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Triterpenes and Sterols from *Terminalia foetidissima* Griff.

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Terminalia foetidissima Griff. is a tree native of the Philippines. Chemical investigation of dichloromethane extract of the leaves of *T. foetidissima* has led to the isolation of cycloeucalenol (**1**), squalene (**2**), long-chain hydrocarbons (**3**) and a mixture of 24-methylene-pollinastanol (**4**), β-sitosterol (**5**) and stigmasterol (**6**) in about 4:3:1 ratio. The structure of compound **1** was elucidated by extensive 1D and 2D NMR spectroscopy and confirmed by comparison of its NMR data with those reported in the literature. The structures of compounds 2-6 were identified by comparison of their NMR data with literature data.

Keywords: *Terminalia foetidissima*, Combretaceae, Cycloeucalenol, Squalene, 24-Methylenepollinastanol, Stigmasterol, β-Sitosterol.

INTRODUCTION

Terminalia foetidissima Griff., locally known as talisay gubat, is native to Southeast Asia *viz*. Myanmar, Thailand, Malaysia, Indonesia and Philippines. The tree is used as a dye and a source of wood, as well as for construction purposes and furniture making [1]. To our best of knowledge, there is no reported study on the chemical constituents of *T. foetidissima*. This study is part of our work on the chemical constituents of native Philippine plants of the genus *Terminalia*. We earlier reported the isolation of squalene, lutein and fatty alcohols from *Terminalia microcarpa* [2]. We report herein the the isolation of cycloeucalenol (**1**), squalene (**2**), long-chain hydrocarbons (**3**), 24-methylenepollinastanol (**4**), β-sitosterol (**5**) and stigmasterol (**6**) (Fig. 1) from the dichloromethane extract of *Terminalia foetidissima*. To the best of our knowledge, this is the first report on the isolation of compounds **1-6** from *Terminalia foetidissima*.

EXPERIMENTAL

NMR spectra were recorded on a JEOL spectrometer in $CDCl_3$ at 600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR spectra. 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: The leaves of *Terminalia foetidissima* Griff. was collected from Mt. Makiling, Los Banos, Laguna, Philippines in February 2018. It was authenticated by Dr. Edwino S. Fernando of Jose Vera Santos Memorial Herbarium, Institute of Biology, University of the Philippines, Diliman, Quezon City, Philippines.

Isolation of chemical constituents of *T. foetidissima*: The leaves of *T. foetidissima* were air-dried (379.6 g), then ground in a blender, soaked in CH_2Cl_2 for 3 days and filtered. The filtrate was concentrated under vacuum to afford a crude extract (7.73 g) which was chromatographed by gradient elution using increasing proportions of acetone in CH_2Cl_2 at 10 % increment by volume. The CH_2Cl_2 fraction was rechromatographed using petroleum ether. The less polar fractions were combined and rechromatographed using petroleum ether to afford compound **3** (28.9 mg) after washing with petroleum ether. The more polar fractions were combined and rechromatographed using 2.5% EtOAc in petroleum ether to afford compound **2** (2.9 mg). Acetone (40 %) in CH_2Cl_2 fraction was rechromatographed using 10 % EtOAc in petroleum ether to yield compound **1** (5.7 mg) and a mixture of compounds **4-6** (15.2 mg) after washing with petroleum ether.

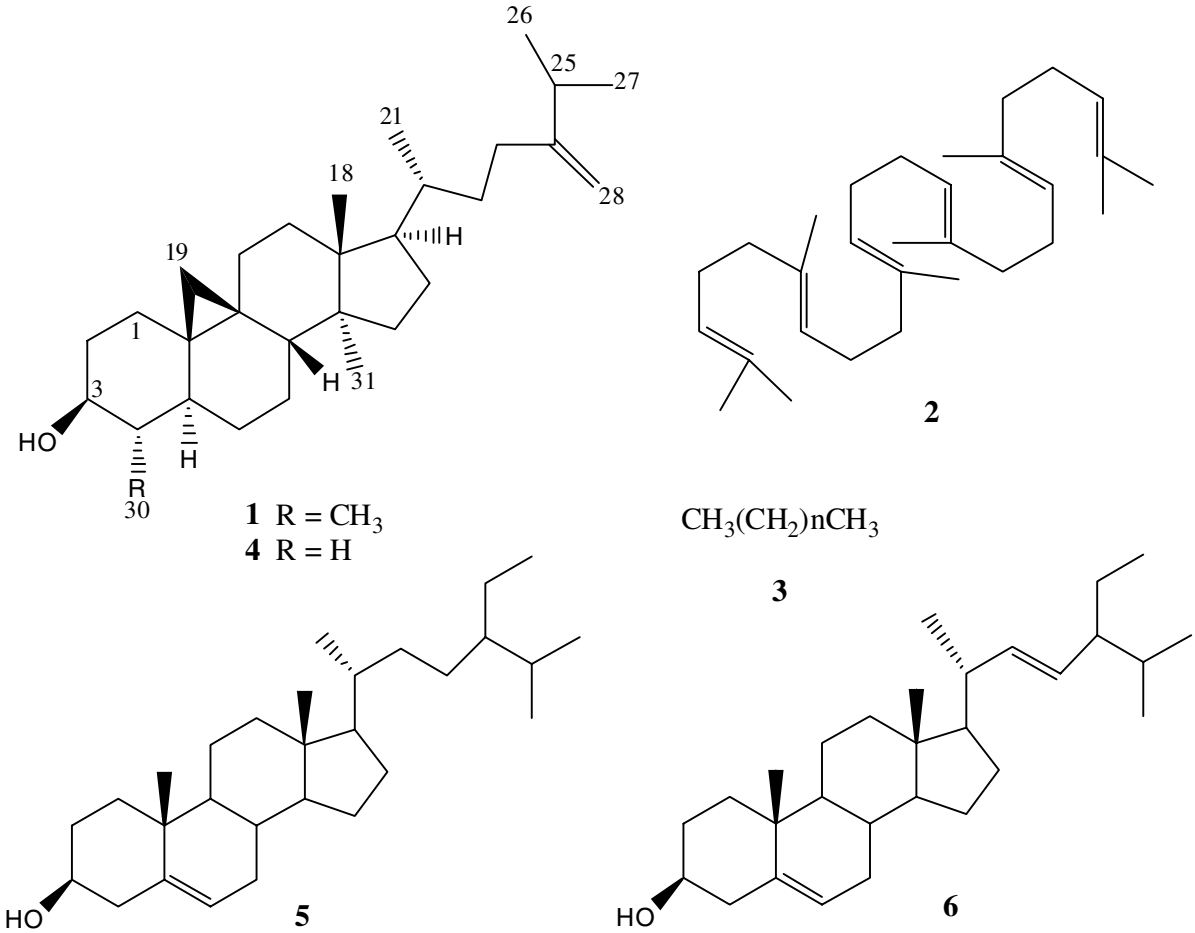

Fig. 1. Chemical structures of cycloeucalenol (**1**), squalene (**2**), long-chain hydrocarbons (**3**), 2,4-methylenepollinastanol (**4**), β-sitosterol (**5**) and stigmasterol (**6**) from *T. foetidissima*

Cycloeucalenol (1): Colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.22 (m, H-3), 0.97 (3H, s, H-18), 0.14 (1H, d, *J* = 3.6 Hz, H-19α), 0.38 (1H, d, *J* = 3.6 Hz, H-19β), 0.89 (3H, d, *J* = 6.6 Hz, H-21), 1.02 (3H, d, *J* = 6.6 Hz, H-26), 1.03 (3H, d, *J* = 6.6 Hz, H-27), 4.66 (brs, H-28), 4.71 (brs, H-28), 0.98 (3H, d, *J* = 6 Hz, H-30), 0.88 (3H, s, H-32); ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.87 (C-1), 34.88 (C-2), 76.68 (C-3), 44.66 (C-4), 43.40 (C-5), 24.76 (C-6), 25.26 (C-7), 46.99 (C-8), 23.64 (C-9), 29.58 (C-10), 27.03 (C-11), 32.94 (C-12), 45.41 (C-13), 48.98 (C-14), 35.42 (C-15), 28.21 (C-16), 52.28 (C-17), 17.91 (C-18), 27.37 (C-19), 36.21 (C-20), 18.42 (C-21), 35.05 (C-22), 31.39 (C-23), 157.04 (C-24), 33.88 (C-25), 22.09 (C-26), 21.96 (C-27), 105.98 (C-28), 14.50 (C-30), 19.22 (C-32).

Squalene (2): Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07-5.14 (6H. =CH), 1.58 (18H, allylic CH_3, *cis*-), 1.66 (6H, allylic CH_3, *trans*-), 1.96-2.06 (20H, allylic CH_2).

Hydrocarbons (3): Colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.26 (brs, -$(CH_2)_n$-), 0.86 (t, 6.6 Hz, terminal CH_3).

24-Methylenepollinastanol (4): Colourless solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.68 (m, H-3), 0.95 (3H, s, H-18), 0.06 (1H, d, *J* = 3.6 Hz, H-19α), 0.41 (1H, *J* = 3.6 Hz, H-19β), 0.90 (3H, d, *J* = 6.6 Hz, H-21), 1.01 (3H, d, *J* = 6.6 Hz, H-26), 1.02 (3H, d, *J* = 6.6 Hz, H-27), 4.65 (brs, H-28), 4.70 (brs, H-28), 0.87 (3H, s, H-32); ^{13}C NMR (150 MHz, $CDCl_3$): 31.38 (C-1), 28.35 (C-2), 71.31 (C-3), 39.83 (C-4), 37.32 (C-5), 27.88 (C-6), 28.12 (C-7), 46.26 (C-8), 23.12 (C-9), 30.58 (C-10), 27.12 (C-11), 32.91 (C-12), 45.46 (C-13), 49.15 (C-14), 35.38 (C-15), 28.12 (C-16), 52.20 (C-17), 17.52 (C-18), 26.07 (C-19), 36.22 (C-20), 18.46 (C-21), 35.14 (C-22), 31.38 (C-23), 157.01 (C-24), 33.88 (C-25), 21.97 (C-26), 22.10 (C-27), 106.00 (C-28), 19.07 (C-32).

β-Sitosterol (5): Colourless solid; ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.26 (C-1), 31.72 (C-2), 71.88 (C-3), 42.39 (C-4), 140.83 (C-5), 121.82 (C-6), 31.96 (C-7), 31.96 (C-8), 50.18 (C-9), 36.58 (C-10), 21.07 (C-11), 39.83 (C-12), 42.28 (C-13), 56.83 (C-14), 24.40 (C-15), 28.12 (C-16), 56.10 (C-17), 11.95 (C-18), 19.39 (C-19), 36.22 (C-20), 18.86 (C-21), 33.88 (C-22), 26.07 (C-23), 45.87 (C-24), 29.18 (C-25), 19.02 (C-26), 19.94 (C-27), 23.12 (C-28), 11.95 (C-29).

Stigmasterol (6): Colourless solid; ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.26 (C-1), 31.72 (C-2), 71.88 (C-3), 42.28 (C-4), 140.83 (C-5), 121.82 (C-6), 31.96 (C-7), 31.96 (C-8), 50.18 (C-9), 36.58 (C-10), 21.07 (C-11), 39.75 (C-12), 42.28 (C-13), 56.83 (C-14), 24.40 (C-15), 28.91 (C-16), 55.99 (C-17), 12.08 (C-18), 19.39 (C-19), 40.48 (C-20), 21.07 (C-21), 138.31 (C-22), 129.32 (C-23), 51.32 (C-24), 31.96 (C-25), 21.32 (C-26), 19.02 (C27), 25.40 (C-28), 12.13 (C-29).

RESULTS AND DISCUSSION

Silica gel chromatography of dichloromethane extract of the leaves of *T. foetidissima* afforded cycloeucalenol (**1**), squalene (**2**), long-chain hydrocarbons (**3**) and a mixture of 24-methylene-

pollinastanol (**4**), β-sitosterol (**5**) and stigmasterol (**6**) in about 4:3:1 ratio. The structures of compounds **1** and **4** were elucidated by extensive 1D and 2D NMR spectroscopy. The NMR spectra of compound **1** are in accordance with data reported in the literature for for cycloeucalenol [3]; compound **2** for squalene [4]; compound **3** for long-chain hydrocarbons [5]; compound **4** for 22-methylenepollinastanol [6]; compound **5** for β-sitosterol [7]; and compound **6** for stigmasterol [7]. The 4:3:1 ratio of 4:5:6 was deduced from the integrations and intensities of ^{1}H NMR resonances of olefinic protons at δ 4.70 and 4.65 for compound **4** [6]; δ 5.35 for compound **5** [7]; and δ 5.35, 5.12 and 5.02 for compound **6** [7].

There are no reported biological activities of *Terminalia foetidissima*, however, squalene (**2**), stigmasterol (**5**) and β-sitosterol (**6**) isolated from the leaves of the tree were reported to exhibit diverse biological activities.

Squalene (**2**) was reported to significantly suppress colonic aberrant crypt foci (ACF) formation and crypt multiplicity, which indicated that it possessed chemopreventive activity against colon carcinogenesis [8]. It showed cardioprotective effect by inhibiting lipid accumulation through its hypolipidemic and antioxidant properties [9]. Furthermore, it exhibited antiproliferative effects on breast cancer cells [10] and showed preventive and therapeutic effects on tumor promotion and regression [11]. A review on the bioactivities of squalene has been reported in the literature [12].

Stigmasterol (**5**) showed therapeutic efficacy against *Ehrlich ascites* carcinoma bearing mice [13], which lowered plasma cholesterol levels, inhibited cholesterol absorption and suppressed hepatic cholesterol synthesis in rats [14] and also showed cytostatic activity against Hep-2 and McCoy cells [15]; markedly inhibited tumour promotion [16] and exhibited antimutagenic [17], topical anti-inflammatory [18], antiosteoarthritic [19] and antioxidant [20] activities.

β-Sitosterol (**6**) inhibited the growth of human breast MCF-7 and MDA-MB-231 adenocarcinoma cells [21] showed to be effective for the treatment of benign prostatic hyperplasia [22]; attenuated β-catenin and PCNA expression and quenched radical *in vitro* in colon carcinogenesis [23]. It is also inhibited the expression of NPC1L1 in the enterocytes to reduce intestinal cholesterol uptake [24] and induced apoptosis mediated by the activation of ERK and the downregulation of Akt in MCA-102 murine fibrosarcoma cells [25].

Conclusion

A dichloromethane extract of the leaves of *Terminalia foetidissima* afforded cycloeucalenol (**1**), squalene (**2**), long-chain hydrocarbons (**3**) and a mixture of 24-methylene-pollinastanol (**4**), β-sitosterol (**5**) and stigmasterol (**6**). Although no biological activities were reported on *T. foetidissima*, compounds **2**, **5** and **6** were reported to exhibit the diverse bioactivities. To the best of our knowledge, this is the first reported study on the chemical constituents of *Terminalia foetidissima* Griff.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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