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Chemical constituents of *Muntingia calabura* L.

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ABSTRACT

*Chemical investigation of the dichloromethane extract of the fruit of Muntingia calaburaafforded squalene (**1**), triglyceride (**2**), a mixture of linoleic acid (**3a**), palmitic acid (**3b**) and α-linolenic acid (**3c**), and a mixture of β-sitosterol (**4a**) and stigmasterol (**4b**). The structures of **1**-**4b** were identified by comparison of their NMR data with those reported in the literature.*

Keywords: *Muntingia calabura*, Muntingiaceae, squalene, triglyceride, β-sitosterol, stigmasterol, linoleic acid, palmitic acid, α-linolenic acid

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INTRODUCTION

Muntingia calabura L. locally known as aratiles is a popular edible fruit in the Philippines. An earlier study reported that the methanol extract of the fruit possessed potent anti-inflammatory activity [1]. Another study reported that the ethanolic extract of the fruit exhibited an LC_{50} value of 1.63 μg mL^{-1} against first instar *P. xylostella* larvae, while the hexane extract gave an LC_{50} value of 5.5 μg mL^{-1} [2]. Furthermore, the acetone, ethanol, methanol and aqueous extracts of the fruitwere found to possess significant antioxidant activities [3].The *M. calabura* leaves exhibited potential antiproliferative and antioxidant activities that could be attributed to their high content of phenolic compounds [4]. The leavesalso exerted potent antityrosinase and antioxidant activities [5]. The aqueous leaf extract at concentrations of10%, 50% and 100% showed significant antinociceptive, anti-inflammatory and antipyretic activities [6]. The chloroform, methanol and aqueous leaf extracts exhibited antibacterial activity against normal *S. aureus* infection [7] and other bacteria [8]. Other studies reported the isolation of cytotoxic chalconesand flavonoids from the leaves [9] and cytotoxic flavonoids from the leaves and stems of *C. calabura*[10]. Furthermore, the aqueous leaf extract of *M. calabura* elicited both a transient and delayed hypotensive effect through the production of NO. The activation of NO/sGC/cGMP signaling pathway may mediate the *M. calabura*-induced hypotension [11]. Steam distillation-extraction of the fruit, followed by GC/MS analyses resulted in the identification of 56 compounds composed of esters (31.4%), alcohols (15.9%), phenolic compounds (11.3%), sesquiterpenoids (10.6%) and furan derivatives (8.3%) [12].

The leaves of *M. calabura*afforded 5-hydroxy-3,7,8-trimethoxyflavone, 3,7-dimethoxy-5-hydroyflavone, 2′,4′-dihydroxy-3′-methoxychalcone, and calaburone [13]. The EtOAc extract from the leaves of *M. calabura* yielded

(2R,3R)-7-methoxy-3,5,8-trihydroxyflavanone, (2S)-5-hydroxy-7-methoxyflavanone, 2',4'-dihydroxychalcone, 4,2', 4'-trihydroxychalcone, 7-hydroxy-isoflavone and 7,3',4'-trimethoxyisoflavone which were found to induce quinone reductase activity [14].The leaves of *M. calabura* afforded 3 new compounds 2,3-dihydroxy-4,3',4',5'-tetramethoxydihydrochalcone, 4,2',4'-trihydroxy-3'-methoxydihydrochalcone, and (2R,3R)-(-)-3,5-dihydroxy-6,7-dimethoxyflavanone and 19 known compounds. 2,3-Dihydroxy-4,3',4',5'-tetramethoxydihydrochalcone, 5,7-dihydroxy-3-methoxyflavone, 5,7-dihydroxy-6-methoxy flavone, 5,4'-dihydroxy-3,7-dimethoxyflavone, (2S)-7,8,3', 4',5'-pentamethoxyflavan, (2S)-5'-hydroxy-7,8,3',4'-tetramethoxyflavan, and methyl gallate exhibited significant anti-platelet aggregation activity [15]. The *M. calabura* extract revealed the presence of phytol (26.26%), n-hexadecanoic acid (11.97%), cyclopropaneoctanoic acid (10.26%), γ-sitosterol (11.15%), stigmasterol (7.20%), and campesterol (4.47%) as main constituents [16]. Another study reported that 8-hydroxy-7,3',4',5'-tetramethoxyflavone, 8,4'-dihydroxy-7,3',5'-trimethoxyflavone, and 3-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl) propan-1-one exhibited effective cytotoxicities (ED_{50} values = 3.56, 3.71, and 3.27 μg/mL, resp.) against the P-388 cell line [17]. Stigmasterol isolated from the roots of *M. calabura* exhibited a potent antifungal activity with a minimum inhibitory concentration of 1 mg/mL against *A. solani* [18].

In this study, the dichloromethane extract of the freeze-dried fruit of *M. calabura* yielded squalene (**1**), triglycerides (**2**), fatty acids (**3**), and a mixture of β-sitosterol (**4a**) and stigmasterol (**4b**) (Fig. 1). To the best of our knowledge this is the first report on the isolation of squalene and triglycerides from *M. calabura*.

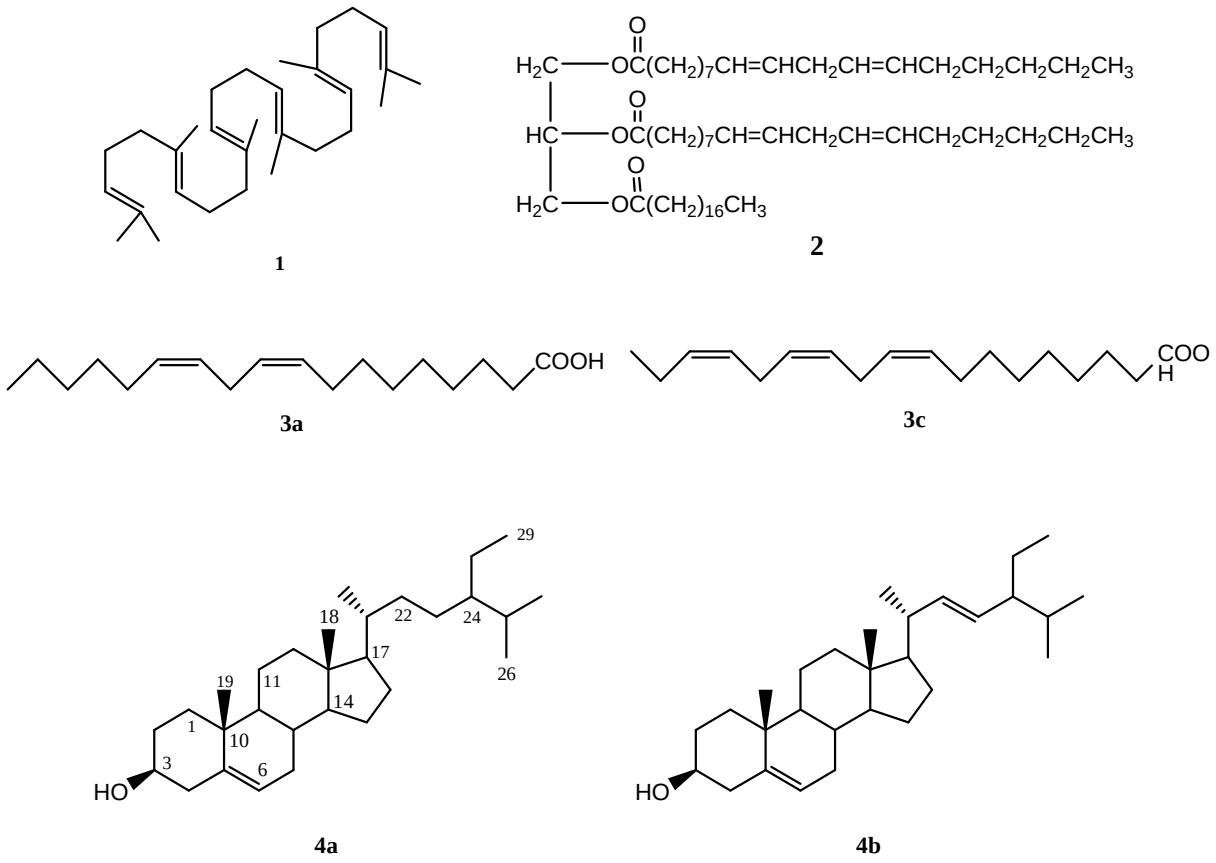

Fig. 1. Chemical structures of squalene (1), triglyceride (2), linoleic acid (3a), α-linolenic acid (3c), β-sitosterol (4a) and stigmasterol (4b) from the fruits of *M. calabura*

MATERIALS AND METHODS

Sample Collection

The ripened fruits from aratiles were harvested from San Pedro, Laguna in June 2014. It was identified as *Muntingia calabura* at the Botany Division, Philippine National Museum.

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.

General Isolation Procedure
A glass column 20 inches in height and 2.0 inches 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 CH_2Cl_2 (10% increment) as eluents. One hundred milliliter fractions were collected. All fractions were monitored by thin layer chromatography. 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. Five milliliter fractions were collected. Final purifications were conducted using Pasteur pipettes as columns. One milliliter fractions were collected.

Extraction and Isolation
Fresh *M. calabura* fruits (700 g) were washed and frozen before lyophilization. The resultant dried berries (281.46 g) were incubated with one liter of CH_2Cl_2 and left in a closed vessel at room temperature for three days. After filtering, CH_2Cl_2 was removed using a rotary evaporator which afforded a 10.0022 g of crude extract.

The crude extract was chromatographed using increasing proportions of acetone in CH_2Cl_2at 10% increment as eluents. The CH_2Cl_2 fraction was rechromatographed (3×) using petroleum ether to afford **1** (1.9 mg). The 20% acetone in CH_2Cl_2 fraction was rechromatographed using 10% EtOAc in petroleum ether. Fractions collected from this rechromatography were combined and washed with petroleum ether, then rechromatographed (2×) using CH_3CN:Et_2O:CH_2Cl_2 (0.5:0.5:9 v/v) to afford a mixture of **4a** and **4b** (7.6 mg).The 50% acetone in CH_2Cl_2 fraction was rechromatographed (2×) in 7.5% EtOAc in petroleum ether to afford **2** (539 mg). The 60% acetone in CH_2Cl_2 fraction was rechromatographed (3×) in 10% EtOAc in petroleum ether to yield **3**(1.4 mg).

Squalene (**1**): ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.69 (C-1), 131.26 (C-2), 124.27 (C-3), 26.66 (C-4), 39.75 (C-5), 134.90 (C-6), 124.30 (C-7), 26.76 (C-8), 39.72 (C-9), 135.10 (C-10), 124.40 (C-11), 28.27 (C-12), 17.67 (C-2′), 16.04 (C-6′), 15.99 (C-10′).

Triglyceride (**2**): ^{13}C NMR (150 MHz, $CDCl_3$): δ 62.07 (2×, glyceryl CH_2); 68.85 (glyceryl CH), 173.22 (2×,C=O α); 172.81 (C=O β); 34.16, 34.02, 33.99 (C-2); 22.55, 22.656, 22.664, 24.81, 24.84, 25.60, 27.16, 27.17, 27.19, 27.22, 29.02, 29.06, 29.09, 29.11, 29.15, 29.17, 29.25, 29.30, 29.32, 29.34, 29.45, 29.50, 29.58, 29.60, 29.63, 29.68, 29.74, 31.50, 31.90 (CH_2); 130.19, 129.97, 129.95, 128.05, 128.03, 127.86, 127.85 (CH=CH); 14.05, 14.09 (terminal CH_3).

β-Sitosterol (**4a**): ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.24 (C-1), 31.64 (C-2), 71.80 (C-3), 42.28 (C-4), 140.74 (C-5), 121.71 (C-6), 31.88 (C-7), 31.90 (C-8), 50.14 (C-9), 36.49 (C-10), 21.07 (C-11), 39.75 (C-12), 42.20 (C-13), 56.75 (C-14), 24.35 (C-15), 28.24 (C-16), 56.03 (C-17), 11.97 (C-18), 19.38 (C-19), 36.13 (C-20), 18.76 (C-21), 33.93 (C-22), 26.04 (C-23), 45.81 (C-24), 29.13 (C-25), 19.02 (C-26), 19.81 (C-27), 23.05 (C-28), 11.85 (C-29).

Stigmasterol (**4b**): ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.24 (C-1), 31.64 (C-2), 71.80 (C-3), 42.28 (C-4), 140.74 (C-5), 121.71 (C-6), 31.88 (C-7), 31.90 (C-8), 50.14 (C-9), 36.49 (C-10), 21.07 (C-11), 39.66 (C-12),42.20 (C-13), 56.75 (C-14), 24.35 (C-15), 28.91 (C-16), 55.93 (C-17), 12.03 (C-18), 19.38 (C-19), 40.49 (C-20),21.07 (C-21), 138.31 (C-22), 129.25 (C-23), 51.22 (C-24), 31.90 (C-25), 21.20 (C-26), 18.97 (C-27), 25.40 (C-28),12.24 (C-29).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extract of the freeze-dried fruits of *M. calabura* yielded squalene (**1**) [19], triglycerides (**2**) [20], fatty acids (**3**) [21], and a mixture of β-sitosterol (**4a**) [22] and stigmasterol (**4b**) [22]. The structures of **1**-**4b** were identified by comparison of their NMR data with those reported in the literature.

Based on the integrations of the triacylglycerol (**2**) protons, the fatty acids attached to the glycerol are linoleic acid (**3a**) [23] and a saturated fatty acid, possibly palmitic acid (**3b**) [24] in a 2:1 ratio.The presence of linoleic acid

(**3a**)was deduced from the methyl triplet at δ 0.86 (t, *J* = 6.6 Hz), the double allylic methylene at δ 2.74 (t, *J* = 6.6 Hz), the olefinic protons at δ 5.32 (m), α-methylene protons at δ 2.30 (t, *J* = 7.2 Hz), and the long-chain methylene protons at δ1.24-1.34 [28]; while the palmitic acid was indicated by the resonances at 2.30 (t, *J* = 7.2 Hz, α-CH_2), 1.60 (m, β-CH_2), 1.24-1.34 (CH_2), 0.85 (t, *J* = 6.6 Hz, CH_3).

The mixture of fatty acids is composed of **3a**, **3b**and α-linolenic acid (**3c**).The presence of **3c** in the mixture was deduced from the methyl triplet at δ 0.96 (t, *J* = 7.8 Hz), the double allylic methylenes at δ 2.78 and the olefinic protons at δ 5.34 (m) [27]. Based on the integrations of the methyls at δ 0.86 (t, *J* = 6.6 Hz)for **3a** and **3b,** and δ 0.96 (t, *J* = 7.8 Hz) for **3c,** and the integrations of the double allylic methylenes at δ 2.74 for **3a** and δ 2.78 for **3c**,the ratio of **3a**,**3b**and **3c** in the fatty acid mixture is 2:1:1, respectively.

The 3:1 ratio of the mixture of **4a**and **4b** was deduced from the integrations of the ^{1}H NMR resonances for the olefinic protons of **4a** at δ 5.33 (dd, *J* = 1.8, 5.4 Hz, H-6) and **4b** at δ 5.33 (dd, *J* = 1.8, 5.4 Hz, H-6), 5.13 (dd, *J* = 9.0, 15.0 Hz, H-22) and 5.00 (dd, *J* = 6.6, 15.0 Hz, H-23).

Although no biological activity tests were conducted on the isolated compounds (**1**-**4b**), literature search revealed that these have diverse biological activities as follows.

Squalene (**1**) 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].

Triacylglycerols (**2**) exhibited antimicrobial activity against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, and *T. mentagrophytes* [30]. Another study reported that triglycerides showed a direct relationship between toxicity and increasing unsaturation, which in turn correlated with increasing susceptibility to oxidation [31].

Linoleic acid (**3a**) belongs to the omega-6 fatty acids. It was reported to be a strong anticarcinogen in a number of animal models. It reduces risk of colon and breast cancer [32] and lowers cardiovascular disease risk and inflammations [33]. Palmitic acid (**3b**), a saturated fatty acid which was reported as a major constituent of *C. ovatum* oil [34] showed selective cytotoxicity to human leukemic cells, induced apoptosis in the human leukemic cell line MOLT-4 and exhibited *in vivo* antitumor activity in mice [35]. Omega-3 polyunsaturated fatty acids (n-3 PUFA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α-linolenic acid (ALA) (**3c**), and their fatty acid ethyl esters, exhibited strong antibacterial activity against various oral pathogens, including *Streptococcus mutans*, *Candida albicans*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*. They also showed anti-inflammatory effects [36]. Peroxisome proliferator-activated receptor-γ (PPAR-γ) and cyclooxygenase-2 (COX-2) inhibition serve as two signaling pathways for the inhibitory effects of α-linolenic acid (ALA) on the human renal cell carcinoma (RCC) cell proliferation [37]. Another study reported that apoptosis of hepatoma cells was induced by the α-linolenic acid enriched diet which correlated with a decrease in arachidonate content in hepatoma cells and decreased cyclooxygenase-2 expression [38]. γ-Linolenic acid (GLA) and α-linolenic acid (ALA) exhibited greater than 90% cytotoxicity between 500 μM and 1 mM against all but two malignant micro-organ cultures tested in 5-10% serum. GLA and ALA killed tumor at concentrations of 2 mM and above in tests using 30-40% serum [39].

β-Sitosterol (**4a**) was reported to exhibit growth inhibitory effects on human breast MCF-7 and MDA-MB-231 adenocarcinoma cells [40]. It was shown to be effective for the treatment of benign prostatic hyperplasia [41]. It attenuated β-catenin and PCNA expression, as well as quenched radical *in-vitro*, making it a potential anticancer drug for colon carcinogenesis [42]. It was reported to induce apoptosis mediated by the activation of ERK and the downregulation of Akt in MCA-102 murine fibrosarcoma cells [43]. It can inhibit the expression of NPC1L1 in the enterocytes to reduce intestinal cholesterol uptake [44].

Stigmasterol (**4b**) shows therapeutic efficacy against Ehrlich ascites carcinoma bearing mice while conferring protection against cancer induced altered physiological conditions [45]. It lowers plasma cholesterol levels, inhibits

intestinal cholesterol and plant sterol absorption, and suppresses hepatic cholesterol and classic bile acid synthesis in Winstar as well as WKY rats [46]. Other studies reported that stigmasterol showed cytostatic activity against Hep-2and McCoy cells [47], markedly inhibited tumour promotion in two stage carcinogenesis experiments [48], exhibited antimutagenic [49], topical anti-inflammatory [50], anti-osteoarthritic [51] and antioxidant [52] activities.

CONCLUSION

Previous literature on *M. calabura* reported mainly on the isolation of chalcones and flavonoids which exhibited cytotoxic and anticancer properties. There were few studies on the isolation of non-polar components of the plant. This study reports on the non-polar constituents from the fruit of *M. calabura* which were reported to exhibit diverse biological activities.

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