A New Phenylethanoid Glycoside From the Leaves of Rosmarinus officinalis With Nitric Oxide Inhibitory Activity

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Abstract
A new phenylethanoid glycoside, named rosmacinalis (1), and 6x known compounds {2-phenylethyl O-α-L-rhamnopyranosyl-(1″→6″)-O-β-D-glucopyranoside (2), clinopodiolide C (3), rosmanol (4), 7α-methoxyrosmanol (5) 7β-methoxyrosmanol (6) and carnosol (7)} were isolated from the leaves of Rosmarinus officinalis. Their structures were determined by extensive analysis of high-resolution electron spray ionization mass spectrum and nuclear magnetic resonance spectral data, as well as by comparison of the spectral data with those reported in the literature. Anti-inflammatory activity of compounds 1-7 was evaluated by their inhibition of NO production in lipopolysaccharide-stimulated RAW 264.7 cells. At a concentration of 100 µM, compounds 1 and 2 exhibited inhibitory rates of 47.1% ± 2.2% and 44.5% ± 1.3%, respectively, while compounds 3-7 showed a cytotoxic effect. After dilution to a concentration of 20 µM, except compound 7, compounds 1-6 did not show a cytotoxic effect. Their NO inhibitory rates ranged from 14.2% ± 1.3% to 31.1% ± 1.9%.

Keywords
Rosmarinus officinalis, rosmacinalis, phenylethanoid, carnosic acid derivative, nitric oxide inhibitor

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Rosmarinus officinalis Linnaeus (Lamiaceae family) is a perennial herb native to the Mediterranean region, where it is commonly known as rosemary. It can be used either in raw materials (fresh and dry) or in processed products (extract and essential oil) for cosmetic, pharmaceutical, and food applications.¹ In traditional medicinal remedies, rosemary leaves are used to treat inflammation-related diseases and pain, enhance circulation, boost the immune system, and promote hair growth.² Rosemary essential oil mainly contains 1,8-cineole, camphor, pinene, borneol, and limonene, which exhibit antidepressant, antimicrobial, anti-allergic, and smooth muscle relaxant effects.³ In natural cosmetics, rosemary is used not only as an antioxidant agent but also as an important fragrance ingredient. Beside essential oil, recent literature has indicated that the biological activities of rosemary have been attributed to phenolic groups, especially rosmarinic acid and carnosic acid derivatives.⁴ Many reports suggest that rosmarinic acid has potential antioxidant and anti-inflammatory activity, and hepatoprotective effects that could be developed for pharmaceutical and cosmetic applications.⁴,⁵ Carnosic acid and its derivatives are phenolic diterpene compounds. Their structures contain an ortho-dihydroquinone fragment, which easily reacts with free radicals produced in biological systems. Carnosic acid compounds play crucial roles because of their antioxidant, anti-inflammatory, and anticarcinogenic activities.⁶–⁸ The finding of phenolic compounds from rosemary therefore attracted medicinal chemists to explore the biomolecules and clarify the therapeutic potential of this medicinal plant.⁹ With the aim of finding natural anti-inflammatory constituents, we describe herein the isolation and identification of 2 phenylethanoid glycosides (1 and 2) and 5 carnosic acid derivatives (5-7) from rosemary leaves (Figure 1). Compound 1 was determined to be a new compound. The anti-inflammatory activity of compounds...
Compound 1 was obtained as a white amorphous powder. Its molecular formula was deduced to be C_{21}H_{32}O_{12} based on the cluster of quasi-molecular ion peaks in the high-resolution electron spray ionization mass spectrum (HR-ESI-MS), including m/z 499.1773 [M + Na]^+ (calculated for [C_{21}H_{32}O_{12}Na]^+, 499.1786), m/z 494.2216 [M+NH_4]^+ (calculated for [C_{21}H_{36}O_{12}N]^+, 494.2232), and m/z 477.1965 [M + H]^+ (calculated for [C_{21}H_{33}O_{12}]^+, 477.1967) (Supplemental Figure S1). The 1H-nuclear magnetic resonance (NMR) spectrum of 1 exhibited signals corresponding to a 1,3,4-trisubstituted benzene moiety (δ_H 6.87 1H, d, J = 2.0 Hz], 6.73 [1H, d, J = 8.0 Hz], 6.70 [1H, dd, J = 2.0 and 8.0 Hz]), 2 anomic protons (δ_H 4.77 [1H, d, J = 1.5 Hz], 4.31 [1H, d, J = 7.5 Hz]), a methoxy group (δ_C 56.5), and a doublet methyl group (δ_H 1.28 [3H, d, J = 6.5 Hz]) (Supplemental Figure S2). The 13C-NMR spectrum of 1 (Supplemental Figure S3) indicated the presence of 21 carbon signals, which were then further classified from the heteronuclear single-quantum coherence spectrum (Supplemental Figure S4) as 6 aromatic carbons (δ_C 148.9, 145.9, 131.6, 122.4, 116.1, 113.8), 2 anomic carbons (δ_C 104.5, 102.3), 8 oxygenated methines (δ_C 78.1, 76.9, 75.1, 74.0, 72.4, 72.1, 71.7, 69.8), 2 oxygenated methylenes (δ_C 72.1, 68.2), 1 aliphatic methylene (δ_C 36.8), 1 methoxy group (δ_C 56.5), and 1 methyl group (δ_H 18.0). In the heteronuclear multiple bond correlation (HMBC) spectra, correlations between H-2 (δ_H 2.87) and C-1′ (δ_C 131.6)/C-2′ (δ_C 113.8)/C-6′ (δ_C 122.4), H-2 (δ_H 6.87)/H-6′ (δ_H 6.70) and C-2 (δ_C 36.8) were observed establishing the connection.
between C-2 and C-1’ (Figure 2). The deshielded carbon signal of C-4′ (δc 145.9) together with HMBC correlations between H-2′ (δh 6.87)/H-6′ (δh 6.70) and C-4′ suggested the presence of a hydroxy group at C-4′. Additionally, HMBC correlations between H-5′ (δh 6.73) and C-5′ (δc 148.9), methoxy protons (δh 3.86), and C-3′ clearly confirmed a methoxy group at C-3′ (Supplemental Figure S5). Besides the 1,3,4-tri-substituted benzenoid moiety, the correlation spectroscopy (COSY) spectrum of I (Supplemental Figure S6) exhibited 3 additional spin systems (Figure 2) of an ethylene group (H-1 [δh 1.40, 2.12, 3.63] and 2 hexose sugar units (H-1′ [δh 4.31]/ H-2′ [δh 4.32]/ H-3′ [δh 5.36]/ H-4′ [δh 4.31]/ H-5′ [δh 5.36]/ H-6′ [δh 3.99, 3.63] and H-1″ [δh 4.77]/ H-2″ [δh 4.78]/ H-3″ [δh 4.68]/ H-4″ [δh 4.38]/ H-5″ [δh 4.69]/ H-6″ [δh 1.28]). Viscinal coupling J values between protons H-1′ and H-2′ (J = 7.5 Hz), H-2′ and H-3′ (J = 9.0 Hz), H-3′ and H-4′ (J = 9.0 Hz), and H-4′ and H-5′ (J = 9.0 Hz) indicated the presence of a β-glucopyranose moiety, while vicinal coupling J values between protons H-1″ and H-2″ (J = 1.5 Hz), H-2″ and H-3″ (J = 3.0 Hz), H-3″ and H-4″ (J = 9.0 Hz), and H-4″ and H-5″ (J = 9.0 Hz) indicated the presence of an α-rhamnopyranose moiety. Furthermore, HMBC correlations of Glc H-1″ (δh 4.31)/ H-1″ (δc 72.1) and Rha H-1″ (δh 4.77)/ Glc C-6″ (δc 68.2) revealed O-glycosidic linkages of the glucose moiety to C-1 and the rhamnose moiety to Glc C-6″, respectively. Finally, the presence of D-glucose and L-rhamnose in the acid hydrolysates products of compound I was confirmed by gas chromatography (GC) analysis of their trimethylsilyl derivatives, as previously described.10 Consequently, compound I was determined to be 2-(4′-hydroxy-3′-methoxyphenyl)-ethyl O-α-L-rhamnopyranosyl-(1″→6″)-O-β-D-glucopyranoside, a new phenylethanoid glycoside and named as rosmacinalis.

Compound 2 was determined to be an additional phenylethanoid glycoside as 2-phenethyl O-α-L-rhamnopyranosyl-(1″→6″)-O-β-D-glucopyranoside, while compounds 3-7 were the abietane diterpenoids clinopodiolide C (3), rosmanol (4), 7α-methoxy rosmanol (5), 7β-methoxyrosmanol (7), and carnosol (7). The NMR spectral data of compounds 2-7 were consistent with those previously reported in the literature (Supplemental Figure S7-S18).11–15 Except for compounds 1-3, phenolic diterpenes 4-7 were previously reported from R. officinalis. Anti-inflammatory activity of compounds 1-7 was evaluated by their ability to inhibit NO production in LPS-stimulated RAW 264.7 cells. First, the cytotoxic effects of the compounds on RAW 264.7 cells were examined to ensure that the NO inhibitory activity was not affected by cytotoxic activity. Each compound was assessed at 2o concentrations, 100 and 20 µM. At a concentration of 100 µM, compounds 1 and 2 did not show a cytotoxic effect, and they exhibited NO inhibitory rates of 47.1% ± 2.2% and 44.5% ± 1.3%, respectively. However, at 100 µM, the effects on NO production of compounds 3-7 were not significant due to their cytotoxic effect (cell viability below 80%, Table 1). At a diluted concentration of 20 µM, compound 7 was cytotoxic, but compounds 1-6 did not show a cytotoxic effect. The NO inhibitory activities of compounds 1-6 were then obtained with inhibitory rates ranging from 14.2% ± 1.3% to 31.1% ± 1.9%. L-NMMA (N(Г-monomethyl-L-arginine) was used as a positive control. Its NO inhibitory values were 92.5% ± 1.1% and 82.2% ± 2.5% at concentrations of 100 and 20 µM, respectively.

### Material and Methods

#### General Experimental Procedures

Optical rotation was measured on a Jasco P-2000 polarimeter. HR-ESI-MS was acquired on an Agilent 6530 Accurate Mass Q-TOF system, and NMR spectra on a Bruker Avance III 500 MHz spectrometer. Flash column chromatography was performed using either silica gel or reversed phase (RP-18) resins as adsorbent. Thin-layer chromatography was carried out on precoated silica gel or reversed phase (RP-18) resins. Traces of compounds were visualized under ultraviolet irradiation (254 and 365 nm) and by spraying with H2SO4 solution (5%) followed by heating with a heat gun.

#### Plant Material

Rosmarinus officinalis L. samples, identified by Dr Nguyen The Cuong at the Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology (VAST), were collected in Ha Giang province in January 2019. A voucher specimen (number: RO.19.01) is kept at the Lab of Pharmaceutical Chemistry, VNU University of Science.

#### Extraction and Isolation

Dried and powdered R. officinalis leaves (2 kg) were ultrasonically extracted with methanol, 3 times (each 5 L for 30 minutes.

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**Table 1. Effect of Compounds 1-7 on NO Production in LPS-Stimulated RAW 264.7 cells**

| Compound | Concentration (µM) | Inhibition (%) | Cell viability (%) |
|----------|-------------------|----------------|--------------------|
| 1        | 20                | 25.3 ± 1.6     | 99.1 ± 1.1         |
|          | 100               | 47.1 ± 2.2     | 99.7 ± 0.9         |
| 2        | 20                | 14.2 ± 1.3     | 99.4 ± 1.8         |
|          | 100               | 44.5 ± 1.3     | 98.4 ± 1.4         |
| 3        | 20                | 31.1 ± 1.9     | 94.6 ± 2.4         |
|          | 100               | 58.7 ± 2.5     | 73.6 ± 3.1         |
| 4        | 20                | 26.7 ± 1.4     | 95.0 ± 2.7         |
|          | 100               | 61.4 ± 1.9     | 43.2 ± 2.2         |
| 5        | 20                | 20.5 ± 2.8     | 95.4 ± 3.0         |
|          | 100               | 56.9 ± 0.9     | 18.3 ± 2.1         |
| 6        | 20                | 22.2 ± 2.1     | 99.0 ± 1.5         |
|          | 100               | 62.3 ± 1.7     | 23.3 ± 1.9         |
| 7        | 20                | 65.8 ± 3.4     | 72.9 ± 3.6         |
|          | 100               | 69.4 ± 1.9     | 21.3 ± 2.4         |
| L-NMMA²  | 20                | 82.2 ± 2.5     | 95.2 ± 2.1         |
|          | 100               | 92.5 ± 1.1     | 85.5 ± 1.6         |

Abbreviations: L-NMMA, NГ-monomethyl-L-arginine; LPS, lipopolysaccharide.

²Positive control compound.
at room temperature). After filtration, the filtrate was evaporated in vacuo to give the methanol extract (156 g). This was suspended in water and successively separated with n-hexane, ethyl acetate, and n-butanol to give n-hexane, ethyl acetate-, and n-butanol-soluble fractions.

The ethyl acetate extract (ROE, 85 g) was loaded on a silica gel column (Φ = 7 cm) and eluted with n-hexane and ethyl acetate (1 L step wise, 40/0, 20/1, 10/1, 5/1, 3/1, 1/1, v/v) to give 6 fractions ROE1-ROE6. Fraction ROE2 was chromatographed on a reverse-phase C-18 column, eluting with acetone/water (5/2, v/v) to give 2 fractions ROE2A and ROE2B. Fraction ROE2A was purified on a reverse-phase C-18 column eluting with acetone/water (2/1, v/v) and then further purified on another reverse-phase C-18 column eluting with methanol/water (3/1, v/v) to give compounds 4 (7.3 mg) and 3 (5.3 mg). Fraction ROE3 was first separated on a reverse-phase C-18 column eluting with acetone/water (2/1, v/v) and then further purified on another reverse-phase C-18 column eluting with methanol/water (3/1, v/v) to give compounds 5 (12.6 mg) and 7 (7.3 mg). Fraction ROE5 was separated on a reverse-phase C-18 column, eluting with acetone/water (5/2, v/v) to give 3e fractions ROE3A-ROE3C. Fractions ROE3A and ROE3B were purified on a reverse-phase C-18 column, eluting with methanol/water (3/1, v/v) to give compounds 4 (45.6 mg) and 5 (29 mg), respectively. The n-butanol extract (ROB, 23 g) was separated by silica gel column chromatography using a solvent system of dichloromethane/methanol/water (4/1/0.1, v/v/v) to give 4 fractions ROB1-ROB4. Fraction ROB1 was purified on a silica gel column, eluting with acetone/dichloromethane/water (3/1/0.2, v/v/v) to give compound 2 (26 mg). Fraction ROB3 was purified on a reverse-phase C-18 column, eluting with methanol/water (1/1, v/v) to give compound 1 (15 mg).

*Rosmacinalis* (I). White amorphous powder, $[\alpha]_D^{25} = -53.8^\circ$ ($\epsilon 0.1$, MeOH); HR-ESI-MS $m/\chi 499.1773$ [M + Na]$^+$ (calculated for $[C_{21}H_{32}O_{12}Na]^+$, 494.2232), and $m/\chi 477.1965$ [M + H]$^+$ (calculated for $[C_{21}H_{32}O_{12}]^+$, 477.1967); $^1$H-NMR (CD$_3$OD, 500 MHz) and $^{13}$C-NMR (CD$_3$OD, 125 MHz) data are given in Table 2.

**Acid hydrolysis and confirmation of monosaccharide.** Please refer to Supplemental Material for more information.

**Nitric Oxide Assay**

The RAW264.7 cells were received from Perugia University, Italy and were maintained in Dulbecco’s modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS), 2 mM L-glutamine, 10 mM HEPES, and 1 mM sodium pyruvate. The cells were dispensed into 96-well plate ($2 \times 10^5$ cells/well) and incubated at $37^\circ C$ in a humidified atmosphere (5% CO$_2$ and 95% air). After 24 hours of incubation, the culture medium was replaced with DMEM without FBS and continuously incubated for 3 hours. The cells were treated with either compounds or vehicle solution and then stimulated with LPS (1 µg/mL) in the next 2 hours. After an additional 24 hours incubation, the cell culture medium (100 µL) was mixed with an equal volume of Griess reagent (Promega, Fitchburg, WI, USA) for 10 minutes and the absorbance was read at 540 nm. The amount of nitrite, an indicator of NO production in the medium, was obtained from a standard curve, which was constructed by NaNO$_2$ serial dilution. L-NMMA was used as a positive control.

Cell viability was determined by adding 10 µL MTT solution (5 mg/mL) and incubating for 4 hours. Formazan crystals were dissolved in 50 µL of DMSO. Absorbance was read at 540 nm and compared with the vehicle group. Data were expressed as mean ± SD of triplicate experiments. Statistical analysis was performed by GraphPad Prism software.

**Table 2. $^1$H-NMR and $^{13}$C-NMR Spectroscopic Data for Compound I in Deuterated Methanol.**

| Position | $\delta_C^{a}$ | $\delta_H^{b}$ (mult., $J$ in Hz) | Position | $\delta_C^{a}$ | $\delta_H^{b}$ (mult., $J$ in Hz) |
|----------|----------------|----------------------------------|----------|----------------|----------------------------------|
| 1        | 72.1           | 4.02 (m)                         | 3"       | 78.1           | 3.36 (t, 9.0)                    |
| 2        | 36.8           | 2.87 (m)                         | 4"       | 71.7           | 3.31 (t, 9.0)                    |
| 1'       | 131.6          | -                                | 5"       | 76.9           | 3.43 (m)                         |
| 2'       | 113.8          | 6.87 (d, 2.0)                    | 6"       | 68.2           | 3.99 (dd, 2.0, 12.0)             |
| 3'       | 148.9          | -                                | 6"-O-Rha | 102.3          | 4.77 (d, 1.5)                    |
| 4'       | 145.9          | -                                | 1"       | 72.1           | 3.84 (dd, 1.5, 3.0)              |
| 5'       | 116.1          | 6.73 (d, 8.0)                    | 2"       | 72.1           | 3.84 (dd, 1.5, 3.0)              |
| 6'       | 122.4          | 6.70 (dd, 2.0, 8.0)              | 3"       | 72.4           | 3.68 (dd, 3.0, 9.0)              |
| 3'-OCH$_3$ | 56.5          | 3.86 (s)                         | 4"       | 74.0           | 3.38 (t, 9.0)                    |
| 1'-O-Glc | 78.1           | 3.43 (t, 9.0)                    | 5"       | 69.8           | 3.69 (m)                         |
| 1""      | 104.5          | 4.31 (d, 7.5)                    | 6"       | 18.0           | 1.28 (d, 6.5)                    |
| 2""      | 75.1           | 3.20 (dd, 7.5, 9.0)              |          |                |                                  |

Abbreviation: NMR, nuclear magnetic resonance.

Measured at $^1{H}$125 MHz, $^{13}$C500 MHz.

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**Supplemental Material for more information**
Conclusions

Two phenylethanoid glycosides, 2-(4′-hydroxy-3′-methoxy phenyl)-ethyl O-a-L-rhamnopyranosyl-(1″→6″-O-β-D-glucopyranoside (rosmacinalis, 1) and 2-phenylethyl O-a-L-rhamnopyranosyl-(1″→6″-O-β-D-glucopyranoside (2) along with 5 carnosic acid derivatives, clinopodioidol C (3), rosmanol (4), 7a-methoxyrosmanol (5), 7β-methoxyrosmanol (6) and carnosol (7) were isolated from the leaves of R. officinalis. Of these, 1 is a new compound. Compounds (1-7) were evaluated for their inhibition of NO production in LPS-activated RAW 264.7 cells. At a concentration of 100 µM, compounds 1 and 2 exhibited inhibitory rates of 47.1% ± 2.2% and 44.5% ± 1.3%, respectively, while compounds 3-7 showed cytotoxic effects. After dilution to a concentration of 20 µM, except compound 7, compounds 1-6 did not show a cytotoxic effect. Their NO inhibitory rates ranged from 14.2% ± 1.3% to 31.1%± 1.9%.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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