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Chemical constituents of *Artocarpus ovatus* Blanco

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ABSTRACT

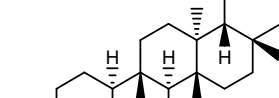
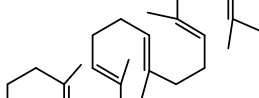
Chemical investigation of the dichloromethane extract of the leaves of *Artocarpus ovatus* Blanco led to the isolation of β -friedelinol (1), squalene (2), polyprenol (3), triacylglycerols (4), and chlorophyll a (5). The structures of 1-5 were identified by comparison of their ¹H and/or ¹³C NMR data with those reported in the literature.

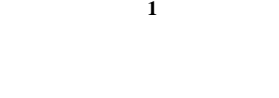

Keywords: *Artocarpus ovatus*, Moraceae, β -friedelinol, squalene, polyprenol, triacylglycerols, chlorophyll a

INTRODUCTION

Artocarpus ovatus Blanco, an endemic Philippine tree, produces strong and durable timber which is used for construction [1-2]. A latex obtained from the tree has potential for use as a chewing gum base [1], while the roasted seeds are eaten [2]. There is no reported study on the chemical constituents of *A. ovatus*. However, congeners of the tree have been studied for their chemical constituents and biological activities. There are about 50 species of the genus *Artocarpus* (Moraceae) which are sources of edible fruit and timber and are used in folk medicines. A review of the chemical constituents, biological and pharmacological activities of *Artocarpus* has been provided [3]. Compounds from *Artocarpus* species exhibit diverse biological activities including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, antiarthritic, tyrosinase inhibitory and cytotoxicity [3]. *Artocarpus* species are used for treatment against inflammation, malarial fever, diarrhoea, diabetes and tapeworm infection. They are rich in phenolic compounds such as flavonoids, stilbenoids, arylbenzofurans and jacalin [3].

This study is part of our research on the chemical constituents of the genus *Artocarpus* found in the Philippines. We earlier reported the isolation of friedelinol, squalene, β -sitosterol, stigmasterol and phytol from the leaves of *A. camansi*, while the stems yielded polyprenol, cycloartenol and cycloartenol acetate [4]. In another study, the leaves of *A. altilis* yielded β -sitosterol, triglycerides, squalene, polyprenol, lutein and fatty acids, while *A. odoratissimus* afforded β -sitosterol, triglycerides and fatty acids from the flesh of the fruit and seeds; and β -sitosterol, fatty acids and hydrocarbons from the fruit rind [5]. Furthermore, the unripe fruit of *A. heterophyllus* afforded cycloartenone, cycloartenol, and a diastereomeric mixture of 2,3-butanediols [6]. Recently, we reported the isolation of lupeol, α -amyirin, β -amyirin, lupeol fatty acid ester, α -amyirin fatty acid ester, β -myrin fatty acid ester, betulin, β ,28-dihydroxyolean-12-ene, oleanolic acid, β -sitosterol, and chlorophyll a from the twigs of *A. ovatus* [7].

4 R, R', R'' = long chain fatty acids

Fig. 1. Chemical constituents of *Artocarpus ovatus* leaves: 3 β -friedelinol (1), squalene (2), polyprenol (3), triacylglycerols (4), and chlorophyll a (5)

General Experimental Procedure

NMR spectra were recorded on a Varian VNMRS spectrometer in CDCl₃ at 600 MHz for ¹H NMR and 150 MHz for ¹³C 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 F₂₅₄ and the plates were visualized by spraying with vanillin/H₂SO₄ solution followed by warming.

The sample was collected from Bataan, Philippines in October 2013. It was identified as *Artocarpus ovatus* Blanco at the Jose Vera Santos Herbarium, Institute of Biology, University of the Philippines, Diliman, Quezon City.

General Isolation Procedure

A glass column 18 inches in height and 1.0 inch internal diameter was packed with silica gel. The crude extract from the leaves were fractionated by silica gel chromatography using increasing proportions of acetone in dichloromethane (10% increment) as eluents. Fifty 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. A glass column 12 inches in height and 0.5 inch internal diameter was used for the rechromatography. Two milliliter fractions were collected. Final purifications were conducted using Pasteur pipettes as columns. One milliliter fractions were collected.

Isolation

The air-dried leaves of *A. ovatus* (336.9 g) were ground in a blender, soaked in CH_2Cl_2 for 3 days and then filtered. The solvent was evaporated under vacuum to afford a crude extract (7.6 g) which was chromatographed using increasing proportions of acetone in CH_2Cl_2 at 10% increment. The 10% acetone in CH_2Cl_2 fraction was rechromatographed (3 \times) in 1% EtOAc in petroleum ether to afford **2** (25 mg) after washing with petroleum ether. The 20% acetone in CH_2Cl_2 fraction was rechromatographed (5 \times) in 10% EtOAc in petroleum ether to afford **3** (8 mg) and **4** (5 mg). The 30% acetone in CH_2Cl_2 fraction was rechromatographed (3 \times) in 10% EtOAc in petroleum ether to yield **1** (6 mg) after washing with petroleum ether. The 40% acetone in CH_2Cl_2 fraction was rechromatographed (4 \times) in 20% EtOAc in petroleum ether to afford **5** (12 mg) after washing with petroleum ether, followed by Et_2O .

3 β -Friedelinol (1): Colorless solid. ^1H NMR (500 MHz, CDCl_3): δ 0.84 (3H, s, H-25), 0.91 (3H, s, H-29), 0.94 (3H, s, H-26), 0.92 (3H, J = 7.8 Hz, H-23), 0.973, 0.968 (6H, s, H-27, H-30), 0.98 (3H, s, H-24), 1.15 (3H, s, H-28), 3.72 (1H, br s, H-3), ^{13}C NMR (150 MHz, CDCl_3): δ 15.77 (C-1), 36.06 (C-2), 72.75 (C-3), 49.15 (C-4), 39.27 (C-5), 41.70 (C-6), 17.53 (C-7), 53.18 (C-8), 37.08 (C-9), 61.32 (C-10), 35.32 (C-11), 30.62 (C-12), 37.82 (C-13), 38.35 (C-14), 32.31 (C-15), 35.54 (C-16), 30.01 (C-17), 42.79 (C-18), 35.16 (C-19), 28.17 (C-20), 32.79 (C-21), 39.66 (C-22), 11.61 (C-23), 16.38 (C-24), 18.23 (C-25), 18.64 (C-26), 20.11 (C-27), 32.08 (C-28), 31.78 (C-29), 35.02 (C-30).

Squalene (2): ^1H NMR (500 MHz, CDCl_3): δ 5.08-5.13 (6H, =CH), 1.58 (18H, allylic CH_3 , *cis*), 1.66 (6H, allylic CH_3 , *trans*), 1.94-2.07 (20H, allylic CH_2). ^{13}C NMR (150 MHz, CDCl_3): δ 25.69 (C-1, C-1'), 131.25 (C-2, 2'), 124.29 (C-3, C-3'), 26.65 (C-4, C-4'), 39.72 (C-5, C-5'), 134.89 (C-6, C-6'), 124.40 (C-7, C-7'), 26.76 (C-8, C-8'), 39.74 (C-9, C-9'), 135.10 (C-10, C-10'), 124.29 (C-11, C-11'), 28.27 (C-12, C-12'), 17.67 (C-13, C-13'), 16.03 (C-14, C-14'), 15.99 (C-15, C-15').

Polyprenol (3): ^1H NMR (600 MHz, CDCl_3): δ 4.07 (2H, d, J = 7.2 Hz, CH_2OH), 5.43 (1H, =CH), 5.09-5.11 (11H, =CH), 1.95-2.08 (40H, allylic CH_2), 1.73 (3H, s, allylic CH_3), 1.66 (21H, allylic CH_3), 1.59 (12H, allylic CH_3). ^{13}C NMR (150 MHz, CDCl_3): δ 59.01, 139.91, 136.08, 135.37, 135.28, 135.23, 135.20, 134.97, 134.90, 131.26, 125.01, 124.98, 124.93, 128.87, 124.51, 124.43, 124.39, 124.35, 124.25, 124.22, 124.14, 124.12, 39.76, 39.74, 39.72, 32.22, 32.20, 32.17, 31.98, 26.76, 26.67, 26.63, 26.39, 26.36, 26.30, 25.69, 23.45, 23.43, 23.36, 17.68, 16.00, 15.99.

Chlorophyll a (4)

^1H NMR (600 MHz, CDCl_3): δ 3.40 (3H, s, H-1a), 7.98 (1H, dd, J = 18, 12 Hz, H-2a), 6.18 (2H, dd, J = 11.4, 1.2 Hz, H-2b), 6.26 (1H, dd, J = 12, 18 Hz, H-2b), 3.23 (3H, s, H-3a), 3.68 (2H, m, H-4a), 1.69 (3H, t, J = 7.2, H-4b), 3.69 (3H, s, H-5a), 4.42 (1H, m, H-7), 2.15, 2.48 (2H, m, H-7a), 2.33, 2.63 (2H, m, H-7b), 4.22 (1H, m, H-8), 1.80 (3H, d, J = 7.2 Hz, H-8a), 6.27 (1H, s, H-10), 3.87 (3H, s, H-10b), 9.44 (1H, s, H- α or H- β), 9.58 (1H, s, H- α or H- β), 8.62 (s, H- δ), 4.46 (2H, m, P1), 5.11 (1H, t, J = 7.2 Hz, P2), 1.56 (3H, br s, P17), 0.82 (6H, d, J = 6.6 Hz, P18 and P19), 0.76 (3H, d, J = 6.6 Hz, P16), 0.74 (3H, d, J = 6.6 Hz, P20).

Triacylglycerols (5): ^1H NMR (600 MHz, CDCl_3): δ 4.27 (dd, 4.2, 11.4, glyceryl CH_2O), 4.12 (dd, 6.0, 11.4, glyceryl CH_2O), 5.25 (m, glyceryl CHO), 2.29 (t, J = 7.2 Hz, α - CH_2), 5.35 (m, olefinic H), 2.75 (t, J = 6.6 Hz, double allylic CH_2), 2.77 (t, J = 6.6 Hz, double allylic CH_2), 1.97-2.08 (allylic, CH_2), 1.58-1.60 (β - CH_2), 1.23-1.36 (CH_2), 0.96 (t, 7.2, CH_3), 0.86 (t, 7.2, CH_3), 0.87 (t, 7.2, CH_3); ^{13}C NMR (150 MHz, CDCl_3): δ 62.09 (glyceryl CH_2), 68.87 (glyceryl CH), 173.31, 173.26 (C=O α), 172.86 (C=O β), 34.02, 34.05, 34.19 (C-2), 19.20, 19.27, 22.57, 22.69, 24.86, 24.83, 25.52, 25.62, 27.17, 27.19, 27.22, 29.05, 29.08, 29.12, 29.17, 29.316, 29.324, 29.34, 29.36.

29.48, 29.52, 29.62, 29.66, 29.70, 29.76, 31.52, 31.90, 31.92 (CH₂), 130.23, 130.02, 130.01, 129.98, 129.71, 129.68, 128.07, 128.06, 127.89, 129.88 (CH=CH), 14.07, 14.12 (terminal CH₃).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extract of the air-dried leaves of *Artocarpus ovatus* led to the isolation of 3 β -friedelinol (1) [8, 9], squalene (2) [10, 11], polyprenol (3) [11, 12], triglycerides (4) [7], and chlorophyll a (5) [7, 11]. The structures of 1-5 were identified by comparison of their ¹H and/or ¹³C NMR data with literature data [8-12].

Although bioassays were not conducted on the isolated compounds, there were previous studies that reported on their biological activities.

3 β -Friedelinol (1) showed only antibacterial activity (MIC = 12.5-100 mg/ml) and no antifungal activity [13].

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 [14]. It showed cardioprotective effect which is related to inhibition of lipid accumulation by its hypolipidemic properties and/or its antioxidant properties [15]. A recent study reported that tocotrienols, carotenoids, squalene and coenzyme Q10 have anti-proliferative effects on breast cancer cells [16]. The preventive and therapeutic potential of squalene containing compounds on tumor promotion and regression have been reported [17]. A recent review on the bioactivities of squalene has been provided [18].

Polyprenols (3) act as co-enzymes of membrane active transport systems for polysaccharides, peptidoglycans and carbohydrate containing biopolymers [19]. Polyprenol from *Ginkgo biloba* L. exhibited hepatoprotective effects against CCl₄-induced hepatotoxicity in rats [20]. Polyprenols from *Ginkgo biloba* L. exhibited antitumor activity [21]. The antidyslipidemic activity of polyprenol from *Coccinia grandis* in high-fat diet-fed hamster model was also reported [22].

Triacylglycerols (4) exhibited antimicrobial activity against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, and *T. mentagrophytes* [23]. Another study reported that triglycerides showed a direct relationship between toxicity and increasing unsaturation, which in turn correlated with increasing susceptibility to oxidation [24].

Chlorophyll a (6) and its various derivatives are used in traditional medicine and for therapeutic purposes [25]. Natural chlorophyll and its derivatives have been studied for wound healing [26], anti-inflammatory properties [27], control of calcium oxalate crystals [28], utilization as effective agents in photodynamic cancer therapy [29-31], and chemopreventive effects in humans [32-33]. A review on digestion, absorption and cancer preventive activity of dietary chlorophyll has been provided [34].

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