Flavonol Glycosides and Novel Iridoid Glycoside from the Leaves of *Morinda citrifolia*

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One new iridoid glycoside and five known flavonol glycosides have been isolated from the leaves of *Morinda citrifolia*. The new iridoid exists as an epimeric mixture in solution. Complete assignments of the proton and carbon chemical shifts for the individual epimers were accomplished on the basis of high-resolution 1D and 2D NMR data. Their antioxidative activities were measured. All of these compounds showed DPPH free radical scavenging activity at the concentration of 30 μM.

Keywords: *Iridoid; epimer; Morinda citrifolia; Rubiaceae; DPPH; antioxidant; flavonoid*

INTRODUCTION

Morinda citrifolia (Rubiaceae), commonly known as noni, is native to certain regions bordering the Indian Ocean, such as Tahiti and Samoa, as well as Hawaii. The plant is a small evergreen tree growing in the open coastal regions and in forest areas up to about 1300 feet above sea level. This plant is identifiable by its straight trunk, large green leaves, and its distinctive, ovid, "grenade-like" yellow fruit. The fruit can grow to a size of 12 cm and results from coalescence of the inferior ovaries of many closely packed flowers. It has a foul taste and a soapy smell when mature. The bark, stem, roots, leaves, and fruits have been used traditionally as a folk remedy for many diseases including diabetes, hypertension, and cancer (*1, 2*). In previous chemical studies, anthraquinones, including damnacanthal, 7-hydroxy-8-methoxy-2-methyl-anthraquinone, morenone 1, and morenone 2, have been found in the roots of noni (*3, 4*). In the seeds of noni, ricinoleic acid has been found (*5*). From the heartwood, two known anthraquinones (morindone and physcion) and one new anthraquinone glycoside have been isolated (*6*). Studies on the chemical components of the flowers of noni have resulted in the identification of one anthraquinone glycoside and two flavone glycosides (*7, 8*). The volatile compounds in the ripe fruits are characterized by a large amount of carboxylic acids, especially octanoic acid and hexanoic acid (*9*). Several nonvolatile compounds, including acetyl derivatives of asperuloside and glucose, have been identified in noni fruit (*10*). Recently, our research group reported five novel glycosides, including glycosides of octanoic and hexanoic acid, from the Hawaiian noni fruits (*11, 12*). However, only two compounds, β-sitosterol and ursolic acid, have been isolated previously from the leaves of this plant (*13*). We have examined the chemical components of the polar *n*-butanol-soluble fraction of the ethanol extract of noni leaves (*14*). In this report, we describe the isolation and structure elucidation of a new iridoid glucoside (**1**), named citrifolinin **B**, together with those of five known flavonol glycosides from the *n*-butanol fraction of *Morinda citrifolia* extract. The DPPH free radical scavenging activities for these compounds were also determined.

MATERIALS AND METHODS

General Procedures. ^{1}H (400 and 600 Hz), ^{13}C (100 and 150 Hz), and 2D NMR spectra were obtained on a Varian AM-600 and AM-400 NMR spectrometer with TMS as internal reference. APCI MS was obtained on a Fisons/VG Platform II mass spectrometer. Thin-layer chromatography was performed on Sigma-Aldrich TLC plates (250 μm thickness, 2−25 μm particle size), with compounds visualized by spraying with 5% (v/v) H_2SO_4 in ethanol solution.

Plant Material. The dried leaves of *Morinda citrifolia* were collected from Bengal, India in 1999 and were identified by Dr. Vladimir Badmaev at the Sarbinsa Corporation. A voucher specimen (HS16) was deposited in the Department of Food Science, Cook College, Rutgers University.

Extraction and Isolation Procedures. The dried noni leaves (5 kg) were extracted with 95% EtOH (4 L) at 50 °C for 1 day. The extract was concentrated to dryness under reduced pressure, and the residue was suspended in water (500 mL) and partitioned successively with hexane (3 × 500 mL), ethyl acetate (3 × 500 mL), and *n*-butanol (3 × 500 mL). The butanol fraction was subjected to a Diaion HP-20 column, and eluted with a water−EtOH (water, 30% EtOH, 70% EtOH, 95% EtOH) solvent system. The fraction (5 g) eluted by 30% EtOH was subjected to silica gel column chromatography with an ethyl acetate−MeOH−H_2O−hexane solvent system (10:1:1:0.5 → 5:1:1:0). In total, 10 fractions were collected. Fraction 1 eluted by ethyl acetate−MeOH−H_2O−hexane (10:1:1:0.5) was subjected to RP-18 silica gel column chromatography with 30% MeOH to give 3 fractions (I−III). Fraction II was rechromatographed on a Sephadex LH-20 eluted by 95% EtOH to give compound **2** (16 mg). Fractions 3 and 4 eluted by ethyl acetate−MeOH−H_2O (10:1:1) were subjected to Sephadex LH-20 eluted by 95% EtOH to afford 21 mg of compound **3** and 25 mg of compound **4**, respectively. Fraction 6 eluted by ethyl acetate−MeOH−H_2O (5:1:1) was subjected to RP-18 silica gel column chromatography with 30% MeOH, and then Sephadex LH-20 eluted by 95% EtOH to give 100 mg of compound **1**, 70 mg of compound **5**, and 80 mg of compound **6**.

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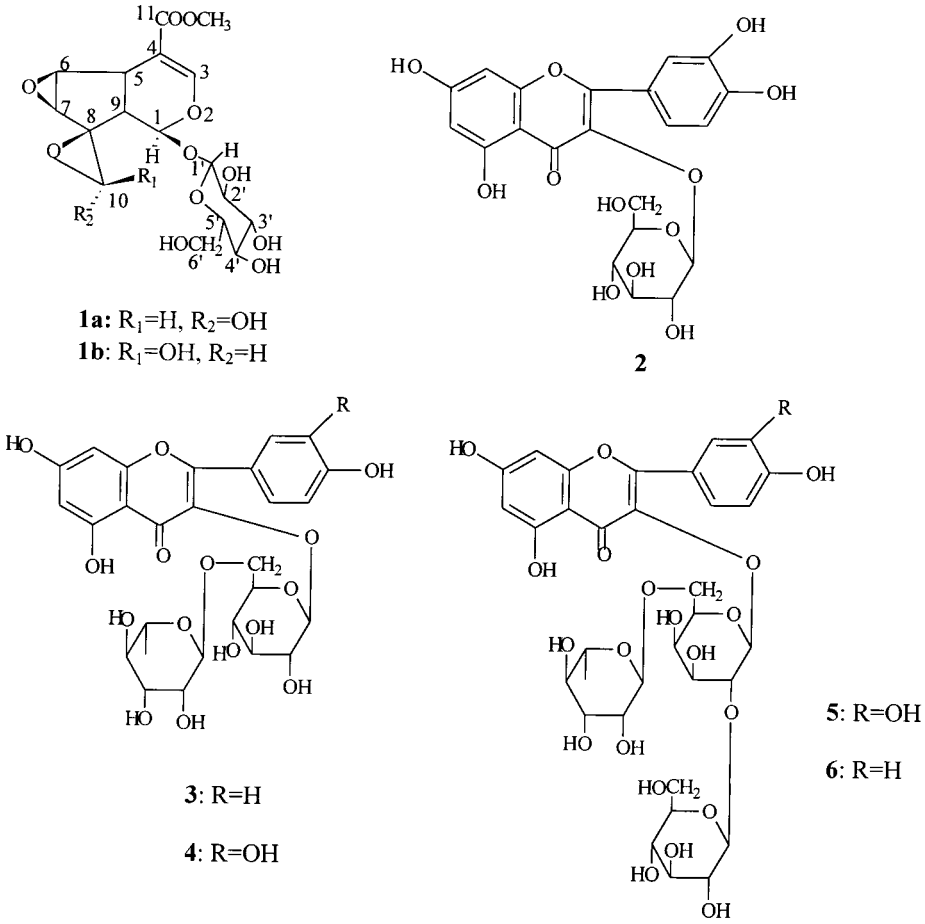

Figure 1. Structures of compounds **1**−**6**.

Spectral Identification of Known Compounds. Quercetin-3-*O*-*β*-D-glucopyranoside (**2**): yellow powder. APCI-MS, *m/z:* 463 $[M-H]^-$. ^1H NMR (CD_3OD, 400 MHz): δ 7.73 (1H, d, J = 2.0 Hz), 7.60 (1H, dd, J = 8.8, 2.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.39 (1H, d, J = 1.6 Hz), 6.21 (1H, d, J = 1.6 Hz), 5.24 (1H, d, J = 7.8 Hz); 3.20−3.80 (6H, m). ^{13}C NMR (CD_3-OD) δ: 179.5 (s), 166.6 (s), 163.1 (s), 159.1 (s), 158.6 (s), 150.0 (s), 146.0 (s), 135.7 (s), 123.3 (s), 123.2 (d), 117.7 (d), 116.1 (d), 108.7 (s), 105.6 (d), 104.5 (d), 95.0 (d), 78.5 (d), 78.2 (d), 75.8 (d), 71.3 (d), 62.7 (t).

Kaempferol-3-*O*-α-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside (**3**): yellow powder. APCI-MS, *m/z:* 593 $[M-H]^-$. ^1H NMR (CD_3OD, 400 MHz): δ 8.07 (2H, d, J = 8.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 6.40 (1H, d, J = 1.8 Hz), 6.21 (1H, d, J = 1.8 Hz), 5.15 (1H, d, J = 7.6 Hz), 4.54 (1H, s), 3.20−3.90 (10H, m), 1.14 (3H, d, J = 5.8 Hz). ^{13}C NMR (CD_3OD) δ: 179.5 (s), 166.4 (s), 163.0 (s), 161.6 (s), 159.5 (s), 158.6 (s), 135.6 (s), 132.5 (d), 122.9 (s), 116.2 (d), 105.7 (s), 104.8 (d), 102.5 (d), 100.2 (d), 95.1 (d), 78.3 (d), 77.3 (d), 75.9 (d), 74.0 (d), 72.4 (d), 72.2 (d), 71.6 (d), 69.8 (d), 68.7 (t), 18.0 (q).

Quercetin-3-*O*-α-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside (**4**): yellow powder. APCI-MS, *m/z:* 609 $[M-H]^-$. ^1H NMR (CD_3OD, 400 MHz) δ: 7.68 (1H, d, J = 2.0 Hz), 7.64 (1H, dd, J = 8.8, 2.0 Hz), 6.85 (1H, d, J = 8.8 Hz), 6.39 (1H, d, J = 1.6 Hz), 6.21 (1H, d, J = 1.6 Hz), 5.10 (1H, d, J = 7.8 Hz), 4.56 (1H, s), 3.20−3.90 (10H, m), 1.14 (3H, d, J = 5.8 Hz). ^{13}C NMR (CD_3OD) δ: 179.4 (s), 166.1 (s), 162.9 (s), 159.4 (s), 158.5 (s), 149.9 (s), 145.9 (s), 135.8 (s), 124.3 (s), 123.3 (d), 118.4 (d), 117.3 (d), 105.7 (s), 103.1 (d), 102.0 (d), 100.7 (d), 95.6 (d), 78.8 (d), 77.8 (d), 75.4 (d), 74.1 (d), 72.5 (d), 72.0 (d), 71.7 (d), 69.6 (d), 68.7, (t), 18.4 (q).

Quercetin-3-*O*-*β*-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-*β*-D-galacopyranoside (**5**): yellow powder. APCI-MS, *m/z:* 771 $[M-H]^-$.; ^1H NMR (C_5D_5N, 600 MHz) δ: 8.39 (1H, d, J = 2.0 Hz), 8.14 (1H, dd, J = 8.8, 2.0 Hz), 7.39 (1H, d, J = 8.8 Hz), 6.91 (1H, d, J = 1.6 Hz), 6.79 (1H, d, J = 1.6 Hz), 6.08 (1H, d, J = 7.8 Hz), 5.81 (1H, d, J = 7.8 Hz), 5.37 (1H, s), 3.80−4.60 (16H, m), 1.25 (3H, d, J = 5.8 Hz). ^{13}C NMR (C_5D_5N) δ: 178.7 (s), 163.9 (s), 162.0 (s), 158.0 (s), 156.9 (s), 150.8 (s), 146.8 (s), 136.0 (s), 122.9 (s), 122.1 (d), 117.9 (d), 116.9 (d), 108.8 (s), 104.4 (d), 102.5 (d), 101.5 (d), 100.4 (d), 95.1 (d), 79.2 (d), 78.5 (d), 78.4 (d), 77.5 (d), 75.4 (d), 74.8 (d), 73.3 (d), 72.5 (d), 72.1 (d), 71.3 (d), 71.1 (d), 69.6 (d), 68.4, (t), 62.4 (t), 18.5 (q).

Kaempferol-3-*O*-*β*-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-*β*-D-galacopyranoside (**6**): yellow powder. APCI-MS, *m/z:* 755 $[M-H]^-$. ^1H NMR (C_5D_5N, 600 MHz) δ: 8.43 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.8 Hz), 7.05 (1H, s), 6.79 (1H, s), 5.83 (1H, d, J = 7.6 Hz), 5.30 (1H, s), 3.80−4.60 (16H, m), 1.25 (3H, d, J = 5.8 Hz). ^{13}C NMR (C_5D_5N) δ: 178.4 (s), 164.2 (s), 162.4 (s), 162.2 (s), 158.9 (s), 157.3 (s), 136.0 (s), 132.2 (d), 121.1 (s), 116.5 (d), 107.1 (s), 104.5 (d), 102.8 (d), 101.8 (d), 100.7 (d), 95.5 (d), 79.5 (d), 78.8 (d), 78.7 (d), 77.8 (d), 76.2 (d), 75.1 (d), 74.2 (d), 72.9 (d), 72.4 (d), 71.7 (d), 71.5 (d), 69.9 (d), 68.9 (d), 62.8 (t), 18.5 (q).

Determination of the DPPH Radical Scavenging Capacity. This method was adapted from Chen and Ho (*26*). DPPH radicals were prepared in ethanol as a 1.0×10^{-4} M solution. This DPPH solution was mixed with different tested compounds (final concentration was 30 μM) and kept in a dark area for 0.5 h. The absorbance of the samples was measured on a spectrophotometer (Milton Roy, model 301) at 517 nm against a blank of ethanol without DPPH. All tests were run in triplicate and averaged.

RESULTS AND DISCUSSION

The *n*-butanol fraction of *Morinda citrifolia* leaves extract was chromatographed successively on Diaion HP-20, silica gel, Sephadex LH-20, and RP-18 silica gel columns to afford one new compound and five known

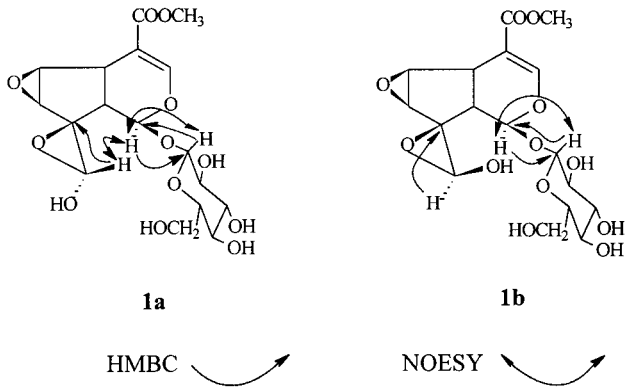

Figure 2. Significant HMBC (H→C) and NOESY correlations of compound **1**.

Table 1. ^{13}C (150 MHz) and ^{1}H (600 MHz) NMR Spectral Data for Compounds 1a and 1b (CD_3OD) (δ in ppm, J in Hz)

	1a		1b	
	δ_C	δ_H	δ_C	δ_H
1	94.7 d	5.95 s	94.1 d	5.93 s
3	154.8 s	7.57 s	154.5 s	7.56 s
4	107.5 s		107.4 s	
5	33.7 d	3.32 m	33.6 d	3.32 m
6	60.9 d	3.88 d 3.6	60.6 d	3.87 d 3.6
7	58.9 d	3.58 d 3.6	58.2 d	3.56 d 3.6
8	82.5 s		82.2 s	
9	46.9 d	2.34 d, 9.6	46.8 d	2.33 d, 9.6
10	98.4 d	4.45 s	98.4 d	4.34 s
11	168.8 s		168.7 s	
11-OCH_3	52.0 s	3.79 s	52.0 s	3.79 s
1′	100.2 d	4.63 d, 7.8	100.0 d	4.62 d, 7.8
2′	74.6 d	3.19 m	74.6 d	3.19 m
3′	78.3 d	3.32 m	78.3 d	3.32 m
4′	71.6 d	3.31 m	71.6 d	3.31 m
5′	78.0 d	3.33 m	78.0 d	3.33 m
6′	62.8 t	3.92 d, 9.6 3.71 dd, 6.6, 11.4	62.8 t	3.92 d, 9.6 3.71 dd, 6.6, 11.4

compounds. Their structures (Figure 1) were established by interpretation and full assignments of 1D and 2D NMR spectroscopic data and comparison with literature data.

Compound **1** was obtained as an amorphous solid. The molecular formula, $C_{17}H_{22}O_{12}$ was determined by negative-ion APCI-MS ($[M - H]^-$ at m/z 417), as well as from its ^{13}C NMR data, and indicated seven degrees of unsaturation. Of great interest was the doubling of the signals in both the ^{1}H and the ^{13}C NMR spectra of **1**, indicating the presence of an epimeric mixture. The ratio of the epimers, as deduced from the integration in the ^{1}H NMR spectrum, was 5:4 (**1a**:**1b**). The ^{1}H NMR spectrum of **1a** showed a singlet for a carbomethoxy group at δ 3.79, a singlet for the C-1 proton at δ 5.95, a doublet (J = 2.0 Hz) for the characteristic C-3 proton of iridoids at δ 7.57, two doublets (J = 3.6 Hz, each) for the C-6, C-7-epoxy protons at δ 3.88 and 3.58, and a doublet (J = 7.8 Hz) for the C-1′ proton at δ 4.63, suggesting that the cyclopentanopyran ring system and the sugar moiety of **1a** were identical to those of 6β,7β-epoxysplendoside (*15*). The major difference was at position 10 in the ^{1}H NMR spectrum. The methene group at position 10 of 6β,7β-epoxysplendoside was substituted by a methine group bearing two oxygen substituents (δ 4.45, s, 1H) in compound **1a**. This also was supported by the ^{13}C NMR data (δ 98.4, d). In addition, **1a** had seven degrees of unsaturation, whereas 6β,7β-epoxysplendoside only had six degrees of unsaturation. These results indicated that an epoxyl group existed between C-8 and C-10.

The ^{13}C NMR spectrum of **1a** exhibited 17 carbon signals (Table 1), with 10 representing the aglycon, one methoxy group (δ 52.0), and six for the glucopyranose unit (δ 100.2, d, C-1′; δ 74.6, d, C-2′; δ 78.3, d, C-3′; δ 71.6, d, C-4′; δ 78.0, d, C-5′; and δ 62.8, t, C-6′). The β-anomeric configuration for the glucose was judged from its large $^{3}J_{H1,H2}$ coupling constants (J = 7.8 Hz) (*16*). HMBC and NOESY correlations between C-1/H-1′, H-1/C-1′, and H-1/H-1′ (Figure 2) suggested that the β-glucopyranose unit was attached at the C-1 position of the aglycon.

The configuration of the C-6, C-7-epoxide group was confirmed from the NMR spectra of **1a** as β ($J_{H1,9} < 1$ Hz, and $\delta_{C1} = 94.7 < 99$ ppm) (*17*, *18*). To determine the stereochemistry at C-8 and C-10, NOESY measurements were carried out on **1**. In the NOESY spectrum, the presence of strong cross-peaks between H-1 and H-10a indicated that the linkage between C-8 and C-10 was α-oriented and H-10 was β in **1a**. Thus, compound **1a** was determined as citrifolinin **Ba** (Structure 1a in Figure 1).

Compound **1b** was almost identical with compound **1a** in all respects except at position 10 (Table 1). In the ^{1}H NMR spectrum of compound **1b**, H-10 appeared at δ 4.34 ppm instead of δ 4.45 ppm as observed in compound **1a**. So **1b** must be the C-10 epimers of **1a**.

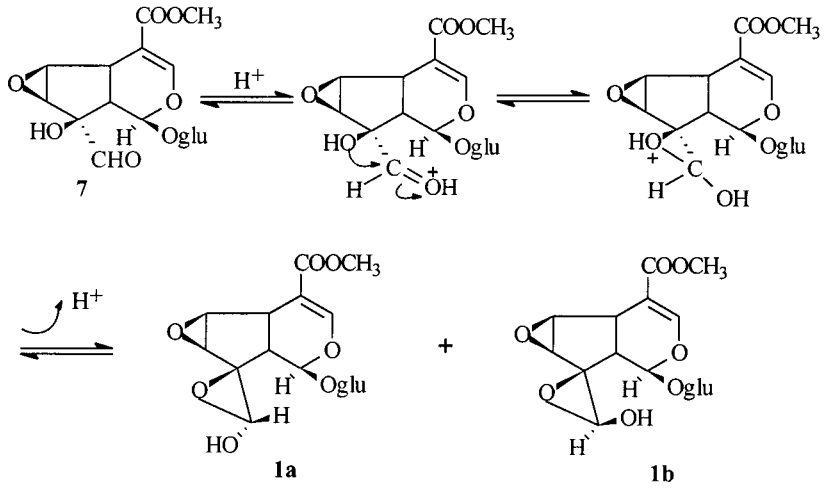

Figure 3. Proposed biosynthetic pathway of Citrifolinoside **B** (**1a**+**1b**).

H-10 was in α position instead of β as observed in **1a**. This was approved by the NOESY spectrum of compound **1**. H-10a showed strong cross-peak with H-1. However, H-10b did not show cross-peak with H-1. Therefore, compound **1b** was determined as citrifolinin **Bb** (Structure 1b in Figure 1). Full assignments of the ^{1}H and ^{13}C NMR signals of **1a** and **1b** were accomplished using HMBC, HMQC, ^{1}H-^{1}H COSY, TOCSY, and NOESY experiments (Table 1).

The different stereochemistry at C-10 in **1a** and **1b** could be explained by involvement of the intramolecular acetalation of compound **7** which was the 6β,7β-epoxy derivative of 10-dehydrogardenoside (*19*) in the proposed biogenetic pathway (Figure 3). According to this pathway, we presumed the existence of compound **7** as a low concentration in these leaves. Because of the instability, as well as the low content of this compound, we did not isolate it.

Actually, the R_f values of these two epimers are significantly different. It should be easy to separate these two compounds. However, when we tried to use the RP-C18 silica gel column, silica gel column, and the prepared TLC plate to separate these two compounds, all efforts failed because of the instability of these two compounds. There is a rapid equilibrium between them.

In addition to the new iridoid glycosides, five known flavonol glycosides, quercetin-3-*O*-β-D-glucopyranoside (**2**), kaempferol-3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**3**), quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**4**), quercetin-3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)] -β-D-galacopyranoside (**5**), and kaempferol-3-*O*-β-D-glucopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→6)]-β-D-galacopyranoside (**6**), have also been isolated in this study. Their structures were identified by comparison of their NMR and MS data with those reported in the literature (*11*, *20*, *21*). It is easy to determine the kinds and the positions of sugar moieties by comparing their ^{13}C data with those in the literature (*22*), because the ^{13}C data are very different between glucose and galactose (*22*). All of these compounds are being reported from the leaves of this plant for the first time.

The antioxidative activities of isolated compounds were measured. All of these compounds showed DPPH free radical scavenging activity at the concentration of 30 μM with 7.7, 85.8, 4.5, 79.9, 81.3, and 28.6%. Flavonoids are phenolic substances isolated from a wide range of vascular plants, with over 8000 individual compounds known. It is suggested that their antioxidative activity is related to their conjugated rings and hydroxyl groups (*23*), so it is not a surprise that quercetin glycosides showed stronger antioxidant activity than kaempferol glycosides.

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