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A New Saponin from the Seeds of *Zizyphus jujuba* var. *spinosa*

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Sour jujube (*Zizyphus jujuba* Miller var. *spinosa* Hu ex H. F. Chou) is a thorny, rhamnaceous deciduous plant distributed widely throughout tropical and subtropical regions. The dried seeds are named sanjoin (Zizyphi Spinosi Semen) in Korean and have a thousand-year history of use in traditional medicine as a sedative for treating mild anxiety, nervousness and sleep-related problems.[1] Previous phytochemical investigations on the seeds of this plant have resulted in the isolation of saponins,[2-6] flavone *C*-glycosides,[7-12] cyclopeptide alkaloids,[1] triterpenoids,[13,14] and others.[6] These compounds exhibit multiple activities, such as hypnotic,[15] histamine-release inhibitory,[4] *anti*-inflammatory[16] and sedative,[16-18] inhibition of foam cell formation,[14] adjuvant,[4] and cardiotonic[19] effects. Our previous studies focused on isolating the flavonoid-*C*-glycosides[7,8] and the sedative activities of these flavonoids.[17,18] In the continuing search for new chemicals and biomarkers from *Z. jujuba* var. *spinosa* for quality control studies of related herbal medicines, 8 flavonoids, along with 3 other known components, were isolated.[20] In the present investigation, we report the isolation and structural elucidation of a new saponin, named jujuboside A_2 (**1**), together with three known saponins, zizyphus saponin III (**2**),[21] jujuboside B (**3**),[2,21] jujuboside A (**4**),[2] and a known sesquiterpene glucoside, dihydrophaseic acid 3-*O*-*β*-D-glucopyranoside (**5**),[22] from the seeds of *Z. jujuba* var. *spinosa*.

Compound **1** was obtained as a colorless amorphous powder. Its molecular formula was established as $C_{58}H_{94}O_{26}$ from the $[M-H]^-$ peak at *m/z* 1205.5961 (Calcd for $C_{58}H_{93}O_{26}$: 1205.5955) in the HR-FAB-MS. The IR absorption bands at 3414, 1647, and 1043 cm^{-1} implied the presence of hydroxyl, double bond, and glycosidic C-O functionalities. Acid hydrolysis of compound **1** with 5% HCl afforded a mixture of ebelin lactone and 17(*Z*)-ebelin lactone as the aglycon[3] and D-glucose, 6-deoxy-L-talose, D-xylose, and L-arabinose as the sugar components identified on GLC analysis of the thiazolidine derivatives.[23] The ^{1}H- and ^{13}C-NMR spectra of **1** suggested the presence of a jujubogenin moiety [δ_H 0.72, 0.97, 1.09, 1.10, 1.38, 1.67, and 1.70 (all s, CH_3-19, CH_3-29, CH_3-18, CH_3-28, CH_3-21, CH_3-26, and CH_3-27), 3.18 (dd, *J* = 4.0, 11.7 Hz, H-3), 5.20 (br t, *J* = 9.5 Hz, H-23), and 5.53 (br d, *J* = 7.9 Hz, H-24)] and five monosaccharide units through easily identifiable signals for anomeric protons and carbons [δ_H 4.86 (d, *J* = 5.2 Hz), 4.90 (d, *J* = 7.7 Hz), 5.00 (d, *J* = 7.6 Hz), 5.43 (d, *J* = 7.3 Hz), and 6.11 (br s); δ_C 104.4, 105.2, 103.6, 106.0, and 101.7)]. The (−)-FAB-MS showed an $[M-H]^-$ ion at *m/z* 1205, which was consistent with a pentasaccharide glycoside carrying two glucose, one 6-deoxy-L-talose, two pentose (xylose and arabinose) units, and an aglycon with a molecular mass of 472. The presence of other

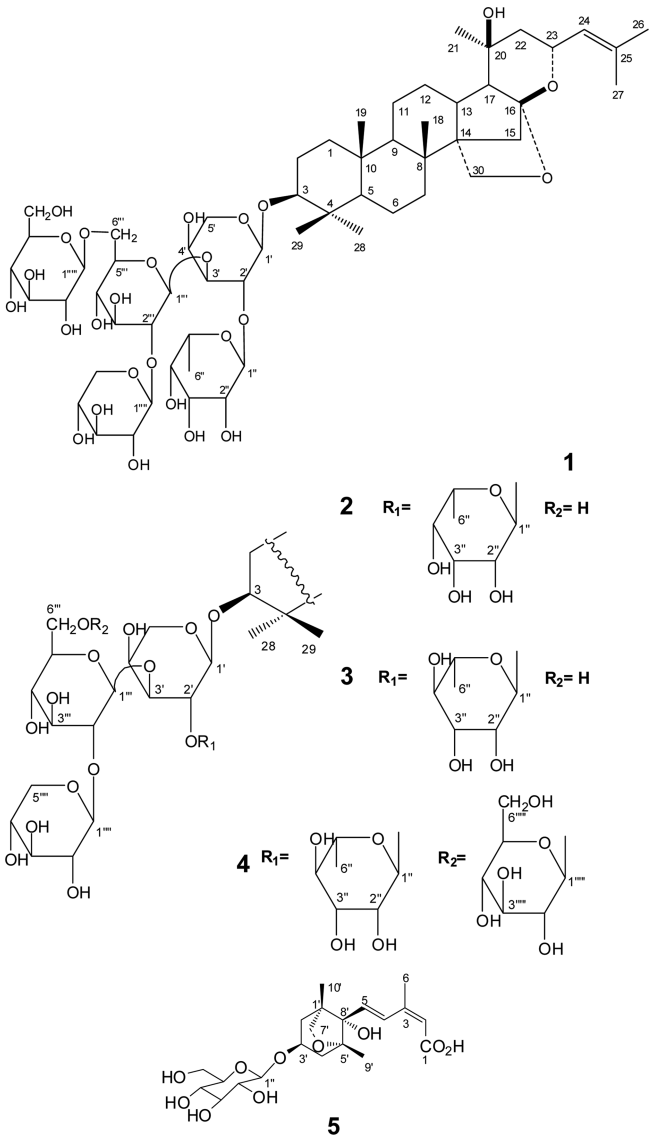

Figure 1. Structural formulas of compounds **1**–**5**.

fragment ions at *m/z* 1073 [(M–H)–132]$^-$, 1059 [(M–H)–146]$^-$, 1043 [(M–H)–162]$^-$, 911 [(M–H)–132–162]$^-$, 749 [(M–H)–132–162–162]$^-$, 603 [(M–H)–132–162–162–146]$^-$, and 471 [(M–H)–132–162–162–146–132]$^-$, supported this suggestion. Complete assignments of the ^{1}H- and ^{13}C-NMR signals of compound **1**, assigned by extensive 2D-NMR experiments, led to the identification of three terminal sugars, *β*-glucopyranosyl, *β*-xylopyranosyl, and 6-deoxy-*α*-talopyranosyl, 2,6-disubstituted *β*-glucopyranosyl, and 2,3-disubstituted *α*-arabinopyranosyl unit. The linkage sites, and sequences of the five saccharides and of the aglycon were confirmed by the HMBC experiments. The HMBC exhibited cross peaks between H-1' of the arabinose and C-3 of aglycon, H-1 of 6-deoxy-talose and C-2' of arabinose, H-1" of the inner glucose and C-3' of arabinose, H-1"" of xylose and C-2"' of the inner glucose, and H-1""" of glucose and C-6"' of the inner glucose. Thus, **1** was elucidated as jujubogenin 3-*O*-*β*-D-glucopyranosyl(1→6)-[*β*-D-xylopyranosyl(1→2)]-*β*-D-glucopyranosyl(1→3)-[6-deoxy-*α*-L-talopyranosyl(1→2)]-*α*-L-arabinopyranoside, named jujuboside A_2 (**1**), which had close similarity to jujuboside A_1, except that D-fucose in jujuboside A_1 was replaced by 6-deoxy-L-talose in **1**. Additionally, by comparing its NMR spectral data with those in the literature,[3] the ^{1}H- and ^{13}C-NMR spectral features of **1** and jujuboside A_1 were identical to each other as indicated in Table 2. The only difference was the ^{13}C-NMR chemical shift assignment of the ^{13}C-NMR chemical signals arising from C-2", C-3" and C-5" of D-fucose in jujuboside A_1 and 6-deoxy-L-talose in **1**. The known compounds were identified as zizyphus saponin III (**2**),[21] jujuboside B (**3**),[2,5,21]

Table 1. ^{1}H-NMR data[a] for sugar moieties of **1**–**4** in pyridine-d_5. δ in ppm, J in Hz

No.	**1**[b]	**2**[b]	**3**[c]	**4**[c]
	Arabinose	Arabinose	Arabinose	Arabinose
1'	4.86 (d, J = 5.2)	4.81 (d, J = 5.1)	4.88 (d, J = 3.8)	4.88 (d, J = 3.5)
2'	4.74 (t, J = 6.4)	4.74 (dd, J = 5.1, 6.9)	4.77 (t, J = 5.3)	4.72 (t, J = 5.0)
3'	4.36 (dd, J = 2.3, 9.5)	4.30 (dd, J = 2.7, 7.2)	4.30–4.34 (m)	4.30 (t, J = 4.4)
4'	4.49–4.54 (m)	4.43–4.48 (m)	4.44–4.50 (m)	4.43–4.52 (m)
5'	3.99 (br d, J = 10.6)	3.70 (dd, J = 2.3, 12.1)	3.71 (br d, J = 11.8)	3.91 (br d, J = 10.7)
	4.26 (dd, J = 3.9, 10.6)	4.23 (dd, J = 5.2, 12.1)	4.22–4.28 (m)	4.32 (dd, J = 4.4, 10.7)
	6-Deoxy-talose	6-Deoxy-talose	Rhamnose	Rhamnose
1"	6.11 (br s)	6.13 (br s)	5.96 (br s)	5.89 (br s)
2"	4.48 (br s)	4.49 (br s)	4.65 (br s)	4.60 (br s)
3"	4.42 (br s)	4.42 (br s)	4.53 (dd, J = 2.9, 9.1)	4.50 (dd, J = 3.3, 8.5)
4"	4.13 (br s)	4.11 (br s)	4.27 (t, J = 8.5)	4.27 (t, J = 8.5)
5"	4.66–4.70 (m)	4.67 (br q, J = 6.3)	4.49–4.55 (m)	4.44–4.53 (m)
6"-CH_3	1.56 (d, J = 6.4)	1.54 (d, J = 6.4)	1.63 (d, J = 6.0)	1.61 (d, J = 6.0)
	Glucose	Glucose	Glucose	Glucose
1"'	5.00 (d, J = 7.6)	5.11 (d, J = 7.6)	5.10 (d, J = 7.4)	4.95 (d, J = 7.6)
2"'	4.14 (t, J = 8.6)	4.11–4.18 (m)	4.10–4.17 (m)	4.09 (t, J = 8.4)
3"'	4.23 (t, J = 9.0)	4.26–4.33 (m)	4.14 (t, J = 8.3)	4.17–4.22 (m)
4"'	4.21 (t, J = 9.0)	4.05–4.12 (m)	4.07 (t, J = 9.0)	4.19 (t, J = 8.7)
5"'	4.03–4.07 (m)	3.91 (ddd, J = 2.5, 5.9, 9.5)	3.87–3.94 (m)	3.99–4.04 (m)
6"'	3.97 (br d, J = 10.5)	4.23 (dd, J = 5.2, 12.1)	4.17–4.21 (m)	3.88 (br d, J = 10.6)
	4.87 (br d, J = 10.5)	4.48 (br d, J = 12.1)	4.45–4.51 (m)	4.84 (br d, J = 10.6)
	Xylose	Xylose	Xylose	Xylose
1""	5.43 (d, J = 7.3)	5.40 (d, J = 7.5)	5.35 (d, J = 7.1)	5.33 (d, J = 6.4)
2""	4.18 (t, J = 7.5)	4.11–4.20 (m)	4.17 (t, J = 8.4)	4.13 (t, J = 7.0)
3""	4.14 (t, J = 8.6)	4.06–4.17 (m)	4.29 (t, J = 10.2)	4.07–4.17 (m)
4""	4.21 (t, J = 9.0)	4.14–4.21 (m)	4.13–4.22 (m)	4.12–4.22 (m)
5""	3.78 (t, J = 10.8)	3.73 (t, J = 11.0)	3.76 (t, J = 10.8)	3.77 (t, J = 11.3)
	4.49 (dd, J = 2.3, 11.9)	4.45 (dd, J = 5.5, 11.8)	4.44–4.50 (m)	4.46 (br d, J = 11.3)
	Glucose			Glucose
1"""	4.90 (d, J = 7.7)			4.85 (d, J = 7.8)
2"""	4.05 (t, J = 8.4)			3.98–4.04 (m)
3"""	4.25 (t, J = 8.8)			4.21 (t, J = 8.6)
4"""	3.84 (t, J = 9.1)			3.80 (t, J = 9.4)
5"""	3.87–3.92 (m)			3.81–3.89 (m)
6"""	4.37 (br d, J = 11.9)			4.29–4.34 (m)
	4.49 (dd, J = 2.3, 11.9)			4.46 (br d, J = 12.1)

[a]All δ_H assignments are based on 2D-NMR (^{1}H-^{1}H COSY, DEPT, HMQC, HMBC). [b]500 MHz. [c]400 MHz.

jujuboside A (**4**),[2,5] and (1*R*,3*S*,5*R*,8*S*,2*Z*,4*E*)-dihydrophaseic acid 3'-*O*-*β*-D-glucopyranoside (**5**)[22] by detailed NMR spectroscopic analysis and by comparing the physical and spectral data with those reported in the literature. Although partial NMR spectral data have been reported for some of the isolated compounds (**2**–**4**), the complete ^{1}H- and ^{13}C-NMR spectral assignments of all the isolated compounds are reported herewith for the first time based on ^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY spectroscopic data as indicated in Tables 1 and 2 and supplementary Table, which led to the revision of chemical shifts for some carbons such as C-18, C-27, C-3, and C-2" in **2**–**4** (Table 2).[5,21] The small *J* value for the H-1 of the arabinopyranosyl moiety of **3** and **4** (3.5–3.8 Hz) suggested that the arabinose ring predominantly adopts $^{1}C_4$ conformation in **3** and **4**, whereas in **1** and **2**, the arabinose ring predominantly adopts $^{4}C_1$ conformation.[23-25]

Selective 1D NOESY data obtained by irradiating the H-1' signal showed the sub-spectrum of the arabinosyl residue, which showed NOEs from H-1' to H-2', H-3', and H-5' in **3** and **4**, and from H-1' to H-3' and H-4' in **1** and **2**, respectively. These results suggest that the rhamnose moiety at C-2' in arabinose increases the population of the $^{1}C_4$ conformation.[23-25] (1'*R*,3'*S*,5'*R*,8'*S*,2*Z*,4*E*)-Dihydrophaseic acid 3'-*O*-*β*-D-glucopyranoside (**5**) has been isolated from several plant species,[22] and our study seems to be the first instance of its isolation from the genus *Zizyphus*. Ten dammarane-type triterpene glycosides such as jujubosides A,[2] B,[2,21] C,[3] E,[5] A_1 (= D),[3,6] B_1,[3] acetyljujubosides B,[3] protojujubosides A,[4] B[4] and B_1[4] have been isolated as the saponin constituents from the seeds of this plant. Among these saponins, jujubosides A, B, and A_1 have been isolated as the major components of Zizyphi Spinosi Semen,[3] but we could not isolate jujuboside A_1 from our sample.

In view of the previous report on the reducing the risk of cardiovascular disease,[26] three major saponins (**1**, **3** and **4**) were evaluated for their antiplatelet effects. Only jujuboside B (**3**) showed a significant inhibitory effect on collagen-, thrombin- and arachidonic acid-induced platelet aggregation.[27]

Table 2. ^{13}C-NMR data[a] of **1**–**4** in pyridine-d_5

No.	$\mathbf{A_1}$[5]	**1**[b]	**2**[b]	**3**[c]	**4**[c]	No.	$\mathbf{A_1}$	**1**[b]	**2**[b]	**3**[c]	**4**[c]
1	38.8	38.8	38.8	38.8	38.8	Arabinose					
2	26.6	26.5	26.6	26.5	26.4	1'	104.5	104.4	104.5	104.2	103.9
3	88.1	88.1	88.0	88.3	88.3	2'	74.6	74.6	74.5	74.9	75.1
4	39.5	39.5	39.6	39.7	39.6	3'	83.1	83.1	82.66	82.2	82.8
5	56.2	56.2	56.2	56.2	56.1	4'	68.5	68.3	68.2	67.8	67.8
6	18.3	18.3	18.3	18.4	18.3	5'	64.5	64.3	64.5	63.6	63.2
7	36.0	36.0	36.0	36.0	36.0	6-Deoxyhexose					
8	37.5	37.5	37.5	37.5	37.5	1"	101.7	101.7	101.8	101.6	101.6
9	53.0	52.9	53.0	53.0	52.9	2"	67.7	72.1	72.1	72.3	72.3
10	37.2	37.2	37.2	37.2	37.2	3"	72.1	67.0	67.1	72.5	72.5
11	21.7	21.7	21.7	21.7	21.7	4"	74.2	74.2	74.2	73.9	73.9
12	28.5	28.5	28.5	28.5	28.5	5"	67.0	67.8	67.8	70.0	70.0
13	37.1	37.1	37.1	37.1	37.1	6"	17.3	17.3	17.3	18.5	18.5
14	53.7	53.7	53.7	53.7	53.7	Glucose					
15	36.9	36.8	36.9	36.8	36.8	1'''	103.6	103.6	103.4	103.7	103.9
16	110.6	110.5	110.5	110.6	110.5	2'''	82.1	82.3	82.74	83.4	83.2
17	54.0	53.9	54.0	54.0	53.9	3'''	78.1	78.1	78.47	78.1	78.0
18	18.9	18.8	18.9	18.9	18.8	4'''	71.4	71.5	71.2	71.2	71.4
19	16.3	16.3	16.3	16.4	16.3	5'''	76.7	76.7	78.5	78.5	76.5
20	68.5	68.4	68.5	68.5	68.4	6'''	70.3	70.3	62.4	62.4	70.3
21	30.0	30.0	30.0	30.0	30.0	Xylose					
22	45.4	45.4	45.5	45.4	45.4	1''''	105.9	106.0	106.0	106.3	106.4
23	68.6	68.5	68.6	68.6	68.5	2''''	75.9	76.0	75.9	76.1	76.2
24	127.1	127.1	127.1	127.1	127.0	3''''	78.1	78.0	78.2	78.3	78.1
25	134.2	134.1	134.1	134.1	134.1	4''''	70.8	70.8	70.9	70.8	70.8
26	25.6	25.5	25.5	25.5	25.5	5''''	67.7	67.7	67.7	67.8	67.8
27	18.3	18.3	18.3	18.3	18.3	Glucose					
28	28.0	28.0	28.0	28.1	28.1	1'''''	105.2	105.2			105.1
29	16.7	16.7	16.7	16.9	16.9	2'''''	75.3	75.3			75.3
30	65.8	65.8	65.8	65.8	65.8	3'''''	78.4	78.4			78.0
						4'''''	71.4	71.5			71.4
						5'''''	78.4	78.4			78.4
						6'''''	62.5	62.5			62.5

[a]All δ_C assignments are based on 2D-NMR (^{1}H-^{1}H COSY, DEPT, HMQC, HMBC). [b]125 MHz. [c]100 MHz.

Experimental Section

Plant Material. The seeds of *Z. jujuba* var. *spinosa* were cultivated at Jinan, Shandong province, China, harvested in October 2009, and authenticated by Dr. J.-H. Lee, one of the authors. A voucher specimen was deposited in the Herbarium of the Traditional Herb Research Center, Korea Food and Drug Administration [no. 11E-1001].

Jujuboside A_2 (1): $[\alpha]_D^{28}$ = –55.4° (c 0.55, MeOH); IR (KBr) cm^{-1}: 3414, 1647, 1043, 980, 813; (–)-FAB-MS *m/z*: 1205 $[M-H]^-$, 1073 $[M-132]^-$, 1059 $[M-146]^-$, 1043 $[M-162]^-$, 911 $[M-132-162]^-$, 749 $[(M-H)-132-162-162]^-$, 603 $[(M-H)-132-162-162-146]^-$; HR-FAB-MS *m/z*: 1205.5961 $[M-H]^-$ (Calcd for $C_{58}H_{93}O_{26}$: 1205.5955); ^{1}H- and ^{13}C-NMR: see Tables 1 and 2.

6-Deoxy-L-talopyranose: $[\alpha]_D^{24}$ = –54.0° (c 0.3, MeOH); FAB-MS *m/z*: 187 $[M+Na]^+$, 165 $[M+H]^+$; ^{1}H-NMR (pyridine-d_5) δ 8.36 (1H, d, J = 3.6 Hz, 1-HO), 6.64 (1H, br s, 2-HO), 6.23 (1H, br s, 3-HO), 6.29 (1H, br s, 4-HO), 5.91 (1H, br s, H-1), 4.49 (1H, br s, H-2), 4.55 (1H, br s, H-3), 4.11 (1H, br s, H-4), 4.61 (1H, q, J = 6.5 Hz, H-5), 1.56 (3H, d, J = 6.5 Hz, 6-CH_3); ^{13}C-NMR (pyridine-d_5) δ 96.5 (C-1), 73.4 (C-2), 67.3 (C-3), 74.5 (C-4), 67.1 (C-5), 17.8 (C-6) for major 6-deoxy-α-L-talopyranose. ^{1}H-NMR (500 MHz, pyridine-d_5) δ 5.07 (1H, br s, H-1), 4.37 (1H, br s, H-2), 3.95 (1H, br s, H-3), 3.91 (1H, br s, H-4), 3.67 (1H, q, J = 6.5 Hz, H-5), 1.53 (3H, d, J = 6.5 Hz, 6-CH_3); ^{13}C-NMR (pyridine-d_5) δ 96.2 (C-1), 73.9 (C-2), 70.8 (C-3), 73.2 (C-4), 71.8 (C-5), 17.8 (C-6) for minor 6-deoxy-β-L-talopyranose. The integrals and the ^{13}C signal intensities provided 6-deoxy-α-L-talopyranose: 6-deoxy-β-L-talopyranose anomer ratio of about 81:19.

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Supporting Informations. General procedures, Extraction and Isolation, Acid Hydrolysis, ^{1}H-NMR data for jujubogenin moiety of **1**–**4** (Table) and NMR and MS spectra of **1** are available as Supporting Information.

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