Cytotoxic Oligostilbenoids from *Vatica odorata*

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Abstract: Five oligostilbenoids, (-)-*trans*-resveratrol-13-O-b-D-glucopyranoside 1, (-)-e-viniferin 2, (-)-lauvifonol 3 and (-)-hopeaphenol 4, (-)-vaticanol B 5, together with a gallic acid derivative, (-)-bergenin 6, were isolated from the acetone and methanol extracts of the tree bark of *Vatica odorata*. Establishment of the structures were made by means of their spectroscopic data, including UV, IR, NMR 1-D and 2-D, mass spectra and X-ray Crystallography analysis. The presence of compounds 1, 3 and 5 could be of chemotaxonomic significance of *Vatica*. Cytotoxic properties of the isolated compounds were evaluated against murine leukemia P-388 cells and *Artemia salina*, resulting that compound 4 was toxic with IC<sub>50</sub> values of 3.2 and 218.5mM respectively.

Key words: Oligostilbenoid, bergenin, *Vatica odorata*, cytotoxicity, P-388 cells.

INTRODUCTION

*Vatica odorata* (Dipterocarpaceae) is a medium size tree ranging from Indo-China to Malaysia, occurs in the lowland area at 350 – 500 m elevation. The plant can be easily identified from other Dipterocarpaceae species due to its hairy rough pink twigs and pale yellow flowers. To date, there are neither medicinal nor commercial values recorded for this particular species although Dipterocarpaceae species were known to produce high quality timber (Symington, 1974). The present investigation is a part of our ongoing studies on the oligostilbenoids of Dipterocarpaceae in which no phytochemical data was ever recorded on *Vatica odorata*.

MATERIALS AND METHODS

2.1 General Experimental Procedures:
Melting points (uncorrected) were determined on a micro-melting point apparatus. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. UV and IR spectra were measured with a Varian 100 Conc and FTIR Spectrum One Perkin-Elmer instruments, respectively. ¹H and ¹³C NMR spectra were recorded with a JEOL ECP400 spectrometer operating at 400 (¹H) and 100 (¹³C) MHz, using residual and deuterated solvent peaks as reference standards. MS spectra were measured at 70eV. HRFABMS were recorded on a JEOL JMS AX-500. Vacuum liquid chromatography (VLC) and radial chromatography were carried out using Merck Si gel 60 GF<sub>254</sub> and, for TLC analysis, precoated Si gel plates (Merck Kieselgel 60 GF<sub>254</sub>, 0.25 mm) were used.

2.2 Plant Material:
Samples of the tree bark of *V. odorata* were collected from Pulau Mata Kail, Belum Forest Reserve, Perak, Malaysia. The plant was identified by botanist, University Putra Malaysia, and a voucher specimen was deposited in the herbarium.

2.3 Extraction and Isolation:
The dried powdered tree bark (0.45 kg) of *V. odorata* was macerated with acetone (3 x 4L) followed by methanol (3 x 4L), and each extract was evaporated under reduced pressure to give dark brown residues.

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dried acetone extract (27.3g) was subjected to vacuum liquid chromatography (silica gel, n-hexane-EtOAc = 4.5:5.5) into five major fractions (A-E). Fraction E (5g) was further fractionated by flash column chromatography (silica gel, CHCl₃-MeOH 10:0 to 1:1) to give three semipurified fractions E1-E3. Recrystallisation of fraction E2 (0.8g) yielded 6 (12mg) while repetitive purification of fraction E1 (1.2g) by radial chromatography (silica gel, EtOAc-MeOH = 10:0 to 8:2 & CHCl₃-MeOH = 95:5) gave 1 (27mg). The MeOH (75g) extract was also subjected to fractionation using VLC (silica gel, n-hexane-EtOAc = 10:0, 8:2, 6:4, 4:6, and 2:8) into five major fractions F-I. Fraction G (2.2g) was refractored by flash column chromatography (silica gel, n-hexane-EtOAc = 10:0 to 8:2) followed by radial chromatography (silica gel, CHCl₃-MeOH = 10:0 to 8:2) afforded 2 (313mg) whereas purification of fraction H (3.7g) by the same methods yielded 5 (100mg). Fractionation of fraction J (6g) was done by flash column chromatography (silica gel, n-hexane-EtOAc = 10:0, 8:2, 6:4, 4:6, and 2:8 & EtOAc-MeOH = 10:0 to 7:3) into six subfractions J1-J6. Purification of subfraction J2 by radial chromatography (silica gel, CHCl₃-MeOH = 10:0, to 1:1) yielded 4 (61mg) while 3 (40mg) was obtained from subfraction J3 using the same method.

RESULTS AND DISCUSSION

We now reported for the first time the isolation of oligostilbenoids namely (-)-trans-resveratrol-3-O-b-D-glucopyranoside (1), (-)-e-viniferin (2), (-)-laevifonol (3), (-)-hopeaphenol (4), (-)-vaticanol B (5) and bergenin (6) from the acetone and methanol extracts of the bark. In addition, the biological activities of the isolated compounds against P-388 cells and Artimina salina, and their chemotaxonomic significance are also described.

Compound (1), isolated as white solids, showed a positive [M+H]+ ion in the high resolution FABMS at m/z 391, corresponding to a molecular formula C₁₄H₁₈O₁₄ which suggested that 1 is a glucoside derivative of a resveratrol. The presence of an anomic proton signal at d₆ 4.93 (d, J = 11.5 Hz) and a pair of doublets at d₆ 7.04 and 6.86 (J = 16.3 Hz) confirmed the existence of glucosyl moiety of trans-resveratrol. Other 1H and 13C chemical shifts were consistent to those reported for trans-resveratrol-3-O-b-D-glucopyranoside (Mattivi, 1995). The connectivity of the b-D-glucopyranoside unit at C-3 of 1 was independently established by the long range correlation observed between the anomeric proton signal of the glucosyl moiety and oxyaryl carbon at d C 158.3 (C-3). The occurrence of 1 was previously reported from V. pauciflora (Ito, 2003), V. rassak (Tanaka, 2000) and V. diospyroides (Soe, 1999). Other isolated oligostilbenoids were identified as (-)-e-(-)-e-viniferin (2), (-)-laevifonol (3), (-)-hopeaphenol (4) and (-)-vaticanol B (5) by spectral analysis and comparison with respective authentic samples.

Compound 6 was isolated as white needles (m. p. 242-244°C) from the most polar fraction of acetone extract. The HREIMS gave molecular ion at m/z 328 which corresponding to molecular formula C₁₄H₁₈O₁₄. Co-TLC and comparison of spectral data with those published confirmed its identity as bergenin which was previously isolated from Vatica (Soe, 1999; Sotheeswaran, 1985; O'Neill, 2004), Shorea (Paquette, 2004; Wollenweber, 1988; Corey, 1995), Vateria (O'Neill, 2004; Ito, 2003; Mishima, 2003) and Hopea (Tanaka, 2001). A single-crystal structure determination provides a relative stereochemistry of bergenin.

While oligostilbenoids found to be the main constituents of Dipterocarpaceae, the occurrence of 2 has no chemotaxonomic significance as it is regarded as the general precursor of oligostilbenoids. However, the presence of compound 1, 3 and 5 in V. odorata could be the important chemical characters for the chemotaxonomical analysis of Vatica as these metabolites were also reported from V. umbonata (Atun, 2004) and Vatica rassak (Tanaka, 2000). Moreover, the occurrence of 3 which is a unique oligostilbenoid formed from a condensation of 2 and ascorbic acid highlights the relationship between Vatica with Shorea.

Interestingly, the isolation of 4 which previously reported from V. umbonata (Atun, 2004) and V. oblingofolia (Zgoda-Pols, 2002) provide a relationship between Vatica and other Dipterocarp genera, given the fact that this metabolite has been found in species of Hopea (Sahidin, 2004; Tanaka, 2000; Sotheeswaran, 1993; Coggon, 1965), Neobalanocarpus (Weber, 2001), Shorea (Ito, 2000; Hakim, 2002), Vateria (Ito, 2001; Mishima, 2003; O'Neill, 2004) and Dipterocarpus (Muhtadi, 2006). Compound 6 which is also known as bergenitol, vakin and ardisic acid, is commonly found in Leguminous plants while its occurrence in Dipterocarp genera is increasingly reported. A preliminary toxicity test of the isolated compounds revealed only 4 was toxic to Artemia salina with IC₅₀ value of 218.5 mM. However, cytotoxic evaluation against P-388 cells indicated that 2, and 4 were found to be active with IC₅₀ values of 18.3 and 3.2 mM respectively. Despite a general observation indicating a smaller size of the oligostilbenoids tends to be more cytotoxic than the larger one, these cytotoxic data suggested that no regular pattern is observed between molecular size and cytotoxic properties of the oligostilbenoids as can be seen by comparison of the cytotoxic properties of compound 2 and 4 with those of 1, 3 and 5.
Fig. 1: Structures of isolated compounds from *Vatica odorata*.

Figure 2: X-Ray crystal structure of (-)-bergenin 6

<table>
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<th>Compounds</th>
<th>IC₅₀, mM</th>
<th>IC₅₀, mM</th>
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<tr>
<td>1</td>
<td>191.8</td>
<td>&gt;1278.8</td>
</tr>
<tr>
<td>2</td>
<td>18.3</td>
<td>&gt;1101.3</td>
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<tr>
<td>3</td>
<td>60.5</td>
<td>&gt;796.2</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
<td>218.5</td>
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<td>5</td>
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<td>6</td>
<td>&gt;304.9</td>
<td>&gt;1524.4</td>
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REFERENCES


Appendix 1: Supporting information

(-)-trans-Resveratrol-13-O-b-D-glucopyranoside (1)

MP: 220-222°C.

$[\alpha]_{D}$: -45° (c 0.1, MeOH).

RF: 0.55 (EtOAc-MeOH, 9.5:0.5).

IR (KBr): 3401, 2920, 1606, 1587, 1514, 1410, 964, 837 cm⁻¹.

UV/Vis $\lambda_{max}$ (MeOH) nm: 205, 215, 226, 306, 318.

$\lambda_{max}$ (MeOH) nm: 205, 215, 226, 306, 318.

H NMR (400 MHz, CD$_3$COCD$_3$: 7.40 (2H, d, J = 8.6 Hz, H-2/H-6), 7.45 (2H, d, J = 8.6 Hz, H-2'/H-6'), 6.80 (2H, br s, J = 7.4 Hz, H-1), 3.46, 3.52, 3.42, 3.54 (4H, m, H-2', H-3', H-4', H-5'), 3.90 (1H, br d, J = 11 Hz, H-6'), 3.74 (1H, br d, J = 11.7 Hz, H-6'b).

IR (KBr): 3401, 2920, 1606, 1587, 1514, 1410, 964, 837 cm⁻¹.

UV/Vis $\lambda_{max}$ (MeOH) nm: 205, 215, 226, 306, 318.

H NMR (400 MHz, CD$_3$COCD$_3$: 7.40 (2H, d, J = 8.6 Hz, H-2/H-6), 6.80 (2H, br s, J = 7.4 Hz, H-1), 3.46, 3.52, 3.42, 3.54 (4H, m, H-2', H-3', H-4', H-5'), 3.90 (1H, br d, J = 11 Hz, H-6'), 3.74 (1H, br d, J = 11.7 Hz, H-6'b).

(-)-e-Viniferin (2)

MP: 184-187°C.

$[\alpha]_{D}$: -39° (c 0.1, MeOH).

RF: 0.62 (CHCl$_3$-MeOH, 8:2).

IR (KBr): 3420, 2920, 1600, 1512, 834 cm⁻¹.

UV/Vis $\lambda_{max}$ (MeOH) nm: 203, 226, 322.

H NMR (400 MHz, CD$_3$COCD$_3$: 7.20 (2H, d, J = 8.4 Hz, H-2a/H-6a), 6.83 (2H, d, J = 8.6 Hz, H-3a/H-5a), 5.41 (1H, d, J = 5.5 Hz, H-7a), 4.46 (1H, d, J = 5.1 Hz, H-8a), 6.24 (3H, br s, H-10a/H-12a/H-14a), 7.17 (2H, d, J = 8.4 Hz, H-2b/H-6b), 6.73 (2H, d, J = 8.4 Hz, H-3b/H-5b), 6.91 (1H, d, J = 16.5 Hz, H-7b), 6.70 (1H, t, J = 16.5 Hz, H-8b), 6.32 (1H, d, J = 2.2 Hz, H-12b), 6.72 (1H, d, J = 2.2 Hz, H-14b).

H NMR (400 MHz, CD$_3$COCD$_3$: 7.20 (2H, d, J = 8.4 Hz, H-2a/H-6a), 6.83 (2H, d, J = 8.6 Hz, H-3a/H-5a), 5.41 (1H, d, J = 5.5 Hz, H-7a), 4.46 (1H, d, J = 5.1 Hz, H-8a), 6.24 (3H, br s, H-10a/H-12a/H-14a), 7.17 (2H, d, J = 8.4 Hz, H-2b/H-6b), 6.73 (2H, d, J = 8.4 Hz, H-3b/H-5b), 6.91 (1H, d, J = 16.5 Hz, H-7b), 6.70 (1H, t, J = 16.5 Hz, H-8b), 6.32 (1H, d, J = 2.2 Hz, H-12b), 6.72 (1H, d, J = 2.2 Hz, H-14b).

13C NMR (100 MHz CD$_3$COCD$_3$: 133.6 (C-1a), 127.9 (C-2a/C-6a), 116.1 (C-3a/C-5a), 158.2 (C-4a), 93.9 (C-7a), 57.1 (C-8a), 147.6 (C-9a), 106.9 (C-10a/C-14a), 159.9 (C-11a/C-13a), 102.1 (C-12a), 129.9 (C-1b), 128.6 (C-2b/C-6b), 116.4 (C-3b/C-5b), 158.2 (C-4b), 123.1 (C-7b), 130.2 (C-8b), 136.3 (C-9b), 119.8 (C-10b), 162.4 (C-11b), 96.8 (C-12b), 159.7 (C-13b), 104.2 (C-14b).

HRMS-EI: m/z [M+] calcd for C$_{28}$H$_{22}$O$_{6}$: 454.1425; found: 454.1416.

(-)-Laevifonol (3)

[\alpha]$_{D}$: -175° (c 0.1, MeOH).

RF: 0.55 (EtOAc-MeOH, 9.5:0.5).

IR (KBr): 3364, 2913, 1789, 1614, 1516, 1454, 1257, 835 cm⁻¹.

UV/Vis $\lambda_{max}$ (MeOH) nm: 203, 226, 284, 298.

H NMR (400 MHz, CD$_3$COCD$_3$: 6.76 (2H, m, H-2a/H-6a), 6.74 (2H, m, H-3a/H-5a), 5.03 (1H, br d, J = 7.3 Hz, H-7a), 3.26 (1H, d, J = 7.4 Hz, H-8a), 5.90 (2H, s, H-10a/H-14a), 6.15 (1H, t, J = 2.2 Hz, H-12a), 5.64 (2H, br s, H-10a/H-14a), 6.17 (1H, d, J = 2.2 Hz, H-12b), 7.13 (1H, br s, H-14b), 4.41 (1H, br s, H-4'), 4.21 (1H, m, H-5'), 3.97 (1H, dd, J = 4.4, 10 Hz, H-6'a), 4.05 (1H, dd, J = 2.2, 10.3 Hz, H-6'b).

13C NMR (100 MHz CD$_3$COCD$_3$: 131.8 (C-1a), 129.1 (C-2a/C-6a), 116.1 (C-3a/C-5a), 158.9 (C-4a), 95.0 (C-7a), 57.1 (C-8a), 146.0 (C-9a), 107.5 (C-10a/C-14a), 159.7 (C-13a), 159.8 (C-11a/C-13a), 102.5 (C-12a), 129.8 (C-1b), 128.2 (C-2b/C-6b), 115.8 (C-3b/C-5b), 158.4 (C-4b), 90.8 (C-7b), 57.1 (C-8b), 132.4 (C-9b), 123.4 (C-10b), 161.4 (C-11b), 97.2 (C-12b), 159.1 (C-13b), 110.0 (C-14b), 173.6 (C-2'), 81.4 (C-3'), 119.2 (C-4'), 90.0 (C-5'), 74.7 (C-6'), 75.9 (C-7'a, 7b').

HRMS-FAB: m/z [M - H]$^+$ calcd for C$_{34}$H$_{28}$O$_{12}$: 627.1318; found: 627.1408.

(-)-Hopeaphenol (4)

MP: 292-295°C.

[\alpha]$_{D}$: -399° (c 0.1, MeOH).

RF: 0.45 (n-Hexane-EtOAc, 1:9).

IR (KBr): 3400, 2898, 1614, 1600, 1515, 1456, 1247, 835 cm⁻¹.

UV/Vis $\lambda_{max}$ (MeOH) nm: 203, 230, 282.
5a/H-3a′/H-5a′), 5.75 (2H, d, J = 12.4 Hz, H-7a/H-7′a), 4.22 (2H, d, J = 12.4 Hz, H-8a/H-8′a), 6.55 (2H, d, J = 2.0 Hz, H-12a/H-12′a), 6.29 (2H, d, J = 2.0 Hz, H-14a/H-14′a), 6.88 (4H, d, J = 8.8 Hz, H-2b/H-6b/H-2′b/H-6′b), 6.55 (4H, d, J = 8.8 Hz, H-3b/H-5b/H-3′b/H-5′b), 5.79 (2H, br s, H-7b/H-7′b), 3.93 (2H, s, H-8b/H-8′b), 5.72 (2H, d, J = 2.2 Hz, H-12b/H-12′b), 5.16 (2H, d, J = 2.2 Hz, H-14b/H-14′b).

13C NMR (100 MHz CD3COCD3): 130.3 (C-1a/C-1′a), 129.6 (C-2a/C-6a/C-2′a/C-6′a), 114.6 (C-3a/C-5a/C-3′a/C-5′a), 157.9 (C-4a/C-4′a), 87.6 (C-7a/C-7′a), 49.1 (C-8a/C-8′a), 141.7 (C-9a/C-9′a), 120.5 (C-10a/C-10′a), 158.2 (C-11a/C-11′a), 100.5 (C-12a/C-12′a), 156.6 (C-14a/C-14′a), 134.5 (C-1-b/C-1′b), 128.6 (C-2b/C-6b/C-2′b/C-6′b), 115.4 (C-3b/C-5b/C-3′b/C-5′b), 154.9 (C-4b/C-4′b), 40.6 (C-7b/C-7′b), 47.6 (C-8b/C-8′b), 113.9 (C-9b/C-9′b), 117.9 (C-10b/C-10′b), 158.6 (C-11b/C-11′b), 94.6 (C-12b/C-12′b), 156.5 (C-13b/C-13′b), 110.6 (C-14b/C-14′b).


(-)-Vaticanol B (5)
MP: 243-245ºC.
[α]D: -48º (c 0.1, MeOH).
Rf: 0.60 (EtOAc-MeOH, 9.5:0.5).
IR (KBr): 3422, 2920, 1600, 1515, 1447, 834 cm−1.
UV/Vis λmax (MeOH) nm: 204, 212, 229, 284.

1H NMR (400 MHz, CD3COCD3): 7.21 (2H, d, J = 8.8, H-2a/H-6a), 6.77 (2H, d, J = 8.4 Hz, H-3a/H-5a), 5.76 (1H, d, J = 11.7 Hz, H-7a), 4.43 (1H, d, J = 11.1 Hz, H-8a), 6.26 (1H, d, J = 2.0 Hz, H-12a), 6.14 (1H, d, J = 2.0 Hz, H-14a), 7.17 (2H, d, J = 8.8 Hz, H-2b/H-6b), 6.68 (2H, d, J = 8.8 Hz, H-3b/H-5b), 5.14 (1H, d, J = 3.9 Hz, H-7b), 3.13 (1H, dd, J = 11.3, 3.9 Hz, H-8b), 6.05 (1H, s, H-12b), 6.38 (2H, d, J = 8.8, H-2c/H-6c), 6.50 (2H, d, J = 8.8, H-3c/H-5c), 4.09 (1H, dd, J = 11.3, 10.8 Hz, H-7c), 4.54 (1H, d, J = 10.8 Hz, H-8c), 6.16 (1H, d, J = 2.0 Hz, H-12c), 6.42 (1H, d, J = 2.0 Hz, H-14c), 7.19 (2H, d, J = 8.4 Hz, H-2d/H-6d), 6.78 (2H, d, J = 8.4 Hz, H-3d/H-5d), 5.34 (1H, d, J = 3.9 Hz, H-7d), 4.66 (1H, d, J = 4.7 Hz, H-8d), 6.08 (2H, d, J = 2.4 Hz, H-10d/H-14d), 6.30 (1H, t, J = 2.4 Hz, H-12d).

13C NMR (100 MHz CD3COCD3): 130.0 (C-1a), 129.4 (C-2a/C-6a), 116.0 (C-3a/C-5a), 157.9 (C-4a), 89.7 (C-7a), 48.2 (C-8a), 141.0 (C-9a), 123.7 (C-10a), 155.0 (C-11a), 109.2 (C-12a), 155.6 (C-13a), 104.9 (C-14a), 132.7 (C-1b), 129.9 (C-2b/C-6b), 114.8 (C-3b/C-5b), 155.2 (C-4b), 36.3 (C-7b), 52.4 (C-8b), 142.5 (C-9b), 114.9 (C-10b), 158.0 (C-11b), 95.7 (C-12b), 154.2 (C-13b), 121.4 (C-14b), 130.6 (C-1c), 128.5 (C-2c/C-6c), 115.1 (C-3c/C-5c), 156.0 (C-4c), 56.9 (C-7c), 48.4 (C-8c), 140.9 (C-9c), 122.6 (C-10c), 160.8 (C-11c), 94.9 (C-12c), 158.7 (C-13c), 106.3 (C-14c), 133.8 (C-1-d), 127.6 (C-2-d/C-6-d), 115.1 (C-3-d/C-5-d), 157.4 (C-4-d), 93.9 (C-7-d), 56.8 (C-8-d), 147.3 (C-9-d), 106.8 (C-10-d/C-14-d), 159.1 (C-11-d/C-13-d), 101.4 (C-12-d).

(-)-Bergenin (6)
MP: 240-242ºC.
[α]D: -30º (c 0.1, MeOH).
Rf: 0.56 (CHCl3-MeOH, 8:2).
IR (KBr): 3420, 2949, 1703, 1613, 1600, 1520, 1464 cm−1.
UV/Vis λmax (MeOH) nm: 215, 274, 315.

1H NMR (400 MHz, CD3COCD3): 3.48 (1H, ovlp. with HOD, H-2), 3.2 (1H, t, J = 8.8 Hz, H-3), 3.64 (1H, t, J = 8.8 Hz, H-4), 3.98 (1H, dd, J = 9.5, 10.3 Hz, H-4a), 6.98 (1H, s, H-7), 4.96 (1H, d, J = 10.3 Hz, H-10b), 3.83 (2H, br d, J = 10.3 Hz, H-11a/H-11b), 3.76 (3H, s, 9-OMe), 4.95 (s, 11-OH), 5.48 (br s, 3-OH), 5.68 (br s, 4-OH), 9.80 (s, 8-OH), 8.45 (s, 10-OH).

13C NMR (100 MHz CD3COCD3): 81.4 (C-2), 70.4 (C-3), 73.4 (C-4), 79.8 (C-4a), 163.2 (C-6), 117.8 (C-6a), 109.2 (C-7), 150.7 (C-8), 140.4 (C-9), 147.8 (C-10), 115.7 (C-10a), 71.8 (C-10b), 60.8 (C-11), 59.6 (9-OMe).