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A new hemiterpene glycoside from the ripe tomatoes

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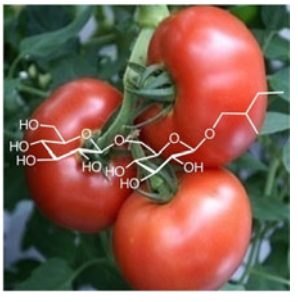

A new hemiterpene glycoside (**1**) was isolated from ripe tomatoes (the fruit of *Lycopersicon esculentum*, Solanaceae) along with eight known compounds. The chemical structure of **1** was determined to be 2-methylbutan-1-ol β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside, based on spectroscopic data as well as chemical evidence. In addition, the radical-scavenging activities of the isolated compounds on the free radical of 1,1-diphenyl-2-picrylhydrazyl were examined. Among the tested compounds, tryptophan, 4-*O*-β-D-glucopyranosyl caffeic acid and dihydro-*p*-coumaryl alcohol γ-*O*-β-D-glucopyranoside demonstrated 42.0%, 50.1% and 76.0% scavenging activities, respectively, at a concentration of 0.5 mM.

Keywords: *Lycopersicon esculentum*; tomato; Solanaceae; hemiterpene glycoside; radical-scavenging effect

1. Introduction

Tomatoes, the fruit of *Lycopersicon esculentum* (syn. *Solanum lycopersicum* L., Solanaceae), are fresh vegetables and are used for cooking and consumption. In previous articles (Fujiwara et al. 2003, 2004; Ono et al. 2006, 2008, 2010; Ohno et al. 2011), we reported the isolation and structural elucidation of chemical constituents from ripe tomatoes of some cultivars ('Momotaro', 'Italian San Marzano', 'Chika' and 'Komomo'). As part of an ongoing study regarding the chemical constituents of tomatoes, here we describe the isolation and structural characterisation of a new hemiterpene glycoside along with eight known compounds from a cultivar known as 'Momotarofight'. In addition, the radical-scavenging activity of the isolated

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compounds on the free radical of 1,1-diphenyl-2-picrylhydrazyl (DPPH) is also described herein.

2. Results and discussion

Smashed ripe tomatoes were successively extracted with H_2O and methanol (MeOH). Each extract was separately subjected to Diaion HP20 column chromatography (Mitsubishi Chemical Industries Co., Ltd., Tokyo, Japan) and eluted with H_2O, MeOH and acetone in turn. The both MeOH eluates were each concentrated *in vacuo* and combined to yield fraction 1; this fraction demonstrated the radical-scavenging activity on DPPH (Ono et al. 2010). Furthermore, fraction 1 was subjected to Sephadex LH-20, silica gel and Chromatorex ODS column chromatography, as well as HPLC on ODS to yield nine compounds (**1**–**9**).

Compound **1** was obtained as an amorphous powder, and exhibited an $[M + Na]^+$ ion peak at *m/z* 435 in the positive ion FAB-MS. The high-resolution (HR)-positive ion FAB-MS suggested that the molecular formula of **1** was $C_{17}H_{32}O_{11}$. The ^{1}H NMR spectrum of **1** exhibited signals due to a primary methyl group [δ 0.80 (3H, t, $J = 7.5$ Hz)], a secondary methyl group [δ 0.94 (3H, d, $J = 7.0$ Hz)] and two anomeric protons [δ 5.15 (1H, d, $J = 7.5$ Hz), 4.76 (1H, d, $J = 8.0$ Hz)]. The ^{13}C NMR spectrum of **1** displayed signals due to a methine carbon (δ 35.4), an oxygenated methylene carbon (δ 62.8), a methylene carbon (δ 26.4) and two methyl carbons (δ 16.8, 11.4) attributed to an aglycone moiety (Agl), along with those due to two hexosyl groups. Accordingly, **1** was determined to be a diglycoside of 2-methylbutan-1-ol. Upon acidic hydrolysis, **1** afforded D-glucose, as confirmed by optical rotation using chiral detection in HPLC analysis. The ^{1}H and ^{13}C NMR signals in **1** were assigned with the aid of ^{1}H–^{1}H COSY, HMQC and HMBC spectra (see Supplementary material, Table S1, Figure S1). The coupling constants of the signals owing to the anomeric and methine protons indicated that the glucosyl groups were of the pyranose type and that glycosidic linkages were of the β-form in the $^4C_1$ conformation. Moreover, the glycosylation shift (+7.7 ppm) (Kasai et al. 1977; Seo et al. 1978) at C-6 of the inner glucosyl group (Glc) in the ^{13}C NMR of **1**, and the HMBC correlations between C-1 of Agl and H-1 of Glc and between C-6 of Glc and H-1 of the terminal glucosyl group (Glc′) suggested that the sugar linkages in **1** were formed at the OH-6 of Glc and the OH-1 of Agl. Consequently, **1** was determined to be 2-methylbutan-1-ol β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside (Figure 1). However, the absolute configuration of Agl of **1** could not be assigned.

Compounds **2**–**9** were identified as corchoionoside C (**2**) (Yoshikawa et al. 1997), tryptophan (**3**), 4-*O*-β-D-glucopyranosyl caffeic acid (**4**) (Cui et al. 1990), dihydroconiferyl 4-*O*-β-D-glucopyranoside (**5**) (Higuchi et al. 1977), dihydro-*p*-coumaryl alcohol γ-*O*-β-D-glucopyranoside (**6**) (Cui et al. 1990), tomato-pregnane (**7**) (Fujiwara et al. 2005), 3-*O*-β-lycotetraosyl 3β,16β-dihydroxy-5α-pregnane-20-carboxylic acid 16,22-lactone (**8**) (Zhou et al. 2006) and esculeoside A (**9**) (Fujiwara et al. 2003, 2004), respectively, based on comparison to the spectral data of authentic samples or to those reported previously. Detailed ^{1}H NMR spectral data of **8** were not previously reported and the some ^{13}C NMR chemical shift assignments of **8** were slightly different (Table S2).

The radical-scavenging activities of **1**–**9** on DPPH were examined. Compounds **3**, **4** and **6** demonstrated 42.0%, 50.1% and 76.0% scavenging activities, respectively, at a concentration of 0.5 mM. However, the activities of the other compounds were less than 10% (data not shown) (Figure S2). In a parallel experiment, a positive control (Trolox) showed 92.3% of DPPH radical-scavenging activity.

Notably, increased alkaline phosphatase activity by **2** (Tung et al. 2009), antioxidative and AGE production inhibition by **3** (Selenge et al. 2013), cytotoxicity by **8** and **9** (Ikeda et al. 2003; Fujiwara et al. 2004) and inhibition of cholesterol ester accumulation in macrophage owing to **9** (Nohara et al. 2010) were previously reported.

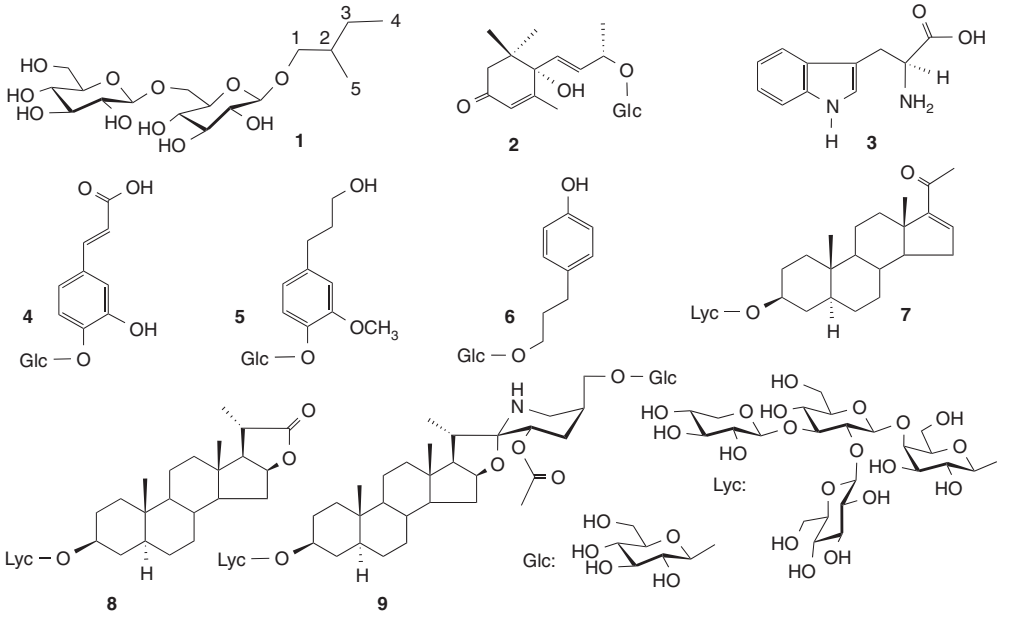

Figure 1. Structures of **1**–**9**.

3. Experimental

3.1. *General experimental procedures*

Optical rotations were performed with a JASCO DIP-1000 KYU digital polarimeter (JASCO Co., Tokyo, Japan). MS were recorded on a JEOL JMS-DX-303HF (JEOL Ltd., Tokyo, Japan). ^{1}H and ^{13}C NMR spectra were recorded with a JEOL alpha-500 spectrometer (JEOL Ltd., Tokyo, Japan), and chemical shifts were given on a δ (ppm) scale with tetramethylsilane as an internal standard. Silica gel 60 (Merck, Art. 1.09385; Merck, Darmstadt, Germany), Sephadex LH-20 (Pharmacia Fine Chemicals, Uppsala, Sweden), Chromatorex ODS (Fuji Silysia Chemical, Ltd., Aichi, Japan) and Diaion HP20 (Mitsubishi Chemical Industries Co., Ltd., Tokyo, Japan) were used for column chromatography. HPLC separation was run on a Shimadzu LC-10AS micro pump (Shimadzu Co., Kyoto, Japan) with a Shimadzu RID-10A RI-detector (Shimadzu Co., Kyoto, Japan). For HPLC column chromatography, COSMOSIL 5C18-AR-II (Nacalai Tesque, Inc., Kyoto, Japan, 20 mm i. d. × 250 mm) was used.

3.2. *Plant material*

The fruits of *L. esculentum* 'Momotarofight' were collected in August 2008 at the farm of Tokai University, Kumamoto Prefecture, Japan.

3.3. *Extraction and isolation*

The smashed ripe fruits of *L. esculentum* (8998 g) were successively extracted with H_2O (8930 mL) and MeOH (8990 mL) at room temperature. The H_2O extract was subjected to Diaion HP20 (H_2O, MeOH, acetone) to yield MeOH-eluted fraction (fr.) (10.3 g) and acetone-eluted fr. (0.1 g). The MeOH extract was concentrated under reduced pressure to yield a syrup (26.9 g), which was subjected to Diaion HP20 (H_2O, MeOH and acetone) to yield MeOH-eluted fr. (3.8 g) and acetone-eluted fr. (0.6 g). Both of the MeOH-eluted fractions (frs.) were combined to yield

fr. 1, which was chromatographed over Sephadex LH-20 [H_2O–MeOH (90% MeOH, 100% MeOH)] to yield frs. 2–4. Chromatography of fr. 2 (5.8 g) over silica gel [$CHCl_3$–MeOH–H_2O (14:2:0.1, 10:2:0.1, 8:2:0.2, 7:3:0.5, 6:4:1, 0:1:0)] furnished frs. 2-1–2-4. Fraction 2-2 (97 mg) was chromatographed over Chromatorex ODS [H_2O–MeOH (30% MeOH, 40% MeOH, 50% MeOH, 60% MeOH, 70% MeOH, 80% MeOH, 90% MeOH, 100% MeOH)] to yield frs. 2-2-1–2-2-4. Fractions 2-2-2 (14 mg) and 2-2-3 (11 mg) were each subjected to HPLC (30% MeOH) to afford **5** (6 mg) from fr. 2-2-2 and **2** (4 mg) from fr. 2-2-3. Chromatography of fr. 2-3 (1.4 g) over Chromatorex ODS [H_2O–MeOH (20% MeOH, 30% MeOH, 40% MeOH, 50% MeOH, 60% MeOH, 70% MeOH, 80% MeOH, 90% MeOH, 100% MeOH)] furnished frs. 2-3-1–2-3-8. Fractions 2-3-2 (17 mg), 2-3-4 (120 mg), 2-3-5 (34 mg) and 2-3-7 (18 mg) were each subjected to HPLC (fr. 2-3-2, 15% MeOH; frs. 2-3-4, 2-3-5, and 2-3-7, 65% MeOH) to yield **1** (7 mg) from fr. 2.3.2, **9** (10 mg) from fr. 2-3-4, **8** (3 mg) from fr. 2-3-5 and **7** (6 mg) from fr. 2-3-7. Fraction 3 (3.7 g) was chromatographed over silica gel [$CHCl_3$–MeOH–H_2O (10:2:0.1, 8:2:0.2, 7:3:0.5, 6:4:1, 0:1:0)] to yield frs. 3-1–3-7. Fraction 3-2 (253 mg) was subjected to Chromatorex ODS [H_2O–MeOH (10% MeOH, 20% MeOH, 30% MeOH, 40% MeOH, 50% MeOH, 60% MeOH, 70% MeOH, 80% MeOH, 100% MeOH)] to yield frs. 3-2-1–3-2-4. Fractions 3-4 (102 mg), 3-6 (143 mg), 3-2-2 (29 mg) and 3-2-3 (30 mg) were each subjected to HPLC (frs. 3-4 and 3-6, 30% MeOH; frs. 3-2-2 and 3-2-3, 20% MeOH) to afford **4** (7 mg) from fr. 3-4, **3** (21 mg) from fr. 3-6, **5** (6 mg) from fr. 3-2-2 and **6** (18 mg) from fr. 3-2-3.

1: Amorphous powder. $[\alpha]_D^{25}$ −42.6° ($c = 0.8$, MeOH). ^{1}H NMR (pyridine-d_5, 500 MHz) δ: 5.15 (1H, d, $J = 7.5$ Hz, Glc′-1), 4.87 (1H, dd, $J = 1.5$ and 11.5 Hz, Glc-6a), 4.76 (1H, d, $J = 8.0$ Hz, Glc-1), 4.54 (1H, dd, $J = 1.5$ and 12.0 Hz, Glc′-6a), 4.39 (1H, dd, $J = 4.5$ and 12.0 Hz, Glc′-6b), 4.36 (1H, dd, $J = 6.5$ and 11.5 Hz, Glc-6b), 4.27* (Glc′-4), 4.26* (Glc′-3), 4.21 (1H, dd, $J = 8.5$ and 8.5 Hz, Glc-3), 4.16 (1H, dd, $J = 8.5$ and 8.5 Hz, Glc-4), 4.11 (1H, m, Glc-5), 4.08* (Agl-1a), 4.06* (Glc′-2), 4.00 (1H, dd, $J = 8.0$ and 8.5 Hz, Glc-2), 3.99 (1H, dd, $J = 6.5$ and 9.5 Hz, Agl-1b), 3.95 (1H, m, Glc′-5), 1.72 (1H, m, Agl-2), 1.51 (1H, m, Agl-3a), 1.11 (1H, m, Agl-3b), 0.94 (3H, d, $J = 7.0$ Hz, Agl-5), 0.80 (3H, t, $J = 7.5$ Hz, Agl-4). Asterisk (*) indicates overlapping signals. ^{13}C NMR (pyridine-d_5, 125 MHz) δ: 105.5 (Glc′-1), 104.9 (Glc-1), 78.5 (Glc-3), 78.5 (Glc′-3), 78.5 (Glc′-5), 77.3 (Glc-5), 75.3 (Glc′-2), 75.1 (Glc-2), 75.0 (Agl-1), 71.8 (Glc-4), 71.7 (Glc′-4), 70.2 (Glc-6), 62.8 (Glc′-6), 35.4 (Agl-2), 26.4 (Agl-3), 16.8 (Agl-5), 11.4 (Agl-4). Positive FAB-MS *m/z*: 435 $[M + Na]^+$. HR-positive FAB-MS *m/z*: 435.1836 (calcd for $C_{17}H_{32}O_{11}Na$: 435.1843).

8: Amorphous powder. $[\alpha]_D^{25}$ −29.3° ($c = 0.4$, MeOH). ^{1}H NMR (pyridine-d_5, 500 MHz) δ: 5.54 [1H, d, $J = 7.5$ Hz, terminal glucosyl group (Glc′)-1], 5.19 [1H, d, $J = 7.5$ Hz, xylosyl group (Xyl)-1], 5.15 [1H, $J = 8.0$ Hz, inner glucosyl group (Glc)-1], 4.99 [1H, ddd, $J = 4.5$, 7.5 and 7.5 Hz, aglycone moiety (Agl)-16], 4.90 [1H, d, $J = 8.0$ Hz, galactosyl group (Gal)], 4.64 (1H, dd, $J = 8.5$ and 11.0 Hz, Gal-6a), 4.61 (1H, d, $J = 3.5$ Hz, Gal-4), 4.52 (1H, dd, $J = 1.5$ and 10.5 Hz, Glc′-6a), 4.49 (1H, dd, $J = 1.5$ and 10.0 Hz, Glc-6a), 4.41 (1H, dd, $J = 7.5$ and 9.5 Hz, Gal-2), 4.37* (Glc′-6b), 4.34 (1H, dd, $J = 8.0$ and 8.5 Hz, Glc-2), 4.23* (Gal-6b), 4.23* (Xyl-5a), 4.18* (Gal-3), 4.18* (Xyl-3), 4.17* (Glc′-4), 4.12* (Xyl-4), 4.11 (1H, dd, $J = 8.5$ and 8.5 Hz, Glc-3), 4.09* (Glc′-3), 4.07 (1H, dd, $J = 7.5$ and 8.5 Hz, Glc′-2), 4.05* (Gal-5), 4.03* (Glc-6b), 3.95 (1H, dd $J = 8.0$ and 8.5 Hz, Xyl-2), 3.94* (Agl-3), 3.93* (Glc′-5), 3.85* (Glc-5), 3.78 (1H, dd, $J = 8.5$ and 8.5 Hz, Glc-4), 3.68 (1H, dd, $J = 10.5$ and 10.5 Hz, Xyl-5b), 2.70 (1H, q, 7.5), 2.17 (1H, ddd, $J = 6.5$, 7.5 and 14.0 Hz, Agl-15a), 2.06 (1H, m, Agl-2a), 1.84 (1H, br d, $J = 7.5$ Hz, Agl-17), 1.81* (Agl-4a), 1.65* (Agl-12a), 1.61* (Agl-2b), 1.50* (Agl-7a), 1.48* (Agl-1a), 1.40* (Agl-4b), 1.39* (Agl-15b), 1.37* (Agl-11a), 1.31 (3H, d, $J = 7.5$ Hz, Agl-21), 1.27* (Agl-8), 1.14* (Agl-6a), 1.11* (Agl-11b), 1.09* (Agl-6b), 1.00 (1H, m, Agl-12b), 0.92* (Agl-14), 0.90* (Agl-5), 0.81* (Agl-7b), 0.79* (Agl-1b), 0.70 (3H, s, Agl-18), 0.62 (3H, s, Agl-19), 0.51 (1H, ddd, $J = 2.5$, 8.5 and 8.5 Hz, Agl-9). Asterisk (*) indicates overlapping signals. ^{13}C NMR (pyridine-d_5, 125 MHz) δ: 181.1 (Agl-22), 105.1 (Glc-1), 104.9 (Xyl-1), 104.8 (Glc′-1), 102.4 (Gal-1), 86.8 (Glc-3), 82.7 (Agl-16), 81.3 (Glc-2), 79.9 (Gal-4), 78.7 (Agl-

3), 78.6 (Xyl-3), 77.8 (Glc′-5), 77.6 (Glc′-3), 77.3 (Glc-5), 76.2 (Glc′-2), 75.6 (Gal-5), 75.4 (Gal-3), 75.1 (Xyl-2), 73.2 (Gal-2), 71.1 (Glc′-4), 70.7 (Xyl-4), 70.5 (Glc-4), 67.3 (Xyl-5), 63.0 (Glc-6), 62.5 (Glc′-6), 60.6 (Gal-6), 59.0 (Agl-17), 54.5 (Agl-9), 54.5 (Agl-14), 44.6 (Agl-5), 41.8 (Agl-13), 38.2 (Agl-12), 37.2 (Agl-1), 36.3 (Agl-20), 35.8 (Agl-10), 34.9 (Agl-8), 34.8 (Agl-4), 33.2 (Agl-15), 32.3 (Agl-7), 29.8 (Agl-2), 28.8 (Agl-6), 20.7 (Agl-11), 17.9 (Agl-21), 13.8 (Agl-18), 12.2 (Agl-19).

3.4. *Acidic hydrolysis of 1*

Compound **1** (1 mg) was heated in 2 M HCl–dioxane (2:1, 1.5 mL) at a temperature of 95°C for 1 h. The reaction mixture was extracted with ethyl acetate. The aqueous layer was neutralised with Amberlite MB-3 (Organo Co., Tokyo, Japan) and then evaporated under reduced pressure to yield a monosaccharide fr. This fr. was analysed by HPLC under the following conditions: column, Shodex RS-Pac DC-613 (Showa Denko, Tokyo, Japan, 6.0 mm i.d. × 150 mm); solvent, $CH_3CN–H_2O$ (3:1); flow rate, 1.0 mL/min; column temperature, 70°C; detector, JASCO OR-2090 plus (Jasco, Tokyo, Japan); pump, JASCO PU-2080 (Jasco; and column oven, JASCO CO-2060 (Jasco). The retention time (t_R) and optical activity of the monosaccharide from **1** were identical with those [t_R (min) 6.9; optical activity, positive] of D-glucose.

3.5. *DPPH radical-scavenging assay*

The DPPH radical-scavenging effect of sample was measured based on the following method (Blois 1958). The standard assay mixture, in a final volume of 200 μL, contained 10 μL of sample, 90 μL of 70% ethanol, 100 μL of 0.1 M sodium acetate buffer (pH 5.5). The reaction was started by the addition of 50 μL of 0.5 mM DPPH freshly prepared in ethanol, allowed to proceed for 30 min at room temperature. The absorbance of the resulting solution was measured at 517 nm using microplate reader (SH-1000Lab, Corona Electric, Ibaragi, Japan). Trolox was used as a positive control. Results presented are the means of four experiments. The DPPH radical-scavenging effect as percentage of breaching rate of DPPH was calculated by the following formula:.

$$\mathrm{DPPH}_{\text{radical-scavenging effect}}(\%) = \left[1 - \frac{A_{\text{sample}} - A_{\text{blank}}}{A_{\text{control}} - A_{\text{blank}}}\right] \times 100,$$

where A_{sample} is the absorbance of the sample and A_{blank} is the absorbance in the presence of neither any samples nor DPPH solution. A_{control} is the absorbance in the absence of the sample.

4. Conclusion

In this study, we isolated and elucidated the structures of nine compounds from the ripe tomatoes ‘Momotarofight’. Among them, one compound was a new hemiterpene glycoside. In addition, three aromatic compounds demonstrated DPPH radical-scavenging activities. We previously isolated and determined the chemical constituents from several other tomato cultivars (‘Momotaro’, ‘Italian San Marzano’, ‘Chika’ and ‘Komomo’). Therefore, screening for those compounds in various biological assays may facilitate the delineation of chemically active constituents from this tomato cultivar. This is a part of our overall goal to fully elucidate the health benefits of tomatoes. Further investigations are warranted to achieve this goal.

Supplementary material

Supplementary material relating to this article is available online, alongside Tables S1 and S2, Figures S1–S14.

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