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ANTIMICROBIAL ACTIVITIES OF *HELICIOPSIS TERMINALIS* TRUNK EXTRACT

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Abstract – Phenolic glucosides, methyl 5-(1,3-dihyroxyphenyl)pentanoate 1-*O*-*β*-D-glucopyranoside (**1**), ethyl 5-(1,3-dihyroxyphenyl)pentanoate 1-*O*-*β*-D-glucopyranoside (**2**), along with 2-(3-methoxy-4-hydroxyphenyl)propane-l,3-diol (**3**), *C*-veratroylglycol (**4**), 6'-[(*E*)-2''-hydroxymethyl-2''-butenoyl] arbutin (**5**), and (8'*Z*)-1,3-dihydroxy-5-[16'-(3'',5''-dihydroxyphenyl)-8'-hexadecen-1'-yl]benzene (6), were isolated from *Heliciopsis terminalis*. Their molecular structures were determined by extensive spectroscopic analyses. The antimicrobial activities of all compounds were evaluated. The results showed that only compound **6** expressed strong antimicrobial activity against Gram-positive bacteria.

Nowadays, infectious diseases are one of the most common causes of morbidity and mortality. Many infections are caused by increasingly drug-resistant microorganisms resulting in difficult-to-treat or untreatable infections. Microbial resistance is generally caused by spontaneous mutations due to the incorrect and inappropriate use of antibiotics. For example, methicillin-resistance *Staphylococcus aureus* (MRSA), a Gram-positive bacterium, is one of the serious antibiotic-resistant bacteria and pathogen causing cutaneous wounds, food poisoning, and opportunistic infections.[1] Plants are a rich source of active compounds against microorganisms, including bacteria, fungi, and protozoa.[2] Thus, numerous studies have been conducted on developing the effectiveness of antibiotics from natural sources.

Heliciopsis terminalis (Kurz) Sleumer is a medium evergreen tree belonging to the Proteaceae family. The plant is distributed in rain forests below 100-1400 meters in southeastern China, Northeast India, and Southeast Asia (Cambodia, Vietnam, Myanmar, and Thailand). Several studies have investigated chemical compounds isolated from the *Heliciopsis* genus, primarily focusing on *H. lobata* and *H. terminalis*. The main constituents identified from the genus included derivatives of arbutin and phenolic glycosides.[3-6] The wood of *H. terminalis* has been used for building, whereas leaves and roots have been applied for traditional medicine in several countries. In China, the roots are traditionally used for mumps and detoxification, while leaves are used for skin disease. Leaves and roots are used to treat pancreatitis in Vietnam. The ground leaves are applied for relieving muscle pain in Thailand.[7,8] Although bisresorcinol has been recently reported as a major constituent of *H. terminalis* and exhibited inhibitory activities towards oxidative, inflammatory, and skin-aging enzymes,[7,9] its antimicrobial activity has not been studied. Therefore, this study aimed to isolate and purify the compounds from *H. terminalis* and determine their antimicrobial activities.

Since ethyl acetate and butanol extracts from *H. terminalis* trunk exhibited some biological activities, their constituents were purified using chromatographic methods, and 6 compounds were obtained as a result. The structure of compounds was determined based on comparing ^{1}H and ^{13}C NMR data with the previous reports and supported by mass spectral data. The ethyl acetate extract contained one previously reported compound, (8'*Z*)-1,3-dihydroxy-5-[16'-(3",5"-dihydroxyphenyl)-8'-hexadecen-1'-yl]benzene (**6**).[10] Two new compounds, named grevilloside C methyl ester (**1**) and grevilloside C ethyl ester (**2**), along with three previously reported compounds, 2-(3-methoxy-4-hydroxyphenyl)propane-l,3-diol (**3**),[11] *C*-veratroylglycol (**4**),[12] and 6'-[(*E*)-2"-hydroxymethyl-2"-butenoyl] arbutin (**5**) were identified in the BuOH extract (Figure 1).[3]

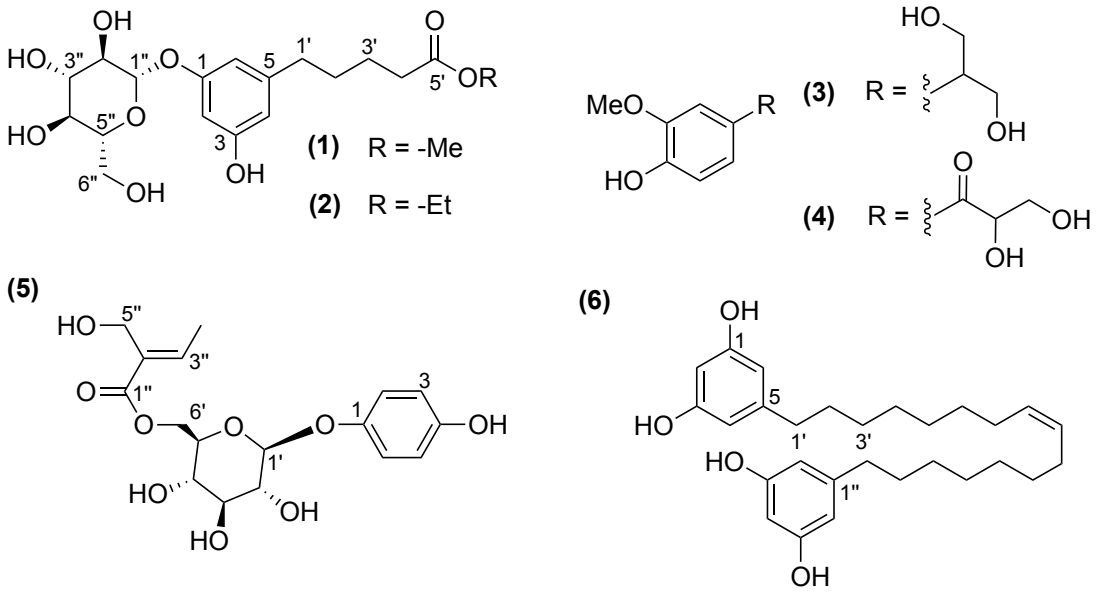

Figure 1. *H. terminalis* compounds

Compound **1** was obtained as a white solid with molecular formula of $C_{18}H_{26}O_9$ determined from HR-ESI-MS at *m/z* 409.1475 $[M+Na]^+$ (calcd for $C_{18}H_{26}O_9Na$: 409.1469). This indicated six degrees of unsaturation, one carbonyl, double bonds, and two rings. The UV absorption at 204 (4.06) nm indicated the presence of an aromatic ring. The IR spectra showed 3370 and 1715 cm^{-1} resulting from hydroxy and carbonyl functionalities, respectively.

In the ^1H NMR spectrum, three typical aromatic signals [δ_H 6.43 (1H, *dd*, *J* = 2.2, 2.2 Hz, H-6), 6.39 (1H, *dd*, *J* = 2.2, 2.2 Hz, H-2), 6.30 (1H, *dd*, *J* = 2.2, 2.2 Hz, H-4) for a 1,3,5-trisubstituted benzene ring, one methoxy group at δ_H 3.64 (3H, s), an anomeric proton at δ_H 4.86 (1H, *d*, *J* = 7.6 Hz, H-1″) were observed. The ^{13}C NMR, DEPT, and HSQC spectra showed six carbons from 19 carbons belonging to *β*-glucopyranose. The signals of one anomeric carbon were at δ_C 102.7 (C-1″), methylene carbons at δ_C 36.7 (C-1′), 31.8 (C-2′), 25.7(C-3′), 34.8 (C-4′), one carbonyl carbon at δ_C 176.1 (C-5′) and six characteristic carbon signals attributable to the benzene ring (δ_C 160.3-102.7). The ^1H and ^{13}C NMR spectroscopic data of **1** was similar to grevilloside E,[13] except for one methylene carbon at δ_C 31.8. The HMBC spectrum (Figure 2) showed the correlations of methoxy proton (3H, δ_H 3.64) with C-5′ (δ_C 176.1). Besides, the correlations of H-1″ (δ_H 4.86) with C-1 (δ_C 160.3) revealed the position of glucopyranoside on C-1. Glucose in the hydrolyzate of **1** was analyzed to be the D-glucose using the chiral detector HPLC. Based on these results, the structure of **1** was characterized as methyl 5-(1,3-dihyroxyphenyl)pentanoate 1-*O*-*β*-D-glucopyranoside, designated as grevilloside C methyl ester.

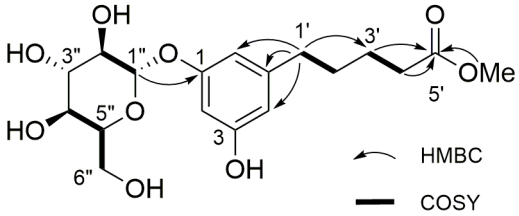

Figure 2. HMBC and ^{1}H-^{1}H COSY of **1**

Compound **2** was obtained as a white amorphous powder with a molecular formula of $C_{19}H_{28}O_9$ determined from HR-ESI-MS at *m/z* 423.1620 $[M+Na]^+$ (calcd for $C_{19}H_{28}O_9Na$: 423.1626). The carbonyl and hydroxy groups were estimated from the IR absorptions at 1679 and 3370 cm^{-1}, respectively. The UV absorption at 204 (3.95) was indicative of the presence of an aromatic ring.

The ^{1}H NMR and ^{13}C NMR spectra of **2** were closely similar to **1**, except for ethoxy protons at δ_H 1.23 (t, J = 7.1 Hz) and δ_H 4.10 (q, J = 7.1 Hz), and two carbons at δ_C 61.6 and δ_C 14.7. The HMBC correlations of H-6′ (δ_H 4.10) with C-5′ (δ_C 175.7) suggested that an ethoxy group connected with the carbonyl group at C-5′. The position of glucopyranoside was confirmed by the correlation between H-1″ (δ_H 4.85) and C-1 (δ_C 160.3) (Figure 3). Glucose in the hydrolysate of **2** was analyzed to be the D-glucose using the chiral detector HPLC. Based on these results, the structure of **2** was characterized as ethyl 5-(1,3-dihyroxyphenyl)pentanoate 1-*O*-*β*-D-glucopyranoside, designated as grevilloside C ethyl ester.

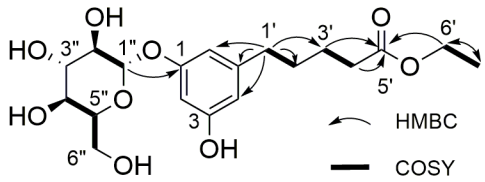

Figure 3. HMBC and ^{1}H-^{1}H COSY of **2**

It should be noted that the formation of ester products from an organic acid and an alcohol solvent, e.g., methanol, used during the extraction or separations could also occur.[13,14] Thus, further investigation and suitable separations are essential.

The effect of isolated compounds from *H. terminalis* extract on the growth of five pathogenic bacteria, including three Gram-positive bacteria (*S. aureus*, MRSA, and *B. subtilis*) and two Gram-negative bacteria (*E. coli* and *P. aeruginosa*), and one pathogenic fungus (*C. albicans*), was determined. Among the tested compounds, only compound **6** (a phenolic) exhibited antimicrobial activity, and only Gram-positive bacteria were effectively inhibited by this compound, suggesting a narrow-spectrum antibacterial activity. In addition, compound **6** had no antifungal activity (Table 1). Typically, the phenolic compounds have diverse activities, and the antimicrobial activity against Gram-positive bacteria rather than Gram-negative

bacteria has also been reported in these compounds. The presence of phenolic hydroxy groups played a pivotal role in cell membrane damage, inhibition of virulent factors, and biofilm suppression by interacting with the cytoplasmic membrane of bacteria.[15] Moreover, a substance similar to compound **6**, (*Z*,*Z*)-5-(trideca-4,7-dienyl)resorcinol exerted its lipophilicity for binding to Gram-positive cell walls and causing breakage of the bacterial cells.[16] The antimicrobial activity against only Gram-positive bacteria of compound **6** was presumed to be from the differences in cell wall structure between Gram-positive and Gram-negative bacteria. The cell wall of Gram-positive bacteria is surrounded by a thick peptidoglycan layer combined with teichoic acid and lipoteichoic acid, while the Gram-negative cell wall is composed of a thin peptidoglycan layer suited inside an outer membrane with lipopolysaccharide. The outer membrane forms an impermeable barrier to large antibiotics and the hydrophilic molecules, preventing the binding of these molecules to the target in the cytoplasm, while being permeable for the hydrophobic molecules. Additionally, the outer membrane contains a pore channel formed by porin proteins that regulate the influx of substances into the bacterial cell.[17] Therefore, the lack of antimicrobial activity of compound **6** against Gram-negative bacteria could be explained by the presence of an impermeable outer membrane in Gram-negative bacteria. However, compound **6** should be further studied for its mechanism and developed into the next generation of antibiotics.

Table 1. Minimum inhibitory concentration (MIC) values of *H. terminalis* compounds against pathogenic bacteria and fungi

Microorganisms		MIC (μg/mL)						
		1	2	3	4	5	6	Positive control *
Gram positive	*S. aureus*	> 100	> 100	> 100	> 100	> 100	3.125	≤ 25
	MRSA	> 100	> 100	> 100	> 100	> 100	3.125	≤ 25
	B. subtilis	> 100	> 100	> 100	> 100	> 100	3.125	≤ 25
Gram negative	*E. coli*	> 100	> 100	> 100	> 100	> 100	> 100	≤ 25
	P. aeruginosa	> 100	> 100	> 100	> 100	> 100	> 100	≤ 25
Fungus	*C. albicans*	> 100	> 100	> 100	> 100	> 100	> 100	≤ 25

*Positive control: oxacillin for bacteria; amphotericin B for fungus

Phenolic glucosides **1** and **2** were identified as the new compounds, while compounds **3**, **4**, and **5** were found in *H. terminalis* for the first time. Compound **6** exhibited various antioxidant, anti-inflammatory, and anti-aging activities, as reported by previous studies, but this study also showed that the compound had strong antimicrobial activity against Gram-positive bacteria.

EXPERIMENTAL

General procedure. ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC, and HMBC spectra were determined with a Bruker Advance III spectrometer at 600 MHz and 150 MHz, respectively, with TMS as an internal standard. IR and UV spectra were recorded on a HORIBA FT-720 and JASCO V-520 UV/Vis spectrophotometer. Optical rotations were measured on JASCO P-1030 spectropolarimeters. Positive ion HR-ESI-MS mass spectra were performed with an LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific). Silica gel column chromatography and open reversed-phase column chromatography (ODS CC) were performed on silica gel 60 (E. Merck, Darmstadt, Germany) and Cosmosil 75C_{18}-OPN (Nacalai Tesque, Kyoto, Japan; Φ = 35 mm, L = 350 mm), respectively. TLC was used on precoated silica gel 60 F_{254} plates (E. Merck; 0.25 mm in thickness) by spraying with a 10% solution of H_2SO_4 in EtOH and heated on a hotplate around 150 °C. HPLC method was performed on the Inertsil ODS column-3 column (Inertsil ODS-3, GL Science, Tokyo, Japan; Φ = 10 mm, L = 25 cm, flow rate 2.00 mL/min), and the eluate ion was monitored with a refractive index monitor. HPLC analysis of sugars after hydrolysis was used on an amino column by using a chiral detector (JASCO OR-2090plus) [Shodex Asahipak NH2P-50, MeCN-H_2O (3:1), flow rate 1.0 mL/min].

Plant material. *H. terminalis* (155 g) timbers used in the present study were collected in Bac Kan province, Vietnam. The collection of *H. terminalis* and its botanical identification was performed by Associate Prof. Dr. Tran Van On of the Hanoi University of Pharmacy (Hanoi, Vietnam). The voucher specimen (HNIP-18473) was extracted with MeOH and partitioned with *n*-hexane. The resulting MeOH layer was then evaporated by a rotary evaporator with the vacuum system at 40 °C until dryness and subsequently partitioned with EtOAc, 1-BuOH, and water. The weight of dried extracts from the EtOAc and 1-BuOH layers were 118.28 g and 29.93 g, respectively.

Extraction and isolation. The EtOAc extract was subjected to silica column chromatography (70-230 mesh) and eluted with $CHCl_3$-MeOH in increasing gradient of polarity to obtain 10 fractions ($CHCl_3$:MeOH 100:0, 30:1, 20:1, 10:1, 7:1, 5:1, 3:1, 3:2, 2:1, 0:100). Compound **3** (132.8 mg; t_R = 20 min) was purified by ODS CC HPLC (70% aq. acetone; flow rate 2 mL/min) from fraction 6-7.

The butanol extract was subjected to chromatography using silica gel and eluted with increasing amounts of $CHCl_3$-MeOH to obtain 11 fractions ($CHCl_3$:MeOH 100:0, 95:5, 92.5:7.5, 9:1, 87.5:12.5, 85:15, 8:2, 7:3, 6:4, 5:5, 0:100). Compound **4** (7.0 mg; t_R = 25 min) and compound **5** (9.7 mg; t_R = 47 min) were purified

by ODS CC HPLC (3% aq. acetone; flow rate 2 mL/min) from fraction 3-1. Fraction 4 (1.99 g) was subjected to ODS CC and eluted with a stepwise gradient of 20% aq. MeOH – 100% MeOH, and 100% acetone to obtain 10 fractions. New compound **1** (21.6 mg; t_R = 59 min) and known compound **6** (6.9 mg; t_R = 16 min) were purified by ODS CC HPLC (17% aq. acetone; flow rate 2 mL/min) from fraction 5-3. Fraction 6 (3.56 g) was subjected to ODS CC and eluted with a stepwise gradient of 10% aq. MeOH – 100% MeOH, and 100% acetone to get 11 fractions. New compound **2** (7.7 mg; t_R = 36 min) was purified by ODS CC HPLC (26% aq. acetone; flow rate 2 mL/min) from fraction 6-4.

Grevilloside C methyl ester (**1**): white solid; $[\alpha]^{26.5}_D$ -37.82(*c* 2.16, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.07) nm; ECD (*c* 0.05 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 270 (-0.24), 229 (-0.37) nm; IR (neat) ν_{max} 3370, 2936, 2865, 1715, 1173 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 6.43 (dd, *J* = 2.2, 2.2 Hz, 1H, H-6), 6.39 (dd, *J* = 2.2, 2.2 Hz, 1H, H-2), 6.30 (dd, *J* = 2.2, 2.2 Hz, 1H, H-4), 4.86 (d, *J* = 7.6 Hz, 1H, H-1'), 3.89 (dd, *J* = 12.1, 2.1 Hz, 1H, H-6''), 3.70 (dd, *J* = 12.1, 5.3 Hz, 1H, H-6''), 3.64 (s, 3H, Me), 3.45 (m, 1H, H-5''), 3.42 (dd, *J* = 9.2, 8.9 Hz, 1H, H-2''), 3.40 (m, 1H, H-3''), 3.39 (m, 1H, H-4''), 2.51 (t, *J* = 7.0 Hz, 2H, H-1'), 2.33 (t, *J* = 7.0 Hz, 2H, H-4'), 1.60 (q, *J* = 7.0 Hz, 4H, H-2', H-3'); ^{13}C NMR (150 MHz, CD_3OD) δ 176.1 (C-5'), 160.3 (C-1), 159.5 (C-3), 145.9 (C-5), 110.7 (C-4), 109.2 (C-6), 102.7 (C-2, C-1''), 78.1 (C-3, C-5''), 75.0 (C-2''), 71.5 (C-4''), 62.6 (C-6''), 52.2 ($-OCH_3$), 36.7 (C-1'), 34.8 (C-4'), 31.8 (C-2'), 25.7 (C-3'); HR-ESI-MS: Calcd for $C_{18}H_{26}O_9Na$ $[M+Na]^+$ *m/z* 409.1475; found *m/z* 409.1469.

Grevilloside C ethyl ester (**2**): white amorphous powder; $[\alpha]^{26.5}_D$ -25.33(*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ε) 223 (3.90) nm; ECD (c 0.05 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 311 (-0.17), 278 (-0.35), 254 (-0.22), 208 (0.48) nm; IR (neat) ν_{max} 3370, 2930, 1679, 1375, 1204 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 6.43 (dd, *J* = 2.2, 2.2 Hz, 1H, H-6), 6.38 (dd, *J* = 2.2, 2.2 Hz, 1H, H-2), 6.30 (dd, *J* = 2.2, 2.2 Hz, 1H, H-4), 4.85 (d, *J* = 7.5 Hz, 1H, H-1''), 4.10 (q, *J* = 7.1 Hz, 2H, H-6'), 3.89 (dd, *J* = 12.0, 2.1 Hz, 1H, H-6''), 3.70 (dd, *J* = 12.0, 5.3 Hz, 1H, H-6''), 3.44 (m, 2H, H-3''), 3.43 (m, 1H, H-2''), 3.39 (m, 1H, H-4''), 2.53 (t, *J* = 7.0 Hz, 2H, H-1'), 1.61 (m, 4H, H-2', H-3'), 2.32 (t, *J* = 7.0 Hz, 2H, H-4'), 1.23 (t, *J* = 7.1 Hz, 3H, H-7'); ^{13}C NMR (150 MHz, CD_3OD) δ 175.7 (C-5'), 160.3 (C-1), 159.5 (C-3), 145.9 (C-5), 110.7 (C-4), 109.2 (C-6), 102.7 (C-2), 102.3 (C-1''), 78.2 (C-3'', C-5''), 75.0 (C-2''), 71.5 (C-4''), 62.6 (C-6''), 61.6 (C-6'), 36.7 (C-1'), 35.1 (C-4'), 31.8 (C-2'), 25.7 (C-3'), 14.7 (C-7'); HR-ESI-MS: Calcd for $C_{19}H_{28}O_9Na$ $[M+Na]^+$ *m/z* 423.1626; found *m/z* 423.1620.

Acid hydrolysis. The isolated compounds **1** and **2** (1.0 mg each) were undergone hydrolysis reaction using 1 M HCl (1.0 mL) and heated at 80 °C for 3 h. The reaction mixtures were neutralized with OH^- resin (amberlite IRA96SB) and the resin was filtered out. The filtrates were extracted with EtOAc. The aqueous fractions were analyzed using HPLC [column: Shodex Asahipak NH 2P-50 4E, 250 × 4.6 mm i.d.; mobile phase: MeCN-H_2O (3:1, v/v); flow rate: 1.0 mL/min; detection: chiral detector (JASCO OR-2090plus)].

The resulting chromatograms were compared to reference standard of D-glucose and displayed a peak of t_R at 14.2 min (positive optical rotation).

Antimicrobial assay. Selected bacterial strains, namely *S. aureus*, MRSA, *B. subtilis*, *E. coli*, and *P. aeruginosa*, were used for antibacterial testing. All bacteria strains were stored in MH broth at –80 °C and grown in culture medium using a 37 °C incubator. For pathogenic fungal, *C. albicans* was stored at –80 °C and maintained in RPMI 1640 at 25 °C and 37 °C incubators. The minimum inhibitory concentration (MIC) of the *H. terminalis* compounds was performed by the microtiter broth dilution method.[18] The stock compounds were dissolved in DMSO. Both Muller Hinton and RPMI 1640 mediums were autoclaved at 121 °C for 15 min and allowed to cool to 37 °C in a water bath for antibacterial and fungi screening, respectively. Each strain of bacteria and fungi was put into a 96-well microplate at 10^4 CFU per 99 μL, and 1 μL of the samples were added. The bacteria plate was incubated at 37 °C, while the fungi plate was incubated at 25 °C. MIC was considered as the lowest concentration of sample without visible growth after 18-24 h incubation. For this assay, the positive control agents were oxacillin for bacteria and amphotericin B for fungi, whereas DMSO and broth were used as negative controls.

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