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Full Length Research Paper

Cytotoxic oligostilbenes from *Shorea hopeifolia*

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Phytochemical and cytotoxicity investigations on the compounds from stem bark of *Shorea hopeifolia* were conducted. Four oligostilbenes of (-)-ε-viniferin (1), (-)-ampelopsin E (2), (-)-hopeaphenol (3) and shoreaphenol (4) together with a coumarin of scopoletin (5) have been isolated and identified from the acetone extract of *S. hopeifolia*. The chemical structures of the isolated compounds were elucidated by spectroscopic methods including UV, IR, NMR and MS, and also by comparison with the literature data. Cytotoxic properties of the isolated compounds were evaluated against human hepatoma (HepG2) and Chang's liver cells. The results indicated that compound 3 was most cytotoxic towards HepG2 cells with CC_{50} value of 4.5 µg/ml.

Key words: Dipterocarpaceae*, Shorea hopeifolia,* oligostilbenes, cytotoxicity.

INTRODUCTION

The Dipterocarpaceae is relatively a large family of tropical plants that consists of 16 genera and approximately 600 species (Cronquist, 1981). *Shorea* is the largest and economically important genus of this family with at least 167 species. This genus is widely distributed in the Southeast Asia regions especially in Malaysia and Indonesia (Symington, 1974). In Peninsula Malaysia, *Shorea* is also known as Balau, Meranti Pa'ang, Meranti Damar Hitam and Meranti Merah (Burkill, 1966). The *Shorea* wood is used for planks, building construction, furniture and plywood industry (Henye, 1987). Meanwhile, the resin is used for varnish glues, torch fuel, medicine for diarrhea, skin diseases, dysentery, gonorrhoea (Misra and Ahmad, 1997) and cosmetic (Westphal and Battermann, 2010). Dipterocarpaceae plants are a rich source of oligostilbenes such as resveratrol dimers, trimers, tetramers, hexamers, heptamers and octamers (Ito, 2011; Lin and Yao, 2006). These compounds exhibited a variety of significant bioactivities including anti-bacterial (Nitta et al., 2002), anti-fungal (Bokel et al., 1988; Kusuma and Tachibana, 2007), anti-babesial (Subeki et al., 2005), anti-tumor (Saroyobudiono et al., 2008; Jang et al., 1997) and anti-HIV (Dai et al., 1998). *Shorea hopeifolia* (Heim.) Sym. (Yellow Meranti) is a species of *Shorea* in the Dipterocarpaceae family. The local name is Damar Siput Jantan, Seraya Kuning Jantan (Malaysia); Damar Kunyit, Karambuku (Indonesia); and Kalunti (Philippines). This species usually grows in Malaysia, Indonesia and Philippines (Ashton, 1995). Chemical analysis of cellulose content, pentosan and lignin was done on *S. hopeifolia* (Sudradjat, 1980), but no study has been carried out in terms of its chemical constituents Thus, the objective of this research was to isolate and characterize oligostilbenes from the acetone extract of the stem bark of *S. hopeifolia* and determine their cytotoxicity against hepatoma and non-malignant cells. In addition, the distribution of these secondary metabolites in *S. hopeifolia* will be described.

MATERIALS AND METHODS

Plant

The stem bark of *S. hopeifolia* was collected from Gunung Angsi, Ulu Bendul Negeri Sembilan, Malaysia and a voucher specimen (WYA180) was deposited at the Herbarium of Universiti Kebangsaan Malaysia (UKMB). This species has been identified by a botanist, Mr. Sani Miran Universiti Kebangsaan Malaysia.

Extraction and isolation

The dried powdered of stem bark of *S. hopeifolia* (300 g) was

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extracted with acetone by Soxhlet apparatus for about 8 h. The extract was concentrated using rotary evaporator to yield a brownish acetone extract (78.1 g, 26%). A portion (30 g) of the acetone extract was fractionated by vacuum liquid chromatography (VLC) eluted with *n*-hexane: EtOAc (increasing polarity of EtOAc). The eluates that showed the same profile on thin layer chromatography (TLC) chromatogram were combined to give five fractions (A to E). Further purification of fraction A (56.0 mg) by column chromatography using $CHCl_3$:MeOH (8.5:1.5) afforded compound 1 (2.0 mg). Fraction B (25.0 mg) was refractionated with radial chromatography (*n*-hexane: EtOAc, 2.5:7.5) followed by preparative TLC ($CHCl_3$:MeOH, 8.5:1.5) to give compound 2 (5.0 mg). Compound 3 (500 mg) was obtained in a pure form after VLC of fraction E. Purification of fraction D (50.0 mg) over preparative TLC (*n*-hexane:EtOAc, 3:7) and Sephadex LH-20 column chromatography afforded compound 4 (6.0 mg). Fraction C (34.5 mg) was further purified by flash column chromatography (*n*-hexane:EtOAc, 8:2) to afford compound 5 (1.5 mg).

Compound identification

^{1}H and ^{13}C-APT nuclear magnetic resonance (NMR) spectra were recorded in acetone-d_6 using JEOL ECP400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Ultraviolet (UV) spectra were recorded on Shimadzu UV-160 (200 to 400 nm). Infrared (IR) spectra were recorded on a Perkin-Elmer GX FTIR spectrometer with chloroform as solvent. Column chromatography was carried out on Kieselgel 60. Melting points were measured by Stuart SMP10 melting point apparatus and were uncorrected. Optical rotations were recorded on JASCO DIP-370 digital polarimeter (589 nm). TLC was performed on pre-coated silica gel (Merck, Kieselgel 60 F_{254} 0.25 mm) and detected by UV light (254 nm) or by $CeSO_4$ spraying reagent followed by heating. ESIMS spectra were recorded on a GCxGC-ToFMS spectrometer.

(-)-ε-Viniferin (1)

Yellow amorphous powder (2.0 mg), mp: 185°C (lit. mp: 190 to 193 °C), optical rotation $[\alpha]_D^{20}$ -40° in MeOH (c = 0.1), UV λ_{max} (MeOH) nm: 229, 325. IR (NaCl) ν_{max} cm^{-1}: 3366, 2920, 1606, 1441, 1241,1168 and 830. ESIMS *m/z* 455 $[M+H]^+$ $C_{28}H_{22}O_6$. ^{1}H NMR δ 7.44 (2H, d, *J* = 8.1 Hz, H-2a/H-6a), 6.85 (2H, d, *J* = 8.8 Hz, H-3a/H-5a), 5.36 (1H, d, *J* = 4.8 Hz, H-7a), 4.36 (1H, d, *J* = 4.8 Hz, H-8a), 6.15 (2H,d, *J* = 2.2 Hz, H-10a/H-14a), 6.22 (1H, d, *J* = 2.2 Hz, H-12a), 7.21 (2H, d, *J* = 8.4 Hz, H-2b/H-6b), 6.82 (2H, d, *J* = 8.2 Hz, H-3b/H-5b), 6.98 (1H, d, *J* = 16.4 Hz, H-7b), 7.07 (1H, d, *J* = 16.8 Hz, H-8b), 6.58 (1H, d, *J* = 2.0 Hz, H-12b) and 6.68 (1H, s, H-14b). ^{13}C-APT NMR δ 133.6 (C-1a), 127.9 (C-2a/6a), 116.1(C-3a/5a), 158.2 (C-4a), 93.9 (C-7a), 57.1 (C-8a), 147.6 (C-9a), 106.9 (C10a/14a), 159.9 (C-11a/13a), 102.1 (C-12a), 129.9 (C-1b), 128.6 (C-2b/6b), 116.4 (C-3b/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) and 104.2 (C-14b).

(-)-Ampelopsin E (2)

White amorphous powder (5.0 mg), mp: 180°C (lit. mp: 184 °C), optical rotation $[\alpha]_D^{20}$ -94° in MeOH (c = 0.1), UV λ_{max} (MeOH) nm: 225, 325. IR (NaCl) ν_{max} cm^{-1}: 3367, 2947, 1655, 1451,1114. ESIMS *m/z* 681 $[M+H]^+$ $C_{42}H_{32}O_9$. ^{1}H NMR δ 4.54 (2H, d, *J*=5.0 Hz, H-8a/H-8c), 5.42 (2H, d, *J*=5.0 Hz, H-7a/H-7c), 6.16 (2H, t, *J*=2.0 Hz, H-12a/H-12c), 6.24 (4H, d, *J*=2.0 Hz, H-10a/H-14a/H-10c/H-14c), 6.45 (1H, s, H-12b), 6.59 (1H, d, *J*=16.0 Hz, H-8b), 6.62 (2H, d, *J*=8.4 Hz, H-3b/H-5b), 6.66 (1H, d, *J* =16 Hz, H-7b), 6.84 (4H, d, *J*=8.4 Hz, H-3a/H-5a/H-3c/H-5c), 6.93 (2H, d, *J*=8.8 Hz, H-2b/H-6b) and 7.24 (2H, d, *J*= 8.4 Hz, H-2a/H-6a/H-2c/H-6c). ^{13}C-APT NMR δ 57.8 (C-8a/8c), 91.2 (C-12b), 93.9 (C-7a/7c), 102.9 (C-12a/12c), 106.7 (C-10a/14a/10c/14c), 115.9 (C-3b/5b), 116.0 (C-3a/5a/3c/5c), 120.0 (C-10b/14b), 122.0 (C-7b), 127.8 (C-2a/6a/2c/6c), 128.2 (C-2b/6b), 129.0 (C-9b), 133.2 (C-1b), 133.6 (C-1a/1c), 133.7 (C-8b), 147.1 (C-9a/9c), 158.1 (C-4b), 158.3 (C-4a/4c),159.7 (C-11a/13a/11c/13c) and 162.5 (C-11b/13b).

(-)-Hopeaphenol (3)

White amorphous powder (500 mg), mp: 292°C (lit. mp: 290°C), optical rotation $[\alpha]_D^{20}$ -396° in MeOH (c = 0.1), UV λ_{max} (MeOH) nm: 203, 230, 282. IR (NaCl) ν_{max} cm^{-1}: 3411, 2950, 1645, 1453. ESIMS *m/z* 907 $[M+H]^+$ $C_{52}H_{42}O_{12}$. ^{1}H NMR δ 3.93 (1H, s, H-8b), 4.21 (1H, d, *J*=12.4 Hz, H-8a), 5.16 (1H, d, *J*=2.1 Hz, H-14b), 5.73 (1H, d, *J*=12.4 Hz, H-7a), 5.80 (1H, br s, H-7b), 5.71 (1H, d, *J*=2.2 Hz, H-12b), 6.29 (1H, br s, H-14a), 6.53 (1H, br s, H-12a), 6.77 (2H, d, *J*=8.0 Hz, H-3a/H-5a), 6.54 (2H, d, *J*= 8.8 Hz, H-3b/H-5b), 6.89 (2H, d, *J*=8.0 Hz, H-2b/H-6b) and 7.12 (2H, d, *J*=8.8 Hz, H-2a/H-6a). ^{13}C-APT NMR δ 41.3 (C-7b), 48.2 (C-8b), 49.8 (C-8a), 88.3 (C-7a), 95.2 (C-12b), 101.1 (C-12a), 106.4 (C-14a), 111.3 (C-14b), 115.2 (C-3b/5b), 116.0 (C-3a/5a), 118.6 (C-10b), 121.1 (C-10a), 129.3 (C-2b/6b), 130.3 (C-2a/6a), 130.9 (C-1a), 135.2 (C-1b), 140.5 (C-9b), 142.4 (C-9a), 155.6 (C-4b), 157.1 (C-13b), 157.2 (C-13a), 158.5 (C-4a), 158.8 (C-11a) and 159.2 (C-11b).

Shoreaphenol (4)

Bright yellow amorphous powder (6.0 mg), mp: 242°C (lit. mp: 240°C), optical rotation $[\alpha]_D^{20}$ +45° in MeOH (c = 0.1), IR (NaCl) ν_{max} cm^{-1}: 3300, 1650, 1605, 1500, 865 and 835. ESIMS *m/z* 467 $[M+H]^+$ $C_{28}H_{18}O_7$. ^{1}H NMR δ 6.12 (1H, br s, H-7b), 6.52 (2H, d, *J*=8.8 Hz, H3b/H-5b), 6.85 (2H, dd, *J*=8.8, 1.1 Hz, H-2b/H-6b), 6.55 (1H, d, *J*=2.6 Hz, H-12a), 6.68(1H, d, *J*=2.6 Hz, H-14a), 6.97(2H, d, *J*=8.8Hz, H-3a/H-5a), 7.69 (2H, d, *J*=8.8 Hz, H-2a/H-6a), 7.02 (1H, d, *J*=2.2 Hz, H-12b), 7.32 (1H, d, *J*=2.1 Hz, H-14b), 8.98 (1H, br s, OH-4a), 8.85 (2H, br s, OH-11a/13b) and 8.38 (1H, br s, OH-4b). ^{13}C-APT NMR δ 56.1 (C-7b), 102.5 (C-12b), 103.1 (C-12a), 108.8 (C-14a), 112.0 (C-14b), 113.9 (C-10a), 115.6 (C-3b/5b), 116.4 (C-8a), 116.7 (C-3a/5a), 122.3 (C-1a), 122.9 (C-10b), 128.4 (C-2b/6b), 129.7 (C-9b), 130.5 (C-1b), 130.9 (C-2a/6a), 135.2 (C-9a), 153.3 (C-7a), 154.9 (C-11b), 156.3 (C-13b), 156.5 (C-4b), 157.7 (C-13a), 158.5 (C-11a), 159.8 (C-4a) and 196.6 (C-8b).

Scopoletin (5)

Pale yellow amorphous powder (1.5 mg), mp: 210°C (lit. mp: 208-210°C), UV λ_{max} (MeOH) nm: 204, 227, 259, 289 and 344. IR (NaCl) ν_{max} cm^{-1}: 3337, 1702, 1606,1566, 1289 and 1141. ESIMS *m/z* 193 $[M+H]^+$ $C_{10}H_8O_4$. ^{1}H NMR δ 3.90 (3H, s, -OCH_3), 6.16 (1H, d, *J*= 9.6 Hz, H-3), 6.78 (1H, s, H-8), 7.20 (1H, s, H-5) and 7.84 (1H, d, *J*=9.5 Hz, H-4). ^{13}C-APT NMR δ 56.7 (OCH_3), 103.8 (C-8), 109.9 (C-5), 112.1 (C-4a), 113.3 (C-3), 144.7 (C-4), 146.0 (C-6), 151.2 (C-8a), 151.9 (C-7) and 161.4 (C-2).

Cell culture

The human hepatoma (HepG2) and non-malignant Chang's liver cell lines were kindly provided by Biocompatibility Laboratory, Department of Biomedical Sciences, Universiti Kebangsaan

Malaysia. The HepG2 cells were cultured in Dulbecco's modified eagle's medium and Chang's liver cells in RPMI 1640 (Flowlab) supplemented with 10% foetal bovine serum (Gibco), penicillin (50 μg ml^{-1}) and streptomycin (50 μg ml^{-1}) (Gibco). Cells were maintained in humidified air with 5% CO_2 at 37°C. Cells were harvested using 0.25% trypsin (Hyclone) when 70 to 80% confluent in culture.

Thiazolyl blue tetrazolium bromide (MTT) assay

Briefly, 200 μl of cells (1 × 10^4 cells) were seeded into 96 well plates and incubated overnight. The following day, cells were then treated with 20 μl of various concentrations of extract (1.56 to 200 μg ml^{-1}) before further incubation for 72 h. At the end of this incubation, 20 μl of MTT (Sigma) (2 mg ml^{-1} in phosphate buffered saline (PBS)) was added to each well and incubated for another 4 h at 37°C. The formazan crystals were dissolved in 100 μl of dimethyl sulfoxide (DMSO) and the absorbance was determined at 570 nm using a multi-plate reader (BioRad). The absorbance value that was determined for cells cultured in complete media without plant extract was based on 100% viable cells. Each concentration of the extract was assayed in triplicate (Ariffin et al., 2009). The 50% cytotoxic concentration (CC_{50}) value was determined.

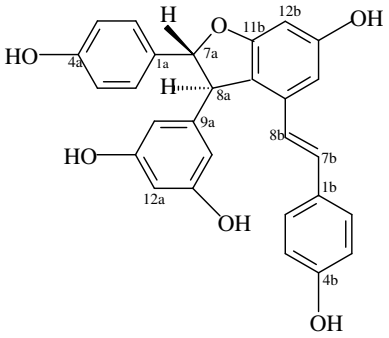
RESULTS AND DISCUSSION

The isolation of acetone extract of the stem bark of *S. hopeifolia* using several chromatographic techniques yielded four oligostilbenes and a coumarin. The structures of the compounds shown in Figure 1 were established on the basis of their spectral data, including UV, IR, NMR, MS, and comparison with literature data.

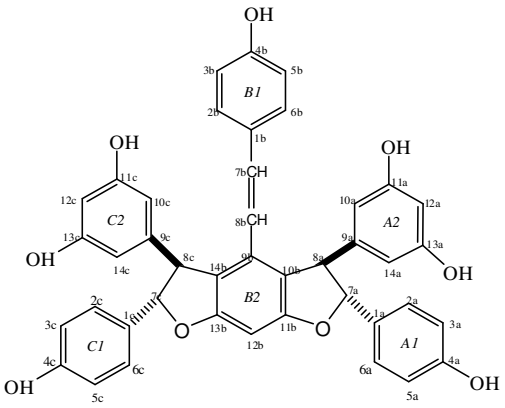
(-)-ε-Viniferin (1) is regarded as the general precursor for the oligostilbenes which was found in many species of *Shorea*, *Hopea*, *Vatica* and *Dipterocarpus,* and it is a chemical marker of Dipterocarpaceae plants. (-)-ε-Viniferin was reported earlier from *Vitis heyneana* (Li et al., 1996). (-)-Ampelopsin E (2) is a trimer stilbene which was first reported in *Ampelopsis brevipedunculata* (Vitaceae) (Oshima and Ueno, 1993). This compound was also found in *Shorea gibbosa* from Yellow Meranti group (Saroyobudiono et al., 2008). The presence of (-)-hopeafenol is very common in *Shorea* species. Previous studies have reported the isolation of these compounds from several species such as *Shorea hemsleyana* (Ito et al., 2000), *Shorea seminis* (Aminah et al., 2002), *Shorea balangeran* (Tukiran et al., 2005), *Shorea robusta* (Sal) (Varshney and Dayal, 2006) and *Shorea ovalis* Blume (Hadi and Noviany, 2009). It is also usually available in other genus such as *Hopea*, *Diptercarpus*, *Neobalanocarpus* and *Vatica*. Based on these facts, it was concluded that (-)-hopeafenol is the chemical marker of the family Dipterocarpaceae. Shoreaphenol (4), a dimer containing benzofuran ring, was reported earlier from *S. robusta* (Balau) and also found in *Shorea talura* (White Meranti) (Saraswathy et al., 1992). Thus, the presence of this compound in some species of *Shorea* could be one important chemical marker for the chemotaxonomical analysis of the genus. Scopoletin (5) is not in the same class with oligostilbenes, but is derived from the same route called shikimic acid pathway which participate in the biosynthesis of most plant phenolics. This compound is commonly present with oligostilbenes in Dipterocarpaceae plants. It was reported for the first time in the family of Dipterocarpaceae from *Shorea worthingtonii* and *Vatica obscura* (Gunawardana et al., 1979). In addition the isolation was also reported from *S. talura* (Venkatramaiah and Rao, 1983) and *Shorea pinanga* Screff (Syah et al., 2009).

The cytotoxic activities of the crude extract, (-)-ε-viniferin, (-)-ampelopsin E, (-)-hopeaphenol, shoreaphenol and scopoletin were evaluated against Chang and HepG2 cell lines. The acetone extract and compounds 1 to 5 were found to be inactive and did not induce cytotoxic effect in Chang's liver cell, a non-maglinant cell line (Table 1). However, the acetone extract, compound 2 and 3 showed cytotoxicity against the HepG2 cells with CC_{50} values of 17.5, 22.5 and 4.5 μg/ml, respectively.

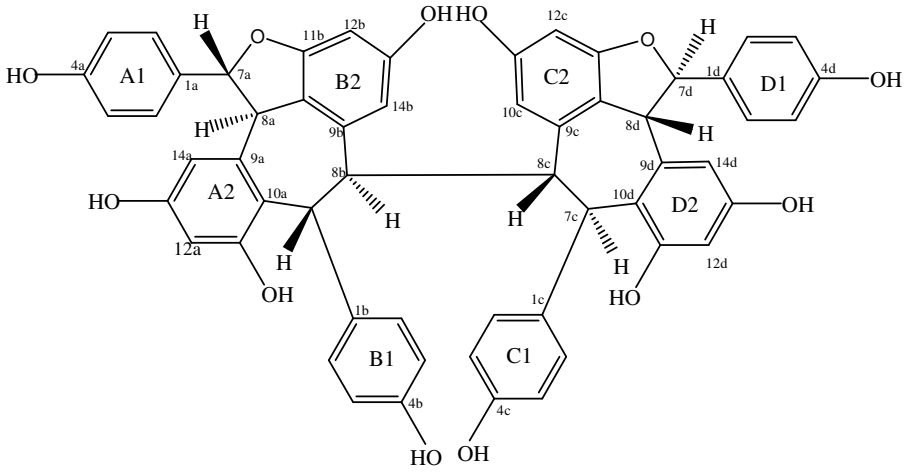
Compounds which demonstrated the CC_{50} value of more than 10 to 25 μg/ml can be considered as weak cytotoxicity while those with the CC_{50} value of less than 5.0 μg/ml were considered very active (Shier, 1991). Compound 3 was the most cytotoxic on HepG2 cells as compared to others. These cytotoxic data showed a correlation between degree of cytotoxicity and the molecular size of oligostilbenes. The larger oligostilbenes are more cytotoxic than the smaller ones. From the results, the number of hydroxyl substituents on the oligomer may play an essential role in the cytotoxicity activity. Difference in activity of stilbenes was also suggested (Yoo et al., 2007). We considered that (-)-hopeaphenol which was the most active compound was the main contributor in synergetic effects of the acetone extract in the increased cytotoxic activity. (-)-Hopeaphenol has also been reported to have potent cytotoxicity on the human epidermoid carcinoma of the sopharynx (Guebailia et al., 2006) and murine leukemia P-388 cells (Latip et al., 2011; Muhtadi et al., 2006; Sahidin et al., 2004). These results, also support previous studies which reported that compound 2 showed strong cytotoxic activity against rat hepatocytes (Oshima and Ueno, 1993) and murine leukemia cells P-388 (Saroyobudiono et al., 2008). Although, compound 1 and 5 are inactive against the Chang and HepG2 cells, they have been reported active against other tumor cells. For example compound 1 showed inhibitory activity on MCF-7 human breast cancer cells (Amico et al., 2009), myeloma cell U266 (Barjot et al., 2007) and human adenocarcinoma colon cells (Marel et al., 2008). Mean-while, compound 5 exhibited cytotoxic activity against human melanoma cell A375 (Khuda-Bukhsh et al., 2010), KB cell lines (Pan et al., 2004) and tumoral lymphocytes cell (Manuele et al., 2006). This study indicates that the crude extract and several pure compounds from stem



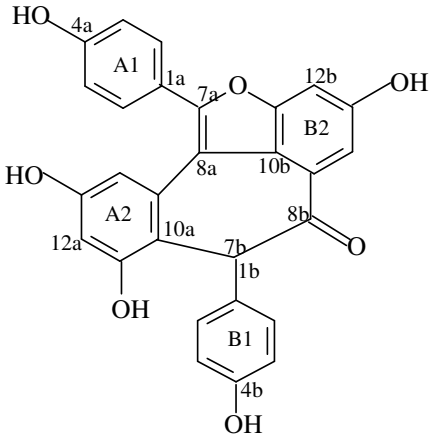
(-)-ε-Viniferin (1)



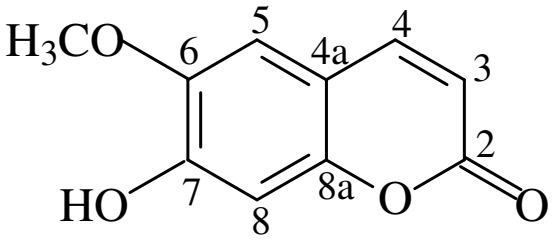
(-)-Ampelopsin E (2)



(-)-Hopeaphenol (3)



Shoreaphenol (4)



Scopoletin (5)

Figure 1. Compounds from stem bark of *S. Hopeifolia*.

Table 1. CC_{50} of compounds and extract in cytotoxicity assay.

Compound	Chang's cell CC_{50} (µg/ml)	HepG2 cell CC_{50} (µg/ml)
(-)-ε-Viniferin (1)	> 200	> 200
(-)-Ampelopsin E (2)	> 200	22.5 ± 0.8
(-)-Hopeaphenol (3)	> 200	4.5 ± 0.3
Shoreaphenol (4)	> 200	> 200
Scopoletin (5)	> 200	> 200
Acetone extract	> 200	17.5 ± 1

bark of *S. hopeifolia* have potentials to be developed as chemoprevention from liver cancers due to the selectivity towards hepatoma cells over non-malignant cells.

Conclusion

Four oligostilbenes of (-)-ε-viniferin (1), (-)-ampelopsin E (2), (-)-hopeaphenol (3), shoreaphenol (4) and a coumarin of scopoletin (5) were isolated from the acetone extract of the stem bark of *S. hopeifolia.* To the best of our knowledge, this is the first report of oligostilbenes from *S. hopeifolia*. Acetone extract of *S. hopeifolia*, (-)-ampelopsin E and (-)-hopeaphenol were cytotoxic to cancer cells but not to normal cells, thus having potential for development as anti-cancer drugs.

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