A New Chromene Derivative and a New Polyalcohol Isolated From the Fungus Xylaria sp. 111A Associated With Garcinia polyantha Leaves

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Abstract
From the crude extract of the plant-associated fungus Xylaria sp. collected in Cameroon, a new 2H-chromene derivative, hexacycloxylariolone (1), and a new polyalcohol, xylatriol (2), were isolated, in addition to 3 known compounds, 2,3-furandiol (3), 1,8-dimethoxynaphthalene (4), and 1-palmitoyl-rac-glycerol (5). Their chemical structures were established on the basis of the interpretation of spectroscopic data. Hexacycloxylariolone (1), 1,8-dimethoxynaphthalene (4), and 1-palmitoyl-rac-glycerol (5) showed antiproliferative activity by inhibiting the growth of Raw 264.7 and THP-1 cancer cell lines.

Keywords
Garcinia polyantha, Xylaria, antiproliferative activity

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Results and Discussion
The Xylaria sp. was isolated from the leaves of G. polyantha and cultivated on an unpolished rice solid medium. The ethyl acetate (EtOAc) extracts of the rice cultures were purified by combined column chromatographies (CCs) using silica gel, and semipreparative high-performance liquid chromatography (HPLC) to yield compounds 1-5 (Figure 1).
Figure 1. Chemical structures of compounds 1-5.

Compound 1 was isolated as a white amorphous powder and was assigned the molecular formula C_{12}H_{13}O_{3} based on the high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) peak at m/z 193.0868 ([M + H]^+), C_{12}H_{13}O_{3}^+, calcld. 193.0865) (Supplemental Figure S1), indicating 6 degrees of unsaturation. Its ultraviolet (UV) spectrum exhibited maxima at 266 and 322 nm, and the infrared (IR) spectrum showed absorptions at 3849, 3741, and 3100 cm\(^{-1}\) for hydroxyl groups. The proton resonances assigned to the relevant carbon atoms by the heteronuclear single quantum coherence spectrum (Supplemental Figures S1, S2 and S4) showed the presence of 12 carbons, which can be sorted into 1 methyl (δ 17.3; 1.16, 3 H, d, J = 6.0 Hz), 2 methines (δ 76.6; 4.02, 1 H, dd, J = 7.2, 4.8 Hz and δ 70.5, 3.74, 1 H, qd, J = 6.0, 4.8 Hz), 5 sp\(^{2}\) methines [δ (132.1, 7.26, 1 H, obs), (132.0; 7.24, 1 H, d, J = 10.8), (130.3; 6.03, 1 H, dd, J = 10.8, 7.2 Hz), (118.4; 6.98, 1 H, dd, J = 7.8, 1.2 Hz), and (115.6; 6.77, 1 H, d, J = 7.8, 1.2 Hz)], 1 olefinic quaternary carbon (δ 115.5) and 2 oxygenated sp\(^{2}\) carbons (δ 160.4 and 140.1). The above nuclear magnetic resonance (NMR) data (Table 2) suggested that compound 1 has a 1,2,3-trisubstituted benzene ring [δ_{H} 7.26 (1H, obs), 6.98 (1H, dd, J = 7.8, 1.2), and 6.77 (1H, dd, J = 7.8, 1.2)]. The benzene ring occupying 4 degrees of unsaturation suggested that compound 1 possessed an additional ring including 1 double bond. In the heteronuclear multiple bond correlation (HMBC) spectrum (Supplemental Figure S5), long-range correlations were observed between H-2 (δ_{H} 4.02) and C-8a (δ_{C} 140.1); H-3 (δ_{H} 6.03) and C-2 (δ_{C} 76.6); and H-4 (δ_{H} 7.24) and C-2. The aromatic proton H-7 (δ_{H} 7.26) showed long-range correlations with the carbon signals C-8a and C-5 (160.4); H-8 (δ_{H} 6.98) showed cross-peaks with the carbon signals C-8a and C-4a (115.5). In the correlation spectroscopy (COSY) (Supplemental Figure S6), cross-peaks were observed between H-6/H-7 and H-7/H-8 of the aromatic protons. From the above evidence, the presence of a 5-mono-substituted chromene ring was postulated. The location of the hydroxyl side chain was confirmed to be at C-2 by the HMBC peaks from H-9 (δ_{H} 3.74) to C-2 and C-10 (δ_{C} 17.3); H-10 (δ_{H} 1.16) to C-2 and C-3 (δ_{C} 130.3); and from H-3 and H-4 to C-2. On that basis, the structure of 1 was established as 2-[(1-hydroxyethyl)-2H-chromen-5-ol, a new secondary metabolite to which the name hexacycloxylarione is given.

Compound 2 was isolated as a white powder. Its molecular formula, C_{16}H_{34}O_{5}, was established from an HR-ESI-MS peak at m/z 171.0997 ([M + Na]^+; C_{16}H_{34}O_{5}Na^+, calcld. 171.0997) (Supplemental Figure S7), indicating no unsaturation. The IR spectrum showed characteristic vibration bands at ν_{max} 3876 and 3741 cm\(^{-1}\) (OH). The ^{1}H NMR and ^{13}C NMR spectra (Supplemental Figures S8 an S9) showed the presence of 7 carbons, which can be sorted into 2 methyls [δ (26.0; 1.89, 3H, d, J = 6.2 Hz) and (11.6; 1.68, 3H, t, J = 7.4 Hz)], 2 methylenes [δ (43.4; 2.33, 2H, m) and (26.7, 2.33, m)], and 3 oxygenated methines [δ (76.8; 3.92, 1H, dtd, J = 9.0, 5.8, 3.3 Hz); (71.8; 4.25, 1H, dtd, J = 8.4, 5.8, 2.4 Hz), and (64.3; 2.33, 1H, m)]. The heteronuclear multiple quantum coherence (HMQC) spectrum (Supplemental Figure S10) in conjunction with the COSY correlation peaks observed from H-1 to H-7 (Supplemental Figure S12) allowed the assignment of 1 spin system in 2. The HMBC peaks from H-1 (δ_{H} 3.74) to C-2 (δ_{C} 64.3) and C-3 (δ_{C} 43.4); H-3 (δ_{C} 2.33) to C-2 and C-4 (δ_{C} 71.8); H-4 (δ_{H} 4.25) to C-2; H-5 (δ_{C} 3.92) to C-4; H-6 (δ_{H} 2.07) to C-5 (δ_{C} 76.8) and C-7 (11.6), and from H-7 (δ_{H} 1.68) to C-5 and C-6 unambiguously established that the hydroxyl groups were linked at C-2, C-4, and C-5, respectively (Figure 2). This finding was further confirmed by the HMBC peaks (Supplemental Figure S11) from 4-OH to C-4, C-3, and C-5 and 5-OH to C-5, C-4, and C-6. On the basis of these data, the planar structure of 2 was elucidated as heptane-2,4,5-triol.

The relative configuration of 2 was established from the nuclear Overhauser effect spectroscopy (NOESY) spectrum where clear NOE correlations between H-2 and H-4 (Supplemental Figure S12) indicate that they are on the same face of the molecule. Besides, no correlation was observed between H-2 and H-5, indicating the α-orientation of H-5. The structure of 2 was found to be (2*S, 3*R, 5*S)-heptane-2,4,5-triol, to which the trivial name xylatriol is given.

The known compounds, 2,3-furandiol (3)\(^{16}\), 1,8-dimethoxynaphthalene (4)\(^{17,18}\), and 1-palmitoyl-rac-glycerol

### Table 1. Antiproliferative Activity of Extract and Compounds 1-5.

| Extract and compounds | THP-1 IC\(_{50}\) (µg/mL) | THP-1 IC\(_{50}\) (µM) | Raw 264.7 IC\(_{50}\) (µg/mL) | Raw 264.7 IC\(_{50}\) (µM) |
|-----------------------|-------------------------|-------------------------|----------------------------|-------------------------|
| Extract               | 12.7                    | 30.1                    | /                          | /                       |
| (1)                   | 82.3                    | 74.6                    | 428.7                      | 388.6                   |
| (2)                   | -                       | -                       | /                          | /                       |
| (3)                   | -                       | -                       | /                          | /                       |
| (4)                   | 94.4                    | 90.5                    | 637.4                      | 611.3                   |
| Paclitaxel            | 3.2                     | 4.5                     | 3.8                        | 5.3                     |

Abbreviation: IC\(_{50}\), half-maximal inhibitory concentration.

“-” indicates >100 µg/mL and “/” indicates not determined.
were identified by comparison of their NMR data with those reported in the literature. The antiproliferative effect of the crude extract and isolated compounds was investigated against cancer cell lines, RAW 264.7 and THP-1. The results presented in Table 1 indicate that the tested samples showed various extents of antiproliferative activity. The crude extract had the most potent cytotoxic activity against THP-1 cells (half-maximal inhibitory concentration [IC50] 12.7 µg/mL) compared with compounds (1) and (5), which showed their inhibitory effects on the growth of THP-1 cells with IC50 values of 82.3 µg/mL and 94.4 µg/mL, respectively. The lowest activity was observed for compounds 2, 3, and 4, which showed less than 50% of cell viability at the concentration of 100 µg/mL; therefore, their IC50 values could not be determined (>100 µg/mL). The IC50 values against RAW 264.7 cells ranged between 30.1 µg/mL and 90.5 µg/mL. Our finding is consistent with the literature since other secondary metabolites such as cytochalasins isolated from Xylaria species were previously pointed out to be promising compounds for applications in medicine as drug candidates for the treatment of cancer. Therefore, the results of this study indicate that the Xylaria sp. is a potential source of compounds that may serve as leads for anticancer drugs.

### Experimental

#### General Experimental Procedures

Optical rotation values were measured with a Horiba SEPA-300 polarimeter. IR and UV spectra were, respectively, recorded with JASCO A-302 IR and Jasco J-20A, Shimadzu UV mini-1240 spectrophotometers. 1H, 13C, and 2D NMR spectra were recorded on Bruker AMX-500 and Jeol ECZ-600 spectrometers. Proton and carbon chemical shifts are reported in δ (ppm) with reference to trimethylsilane (TMS). Coupling constants (J) are given in Hz. Homonuclear 1H-1H connectivity was determined by the COSY 45 experiment and 1-bond 1H-13C connectivity by HMQC. 1H-13C connectivity over 2 or 3 bonds was detected by HMBC. The ESI-MS were recorded on a Double-Focusing Mass Spectrometer (Varian MAT 311A). HR-ESI-MS were recorded on JEOL HX 110 and Synapt G2 Mass Spectrometers. Column chromatography was carried out on silica gel 60 (70-230 and 240-320 mesh sizes, E. Merck), and semipreparative HPLC with a Shimadzu pump and UV LC-10A detector (set at 210 nm) on a Mightysil ODS column (250 × 6.0 mm i.d.) at a flow rate of 1.5 mL/min. Precoated silica gel thin-layer chromatography plates supported on aluminum sheets (E. Merck, F254) were used to check the purity of compounds, which were detected either by spraying with 10% vanillin in sulfuric acid followed by heating or by UV irradiation. The vanillin/sulfuric acid spray reagent was prepared by dissolving 1.0 g of vanillin in 100 mL of concentrated sulfuric acid.
Fungal Material

The fungal strain *Xylaria* sp. 111A was isolated from a healthy leaf of *G. polysantha* collected in Yaoundé (Cameroon). The plant material was authenticated by Mr NANA Victor of the National Herbarium of Cameroon in Yaoundé, where a voucher specimen (21337/SRF/Cam/Mt Kala) is deposited. The healthy leaf was aseptically cleaned successively with 70% ethanol (EtOH) for 1 minute, 5% sodium hypochlorite for 5 minutes, 70% EtOH for 1 minute, and then rinsed in sterile water 2 times. The aseptically clean samples were dried on sterilized paper and cut into 1-cm pieces. The pieces were placed on plates of potato dextrose agar (PDA) containing chloramphenicol (100 mg/L). After incubation at 25 °C for 7 days, the hyphal tips of the fungi on the plates were removed from the agar plates and transferred to new PDA plates (slant). The strain 111A was isolated and grown on slants of PDA as silver to black colored culture. This strain was identified as *Xylaria sp.* by BEX Co. LTD., Japan, using DNA analysis of the 18S rDNA regions and deposited at the laboratory in the Faculty of Agriculture of Yamagata University, Japan.

Extraction and Isolation

*Xylaria* sp. was cultivated in 10 Erlenmeyer flasks (1000 mL each) containing 50 g of sterile steamed unpollished rice. Each flask received about 5 small pieces of the mycelium from the PDA plate under sterile conditions. After 4 weeks of growing at 25 °C, the moldy unpollished rice was extracted with EtOAc (2.0 L), and then taken to dryness. The resulting extract was further partitioned into *n*-hexane fraction (0.5 L), EtOAc fraction (0.5 L), and aqueous fraction (0.5 L). The EtOAc fraction (3.5 g) was chromatographed on a silica gel column using stepwise elution (chloroform [CHCl3]/EtOAc 100:0-0:100, v/v, respectively, to afford fractions A, B, C, and D. Fraction A (0.8 g) was further chromatographed on a silica gel column using stepwise elution (chloroform [CHCl3]/EtOAc to afford fractions A-1 to A-6. Fractions A-3 (43 mg) (CHCl3/EtOAc 50:50, v/v) and A-4 (72 mg) (CHCl3/EtOAc 40:60, v/v) were further separated by octadecyl silica gel column chromatography eluting with isocratic acetonitrile-water (60:40) to yield 1 (2.1 mg) and 3 (10.2 mg). Fractions B and C (*n*-hexane/EtOAc 30/80, 40/60) were combined (1.8 g) and further column chromatography on silica gel using a gradient of CHCl3/EtOAc 100:0-0:100, v/v afforded 2 (14.6 mg), 4 (10.3 mg), and 5 (11.1 mg).

**Hexacycloxylariolone (1).** White powder. [α]D25 = +0.55 (c 0.03, MeOH). UV (MeOH): 266 and 322 nm IR (ν = 3876, 3741, 3100, 1673, 1631, 1531, and 1295. HR-ESI-MS: m/z 193.0868 [M + H]+, (calcd. for C12H13O3 m/z 193.0865). 1H and 13C NMR see Table 2.

**Xylatriol (2).** White powder. [α]D25 = +6.7 (c 0.3, MeOH). IR (ν = 3876, 3741, 1708 and 1527 cm−1, HR-ESI-MS: m/z 171.0990 [M + Na]+, (calcd. for C7H16O3Na m/z 171.0997). 1H and 13C NMR see Table 2.

Antiproliferative Activity

The mouse macrophages Raw 264.7 cell line and the THP-1 human monocytic leukemia cell line were cultured, respectively, in Dulbecco’s modified Eagle’s medium and Roswell Park Memorial Institute 1640 culture medium containing 2 mM l-glutamine supplemented with 0.1% 2-mercaptoethanol. All the culture media were supplemented with 10% fetal calf serum and 1% antibiotics comprising 100 IU/mL penicillin and 100 µL/mL streptomycin. Cells were maintained at 37 °C in a humidified atmosphere containing 5% carbon dioxide.

Cell proliferation was evaluated using the cell proliferation reagent WST-1 (2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfoaphenyl)-2H-tetrazolium) (Roche Diagnostics, Germany), according to the manufacturer’s instructions. Cells were seeded (104 cells/100 µL per well) in 96-well plates in triplicate and incubated overnight. The next day, the cells were exposed to different concentrations (1 µg/mL, 10 µg/mL, 30 µg/mL, 60 µg/mL, and 100 µg/mL) of either extract or compounds and incubated for 48 hours. Then the medium in each well was aspirated, and WST-1 solution, diluted 1:10 with fresh medium, was added to each well, and the plates incubated at 37 °C for 60 minutes. The absorbance was recorded at 450 nm/690 nm using a Synergy Multi-Mode Microplate Reader (BioTek). Results were expressed as the percentage of viable cells relative to the control without treatment. A concentration-response analysis was performed to determine the compound concentrations required to inhibit the growth of cancer cells by 50% (IC50) using GraphPad Prism software.

Conclusion

The chemical investigation of *Xylaria* sp. obtained from *G. polysantha* led to the isolation of a new 2H-chromene derivative, hexacycloxylariolone (1), and a new polyalcohol xylatriol (2), along with 3 known compounds, 2,3-furandiol (3), 1,8-dimethoxynaphthalene (4), and 1-palmitoyl-rac-glycerol (5). An antiproliferative in vitro bioassay was used to evaluate the crude extract and isolated compounds against Raw 264.7 and THP-1 cancer cell lines. The crude extract, hexacycloxylariolone (1), 1,8-dimethoxynaphthalene (4), and 1-palmitoyl-rac-glycerol (5) showed moderate antiproliferative activity. None of the isolated compounds has been reported from the host plant. This finding could provide new perspectives in the study of the chemical diversity of endophytes from other parts of this plant.

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Declaration of Conflicting Interests

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