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Chemical Constituents of *Macaranga grandifolia*

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The chemical analysis of dichloromethane (DCM) extract of *Macaranga grandifolia* (Blanco) Merr. resulted in the isolation and identification of several compounds. From the leaves, vedelianin (**1**), squalene (**2**), β-carotene (**3**) and polyprenol (**4**) were isolated. The barks contained a mixture of stigmasterol (**5a**) and β-sitosterol (**5b**). Additionally, the fruits yielded saturated fatty acid (**6**). The elucidation of structure **1** was accomplished through the utilization of comprehensive 1D and 2D NMR spectroscopic techniques. The identification of the structures of compounds **2-6** was achieved through a comparative analysis of their nuclear magnetic resonance (NMR) data with the literature data.

Keywords: *Macaranga grandifolia* (Blanco) Merr., Vedelianin, Squalene, β-Carotene, Polyprenol, Stigmasterol, β-Sitosterol.

INTRODUCTION

Macaranga Thou. is a genus of the spurge botanical family Euphorbiaceaes [1] and the solitary genus within Macaranginae to consist of approximately 300 species. This genus is widely distributed in tropical countries mainly in Africa, Madagascar, Southeast Asia, Australia and some parts of the Pacific regions [2]. *Macaranga* species have been used as traditional medicine in treating swellings, cuts, boils, stomach-aches, fever, fungal infections, inflammation, skin itches, and icteric hepatitis by local healers [3-5]. The phytochemical investigation of the different species of *Macaranga* showed numerous varieties of secondary metabolites such as tannins, coumarins, steroids, chalcones, terpenes, and phenolic compounds, specifically prenylated flavonoids and stilbenes, which are considered as the major constituents of the genus [2,3,6].

Currently, only 12% of the 300 species of the aforementioned genus have been studied for their inherent phytochemical profiles. *M. tanarius* whose origin is native to the Philippines and is widely distributed throughout the country [7,8]. This ornamental plant is the most studied *Macaranga* species and has reported antioxidant [9], antiplasmodial [10] and cytotoxicity activities [1,11]. A published work described that *n*-hexane:ethanol dried supernatant mixture of the leaves of *M. tanarius* showed antihyperlipidemic and hepatoprotective activity [12].

There has been limited investigations of the plants of this genus. One of the plants is *Macaranga grandifolia* (Blanco) Merr., an endemic tree in the Philippines [13] and locally known as Binuñgang-malapad or Takip-asin. This flowering plant's habitat is usually in a humid forest at low altitude of different provinces in Luzon region. *M. grandifolia* is usually mistaken for *M. tanarius* because of their similar characteristics, even though *M. grandifolia* can grow up to 4 to 10 m tall and its leaves can range from 60-100 cm wide, whereas *M. tanarius* can grow up to 4 to 8 m tall and its leaves ranges from 10 to 25 cm in diameter [7,8]. The leaves of *M. grandifolia* are locally employed to wrap food due to its large size, while the leaf ash is eaten for enlarged bellies and the resin is used as astringent gargle for mouth ulcer [7,13].

This study chronicles the methodology that was used and the chemical characterization of vedelianin (**1**), squalene

(**2**), β-carotene (**3**) and polyprenol (**4**) which were found in the leaves; a mixture of stigmasterol (**5a**) and β-sitosterol (**5b**) from the bark and saturated fatty acid (**6**) (Fig. 1) from the fruits of *M. grandifolia*. To the best of our knowledge, the chemical characterizations of *M. grandifolia* has not been reported in any other work.

EXPERIMENTAL

Characterization: A Varian VNMRS spectrometer, 600 MHz for ^{1}H NMR and 150 MHz ^{13}C NMR, was employed to generate the NMR data. The samples were diluted in deuterated chloroform before placing in covered 5 mm NMR capillary tubes. Silica gel 60, 70-230 mesh, was the stationary adsorbent used for column chromatography. Thin layer chromatography (TLC) was carried out on polymer coated silica gel F_{254} plates. A vanillin and sulfuric acid solution was used as the visualizing agent for the TLC plates.

Plant selection and collection: *M. grandifolia* (Blanco) Merr. was collected from the Province of Bataan, Philippines circa 2019 in September. Certification of the identity of this endemic flowering plant was accomplished at the University of the Philippines, College of Science at the Institute of Biology, Jose Vera Santos Memorial Herbarium.

Purification and isolation protocol: Columns for gravity chromatography with the following dimensions: a height of 50.8 cm with an internal diameter (I.D.) of 5.8 cm, was used with silica gel resin. Silica gel chromatography using eluents of increasing incremental quantities of acetone in dichloride methane (DCM) (from 0% to 100% acetone) was used to fractionate the crude extract. Eluates of approximately one hundred milliliters of each mobile phase solvent system were collected in test tubes. Each individual fraction was visualized *via* TLC for any noteworthy spots. Eluates with similar retention factors were pooled together for further column chromatography using suitable solvent eluents until single component isolates were substantiated by TLC. Columns with the specifications: a height of 30.48 cm and an I.D. of 0.5 cm, incorporated with silica gel, was the stationary phase of the succeeding procedure. The volume of the fraction collection was set at 5 mL. Modified Pasteur pipettes served as the columns for the last purifications steps of which 1 mL fractions were set aside for drying and subsequent NMR experiments.

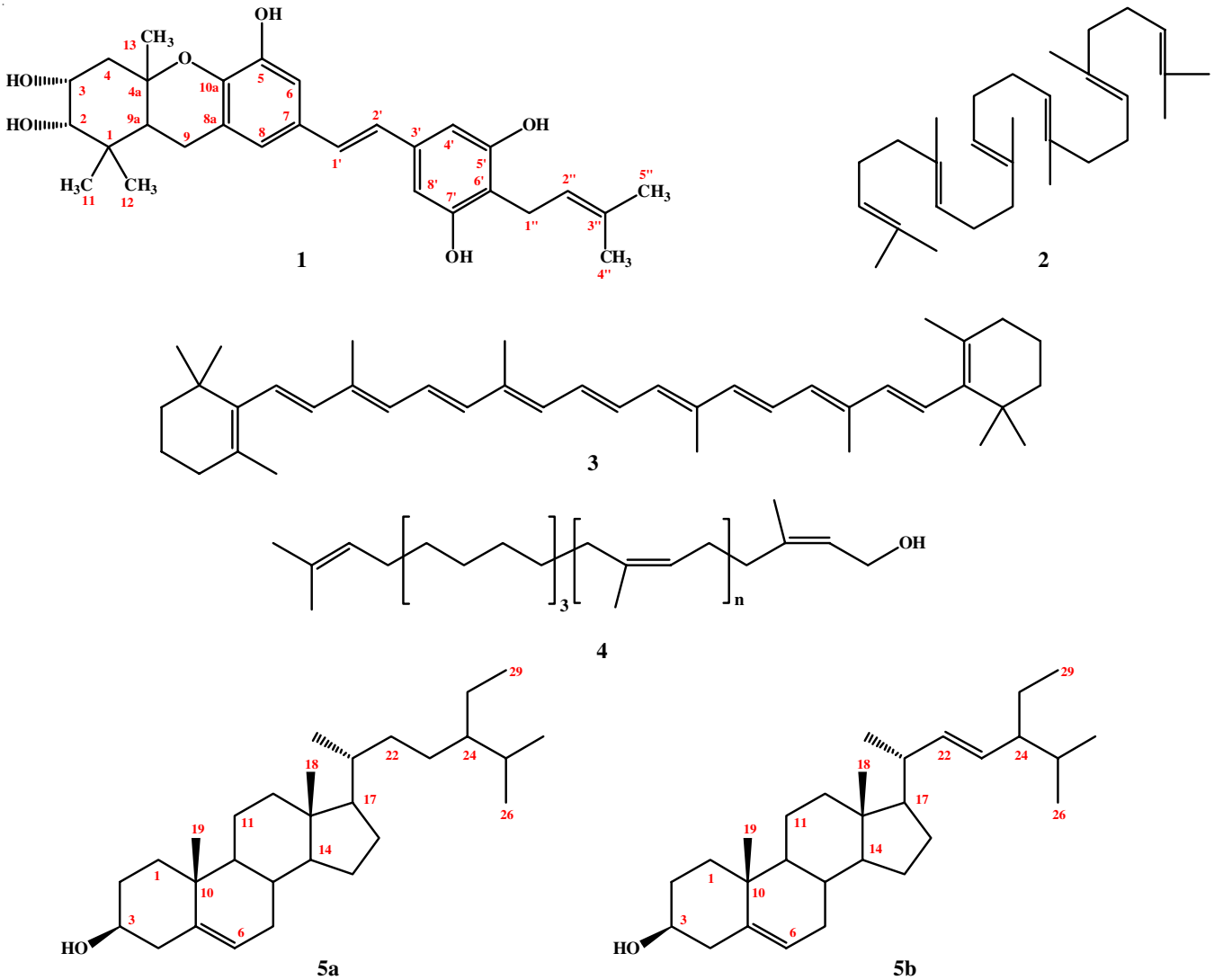

Fig. 1. Chemical structure of compounds **1-5**

Sample preparation: Maceration extraction of the leaves (328.6 g) was done using DCM as the extracting solvent. The resultant mixture was incubated for 3 days and filtered using Whatman filter paper. The concentrated filtered eluates weighed 7.20 g and were obtained using rotary evaporation. The crude extract underwent purification by column gravity chromatography with different solvent systems using varying concentrations of acetone in DCM at 10% incremental increase for each elution. Both the 70% and 80% acetone in DCM eluates were pooled together for additional chromatography using the solvent system 1:1:8, v/v of acetonitrile:diethyl ether:DCM, which recovered compound **1** (13.9 mg). Three fractions specifically; DCM, 10% and 20% acetone in DCM were collected and underwent chromatography *via* elution of first petroleum ether, afterwards 1%, then 2.5% and finally 7.5% ethyl acetate (EtOAc) in petroleum ether. All the eluates from petroleum ether were collected which acquired compound **2** (4.2 mg). The fractions derived from 1% and 2.5% EtOAc in petroleum ether were intermixed and yield constituent **3** (14.7 mg). Compound **4** (7.8 mg) was recovered from the 7.5% EtOAc in petroleum ether fraction.

Sample preparation and isolation methodology for the bark: The bark of *M. grandifolia,* which was dried at ambient temperatures, afforded approximately 256.60 g. The sample was pulverized before maceration extraction, as stated in the aforementioned methodology for the purification of constituents from the leaves. After removal of DCM *via* rotary evaporator, the crude extract was weighed 0.6072 g. The DCM eluate from the crude extract was further purified through two different sets of column chromatography using DCM as eluent and resulted in the recovery of a 2.1 mg mixture of compounds **5a** and **5b**.

Sample preparation and isolation for the fruits: The lyophilized fruits, which was approximately 6.0012 g, were pulverized and underwent the same initial incubation with DCM as described above. After vacuum concentration, 0.6305 g of residue was extracted. Increasing acetone concentrations in DCM by 10% volume intervals were used to chromatograph the crude residue. Isolate **6** (0.4 mg) was obtained after subsequent chromatography of the fraction recovered from 40% acetone in DCM using 20% EtOAc in petroleum ether.

Vedelianin (1): Yellowish brown solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.91 (1H, d, *J* = 1.8 Hz, H-6), 6.85 (1H, d, *J* = 16.2 Hz, H-1′), 6.74 (1H, d, *J* = 1.2 Hz, H-8), 6.74 (1H, d, *J* = 16.2, H-2′), 6.52 (2H, H-4′, H-8′), 5.25 (1H, m, H-2″), 4.24 (1H, d, *J* = 3.6 Hz, H-3), 3.40 (3H, d, *J* = 3.6 Hz, H-2, H-1″), 2.74 (2H, m, H-9), 2.39 (1H, dd, *J* = 3.6, 14.4 Hz, H-4), 1.98 (1H, dd, *J* = 3.6, 14.4 Hz, H-4), 1.81 (s, H-5″), 1.78 (s, H-9a), 1.74 (s, H-4″), 1.43 (s, H-13), 1.11 (s, H-12), 1.07 (s, H-11); ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.07 (C-5′), 155.07 (C-7′), 145.28 (C-5), 139.71 (C-10a), 137.21 (C-3′), 135.41 (C-3″), 129.60 (C-7), 128.57 (C-1′), 125.96 (C-2′), 122.24 (C-8a), 121.47 (C-2″), 119.49 (C-8), 112.74 (C-6′), 109.65 (C-6), 106.18 (C-4′), 106.18 (C-8′), 77.57 (C-4a), 77.54 (C-2), 70.67 (C-3), 47.36 (C-9a), 43.25 (C-4), 38.11 (C-1), 28.94 (C-12), 25.79 (C-4″), 22.58 (C-9), 22.51 (C-1″), 21.59 (C-13), 17.89 (C-5″), 15.99 (C-11).

Squalene (2): Colourless oil, ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.08-5.13 (6H =CH), 1.94-2.08 (20H, allylic CH_2), 1.66 (6H, allylic Me, *trans*), 1.58 (18H, allylic Me, *cis*).

β-Carotene (**3**): Red orange solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.09-6.63 (=CH), 1.97 (12H, s, allylic CH_3), 1.70 (6H, s, allylic CH_3), 1.01 (12H, s, CH_3).

Polyprenol (4): ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.07 (2H, d, *J* = 6.6 Hz, CH_2OH), 5.41 (1H, =CH), 5.08-5.11 (11H, =CH), 1.94-2.07 (40H, allylic CH_2), 1.73 (3H, allylic CH_3), 1.66 (21H, allylic CH_3), 1.58 (12H, allylic CH_3).

Stigmasterol (5a): Colourless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, *J* = 4.8 Hz, H-6), 5.12 (dd, *J* = 8.4, 16.0 Hz, H-22), 5.00 (dd, *J* = 8.4, 15.0 Hz, H-23), 3.50 (m, H-3), 1.00 (s, CH_3-19), 1.00 (d, *J* = 6.6 Hz, CH_3-21), 0.83 (d, *J* = 6.6 Hz, CH_3-26), 0.83 (d, *J* = 6.6 Hz, CH_3-27), 0.79 (t, *J* = 7.2 Hz, CH_3-29), 0.68 (s, CH_3-18).

β-Sitosterol (5b): Colourless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, *J* = 4.8 Hz, H-6), 3.50 (m, H-3), 2.26, 2.22 (H_2-4), 1.00 (s, CH_3-19), 0.91 (d, *J* = 7.2 Hz, CH_3-21), 0.88 (t, *J* = 6.6 Hz, CH_3-29), 0.83 (d, *J* = 6.6 Hz, CH_3-27), 0.80 (d, *J* = 7.2 Hz, CH_3-26), 0.66 (s, CH_3-18).

Saturated fatty acid (6): Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.33 (t, *J* = 7.8 Hz, α-CH_2), 1.60 (m, β-CH_2), 1.23-1.35 (CH_2), 0.86 (t, *J* = 7.2 Hz, CH_3).

RESULTS AND DISCUSSION

Extensive normal phase chromatography of the maceration infusions of DCM extracts of *M. grandifolia* was able to purify compounds **1-6**. The confirmation of molecule **1** was through both one-dimensional and two-dimensional NMR spectroscopic techniques. The NMR spectrum data for the isolated constituents **2** for squalene [14], **3** for β-carotene [15], **4** for polyprenol [15] and **5a** and **5b** for stigmasterol and β-sitosterol, respectively [16] and **6** for a saturated fatty acid [17], was compared to the reported NMR spectra, and the results were able to successfully characterize these isolates which are in concurrence with these reported findings.

Providing that neither *in vivo* nor *in vitro* experiments were conducted on the isolated constituents (**1-6**), a thorough examination of all available literature was conducted with the help of reference management tools such as Mendeley Reference Manager and Google Scholar. The sources divulged that the aforementioned molecules compounds have some noted pharmacological activities.

Vedelianin (**1**) is a derivative of hexahydroxanthane, which can be classified as a substituted cyclized geranylstilbene. Its purification and characterization were initially conducted through the trails of methanol on the leaves of *M. vedeliana* [18]. The structure of vedelianin from *M. vedeliana* was first reported in 1992, wherein the pharmacognosy of this molecule was found to be hypotensive. Vedelianin was also found in different species of *Macaranga*; fruits of *M. alnifolia* [19], from the leaves of *M. schweinfurthii* [20], leaves of *M. indica* [5] and leaves of *M. barteri* [2] and from the fruits of *M. tanarius* [1,11]. This compound exhibited a highly significant cytotoxicity activity against U87, A459 [1], MCF7, PC3, HeLa [2], KB, HepG-2, LU [4] and A2780 [20]. Because of its plausible

antiproliferative action, Topczewski & Wiemer [21] developed a synthetic methodology to yield (+)-vedelianin in a nonracemic form through a Shi epoxidation *via* 18 steps from vanillin.

Squalene (**2**) was reported to effectively inhibit chemically induced tumors on different rodent cell tissues, specifically in the lungs, colon and skin. One of its critical roles is reducing free radical oxidative damage to the skin [22], which makes squalene a natural antioxidant. Dietary supplement of squalene enhances the immune system performance and improves macrophage function [23]. Also, this compound has been correlated to the prevention of human disease due to the systemic influences on autoimmune adverse disorders, dendritic and T cell production, anti-inflammatory regulators and the strengthening of the immune palisade [24]. In addition to its biological properties, squalene is currently employed in the formulation of suspension-based adjuvants, namely AS03 and MF59, which are utilized in vaccinations, particularly for the prevention of human influenza [25].

β-Carotene (**3**) exhibited antimicrobial inhibition towards *Pseudomonas aeruginosa* and *Aspergillus niger* and was minimally inhibitory for *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Trichophyton mentagrophytes* [26]. The antioxidant capacity of β-carotene from *ex vivo* investigations obtained in the LDL fraction in human body have established the ameliorative effect of β-carotene [27].

Polyprenol (**4**) from *Ginkgo biloba* exhibited an antibacterial property against *Staphylococcus aureus*, with MIC value of 33.0 μg/mL [28]. Moreover, polyprenol extracted from *Abies sibirica* L. was reported to be a hepatoprotective agent that might be suitable for use in the supplementation of food, in industries such as in cosmetic manufacturing and as a concomitant adjuvant with accepted medical protocols for human disorders [29]. Furthermore, polyprenol has been utilized in the medication of the neurodegenerative illness Alzheimer's. It was found that treatment of polyprenols on selected cerebral divisions of APP/PS1 rodents (9 months) reduced the apoptotic cells, which exhibited the neuroprotective activity in APP/PS1 mice [30]. This molecule has also been seen to improve cellular barrier features, provide protection to the liver, induce inhibition of viral infections and cause the prevention of tumor formation [31-34].

Stigmasterol (**5a**) exhibited a antimicrobial activity similar to ciprofloxacin, a standard antimicrobial drug. It also was found to impede the proliferation of *Candida* spp. much like fluconazole, a well-known antimycotic medicine. Additionally, there has been cited that the minimum inhibitory concentration (MIC) and the minimum bactericidal/fungicidal dilution (MBC/MFC) of compound **5a** vary from 6.25 μg/mL to 25 μg/mL and from 12.5 μg/mL to 50 μg/mL, respectively [35]. Stigmasterol exhibited various biological activities such as anti-osteoarthritic, antitumor, antihypercholesterolemic, antioxidant, cytotoxicity, hypoglycemic and CNS activities [36].

β-Sitosterol (**5b**) also displayed several biological activities like antipyretic, antioxidant, antimicrobial, antidiabetic, anti-inflammatory, antihypercholesterolemic, antiarthritic, anti-pulmonary tuberculosis, immune modulation and anti-HIV and anticancerogenic activities [37]. Compound **5b** reduced β-catenin and PCNA regulation, which hypothetically could be considered as an adjuvant in colon cancer treatment [38] and showed promising results in 1,2-dimethylhydrazine (DMH) stimulated colonic preneoplastic progression in Wistar rats as demonstrated by the observed radical scavenging ability [39].

Conclusion

The leaves of *Macaranga grandifolia* were subjected to extraction with dichloromethane, resulting in the isolation of vedelianin (**1**), squalene (**2**), β-carotene (**3**) and polyprenol (**4**). On the other hand, the bark of *M. grandifolia* yielded a mixture of stigmasterol (**5a**) and β-sitosterol (**5b**). Additionally, the fruits of *M. grandifolia* were found to contain saturated fatty acid (**6**), which has been reported to exhibit various biological activities.

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CONFLICT OF INTEREST

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

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