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Chemical Constituents of Mistletoe (*Viscum album* L. var. *coloratum* Ohwi)

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Abstract : *Six compounds from the stems and leaves of Viscum album L. var. coloratum Ohwi were isolated and characterized. The structure of six compounds was elucidated as adenosine (1), thymidine (2), syringing (3), 1,5-dimethyl-6,8-dioxatricyclo[4.2.1.0^{3,9}]nonane-3-methyl-2,4-pentadienoic acid (4), homoeriodictyol-7-O-β-apiosyl-(1→2)-O-β-glucoside (5) and homoeriodictyol-7-O-β-apiosyl-(1→5)-O-β-apiosyl-(1→2)-O-β-glucoside (6) based on the NMR and MS spectral evidence.*

Keywords *- Viscum album L. var. coloratum., NMR, adenosine, thymidine, dioxatricyclo[4.2.1.0^{3,9}]nonane, flavanone glycoside*

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I. Introduction

The plant of mistletoe, *Viscum album* L. var. *coloratum* Ohwi (Loranthaceae), is an evergreen hemi-parasitic plant which grows on various host tree and shrubs. Various kinds of *Quercus* spp., *Prunus* spp., *Fagus* spp., *Celtis* spp. and *Acer* spp. are well known as the host plant [1]. Mistletoe is widely found in Asia such as Korea, Japan, China and in Europe and North Africa. The stems and leaves of mistletoe were traditionally used as medicinal plant to treat hemorrhage, pleurisy, gout, heart disease, arthritis, and hypertension etc [2-4]. Previous phytochemical investigations have revealed that triterpenoids, lignans, diarylheptanoids and flavonoids are the major secondary metabolites of mistletoe [4-7], and anticancer, antimycobacterial, antiviral, antioxidant activities and immunostimulating properties of mistletoe extracts have been reported [8-11]. In addition, mistletoe is used in treatments of cardiovascular disease that is linked to the presence of flavonoids [12] and is an important medicinal plant suitable for commercial production. In the present study, we reported the isolation and structural determination of flavanone glycosides and several new compounds from the stems and leaves of mistletoe.

II. Material and Methods

Plant material

Mistletoe was collected on the host plant *Quercus crispula* Blume (Fagaceae), in June 2009. The leaves and stems of the plant were dried at the room temperature and ground into a fine powder.

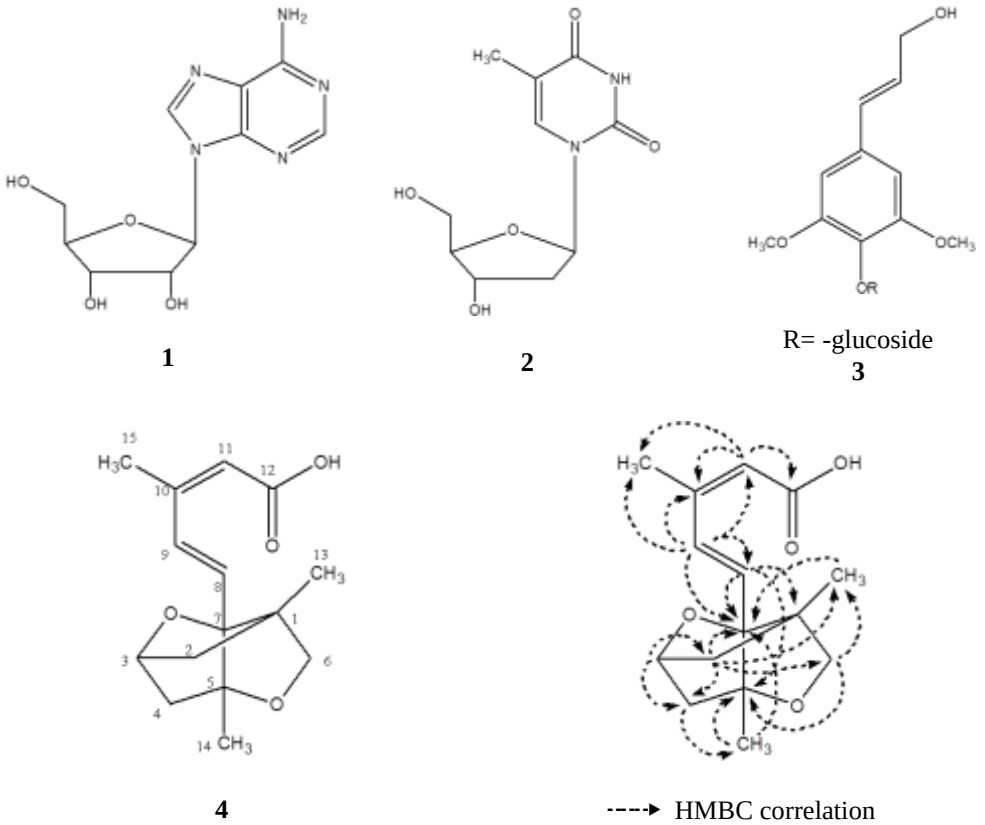
Extraction and Isolation

The powder (100g) was extracted 2 times with 80% MeOH and after that 2 times with 80% acetone. The MeOH solvent was removed by evaporation under reduced pressure (ca. 40°C) to give the crude extracts. The crude extracts were suspended in 500 mL water and then defatted with 500 mL *n*-hexane 3 times. The hexane-insoluble layer was applied to an MCI GEL CHP-20 (4.0 cm i.d. × 18 cm) column using H_2O–MeOH mixture (2L each) to give fraction I (10% MeOH), fraction II (30% MeOH), fraction III (50% MeOH) and fraction IV (75% MeOH). Fraction I was further separated by preparative HPLC to give compound 1 (18mg) and compound 2 (11mg). Fraction II was further separated by preparative HPLC to give compound 3 (142mg). Fraction III was further separated by preparative HPLC to give compound 4 (23mg), compound 5 (39mg) and compound 6 (19mg). HPLC was carried out using the Shimadzu (Kyoto, Japan) preparative HPLC system comprising an LC-6A pump and an SPD-10A detector. The separation column was TSKgel ODS-80TM (21.5 mm i.d. x 30 cm, Tosoh) with solvent H_2O–acetonitrile–formic acid (95:5:1) and/or H_2O–acetonitrile–formic acid (85:15:1). ^{1}H and ^{13}C-NMR spectra were measured with a JEOL JNM-ECA 600 spectrometer in DMSO-*d6*, CD_3OD. HR-ESI-TOF-MS spectra were recorded on a JEOL JMS-T100LC spectrometer.

III. Results And Discussion

Six compounds were obtained by separating and purifying extracts of the stems and leaves of mistletoe. The structures of these compounds were elucidated using 1D, 2D NMR and MS spectra data. Compound 1 was obtained as a white powder. The HR-ESI-TOF-MS analysis of compound 1 displayed a molecular ion peak $[M+H]^+$ at *m/z* 268.1. In the ^{1}H and ^{13}C-NMR (600 MHz, DMSO-d_6) spectrum of compound 1, proton signals at δ 8.33 (1H, s), 8.13 (1H, s) and 7.31 (2H, s), and carbon signals at δ 156.1, 152.3, 149.0, 139.9, 119.3 evidenced the presence of an adenine moiety. Compound 1 was showed characteristic chemical shifts of a deoxyribose moiety at δ 5.87 (1H, d, *J* = 6.3), 5.41 (1H, d, *J* = 6.3, OH), 5.39 (1H, m, OH), 5.14 (1H, d, *J* = 4.4, OH), 4.62 (1H, dd, *J* = 4.9, 6.3), 4.14 (1H, ddd, *J* = 2.9, 4.9, 7.8), 3.96(1H, q, *J* = 3.4), 3.67 (1H, ddd, *J* = 3.4, 4.4, 12.2) and 3.55 (1H, m). Based on these data and literatures [13-15], compound 1 was identified as adenosine.

Compound 2 was obtained as a white powder. The HR-ESI-TOF-MS analysis of compound 2 displayed a molecular ion peak $[M+H]^+$ at m/z 243.1. In the ^{1}H and ^{13}C-NMR (600 MHz, CD_3OD) spectrum, proton signals at δ 6.26 (1H, t, *J* = 6.8), 4.39 (1H, dt, *J* = 6.4, 6.3), 3.90 (1H, q, *J* = 6.8), 3.79 (1H, dd, *J* = 3.4, 12.2), 3.72 (1H, dd, *J* = 3.4, 12.2), 2.24-2.20 (2H, m) and carbon signals at δ 88.8, 86.3, 72.2, 62.8 and 41.2 indicated the presence of a 2′-deoxyribose moiety. The proton signals at δ 7.69 (1H, d, *J* = 1.0), 1.87 (3H, d, *J* = 1.4) and carbon resonances at δ 166.4, 152.4, 138.2, 111.5 and 12.7 evidenced the presence of a thymine moiety. Based on these data and literatures [15, 16], compound 2 was identified as thymidine.



1 **2** **3** **4**

Fig.1. Chemical structure of compound 1-4, HMBC correlation of compound 4

Compound 3 was obtained as a yellow-white powder. The HR-ESI-TOF-MS analysis of compound 3 displayed a molecular ion peak $[M+H]^+$ at m/z 373.3. The ^{1}H-NMR spectrum (600 MHz, CD_3OD) showed the presence of a symmetric tetra-substituted aromatic proton at δ 6.74 (2H, s) and another singlet at δ 3.86 (6H, s) attributable to two methoxy protons. The observation of two characteristic doublet of triplets signals at δ 6.55 (1H, *J*=1.4, 15.6) and δ 6.32 (1H, *J*=5.4, 15.6) suggested the presence of a *trans*-olefinic protons directly linked to a methylene group. An anomeric proton of glucose H-1′ (δ 4.86) showed a correlation with C-4 (δ 134.0) in the HMBC spectrum. Based on these data and literatures [1, 17], compound 3 was identified as syringin.

Compound 4 was obtained as a yellow amorphous powder. Its molecular formula $C_{15}H_{20}O_4$ was deduced from the ion peak $[M + H]^+$ at *m/z* 265.2 in the positive HR-ESI-TOF-MS. The structural assignment of compound 4 was based on ^{1}H and ^{13}C-NMR along with COSY, HSQC and HMBC correlations. The ^{1}H-NMR (600 MHz, CD_3OD) spectrum of compound 4 showed the presence of three tertiary methyl signals at δ 0.92 (s, H-13), 1.14 (s, H-14) and 2.07 (d, *J* = 1.0, H-15), three methylenes signals at δ 1.85 (H-2a), 1.65 (H-2b), 2.03

(H-4a), 1.73 (H-4b), 3.80 (H-6a) and 3.70 (H-6b), a oxygenated methine signal at δ 4.11 (m, H-4), trans-olefinic signals at δ 6.51 (d, *J* = 16.1, H-8) and 7.97 (d, *J* = 16.1, H-9), a singlet olefin signal at δ 5.75 (H-11). The ^{13}C-NMR spectrum of compound 4 showed the presence of three tertiary methyl signals at δ 16.3 (C-13), 19.6 (C-14) and 21.2 (C-15), three methylenes signals at δ 44.5 (C-2), 46.0 (C-4) and 77.3 (C-6), a oxygenated methine signal at δ 66.0 (C-3), three olefinic signals at δ 135.2 (C-8), 131.8 (C-9) and 119.2 (C-11), five quaternary signals at δ 49.4 (C-1), 87.8 (C-5), 83.2 (C-7), 151.4 (C-10) and 169.6 (C-12). The significant correlations were observed between protons [(H-2a / H-2b); (H-3 / H-2a, 2b, 4a, 4b); (H-4a / H-4b); (H6a / H-6b); (H-8 / H-9)] in the COSY spectrum. In the HSQC spectrum, three methyl signals at δ 0.92 (s), 1.14 (s) and 2.07 (d, *J* = 1.0) corresponding to the carbon signals at δ 16.3, 19.6 and 21.2 were observed. The remaining carbon and proton signals were to evaluate the position based on the results from HSQC spectrum. The significant correlations were observed between protons and carbons [(H-13 / C-1, 2, 6, 7); (H-13 / C-4, 5, 7); (H-2 / C-1, 3, 4, 6, 7, 13); (H3 / C-2, 4); (H-4 / C-2, 3, 5, 7, 14); (H-6 / C-1, 2, 5, 7, 13)] in the HMBC spectrum. Since H-6 exhibited long-range correlation to C-5, it was considered that C-6 formed a furan ring to C-5 through an oxygen atom. Its structure was assumed to be the presence of a 6,8-dioxatricyclo[4.2.1.0^{3,9}]nonane skeleton [18-20]. In addition, the correlations were also observed between [(H-15 / C-9, 10, 11); (H-8 / C-1, 2, 6, 9, 10); (H-9 / C-1, 8, 10, 11, 15); (H-11 / C-9, 10, 12, 15)] in the HMBC spectrum. Its structure was assumed to be the presence of a 3-methyl-2,4-pentadienoic acid skeleton [21, 22]. Based on these data, the structure of compound 4 was elucidated as 1,5-dimethyl-6,8-dioxatricyclo [4.2.1.0^{3,9}]nonane-3-methyl-2,4- pentadienoic acid.

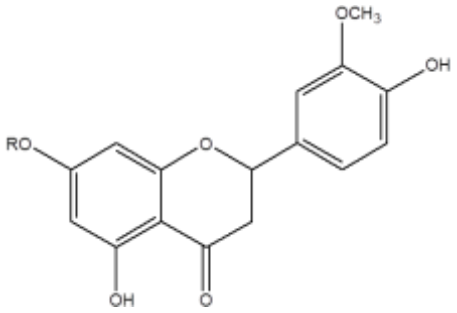
Table 1. ^{13}C-NMR spectrum data for compound 5 and 6

Position	Comp.5	Comp.6	Position	Comp.5	Comp.6
2	79.1	78.9	1″	97.8	97.6
3	42.3	42.3	2″	76.8	76.6
4	197.4	197.3	3″	75.7	75.8
5	163.0	162.9	4″	69.8	70.0
6	96.5	96.3	5″	77.0	77.0
7	165.1	164.9	6″	60.5	60.5
8	95.3	95.3	1‴	108.8	108.9
9	162.9	162.8	2‴	76.1	76.5
10	103.3	103.3	3‴	79.3	78.0
1′	129.3	129.2	4‴	74.0	74.0
2′	111.3	111.2	5‴	64.3	69.5
3′	147.6	147.6	1⁗		108.8
4′	147.1	147.0	2⁗		76.3
5′	115.3	115.2	3⁗		79.1
6′	120.0	119.9	4⁗		73.4
			5⁗		63.5
OMe	55.8	55.7			

Compound 5 was obtained as a yellow amorphous powder. The HR-ESI-TOF-MS analysis of compound 5 displayed a molecular ion peak $[M + H]^+$ at *m/z* 597.5. The structural assignment of compound 5 was based on ^{1}H and ^{13}C-NMR along with COSY, HSQC and HMBC correlations. In the ^{1}H-NMR spectrum (600 MHz, DMSO-d_6), a typical three protons ABX spin system at δ 3.40 (1H, m), 2.74 (1H, dd, *J* = 3.1, 17.3) and 5.49 (1H, dd, *J* = 2.7, 12.2) showed a flavanone skeleton. The ^{1}H-NMR spectrum showed three aromatic proton signals at δ 7.11 (br. s), 6.80 (d, *J* = 8.2), and 6.92 (d, *J* = 8.2) attributable to the B ring and two meta-coupling protons at δ 6.16 (br. s), 6.11 (d, *J* = 2.0) assignable to the A ring. One methoxyl group at δ 3.79 (3H, s) was correlated to C-3′ (δ 147.6) signal in the HMBC spectrum. These evidences suggested the flavanone moiety was homoeriodictyol [23]. In addition, two anomeric proton resonances corresponding to *O*-linked sugars were displayed in ^{1}H-NMR spectrum as one doublet at δ 5.09 (1H, d, *J* = 7.5) and one singlet at δ 5.32 (1H, s). Based on the analysis of 1D and 2D NMR data of compound 5, the two sugar units were elucidated as glucosyl and apiosyl moiety, respectively. The HMBC correlation between apiose proton H-1‴ (δ 5.32) and glucose C-2″ (δ 76.8) suggested the interglycosidic linkage. A correlation between glucose proton H-1″ (δ 5.09) and C-7 (δ 165.1) in the HMBC spectrum defined the site of *O*-glycosylation. Based on these data and literatures [23, 24], compound 5 was identified as homoeriodictyol-7-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (viscumneoside III).

Compound 6 was obtained as a yellow amorphous powder. The HR-ESI-TOF-MS analysis of compound 6 displayed a molecular ion peak $[M + H]^+$ at *m/z* 729.6. The structural assignment of compound 6 was based on ^{1}H and ^{13}C-NMR along with COSY, HSQC and HMBC correlations. Comparison of the ^{1}H and ^{13}C-NMR of compound 6 with those of compound 5 showed that they have same flavanon moiety (Table 1). On

the other hand, the ^{1}H-NMR spectrum (600 MHz, DMSO-d_6) of compound 6 showed three anomeric protons at δ 5.11 (1H, d, *J* = 7.5), 5.28 (1H, s) and 4.68 (1H, d, *J* = 2.7). Comparison of the NMR data of compound 6 with those of viscumneoside V implied similar interglycosidic linkages of one glucosyl and two apiosyl moieties [24-26]. Furthermore, HMBC correlations between glucose proton H-1″ (δ 5.11) and C-7 (δ 164.9); between apiose proton H-1‴ (δ 5.28) and glucose C-2″ (δ 76.6); and between apiose proton H-1⁗ (δ 4.68) and apiose C-5‴ (δ 69.5) were observed. Thus, the sugar moiety was identified as *O*-*β*-apiosyl-(1→5)-*O*-*β*-apiosyl-(1→2)-*O*-*β*--glucoside and located at C-7. Based on these data and literatures [24-26], compound 6 was identified as homoeriodictyol-7-*O*-*β*-apiosyl-(1→5)-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (viscumneoside V).



compound 5:
R= -apiosyl-(1→2)-*O*-glucoside

compound 6:
R= -apiosyl-(1→5)-*O*-apiosyl-(1→2)-*O*-glucoside

Fig.2. Chemical structure of compound 5 and 6

Adenosine (1), white powder. HR-ESI-TOF-MS *m/z* 268.1 $[M+H]^+$ (calcd for $C_{10}H_{14}N_5O_4$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ, ppm, *J*/Hz): 8.33 (1H, s, H-2), 8.13 (1H, s, H-8), 7.31 (2H, s, NH_2), 5.87 (1H, d, *J* = 6.3, H-1′), 5.41 (1H, d, *J* = 6.3, 2′-OH), 5.39 (1H, m, 5′-OH), 5.14 (1H, d, *J* = 4.4, 3′-OH), 4.62 (1H, dd, *J* = 4.9, 6.3, H-2′), 4.14 (1H, ddd, *J* = 2.9, 4.9, 7.8, H-3′), 3.96 (1H, q, *J* = 3.4, H-4′), 3.67 (1H, ddd, *J* = 3.4, 4.4, 12.2, H-5′a), and 3.55 (1H, m, H-5′b). ^{13}C-NMR (150 MHz, DMSO-d_6, δ): 156.1 (C-6), 152.3 (C-2), 149.0 (C-4), 139.9 (C-8), 119.3 (C-5), 87.9 (C-1′), 85.9 (C-4′), 73.4 (C-2′), 70.6 (C-3′) and 61.6 (C-5′).

Thymidine (2), white powder. HR-ESI-TOF-MS *m/z* 243.1 $[M+H]^+$ (calcd for $C_{10}H_{14}N_2O_5$). ^{1}H-NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 7.69 (1H, d, *J* = 1.0, H-6), 6.26 (1H, t, *J* = 6.8, H-1′), 4.39 (1H, dt, *J* = 6.4, 6.3, H-3′), 3.90 (1H, q, *J* = 6.8, H-4′), 3.79 (1H, dd, *J* = 3.4, 12.2, H-5′a), 3.72 (1H, dd, *J* = 3.4, 12.2, H-5′b), 2.24 - 2.20 (2H, m, H-2′a, H-2′b), and 1.87 (3H, d, *J* = 1.4, CH_3). ^{13}C-NMR (150MHz, CD_3OD, δ): 166.4 (C-4), 152.4 (C-2), 138.2 (C-6), 111.5 (C-5), 88.8 (C-4′), 86.3 (C-1′), 72.2 (C-3′), 62.8 (C-5′), 41.2 (C-2′) and 12.4 (CH_3).

Syringin (3), yellow-white powder. HR-ESI-TOF-MS *m/z* 373.3 $[M+H]^+$ (calcd for $C_{17}H_{25}O_9$). ^{1}H-NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 6.74 (2H, s, H-2, 6), 6.54 (1H, dt, *J* = 15.6, 1.4, H-7), 6.32(1H, dt, *J* = 15.6, 5.4, H-8), 4.22 (1H, dd, *J* = 1.4, 5.4, H-9a, 9b), 3.86 (6H, s, 3, 5-OMe), 4.86 (1H, d, *J* = 7.8, H-1′), 3.77 (1H, dd, *J* = 3.4, 12.2, H-6′a), 3.65 (1H, dd, *J* = 5.4, 12.2, H-6′b), 3.47 (1H, m, H-2′), 3.41 - 3.40 (1H, m, H-4′), and 3.22 - 3.19 (1H, m, H-5′). ^{13}C-NMR (150 MHz, CD_3OD, δ): 154.8 (C-2, 6), 134.0 (C-4), 133.2 (C-1), 129.5 (C-8), 128.4 (C-7), 105.8 (C-3, 5), 103.4 (C-1′), 76.9 (C-5′), 76.5 (C-3′), 74.7 (C-2′), 70.1 (C-4′), 62.5 (C-9), 61.6 (C-6′) and 55.6 (OMe).

1,5-dimethyl-6,8-dioxatricyclo[4.2.1.$0^{3,9}$]nonane-3-methyl-2,4-pentadienoic acid (4), yellow amorphous powder. HR-ESI-TOF-MS *m/z* 265.2 $[M+H]^+$ (calcd for $C_{15}H_{20}O_4$). ^{1}H-NMR (600 MHz, CD_3OD, δ, ppm, *J*/Hz): 7.97 (1H, d, *J* = 16.1, H-9), 6.51 (1H, d, *J* = 16.1, H-8), 5.75 (1H, s, H-11), 4.11 (1H, m, H-4), 3.80 (1H, dd, *J* = 1.4, 7.3, H-6a), 3.70 (1H, d, *J* = 7.3, H-6b), 2.07 (3H, d, *J* = 1.0, H-15), 2.03 (1H, ddd, *J* = 1.5, 6.8, 13.7, H-4a), 1.85 (1H, ddd, *J* = 1.5, 6.8, 13.7, H-2a), 1.73 (1H, dd, *J* = 10.2, 13.7, H-4b), 1.65 (1H, ddd, *J* = 2.0, 11.2, 13.2, H-2b), 1.14 (3H, s, H-14) and 0.92 (3H, s, H-13). ^{13}C-NMR (150MHz, CD_3OD, δ): 169.6 (C-12), 151.4 (C-10), 135.2 (C-8), 131.8 (C-9), 119.2 (C-11), 87.8 (C-5), 83.2 (C-7), 77.3 (C-6), 66.0 (C-3), 49.4 (C-1), 46.0 (C-4), 44.5 (C-2), 21.2 (C-15), 16.3 (C-13) and 19.6 (C-14).

homoeriodictyol-7-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (viscumneoside III) (5), yellow amorphous powder. HR-ESI-TOF-MS *m/z* 597.5 $[M+H]^+$ (calcd for $C_{27}H_{33}O_{15}$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ, ppm, *J*/Hz): 12.07 (5-OH), 9.21 (4′-OH), 7.11 (1H, s, H-2′), 6.92 (1H, d, *J* = 8.2, H-6′), 6.80 (1H, d, *J* = 8.2, H-5′), 6.16 (1H, s, H-8), 6.11 (1H, d, *J* = 2.0, H-6), 5.49 (1H, dd, *J* = 2.7, 12.2, H-2), 5.32 (1H, s, H-1‴), 5.09 (1H, d, *J* = 7.5, H-1″), 3.85 (1H, dd, *J* = 3.4, 9.5, H-4‴a), 3.79 (3H, s, OMe), 3.74 (1H, d, *J* = 3.4, H-2‴), 3.67 (1H, dd, *J* = 3.4, 9.5, H-6″a), 3.63 (1H, d, *J* = 9.5, H-4‴b), 3.44-3.48 (3H, m, H-2″, H-3″, H-6″b), 3.40 (1H, m, H-3a), 3.38 (1H, m, H-5″), 3.29 (2H, m, H-5‴), 3.17 (1H, m, H-4″) and 2.74 (1H, dd, *J* = 3.1, 17.3, H-3b).

homoeriodictyol-7-*O*-*β*-apiosyl-(1→5)-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (viscumneoside V) (6), yellow amorphous powder. HR-ESI-TOF-MS *m/z* 729.6 $[M+H]^+$ (calcd for $C_{32}H_{41}O_{19}$). ^{1}H-NMR (600 MHz, DMSO-d_6, δ, ppm, *J*/Hz): 12.07 (5-OH), 9.20 (4′-OH), 7.11 (1H, s, H-2′), 6.92 (1H, d, *J* = 8.2, H-6′), 6.79 (1H, d, *J* = 8.2, H-5′), 6.12 (1H, d, *J* = 2.0, H-8), 6.09 (1H, s, H-6), 5.48 (1H, m, H-2), 5.28 (1H, s, H-1‴), 5.11 (1H,

dd, *J* = 7.5, H-1″), 4.68 (1H, d, *J* = 2.7, H-1‴), 3.83 (1H, d, 9.5, H-4‴a), 3.79 (3H, s, OMe) , 3.75 (1H, m, H-4‴a), 3.73 (1H, m, H-4‴b), 3.64 (3H, m, H-6″a, H-2‴, H-5‴a), 3.52 (1H, dd, *J* = 4.7, 9.5, H-4‴b), 3.44-3.46 (6H, m, H-2″, H-3″, H-4″, H-6″b, H-5‴b, H-2‴), 3.41 (1H, m, H-3a), 3.28 (1H, m, H-5″), 3.27 (2H, s, H-5‴) and 2.71 (1H, dd, *J* = 3.4, 17.0, H-3b).

IV. Conclusion

Six compounds from the stems and leaves of mistletoe were isolated and characterized. The structure of six compounds was elucidated as adenosine (1), thymidine (2), syringing (3), 1,5-dimethyl-6,8-dioxatricyclo[4.2.1.$0^{3,9}$]nonane-3-methyl-2,4-pentadienoic acid (4), homoeriodictyol-7-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (5) and homoeriodictyol-7-*O*-*β*-apiosyl-(1→5)-*O*-*β*-apiosyl-(1→2)-*O*-*β*-glucoside (6) based on the NMR and MS spectral evidence. Compounds 1, 2 and 4 were isolated from mistletoe for the first time in this investigation.

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