Note

New Triterpenoids from the Stems of *Cornus walteri*Seoung Rak Lee,^a Joo-Won Nam,^b and Ki Hyun Kim^{*a}^aSchool of Pharmacy, Sungkyunkwan University; Suwon 440–746, Korea: and ^bCollege of Pharmacy, Yeungnam University; Gyeongsan, Gyeongbuk 38541, Korea.

Received March 28, 2017; accepted May 1, 2017

A new 28-norlupane triterpenoid, 3-acetate-28-norlup-20(29)-en-3 β -hydroxy-17 β -hydroperoxide (**1**) and a new tirucallane triterpenoid, cornusalterin M (**2**), together with one known triterpenoid, 3-acetate-28-norlup-20(29)-en-3 β ,17 β -diol (**3**), were isolated from a MeOH extract of the stems of *Cornus walteri*. The chemical structures of the new compounds (**1** and **2**) were elucidated based on comprehensive one- and two-dimensional (1D and 2D) NMR spectroscopic experiments and high resolution-electrospray ionization (HR-ESI)-MS. Among the isolates, compound **1** was a relatively rare triterpenoid identified as a 28-norlupane-type triterpene with a 17 β -hydroperoxide group and compound **3** was previously reported but only as a synthetic product. The cytotoxic activities of the isolated compounds **1**–**3** were evaluated by determining their inhibitory effects on human tumor cell lines (A549 (non-small cell lung carcinoma), SK-OV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT-15 (colon adenocarcinoma)).

Key words *Cornus walteri*; Cornaceae; 28-norlupane triterpene; tirucallane triterpene

Cornus walteri WAGNER (Cornaceae) is a deciduous tree that mainly grows in the valley areas of Korea and China. In Chinese traditional medicine, the fruits and leaves of *C. walteri* have been widely utilized for the alleviation of skin inflammatory symptoms and the treatment of glycosuria.^{1–3} In addition, the leaves have been used for the treatment of diarrheal symptoms as a traditional medicine in Korea.⁴ A variety of therapeutic activities including anti-inflammatory, anti-obesity, and anti-hyperglycemic effects have been reported for the extracts of *C. walteri*.^{5,6} Additionally, the anti-photoaging activity of this source was investigated in a recent study.² As part of our continuing efforts to explore structurally novel and bioactive constituents from natural sources,^{7–14} our recent phytochemical studies of the stems of *C. walteri* reported the isolation and identification of bioactive compounds, tirucallane triterpenoids and δ -valerolactones with cytotoxic and anti-inflammatory activities.^{15,16} In our ongoing search for bioactive constituents from this source, we further investigated the MeOH extract of the stems of *C. walteri* through extensive chromatographic purifications, which resulted in the isolation of a new 28-norlupane triterpenoid, 3-acetate-28-norlup-20(29)-en-3 β -hydroxy-17 β -hydroperoxide (**1**) and a new tirucallane triterpene, (20 α ,24 S)-20,24-dihydroxy-tirucall-25(26)-ene-3-one (**2**), along with one known triterpenoid, 3-acetate-28-norlup-20(29)-en-3 β ,17 β -diol (**3**) (Fig. 1). In the present study, we report the isolation and structural elucidation of the isolated compounds and their cytotoxic activities.

Results and Discussion

Compound **1** was isolated as a white amorphous powder, and possessed the molecular formula of C₃₁H₅₀O₄ as deduced from the positive-ion mode high resolution electrospray ionization (HR-ESI)-MS data at m/z 487.3792 [M+H]⁺ (Calcd for C₃₁H₅₁O₄, 487.3787). The characteristic absorption band (3405 cm^{−1}) obtained from the IR spectrum of **1** suggested the presence of a hydroxyl group. The ¹H-NMR spectrum of **1** displayed a typical pattern of a lupane-type triterpene, with six tertiary methyls [δ_H 0.86, 0.87, 0.88, 0.96, 1.05, and

1.69 (each 3H, s)] including a vinylic methyl at δ_H 1.69 (s); an oxygenated methine [δ_H 4.50 (1H, dd, J =11.0, 6.0 Hz)]; and an olefinic methylene [δ_H 4.62 (1H, brs), 4.72 (1H, brs)]. The ¹³C-NMR data of **1**, with the aid of heteronuclear single quantum coherence spectroscopy (HSQC) analysis, showed 31 carbon signals, which were classified as seven quaternary carbons (δ_C 37.4, 38.7, 41.1, 42.3, 91.8, 150.2, and 171.2); six methines (δ_C 36.9, 48.2, 49.4, 50.8, 55.7, and 81.2) including an distinguished oxygenated carbon (δ_C 81.2); eleven methylenes (δ_C 18.5, 21.2, 23.9, 25.5, 27.2, 27.5, 29.7, 32.4, 34.6, 38.0, and 110.0) including an olefinic methylene (δ_C 110.0); and seven methyls (δ_C 14.2, 16.4, 16.5, 16.7, 19.4, 21.5, and 28.2). Detailed inspection of its NMR data revealed that compound **1** was almost identical to 3-acetate-28-norlup-20(29)-ene-3 β ,17 β -diol (**3**), except for the oxygenated quaternary carbon of C-17 (δ_C 91.8) in **1**, instead of the corresponding one (δ_C 80.4) in **3**.¹⁷ The existence of the hydroperoxide group at C-17 was confirmed based on the characteristic carbon chemical shift of C-17 (δ_C 91.8),¹⁸ along with heteronuclear multiple bond correlation (HMBC) correlations from H-13 (δ_H 1.85), H₂-15 (δ_H 1.37 and 1.98), and H-19 (δ_H 2.61) to C-17 (δ_C 91.8) (Fig. 2). The gross structure of **1** was confirmed by the cross peaks in the ¹H–¹H correlation spectroscopy (COSY) and HMBC spectra (Fig. 2). The β -configuration of the hydroperoxide group of C-17 in **1** was unambiguously determined by comparing the chemical shift (δ_C 91.8) of C-17 with that of 28-norlup-20(29)-en-3 β -hydroxy-17 β -hydroperoxide [α -form= δ_C 93.4 (C-17); β -form= δ_C 91.6 (C-17) in CDCl₃].¹⁸ The nuclear Overhauser spectroscopy (NOESY) correlations of H₃-25/H₃-26, H-13/H₃-26, H-13/H-19, H-9/H₃-27, H-18/H₃-27, H-18/H₂-29, H-5/H-9, and H-3/H-5 as well as aspects of the biosynthetic pathway suggested that the relative configuration of **1** was the same as compound **3**. Accordingly, the chemical structure of **1** was determined to be 3-acetate-28-norlup-20(29)-en-3 β -hydroxy-17 β -hydroperoxide.

Compound **2** was isolated as a white amorphous powder with the molecular formula of C₃₀H₅₀O₃ determined by the HR-ESI-MS data at m/z 459.3836 [M+H]⁺ (Calcd for

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Fig. 1. The Chemical Structures of Compounds **1–3** from *C. walteri*

Fig. 2. Key ^1H – ^1H COSY (—) and HMBC (---) Correlations of **1** and **2**

$\text{C}_{30}\text{H}_{51}\text{O}_3$, 459.3838). The IR spectrum of **2** suggested the existence of hydroxyl groups and a ketone moiety from the distinguished absorption bands (3410 and 1730 cm^{-1} , respectively). The ^1H -NMR data of **2** showed the characteristic seven tertiary methyls [δ_{H} 0.93, 0.97, 1.04 ($\times 2$), 1.07, 1.12, and 1.71 (each 3H, s)] including a vinylic methyl at δ_{H} 1.71 (s); an oxygenated methine [δ_{H} 3.96 (1H, t, $J=6.0\text{ Hz}$)] and an olefinic methylene [δ_{H} 4.82 (1H, brs), 4.90 (1H, brs)]. The ^{13}C -NMR spectrum revealed 30 carbon resonances, which were classified by HSQC data as seven quaternary carbons (δ_{C} 37.0, 42.4, 47.8, 50.2, 74.7, 147.8, and 220.0); five methines (δ_{C} 42.5, 49.9, 50.3, 55.3, and 76.3) including an oxygenated carbon (δ_{C} 76.3); eleven methylenes (δ_{C} 22.0, 24.1, 24.6, 27.5, 29.0, 31.1, 33.9, 34.5, 36.8, 40.3, and 110.5) including an olefinic methylene (δ_{C} 110.5); and seven methyls (δ_{C} 14.5, 15.4, 15.7, 19.6, 20.3, 26.1, and 27.6). The NMR data of **2** was similar to the data from cornusalterins A–E identified from *C. walteri* by our group,¹⁵⁾ which suggested that compound **2** was a tirucallane-type triterpene. Detailed interpretation of COSY and HMBC data led to elucidation of the gross structure of **2** (Fig. 2). The hydroxyl group at C-20 was confirmed based on the down-field shifted carbon chemical shift (δ_{C} 74.7) of C-20 and HMBC correlations from H-17 (δ_{H} 1.52) and H₃-21 (δ_{H} 1.12) to C-20 (δ_{C} 74.7) (Fig. 2). The hydroxyl group of C-20 was confirmed to be α -oriented based on the NOESY correlations of H-17/H₃-21 and H₃-18/H₃-21¹⁹⁾ (Fig. 3). In addition, the presence of a hydroxyl group at C-24 and $\Delta^{25,26}$ -double bond was unambiguously identified by the HMBC correlations of H-24/C-25, H-24/C-26, H-24/C-27, H₂-26/C-24, H₂-26/C-27, H₃-27/C-24, and H₃-27/C-26 (Fig. 2). The absolute configuration of C-24 was assigned as 24*S* based on the comparison of the coupling constant and chemical shifts [δ_{H} 3.96 (1H, t, $J=6.0\text{ Hz}$); δ_{C} 76.3] of C-24 with those previously reported [$24R=\delta_{\text{H}}$ 4.26 (1H, t, $J=6.8\text{ Hz}$); δ_{C} 90.5 and $24S=\delta_{\text{H}}$ 3.97 (1H, t, $J=6.1\text{ Hz}$) and δ_{C} 76.9 in CDCl_3] in the related compound.²⁰⁾ Finally, the other relative configuration of **2** was determined by analysis of the NOESY data. Thus, the chemical structure of **2** was elucidated

Fig. 3. Key NOESY (---) Correlations of **2**

as (20 α ,24*S*)-20,24-dihydroxy-tirucall-25(26)-ene-3-one and named as cornusalterin M.

The known compound **3** was identified as 3-acetate-28-norlup-20(29)-en-3 β ,17 β -diol by detailed comparison of its physical and spectroscopic data with previously reported values.¹⁷⁾ To the best of our knowledge, the two norlupane-type triterpenes (**1** and **3**) had been not reported from *C. walteri* and compound **3** was reported as a natural product in this study for the first time since it was previously only reported as a synthetic product.

The cytotoxic activities of the isolated compounds **1–3** were evaluated by determining their inhibitory effects on human tumor cell lines (A549 (non-small cell lung carcinoma), SK-OV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT-15 (colon adenocarcinoma)) using the sulforhodamine B (SRB) bioassay. However, the three tested compounds were inactive (IC_{50} : $>10.0\text{ }\mu\text{M}$).

Experimental

General Experimental Procedures Optical rotations were measured on a Jasco P-1020 polarimeter. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer. UV spectra were recorded with a Shimadzu UV-1601 UV-visible spectrophotometer. ESI and HR-ESI mass spectra

were recorded on a SI-2/LCQ DecaXP LC-MS. NMR spectra, including ^1H – ^1H COSY, HSQC, HMBC, and NOESY experiments, were recorded on a Varian UNITY INOVA 500 NMR spectrometer operating at 500 MHz (^1H) and 125 MHz (^{13}C), with chemical shifts given in ppm (δ). Preparative HPLC was performed using a Gilson 306 pump with a Shodex refractive index detector. A silica gel 60 (Merck, 230–400 mesh) and an RP-C₁₈ silica gel (Merck, 230–400 mesh) were used for column chromatography. Merck precoated silica gel F₂₅₄ plates and RP-18F_{254s} plates were used for TLC. Spots were detected on TLC under UV light or by heating after spraying with anisaldehyde–sulfuric acid.

Plant Materials The stems of *C. walteri* were acquired from Jeju Island, Korea, in October 2014. The plant was identified by one of the authors (K.H.K.). A voucher specimen (SKKU MC-2014) was deposited in the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Extraction and Isolation The stems of *C. walteri* (2.5 kg) were dried, mashed, and extracted with 80% MeOH (4L×3) twice at room temperature and filtered. The filtrate was evaporated *in vacuo* to obtain a slurry of the MeOH extract (220 g). The MeOH extract was dissolved in distilled water (800 mL) and then successively solvent-partitioned with *n*-hexane, CHCl₃ and *n*-BuOH, affording dried residues weighing 9, 25, and 43 g. The *n*-hexane-soluble fraction (9 g) was subjected to a silica gel (230–400 mesh) column eluted with a gradient solvent system of *n*-hexane–EtOAc (3:1 to 1:1, v/v) to afford five fractions (H1–H5). Fraction H1 (3.3 g) was fractionated by an RP-C₁₈ silica gel (230–400 mesh) column with an isocratic solvent system of 100% MeOH to give five subfractions (H11–H15). Subfraction H13 (750 mg) was loaded onto a silica gel (230–400 mesh) column with *n*-hexane–EtOAc (7:1, v/v) and then successively followed by semi-preparative reverse-phase HPLC (Econosil C18 column, 250×10.0 mm, 5 μm , flow rate: 2 mL/min) utilizing 100% MeOH to provide compounds **1** (6 mg) and **3** (5 mg). Fraction H5 (0.5 g) was fractionated by an RP-C₁₈ silica gel (230–400 mesh) column with an isocratic solvent system of 85% MeOH to give five subfractions (H51–55). Compound **2** (10 mg) was purified from subfraction H54 (120 mg) by semi-preparative normal-phase HPLC (Apollo Silica column, 250×10.0 mm, 5 μm , flow rate: 2 mL/min) with an isocratic solvent system of CHCl₃–MeOH (22:1, v/v).

3-Acetate-28-norlup-20(29)-en-3 β -hydroxy-17 β -hydroperoxide (**1**)

White amorphous powder; $[\alpha]_{\text{D}}^{25} + 17.9$ ($c = 0.10$, MeOH); IR (KBr) ν_{max} 3405, 2947, 1723, 1632, 1354, 1032, 670 cm^{-1} ; ^1H -NMR (CDCl₃, 500 MHz) δ : 4.72 (1H, brs, H-29b), 4.62 (1H, brs, H-29a), 4.50 (1H, dd, $J = 11.0, 6.0$ Hz, H-3), 2.61 (1H, m, H-19), 2.31 (1H, m, H-21 α), 2.20 (1H, m, H-22 α), 2.06 (3H, s, OAc), 1.98 (1H, m, H-15 α), 1.86 (2H, m, H-1 α , H-16 α), 1.85 (1H, m, H-13), 1.69 (1H, m, H-2 α), 1.69 (3H, s, H-30), 1.68 (1H, m, H-18), 1.66 (1H, m, H-12 α), 1.65 (1H, m, H-6 α), 1.61 (1H, m, H-2 β), 1.48 (1H, m, H-11 α), 1.43 (1H, m, H-21 β), 1.41 (2H, m, H-7 α , H-7 β), 1.37 (1H, m, H-15 β), 1.36 (1H, m, H-6 β), 1.35 (1H, m, H-22 β), 1.25 (1H, m, H-9), 1.19 (1H, m, H-12 β), 1.17 (1H, m, H-11 β), 1.08 (1H, m, H-1 β), 1.07 (1H, m, H-16 β), 1.05 (3H, s, H-26), 0.96 (3H, s, H-23), 0.88 (3H, s, H-27), 0.87 (3H, s, H-25), 0.86 (3H, s, H-24), 0.79 (1H, m, H-5); ^{13}C -NMR (CDCl₃, 125 MHz) δ : 171.2 (OAc), 150.2 (C-20), 110.0 (C-29), 91.8 (C-17), 81.2 (C-3), 55.7 (C-5), 50.8 (C-9), 49.4 (C-18), 48.2

(C-19), 42.3 (C-14), 41.1 (C-8), 38.7 (C-4), 38.0 (C-1), 37.4 (C-10), 36.9 (C-13), 34.6 (C-7), 32.4 (C-22), 29.7 (C-15), 28.2 (C-23), 27.5 (C-21), 27.2 (C-16), 25.5 (C-12), 23.9 (C-2), 21.5 (OAc), 21.2 (C-11), 19.4 (C-30), 18.5 (C-6), 16.7 (C-24), 16.5 (C-25), 16.4 (C-26), 14.2 (C-27); HR-ESI-MS (positive-ion mode) m/z : 487.3792 $[\text{M}+\text{H}]^+$ (Calcd for C₃₁H₅₁O₄, 487.3787).

Cornusalterin M (**2**)

white amorphous powder; $[\alpha]_{\text{D}}^{25} - 32.9$ ($c = 0.10$, MeOH); IR (KBr) ν_{max} 3410, 2931, 1730, 1662, 1367, 1051, 679 cm^{-1} ; ^1H -NMR (CDCl₃, 500 MHz) δ : 4.90 (1H, brs, H-26b), 4.82 (1H, brs, H-26a), 3.96 (1H, t, $J = 6.0$ Hz, H-24), 2.49 (1H, m, H-2 β), 1.94 (1H, m, H-2 α), 1.82 (1H, m, H-23b), 1.78 (1H, m, H-1 β), 1.74 (2H, m, H-12 β , H-16 β), 1.73 (1H, m, H-6 α), 1.71 (3H, s, H-27), 1.61 (1H, m, H-23a), 1.60 (1H, m, H-15 β), 1.56 (1H, m, H-16 α), 1.53 (1H, m, H-7 α), 1.52 (1H, m, H-17), 1.51 (1H, m, H-11 α), 1.50 (1H, m, H-6 β), 1.44 (1H, m, H-8), 1.42 (2H, m, H-22), 1.35 (1H, m, H-9), 1.31 (2H, m, H-7 β , H-15 α), 1.30 (1H, m, H-1 α), 1.25 (1H, m, H-12 α), 1.12 (3H, s, H-21), 1.10 (1H, m, H-11 β), 1.07 (3H, s, H-19), 1.04 (each 3H, s, H-28, H-29), 0.97 (3H, s, H-30), 0.93 (3H, s, H-18), 0.77 (1H, m, H-5); ^{13}C -NMR (CDCl₃, 125 MHz) δ : 220.0 (C-3), 147.8 (C-25), 110.5 (C-26), 76.3 (C-24), 74.7 (C-20), 55.3 (C-5), 50.3 (C-9), 50.2 (C-14), 49.9 (C-17), 47.8 (C-4), 42.5 (C-8), 42.4 (C-13), 40.3 (C-1), 37.0 (C-10), 36.8 (C-22), 34.5 (C-7), 33.9 (C-2), 31.1 (C-15), 29.0 (C-23), 27.6 (C-28), 27.5 (C-16), 26.1 (C-21), 24.6 (C-12), 24.1 (C-11), 22.0 (C-6), 20.3 (C-29), 19.6 (C-27), 15.7 (C-30), 15.4 (C-19), 14.5 (C-18); HR-ESI-MS (positive-ion mode) m/z : 459.3836 $[\text{M}+\text{H}]^+$ (Calcd for C₃₀H₅₁O₃, 459.3838).

Cytotoxicity Assay A sulforhodamine B (SRB) bioassay was used to determine the cytotoxicity of each isolated compound against four cultured human tumor cell lines.^{21–26} The cell lines used were A549, SK-OV-3, SK-MEL-2, and HCT-15. Doxorubicin was used as a positive control. The cytotoxicity of doxorubicin against the A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines was IC₅₀ 0.010, 0.001, 0.001, and 0.028 μM , respectively.

Acknowledgments This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2015R1C1A1A02037383) and by the Ministry of Education (NRF-2012R1A5A2A28671860).

Conflict of Interest The authors declare no conflict of interest.

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