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ORIGINAL ARTICLE

Glucosylated caffeoylquinic acid derivatives from the flower buds of *Lonicera japonica*

Yang Yu[a], Zhibo Jiang[a], Weixia Song[a], Yongchun Yang[a], Yuhuan Li[b], Jiandong Jiang[a,b], Jiangong Shi[a,*]

[a]*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*
[b]*Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*

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Abstract Three new glucosylated caffeoylquinic acid isomers (**1**–**3**), along with six known compounds, have been isolated from an aqueous extract of the flower buds of *Lonicera japonica*. Structures of the new compounds were determined by spectroscopic and chemical methods as (−)-4-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl)quinic acid (**1**), (−)-3-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl)quinic acid (**2**), and (−)-5-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl)quinic acid (**3**), respectively. In the preliminary *in vitro* assays, two known compounds methyl caffeate and 2′-*O*-methyladenosine showed inhibitory activity against Coxsackie virus B3 with IC_{50} values of 3.70 μmol/L and 6.41 μmol/L and SI values of 7.8 and 12.1, respectively.

*Corresponding author. Tel.: +86 10 83154789; fax: +86 10 63037757.
E-mail address: shijg@imm.ac.cn (Jiangong Shi).

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1. Introduction

The flower buds of *Lonicera japonica* Thunb. (Caprifoliaceae), known as Jin Yin Hua in Chinese, are used for treating influenza, cold fever, and infections in traditional Chinese medicine[1]. Caffeoyl quinic acids, secoiridoids, flavonoids, saponins, cerebrosides, polyphenols and nitrogen containing iridoids[2–9] were mainly isolated from alcoholic extracts of this medicine. As part of a program to assess the chemical and biological diversity of traditional Chinese medicines, we conducted detailed chemical analysis of an aqueous extract of the flower buds of *L. japonica*, since the flower bud decoction is practically used. Our previous studies on the aqueous extract led to the isolation of 27 homosecoiridoids containing *N*-substituted pyridinium units (lonijaposides A–W) and phenylpyruvic acid derived moieties (lonipheny-ruviridosides A–D)[10–12], two *β*-amino-acid-coupled secoiridoids (serinosecologanin and threonosecologanin)[13], and two 1-(6′-*O*-acyl-*β*-D-glucopyranosyl)pyridinium-3-carboxylates (lonijaponinicotinosides A and B)[14], as well as 19 known compounds. In addition, the decocted flower bud residue was further extracted with EtOH (95%), and six new aromatic glycosides and 48 known compounds were characterized from the EtOH extract[15,16]. The study continues on the aqueous extract, leading to the isolation of three glucosylated caffeoylquinic acid isomers (**1**–**3**) (Fig. 1), together with six known compounds. We report herein the isolation, structure determination and biological activity of the new isolates.

2. Results and discussion

Compound **1** was obtained as a white amorphous powder with $[\alpha]_D^{20}$ of −78.6 (*c* 0.10, H_2O). The IR spectrum of **1** displayed absorption bands for hydroxyl (3335 cm^{-1}), carbonyl (1693 cm^{-1}), double bond (1631 cm^{-1}), and aromatic ring (1609 cm^{-1} and 1508 cm^{-1}) functional groups. The molecular formula $C_{22}H_{28}O_{14}$ was indicated by HR-ESI-MS at *m/z* 515.1392 $[M-H]^-$ and the NMR spectral data (Table 1). The NMR spectra of **1** displayed characteristic resonances for the caffeoylquinic acid analogues[17] except for the presence of additional signals assignable to a *β*-glucopyranosyl moiety. This suggested that **1** was a caffeoylquinic acid *β*-glucopyranoside. The suggestion was confirmed by alkali hydrolysis of **1** with 2 mol/L NaOH. From the hydrolysate, two products were isolated and identified by comparison of their specific rotation $[\alpha]_D^{20}$ and spectral data with the reported data to be (−)-quinic acid[18] and (−)-4-*O*-*β*-D-glucopyranosylcaffeic acid[19,20], respectively. The linkage of the structure moieties was further deduced by 2D NMR spectroscopic

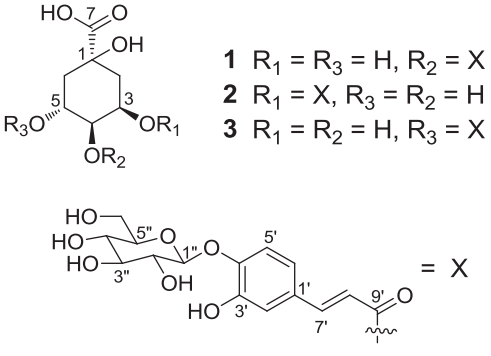

Figure 1 The structures of compounds **1**–**3**.

data analysis. Particularly, in the ^1H-^1H gCOSY spectrum, cross peaks H_2-2/H-3/H-4/H-5/H_2-6, H-5′/H-6′, H-7′/H-8′, and H-1″/H-2″/H-3″/H-4″/H-5″/H_2-6″ (Fig. 2) proved the presence of vicinal coupling extensions of the quinic acid, caffeoyl, and *β*-glucopyranosyl units in **1**. In the HMBC spectrum, correlations from H-4 to C-9′ and from H-1″ to C-4′, together with the chemical shifts of these proton and carbon resonances, revealed that the caffeoyl unit was located at C-4 of the quinic acid moiety and the *β*-glucopyranosyloxy group at C-4′ of the caffeoyl unit. Therefore, the structure of compound **1** was determined as (−)-4-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl)quinic acid.

Compound **2**, a white amorphous powder with $[\alpha]_D^{20}$ of 71.7 (*c* 0.15, H_2O), showed spectral data similar with those of **1** (see Table 1 and Section 3), indicating that it was an isomer of **1**. Comparison of the NMR spectral data of **2** with those of **1** suggested that the 4-*O*-*β*-D-glucopyranosylcaffeoyloxy moiety was at C-3 of the quinic acid unit in **2** instead of at C-4 in **1**. This was confirmed by 2D NMR data analysis and alkali hydrolysis of **2**. Especially, the COSY cross peaks H_2-2/H-3/H-4/H-5/H_2-6 and the HMBC correlations from H-3 to C-9′ and from H-1″ to C-4′, together with their shifts, proved that the caffeoyl was located at C-3 of the quinic acid unit and the glucopyranosyloxy group at C-4′ of the caffeoyl unit. Alkali hydrolysis of **2** produced the same products as those from **1**. Thus, the structure of compound **2** was determined as (−)-3-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl) quinic acid.

Compound **3**, a white amorphous powder with $[\alpha]_D^{20}$ of −74.2 (*c* 0.10, H_2O), was another isomer of glucosylated caffeoylquinic acid, as indicated by the spectral data (see Table 1 and Section 3). Comparison of the NMR data between **3** and **2** indicated that H-3 and C-3, C-4, and C-6 were shielded by $\Delta\delta_H$ −1.15 and $\Delta\delta_C$ −3.0, −1.7, and −3.1 ppm, respectively, whereas H-5 and C-2 and C-5 were deshielded by $\Delta\delta_H$ +1.1, $\Delta\delta_C$ +1.4 and +4.4 ppm, respectively. This demonstrated that the caffeoyl unit was located at C-5 in **3**. Thus, the structure of compound **3** was assigned as (−)-5-*O*-(4-*O*-*β*-D-glucopyranosylcaffeoyl)quinic acid, which was also confirmed by the COSY cross peaks H_2-2/H-3/H-4/H-5/H_2-6 and the HMBC correlations from H-1″ to C-4′, as well as by alkali hydrolysis that generated (−)-quinic acid and (−)-4-*O*-*β*-D-glucopyranosylcaffeic acid. A literature survey indicated that the structure of **3** was reported in several literatures.[21–24]. However, detailed structural elucidation and physical-chemical properties of the compound were not documented in the literatures.

Although the ^1H NMR spectra of compounds **1**–**3** in D_2O were acquired at 500 or 600 MHz, the partially overlapping resonances were broadened with a low resolution (see Supporting information). Especially, in the ^{13}C NMR spectra, the carbon resonances of the quinic acid moieties were broadened with intensities lower than those of the other units. This demonstrates that the conformation of the quinic acid moieties in these compounds is unstable and that a dynamic conformational fluctuation of the quinic acid moieties should have occurred in the D_2O solutions of **1**–**3**. In addition, two *α*-D-glucopyranosylated caffeoylquinic acid isomers were recently reported from the leaves of *Moringa oleifera*[25], which are only different from compound **1** in the *α*-configuration of the D-glucopyranosyl unit. Interestingly, the reported isomers had the specific rotation data with the signs opposite to and the magnitudes similar to those of **1**–**3**.

The known compounds were identified by comparing the spectroscopic data with those reported in the corresponding literatures as methyl caffeate[20], 4-*O*-caffeoylquinic acid methyl ester (cryptochlorogenic acid methyl ester)[26,27], methyl 4-*O*-*β*-D-glucopyranosylcaffeate[28,29], guanosine[30], 2′-*O*-methyladenosine

Table 1 ^{1}H and ^{13}C NMR spectral data (δ) for compounds **1–3**.[a]

No.	Compound **1**		Compound **2**		Compound **3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		76.0		75.7		76.0
2a	2.23 m	37.6	2.28 brd (15.0)	35.9	2.21 m	37.3
2b	2.10 m		2.19 brd (15.0)		2.07 m	
3	4.37 m	68.5	5.42 brd (1.8)	73.3	4.27 m	70.3
4	4.94 brd (8.0)	78.1	3.79 m	74.1	3.90 m	72.4
5	4.35 m	65.1	4.21 m	67.2	5.31 m	71.6
6a	2.25 m	40.9	2.21 brd (15.0)	40.8	2.25 m	37.7
6b	2.12 m		1.98 dd (15.0, 12.0)		2.10 m	
7		179.3		179.7		178.7
1′		130.2		130.3		130.1
2′	7.21 s	116.0	7.21 s	116.0	7.17 s	115.9
3′		146.2		146.2		146.2
4′		147.4		147.3		147.5
5′	7.17 s	116.7	7.18 s	116.8	7.16 s	116.7
6′	7.17 s	122.9	7.18 s	122.8	7.16 s	122.9
7′	7.68 d (16.0)	146.5	7.64 d (15.6)	146.2	7.58 d (14.5)	146.2
8′	6.49 d (16.0)	116.6	6.47 d (15.6)	117.1	6.38 d (14.5)	116.7
9′		169.2		169.4		169.0
1″	5.13 d (5.0)	101.1	5.13 d (6.6)	101.1	5.11 d (6.0)[b]	101.2
2″	3.65 m	73.4	3.64 m	73.4	3.64 m	73.4
3″	3.66 m	76.0	3.66 m	76.0	3.65 m	76.0
4″	3.54 dd (8.5, 9.0)	69.9	3.54 dd (8.0, 8.0)	69.9	3.55 m	70.0
5″	3.64 m	76.8	3.64 m	76.8	3.64 m	76.8
6″a	3.94 d (12.5)	61.1	3.94 brd (12.0)	61.1	3.94 d (12.0)	61.1
6″b	3.78 dd (12.5, 5.0)		3.79 dd (12.0, 5.4)		3.79 dd (12.0, 5.0)	

[a]Data (δ) were measured in D_2O at 500 MHz (**1** and **3**) and 600 Mz (**2**) for ^{1}H and 125 MHz for ^{13}C (**1–3**). Proton coupling constants (J) in Hz are given in parentheses. The assignments were based on ^{1}H-^{1}H COSY, HSQC, and HMBC experiments; the data for proton resonances were presented as calculated using the solvent peak (δ 4.80 ppm) as the reference, and for carbon resonances as calculated using the methanol peak (δ 49.50 ppm) as the reference.

[b]The signal split was not resolved in the ^{1}H NMR spectrum and the coupling constant was presented as the half width of the peak.

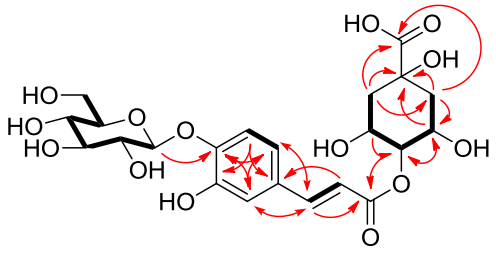

Figure 2 The ^{1}H-^{1}H COSY (thick lines) and key HMBC correlations (arrows, from ^{1}H to ^{13}C) of compound **1**.

(cordysinin B)[31], and (−)-dihydrophaseic acid 4′-*O*-*β*-D-glucopyranoside[32].

In the preliminary *in vitro* assays, methyl caffeate and 2′-*O*-methyladenosine showed inhibitory activity against Coxsackie virus B3 with IC_{50} values of 3.70 μmol/L and 6.41 μmol/L and SI values of 7.8 and 12.1, respectively, and the positive control Pleconaril gave an IC_{50} of 0.000370 μmol/L and an SI value of 41648.7; while other isolates were inactive in the concentration of 10 μmol/L. These results, together with our previous studies[10–16], reveal that the diverse constituents have pharmacological contributions to the traditional uses of the flower buds of *L. japonica*.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on P-2000 polarimeter (JASCO, Tokyo, Japan). UV spectra were measured on a JASCOP-650 spectrometer (JASCO). CD spectra were recorded on a J-815 CD spectrometer (JASCO). IR spectra were recorded on a Nicolet 5700 FT-IR microscope transmission (Thermo Electron Corporation, Madison, USA). NMR spectra were obtained at 500 MHz or 600 MHz for ^{1}H, and 125 MHz for ^{13}C, respectively, on an Inova 500 or SYS 600 MHz spectrometers (Varian Associates Inc., Palo Alto, USA) in D_2O with solvent peaks used as references (unless otherwise noted). ESI-MS and HR-ESI-MS data were measured using an AccuToFCS JMS-T100CS spectrometer (Agilent Technologies, Ltd., Santa Clara, USA). Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Inc., Qingdao, China) and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden). HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector (Waters Corporation, Milford, USA), with an Prevail (250 mm × 10 mm i.d.) column packed with C18 (5 μm) (Alltech Associates Inc., Deerfield, USA). TLC was carried out with glass precoated silica gel

GF_{254} plates (Qingdao Marine Chemical Inc.). Spots were visualized under UV light or by spraying with 7% H_2SO_4 in 95% EtOH followed by heating. Unless otherwise noted, all chemicals were obtained from commercially available sources and were used without further purification.

3.2. Plant material

The flower buds of *L. japonica* were collected in May 2005 from Shangqiu, Henan Province, China. Plant identity was verified by Mr. Lin Ma (Institute of Materia Medica, Beijing 100050, China). A voucher specimen (No. ZH02273) was deposited at the herbarium of the Department of Chemistry of Natural Products, Institute of Materia Medica.

3.3. Extraction and isolation

For the extraction and preliminary fractionation of the extract, see Ref. 10. Fraction B_3-10 (22.1 g) was separated by MPLC over RP silica gel and eluted with a gradient of EtOH (0–50%) in H_2O to give subfractions (B_3-10-1–B_3-10-13). Fraction B_4-5 (3.7 g) was further separated by flash chromatography over RP silica gel and eluted with a gradient of MeOH (0–50%) in H_2O to give subfractions (B_4-5-1–B_4-5-4). B_4-5-2 (765 mg) and B_4-5-3 (940 mg) were separately subjected to RP-HPLC using CH_3CN/H_2O (7:93, *v*/*v*) containing 0.1% HOAc as the mobile phase (1.5 mL/min) to afford **2** (20 mg, t_R = 27.6 min) from B_4-5-2 and **1** (23 mg, t_R = 26.3 min) and **3** (37 mg, t_R = 28.9 min) from B_4-5-3.

3.3.1. (–)-4-O-(4-O-β-D-glucopyranosylcaffeoyl)-quinic acid (*1*)

White amorphous powder; $[\alpha]_D^{20}$ −78.6 (*c* 0.10, H_2O); UV (H_2O) λ_{max} (logε): 195 (4.48), 212 (4.34, sh), 228 (4.15, sh), 236 (4.12, sh), 291 (4.28), 317 (4.23, sh); CD (H_2O): $\Delta\varepsilon_{204\ nm}$ (−1.87), $\Delta\varepsilon_{231\ nm}$ (−1.01), $\Delta\varepsilon_{278\ nm}$ (-0.35), $\Delta\varepsilon_{294\ nm}$ (−0.56), $\Delta\varepsilon_{311\ nm}$ (−0.63), $\Delta\varepsilon_{325\ nm}$ (−0.59); IR ν_{max}: 3335, 2927, 1693, 1631, 1609, 1508, 1440, 1354, 1266, 1166, 1127, 1073, 1045, 982, 895, 856, 812, 627 cm^{-1}; ^1H NMR (D_2O, 500 MHz) and ^{13}C NMR (D_2O, 125 MHz) spectral data, see Table 1; ESI-MS: *m*/*z* 515 $[M-H]^-$; (−)-HR-ESI-MS: *m*/*z* 515.1392 $[M-H]^-$ (Calcd. for $C_{22}H_{27}O_{14}$, 515.1406).

3.3.2. (–)-3-O-(4-O-β-D-glucopyranosylcaffeoyl)-quinic acid (*2*)

White amorphous powder; $[\alpha]_D^{20}$ −71.7 (*c* 0.15, H_2O); UV (H_2O) λ_{max} (logε): 214 (4.54), 237 (4.36, sh), 291 (4.54), 315(4.48); CD (H_2O): $\Delta\varepsilon_{203\ nm}$ (−2.82), $\Delta\varepsilon_{219\ nm}$ (+0.43), $\Delta\varepsilon_{231\ nm}$ (−0.81), $\Delta\varepsilon_{246\ nm}$ (−0.43), $\Delta\varepsilon_{270\ nm}$ (+0.33), $\Delta\varepsilon_{285\ nm}$ (+0.41), $\Delta\varepsilon_{299\ nm}$ (+0.04), $\Delta\varepsilon_{316\ nm}$ (−0.35), $\Delta\varepsilon_{328\ nm}$ (−0.22); IR ν_{max}: 3329, 2919, 2852, 1693, 1630, 1607, 1509, 1439, 1371, 1308, 1268, 1155, 1118, 1073, 1041, 988, 857, 807, 610 cm^{-1}; ^1H NMR (D_2O, 600 MHz) and ^{13}C NMR (D_2O, 125 MHz) spectral data, see Table 1; ESI-MS: *m*/*z* 517 $[M+H]^+$, 539 $[M+Na]^+$, 555 $[M+K]^+$, 515 $[M-H]^-$; (−)-HR-ESI-MS: *m*/*z* 515.1410 $[M-H]^-$ (Calculated for $C_{22}H_{27}O_{14}$, 515.1406).

3.3.3. (–)-5-O-(4-O-β-D-glucopyranosylcaffeoyl)-quinic acid (*3*)

White amorphous powder; $[\alpha]_D^{20}$ −74.2 (*c* 0.10, H_2O); UV (H_2O) λ_{max} (logε): 212 (4.21, sh), 228 (4.01, sh), 289 (4.12), 319 (4.06); CD (H_2O): $\Delta\varepsilon_{203\ nm}$ (−2.21), $\Delta\varepsilon_{227\ nm}$ (−1.73), $\Delta\varepsilon_{235\ nm}$ (−1.33), $\Delta\varepsilon_{262\ nm}$ (+0.03), $\Delta\varepsilon_{299\ nm}$ (−0.36), $\Delta\varepsilon_{319\ nm}$ (−0.63), $\Delta\varepsilon_{331\ nm}$ (−0.40); IR ν_{max}: 3395, 2926, 1694, 1633, 1611, 1509, 1440, 1308, 1268, 1183, 1126, 1075, 1042, 984, 916, 857, 808, 620 cm^{-1}; ^1H NMR (D_2O, 500 MHz) and ^{13}C NMR (D_2O, 125 MHz) spectral data, see Table 1; ESI-MS: *m*/*z* 539 $[M+Na]^+$, 555 $[M+K]^+$, 515 $[M-H]^-$; (+)-HR-ESI-MS: *m*/*z* 515.1386 $[M-H]^-$ (Calcd. for $C_{22}H_{27}O_{14}$, 515.1406).

3.4. Alkali hydrolysis of *1–3*

A solution of each compound (**1–3**, 8–12 mg) was hydrolyzed with 2 mol/L NaOH (2.0 mL) at room temperature for 2 h. The reaction mixture was neutralized with 2 mol/L HCl, then extracted with EtOAc (5 mL for 3 times). The EtOAc phases were separately concentrated to dryness, and isolated by RP-HPLC using CH_3CN-H_2O (8:92, *v*/*v*) containing 0.1% HOAc as the mobile phase to yield the products (−)-quinic acid and (−)-4-*O*-β-glucopyranosylcaffeic acid with $[\alpha]_D^{20}$ values of −43.8 to −44.3 (*c* 0.04–0.06, H_2O) and −86.1 to −87.6 (*c* 0.53–0.90, MeOH), respectively, of which the NMR spectral data were in agreement with those reported in the literatures[18,20].

3.5. Anti-influenza virus and Coxsackie virus assay

See Ref. 33.

Acknowledgments

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.apsb.2015.01.012.

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