PHENOLIC CONSTITUENTS FROM THE STEM BARKS OF RHIZOPHORA APICULATA BLUME

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Abstract. Using various chromatographic separations, seven phenolic derivatives (1-7) were isolated from a methanolic extract of the stem barks of Rhizophora apiculata Blume. Their structures were elucidated to be dunnianoside E (1), (+)-dihydroquercetin (2), 2,6-dimethoxy-[1,4]benzoquinone (3), 2,4,6-trimethoxyphenol (4), 3,4,5-trimethoxybenzyl alcohol (5), hydroxytyrosol (6), and methyl 3,4-dihydroxycinnamate (7) by a detailed analysis via spectroscopic techniques (1D-, 2D-NMR, and ESI-MS data) as well as comparison with those previously reported. This is the first report of compounds 1 and 4-7 from the Rhizophora genus.

Keywords: Rhizophora apiculata, Rhizophoraceae, phenolic.

Classification numbers: 1.1.1; 1.1.6.

1. INTRODUCTION

More than 84 species in 24 genera from 16 families of mangrove plants have been discovered across the world, which is composed of a large group of different salt-tolerant plants. These species are distributed worldwide, especially in tropical and subtropical intertidal estuarine areas [1, 2]. Of the recognized mangrove species, the family Rhizophoraceae constitutes a true mangrove, which contains 24 species in four genera, including Bruguiera (7 species), Ceriops (5 species), Kandelia (2 species), and Rhizophora (10 species) [1, 3]. In recent years, Rhizophora plants have attracted extensive scientific interests due to their chemical and pharmacological properties and proved to be a rich source of benzoquinones, flavonoids, terpenoids, and phenolic compounds [4 - 9].
Previous phytochemical investigations on *Rhizophora apiculata* Blume (synonym *R. candelaria* DC.) have resulted in the isolation of various classes of compounds including aliphatic alcohols [10], alkaloids [6, 11], flavonoids [6], phenolic derivatives [6], and terpenoids [5, 12, 13]. Some of these compounds have shown interesting biological properties including antibiotics [11], anticancer [4], antimicrobial [4], antioxidant [4, 14-17], antiviral [18], and hepatoprotective effects [19].

In our continuing search for phenolic compounds from the Vietnamese mangrove plants [20-22], the stem barks of *R. apiculata* were investigated on the chemical constituents. The current paper discusses the detailed structure elucidation of seven phenolic derivatives (1-7, Figure 1) from this plant.

![Figure 1. Structures of compounds 1-7 isolated from *R. apiculata*.](image)

### 2. EXPERIMENTAL

#### 2.1. General experimental procedures

The instruments used to isolate compounds, measure optical rotation, and record IR, NMR, ESI-MS data collection, TLC, and MPLC were carried out in a manner similar to procedures described in a previous paper [23].

#### 2.2. Plant material

The stem barks of *Rhizophora apiculata* Blume were collected at Ca Mau National Park, Ca Mau province, Viet Nam in May 2018, and taxonomically identified by Dr. Nguyen The Cuong (Institute of Ecology and Biological Resources, VAST). A voucher specimen (TĐPCCC-2018.02) was deposited at the Herbarium of Institute of Marine Biochemistry (IMBC) and Institute of Ecology and Biological Resources, VAST.
2.3. Extraction and isolation

The dried stem barks of R. apiculata (2.5 kg) were cut into pieces and extracted with 95 % aqueous MeOH by percolation at room temperature to obtain 250 g of extract. The concentrated methanol extract was suspended in water and defatted with n-hexane and then was partitioned into an ethyl acetate-soluble fraction.

The EtOAc-soluble fraction (E, 21.5 g) was separated on silica gel MPLC (column: Biotence SNAP Cartridge, KP-SIL, 100 g) using a mobile phase of CH₃Cl₂–EtOAc (0 - 5 min 50 % EtOAc, 6 - 65 min 50 - 75 % EtOAc, 66 - 75 min 100 % EtOAc, 76 - 90 min 100 % MeOH, 15 mL/min, 90 min) to give ten fractions (E-1 to E-10). This MPLC procedure was repeated 5 times using the same conditions before further isolation. By TLC monitoring, fractions E-5 was further separated on a silica gel column chromatography (CC), using dichloromethane-acetone (10:1:1, v/v) as the mobile phase, to give four subfractions (E-5.1 to E-5.4). Precipitates from fraction E-5.1 eluted by dichloromethane-acetone (60:1) were collected, dissolved in MeOH, and purified on Sephadex LH-20 (eluted with MeOH) to yield 3 (5.5 mg) and 4 (10 mg). In a similar process to that described above, subfraction E-5.2 was chromatographed over an open ODS column eluted with acetone-water (2:3, 3:2, v/v) to give one subfraction E-1.2.1 and compounds 5 (2.1 mg) and 7 (2.5 mg). Similarly, subfraction E-8 was separated by separation on a Sephadex LH-20 column and was eluted with a gradient solvent mixture of MeOH–H₂O (gradient 1:3; 1:1; 2:1, 3:1; to pure MeOH) to yield three fractions (E-8.1 to E-8.3), based on TLC analysis. The fractionation W-8.2 was separated via silica gel CC and eluted repeatedly with n-hexane-acetone (1:1, v/v) to yield two subfractions (E-8.2a to E-8.2b). Subfraction E-8.2b was subjected to a silica gel CC (Φ20 mm, L800 mm with a solvent mixture of n-hexane-EtOAc, 1:1:2), and then an open YMC*GEL column (Φ15 mm, L800 mm, 65 → 100 %, H₂O-MeOH) to afford compound 6 (2.2 mg). Finally, when the same steps were repeated as per above, compounds 1 (6.5 mg) and 2 (6.5 mg) were also obtained by purifying subfraction E-10 on YMC*GEL column (Φ20 mm, L 700 mm) and followed by passage over a Sephadex LH-20 column (Φ15 mm, L900 mm) using a mixture of MeOH-H₂O (1:2).

Dunnianoside E (1): White, amorphous powder; [α]D20 +22.6 (c 0.15, MeOH); UV (MeOH) λmax (log ε) 204 (4.17) and 258 (3.87) nm; IR (KBr) νmax 3350, 2943, 1680, 1610, 1521, 1458, 1334, 1290, 1205, 1167, 1086, 975, and 851 cm⁻¹; ¹H-NMR (500 MHz, CD₃OD) and ¹³C-NMR (125 MHz, CD₃OD) spectroscopic data, see Table 1; ESI-MS m/z 423 [M + H]⁺ (C₂₀H₂₅O₁₀H⁺) and 445 [M + Na]⁺ (C₂₀H₂₂NaO₁₀H⁺), C₃₀H₃₂O₁₀, m = 422.

(+)-Dihydroquercetin (2): Yellow, amorphous solid; [α]D20 +28.7 (c 0.15, MeOH); UV (MeOH) λmax 277 nm; ¹H-NMR (500 MHz, CD₃OD) and ¹³C-NMR (125 MHz, CD₃OD) spectroscopic data, see Table 2; ESI-MS m/z 291 [M + H]⁺ (C₁₅H₁₃O₆H⁺), C₁₃H₁₀O₆, M = 290.

2,6-Dimethoxy-[1,4]benzoquinone (3): Yellow, amorphous powder; mp: 25 – 26 °C; IR (KBr) 1600, 1645, 1696, and 1320 cm⁻¹; ¹H-NMR (500 MHz, DMSO-d₆): δH 3.77 (6H, s, 2-OCH₃ and 6-OCH₃), and 5.94 (2H, s, H-3 and H-5); ¹³C-NMR (125 MHz, DMSO-d₆): δC 166.3 (C-1), 157.0 (C-2 and C-6), 106.8 (C-3 and C-5), 175.7 (C-4), and 56.0 (2-OCH₃ and 6-OCH₃); C₈H₈O₄, M = 168.

2,4,6-Trimethoxyphenol (4): White, amorphous powder; mp: 62 – 64 °C; ¹H-NMR (500 MHz, CD₃OD): δH 3.69 (3H, s, 4-OCH₃), 3.78 (6H, s, 2-OCH₃ and 6-OCH₃), and 6.11 (2H, s, H-3 and H-5); ¹³C-NMR (125 MHz, CD₃OD): δC 132.2 (C-1), 154.9 (C-2 and H-6), 94.01 (C-3 and H-5), 155.4 (C-4), 56.4 (2-OCH₃ and 6-OCH₃), and 61.3 (4-OCH₃); ESI-MS m/z 185 [M + H]⁺ (C₁₃H₁₀O₄⁺), C₁₂H₉O₄, m = 184.
3,4,5-Trimethoxybenzyl alcohol (5): White, amorphous powder; mp. 36 – 38 °C; UV (MeOH) λ_max 264 nm; IR (KBr) ν_max 3400, 2945, 1594, 1461, 1425, 1330, 1238, 1128, 1059, and 831 cm⁻¹; ¹H-NMR (500 MHz, CD₂OD): δ_H 3.84 (3H, s, 4-OCH₃), 3.87 (6H, s, 3-OCH₃ and 5-OCH₃), 4.64 (2H, s, H-7), and 6.61 (2H, s, H-2 and H-6); ¹³C-NMR (125 MHz, CD₂OD): δ_C 136.6 (C-1), 103.9 (C-2 and C-6), 153.4 (C-3 and C-5), 137.5 (C-4), 65.0 (C-7), 56.1 (3-OCH₃ and 5-OCH₃), and 60.8 (4-OCH₃); ESI-MS m/z 197 [M - H]⁺ (C₁₀H₁₃O₄), C₁₀H₁₄O₄, M = 198.

Hydroxytyrosol (6): Brown oil; IR (KBr) ν_max 3376, 2946, 1605, and 1448 cm⁻¹; ¹H-NMR (500 MHz, CD₂OD): δ_H 2.68 (2H, t, J = 7.0 Hz, H-7), 3.69 (2H, t, J = 7.0 Hz, H-8), 6.55 (1H, dd, J = 8.0, 2.0 Hz, H-6), 7.05 (1H, d, J = 2.0 Hz, H-2), and 7.56 (1H, d, J = 15.5 Hz, H-7); ¹³C-NMR (125 MHz, CD₂OD): δ_C 131.8 (C-1), 117.0 (C-2), 146.4 (C-3), 146.1 (C-4), 116.3 (C-5), 121.2 (C-6), 39.6 (C-7), and 64.5 (C-8); ESI-MS m/z 155 [M + H]⁺ (C₈H₁₁O₃), C₈H₁₀O₃, M = 154.

Methyl 3,4-dihydroxycinnamate (7): White, amorphous powder; mp. 158 °C; IR (KBr) ν_max 3500, 3450, 3320, 3019, 1705, 1258, and 1178 cm⁻¹; ¹H-NMR (500 MHz, CD₂OD): δ_H 3.77 (3H, s, 9-OCH₃), 6.27 (1H, d, J = 15.5 Hz, H-8), 6.80 (1H, d, J = 8.0 Hz, H-5), 6.96 (1H, dd, J = 8.0, 2.0 Hz, H-6), 7.05 (1H, d, J = 2.0 Hz, H-2), and 7.56 (1H, dd, J = 15.5 Hz, H-7); ¹³C-NMR (125 MHz, CD₂OD): δ_C 127.7 (C-1), 115.1 (C-2), 146.8 (C-3), 149.6 (C-4), 116.5 (C-5), 122.9 (C-6), 146.9 (C-7), 114.8 (C-8), 169.7 (C-9), and 51.9 (9-OCH₃); ESI-MS m/z 195 [M + H]⁺ (C₁₀H₁₃O₄), C₁₀H₁₄O₄, M = 194.

3. RESULTS AND DISCUSSION

Compound 1 was obtained as a white, amorphous powder, with a negative optical rotation [α]₀ = 22.6 (c 0.15, MeOH). Its molecular formula was found to be C₂₀H₂₂O₁₀ (10 indices of hydrogen deficiency) via the ¹³C NMR spectroscopic data and positive ESI-MS ions at m/z 423 [M + H]⁺ and 445 [M + Na]⁺. The ¹H-NMR spectroscopic data showed three aromatic protons attributed to a 1,2,4-trisubstituted aromatic ring [δ_H 6.46 (1H, d, J = 2.5 Hz, H-3), 6.19 (1H, dd, J = 8.5, 2.5 Hz, H-5), and 6.97 (1H, d, J = 8.5 Hz, H-6), fragment A], two doublets assignable to a symmetrical 1,4 disubstituted aromatic ring [δ_H 7.88 (2H, d, J = 8.5 Hz, H-2" and H-6") and 6.86 (2H, d, J = 8.5 Hz, H-3" and H-5")], fragment B, an aromatic methoxy signal [δ_H 3.79 (3H, s, 3-OCH₃)], together with one glucosidic moiety as evidenced by the presence of an anomeric proton signal [δ_H 4.73 (1H, d, J = 7.5 Hz, H-1')], and other proton signals [δ_H 3.50 (1H, dd, J = 9.0, 7.5 Hz, H-2'), 3.53 (1H, overlapped signal, H-3'), 3.46 (1H, overlapped signal, H-4'), 3.68 (1H, m, H-5'), 4.66 (1H, dd, J = 11.5, 2.0 Hz, H-6'a), and 4.35 (1H, dd, J = 11.5, 5.0 Hz, H-6'b) (Table 1). Moreover, the anomeric proton signal of H-1' was attributed to a β-glucosyl unit (a trans-diaxial configuration of H-1' and H-2') from the large coupling constant (J₁₂ = 7.5 Hz).

![Figure 2. Key HMBC correlations of 1.](image-url)
Table 1. $^1$H- and $^{13}$C-NMR spectroscopic data for 1 and reference compound (in CD$_3$OD).

| Position | $^2\delta_C$ | $^2\delta_C$ | $^2\delta_H$ mult. ($J$ in Hz) |
|----------|--------------|--------------|-------------------------------|
| 1        | 140.6        | 140.8        | -                             |
| 2        | 152.0        | 152.1        | -                             |
| 3        | 101.6        | 101.9        | 6.46 d (2.5)                  |
| 4        | 154.9        | 154.9        | -                             |
| 5        | 107.0        | 107.5        | 6.19 dd (8.5, 2.5)            |
| 6        | 120.7        | 120.7        | 6.97 d (8.5)                  |
| 1'       | 104.0        | 104.2        | 4.73 d (7.5)                  |
| 2'       | 74.7         | 75.0         | 3.50 dd (9.0, 7.5)            |
| 3'       | 77.7         | 77.8         | 3.53*                         |
| 4'       | 71.6         | 72.0         | 3.46*                         |
| 5'       | 75.2         | 75.6         | 3.68 m                        |
| 6'       | 64.6         | 64.9         | 4.66 dd (11.5, 2.0)           |
|          |              |              | 4.35 dd (11.5, 5.0)           |
| 1''      | 122.2        | 122.2        | -                             |
| 2'', 6'' | 132.5        | 132.9        | 7.88 d (8.5)                  |
| 3'', 5'' | 116.1        | 116.2        | 6.86 d (8.5)                  |
| 4''      | 163.0        | 163.5        | -                             |
| 7''      | 166.4        | 167.9        | -                             |
| 3-OCH$_3$| 56.3         | 56.5         | 3.79 s                        |

*125 MHz, 500 MHz. *Overlapped signals. $^2\delta_C$ of dunnianoside E [24]. Assignments were confirmed by HMQC and HMBC experiments.

The $^{13}$C-NMR and HSQC spectroscopic data of 1 revealed the presence of 20 carbon signals, including a carbonyl ($\delta_C$ 167.9), a methoxyl group ($\delta_C$ 56.5), and 12 aromatic carbon atoms, as well as signals from one glycoside moiety [$\delta_C$ 104.2 (C-1’), 75.0 (C-2’), 77.8 (C-3’), 72.0 (C-4’), 75.6 (C-5’), and 64.9 (C-6’)] (Table 1). The sugar moiety was confirmed as β-D-glucose, which was linked to the aglycone at C-1 (fragment A) and C-7’ (fragment B) positions in 1. This relationship was supported by the HMBC experiments, in which correlations were observed for the resonances between $\delta_H$ 4.73 (H-1’)/4.66/4.35 (H-6’) with the signals of C-1 ($\delta_C$ 140.8) and C-7’ ($\delta_C$ 167.9). On the other hand, the locations of two hydroxy groups and a methoxyl group were assigned to C-4, C-4”, and C-2 by the HMBC correlations between $\delta_H$ 6.46 (H-3)/6.19 (H-5) and $\delta_C$ 154.9 (C-4’); $\delta_H$ 6.86 (H-3”/H-5”) and $\delta_C$ 163.5 (C-4”), as well as between $\delta_H$ 3.79 (OCH$_3$), 6.46 (H-3), and 6.97 (H-6) with C-2 ($\delta_C$ 152.1), respectively (Figure 2). These spectroscopic data suggested that 1 is a phenolic glycoside which indicated the presence of a glucosyl unit, a 2-methoxyl,4-hydroxyphenyl, and a 4-hydroxybenzoyl moiety [24].

By comparing the NMR spectroscopic data of 1 with reported literature which found that they were similar, it was suggested that 1 was dunnianoside E [24] (Table 1). Furthermore, the ESI-MS data of 1 exhibited a protonated molecular ion peak at m/z 423 [M + H]$^+$ and a sodium adduct molecular ion peak at m/z 445 [M + Na]$^+$, determining the molecular formula of C$_{30}$H$_{42}$O$_{16}$. From the above evidence, the structure of 1 was determined as 4-hydroxy-2-methoxyphenyl 1-O-β-D-[6'-O-(p-hydroxybenzoyl)]glucopyranoside (named dunnianoside E). This compound was previously obtained from the roots of Illicium dunnianum [24].

Compound 2 was isolated as a yellow, amorphous solid. Its molecular formula was determined to be C$_{13}$H$_{18}$O$_{8}$ based on a protonated molecular ion peak at m/z 291 [M + H]$^+$ and $^{13}$C-NMR spectroscopic data, consistent with nine degrees of unsaturation. Analysis of the $^1$H-
Table 2. $^1$H- and $^{13}$C-NMR spectroscopic data for 2 (in CD$_3$OD) and reference compound.

| Position | $^1$H | $^{13}$C | $^1$H | $^{13}$C | $^1$H, $^{13}$C |
|----------|------|--------|------|--------|----------------|
| 2        | 80.0 | 83.0   | 82.8 | 4.59   | d (7.5)       |
| 3        | 67.7 | 69.0   | 68.7 | 4.00   | m             |
| 4        | 29.4 | 28.7   | 28.4 | 2.87   | d (16.5, 5.5) |
|          |      |        |      |        | 2.53 d (16.5, 8.0) |
| 5        | 157.9| 157.7  | 157.7| -      |                |
| 6        | 96.0 | 96.4   | 96.3 | 5.95   | d (1.5)       |
| 7        | 158.2| 158.0  | 157.2| -      |                |
| 8        | 96.5 | 95.6   | 95.5 | 5.88   | d (1.5)       |
| 9        | 157.9| 157.1  | 156.8| -      |                |
| 10       | 100.2| 100.9  | 100.8| -      |                |
| 1'       | 132.5| 132.4  | 132.2| -      |                |
| 2'       | 115.5| 115.4  | 115.2| 6.86   | d (2.0)       |
| 3'       | 146.1| 146.4  | 146.1| -      |                |
| 4'       | 146.0| 146.4  | 146.2| -      |                |
| 5'       | 116.0| 116.2  | 116.1| 6.77   | d (8.0)       |
| 6'       | 119.5| 120.2  | 120.0| 6.75   | dd (8.0, 2.0) |

$^a$125 MHz. $^b$500 MHz. $^c$δ of (+)-catechin [25] and $^d$δ of (−)-epicatechin [25]. Assignments were confirmed by HMQC and HMBC experiments.

Figure 3. Key HMBC correlations of 2.

$^{13}$C-NMR, and HSQC spectroscopic data of 2 displayed signals for all 15 carbons and 14 protons, suggesting the presence of the following partial structures: an AB spin system appearing as two doublet signals [$\delta_H$ 5.95 (1H, d, $J = 1.5$ Hz, H-6)/$\delta_C$ 96.3 (C-6) and 5.88 (1H, d, $J = 1.5$ Hz, H-8)/$\delta_C$ 95.5 (C-8)], typical of a meta-dihydroxylated A-ring; an ABX spin system [$\delta_H$ 6.86 (1H, d, $J = 2.0$ Hz, H-2')/$\delta_C$ 115.2 (C-2')], 6.77 (1H, d, $J = 8.0$ Hz, H-5')/$\delta_C$ 116.1 (C-5'), and 6.75 (1H, dd, $J = 8.0, 2.0$ Hz, H-6')/$\delta_C$ 120.0 (C-6'), characteristic of a 3,4-dihydroxylated B-ring, along with the occurrence of a flavan-3-ol skeleton in the molecule could be determined from the characteristic signals at $\delta_H$ 4.59 (1H, d, $J = 7.5$ Hz, H-2)/$\delta_C$ 82.8 (C-2), 4.00 (1H, m, H-3)/$\delta_C$ 68.7 (C-3), and 2.87 (1H, dd, $J = 16.5, 5.5$ Hz, H-4a), 2.53 (1H, dd, $J = 16.5, 8.0$ Hz, H-4b)/$\delta_C$ 28.4 (C-4) (Table 2). Furthermore, a large coupling constant of H-2 and H-3 ($J_{2,3} = 7.5$ Hz) and on the basis of the optical rotation ($[\alpha]^2_D +28.7$), confirmed a 2,3-trans configuration in 2 [25, 26]. Based on the above analysis, the relative configuration was assigned for 2. The comparison NMR spectroscopic data of 2 (Table 2) were similar to those of (+)-dihydroquercetin [25]. Detailed analysis of other HMBC correlations (Figure 3) confirmed the structure of 2 as (+)-dihydroquercetin (named (+)-catechin). Compound 2 was previously isolated from the stems and twigs of R. stylosa [27].
Based on the spectroscopic analysis and comparison with literature values, the remaining compounds were identified as 2,6-dimethoxy-[1,4]benzoquinone (3) [28], 2,4,6-trimethoxyphenol (4) [29], 3,4,5-trimethoxymethyl alcohol (5) [30], hydroxytyrosol (6) [31], and methyl 3,4-dihydroxycinnamate (7) [32].

4. CONCLUSIONS

Seven phenolic compounds, including dunnianoside E (1), (+)-dihydroquercetin (2), 2,6-dimethoxy-1,4-benzoquinone (3), 2,4,6-trimethoxyphenol (4), 3,4,5-trimethoxymethyl alcohol (5), hydroxytyrosol (6), and methyl 3,4-dihydroxycinnamate (7), were isolated from a methanolic extract of Rhizophora apiculata stem barks. This is the first report of phenolic derivatives 1 and 4-7 from the Rhizophora genus. The structures of these isolates were accomplished using comprehensive spectroscopic methods and comparison with those reported.

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