Antioxidative Caffeoylquinic Acid Derivatives in the Roots of Burdock (*Arctium lappa* L.)

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Five antioxidative caffeoylquinic acid derivatives were isolated from the roots of burdock (*Arctium lappa* L.), an edible plant in Japan. Their structures were established as 1-*O*-,5-*O*-dicaffeoylquinic acid (**1**), 1-*O*-,5-*O*-dicaffeoyl-3-*O*-succinylquinic acid (**2**), 1-*O*-,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid (**3**), 1-*O*-,5-*O*-dicaffeoyl-3-*O*-,4-*O*-disuccinylquinic acid (**4**), and 1-*O*-,3-*O*-,5-*O*-tricaffeoyl-4-*O*-succinylquinic acid (**5**) on the basis of chemical and spectral (NMR, MS) evidence. The antioxidant activities were measured in a hexane/2-propanol solution of methyl linoleate in the presence of a radical initiator. The antioxidant efficiency increased in the order of α-tocopherol < chlorogenic acid < caffeic acid < (**1**) = (**2**) = (**3**) = (**4**) < (**5**).

Keywords: *Antioxidants; caffeoylquinic acids; Arctium lappa*

INTRODUCTION

Dietary antioxidants are supposed to protect cell membranes against damages caused by oxygen radicals. For this reason, an extensive search for novel natural antioxidants has been undertaken (Su et al., 1988; Masuda and Jitoe, 1994; Tsushida et al., 1994). We have also started an investigation concerning antioxidants in Japanese vegetables and found that methanol extracts of the roots of burdock (*Arctium lappa* L.; Japanese name, gobou) showed a significant antioxidant activity in an *in vitro* fatty acid peroxidation assay. The roots of burdock are commonly consumed as vegetables in Japan. Many terpenoids and sulfur-containing acetylenic compounds have been isolated from the roots of the plant (Yochkova et al., 1990; Washino et al., 1985, 1987). Although quinic acid derivatives in the plant were already investigated (Nakabayashi, 1968), detailed analyses of the structures of the compounds had not been shown. In the course of our investigation of antioxidative vegetable constituents, we isolated and characterized one known and four novel caffeoylquinic acid derivatives as antioxidative principles in burdock roots.

EXPERIMENTAL PROCEDURES

General Procedures and Materials. Specific rotations were measured on a JASCO DIP-370. Circular dichroism (CD) spectra were measured on a JASCO J-720W. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured at 500 and 125 MHz, respectively, on a Bruker AM-500. Field desorption mass spectrometry (FD-MS) was carried out with a JEOL JMS 01SG-2 and electron impact (EI) MS on a JEOL JMS DX300.

Fresh roots of *A. lappa* were available from the market. Dimethyl sulfate, anhydrous potassium carbonate, methyl linoleate, and 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN) were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Methyl linoleate was purified by column chromatography with Florisil to remove any peroxides before use (Carroll, 1961).

Extraction and Isolation. Roots (100 g) of *A. lappa* were extracted with 1 L of methanol. The methanol extracts dispersed into water were washed with hexane and then partitioned between ethyl acetate and water. The ethyl acetate layer was extracted with 5% sodium bicarbonate solution. The resulting acidic fraction (106.4 mg) was applied to Sephadex LH-20 column chromatography (140 mL). The column was continuously eluted with methanol, and the eluate from 160 to 240 mL (elution volume) afforded a mixture of quinic acid derivatives. Further purification was achieved by high-performance liquid chromatography (HPLC) [Inertsil PREP ODS (20.0 × 250 mm); acetonitrile/1% acetic acid (1/4); flow rate, 5 mL/min; UV detector, 254 nm] to yield **1** (26.5 mg), **2** (41.7 mg), **3** (8.4 mg), **4** (7.7 mg), and **5** (10.3 mg).

Methylation of Compounds 2–5. In the case of **2**, to a mixture of anhydrous potassium carbonate (120 mg) and dimethyl sulfate (70 μL) was added **2** (8 mg) in acetone (2 mL) with stirring, and the mixture was refluxed for 30 min. The reaction mixture was filtered to remove potassium carbonate and concentrated to dryness. The residue was dissolved in ethyl acetate, and the organic layer was washed with water and concentrated *in vacuo*. The residue was purified by silica gel thin layer chromatography (TLC) [hexane/acetone (1:1 v/v)]. Compounds **3**–**5** were also methylated according to the same procedure.

Antioxidant Assay in Solution. To a reaction mixture containing 110 μmol of methyl linoleate and an appropriate concentration of a sample in 1 mL of hexane/2-propanol (1:1 v/v) was added 11 μmol of AMVN in 0.1 mL of hexane/2-propanol (1:1 v/v). The mixture was incubated at 37 °C for 1.5 h and then subjected to the HPLC analysis to determine methyl linoleate hydroperoxide (Murase et al., 1993).

RESULTS AND DISCUSSION

Structural Determination of Compounds 1–5. Physicochemical properties of the isolates were as follows.

Compound 1: colorless oil; $[\alpha]_D$ +117° (methanol, *c* 0.3); NMR see Tables 1 and 2.

Compound 2: colorless oil; $[\alpha]_D$ +41° (methanol, *c* 0.3); UV λ_{max} (methanol) 328, 305 (sh), 246, 220; CD (methanol) 348 ($\Delta\epsilon$, 25.7), 323 (0.0), 291 (−9.3); NMR see Tables 1 and 2.

Compound 3: colorless oil; $[\alpha]_D$ +75° (methanol, *c* 0.6); NMR see Tables 1 and 2.

Compound 4: colorless oil; $[\alpha]_D$ +45° (methanol, *c* 0.3); NMR see Tables 1 and 2.

Compound 5: colorless oil; $[\alpha]_D$ −95° (methanol, *c* 0.3); NMR see Tables 1 and 2.

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Table 1. ^{1}H NMR Spectral Data of Compounds 1–5 (500 MHz, Acetone-d_6, J in Hertz)

H	1[a]	2	3	4	5
2_{eq}	2.42–2.48 m	2.53–2.67 m	2.50–2.66 m	2.52–2.72 m	2.75 m
2_{ax}	2.42–2.48 m	2.53–2.67 m	2.50–2.66 m	2.52–2.72 m	2.85 m
3	4.29 m	5.52 m	4.44 m	5.62 m	5.69 m
4	3.78 dd	4.03 dd	5.08 dd	5.24 dd	5.31 dd
5	5.38 ddd	5.44 ddd	5.64 ddd	5.60 ddd	5.73 ddd
6_{eq}	2.56 dd	2.53–2.67 m	2.50–2.66 m	2.52–2.72 m	2.65 dd
6_{ax}	2.05 dd	2.13 m	2.14 dd	2.19 dd	2.19 dd
2′	7.05 d, 7.06 d	7.17 d, 7.22 d	7.15 d, 7.17 d	7.15 d, 7.22 d	6.99 d, 7.16 d, 7.23 d
5′	6.78 d, 6.78 d	6.88 d, 6.88 d	6.86 d, 6.87 d	6.86 d, 6.87 d	6.63 d, 6.85 d, 6.86 d
6′	6.96 dd, 6.96 dd	7.06 dd, 7.11 dd	7.04 dd, 7.06 dd	7.04 dd, 7.11 dd	6.72 dd, 7.05 dd, 7.06 dd
7′	7.57 d, 7.57 d	7.59 d, 7.64 d	7.55 d, 7.60 d	7.56 d, 7.65 d	7.51 d, 7.57 d, 7.65 d
8′	6.26 d, 6.29 d	6.28 d, 6.39 d	6.23 d, 6.32 d	6.25 d, 6.42 d	6.22 d, 6.26 d, 6.45 d
2″		2.53–2.67 m	2.50–2.66 m	2.52–2.72 m	2.47–2.59 m
3″		2.53–2.67 m	2.50–2.66 m	2.52–2.72 m	2.47–2.59 m
$J_{2ax,3}$			4.0	3.8	3.0
$J_{2eq,2ax}$			13.7	13.6	10.6
$J_{3,4}$	3.5	3.6	3.2	3.7	3.6
$J_{4,5}$	8.3	8.7	8.7	9.3	10.0
$J_{5,6eq}$	3.7	4.0	4.2	5.1	3.6
$J_{5,6ax}$	8.7	8.9	9.3	9.7	10.0
$J_{6eq,6ax}$	13.6				15.6
$J_{2',6'}$	2.0, 2.0	2.0, 2.0	2.0, 2.0	2.0, 2.0	2.0, 2.0, 2.0
$J_{5',6'}$	8.1, 8.1	8.1, 8.1	8.1, 8.1	8.2, 8.2	8.0, 8.0, 8.3
$J_{7',8'}$	15.8, 15.8	16.0, 16.0	15.9, 15.9	15.9, 15.9	15.9, 15.9, 15.0

[a] Measured in methanol-d_4.

Table 2. ^{13}C NMR Spectral Data of Compounds 1–5 (125 MHz, Acetone-d_6)

C	1[a]	2[b]	3	4	5
1	81.0	79.7	79.6	79.3	79.5
2	35.6	32.7	35.0	32.6	32.5
3	69.4	70.8	66.9	69.0	68.8
4	72.8	72.1	75.0	72.2	72.8
5	71.5	70.8	67.6	67.6	67.5
6	36.9	36.9	37.4	37.3	38.0
7	174.9	173.8	173.9	173.6	173.3
1′	127.8, 127.8	127.4, 127.6	127.6, 127.6	127.4, 127.5	127.2, 127.3, 127.5
2′	115.2, 115.2	115.3,[d] 115.4[d]	115.3,[d] 115.7	115.4, 115.5[d]	116.3, 116.5,[d] 116.6[d]
3′	146.8, 146.8	146.2,[e] 146.3[e]	146.2,[e] 146.3[e]	146.3, 146.3	146.0, 146.2, 146.3
4′	149.6, 149.8	148.8, 149.0	148.8, 148.8	148.9, 149.0	148.7, 148.8, 149.1
5′	116.5, 116.5	116.3, 116.4	116.3, 116.4	116.3, 116.4	116.3, 116.3, 116.6[d]
6′	123.0, 123.1	122.6, 122.7	122.6, 122.7	122.7, 122.8	121.4, 122.7, 122.7
7′	147.3, 147.5	146.1,[e] 146.8	146.3,[e] 146.3[e]	146.5, 147.0	146.5, 146.5, 146.9
8′	115.1, 115.2	115.3,[d] 115.5[d]	115.2,[d] 115.3[d]	115.0, 115.2[d]	115.1, 115.3, 115.8
9′	168.0, 168.7	166.9, 166.9	166.3, 166.5	166.3, 166.5	166.2, 166.6, 166.8
1″		172.3	172.2	172.1, 173.2	172.1
2″		29.8[c]	29.8[c]	29.6,[c] 29.8[c]	29.7[c]
3″		29.2[c]	29.2[c]	29.0,[c] 29.1[c]	29.0[c]
4″		172.3	172.2	172.1, 172.5	172.1

[a] Measured in methanol-d_4. [b] Assignments based on the heteronuclear multiple quantum coherence (HMQC) spectrum. [c] Signals were observed in the distortionless enhancement by polarization transfer (DEPT) experiments. [d,e] Assignment interchangeable.

Compound **1** was identified as 1-*O*-,5-*O*-dicaffeoylquinic acid by comparison of the ^{1}H and ^{13}C NMR data with the literature data (Merfort, 1992).

Compounds **2**–**5** gave no significant peaks by FD-MS. Therefore, these compounds were methylated, and their molecular weights were determined from the mass spectral data of the corresponding methylated compounds.

Methylated Compound 2: FD-MS m/z 700 $[M]^+$; EI-MS m/z (rel int) 700 ($[M]^+$, 2), 208 (61), 191 (95), 44 (100); high-resolution (HR) EI-MS m/z 700.2392 ($[M]^+$, calcd for $C_{35}H_{40}O_{15}$, 700.2367); ^{1}H NMR (500 MHz, acetone-d_6, J in Hz) δ 2.13 (1H, m, H_{ax}-6), 2.49–2.78 (7H, m, H_{eq}-2, H_{ax}-2, H_{eq}-6, H-2″ and H-3″), 3.54 (3H, s, CH_3O at 7), 3.68 (3H, s, CH_3O at 1″), 3.85 (3H, s, CH_3O at 4′), 3.86 (3H, s, CH_3O at 4′), 3.88 (3H, s, CH_3O at 3′), 3.90 (3H, s, CH_3O at 3′), 4.33 (1H, dd, J = 3.6, 8.7, H-4), 5.41 (1H, ddd, J = 3.5, 8.7, 8.7, H-5), 5.46 (1H, m, H-3), 6.42 (1H, d, J = 16.0, H-8′), 6.54 (1H, d, J = 16.0, H-8′), 6.99 (1H, d, J = 8.2, H-5′), 7.01 (1H, d, J = 8.2, H-5′), 7.20 (1H, dd, J = 2.0, 8.2, H-6′), 7.24 (1H, dd, J = 2.0, 8.2, H-6′), 7.33 (1H, d, J = 2.0, H-2′), 7.39 (1H, d, J = 2.0, H-2′), 7.65 (1H, d, J = 16.0, H-7′), 7.69 (1H, d, J = 16.0, H-7′); ^{13}C NMR (125 MHz, acetone-d_6) δ 29.3 (C-3″), 29.9 (C-2″), 32.6 (C-2), 36.9 (C-6), 51.8 (CH_3O at 7), 52.8 (CH_3O at 4″), 56.1 (CH_3O at 3′), 56.1 (CH_3O at 3′), 56.1 (CH_3O at 4′), 56.1 (CH_3O at 4′), 70.8 (C-3), 70.8 (C-5), 72.0 (C-4), 79.8 (C-1), 110.9 (C-2′), 110.9 (C-2′), 112.3 (C-5′), 112.3 (C-5′), 115.7 (C-8′), 116.2 (C-8′), 123.8 (C-6′), 124.2 (C-6′), 128.0 (C-1′), 128.1 (C-1′), 146.0 (C-7′), 147.0 (C-7′), 150.6 (C-3′), 150.6 (C-3′), 152.7 (C-4′), 152.8 (C-4′), 166.3 (C-9′), 166.8 (C-9′), 171.9 (C-4″), 172.2 (C-1″), 173.1 (C-7).

Methylated Compound 3: FD-MS m/z 700 $[M]^+$; EI-MS m/z (rel int) 700 ($[M]^+$, 3), 208 (23), 191 (100), 164 (12), 115 (18), 55 (11); HR EI-MS m/z 700.2373 ($[M]^+$, calcd for $C_{35}H_{40}O_{15}$, 700.2367).

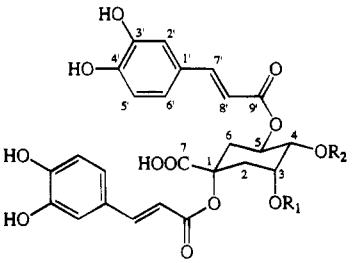
Methylated Compound 4: FD-MS m/z 814 $[M]^+$; EI-MS m/z (rel int) 814 ($[M]^+$, 10), 208 (59), 191 (100), 115

(84), 55 (52), 44 (51); HR EI-MS m/z 814.2691 ([M]$^+$, calcd for $C_{40}H_{46}O_{18}$, 814.2685).

Methylated Compound 5: FD-MS m/z 890 [M]$^+$; EI-MS m/z (rel int) 890 ([M]$^+$, 4), 208 (33), 191 (100), 115 (26); HR EI-MS m/z 890.2971 ([M]$^+$, calcd for $C_{46}H_{50}O_{18}$, 890.2995).

The molecular formula of methylated **2** was suggested to be $C_{35}H_{40}O_{15}$ by HR EI-MS. The ^{1}H NMR spectrum of methylated **2** indicated the presence of six methyl groups. From these results, the chemical formula of **2** was determined as $C_{29}H_{35}O_{15}$. The ^{1}H NMR spectrum of **2** exhibited signals for two caffeic acid and a quinic acid moiety (Table 1). Four doublets with coupling constants of 15.8 Hz appeared for the *trans* olefinic protons H-7′ and H-8′. The six aromatic protons (H-2′, H-5′, and H-6′) exhibited as two ABX systems, indicating the presence of 1,2,4-trisubstituted benzenes. The signals of H-3 (equatorial), H-4 (axial), and H-5 (axial) of the quinic acid moiety were assigned according to their multiplicity and their spin−spin coupling constants. The ^{1}H NMR signals at δ 2.53−2.67, the ^{13}C NMR signals (Table 2) at δ 29.2 and 29.8, and the signals of carbonyl carbons (δ 172.3, 2C) indicated the presence of a succinic acid moiety. The location of caffeoyl and succinyl substitution on the quinic acid moiety was determined by the insensitive nuclei assigned by polarization transfer (INAPT; Bax, 1984) experiments. In the INAPT spectra, the correlations between H-3 and C-1″ and between H-5 and one of the C-9′s indicated that the succinyl residue and caffeoyl residue were esterified at 3-OH and 5-OH, respectively. The second caffeoyl residue seemed to attach at 1-OH because the signal of H-4 (δ 3.78) was not shifted downfield as H-3 (δ 5.52) and H-5 (δ 5.44), showing no acyl substitution at 4-OH. Further evidence for the caffeoyl esterification at C-1 was provided by the NMR analysis of methylated **2**. From the heteronuclear multiple bond correlation (HMBC) spectrum of methylated **2**, four methyl signals at δ_H 3.85, 3.86, 3.88, and 3.90 correlated with C-3′ (2C) and C-4′ (2C) and two methyl protons at δ 3.54 and 3.68 correlated with C-7 and C-4″, respectively. No methyl signals correlated with caffeoyl carbonyls appeared, indicating that 1-OH of the quinic residue was esterified with one of the caffeoyl carboxyls rather than there being an ether linkage with the phenolic OH. Therefore, the structure of compound **2** was established as 1-*O*,5-*O*-dicaffeoyl-3-*O*-succinylquinic acid. The absolute configuration of **2** was determined by CD. Since the CD spectrum of **2** shows positive first and negative second Cotton effects, the two caffeoyl residues should constitute a right-handed screw, and thus both C-1 and C-5 of the quinic acid moiety have *R* configuration. Hence, it was confirmed that the parent quinic acid of **2** was (−)-quinic acid.

The molecular formulas of compounds **3**, **4**, and **5** were suggested to be $C_{29}H_{35}O_{15}$, $C_{33}H_{39}O_{18}$, and $C_{38}H_{41}O_{18}$, respectively, by FD-MS of their methylated compounds in conjunction with the ^{1}H and ^{13}C NMR data. The NMR data of **3** (Tables 1 and 2) were similar to those of **2** except for the chemical shifts of H-3 (δ 4.44) and H-4 (δ 5.08). The following correlations were observed in the INAPT experiments of **3**: H-4 with C-1″ and H-5 with C-9′. Therefore, the structure of **3** was determined as 1-*O*-,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid. In a similar manner, the structures of **4** and **5** were established as 1-*O*-,5-*O*-dicaffeoyl-3-*O*-,4-*O*-disuccinylquinic acid and 1-*O*-,3-*O*-,5-*O*-tricaffeoyl-4-*O*-succinylquinic acid by analyses of ^{1}H and ^{13}C NMR data (Tables 1 and 2) and INAPT experiments. The chemical structures of the compounds **1**−**5** were thus elucidated as shown in Figure 1.



	R_1	R_2
1	H	H
2	succinyl	H
3	H	succinyl
4	succinyl	succinyl
5	caffeoyl	succinyl

Figure 1. Structures of compounds **1**−**5**.

Compounds **2**−**5** are novel compounds. These compounds are very interesting because the quinic acid moiety is esterified with succinic acid. The antioxidative compound (**SP-2**), isolated from *Chrysanthemum coronatium* L., was presumed to be 3-*O*-,5-*O*-dicaffeoylquinic acid conjugated with the residue which had a molecular weight of 118 by secondary ion MS (Tsushida et al., 1994). Since the molecular weight is identical to that of succinic acid and *C. coronatium* is classified in the same family (Asteraceae) as *A. lappa*, **SP-2** would be a dicaffeoylsuccinylquinic acid. Hence, caffeoylsuccinylquinic acid might be a common compound in the plants of Asteraceae.

Antioxidant Activities of Compounds 1−5. Antioxidant activities of **1**−**5** were investigated by measuring the hydroperoxidation of methyl linoleate via radical chain reaction (Figure 2). The antioxidant efficiency of these compounds increased in the order α-tocopherol < chlorogenic acid < caffeic acid < (**1**) = (**2**) = (**3**) = (**4**) < (**5**). This result indicated that in this particular system caffeic acid derivatives were more effective than α-tocopherol, that the activity of caffeoylquinic acids on a molar basis increased in proportion to the number of caffeoyl residue, and that esterification with quinic acid lowered the activity of caffeic acid in this system.

Although a number of investigations related to the antioxidant activity of caffeoylquinic acids have been undertaken, their results were different depending upon the system of experiments. Chlorogenic acid and 3-*O*-,5-*O*-, 4-*O*-,5-*O*-, and 3-*O*-,4-*O*-dicaffeoylquinic acids (isochlorogenic acids) from sweetpotato were assessed as antioxidants in a linoleic acid−aqueous system (Hayase and Kato, 1984). Kimura et al. (1984) reported that isochlorogenic acids inhibited lipid peroxidation in mitochondria and microsomal fraction prepared from rat liver tissue, and the inhibitory effects of these compounds were markedly higher than those of caffeic acid and chlorogenic acid (Kimura et al., 1984). In the mouse liver homogenate system, antioxidant activities of caffeic acid, isochlorogenic acids, and cynarin (1-*O*-,3-*O*-dicaf-

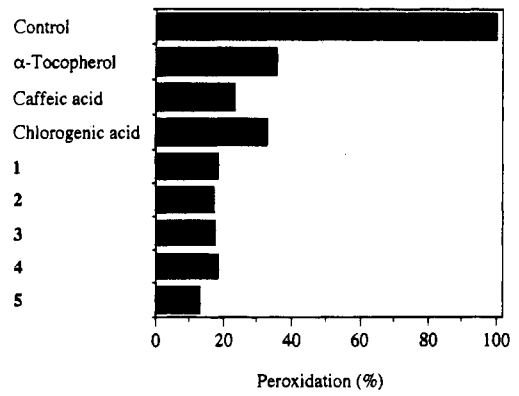


Figure 2. Effect of isolated caffeoylquinic acids and related compounds on the oxidation of methyl linoleate in solution. Final concentration of each sample was 100 μM in the reaction mixture (total volume, 1.1 mL) containing 100 mM methyl linoleate and 10 mM AMVN. Antioxidant activity was presented by the relative values compared to the control experiment (no additive). Hydroperoxidation efficiency in the control experiment was estimated to be approximately 2.2% by the previous data (Murase et al., 1993).

feoylquinic acid) were also reported (Fraga et al., 1987). However, Adzet et al. (1987) reported that quinic acid, chlorogenic acid, and isochlorogenic acids did not have hepatoprotective activity against carbon tetrachloride toxicity in isolated rat hepatocytes, although caffeic acid and cynarin did show activity (Adzet et al., 1987). The activity of cynarin may be due to its antioxidant activity, which prevents the carbon tetrachloride-induced oxidation of the phospholipids that are constituents of the hepatocyte membrane.

Compounds **1**–**5** are expected to have activities similar to those reported for caffeoylquinic acids, although the effects on the whole animal and the structure–activity relationship relating to caffeoylquinic acids remain obscure. Since caffeoylquinic acids are widely distributed in various foods, detailed investigations on the biological effects of the compounds would be quite valuable. Further investigation into the antioxidant activities of the isolates in a biological system and a search for related compounds in other Asteraceae vegetables are now in progress.

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