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Chemical Constituents of *Hoya cagayanensis* C. M. Burton

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ABSTRACT

Chemical investigation of the dichloromethane extracts of *Hoya cagayanensis* led to the isolation of dihydrocanaric acid (**1**), lupeol (**2**), lupenone (**3**) and saturated hydrocarbons from the stems; and 2-hydroxyethyl benzoate (**4**) and a mixture of β-sitosterol (**5a**) and stigmasterol (**5b**) from the leaves. The structures of **1** and **4** were elucidated by extensive 1D and 2D NMR spectroscopy. The structures of **2**, **3**, **5a** and **5b** were identified by comparison of their NMR data with literature data.

INTRODUCTION

Hoya is a genus of flowering plants in the family Apocynaceae. Most are epiphytic vines with succulent leaves and attractive clusters of flowers. There are at least 109 species of *Hoya* found in the Philippines, 88 of these are endemic to the country (Aurigue, 2013). Among them is *Hoya cagayanensis* C. M. Burton, first discovered in Cagayan province but also collected from Laguna and Quezon provinces in Luzon island, Philippines. It has become popular as an ornamental plant among collectors in the country and also abroad due to its spice-scented flowers, lush foliage, and ease of culture. No report on their ethnobotany or chemical analysis have been found. This study is part of our research on the chemical constituents of Philippine endemic and indigenous hoyas. We earlier reported the isolation of lupenone and lupeol from the roots; lupeol, squalene and β-sitosterol from the leaves; and betulin from the stems of *H. mindorensis* Schlechter (Ebajo *et al.*, 2014). In another study, we reported the isolation of lupeol, α-amyrin, β-amyrin, lupeol acetate, α-amyrin acetate, and β-amyrin acetate from the stems; and α-amyrin, bauerenol, squalene, lutein, β-sitosterol, and stigmasterol from the leaves of *H. multiflora* Blume (Ebajo *et al.*, 2015a). The isolation of β-amyrin cinnamate and taraxerol from the stems; and taraxerol, triglycerides, chlorophyll a, and a mixture of β-sitosterol and stigmasterol from the leaves of H. wayetii Kloppenb. has been reported (Ebajo *et al.*, 2015b). Furthermore, the isolation of taraxerol, taraxerone, a mixture of β-sitosterol and stigmasterol, and a mixture of α-amyrin cinnamate and β-amyrin cinnamate from the stems; taraxerol, taraxerone, and β-sitosterol from the roots; a mixture of α-amyrin cinnamate and β-amyrin cinnamate from the flowers; and squalene, β-sitosterol, and saturated hydrocarbons from the leaves of *H. buotii* has been reported (Ebajo *et al.*, 2015c).

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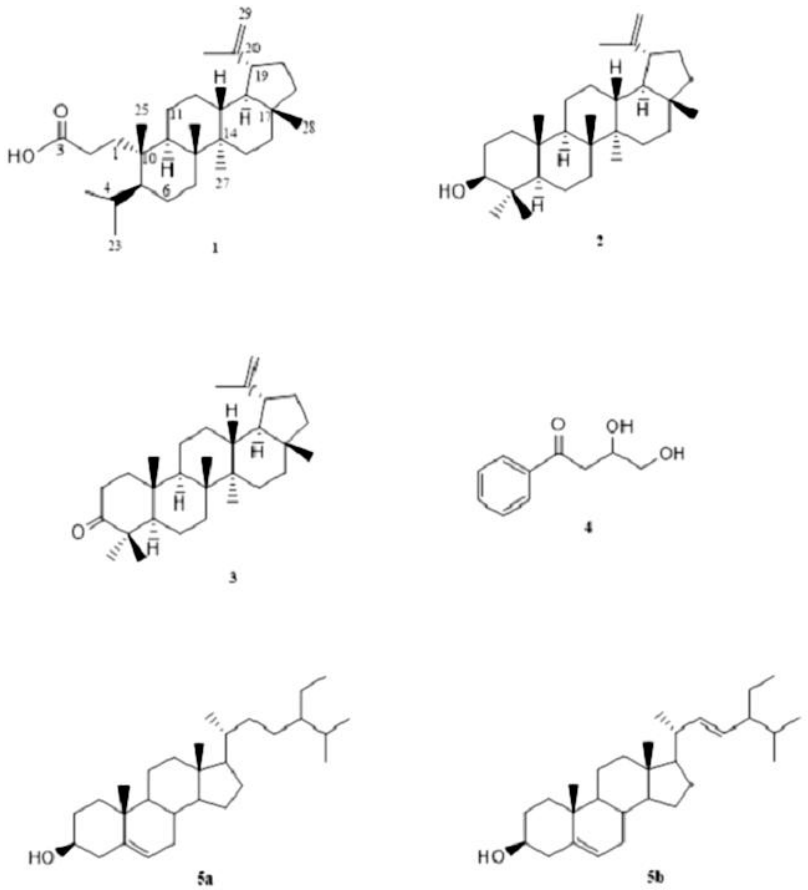

Fig. 1: Chemical structures of dihydrocanaric acid (**1**), lupeol (**2**), lupenone (**3**), 2-hydroxyethyl benzoate (**4**), β-sitosterol (**5a**) and stigmasterol (**5b**) from *H. cagayanensis.*

Recently, we reported the isolation of β-amyrin cinnamate, squalene, β-sitosterol, a mixture of β-amyrin, α-amyrin and lupeol and saturated hydrocarbons from the leaves; and squalene, taraxerol, lupeol cinnamate, and a mixture of β-sitosterol and stigmasterol from the stems of *H. diversifolia* (Panajon *et al.*, 2016a). Moreover, the isolation of taraxerol, β-sitosterol and stigmasterol from *H. pubicalyx* was reported (Panajon *et al.*, 2016b). Lastly, we reported the isolation of taraxerol, taraxeryl acetate, and a mixture of α-amyrin acetate and β-amyrin acetate from *H. paziae* (Borlagdan *et al.*, 2016).

We report herein the isolation of hydrocanaric acid (**1**), lupeol (**2**), lupenone (**3**), and saturated hydrocarbons from the stems; and 2-hydroxyethyl benzoate (**4**) and a mixture of β-sitosterol (**5a**) and stigmasterol (**5b**) from the leaves of *H. cagayanensis.* To the best of our knowledge this is the first report on the isolation of **1-5** and hydrocarbons from *H. cagayanensis.*

MATERIALS AND METHODS

General Experimental Procedure

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were acquired in $CDCl_3$ on a 500 MHz Agilent DD2 NMR spectrometer with referencing to solvent signals (δ 7.26 and 77.0 ppm).

Two dimensional NMR experiments recorded included gCOSY, HSQCAD, and gHMBCAD NMR experiments. 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

Stem cuttings were taken from two large specimen plants of *H. cagayanensis* cultivated at the Philippine Nuclear Research Institute *Hoya* Germplasm Collection under MTA No. 2015-06 dated August 13, 2015 and MTA No. 2016-04 dated June 24, 2016. Accession No. PNRI-H.23 is grown from a cutting that originally came from Quezon province and was subsequently propagated since 1997. It was identified and authenticated by Dr. Simeona V. Siar of the Institute of Plant Breeding, University of the Philippines-Los Baños on February 26, 2008.

General Isolation Procedure

The air-dried stems (81.25 g) and leaves (61.95 g) of *H. cagayanensis* were ground in a blender, soaked in CH_2Cl_2 for three days and then filtered. The filtrates were concentrated under vacuum to afford crude extracts of stems (4.79 g) and leaves (4.00

g) which were separately chromatographed by gradient elution with CH_2Cl_2, followed by increasing amounts of acetone at 10% increments by volume as eluents. A glass column 12 inches in height and 0.5 inch internal diameter was used for the fractionation of crude extracts.

Two millilitre 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. Rechromatography and final purifications were conducted using Pasteur pipettes as columns. One millilitre fractions were collected.

Isolation of the Chemical Constituents of the Stems

The crude leaves extract (4.00 g) was chromatographed using increasing proportions of acetone in CH_2Cl_2 (10% increment) as eluents. The CH_2Cl_2 fraction was rechromatographed (2 ×) using petroleum ether to afford hydrocarbons (5 mg) after washing with petroleum ether. The 20% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) using 5% EtOAc in petroleum ether to yield **3** (10 mg) after washing with petroleum ether.

The 30% acetone in CH_2Cl_2 fraction was rechromatographed (2 ×) using 10% EtOAc in petroleum ether to yield **2** (3 mg) after washing with petroleum ether. The 40% acetone in CH_2Cl_2 fractions was rechromatographed (3 ×) using 15% EtOAc in petroleum ether to yield **1** (7 mg) after washing with petroleum ether.

Isolation of the Chemical Constituents of the Leaves

The crude stems extract (4.79 g) was chromatographed using increasing proportions of acetone in CH_2Cl_2 (10% increment) as eluents. The CH_2Cl_2 fraction was rechromatographed (3 ×) using 10% EtOAc in petroleum ether to yield a mixture of **5a** and **5b** (12 mg) after washing with petroleum ether. The 70% acetone in CH_2Cl_2 fraction was rechromatographed using 15% EtOAc in petroleum ether. Fractions collected from this column were combined and rechromatographed using CH_3CN:Et_2O: CH_2Cl_2 (0.5:0.5:9, v/v) to afford **4** (3 mg) after washing with petroleum ether.

Dihydrocanaric acid (1)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.58, 1.68 (H_2-1), 2.20 (H_2-2), 1.87 (H-4), 0.97 (H-5), 1.36 (H_2-6), 1.33, 1.38 (H_2-7), 1.44 (H-9), 1.23, 1.36 (H_2-11), 1.05, 1.68 (H_2-12), 1.66 (H-13), 1.05, 1.66 1.38 (H_2-15), 1.37, 1.47 (H_2-16), 1.37 (H-18), 2.37 (H-19), 1.33, 1.92 (H_2-21), 1.20, 1.38 (H_2-22), 0.90 (d, *J* = 7.0 Hz, H_3-23), 0.79 (d, *J = 6.5* Hz, H_3-24), 0.81 (s, H_3-25), 1.04 (s, H_3-26), 0.94 (s, H_3-27), 0.78 (s, H_3-28), 4.57, 4.68 (br s, H_2-29), 1.68 (br s, H_3-30); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 32.7 (C-1), 28.5 (C-2), 180.7 (C-3), 25.4 (C-4), 47.3 (C-5), 18.2 (C-6), 33.0 (C-7), 40.6 (C-8), 40.8 (C-9), 39.9 (C-10), 21.6 (C-11), 25.1 (C-12), 38.1 (C-13), 43.2 (C-14), 27.5 (C-15), 35.5 (C-16), 43.0 (C-17), 48.2 (C-18), 48.0 (C-19), 150.9 (C-20), 29.8 (C-21), 40.0 (C-22), 24.8 (C-23), 18.8 (C-24), 19.6 (C-25), 15.9 (C-26), 14.4 (C-27), 18.0 (C-28), 109.4 (C-29), 19.3 (C-30).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extract of *H. cagayanensis* yielded **1**–**5** and hydrocarbons. The structures of **1** and **4** were elucidated by extensive 1D and 2D NMR spectroscopy. The NMR data of **1** are similar to those of canaric acid (Lopes *et al.*, 1999), except at C-4 and C-24 where their structures differ. In canaric acid, a double bond is found between C-4 and C-24, while a single bond is present in **1**. There are also differences in the chemical shifts of the protons and carbons close to C-4 and C-24. The NMR spectra of **2** are in accordance with data reported in the literature for lupeol (Ebajo *et al.*, 2015a), **3** for lupenone (Prakash *et al.*, 2012); **4** for 2-hydroxyethyl benzoate (Sharghi and Sarvari, 2003); **5a** for *β*-sitosterol (Ebajo *et al.*, 2015a), **5b** for stigmasterol (Ebajo *et al.*, 2015a) and hydrocarbons (Ebajo *et al.*, 2015c).

Although there is no reported biological acitivity for *H. cagayanensis*, the compounds (**1**-**3** and **5a**-**5b**) isolated from the plant were reported to possess diverse activities.

An earlier study reported that dihydrocanaric acid (**1**) exhibited growth inhibitory activity against both HeLa and SW480 cells (Sadhu *et al.*, 2008). It was also reported as a powerful anti-oxidant (Ghosh *et al.*, 2010).

Lupeol (**2**) exhibited antiurolithiatic and diuretic activity (Vidya *et al.*, 2002). It prevented the formation of vesical calculi and reduced the size of the preformed stones in rats (Anand *et al.*, 1994). It also showed antifungal activity against *Fusarium oxysporum* and *Penicillium notatum (*Manzano *et al.*, 2013). Lupeol significantly reduced the 451Lu tumor growth in athymic nude mice (Saleem et al., 2008), inhibited the proliferation of MDA-MB-231 human breast cancer cells in a dose dependent manner (Lambertini *et al.*, 2005), and induced growth inhibition and apoptosis in hepatocellular carcinoma SMMC7721 cells by down-regulation of the death receptor 3 (DR3) expression (Zhang *et al.*, 2009). Lupeol and lupeol acetate (**2a**) have shown hypotensive activity (Saleem *et al.*, 2003), while **1a** also exhibited antidyslipidemic activity in hamster at 100 mg/Kg body weight (Reddy *et al.*, 2009). It exhibited potent anti-inflammatory activity in an allergic airway inflammation model by a significant reduction in eosinophils infiltration and in Th2-associated cytokines levels that trigger the immune responses in asthma (Vasconcelos *et al.*, 2008). A review on the biological activities of lupeol has been provided (Gallo and Sarachine, 2009).

Lupenone (**3**) inhibits adipocyte differentiation by suppressing PPARγ and C/EBPα protein levels (Ahn and Oh, 2013). It also increases the tyrosinase enzyme expression via mitogen-activated protein kinase phosphorylated extracellular signal regulated kinases 1 and 2 phosphorylation inhibition which results to stimulation of melanogenesis. This suggests that lupenone could be a possible treatment for hypopigmentation (Villareal *et al.*, 2013). β-Sitosterol (**5a**) has been reported to have growth inhibitory effects on human breast MCF-7 and MDA-MB-231 adenocarcinoma cells (Awad *et al.* 2007). It was shown to be effective for the treatment of benign prostatic hyperplasia

(Jayaprakasya *et al.*, 2007). It was observed to attenuate β-catenin and PCNA expression, as well as quench free radical *in vitro*, making it a potential anticancer drug for colon carcinogenesis (Baskar, *et al.*, 2010), and inhibit the expression of NPC1L1 in the enterocytes to reduce intestinal cholesterol uptake (Jesch *et al.*, 2009). It was also reported to induce apoptosis mediated by the activation of ERK and the downregulation of Akt in MCA-102 murine fibrosarcoma cells (Moon *et al.*, 2007).

On the other hand, stigmasterol (**5b**) shows therapeutic efficacy against Ehrlich ascites carcinoma in mice while conferring protection against cancer induced altered physiological conditions (Ghosh *et al.*, 2011). It has been reported to lower plasma cholesterol levels, inhibit intestinal cholesterol and plant sterol absorption, and suppress hepatic cholesterol and classic bile acid synthesis in Winstar and WKY rats (Batta *et al.*, 2006). In other studies, stigmasterol showed cytostatic activity against Hep-2 and McCoy cells (Gomez *et al.*, 2001), markedly inhibited tumour promotion in two stage carcinogenesis experiments (Kasahara *et al.*, 1994), and exhibited antimutagenic (Lim *et al.*, 2005), topical anti-inflammatory (Garcia *et al.*, 1999), antiosteoarthritic (Gabay *et al.*, 2010) and antioxidant (Panda *et al.*, 2009) activities.

CONCLUSION

H. cagayanensis shares similar chemical characteristics with other members of the Philippine native *hoyas*: *H. mindorensis* (Ebajo *et al.*, 2014), *H. multifora* (Ebajo *et al.*, 2015a), and *H. diversifolia* (Panajon *et al.*, 2016a) which yielded lupeol (**2**); *H. mindorensis* (Ebajo *et al.*, 2014) which contained lupenone (**3**); *H. mindorensis* (Ebajo *et al.*, 2014), *H. multifora* (Ebajo *et al.*, 2015a), *H. wayetii* (Ebajo *et al.*, 2015b), *H. buotii* (Ebajo *et al.*, 2015c), *H. diversifolia* (Panajon *et al.*, 2016a), *and H. pubicalyx* (Panajon *et al.*, 2016b) which afforded β-sitosterol (**5a**); *H. multifora* (Ebajo *et al.*, 2015a), *H. wayetii* (Ebajo *et al.*, 2015b), *H. buotii* (Ebajo *et al.*, 2015c), *and H. pubicalyx* (Panajon *et al.*, 2016b) which contained stigmasterol (**5b**); and *H. buotii* (Ebajo *et al.*, 2015c) and *H. diversifolia* (Panajon *et al.*, 2016a) which yielded saturated hydrocarbons. This is the first report on the isolation of dihydrocanaric acid (**1**) and 2-hydroxyethyl benzoate (**4**) from Philippine native hoyas.

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Conflict of Interests: The authors' declare no conflict of interest.

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