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NEW FLAVONE GLYCOSIDES FROM *Astragalus tanae* ENDEMIC TO GEORGIA

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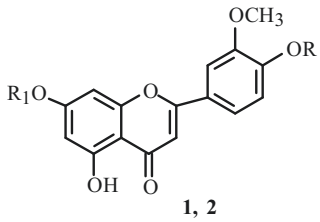
The new flavone glycosides tanoside I and II in addition to three known flavonoids and daucosterol were isolated from the Georgian endemic species Astragalus tanae *Sosn. Their structures were elucidated as chrysoeriol-7-*O-β-*D-glucopyranosyl-4′-*O-α-*L-rhamnopyranoside, chrysoeriol-4′-*O-α-*L-rhamnopyranoside, kaempferol-3-*O-β-*D-glucopyranosyl(2→1)-*O-α-*L-rhamnopyranoside (kaempferol-3-*O-β-*D-neohesperidoside), tamarixin, apigenin, and* β-*sitosterol-3-*O-β-*D-glucopyranoside (daucosterol).*

Keywords: *Astragalus tanae*, flavonoids, glucosides, chrysoeriol, tanoside I, tanoside II, tamarixin, kaempferol-3-*O-β*-D-neohesperidoside, daucosterol.

Plants of the genus *Astragalus* provide raw material for biologically active additives [1–3] and valuable excipients used in the pharmaceutical industry and other sectors [4] and the manufacturing of medicines [5, 6].

Astragalus tanae Sosn. is one of 16 endemic species of the 72 species inhabiting Georgia [7]. Flavonoid kaempferol derivatives [8] and triterpenes [9] were previously isolated and characterized from *A. tanae*. Later, new flavone glycosides (**1** and **2**), three known flavonoids (**3**–**5**), and a sterol glycoside (**6**) were isolated and identified. The present work describes them.



1, 2

1: R = Rha*p*; R_1 = Glc*p*
2: R = Rha*p*; R_1 = H

Compounds **1**–**6** were isolated by fractionation of total extracted substances from aerial parts over Sephadex LH-20 followed by separation of the obtained fractions by HPLC and separation over silica gel of total slightly polar substances.

Compound **1** formed pale-yellow crystals of molecular formula $C_{28}H_{32}O_{15}$ that was established using ESI-MS (*m*/*z* 607.5356, $[M - H]^-$). The IR spectrum showed vibrations for OH (3400 cm^{-1}) and carbonyl (1653) and characteristic absorption bands for aromatic systems (1606, 1554, 1495). A Bryant cyanidin test was positive [10], confirming that the compound was a flavonoid glycoside. The UV spectrum showed absorption maxima at 260 and 345 nm, which was typical of flavones. The PMR spectrum (Table 1) exhibited the H-3 resonance at 6.80 ppm. A resonance for the corresponding C atom appeared at δ 103.9 in the ^{13}C NMR spectrum. Addition of ionizing and complexing reagents established that the substituents in the aglycon were located on C-7, C-3′, and C-4′; C-3 lacked a hydroxyl; and the molecule was *ortho*-substituted. Acid hydrolysis formed the sugars D-glucose and L-rhamnose.

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TABLE 1. PMR and ^{13}C NMR Spectra of **1** and **2** (CD_3OD, δ, ppm, J/Hz)

C atom	**1**			**2**		
	δ_H	δ_C	HMBC (H→C)	δ_H	δ_C	HMBC (H→C)
2	–	164.4	–	–	164.5	–
3	6.80 (s)	103.9	2, 4, 10	6.45 (s)	104.2	2, 4, 10
4	–	182.5	–	–	182.1	–
5	–	161.9	–	–	161.7	–
6	6.55 (d, J = 2.0)	99.2	5, 7, 8, 10	6.20 (d, J = 2.0)	99.3	5, 7, 8, 10
7	–	164.3	–	–	163.9	–
8	6.92 (d, J = 2.0)	95.0	7, 9, 10	6.71 (d, J = 2.0)	95.1	6, 7, 9, 10
9	–	157.9	–	–	156.9	–
10	–	104.7	–	–	104.5	–
1′	–	122.8	–	–	122.7	–
2′	7.68 (d, J = 2.1)	110.6	1′, 3′, 4′	7.60 (d, J = 2.1)	110.5	1′, 3′, 4′
3′	–	149.1	–	–	149.4	–
4′	–	151.3	–	–	150.8	–
5′	7.34 (d, J = 8.3)	116.1	1′, 3′, 4′, 6′	7.32 (d, J = 8.3)	116.2	1′ 3′, 4′, 6′
6′	7.62 (dd, J = 8.3, 2.1)	120.8	1′, 2′, 5′	7.55 (dd, J = 2.1, 8.3)	120.5	1′, 2′, 5′, 4′
3′-OCH_3	3.97 (s)	56.3	3′	3.98 (s)	56.4	3′
D-Glc*p*						
1″	5.12 (d, J = 7.6)	100.6	7			
2″	3.32 (d, J = 11.4)	75.1	1″, 3″			
3″	3.55 (d, J = 11.4)	76.6	2″			
4″	3.20–3.80 (m)	71.3	3″, 5″			
5″	3.20–3.86 (m)	77.1	4″, 6″			
6″	3.72 (dd, J = 12.0, 4.2) 3.58 (dd, J = 12.0, 4.5)	63.2	4″, 5″			
L-Rha*p*						
1‴	5.55 (d, J = 4)	99.6	4′	5.52 (d, J = 4)	98.8	4′, 2‴
2‴	4.62 (dd, J = 1.7, 3.2)	70.2	1‴, 3‴	4.51 (dd, J = 1.7, 3.2)	72.1	1‴, 3‴
3‴	3.94 (dd, J = 3.2, 9.3)	70.3	2‴	3.87 (dd, J = 3.2, 9.3)	69.8	2‴
4‴	3.20–3.80 (m)	71.7	3‴	3.24–3.83 (m)	73.4	3‴, 5‴
5‴	3.20–3.86 (m)	67.9	4‴, 6‴	3.24–3.89 (m)	67.7	4‴, 6‴
6‴ (CH_3)	0.99 (d, J = 6)	18.1	5‴	1.22 (d, J = 6)	18.0	4‴, 5‴

The PMR spectrum showed six resonances for aromatic protons at 6.5–7.7 ppm and resonances for anomeric protons at 5.55 and 5.12 ppm. The SSCC (J = 2.0 Hz) of doublets at δ 6.55 (H-6) and δ 6.92 (H-8) were indicative of *meta*-coupling of aromatic protons. Doublets at δ 7.68 (H-2′), 7.34 (H-5′), and 7.62 (H-6′) suggested that the protons in the flavonoid side aromatic ring were asymmetric.

A singlet at 3.97 ppm and the corresponding resonance at 56.3 ppm in the ^{13}C NMR spectrum were consistent with a methoxyl in the molecule (Table 1). A correlation between resonances at δ 149.1 and 3.97 indicated that the methoxyl was bonded to C-3′. The ^{13}C NMR spectrum contained chemical shifts for 28 C atoms. UV spectra of the aglycon obtained by acid hydrolysis confirmed that C-3′ was substituted by a methoxyl. Methyl protons of L-rhamnose appeared at 0.99 ppm and correlated with a resonance at 18.1 ppm in the ^{13}C NMR spectrum. Based on these results, the aglycon of **1** was 3′-methoxyapigenin or chrysoeriol [11–13].

The site of attachment of the sugar to the aglycon was established using a heteronuclear correlation spectrum (HMBC) in which correlations were observed between the D-glucose (δ 5.12) and L-rhamnose anomeric protons (δ 5.55) and C-7 (δ 164.3) and C-4′ (δ 151.3), respectively.

Considering these results, **1** was chrysoeriol-7-*O*-*β*-D-glucopyranosyl-4′-*O*-*α*-L-rhamnopyranoside. A flavone glycoside with this structure has not been reported so **1** was new and called tanoside I (**1**).

Compound **2** was also pale-yellow crystals with molecular formula $C_{22}H_{22}O_{10}$ that was established by ESI-MS (*m*/*z* 445.3967 $[M - H]^-$). The IR spectrum showed vibrations for OH (3460 cm^{-1}), carbonyl (1654 cm^{-1}), and aromatic systems (1606, 1415, 1252 cm^{-1}). A Bryant cyanidin test was positive [10]. The UV spectrum showed absorption maxima at 270 and 340 nm that were typical of flavones. Addition of ionizing and complexing reagents indicated that substituents in the

aglycon were located on C-7, C-3′, and C-4′; C-3 lacked an OH; and the molecule was *ortho*-substituted. Proton H-3 (Table 1) appeared at 6.45 ppm in the PMR spectrum, which also showed six resonances for aromatic protons at 6.20–7.62 ppm and a resonance for an anomeric proton at 5.52 ppm. The methoxyl gave a singlet at 3.98 ppm and the corresponding ^{13}C resonance at δ 56.4. The ^{13}C NMR spectrum had chemical shifts for 22 C atoms (Table 1). A correlation between resonances at δ 149.4 and 3.98 ppm proved that the methoxyl was bonded to C-3′. Methyl protons of L-rhamnose were found at 1.22 ppm and correlated with a ^{13}C resonance at δ 18.0. Acid hydrolysis gave L-rhamnose and the aglycon, which was identical to that of **1**. Based on the experimental results, the aglycon of **2** was chrysoeriol.

The location of the sugar in **2** was established by a correlation between the L-rhamnose anomeric proton (δ 5.52) and the C-4′ resonance (δ 150.8) in the HMBC spectrum.

According to the results, **2** was chrysoeriol-4′-*O*-α-L-rhamnopyranoside. A flavonoid with this structure has not been reported so **2** was a new compound and was called tanoside II.

Compounds **3**–**5** were identified as the known flavonoids apigenin (**3**) [5, 11], tamarixin (**4**) [14], and kaempferol-3-*O*-β-D-glucopyranosyl(2→1)-α-L-rhamnopyranoside (**5**) [15]. Compound **6** was characterized as β-sitosterol-3-*O*-β-D-glucopyranoside or daucosterol [16].

EXPERIMENTAL

General Comments. UV and IR spectra were taken on Jasco V-730 and Jasco FT/IR-4600 V-730 instruments. NMR spectra were recorded in CD_3OD (99.95%, Sigma-Aldrich) on a Bruker DRX 600 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) equipped with a Bruker 5-mm TCI CryoProbe at 300 K. Mass spectra were taken using an Agilent 6240 ESI-MS. HPLC was performed on a Waters 590 apparatus equipped with a Waters R401 refractive-index detector and a Waters Bondapak™ C_{18} chromatography column (8 × 300 mm). Column chromatography used Kieselgel 60 (0.06–0.2 mm, Carl Roth GmbH) and Sephadex LH-20 (Pharmacia); TLC, silica gel 60 F_{254} plates (Merck); paper chromatography (PC), FN-11 (Whatman). The solvent systems for TLC and PC were *n*-BuOH–AcOH–H_2O (60:15:25, 1); $CHCl_3$–MeOH (10:1, 2); and C_5H_5N–C_6H_6–*n*-BuOH–H_2O (3:1:5:3, 3). TLC plates were detected by spraying $Ce(SO_4)_2$ solution in dilute H_2SO_4 followed by heating at 110°C for 2–3 min. Sugars in paper chromatograms were detected using anilinium phthalate reagent.

Plant Material. *A. tanae* Sosn. (Leguminosae) was collected in the environs of Tbilisi (Digmistskali gorge, Didgori) at the end of June 2013 during flowering. Specimens were determined at the Direction of Pharmacobotany, I. Kutateladze Institute of Pharmacochemistry (Tbilisi, Georgia), herbarium No. 13 076.

Extraction and Isolation. Air-dried milled flowers (0.7 kg) were extracted with EtOH (80%). The obtained extract was evaporated to a watery residue. A viscous resinous precipitate was filtered off. The residue on the filter did not contain flavonoids and triterpenoids according to TLC. The filtrate was purified by $CHCl_3$. White needle-like crystals precipitated at the interface between the layers and turned out to be a mixture of two compounds [9]. The crystalline precipitate was separated. The remaining aqueous layer was extracted sequentially with $CHCl_3$ (4 × 200 mL) and EtOAc (5 × 200 mL).

The obtained $CHCl_3$ extract was evaporated. The solid (2 g) was separated over a silica gel column (1.5 × 40 cm) with elution by $CHCl_3$ and $CHCl_3$–MeOH mixtures with increasing concentration of the latter. Fraction 26 yielded yellow crystals (compound **3**, 12 mg); fractions 30 and 31, white crystals (**6**, 10 mg).

The dry solid (3 g) obtained by evaporating the aqueous layer was dissolved in MeOH (15 mL). The insoluble part was separated by centrifugation. The liquid was transferred to a Sephadex LH-20 column (100 × 5 cm) and eluted by MeOH to produce 97 fractions (10 mL each). Fractions that had identical compositions by TLC using system 1 were combined. Fraction 35 afforded **5** (11 mg); combined 37–49, **1** (9 mg).

Separation of the EtOAc fraction by isocratic HPLC (40% MeOH, flow rate 2.5 mL/min) produced **2** (8 mg) and **4** (6 mg).

Chrysoeriol-7-*O*-β-D-glucopyranosyl-4′-*O*-α-L-rhamnopyranoside or tanoside I (1), yellow crystals, mp 256–259°C. IR spectrum (KBr, ν, cm^{-1}): 3400 (OH), 1653, 1606, 1554, 1495, 1354. UV spectrum (MeOH, λ_{max}, nm): 260, 345; +NaOMe – 268, 350; +$AlCl_3$ – 271, 396; + $AlCl_3$/HCl – 270, 390; + NaOAc – 263, 345. Mass spectrum, *m/z*: 607.5356 $[M - H]^-$ (calcd for $C_{28}H_{32}O_{15}$, 608.5386); 299 $[M - H - Glc - Rha]^-$; 284 $[M - H - Glc - Rha - CH_3]^-$; 445 $[M - H - Glc]^-$; 461 $[M - H - Rha]^-$.

Acid Hydrolysis of 1. A MeOH solution of **1** (3 mg) was treated with H_2SO_4 solution (5%), hydrolyzed on a water bath at 80°C for 2 h, cooled, diluted with H_2O, and extracted with EtOAc. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness. The solid was dissolved in MeOH, after which the aglycon crystallized,

mp 325–330°C. UV spectrum (MeOH, λ_{max}, nm): 265, 345; +NaOMe – 267, 405; +$AlCl_3$ – 274, 396; + $AlCl_3$/HCl – 275, 394; + NaOAc – 274, 355. The aqueous fraction was neutralized by AV-17 anion-exchanger (OH^--form). Sugars were identified by comparing paper chromatograms with authentic D-glucose and L-rhamnose using system 3.

Chrysoeriol-4′-*O*-α-L-rhamnopyranoside or tanoside II (2), yellow crystals, mp 272–275°C. IR spectrum (KBr, ν, cm^{-1}): 3460 (OH), 1654, 1606, 1415, 1252. UV spectrum (MeOH, λ_{max}, nm): 266, 346; +NaOMe – 265, 345; +$AlCl_3$ – 270, 380; + $AlCl_3$/HCl – 280, 360; + NaOAc – 282, 346. Mass spectrum, *m/z*: 445.3967 $[M - H]^-$ (calcd for $C_{22}H_{22}O_{10}$, 446.3978), 299.2671 $[M - H - Rha]^-$; 284.2581 $[M - H - Rha - CH_3]^-$. Table 1 lists the PMR and ^{13}C NMR spectra.

Acid hydrolysis of 2 (3 mg) was performed analogously to that for **1** to produce the aglycon, mp 327–330°C. UV spectrum (MeOH, λ_{max}, nm): 260, 343; +NaOMe – 265, 400; +$AlCl_3$ – 267, 396; + $AlCl_3$ + HCl – 273, 394; + NaOAc – 263, 345. The sugar component was identified as L-rhamnose.

Apigenin (3), pale-yellow crystals, mp 340–342°C, sublimes at 230°C. Mass spectrum, *m/z*: 269.0533 $[M - H]^-$ (calcd for $C_{15}H_{10}O_5$, 270.0528). ^1H NMR spectrum (δ, ppm, J/Hz): 7.55 (2H, d, J = 8.9, H-2′, 6′), 7.41 (2H, d, J = 8.9, H-3′, 5′), 7.18 (1H, d, J = 2.0, H-8), 7.10 (1H, s, H-3), 7.01 (1H, d, J = 2.0, H-6). ^{13}C NMR spectrum (δ, ppm): 165.2 (C-2), 104.3 (C-3), 183.1 (C-4), 162.1 (C-5), 100.2 (C-6), 164.9 (C-7), 95.6 (C-8), 159.7 (C-9), 105.1 (C-10), 122.7 (C-1′), 129.8 (C-2′, 6′), 117.4 (C-3′, 5′), 161.8 (C-4′).

Tamarixin or tamarixetin-3-*O*-β-D-glucopyranoside (4), pale-yellow crystals, mp 315°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3400 (OH), 1652, 1600, 1561, 1506, 1290, 1207, 1165. UV spectrum (MeOH, λ_{max}, nm): 255, 288, 375; + $AlCl_3$: 270, 300, 390; + $AlCl_3$/HCl: 270, 300, 375; + NaOMe: 270, 330, 410. Mass spectrum, *m/z*: 477.401 $[M - H]^-$ (calcd for $C_{22}H_{22}O_{12}$, 478.406); 315.230 $[M - H - Glc]^-$; 300.042 $[M - H - Glc - CH_3]^-$. ^1H NMR spectrum (δ, ppm, J/Hz): 7.96 (1H, d, J = 2.0, H-2′), 7.63 (1H, dd, J = 2.0, 8.4, H-6′), 6.92 (1H, d, J = 8.4, H-5′), 6.44 (1H, d, J = 2.0, H-8), 6.23 (1H, d, J = 2.0, H-6), 5.48 (1H, d, J = 7.2, H-1″), 3.30–3.75 (m, D-glucose protons), 3.96 (3H, s, 4′-OC<u>H</u>$_3$). ^{13}C NMR spectrum (δ, ppm): 160.2 (C-2), 136.7 (C-3), 173.9 (C-4), 164.1 (C-5), 100.1 (C-6), 167.7 (C-7), 94.4 (C-8), 159.8 (C-9), 104.9 (C-10), 125.2 (C-1′), 114.9 (C-2′), 152.4 (C-3′), 150.3 (C-4′), 115.1 (C-5′), 129.8 (C-6′), 105.4 (C-1″), 75.1 (C-2″), 77.8 (C-3″), 71.4 (C-4″), 78.7 (C-5″), 63.4 (C-6″).

Kaempferol-3-*O*-β-D-glucopyranosyl(2→1)-*O*-α-L-rhamnopyranoside or kaempferol-3-*O*-β-D-neohesperidoside (5), yellow compound, mp 195–199°C. IR spectrum (KBr, ν, cm^{-1}): 3400 (OH), 1662, 1615, 1514, 1494. UV spectrum (MeOH, λ_{max}, nm): 266, 295, 350; +NaOMe – 276, 320, 405; +$AlCl_3$ – 275, 315, 390; + $AlCl_3$/HCl – 275, 310, 386; + NaOAc – 272, 316, 390. Mass spectrum, *m/z*: 593.513 $[M - H]^-$ (calcd for $C_{27}H_{30}O_{15}$, 594.5121); 447.192 $[M - H - Rha]^-$; 285.219 $[M - H - Rha - Glc]^-$. ^1H NMR spectrum (δ, ppm, J/Hz): 8.10 (1H, d, J = 2.1, H-2′, 6′), 6.92 (1H, dd, J = 2.1, 8.3, H-3′, 5′), 6.42 (1H, d, J = 2.0, H-8), 6.22 (1H, d, J = 2.0, H-6), 5.76 (1H, d, J = 7.2, Glc H-1), 5.22 (1H, s, Rha H-1), 3.40–4.45 (m, sugar protons), 1.29 (3H, d, J = 6, C<u>H</u>$_3$-Rha). ^{13}C NMR spectrum (δ, ppm): 155.4 (C-2), 133.6 (C-3), 178.1 (C-4), 161.5 (C-5), 98.6 (C-6), 164.3 (C-7), 94.0 (C-8), 156.7 (C-9), 104.3 (C-10), 120.5 (C-1′), 131.2 (C-2′), 115.2 (C-3′), 160.2 (C-4′), 115.2 (C-5′), 131.2 (C-6′), 99.0 (C-1″), 77.3 (C-2″), 76.7 (C-3″), 70.4 (C-4″), 77.0 (C-5″), 62.7 (C-6″), 100.4 (C-1‴), 71.0 (C-2‴), 71.7 (C-3‴), 72.0 (C-4‴), 66.7 (C-5‴), 17.8 (<u>C</u>H$_3$-Rha).

β-Sitosterol-3-*O*-β-D-glucopyranoside or daucosterol (6), white crystals, mp 289–292°C. Mass spectrum, *m/z* 576.86, $C_{35}H_{60}O_6$. IR spectrum (KBr, ν, cm^{-1}): 3425 (OH), 2960 (CH_3), 1460, 1075, 1020 (CH-CH). ^1H NMR spectrum (δ, ppm, J/Hz): 0.74 (3H, s, CH_3-18), 0.84 (3H, d, J = 6.8, CH_3-27), 0.87 (3H, d, J = 5.5, CH_3-26), 0.88 (3H, t, J = 7.4, CH_3-29), 0.95 (3H, d, J = 5.1, CH_3-21), 0.93 (1H, m, H-24), 0.96 (1H, m, H-9), 1.02 (1H, m, H_a-11), 1.03 (1H, m, H-14), 1.05 (3H, s, CH_3-19), 1.09 (1H, m, H_a-1), 1.12 (1H, m, H_a-15), 1.14 (1H, m, H-17), 1.19 (1H, m, H_a-12), 1.22 (2H, m, H-23), 1.28 (2H, m, H-28), 1.33 (1H, m, H_a-16), 1.32 (1H, m, H_a-22), 1.40 (1H, m, H-20), 1.45 (2H, m, H_b-11), 1.48 (1H, m, H-8), 1.55 (1H, m, H_a-7), 1.55 (1H, m, H_b-22), 1.61 (1H, m, H_b-15), 1.63 (1H, m, H_a-2), 1.69 (1H, m, H-25), 1.88 (1H, m, H_b-16), 1.89 (1H, m, H_b-1), 1.93 (1H, m, H_b-2), 1.99 (1H, m, H_b-7), 2.05 (1H, m, H_b-12), 2.27 (1H, br.t, J = 10.0, H_a-4), 2.43 (1H, m, H_b-4), 3.16 (1H, dd, J = 7.8, 9.0, H-2′), 3.27 (1H, m, H-5′), 3.28 (1H, m, H-4′), 3.36 (1H, dd, J = 9.0, 9.0, H-3′), 3.59 (1H, m, H-3), 3.66 (1H, dd, J = 4.7, 12.0, H_a-6′), 3.90 (1H, dd, J = 1.7, 12.0, H_b-6′), 4.39 (1H, dd, J = 7.8, H-1′), 5.38 (1H, d, J = 5.0, H-6). ^{13}C NMR spectrum (δ, ppm): 38.2 (C-1), 30.4 (C-2), 79.7 (C-3), 39.4 (C-4), 141.8 (C-5), 122.5 (C-6), 32.7 (C-7), 33.0 (C-8), 51.4 (C-9), 37.6 (C-10), 21.8 (C-11), 40.8 (C-12), 43.4 (C-13), 57.8 (C-14), 25.3 (C-15), 29.0 (C-16), 57.1 (C-17), 12.0 (C-18), 19.7 (C-19), 37.1 (C-20), 19.1 (C-21), 32.8 (C-22), 27.0 (C-23), 47.1 (C-24), 30.0 (C-25), 19.6 (C-26), 19.6 (C-27), 23.9 (C-28), 12.0 (C-29), 102.1 (C-1′), 74.8 (C-2′), 77.9 (C-3′), 71.4 (C-4′), 77.7 (C-5′), 62.7 (C-6′).

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