Available online on www.ijppr.com
International Journal of Pharmacognosy and Phytochemical Research 2015; 7(4); 718-722

ISSN: 0975-4873

Research Article

Triterpenes from *Calophyllum inophyllum* Linn.

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Available Online: 25th June, 2015

ABSTRACT
Chemical investigation of the dichloromethane extracts of *Calophyllum inophyllum* Linn. afforded friedelin (**1**), squalene (**2**), canophyllic acid (**3**), and a mixture of canophyllalic acid (**4a**) and canophyllol (**4b**) from the leaves; and **1** and taraxasterol (**5**) from the twigs. The structures of **3-5** were elucidated by extensive 1D and 2D NMR spectroscopy, while those of **1** and **2** were identified by comparison of their NMR data with those reported in the literature.

Keywords: *Calophyllum inophyllum*, Clusiaceae, friedelin, squalene, canophyllic acid, canophyllalic acid, canophyllol, taraxasterol

INTRODUCTION

Calophyllum inophyllum Linn. belongs to the mangosteen family (Clusiaceae). This latex-rich tropical tree is known to the world as the Indian laurel or Alexandrian laurel. In the Philippines, it is popularly called *bitaog*. It is used in traditional folk medicine to treat eye diseases, wounds, rheumatism, and inflammation[1,2]. Earlier studies reported on the chemical constituents and bioactivities of the plant extracts. Extracts from the nut and root bark of the plant yielded calophyllolide which exhibited significant cytotoxic activity against human epidermoid carcinoma of the nasopharynx cancer cell line (KB)[3]. A prenylated xanthone and other known compounds from the twigs of the plants exhibited cytotoxicity against chronic myelogenous leukemia cells (K562)[4]. A friedelane-type triterpene, along with other known triterpenoids, isolated and characterized from the leaves and stems of the plant, showed inhibitory effects on human leukemia HL-60 cells[5]. Ethanolic and water extracts from the plant's bark exhibited significant anti-HIV-IN (HIV-1 integrase) enzyme inhibition[6]. Calophyllic acid, isocalophyllic acid, and canophyllic acid from the leaves of *C. inophyllum* exhibited dose-dependent lipid lowering activity and antioxidant property[7]. Initial screening of crude extracts from the leaves of *C. inophyllum* showed moderate bioactivity against human breast cancer cells (MCF-7) and human colonic cancer cells (HT-29)[8]. Another study reported the isolation of canophyllol, 3-oxo-28-friedelanoic acid, canophyllic acid, friedelin and epifriedelinol from *C. inophyllum*[9].

We report herein the isolation of friedelin (**1**), squalene (**2**), canophyllic acid (**3**), canophyllalic acid (**4a**), and canophyllol (**4b**) from the leaves; and **1** and taraxasterol (**5**) from the twigs of *C. inophyllum* (Fig. 1).

MATERIALS AND METHODS

General Experimental Procedure

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were acquired in $CDCl_3$ on a 500 MHz Agilent DD2 NMR spectrometer with referencing to solvent signals (δ 7.26 and 77.0 ppm). Two-dimensional NMR experiments recorded included gCOSY, HSQCAD, and gHMBCAD NMR experiments. Column chromatography was performed with silica gel 60 (70-230 mesh). Thin layer chromatography was performed with plastic backed plates coated with silica gel F_{254} and the plates were visualized by spraying with vanillin/H_2SO_4 solution followed by warming.

Sample Collection

Samples of leaves and twigs of *Calophyllum inophyllum* Linn. were collected from the De La Salle University – Science and Technology Complex (DLSU-STC) riparian forest in February 2014. The samples were authenticated by one of the authors (EHM) and deposited at the De La Salle University Herbarium with voucher specimen # 917.

General Isolation Procedure

The air-dried leaves (193 g), and stems (120 g) of *C. inophyllum* Linn. were ground in a blender, soaked in CH_2Cl_2 for three days and then filtered. The filtrates were concentrated under vacuum to afford crude extracts of

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leaves (9.5 g), and stems (4 g) which were each chromatographed by gradient elution with CH_2Cl_2, followed by increasing amounts of acetone at 10% increment by volume as eluents. A glass column 12 inches in height and 0.5 inch internal diameter was used for the fractionation of crude extracts. Two milliliter fractions were collected. Fractions with spots of the same R_f values were combined and rechromatographed in appropriate solvent systems until TLC pure isolates were obtained. Rechromatography and final purifications were conducted using Pasteur pipettes as columns. One milliliter fractions were collected.

Isolation of Chemical Constituents of the Leaves

The CH_2Cl_2 fraction from the chromatography of the crude extract was rechromatographed (3 ×) using petroleum ether to afford **2** (12 mg). The 30% acetone in CH_2Cl_2 fraction from the chromatography of the crude extract was rechromatographed (3 ×) using 15% EtOAc in petroleum ether to afford **1** (8 mg). The 40% acetone in CH_2Cl_2 fraction from the chromatography of the crude extract was rechromatographed using 20% EtOAc in petroleum ether. The more polar fractions were rechromatographed using 20% EtOAc in petroleum ether to afford **3** (4 mg) after trituration with petroleum ether. The less polar fractions were rechromatographed (2 ×) using 20% EtOAc in petroleum ether to afford a mixture of **4a** and **4b** (5 mg) after trituration with petroleum ether.

Isolation of Chemical Constituents of the Twigs

The 10% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) using 10% EtOAc in petroleum ether to afford **1** (7 mg) after washing with petroleum ether. The 40% acetone in CH_2Cl_2 fraction was rechromatographed (4 ×) using 15% EtOAc in petroleum ether to afford **5** (6 mg) after washing with petroleum ether.

Friedelin (1): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72 (3H, s, H-24), 0.87 (3H, s, H-25), 0.88 (3H, d, *J* = 6.5 Hz, H-23), 0.95 (3H, s, H-29), 0.997 (3H, s, H-28), 1.00 (3H, s, H-26), 1.05 (3H, s, H-27), 1.18 (3H, s, H-30). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3 (C-1), 41.5 (C-2), 213.2 (C-3), 58.2 (C-4), 42.1 (C-5), 41.3 (C-6), 18.2 (C-7), 53.1 (C-8), 37.4 (C-9), 59.4 (C-10), 35.6 (C-11), 30.5 (C-12), 39.7 (C-13), 38.3 (C-14), 32.4 (C-15), 36.0 (C-16), 30.0 (C-17), 42.8 (C-18), 35.3 (C-19), 28.2 (C-20), 32.8 (C-21), 39.2 (C-22), 6.8 (C-23), 14.6 (C-24), 17.9 (C-25), 20.2 (C-26), 18.7 (C-27), 32.1 (C-28), 35.0 (C-29), 31.8 (C-30).

Squalene (2): ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.09-5.15 (6H, =CH), 1.60 (18H, allylic CH_3, *cis*), 1.68 (6H, allylic CH_3, *trans*), 1.96-2.10 (20H, allylic CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.1, 134.9, (C-6, C-10), 131.2 (C-2), 124.4, 124.30, 124.27 (C-3, C-7, C-11), 39.72, 39.75 (C-5, C-9), 28.3 (C-12), 26.8, 26.7 (C-4, C-8), 25.7 (C-1), 17.7 (C-2′), 16.02, 15.98 (C-6′, C-10′).

Canophyllic acid (**3**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, s, H-26), 0.85 (3H, s, H-25), 0.93 (3H, d, J = 6 Hz, H-23), 0.94 (3H, s, H-29), 0.95 (3H, s, H-24), 1.00 (3H, s, H-27), 1.05 (3H, s, H-30), 3.73 (1H, m, H-3); ^{13}C NMR (125 MHz $CDCl_3$): δ 15.8 (C-1), 36.0 (C-2), 72.7 (C-3), 49.2 (C-4), 38.9 (C-5), 41.5 (C-6), 17.4 (C-7), 53.1 (C-8), 37.3 (C-9), 61.2 (C-10), 20.5 (C-11), 31.2 (C-12), 37.8 (C-13), 38.9 (C-14), 28.4 (C-15), 32.6 (C-16), 37.8 (C-17), 37.8 (C-18), 35.2 (C-19), 28.4 (C-20), 34.9 (C-21), 32.6 (C-22), 11.6 (C-23), 16.4 (C-24), 17.8 (C-25), 20.5 (C-26), 18.5 (C-27), 181.6 (C-28), 29.8 (C-29), 34.5 (C-30).

Canophyllalic acid (4a): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.71 (3H, s, H-24), 0.83 (3H, s, H-26), 0.858 (3H, s, H-25), 0.862 (3H, d, J = 7 Hz, H-23), 0.91 (3H, s, H-29), 1.04 (each 3H, s, H-27, 30); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2 (C-1), 42.1 (C-2), 213.1 (C-3), 58.2 (C-4), 44.7 (C-5), 41.5 (C-6), 18.1 (C-7), 53.0 (C-8), 37.8 (C-9), 59.3 (C-10), 21.44 (C-11), 31.0 (C-12), 41.1 (C-13), 38.9 (C-14), 29.1 (C-15), 32.6 (C-16), 37.6 (C-17), 37.7 (C-18), 35.4 (C-19), 28.4 (C-20), 34.9 (C-21), 32.6 (C-22), 6.8 (C-23), 14.6 (C-24), 17.5 (C-25), 20.6 (C-26), 18.5 (C-27), 182.0 (C-28), 29.7 (C-29), 34.5 (C-30).

Canophyllol (4b): ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.72 (3H, s, H-24), 0.87 (3H, d, J = 7 Hz, H-23), 0.86 (3H, s, H-25), 0.91 (3H, s, H-29), 0.98 (3H, s, H-26), 0.99 (3H, s, H-27), 1.13 (3H, s, H-30), 3.63 (1H, br s, H-28); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2 (C-1), 41.5 (C-2), 213.1 (C-3), 58.2 (C-4), 42.1 (C-5), 41.2 (C-6), 18.2 (C-7), 52.5 (C-8), 37.4 (C-9), 59.5 (C-10), 34.5 (C-11), 28.1 (C-12), 38.1 (C-13), 37.4 (C-14), 29.1 (C-15), 31.4 (C-16), 35.1 (C-17), 39.4 (C-18), 33.3 (C-19), 30.1 (C-20), 31.4 (C-21), 41.5 (C-22), 6.8 (C-23), 14.6 (C-24), 19.2 (C-25), 19.1 (C-26), 18.1 (C-27), 68.0 (C-28), 34.2 (C-29), 32.8 (C-30).

Taraxasterol (5): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (3H, s, H-24), 0.849 (3H, s, H-25), 0.852 (3H, s, H-28), 0.93 (3H, s, H-27), 0.97 (3H, s, H-23), 1.01 (3H, d, J = 7.1 Hz, H-29), 1.02 (3H, s, H-26), 3.20 (1H, dd, J= 11, 5.5 Hz, H-3), 4.60 (1H, H-30b), 4.62 (1H, H-30a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.8 (C-1), 27.4 (C-2), 79.0 (C-3), 38.9 (C-4), 55.4 (C-5), 18.3 (C-6), 34.1 (C-7), 40.9 (C-8), 50.5 (C-9), 37.1 (C-10), 21.4 (C-11), 26.2 (C-12), 39.2 (C-13), 42.0 (C-14), 26.7 (C-15), 38.3 (C-16), 34.5 (C-17), 48.7 (C-18), 39.4 (C-19), 154.6 (C-20), 25.6 (C-21), 38.9 (C-22), 28.0 (C-23), 15.4 (C-24), 16.8 (C-25), 15.9 (C-26), 14.8 (C-27), 19.5 (C-28), 25.5 (C-29), 107.1 (C-30).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extracts of *Calophyllum inophyllum* yielded friedelin (**1**)[10], squalene (**2**)[11,12], canophyllic acid (**3**), and a mixture of canophyllalic acid (**4a**)[13-15] and canophyllol (**4b**)[13,16] from the leaves; and **1** and taraxasterol (**5**)[14,17] from the twigs. The structures of **3-5** were elucidated by extensive 1D and 2D NMR spectroscopy. The structures of **1** and **2** were identified by comparison of their NMR data with those reported in the literature for friedelin[10] and squalene[11,12], respectively.

Although no biological activity tests were conducted on the isolated triterpenes (**1-5**), a literature search of these compounds revealed that these have diverse bioactivities. Friedelin (**1**) was reported to possess potent anti-inflammatory, analgesic and antipyretic activities[18]. It exhibited antinociceptive effects in models of orofacial nociception in rodents[19]. The *in vitro* antimycobacterial activity of **1** was investigated and shown to exhibit an MIC value at 4.9 µg/mL against *Bacillus calmette* Guerin (BCG)[20]. Triterpene **1** was also shown to exhibit good antibacterial activity against *Staphylococcus aureus,*

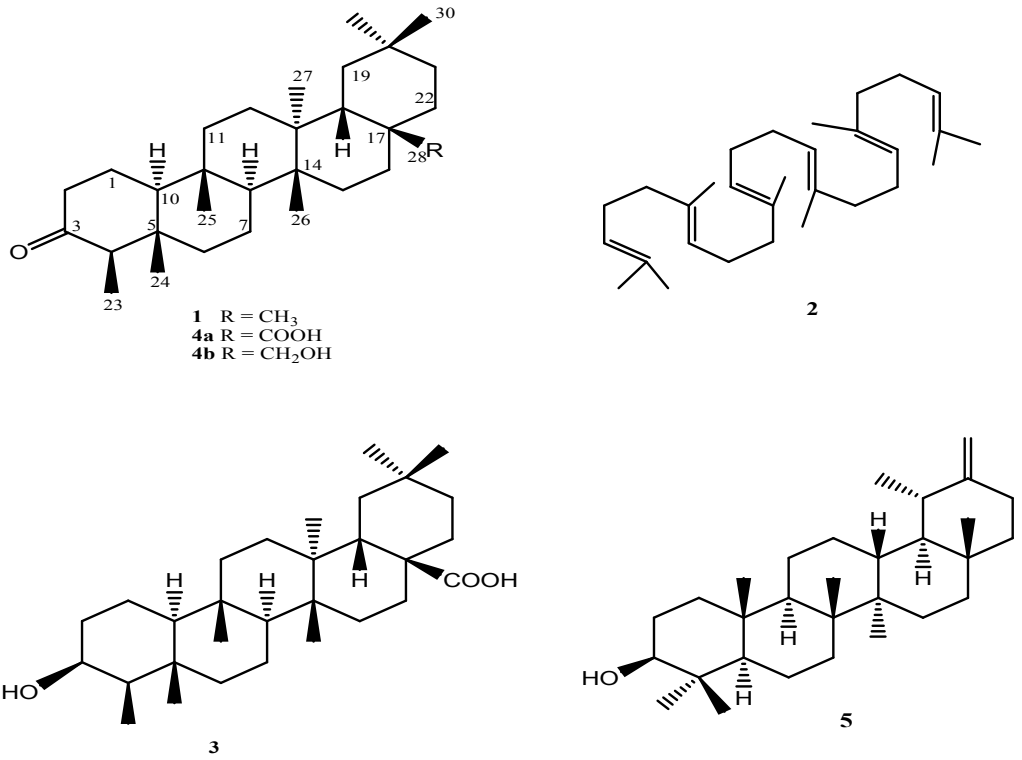

Figure 1: Chemical structures of friedelin (**1**), squalene (**2**), canophyllic acid (**3**), canophyllalic acid (**4a**), canophyllol (**4b**), and taraxasterol (**5**) from *Calophyllum inophyllum.*

Corynebacterium diptheriae, Salmonella typhi, Klebsiella pneumonia, and *Proteus mirabilis.* It was highly active against most of the pathogenic fungi tested such as *Aspergillus niger, Pseudallescheria boydii,* and *Trichophyton schoenleinii*[21]. The antiproliferative effect of **1** on both HeLa and HSC-1 cells has been reported[22]. Another study reported that **1** exhibited the strongest inhibitory effect against HeLa cancer cell with IC_{50} value of 3.54±0.30 μg/mL[23]. Compound **1** also displayed strong cytotoxic activities on the proliferation of four human cancer cells namely, A375, L292, HeLa and THP-1[24].

Squalene (**2**) was reported to significantly suppress colonic ACF formation and crypt multiplicity which strengthened the hypothesis that it possesses chemopreventive activity against colon carcinogenesis[25]. It showed cardioprotective effect which is related to inhibition of lipid accumulation by its hypolipidemic properties and/or its antioxidant properties[26]. A recent study reported that tocotrienols, carotenoids, squalene and coenzyme Q10 have anti-proliferative effects on breast cancer cells[27]. The preventive and therapeutic potential of squalene containing compounds on tumor promotion and regression have been reported[28]. A recent review on the bioactivities of squalene has been provided[29].

Canophyllic acid (**3**) showed dose dependent lipid lowering activity in *in vivo* experiments[30]. In another study, **3** showed inhibitory activity against human leukemia HL-60 cells with growth inhibition (IG_{50}) value of 4.64±0.27 μM[11]. Furthermore, **3** was reported to exhibit bactericidal activity against *Proteus mirabilis*[19].

An earlier study reported that canophyllalic acid (**4a**) exhibited antioxidant activity and showed very weak antidyslipidemic activity as it lowered the total cholesterol and total triglycerides by 10%[30]. In another study, **4a** showed inhibitory activity against human leukemia HL-60 cells with growth inhibition (IG_{50}) value of 2.67±0.49 μM[11].

Canophyllol (**4b**) exhibited antifungal activity against *Candida albicans, Microsporum canis, Fusarium oxisporum* var. *lycopersici*, and *Rhizoctonia solani* with % inhibition of 15.45, 5.97, 1.90, and 25.93, respectively[19]. Triterpene **4b** also showed antimicrobial activity against *Staphylococcus aureus, Carynebacterium diptheriae, Klebsiella pneumonia,* and *Proteus mirabillis* with zone of growth inhibition of 5.50, 4.53, 3.00, and 3.50, respectively[19]. Compound **4b** was reported to exhibit antiplasmodial activity against the W2 strain of *Plasmodium falciparum* with an IC_{50} value of 15.0μM±0.1[31]. Furthermore, *in vivo* assays indicated that **4b** acts as a selective postemergence herbicides at 100 μM by reducing biomass production in the weed *Physalis ixocarpa*[32]. In another study, several compounds were screened for cytokine-inducing activity on human PBMCs to investigate their antitumor effects, and **4b** was found to demonstrate the most effective induction of the cytokines[33].

Taraxasterol (**5**) exhibited inhibitory effects on Epstein-Barr virus early antigen induction and showed potent anti-mammary tumor activity[34]. In another study, **5** was shown to possess strong anti-inflammatory activity[35,36], and exhibit antihyperlipidemic activity[37] and antimicrobial activity against *Staphylococcus aureus*[38].

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CONCLUSION

Calophyllum inophyllum is used in traditional folk medicine to treat eye diseases, wounds, rheumatism, and inflammation. A study reported that the crude extracts of *C. inophyllum* exhibited cytotoxic and anticancer properties. This study reports on the isolation of triterpenes with diverse biological activities. Friedelin (**1**) and taraxasterol (**5**) were reported to exhibit anti-inflammatory properties. Triterpene **1**, canophyllic acid (**3**), canophyllol (**4b**), and **5** were also shown to possess antimicrobial properties and thus could be used for the treatment of wounds. All the triterpenes (**1**-**5**) isolated from *C. inophyllum* have been reported to possess cytotoxic and anticancer properties.

ACKNOWLEDGEMENT

A research grant from the De La Salle University Science Foundation through the University Research Coordination Office is gratefully acknowledged.

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