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Chemical Constituents of *Cordia dichotoma* G. Forst.

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ABSTRACT

Chemical investigation of the dichloromethane extracts of *Cordia dichotoma* G. Forst led to the isolation of β-sitosteryl-3β-glucopyranoside-6'-*O*-palmitate (**1**), nervonyl 4-hydroxy-*trans*-cinnamate ester (**2**), β-sitosterol (**3**), and chlorophyll a (**4**) from the leaves; and **4** and 1,2-dilinoleoyl-3-linolenoylglycerol (**5**) from the twigs. The structures of **1**-**5** were identified by comparison of their NMR data with those reported in the literature. The fatty acids in **1**, **2** and **5** were deduced from ESI-MS data.

INTRODUCTION

Cordia dichotoma G. Forst. belongs to the family Boraginaceae. This medium sized tree grows widespread in the Philippines where it is locally known as *anonang*. It yields edible fruits from which a very sticky white substance could be extracted for gluing purposes. The leaves, fruit, bark and seed have been reported to exhibit antidiabetic, antiulcer, anti-inflammatory, immune-modulator and analgesic activities (Jamkhande *et al*., 2013). The leaves, seed, fruit, bark, and roots are well-known to have different medicinal uses: antidiabetic, anthelmintic, antilarvicidal, hepatoprotective, immuno-modulator, antidysentery, antidyspepsia, anti-inflammatory, anti-ulcer, diuretic and laxative (Patel *et al*., 2011). The crude ethanol extract from the leaves showed antilarvicidal potency against the brine shrimp *Artemia salina* (Sharker *et al*., 2013). Initial studies indicated potential antioxidant properties based on direct measurement of radical scavenging activity of crude extracts from the tree's bark (Nariya *et al*., 2013). Crude methanolic extract of the bark showed inhibition of number of implants in laboratory female rats (Katolkar *et al*., 2012). In a related study, leaf extract from the tree showed anti-implantation activity, suggesting its possible use as a natural contraceptive drug (Bhattacharya and Saha, 2013).

The fruit, leaves and seed contain pyrrolizidine alkaloids, coumarins, flavonoids, saponins, terpenes and sterols (Jamkhande *et al*., 2013). Taxifolin from the seeds of *C. dichotoma* showed promising DPPH free radical scavenging activity at a concentration of 100 µg/mL (Mahasweta *et al*., 2014). Another study reported that apigenin (5 mg/kg, p.o.) from *C. dichotoma* showed significant healing and reduction in inflammatory enzymes when screened for ulcerative colitis (Ganjare *et al*., 2011). The fatty oil content in the seeds of *C. dichotoma* was found to be 7.60% with stearic, oleic and linoleic acids as the major constituents (Rameshwar *et al*., 2006). Three flavonoids, kaempferol, quercetin and isorhamnetin, were isolated from the butanol fraction of fruits of *C. dichotoma* (Kuppast *et al*., 2006).

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Six flavonol glycosides and two phenolic compounds were isolated from butanol extract of the leaves of *C. dichotoma* with rosmarinic acid as a major constituent (Wang *et al*., 1996). In another study, the ethanolic extracts were reported to contain polyphenolic compounds (1.0%), triterpenoids (0.075%), amino acids (1.39%), and rosmarinic acid (0.0028%) (Tian *et al*., 2014). A review on the chemical constituents and medicinal uses of *Cordia dichotoma* has been provided (Priyanka and Shrikant, 2014). We report herein the isolation of β-sitosteryl-3β-glucopyranoside-6'-*O*-palmitate (**1**), nervonyl 4-hydroxy-*trans*-cinnamate ester (**2**), β-sitosterol (**3**), and chlorophyll a (**4**) from the leaves; and **3** and 1,2-dilinoleoyl-3-linolenoylglycerol (**5**) from the twigs of *C. dichotoma* (Fig. 1). To the best of our knowledge this is the first report on the isolation of **1**-**2** from *C. dichotoma*.

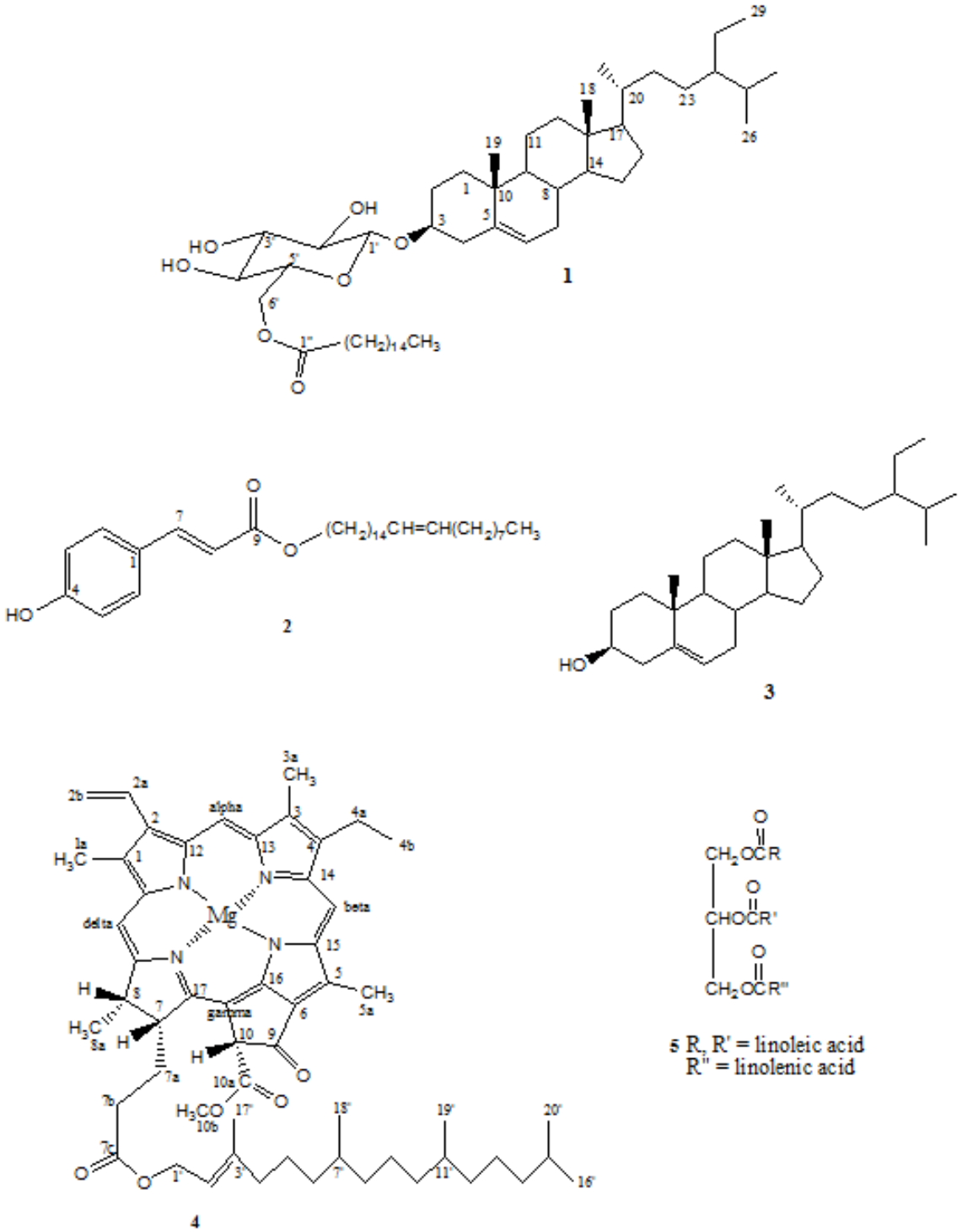

Fig. 1: Chemical structures of β-Sitosteryl-3β-glucopyranoside-6'-*O*-palmitate (**1**), nervonyl 4-hydroxy-*trans*-cinnamate ester (**2**), β-sitosterol (**3**), chlorophyll a (**4**), and 1,2-dilinoleoyl-3-linolenoylglycerol (**5**) from *C. dichotoma*.

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). Mass spectral analysis was conducted on the Bruker Daltonics micro TOF Q – II mass spectrometer employing ESI – Qq – TOF in positive mode. Data analysis was processed using the Bruker Compass Data Analysis 4.0 application. 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

Samples of leaves and twigs of *Cordia dichotoma* G. Forst. were collected from the De La Salle University – Science and Technology Complex (DLSU-STC) riparian forest in February 2014. The samples were authenticated by one of the authors (EHM) and deposited at the De La Salle University Herbarium with voucher specimen # 916.

General Isolation Procedure

The air-dried leaves (300 g) and stems (121.4 g) of *C. dichotoma* 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 leaves (6.3 g), and stems (1.0 g) which were each chromatographed by gradient elution with CH_2Cl_2, followed by increasing amounts of acetone at 10% increment 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 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. Subsequent chromatography and final purifications were conducted using Pasteur pipettes as columns. One milliliter fractions were collected.

Isolation of Chemical Constituents of the Leaves

The 20% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) using 15% EtOAc in petroleum ether to afford **2** (1 mg). The 30% acetone in CH_2Cl_2 fraction was rechromatographed (2 ×) using 20% EtOAc in petroleum ether to afford **3** (6 mg) after washing with petroleum ether. The 40% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) using CH_3CN:Et_2O:CH_2Cl_2 (0.5:0.5:9 by volume ratio) to afford **4** (4 mg) after washing with petroleum ether, followed by Et_2O. The 60% acetone in CH_2Cl_2 fraction was rechromatographed (4 ×) using CH_3CN:Et_2O:CH_2Cl_2 (2:2:6 by volume ratio) to afford **1** (5 mg) after trituration with petroleum ether.

Isolation of Chemical Constituents of the Twigs

The 10% acetone in CH_2Cl_2 fraction was rechromatographed (2 ×) using 5% EtOAc in petroleum ether to afford **5** (7 mg). The 40% acetone in CH_2Cl_2 fraction was rechromatographed (3 ×) using 20% EtOAc in petroleum ether to afford **3** (3 mg) after washing with petroleum ether.

***β-Sitosteryl-3β-glucopyranoside-6'-O-palmitate* (1)**

^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz) see Table 1. ESI-MS *m/z* 815.5130 $[M+H]^+$ (calcd. 815.6759 for $C_{51}H_{91}O_7$).

***Nervonyl 4-hydroxy-trans-cinnamate ester* (2)**

^{1}H NMR (500 MHz, $CDCl_3$): 6.83 (d, *J* = 8.8, H-2), 7.43 (d, *J* = 8.8, H-3, H-5), 6.83 (d, *J* = 8.8, H-6), 7.62 (d, *J* = 16.0, H-7), 6.30 (d, *J* = 16.0, H-8), 4.20 (t, *J* = 6.8, H-1'), 1.70 (H-2'), 1.23-1.40 (H-3'–H-n'), 0.88 (t, *J* = 6.4, Me). ESI-MS *m/z* 507.3273 $[M+Na]^+$ (calcd. 507.3809 for $C_{32}H_{52}NaO_3$).

***β-Sitosterol* (3)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (m, H-3), 2.28, 2.23 (H_2-4), 5.34 (dd, *J* = 5.0, 2.0 Hz, H-6), 0.67 (s, CH_3-18), 1.00 (s, CH_3-19), 0.91 (d, *J* = 6.5 Hz, CH_3-21), 0.80 (d, *J* = 7.0 Hz, CH_3-26), 0.83 (d, *J* = 7.0 Hz, CH_3-27), 0.87 (t, *J* = 7.0 Hz, CH_3-29). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.2 (C-1), 31.7 (C-2), 71.8 (C-3), 42.3 (C-4), 140.8 (C-5), 121.7 (C-6), 31.9 (C-7), 31.9 (C-8), 50.1 (C-9), 36.1 (C-10), 21.1 (C-11), 39.8 (C-12), 42.3 (C-13), 56.8 (C-14), 24.3 (C-15), 28.2 (C-16), 56.0 (C-17), 11.8 (C-18), 19.4 (C-19), 36.5 (C-20), 19.0 (C-21), 33.9 (C-22), 29.1 (C-23), 45.8 (C-24), 26.1 (C-25), 18.8 (C-26), 19.8 (C-27), 23.1 (C-28), 12.0 (C-29).

Chlorophyll a (4)

^{1}H NMR (500 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, H2-7b), 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, H-1'), 5.11 (1H, t, *J* = 7.2 Hz, H-2'), 1.56 (3H, br s, H-17'), 0.82 (6H, d, *J* = 6.6 Hz, H-18' and H-19'), 0.76 (3H, d, *J* = 6.6 Hz, H-16'), 0.74 (3H, d, *J* = 6.6 Hz, H-20').

1,2-dilinoleoyl-3-linolenoylglycerol (5)

^{1}H 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), 1.97-2.08 (allylic, CH_2), 1.58-1.60 (β-CH_2), 1.23-1.36 (CH_2), 0.86 (t, *J* = 7.2, CH_3). ESI-MS *m/z* 877.7404 $[M+H]^+$ (calcd. 877.7280 for $C_{57}H_{97}O_6$), *m/z* 621.4938 $[DAG_{1,2}+Na]^+$ (calcd. 621.4853 for $C_{39}H_{66}NaO_4$), *m/z* 597.4948 $[DAG_{2,3}+H]^+$ (calcd. 597.4877 for $C_{39}H_{65}O_4$).

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extracts of *C. dichotoma* yielded **1**-**4** from the leaves; and **3** and **5** from the twigs. The structure of **1** was identified by comparison of its ^{1}H and ^{13}C NMR data (Table 1) with those reported in the literature for β-sitosteryl-3β-glucopyranoside-6'-*O*-palmitate (**1**) (Nguyen *et al.*, 2004).

The fatty acid in **1** was identified as palmitic acid through ESI-MS which gave an *m/z* 815.5130 $[M+H]^+$ corresponding to the molecular formula of $C_{51}H_{91}O_7$. The structures of **2**-**5** were identified as nervonyl 4-hydroxy-*trans*-cinnamate ester (**2**) (Ragasa *et al*., 2013a; Venkateswarlu *et al*., 2006), β-sitosterol (**3**) (Ragasa *et al*., 2014), chlorophyll a (**4**) (Ragasa *et al*., 2015) and 1,2-dilinoleoyl-3-linolenoylglycerol (**5**) (Ragasa *et al*., 2015) by comparison of their NMR data with those reported in the literature. The fatty acid which was esterified to the cinnamate in **2** was identified as nervonic acid based on ESI-MS. Compound **2** gave an *m/z* 507.3273 $[M+Na]^+$ which corresponded to a molecular formula of $C_{32}H_{52}NaO_3$. The triacylglycerol (**5**) was identified as 1,2-dilinoleoyl-3-linolenoylglycerol based on ESI-MS analysis. Compound **5** gave an *m/z* 877.7404 $[M+H]^+$ corresponding to the molecular formula of $C_{57}H_{97}O_6$; diacylglycerol *m/z* 621.4938 $[DAG_{1,2}+Na]^+$ corresponding to the molecular formula of $C_{39}H_{66}NaO_4$; and *m/z* 597.4948 $[DAG_{2,3}+H]^+$ corresponding to the molecular formula of $C_{39}H_{65}O_4$, which are consistent with linoleic acid (18:2) at C-1, linoleic acid (18:2) at C-2, and linolenic acid (18:3) at C-3 of **5**.

Table 1 Comparison of 125 MHz ^{13}C NMR and 500 MHz ^{1}H NMR data of **1** in $CDCl_3$ with the 150 MHz ^{13}C NMR and 600 MHz ^{1}H NMR data of β-sitosteryl-3β-glucopyranoside-6'-*O*-palmitate (SGP) in $CDCl_3$ (Nguyen et al., 2001).

Position β-Sitosterol	^{13}C, δ (1)	^{13}C, δ (SGP)	^{1}H, δ (1)	^{1}H, δ (SGP)
1	37.3	37.27		1.06 (m), 1.85 (m)
2	29.7	29.70		1.61 (m), 1.95 (m)
3	79.5	79.65	3.54 (1H, m)	3.54 (1H, m)
4	38.9	38.91		2.27 (1H, m), 2.36 (1H, m)
5	140.3	140.30		–
6	122.1	122.14	5.36 (1H, m)	5.38 (1H, m)
7	31.9	31.94		1.98 (2H, m)
8	31.9	31.88		1.52 (1H, m)
9	50.2	50.15		0.93 (1H, m)
10	36.7	36.70		–
11	21.1	21.07		1.02 (m), 1.56 (m)
12	39.7	39.76		1.18 (m), 2.02 (m)
13	42.3	42.33		–
14	56.7	56.76		1.01 (m)
15	24.3	24.30		1.08 (m), 1.12 (m)
16	28.2	28.26		1.83 (m), 1.86 (m)
17	56.1	56.11		1.12 (m)
18	11.8	11.85	0.68 (3H, s)	0.68 (3H, s)
19	19.3	19.37	1.00 (3H, s)	1.00 (3H, s)
20	36.1	36.19		1.36 (m)
21	18.8	18.76	0.92 (3H, d, 6.0)	0.92 (3H, d, 6.4)
22	33.9	33.94		1.00 (s), 1.34 (m)
23	26.1	26.10		1.18 (2H, m)
24	45.8	45.81		0.95 (m)
25	29.1	29.16		1.66 (m)
26	19.0	19.02	0.82 (3H, d, 7.0)	0.82 (3H, d, 6.8)
27	19.8	19.82	0.83 (3H, d, 7.0)	0.84 (3H, d, 6.8)
28	23.1	23.06		1.26 (bs)
29	12.0	11.97	0.84 (3H, t, 8.0)	0.84 (3H, t, 7.6)
Glucopyranoside				
1'	101.2	101.24	4.38 (1H, d, 7.5)	4.38 (1H, d, 7.7)
2'	73.6	73.45	3.36 (1H, dd, 7.5, 9.0)	3.35 (1H, dd, 7.7, 8.7)
3'	76.0	76.07	3.58 (1H, dd, 9.0, 10.0)	3.57 (1H, dd, 8.7, 9.9)
4'	70.1	70.23	3.38 (1H, dd, 9.0, 10.0)	3.38 (1H, dd, 9.9, 8.6)
5'	74.0	73.82	3.45 (1H, m)	3.45 (1H, m)
6'	63.2	63.41	4.27 (1H, dd, 12.0, 2.0)	4.29 (1H, dd, 12.1, 1.7)
			4.42 (1H, dd, 5.0, 12.0)	4.42 (1H, dd, 5.3, 12.1)
Palmitic acid				
1"	174.7	174.56		–
2"	34.2	34.26	2.34 (2H, t, 7.5)	2.34 (2H, t, 7.6)
3"	24.9	24.97	1.61 (2H, m)	1.61 (m)
4"	29.3	29.26		1.28 (bs)
5"	29.5	29.45		1.26 (bs)
6"	29.7	29.68		1.26 (bs)
7-12"	29.7	29.78		1.26 (bs)
13"	29.4	29.40		1.26 (bs)
14"	31.9	31.94		1.26 (bs)
15"	22.7	22.70		1.30 (bs)
16"	14.1	14.13	0.88 (3H, t, 7.0)	0.88 (3H, t, 7.1)

Although no biological activity tests were conducted on the isolated compounds, a literature search of **1-4** revealed that these have diverse bioactivities.

α-Sitosteryl-3α-glucopyranoside-6'-*O*-palmitate (**1**) was reported to exhibit cytotoxicity against Bowes (melanoma) and MCF7 (breast) cancer cell lines with IC_{50} values of 152 µM and 113 µM, respectively (Nguyen *et al.*, 2004). Furthermore, **1** exhibited cytotoxicity against human stomach adenocarcinoma (AGS) cell line with 60.28% growth inhibition (Tsai *et al*., 2010). In search of substances that inhibit the hemolytic activity of human serum against erythrocytes, **1** was evaluated on its anti-complement activity. Compound **1** was found to exhibit potent anti-complement activity (IC_{50} = 1.0 ± 0.1 µM) on the classical pathway of the complement, as compared to the positive control, tiliroside (IC_{50} = 76.5 ± 1.1 µM) (Yoon *et al.*, 2005).

A study reported that alkyl 4-hydroxy-*trans*-cinnamate ester compounds: docosyl and tetracosyl 4-hydroxy-*trans*-cinnamate caused NUGC cells to survive 67% on treatment with 50 µM (Kuo *et al.*, 2002). Furthermore, in the superoxide scavenging activity, alkyl 4-hydroxy-*trans*-cinnamate ester compounds: 1-tetradecyl 4-hydroxycinnamate and 1-eicosanyl 4-hydroxycinnamate exhibited IC_{50} values of 416 µM and 477 µM, respectively. In the DPPH radical scavenging activity, both compounds gave IC_{50} values of >100 µM (Venkateswarlu *et al*., 2006).

β-Sitosterol (**3**) was observed to have growth inhibitory effects on human breast MCF-7 and MDA-MB-231adenocarcinoma cells (Awad *et al.*, 2007). It was shown to be effective for the treatment of benign prostatic hyperplasia (Jayaprakasha *et al.*, 2007). It was also reported to attenuate β-catenin and PCNA expression, as well as quench radical *in-vitro*, making it a potential anticancer drug for colon carcinogenesis (Baskar *et al.*, 2010). It can inhibit the expression of NPC1L1 in the enterocytes to reduce intestinal cholesterol uptake (Jesch *et al.*, 2009). It was 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).

Chlorophyll (**4**) and its various derivatives are used in traditional medicine and for therapeutic purposes (Edwards, 1954). Natural chlorophyll and its derivatives have been studied for wound healing (Kephart, 1955), anti-inflammatory properties (Larato and Pfao, 1970), control of calcium oxalate crystals (Tawashi *et al.*, 1980), utilization as effective agents in photodynamic cancer therapy (Sternberg *et al.*, 1998; Nourse *et al.*, 1988; Henderson *et al.*, 1997), and chemopreventive effects in humans (Egner *et al.*, 2001; Egner *et al.*, 2003). A review on digestion, absorption and cancer preventive activity of dietary chlorophyll has been provided (Ferruzzi and Blakeslee, 2007).

CONCLUSION

Cordia dichotoma is a medicinal tree with many reported biological activities. This study reports on the isolation of compounds (**1-5**) from the dichloromethane extracts of the leaves and stems of *C. dichotoma*. Compounds **1**–**4** have been reported to possess anticancer and cytotoxic properties. The antioxidant property of **2**, cholesterol lowering effect of **3** and wound healing effect of **4** have also been reported. Thus, the medicinal properties of *C. dichotoma* maybe partly attributed to **1-4** which were reported to exhibit diverse biological activities.

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