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Isolation of Flavonol Rhamnosides from *Loranthus tanakae* and Cytotoxic Effect of Them on Human Tumor Cell Lines

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Loranthus tanakae Fr. *et* Sav. (Loranthaceae) is a species of mistletoe, a semiparasitic plant growing on the branches of *Quercus* and *Betula* species as host trees. In our ongoing search for bioactive compounds from endemic species in Korea, we have investigated to isolate the chemical constituents responsible for the antitumor effect of the MeOH extract of *L. tanakae*. The ethylacetate soluble part of the MeOH extract demonstrated a marginal inhibition on the proliferation of the tumor cell lines such as A549 (non small cell lung), SK-OV-3 (ovary), SK-MEL-2 (melanoma), XF498 (central nerve system), and HCT-15 (colon) *in vitro*. Thus, the activity-guided isolation procedure upon the ethylacetate soluble part of the extract has been carried out and finally four flavonoid rhamnopyranosides (**1**-**4**) were isolated as active principle. The structures of **1**-**4** were elucidated by the physicochemical and spectral data as rhamnetin 3-*O*-α-L-rhamnoside (**1**), quercetin 3-*O*-α-L-rhamnoside (**2**), rhamnocitrin 3-*O*-α-L-rhamnoside (**3**), and kaempferol 3-*O*-α-L-rhamnoside (**4**).

Key words: *Loranthus tanakae*, Mistletoe, Cytotoxicity, Flavonoid rhamnosides

INTRODUCTION

Loranthus species in semiparasitic plants are known to produce variety of bioactive compounds; *i.e.*, sesquiterpene lactones from *Loranthus parasiticus* for the treatment of schizophrenia (Okuda *et al.*, 1987) and (+)-catechin, 3,4-dimethoxycinnamyl alcohol and 3,4,5-trimethoxycinnamyl alcohol from *L. globosus* for the antimicrobial and antifungal properties (Sadik *et al.*, 2003). Many other chemical components such as triterpenoids from *L. grewinkii* (Rahman *et al.*, 1973), and *L. falcatus* (Anjaneyulu *et al.*, 1977), flavonoids from the leaves of *L. kaoi* (Lin and Lin, 1999) and from *L. europaeus* (Harvala *et al.*, 1984), a cytotoxin from *L. parasiticus* (Zhou *et al.*, 1993), and phenolics from *L. longiflorus* (Indrani and Balsubramanian, 1985) have been reported so far.

Other biological activities such as antihypertensive effect (Obatomi *et al.*, 1996), antiviral activity of *L. parasiticus* (Kusumoto *et al.*, 1992), anti-diabetic properties of *L. bengwensis* (Obatomi *et al.*, 1994), smooth muscle contracting activity (Chantarasomboon *et al.*, 1974) were also evaluated for the extracts of the species.

Loranthus tanakae Fr. *et* Sav. (Loranthaceae) (Joe, 1992) is a kind of mistletoe in *Loranthus* genus exclusively found in Korea and Japan, which is growing on the branches of *Quercus* and *Betula* species as host trees. In our ongoing research for bioactive compounds from endemic species in Korea, we have found that the MeOH extract of the species had exhibited a moderate cytotoxicity against cultured human tumor cell lines *in vitro*. The phytochemical investigation, therefore, has been carried out to isolate the active constituents by way of the cytotoxicity-guided fractionation procedure combined with the SRB (sulforhodamine-B) method (Skehan *et al.*, 1990) for cytotoxicity evaluation.

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MATERIALS AND METHODS

General

The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AMX 500 NMR spectrometer. Chemical shifts were referenced to the respective residual solvent peaks, and the values were recorded in δ. The column chromatography was carried out with prepacked silica gel 60

(150×15 mm, 230-400 mesh, Merck Co, Germany) and LiChroprep RP-18 (150×15 mm, 25-40 μm, Merck Co, Germany) columns. The TLCs were performed on precoated Merck Kieselgel 60 F_{254} plate (0.25 mm) and spots were detected under UV light (UV-254, Model UVGL-58, U.S.A.) followed by Vanillin-H_2SO_4 reagent. Solvents and reagents were obtained from commercial sources and used without further purification.

Plant material

The stem parts of the plant, *L. tanakae,* were collected during November 2000 from Balwang Mt (800 m altitude), Kangwon Province, Korea. The plant was authenticated by Dr. Sungsik Kim, Kwangnung National Arboretum, Korea. A voucher specimen (Lt20112) is deposited at the Herbarium of Kookmin University, College of Forest Science, Korea.

Extraction and isolation

The air-dried and ground of the stem part of *L. tanakae* (500 g) was extracted with hot MeOH (800 mL×3) for 4 hours. The MeOH solutions were combined, filtered, and evaporated under a vacuum. The dried MeOH extract (85 g, 17%) was suspended in a mixture of MeOH/water (800 mL, 90:10) and then partitioned with *n*-hexane (500 mL ×3) to afford a dried hexane fraction (8 g). The aqueous MeOH solution was evaporated to remove MeOH and then suspended in water (600 mL). The aqueous solution was percolated with $CHCl_3$ (500 mL×2), followed by EtOAc (700 mL×3) and BuOH (700 mL×3) and finally the residual extract to give upon concentration $CHCl_3$ (5.5 g), EtOAc (23 g), BuOH (6 g), and aqueous (40 g) fractions, respectively. Each fractions were evaluated for the anti-proliferative activity on the tumor cell lines. Consequently, it was shown that the activity resided predominantly in the EtOAc fraction (ED_{50} value against A549 cell was estimated as 55 μg/mL). Thus, a part (2.3 g) of EtOAc fraction was subjected to column chromatography on pre-packed silica gel column (20 mm i.d.×200 mm) to give subfraction A (48 mg), B (31 mg), C (21 mg), D (24 mg), and E (35 mg). Subfraction A was purified by pre-packed semipreparative RPMPLC (12 mm i.d.×150 mm) using 50% MeOH-H_2O as solvent to afford yellow solid **1** [15 mg; R_f 0.31, ODS, solvent; MeOH/H_2O (3:1)].

Separation of subfraction B with pre-packed semipreparative RPMPLC (12 mm i.d.×150 mm) using 50% MeOH-H_2O as solvent afforded yellow solid **2** [16 mg; R_f 0.29, ODS, solvent; MeOH/H_2O (3:1)], followed by **3** (12 mg; R_f 0.26). Subfraction C was separated by pre-packed semipreparative RPMPLC (12 mm i.d.×150 mm) using 60% MeOH-H_2O as solvent, which afforded yellow solids **3** (8mg) and **4** [18 mg; R_f 0.34, ODS, solvent; MeOH/H_2O (3:1)].

Rhamnetin 3-*O*-α-L-rhamnopyranoside (1)

Rhamnitrin, Yellow powder, ^{1}H-NMR (500 MHz, CD_3OD) δ : 0.86 (3H, d, *J* = 6.1 Hz, H-6"), 3.32 (1H, d, *J* = 9.6 Hz, H-4"), 3.36 (1H, m, H-5"), 3.69 (1H, d, *J* = 6.8Hz, H-3"), 3.84 (3H, s, -OCH_3), 4.18 (1H, m, H-2"), 5.30 (1H, d, *J* = 1.2 Hz H-1"), 6.14 (1H, *J* = 1.8 Hz, H-6), 6.30 (1H, *J* = 1.8 Hz, H-8), 6.86 (1H, d, *J* = 8.0 Hz, H-5), 7.26 (1H, d, *J* = 8.0 Hz, H-6), 7.29 (1H, *J* = 2.4 Hz, H-2); ^{13}C-NMR (125 MHz, CD_3OD) δ : 17.5 (C-6"), 51.8 (-OCH_3), 72.0 (C-2"), 72.0 (C-5"), 72.3 (C-3"), 73.4 (C-4"), 95.4 (C-8), 100.8 (C-6), 103.7 (C-1"), 105.9 (C-10), 116.5 (C-5'), 117.0 (C-2'), 123.2 (C-6'), 123.4 (C-1'), 136.5 (C-3), 146.8 (C-3'), 150.2 (C-2), 158.9 (C-9), 159.3 (C-4'), 163.1 (C-5), 167.3 (C-7), 179.8 (C-4).

Quercetin 3-*O*-α-L-rhamnopyranoside (2)

quercitrin, Yellow powder, ^{1}H-NMR (500 MHz, CD_3OD) δ : 0.86 (3H, d, *J* = 6.1 Hz, H-6"), 3.32 (1H, d, *J* = 9.6 Hz, H-4"), 3.35 (1H, m, H-5"), 3.70 (1H, d, *J* = 6.7 Hz, H-3"), 4.17 (1H, m, H-2"), 5.29 (1H, d, *J* = 1.2 Hz, H-1"), 6.13 (1H, d, *J* = 2.5 Hz, H-6), 6.29 (1H, d, *J* = 2.5 Hz, H-8), 6.86 (1H, d, *J* = 7.9 Hz, H-5'), 7.25 (1H, d, *J* = 7.9 Hz, H-6'), 7.28 (1H, s, H-2'); ^{13}C-NMR (125 MHz, CD_3OD) δ : 17.7 (C-6"), 71.9 (C-2"), 72.0 (C-5"), 72.2 (C-3"), 73.4 (C-4"), 95.3 (C-8), 100.2 (C-6), 103.5 (C-1"), 105.6 (C-10), 116.4 (C-5'), 116.9 (C-2'), 122.8 (C-6'), 123.1 (C-1'), 136.2 (C-3), 146.4 (C-3'), 149.9 (C-2), 158.6 (C-9), 159.2 (C-4'), 163.2 (C-5), 167.2 (C-7), 179.6 (C-4).

Rhamnocitrin 3-*O*-α-L-rhamnopyranoside (3)

Yellow powder, ^{1}H-NMR (500 MHz, CD_3OD) δ : 0.86 (3H, d, *J* = 6.4 Hz, H-6"), 3.35 (1H, d, *J* = 9.8 Hz, H-4"), 3.43 (1H, m, H-5"), 3.80 (1H, d, *J* = 6.7 Hz, H-3"), 3.84 (3H, s, -OCH_3), 4.18 (1H, m, H-2"), 5.30 (1H, d, *J* = 1.2Hz, H-1"), 6.16 (1H, d, *J* = 2.5 Hz, H-6), 6.32 (1H, d, *J* = 2.5 Hz, H-8), 6.87 (1H, d, *J* = 8.0 Hz, H-3), 6.87 (1H, d, *J* = 8.0 Hz, H-5'), 7.89 (1H, d, *J* = 8.0 Hz, H-2'), 7.89 (1H, d, *J* = 8.0 Hz, H-2'); ^{13}C-NMR (125 MHz, CD_3OD) δ : 17.5 (C-6"), 48.7 (-OCH_3), 70.1 (C-2"), 70.4 (C-5"), 70.7 (C-3"), 71.1 (C-4"), 92.4 (C-8), 98.0 (C-6), 101.8 (C-1"), 105.2 (C-10), 115.5 (C-3'), 115.5 (C-5'), 120.4 (C-1'), 130.7 (C-2'), 130.7 (C-6'), 134.6 (C-3), 156.5 (C-9), 157.6 (C-2), 160.2 (C-4), 161.0 (C-5), 165.2 (C-7), 177.9 (C-4).

Kaempferol 3-*O*-α-L-rhamnopyranoside (4)

afzelin, Yellow powder, ^{1}H-NMR (500 MHz, CD_3OD) δ : 0.84 (3H, d, *J* = 6.5 Hz, H-6"), 3.32 (1H, d, *J* = 9.4 Hz, H-4"), 3.45 (1H, m, H-5"), 3.98 (1H, d, *J* = 6.5 Hz, H-3"), 4.20 (1H, m, H-2"), 5.29 (1H, d, *J* = 1.2Hz, H-1"), 6.20 (1H, d, *J* = 2.5 Hz, H-6), 6.40 (1H, d, *J* = 2.5 Hz, H-8), 6.84 (2H, d, *J* = 8.0 Hz, H-3', H-5'), 8.00 (2H, d, *J* = 8.0 Hz, H-2', H-6'); ^{13}C-NMR (125 MHz, CD_3OD) δ : 17.5 (C-6"), 70.1 (C-2"), 70.3 (C-5"), 70.6 (C-3"), 71.1 (C-4"), 93.8

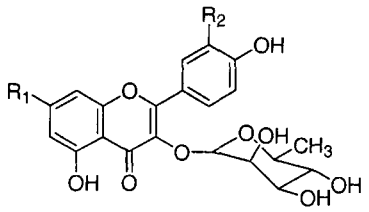
(C-8), 98.7 (C-6), 101.8 (C-1"), 104.1 (C-10), 115.4 (C-3'), 115.4 (C-5'), 120.5 (C-1'), 130.6 (C-2'), 130.6 (C-6'), 134.2 (C-3), 156.5 (C-9), 157.3 (C-2), 160.0 (C-4'), 161.3 (C-5), 164.2 (C-7), 177.7 (C-4).

Inhibition of tumor cell proliferation

Tumor cells used in the experiment, *i.e.*, A549 (non small cell lung), SK-OV-3 (ovary), SK-MEL-2 (skin), XF498 (central nerve system) and HCT-15(colon) were obtained from the National Cancer Institute (NCI) in the USA. The viability of the tumor cell lines after treatment of the test materials was determined using the SRB method, currently adopted in the NCI's *in vitro* anti-cancer drug screening (Skehan *et al.*, 1990), *i.e.*, estimating the inhibition rate of cell proliferation after continuous exposure to test materials for 48 h at 37°C in a CO_2 incubator. Detailed experimental procedures were described on the previous paper (Ryu *et al.*, 1992).

RESULTS AND DISCUSSION

The MeOH extract of the twigs of *L. tanakae* was partitioned with *n*-hexane, $CHCl_3$, EtOAc, BuOH, successively to give corresponding $CHCl_3$, EtOAc, BuOH fractions and the remnant aqueous fraction. Among these fractions, only the EtOAc soluble part exhibited a modest cytotoxicity against examined tumor cell lines *in vitro*. Thus, the EtOAc soluble part was subjected to repeated column chromatography on the silica gel and reversed-phase C-18 to yield flavonol rhamnosides **1-4**. The structural identifications of these compounds were elucidated from the ^{1}H- and ^{13}C-NMR spectral data interpretation and by comparison with published spectral data (Harvela, 1984; Haraguchi *et al.*, 1988). Rhamnetin 3-*O*-α-L-rhamnopyranoside (**1**) was obtained as a yellow powder. The ^{1}H-NMR spectrum of **1** showed three *meta*-coupled doublets at δ 6.14 (1H, *J* = 1.8 Hz, H-6), δ 6.30 (1H, *J* = 1.8 Hz, H-8), and δ 7.29 (1H, *J* = 2.4 Hz, H-2'), two *ortho*-coupled doublets at δ 6.86 (1H, *J* = 8.0 Hz, H-5') and δ 7.26 (1H, *J* = 8.0 Hz, H-6') along with δ 179.8 (C-4) in the ^{13}C-NMR spectrum indicating a typical flavonoid skeleton. A doublet at δ 0.86 (3H, *J* = 6.1 Hz) and a doublet at δ 5.30 (1H, *J* = 1.2 Hz, H-1") in the ^{1}H-NMR spectrum suggested the presence of rhamnose in its structure (Markham, 1982). Two carbon signals at δ 136.5 (C-3) and δ 150.2 (C-2) in the ^{13}C-NMR spectrum suggested that the sugar moiety was attached to the O-atom at C-3 of the aglycone. The spectrum of **1** also revealed the rhamnosyl moiety to be α-linked ($J_{H\text{-}1\text{-}H\text{-}2}$ = 1.2 Hz) and in the pyranose form (Harborne, 1994). The presence of methoxyl group was confirmed by a singlet signal at δ 3.84 (3H) in the ^{1}H-NMR and δ 51.8 in the ^{13}C-NMR spectra. The chemical shifts observed for **1** were in good agreement with those measured with other flavonol



1 rhamnetin 3-rhamnoside $R_1 = OCH_3$, $R_2 = OH$
2 quercetin 3-rhamnoside $R_1 = OH$, $R_2 = OH$
3 rhamnocitrin 3-rhamnoside $R_1 = OCH_3$, $R_2 = H$
4 kaempferol 3-rhamnoside $R_1 = OH$, $R_2 = H$

Fig. 1. Structure of compounds **1-4**

3-rhamnoside. Based on the spectral data of **1** and the comparison with literature values, **1** was identified as rhamnetin 3-*O*-α-L-rhamnopyranoside.

Quercetin 3-O-α-L-rhamnopyranoside (**2**) was obtained as a yellow powder. The spectral data of **2** were quite similar to those of **1**, except for the absence of a methoxyl group signal at δ 3.84 (3H) in the ^{1}H-NMR and δ 51.8 in the ^{13}C-NMR spectra of **1**. These observations suggested that **2** was the C-8 hydroxy derivative of **1** and characterized as quercetin 3-*O*-α-L-rhamnopyranoside (Zhong *et al.*, 1997).

Rhamnocitrin 3-O-α-L-rhamnopyranoside (**3**) was obtained as a yellow powder. A singlet signal at δ 3.84 (3H) in the ^{1}H-NMR spectrum was assigned to the methoxyl protons. Two *ortho*-coupled doublets centered at δ 6.87 (*J* = 8.0 Hz, H-3') and δ 7.89 (*J* = 8.0 Hz, H-2') integrating four protons of an AB system were due to the protons on a *para*-disubstituted benzene ring. A doublet at δ 0.86 (3H, d, *J* = 6.4 Hz, H-6") and peaks between δ 3.3-4.2 indicated the presence of rhamnosyl moiety and the α-linkage of the sugar to the aglycone was also confirmed by a doublet at δ 5.30 (1H, *J* = 1.2 Hz, H-1"). On the basis of the above spectral evidences, **3** was suggested to rhamnocitrin 3-rhamnoside. The spectral data of **3** were in good agreement with the previous data of rhamnocitrin 3-*O*-α-L-rhamnopyranoside.

Kaempferol 3-O-α-L-rhamnopyranoside (**4**) was obtained as a yellow powder. The ^{1}H-NMR spectrum of **4** exhibited one set of *meta*-coupled aromatic protons at δ 6.20, (1H, *J* = 2.5 Hz, H-6) and δ 6.40 (1H, *J* = 2.5 Hz, H-8) and two sets of *ortho*-coupled aromatic protons at δ 8.00 (2H, *J* = 8.0 Hz) and δ 6.84 (2H, *J* = 8.0 Hz). These signals were assigned to H-6, H-8, H-2' and H-6', and H-3' and H-5' of 4', 5, 7-trihydroxyflavone skeleton, respectively. The spectral data of **4** were quite similar to those of **3**, except for the absence of a methoxyl group signal at δ 3.84 (3H) in the ^{1}H-NMR and δ 48.7 in the ^{13}C-NMR spectra of **3**. The carbon chemical shifts were assigned by comparison with literature values (Silva *et al.*, 1997). Based on the spectral evidences, **4** was identified as kaempferol 3-*O*-α-L-

Table I. Inhibition of cell proliferation by flavonol rhamnosides from *Loranthus tanakae*

	ED_{50} (μg/mL)[a]				
	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	>100	>100	>100	>100	>100
2	70.2±0.3[b]	45.8±0.3	41.5±0.4	81.3±0.5	>100
3	42.1±0.4	24.1±0.5	34.1±0.2	50.2±0.5	85.2±0.1
4	40.6±0.5	34.5±0.4	33.9±0.3	>100	>100
Quercetin	5.8±0.2	6.3±0.2	4.7±0.3	6.0±0.1	4.8±0.1
kaempferol	7.6±0.2	8.2±0.3	6.9±0.2	8.2±0.1	5.1±0.1
Cisplatin	1.4±0.2	1.9±0.3	0.8±0.2	0.9±0.3	2.2±0.4

[a]ED_{50} value of compound against each cancer cell line, which was defined as a concentration that caused 50% inhibition of cell proliferation *in vitro*.

[b]Data are mean±S.E.M. of three distinct experiments.

rhamnopyranoside.

All isolates **1-4** were comprised in flavonol component which possessed a α-linked rhamnosyl moiety as a common feature.

The ED_{50} value (a concentration that caused 50% inhibition of cell proliferation) of compound against each cancer cell line was summarized in Table I. Each isolated components **1-4** were exhibited to give a moderate inhibition upon the proliferation of cultured human tumor cell lines, A549 (non small cell lung), SK-OV-3 (ovary), SK-MEL-2 (skin), XF498 (central nerve system) and HCT-15 (colon), respectively. However, the corresponding flavonol of **2** and **4**, quercetin and kaempferol was found to give inhibition upon the proliferation of examined tumor cell lines with much higher potency. These results suggested that the anti-proliferative activity of flavonol rhamnoside **1-4** on the tumor cell lines might be ascribed to the flavonol skeleton not to the rhamnosidic moiety.

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