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Triterpenes from *Shorea negrosensis*

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ABSTRACT

*Chemical investigations of the dichloromethane extracts of Shorea negrosensis (Foxw.) led to the isolation of friedelin (**1**), 3β-friedelinol (**2**), oleanolic acid (**3**), ursolic acid (**4**), squalene (**5**) and chlorophyll a (**6**) from the leaves, while the twigs yielded **1**, **3** and **4**. The structures of **1-6** were identified by comparison of their ^{1}H and/or ^{13}C NMR data with those reported in the literature.*

***Keywords*:** *Shorea negrosensis*, Dipterocarpaceae, friedelin, 3β-friedelinol, oleanolic acid, ursolic acid, squalene, chlorophyll a

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INTRODUCTION

Shorea negrosensis (Foxw.) of the family Dipterocarpaceae, commonly known as red lauan or Philippine red mahogany, is a tree endemic to the Philippines, growing gregariously in evergreen, semi-evergreen and dipterocarp forests at low altitudes, and reaching up to 50 m in height [1, 2]. Red lauan produces valuable and strong bark, pulp and timber which are generally used for exterior and interior joinery, shop fittings, hand tools, boat building and flooring [3]. The plant's bark contains tannins that are useful as adhesives and as tanning agent for leather, while its wood extractives are reported to be tumor inhibiting [1, 4]. Illegal logging and unabated cutting of the tree for timber and furniture resulted to the tree being classified by IUCN as critically endangered [5, 6]. An earlier study reported that the hexane extract of *S. negrosensis* afforded 1-tetracosanol, 1-hexacosanol, Ψ-taraxasterone, β-sitosterol, β-sitosteryl oleate, 24-methylenecycloartanol, 24-methylenecycloartanone, and 24-methylenecycloartanyl oleate [7].

This study was conducted as part of our research on the chemical constituents of the genus *Shorea* which are found in the Philippines. We earlier reported the isolation of shoreic acid from *Shorea guiso* which exhibited low antimicrobial activity against *E. coli, P. aeruginosa, S. aureus, B. subtilis, C. albicans and T. mentagrophytes*. *S. guiso* is another critically endangered tree which is used for furniture and timber [8]. Recently, we reported the isolation of lup-20(29)-en-3-one, olean-12-en-3-one, urs-12-en-3-one, lutein, chlorophyll a and β-sitosterol from *Shorea contorta*, another endemic Philippine tree. This tree is commonly known as white lauan which is also used

for furniture and timber. It is classified as critically endangered by IUCN due to illegal logging and unabated cutting of the tree [9]. A chemotaxonomic study on the family Diptorecarpaceae reported the isolation of sesqui and triterpenic constituents from the genus *Shorea* [10].

We report herein the isolation and identification of friedelin (**1**), 3β-friedelinol (**2**), oleanolic acid (**3**), ursolic acid (**4**), squalene (**5**) and chlorophyll a (**6**) from the leaves; and **1**, **3** and **4** from the twigs of *S. negrosensis* (Fig. 1). To the best of our knowledge this is the first report on the isolation of these compounds from *S. negrosensis.*

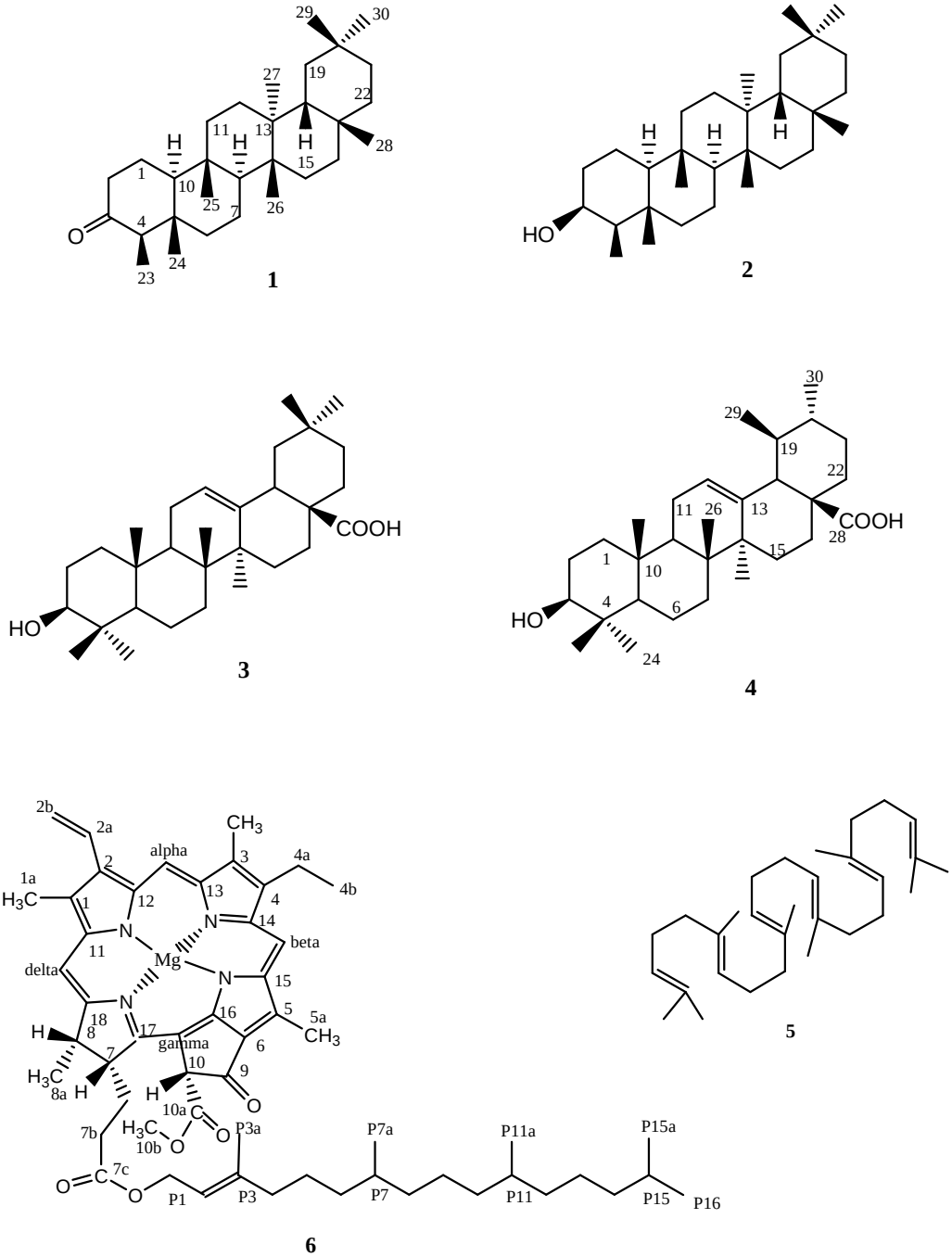

Fig. 1. Chemical constituents of *S. negrosensis*: friedelin (1), 3β-friedelinol (2), oleanolic acid (3), ursolic acid (4), squalene (5) and chlorophyll a (6)

MATERIALS AND METHODS

General Experimental Procedure

NMR spectra were recorded on a Varian VNMRS 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.

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 dichloromethane (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.

Sample Collection

The sample was collected from Pola, Oriental Mindoro, Philippines in January 2014. It was identified as *Shorea negrosensis* Foxw. at the Bureau of Plant Industry, Malate, Manila, Philippines.

Isolation

The air-dried leaves of *Shorea negrosensis* (539 g) was 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 (15 g) which was chromatographed using increasing proportions of acetone in CH_2Cl_2 at 10% increment. The CH_2Cl_2 and 10% acetone in CH_2Cl_2 fractions were combined and rechromatographed (3 ×) in 1% EtOAc in petroleum ether to afford **5** (7 mg). The 30% acetone in CH_2Cl_2 fraction was rechromatographed (4 ×) in 10% EtOAc in petroleum ether to afford a mixture of **1** and **2** (12 mg) after washing with petroleum ether. The 40% acetone in CH_2Cl_2 fraction was rechromatographed (5 ×) in 20% EtOAc in petroleum ether to afford **6** (10 mg) after washing with petroleum ether, followed by Et_2O. The 70% to 90% acetone in CH_2Cl_2 fractions were combined and rechromatographed (4 ×) using CH_3CN:Et_2O:CH_2Cl_2 (1:1:8, v/v) to afford a mixture of **3** and **4** (7 mg) after trituration with petroleum ether.

The air-dried twigs of *Shorea negrosensis* (440 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 (3 g) which was chromatographed using increasing proportions of acetone in CH_2Cl_2 at 10% increment. The 40% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) in 7.5% EtOAc in petroleum ether to afford **1** (4 mg) after washing with petroleum ether. The 70% to 90% acetone in CH_2Cl_2 fractions were combined and rechromatographed (5 ×) using CH_3CN:Et_2O:CH_2Cl_2 (1:1:8, v/v) to afford a mixture of **3** and **4** (5 mg) after trituration with petroleum ether.

Friedelin (**1**): Colorless solid. ^1H NMR (600 MHz, $CDCl_3$): δ 2.28, 2.37 (H_2-2), 2.23 (H-4), 0.86 (H_3-23, d, J = 7:2 Hz), 0.71 (H_3-24, s), 0.84 (H_3-25, s), 0.99 (H_3-26, s), 1.03 (H_3-27, s), 0.98 (H_3-28, s), 0.93 (H_3-29, s), 1.16 (H_3-30); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.28 (C-1), 41.53 (C-2), 213.27 (C-3), 58.22 (C-4), 42.15 (C-5), 41.28 (C-6), 18.23 (C-7), 53.09 (C-8), 37.43 (C-9), 59.46 (C-10), 35.61 (C-11), 30.50 (C-12), 39.69 (C-13), 38.29 (C-14), 32.41 (C-15), 36.06 (C-16), 30.00 (C-17), 42.79 (C-18), 35.33 (C-19), 28.17 (C-20), 32.79 (C-21), 39.25 (C-22), 6.82 (C-23), 14.65 (C-24), 17.94 (C-25), 20.25 (C-26), 18.66 (C-27), 32.08 (C-28), 35.02 (C-29), 31.77 (C-30).

3β-Friedelinol (**2**): Colorless solid. ^{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), 35.33 (C-11), 30.63 (C-12), 37.80 (C-13), 38.29 (C-14), 32.31 (C-15), 35.54 (C-16), 30.00 (C-17), 42.79 (C-18), 35.17 (C-19), 28.17 (C-20), 32.79 (C-21), 39.69 (C-22), 11.62 (C-23), 16.38 (C-24), 18.23 (C-25), 18.64 (C-26), 20.11 (C-27), 32.08 (C-28), 31.77 (C-29), 35.02 (C-30).

Oleanolic acid (**3**): Colorless solid. ^1H NMR (600 MHz, $CDCl_3$): δ ^1H NMR ($CDCl_3$, 500 MHz) δ 3.20 (dd, J = 4.2, 11.4 Hz, H-3α), 5.26 (t, J = 3.6 Hz, H-12), 2.81 (dd, J = 4.2, 13.8 Hz, H-18), 0.96 (s, H_3-23), 0.73 (s, H_3-24), 0.89 (s, H_3-25), 0.75 (s, H_3-26), 1.11 (s, H_3-27), 0.91 (s, H_3-29), 0.88 (s, H_3-30); ^{13}C NMR (150 MHz, $CDCl_3$): δ 38.38 (C-1), 27.17 (C-2), 77.00 (C-3), 38.74 (C-4), 55.19 (C-5), 18.28 (C-6), 32.61 (C-7), 39.25 (C-8), 47.60 (C-9), 37.06 (C-

10), 23.38 (C-11), 122.63 (C-12), 143.56 (C-13), 41.61 (C-14), 27.67 (C-15), 22.93 (C-16), 46.49 (C-17), 41.01 (C-18), 45.86 (C-19), 30.66 (C-20), 33.78 (C-21), 32.42 (C-22), 28.09 (C-23), 15.53 (C-24), 15.31 (C-25), 17.09 (C-26), 25.91 (C-27), 182.55 (C-28), 33.05 (C-29), 23.56 (C-30).

Ursolic Acid (**4**): colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.20 (1H, dd, *J* = 4.2, 11.4 Hz, H-3α), 5.23 (1H, t, *J* = 3.6 Hz, H-12), 2.18 (1H, d, *J* =11.4 Hz, H-18), 1.23 (3H, s, Me-23), 0.97 (3H, s, Me-24), 0.77 (3H, s, Me-25), 1.06 (3H, s, Me-26), 1.12 (3H, s, Me-27), 0.93 (3H, d, *J* = 6.6 Hz, Me-29), 0.91 (3H, d, *J* = 5.9 Hz, Me-30). ^{13}C NMR (150 MHz, $CDCl_3$): δ 36.99 (C-1), 28.12 (C-2), 79.04 (C-3), 38.57 (C-4), 55.19 (C-5), 18.28 (C-6), 32.90 (C-7), 39.46 (C-8), 47.51 (C-9), 38.74 (C-10), 23.27 (C-11), 125.84 (C-12), 137.92 (C-13), 41.93 (C-14), 27.20 (C-15), 24.11 (C-16), 47.90 (C-17), 52.60 (C-18), 39.02 (C-19), 38.81 (C-20), 30.58 (C-21), 36.68 (C-22), 28.00 (C-23), 15.46 (C-24), 15.58 (C-25), 17.09 (C-26), 23.56 (C-27), 182.27 (C-28), 16.97 (C-29), 21.17 (C-30).

Squalene (**5**): colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.07-5.12 (6H, =CH), 1.58 (18H, allylic CH_3, *cis*), 1.66 (6H, allylic CH_3, *trans*), 1.94-2.07 (20H, allylic CH_2).

Chlorophyll a (**6**): dark green crystals. ^{13}C NMR (150 MHz, $CDCl_3$): δ 131.85 (C-1), 12.12 (C-1a), 136.51 (C-2), 129.05 (C-2a), 122.79 (C-2b), 136.18 (C-3), 11.26 (C-3a), 145.23 (C-4), 19.47 (C-4a), 17.42 (C-4b), 137.93 (C-5), 12.12 (C-5a), 129.05 (C-6), 51.12 (C-7), 29.80 (C-7a), 31.16 (C-7b), 172.93 (C-7c), 50.10 (C-8), 23.06 (C-8a), 189.64 (C-9), 64.69 (C-10), 169.60 (C-10a), 52.84 (C-10b), 142.84 (C-11), 136.28 (C-12), 155.66 (C-13), 150.99 (C-14), 129.10 (C-15), 149.65 (C-16), 161.24 (C-17), 172.93 (C-18), 97.55 (C-α), 104.44 (C-β), 105.22 (C-γ), 93.12 (C-δ), 61.45 (P-1), 117.69 (P-2), 142.03 (P-3), 16.27 (P-3a), 39.77 (P-4), 24.97 (P-5), 36.62 (P-6), 32.60 (P-7), 19.64 (P-7a), 37.30 (P-8), 24.40 (P-9), 37.37 (P-10), 32.74 (P-11), 19.70 (P-11a), 37.24 (P-12), 24.76 (P-13), 39.33 (P-14), 27.95 (P-15), 22.60 (P-15a), 22.70 (P-16).

RESULTS AND DISCUSSION

Silica gel chromatography of the dicloromethane extracts of *Shorea negrosensis* (Foxw.) led to the isolation of a mixture of friedelin (**1**) [11] and 3β-friedelinol (**2**) [12, 13] in a 2.5:1 ratio, a mixture of oleanolic acid (**3**) [14, 15] and ursolic acid (**4**) [13, 14] in a 3:1 ratio, squalene (**5**) [16] and chlorophyll a (**6**) [17] from the leaves, while the twigs yielded **1** and a mixture of **3** and **4** in a 3:2 ratio. The 2.5:1 ratio of **1** and **2** was deduced from the intensities of the corresponding ^{13}C NMR resonances. The ratios of **3** and **4** were deduced from the integrations of the ^{1}H NMR resonances for the olefinic protons of **3** at δ 5.26 (t, *J* = 3.6 Hz) and **4** at δ 5.23 (t, *J* = 3.6 Hz) and the H-18 proton of oleanolic acid at δ 2.81. The structures of **1**-**6** were identified by comparison of their ^{1}H and/or ^{13}C NMR data with those reported in the literature [11-17].

Although no biological activity tests were conducted on the isolated compounds (**1**-**6**), literature search revealed that these have diverse bioactivities as follows.

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]. The high efficiency antiproliferative effect of **1** on both HeLa and HSC-1 cells has been reported [21]. Another study reported that it exhibited the strongest inhibitory effect against HeLa cancer cell with IC_{50} value of 3.54±0.30 μg/ml [22]. It also displayed strong cytotoxic activities on the proliferation of four human cancer cells namely, A375, L292, HeLa and THP-1 [23]. 3β-Friedelinol (**2**) showed only antibacterial activity (MIC = 12.5-100 mg/ml) and no antifungal activity [24].

Ursolic acid (**3**) was found to induce apoptosis in tumor cells by activation of caspases and modulation of other pathways involved in cell proliferation and migration. It decreases proliferation of cells and induces apoptosis, thereby inhibiting growth of tumor cells both *in vitro* and *in vivo* [25]. An earlier study reported that it exhibited anti-tumor activity against human colon carcinoma cell line HCT15 [26]. Moreover, it inhibited the growth of colon cancer-initiating cells by targeting STAT3 [27]. Furthermore, it has potential therapeutic use in prostate cancer through its antiproliferative and apoptotic effects [28]. A recent study reported that it inhibited cell growth and proliferation of Jurkat leukemic T-cells, as well as suppressed PMA/PHA induced IL-2 and TNF-α production in a concentration and time dependent manner [29]. Another study reported that ursolic acid-activated autophagy

induced cytotoxicity and reduced tumor growth of cervical cancer cells TC-1 in a concentration-dependent manner [30].

Oleanolic acid (**4**) exhibited anti-inflammatory effects by inhibiting hyperpermeability, the expression of CAMs, and the adhesion and migration of leukocytes [31]. It showed anti-inflammatory activities through the inhibition of the HMGB1 signaling pathway [32]. It exhibited anti-inflammatory, hepatoprotective, gastroprotective, immunoregulatory and anti-ulcer activities [33], and gastroprotective effect on experimentally induced gastric lesions in rats and mice [34]. It was also reported to inhibit mouse skin tumor [35], protect against hepatotoxicants and treat hepatitis [36], and showed significant antitumor activity on human colon carcinoma cell line HCT 15 [37].
Squalene (**5**) was reported to significantly suppress colonic ACF formation and crypt multiplicity which strengthened the hypothesis that it possesses chemopreventive activity against colon carcinogenesis [38]. It showed cardioprotective effect which is related to inhibition of lipid accumulation by its hypolipidemic properties and/or its antioxidant properties [39]. A recent study reported that tocotrienols, carotenoids, squalene and coenzyme Q10 have anti-proliferative effects on breast cancer cells [40]. The preventive and therapeutic potential of squalene containing compounds on tumor promotion and regression have been reported [41]. A recent review on the bioactivities of squalene has been provided [42].

Chlorophyll a (**6**) and its various derivatives are used in traditional medicine and for therapeutic purposes [43]. Natural chlorophyll and its derivatives have been studied for wound healing [44], anti-inflammatory properties [45], control of calcium oxalate crystals [46], utilization as effective agents in photodynamic cancer therapy [47-49], and chemopreventive effects in humans [50, 51]. A review on digestion, absorption and cancer preventive activity of dietary chlorophyll has been provided [52].

CONCLUSION

The wood extractives of *S. negrosensis* were reported to exhibit tumor inhibiting properties. It is interesting to note that except for 3β-friedelinol (**2**), all the compounds (**1**, **3**-**6**) isolated were reported to exhibit anticancer and antitumor properties. Thus, the tumor inhibiting properties of *S. negrosensis* may be attributed to the synergistic effects of these compounds among others in the extracts.

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