabinopyranoside, terminal glucopyranoside and terminal rhamnopyranoside, leading to the formulation of the sugar moiety of **9** as Rha-(1→2)-[(Glc-(1→3)]-Ara or Glc-(1→2)-[Rha-(1→3)]-Ara. The locations of rhamnosyl and glucosyl linkages on the arabinose moiety



	R¹	R²	R³
1:	–Ara(p)[2]–Rha	–H	–OH
2:	–Ara(p)[2]–Rha	–Glc[6]–Glc[4]–Rha	–OH
3:	–GlcUA[4]–Ara(f)	–Glc	–H
4:	–Ara(p)[2]–Rha [3] Glc	–Glc[6]–Glc[4]–Rha	–OH
5:	–Ara(p)[2]–Rha [3] Glc	–Glc[6]–Glc[4]–Rha	–H
6:	–GlcUA[3]–Glc	–H	–H
7:	–GlcUA[2]–Ara(p) [3] Glc	–Glc	–H
8:	–H	–H	–OH
9:	–Ara(p)[2]–Rha [3] Glc	–H	–OH
11:	–H	–H	–H
12:	–Ara(p)[2]–Rha [3] Glc	–H	–H
13:	–GlcUA	–H	–H
14:	–GlcUA[2]–Ara(p) [3] Glc	–H	–H

Ara(p): α-arabinopyranosyl, Ara(f): α-arabinofuranosyl, Rha: α-rhamnopyranosyl, Glc: β-glucopyranosyl, GlcUA: β-glucuronopyranosyl

Chart 1

were confirmed as follows. In the two dimensional nuclear Overhauser effect correlation spectroscopy (2D NOESY) spectrum of **9**, cross peaks were observed between H-1 of the rhamnoside moiety and H-2 of the arabinoside moiety as well as between H-1 of the glucoside moiety and H-3 of the arabinoside moiety. The anomeric configuration of each sugar unit was determined by ^{1}H- and ^{13}C-NMR spectroscopy. Based on these results, the structure of **4** was formulated as shown in Chart 1.

The new saponin **5** afforded oleanolic acid (**11**), glucose, rhamnose and arabinose on acid hydrolysis. The ^{13}C-NMR spectrum of **5** showed that **5** is a bisdesmoside of **11** having six monosaccharide units. The selective cleavage of the ester-glycoside linkage (*vide supra*) of **5** gave **12** as a prosapogenin and a methyl trisaccharide, **10**. The carbon signals due to the sugar moiety of **12** were almost superimposable on those of **9**. Furthermore, the 2D NOESY spectrum of **12** also showed the same correlation as in the case of **9**. These observations led to the formulation of **5** as shown in Chart 1.

On acid hydrolysis, the new saponin **6** gave oleanolic acid (**11**), glucose and glucuronic acid. Based on analysis of the ^{1}H- and ^{13}C-NMR spectra, **6** was formulated as a monodesmoside of **11** (3-*O*-glycoside). In a comparison of the ^{13}C-NMR spectrum of **6** with that of 3-*O*-β-glucuronopyranosyl oleanolic acid (**13**),[6] on going from **13** to **6**, the signals due to C-3 of the glucuronide moiety were displaced downfield by 10.6 ppm, and the signals due to C-2 and C-4 were moved upfield by 0.8 and 0.8 ppm, respectively, while other signals remained almost unshifted. It follows that **6** can be formulated as shown in Chart 1.

On acid hydrolysis, the new saponin **7** gave oleanolic acid (**11**), arabinose, glucose and glucuronic acid. Inspection of the ^{13}C-NMR spectrum of **7** suggested that **7** is a bisdesmoside of **11** with four monosaccharide units. On alkaline hydrolysis, **7** yielded a prosapogenin, **14**, and 1,6-anhydroglucose, indicating the presence of a β-glucopyranosyl ester at the 28-carboxyl group of **7**.[6] Acid hydrolysis of **14** gave **11**, arabinose, glucose and glucuronic acid. On mild acid hydrolysis, **14** yielded two partially hydrolyzed products which were identified as **6** and **13** by comparison of the physical and spectral data with those of authentic samples. The comparison of the ^{13}C-NMR spectrum of **14** with that of **6**, with a consideration of the glycosylation shifts, established the position of the arabinose to be at C-2 of the glucuronide moiety. These results suggested that **7** can be formulated as shown in Chart 1.

These new saponins, **4**—**7**, are named kalopanaxsaponins, C, D, E and F, respectively.

Experimental

Melting points were measured with a micro hot-stage and are uncorrected. Optical rotations were taken on a Union PM-101 automatic digital polarimeter. NMR spectra were recorded on JEOL FX-100 and GX-400 spectrometers in C_5D_5N solution using tetramethylsilane (TMS) as an internal standard. For gas-liquid chromatography (GLC), a Shimadzu GC-6A apparatus was used. GC-MS were taken on a Shimadzu GCMS-7000S; glass column (2.6 mm × 1.5 m) packed with 5% ECNSS-M on Chromosorb W, injection temperature 220 °C, column temperature 175 °C, carrier gas, He at 15 ml/min, separator temperature 270 °C, ionization voltage 70 eV, accelerating voltage 1.5 kV. HPLC was carried out on a column of TSK-gel ODS-120T (21.5 mm × 30 cm) with a Toyo Soda HLC 803D pump and a Toyo Soda RI-8 differential refractometer as a detector. For column chromatography, Kieselgel 60 (70—230 mesh, Merck) was used.

Acid hydrolysis of saponins followed by identification of the resulting

TABLE I. ^{13}C-NMR Chemical Shifts of Aglycone Moieties in C_5D_5N

Carbon No.	1	2	4	9	5	12	7	14	3	6	13[6]
1	38.9	39.0	39.0	39.1	39.1	39.2	38.6	38.6	38.8	38.8	38.8
2	26.0	26.0	26.0	26.2	26.5	26.5	26.1	26.2	26.2	26.5	26.4
3	81.1	81.0	81.0	80.6	88.2	88.2	89.7	89.7	89.7	89.3	89.5
4	47.7	47.7	47.7	47.8	39.5	39.6	39.6	39.7	39.7	39.5	39.5
5	43.5	43.4	43.4	43.5	56.0	56.0	55.7	55.8	55.7	55.9	55.9
6	18.5	18.5	18.4	18.5	18.5	18.5	18.5	18.5	18.4	18.6	18.5
7	32.8	33.1	33.1	33.2	33.1	33.2	33.1	33.2	33.1	33.2	33.3
8	39.7	39.9	39.8	39.7	39.9	39.7	39.6	39.7	39.9	39.9	39.9
9	48.1	48.2	48.3	48.2	48.1	48.0	48.0	48.0	48.0	48.1	48.5
10	36.8	36.8	36.8	36.9	37.0	37.0	36.8	36.9	36.9	37.1	37.1
11	23.8	23.6	23.6	23.8	23.7	23.7	23.6	23.7	23.7	23.8	23.7
12	122.6	122.9	122.6	122.6	122.5	122.5	122.6	122.6	122.5	122.6	122.6
13	144.8	144.1	144.0	144.8	144.1	144.8	144.1	144.8	144.2	144.8	144.8
14	42.1	42.1	42.1	42.1	42.1	42.1	42.1	42.1	42.1	42.3	42.3
15	28.3	28.0	28.3	28.2	28.1	28.1	27.7	28.3	28.2	28.2	28.2
16	23.8	23.6	23.6	23.8	23.7	23.7	23.6	23.7	23.7	23.8	23.7
17	46.6	47.0	46.9	46.6	47.0	46.6	46.9	46.6	47.0	46.7	48.0
18	41.9	41.6	41.7	42.1	41.6	41.9	41.7	41.9	41.7	42.1	42.3
19	46.4	46.3	46.6	46.6	46.6	46.6	46.9	46.6	46.7	46.7	46.8
20	30.9	30.7	30.7	30.9	30.7	30.9	30.7	30.9	30.8	30.9	30.9
21	34.2	34.0	34.2	34.3	33.7	34.2	34.0	34.2	34.0	34.4	34.4
22	32.6	32.7	33.1	33.2	32.9	33.2	33.1	33.2	32.6	33.2	33.3
23	63.9	64.0	63.8	63.9	28.1	28.1	27.7	27.7	28.2	28.2	28.3
24	13.9	13.9	13.9	14.0	17.0	17.0	16.3	16.3	17.0	16.9	16.9
25	16.0	16.1	16.2	16.1	15.7	15.5	15.5	15.4	15.5	15.4	15.4
26	17.4	17.5	17.4	17.4	17.5	17.4	17.4	17.3	17.4	17.4	17.4
27	26.1	26.0	26.1	26.2	26.1	26.2	26.1	26.2	26.2	26.2	26.4
28	180.1	176.5	176.5	180.2	176.5	180.1	176.8	180.1	176.5	180.0	180.0
29	32.8	33.1	33.1	33.2	33.1	33.2	33.1	33.2	33.1	33.2	33.3
30	23.8	23.6	23.6	23.8	23.7	23.7	23.6	23.7	23.7	23.8	23.7

TABLE II. ^{13}C-NMR Chemical Shifts of Sugar Moieties in C_5D_5N

Carbon No.	1	2	4	9	5	12	Carbon No.	7	14	3	6	13[6]
3-*O*-Sugar												
Ara 1	104.2	104.2[a]	104.6[a]	104.9[a]	104.6[a]	104.6	GlcUA 1	105.1	105.2	106.8	106.4	106.3
Ara 2	75.8	75.7[c]	74.8	74.4[b]	74.6[d]	74.8[a]	GlcUA 2	78.8	79.0	75.4	74.2	75.0
Ara 3	74.5[b]	74.4	83.0	83.1	81.9	82.1	GlcUA 3	87.7	87.8	76.3	87.9	77.3
Ara 4	69.6	69.6	68.7	68.2	68.1	68.1	GlcUA 4	72.8	72.8	78.9[a]	71.7[a]	72.5
Ara 5	65.5	65.5	65.5	65.5	64.7	64.8	GlcUA 5	77.2	77.2	76.3	77.2	77.3
Rha 1	101.6	101.6	101.6	101.7[a]	101.8	101.8	GlcUA 6	172.0	171.8	172.3	172.0	172.5
Rha 2	72.3[a]	72.2[b]	72.4	72.5[b]	72.4	72.3	Glc 1	104.6	104.6		105.7	
Rha 3	72.5[a]	72.5[b]	72.4	72.5	72.4	72.3	Glc 2	76.0	76.1		75.4	
Rha 4	74.0[b]	73.8	73.8	73.9	73.8[c]	73.8	Glc 3	77.2	77.2		78.1[b]	
Rha 5	69.2	69.1	69.8	69.8	70.0	69.9	Glc 4	71.8[a]	71.8[a]		71.6[a]	
Rha 6	18.5	18.5	18.4	18.5	18.5	18.5	Glc 5	78.8	79.0		78.5[b]	
Glc 1			104.2[a]	104.2	104.5[a]	104.6	Glc 6	61.9	61.9		62.6	
Glc 2			74.8	74.9	74.8[d]	74.9[a]	Ara 1	105.1	105.2	108.3		
Glc 3			78.3	78.5	78.1[c]	78.1[b]	Ara 2	71.3[a]	71.3[a]	82.4		
Glc 4			71.2	71.4	71.4	71.4	Ara 3	75.2	75.3	78.2[a]		
Glc 5			78.3	78.3	78.3[c]	78.5[b]	Ara 4	70.0	70.0	87.4		
Glc 6			62.4	62.5	62.5	62.4	Ara 5	67.0	67.1	62.5[b]		
28-*O*-Sugar												
Inner Glc 1		95.6	95.6		95.6		Glc 1	95.7		95.8		
Glc 2		73.8	73.8		73.8[c]		Glc 2	74.0		74.1		
Glc 3		78.3	78.3		78.1		Glc 3	78.8		78.9[a]		
Glc 4		70.7[d]	70.6[b]		70.7[b]		Glc 4	71.0[a]		71.2		
Glc 5		76.5	76.4		76.4		Glc 5	78.8		78.2[a]		
Glc 6		70.0	70.2[b]		70.0		Glc 6	61.9		62.2[b]		
Outer Glc 1		104.7[a]	104.6[a]		104.6							
Glc 2		75.3[c]	75.3		75.3							
Glc 3		76.5	76.4		76.4							
Glc 4		78.6	78.3		78.3							
Glc 5		77.0	77.0		77.1							
Glc 6		61.2	61.2		61.2							
Rha 1		102.6	102.6		102.6							
Rha 2		72.5[b]	72.4		72.4							
Rha 3		72.3[b]	72.4		72.4							
Rha 4		73.8	73.8		73.8[c]							
Rha 5		70.2[d]	70.2		70.2[b]							
Rha 6		18.5	18.4		18.5							

a—*d*) These assignments may be interchanged in each column.

monosaccharides and determination of the sugar sequence by methylation analysis were carried out as described in the previous paper.[6,7]

Extraction and Separation of Saponins The dried roots of *Kalopanax septemlobus* (2 kg), collected in Jilin, China, were extracted with hot MeOH. A suspension of the MeOH extract (221 g) in H_2O was washed with AcOEt and then extracted with 1-BuOH. The BuOH layer was concentrated to dryness to give a crude saponin (119 g), which was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (30:10:1 and 6:4:1, homogeneous, successively) to give six fractions, frs. A, B, C, D, E and F in order of elution. Fraction A was crystallized from MeOH to give **1** (0.02%). Fractions B, C, and D were purified by HPLC with 60—70% MeOH (flow rate, 6 ml/min) to give **6** (0.002%) from fr. B, **2** (1.64%) from fr. C, **4** (0.08%) from fr. D and **5** (0.03%) from fr. E. Fraction F was chromatographed on silica gel with $CHCl_3$–MeOH–H_2O (14:6:1, homogeneous) to give **7** (0.02%) and **3** (0.01%). **1**: Colorless needles (MeOH), mp 249—250 °C (dec.), $[\alpha]_D^{22}$ +18.0° (*c*=0.61, MeOH). **2**: A white powder, $[\alpha]_D^{22}$ −7.6° (*c*=0.92, MeOH). **3**: A white powder, $[\alpha]_D^{25}$ −12.7° (*c*=0.61, MeOH). **4**: A white powder, $[\alpha]_D^{22}$ −19.3° (*c*=0.88, MeOH). *Anal.* Calcd for $C_{65}H_{106}O_{31}\cdot H_2O$: C, 55.70; H, 7.77. Found: C, 55.81; H, 7.57. ^{1}H-NMR δ: 0.88 (9H, s), 0.96 (3H, s), 1.04 (3H, s), 1.17 (3H, s), 1.62 (6H, d, *J*=6 Hz, Me of Rha), 5.40 (1H, s, H-12), 4.90, 4.98 5.06, 6.13 (each 1H, d, *J*=7 Hz, anomeric H), 5.68, 6.01 (each 1H, s, anomeric H of Rha). **5**: Colorless needles (MeOH), mp 235—236 °C, $[\alpha]_D^{22}$ −24.6° (*c*=0.57, MeOH). *Anal.* Calcd for $C_{65}H_{106}O_{30}$: C, 57.09; H, 7.81. Found: C, 56.97; H, 7.95. ^{1}H-NMR δ: 0.91 (9H, s), 1.07 (6H, s), 1.17 (3H, s), 1.25 (3H, s), 1.55, 1.62 (each 3H, d, *J*=5 Hz, Me of Rha), 5.48 (1H, s, H-12), 4.91 (2H), 4.99 (1H), 6.12 (1H) (each d, *J*=7 Hz, anomeric H), 5.66, 5.92 (each 1H, s, anomeric H of Rha). **6**: A white powder, $[\alpha]_D^{20}$ +14.2° (*c*=0.60, MeOH). *Anal.* Calcd for $C_{42}H_{66}O_{14}\cdot H_2O$: C, 82.29; H, 11.18. Found: C, 82.00; H, 11.48. ^{1}H-NMR δ: 0.84 (3H, s), 0.97 (9H, s), 1.28 (9H, s), 5.41 (1H, s, H-12), 4.92, 5.16 (each 1H, d, *J*=7 Hz, anomeric H). **7**: A white powder, $[\alpha]_D^{24}$ +7.1° (*c*=0.70, H_2O). *Anal.* Calcd for $C_{53}H_{84}O_{23}\cdot H_2O$: C, 57.49; H, 7.83. Found: C, 57.37; H, 7.95. ^{13}C-NMR data of **1**—**7** were given in Tables I and II.

Aglycones of 4—7 A solution of saponin in 2 N HCl–MeOH was heated under reflux and then neutralized with Ag_2CO_3. The precipitate was filtered off and the filtrate was concentrated. The residue was crystallized from MeOH to give **8** from **4** and **11** from **5**, **6** and **7**; these products were identified as hederagenin and oleanolic acid, respectively, by comparison of the melting point and spectral data with those of authentic samples.

Selective Cleavage of the Ester-Glycoside Linkage of 4 and 5 According to the reported method,[5] **4** and **5** afforded **9** and **12**, respectively, along with a common methyl trisaccharide **10**, which was identified by comparison of the ^{13}C-NMR spectrum with that of an authentic sample. **9**: A white powder, $[\alpha]_D^{24}$ +3.7° (*c*=0.54, MeOH). *Anal.* Calcd for $C_{47}H_{76}O_{17}\cdot H_2O$: C, 60.62; H, 8.44. Found: C, 60.61; H, 8.54. ^{1}H-NMR δ: 0.86 (3H, s), 0.92 (6H, s), 0.98 (3H, s), 1.07 (3H, s), 1.22 (3H, s), 5.46 (1H, s, H-12), 4.99, 5.08 (each 1H, d, *J*=7 Hz, anomeric H), 6.21 (1H, s, anomeric H of Rha). **12**: A white powder, $[\alpha]_D^{25}$ −3.3° (*c*=0.61, MeOH). *Anal.* Calcd for $C_{47}H_{76}O_{16}\cdot H_2O$: C, 61.69; H, 8.59. Found: C, 61.87; H, 8.60. ^{1}H-NMR δ: 0.94 (3H, s), 0.98 (6H, s), 1.01 (3H, s), 1.12 (3H, s), 1.22 (3H, s), 1.32 (3H, s), 1.62 (3H, d, *J*=5 Hz, Me of Rha), 5.48 (1H, s, H-12), 4.88 (1H, d, *J*=6 Hz, anomeric H), 5.10 (1H, d, *J*=7 Hz, anomeric H), 6.16 (1H, s, anomeric H of Rha).

Alkaline Saponification of 7 According to the reported method,[6] alkaline saponification of **7** with 0.5 N aqueous KOH afforded **14** along with 1,6-anhydroglucose. **14**: A white powder, $[\alpha]_D^{24}$ +16.4° (*c*=0.61, MeOH). *Anal.* Calcd for $C_{47}H_{74}O_{18}\cdot 2H_2O$: C, 58.39; H, 8.17. Found: C, 58.35; H, 7.96.

Partial Hydrolysis of 14 A solution of **14** (60 mg) in aqueous 1.5% H_2SO_4 (15 ml) was heated at 70 °C for 16 h. The reaction mixture was diluted with H_2O and then extracted with 1-BuOH saturated with H_2O. The BuOH layer was washed with H_2O and concentrated to dryness. The residue was purified by silica gel column chromatography with $CHCl_3$–MeOH–H_2O (14 : 6 : 1, homogeneous) to give **13** (11 mg) and **6** (13 mg), identification of which was achieved by comparison of the ^1H- and ^{13}C-NMR spectra, as well as optical rotation, with those of authentic samples.

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