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Chemical Constituents and Cytotoxic Activity of *Polyalthia cauliflora* var. *cauliflora*

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ABSTRACT

Phytochemical investigation of the stem bark of *Polyalthia cauliflora* var. *cauliflora* has led to the isolation of two chalcones and an alkaloid; 2', 4'-dihydroxy-3'-methoxychalcone (1), 2', 4'-dihydroxychalcone (2) and liriodenine (3). 2', 4'-dihydroxy-3'-methoxychalcone (1) n was found to be cytotoxic against HL-60, MCF-7 and HeLa cancer cell lines with IC_{50} value of 12.2, 5.1 and 12.5 μg mL^{-1}, respectively. 2', 4'-dihydroxy-3'-methoxychalcone may prove to be useful in cancer treatment and prevention. The aims of this study were to extract, fractionate and isolate the chemical constituents from the stem bark of *Polyalthia cauliflora* var. *cauliflora*. Various chromatographic techniques including glass column chromatography, preparative thin layer chromatography and centrifugal chromatography had been used in this study. The isolated compounds were elucidated using several spectroscopic techniques including ^{1}H and ^{13}C NMR, IR, UV-Vis, mass spectroscopy and comparison with literature. Potential and sufficient amount of compounds were subjected to cytotoxic activity against HL-60, MCF-7 and HeLa cancer cell lines.

Key words: Annonaceae, *Polyalthia cauliflora*, chalcone, alkaloid, cytotoxic

INTRODUCTION

Annonaceae, a family of flowering plant consisting of trees, shrubs or rarely lianas is also known as custard apple family or 'kenanga' in Malaysia. It is the largest family in Magnoliales where it contains more than 130 genera and about 2300 to 2500 species (Mabberley, 1987). The genus *Polyalthia* (Annonaceae) consists of about 120 species of shrubs and trees. This genus is widely distributed in tropical and subtropical (Connolly *et al*., 1996). Alkaloid, terpenes, benzopyrans and flavonoids have been isolated from *Polyalthia* species (Abu Zarga and Shamma, 1982; Gonzalez *et al*., 1995; Islam *et al*., 2001; Kijjoa *et al*., 1990). Previous chemical investigation on *Polyalthia beccarii* (Hooker, 1875) and *Polyalthia cauliflora* Jossang *et al*. (1982) reported several bisaporphine-typed of alkaloids.

Polyalthia has been used as folk medicine in many tropical countries. In India, *Polyalthia* plants has been used as bitter tonic, abortifacient, febrifuge, a cure for scorpion stings, high blood pressure and as respiratory stimulant (Padmaa and Khosa, 2009). In addition, seeds and bark of *P. longifolia* are used as febrifuge in the Balasore district of Orissa (Raghunathan and Mitra, 1982). In Thai, a water decoction of the root of *P. evecta* has been used by the North-Eastern natives as a galactagogue (Kanokmedhakul *et al*., 1998). Furthermore, *P. lateriflora* was used to

treat skin infection (Wiart, 2000) and the alkaloids isolated from its stem bark have been reported for antibacterial and antifungal activities (Hasan *et al*., 1988). *Polyalthia cauliflora* was used by the Kelabit community in Bario, Sarawak for birth control (Fasihuddin *et al*., 1995).

Chalcone, a type of compound isolated from *P. cauliflora* var. *cauliflora* is an aromatic ketone which forms the central core for a variety of important biological compounds (Mandge *et al*., 2007). Chalcones and their derivatives are also medicinally important as they were reported to display various biological activities such as antioxidant, antimicrobial, antibacterial, antifungal, antitumor and anti-inflamantory (Alam *et al*., 2004; Alam and Mostahar, 2005; Azad *et al*., 2007; Lotulung *et al*., 2008; Oyedapo *et al*., 2008). Some chalcones showed the ability to block voltage-dependent potassium channels (Yarishkin *et al*., 2008). Chalcone is an intermediate in the biosynthesis of flavonoid which substance is widespread in plants with an array of biological activities (Martens and Mithofer, 2005; Mostahar *et al*., 2007).

The intention of this study was to isolate the chemical constituents from the methanolic extract of the stem bark of *P. cauliflora* var. *cauliflora*. The isolation and purification of the non alkaloid fraction has led to the isolation of two chalcone; 2', 4'-dihydroxy-3'-methoxychalcone and 2', 4'-dihydroxychalcone while the isolation of the alkaloidal fraction yielded an alkaloid; liriodenine.

MATERIALS AND METHODS

General experimental procedures: The ^{1}H-NMR and ^{13}C-NMR were recorded in chloroform-D on Bruker 300 Ultrashield NMR spectrometer measured at 300 and 75 MHZ. Chemical shifts are reported in ppm and the coupling constants are given in Hz. Melting point was taken on a hot stage Gallen Kamp melting point apparatus with microscope and was uncorrected. The Infrared (IR) was recorded on the Perkin Elmer spectrum one FT-IR spectrometer. The Ultraviolet (UV) spectra were recorded on Shimadzu UV-Vis 160i. The mass spectra were measured on Perkin Elmer Clarus 600T spectrometer 70 eV. Glass column used silica gel 60 230-400 mesh ASTM (Merck 1.09385), centrifugal thin layer chromatography used silica gel 60 PF_{254} (Merck catalog number: 1.07749). Aluminum supported silica gel 60 F_{254} was used for analytical thin layer chromatography while glass supported silica gel 60 F_{254} was used for preparative thin layer chromatography.

Extraction and isolation: The stem bark of *P. cauliflora* var. *cauliflora* was collected from Kuala Keniam, Pahang and a voucher specimen (UiTM64/2008) was deposited at the Faculty of Applied Sciences Herbarium, Universiti Teknologi Mara (UiTM), Malaysia. The stem bark (350 g) was air-dried, ground and macerated in methanol for several times. The extract was filtered and concentrated under reduced pressure. The crude extract (16.25 g) was subjected to acid-base extraction yielding a non-alkaloidal fraction that was subjected to silica gel column chromatography and eluted with hexane 100% and increasing polarity with DCM, EA and MeOH to afford 52 fractions. Fractions with similar profile on analytical TLC were pooled together to yield 12 sub fractions. Sub fraction 10 was subjected to purification by multiple development of Preparative Thin Layer Chromatography (PTLC) using hexane: ethyl acetate 9:1 system to afford compound 1. Re-column chromatography and further purification using multiple development-preparative thin layer chromatography [Hex:DCM (4:6)] of subfraction 12 gave compound 2. as yellow oil. The alkaloidal crude (4.9374 g) was subjected to fractionation using Vacuum Liquid Chromatography (VLC) with various composition of solvent system [Hex: DCM (5:5, 0:10) and DCM: MeOH (9.5:0.5, 9:1, 8.5:1.5, 8:2,5:5, 0:10)] to yield 11 fractions. Fraction 3 was subjected to centrifugal chromatography to afford compound 3.

2', 4'-dihydroxy-3'-methoxychalcone (1): Yellow oil MS m/z: 270 $C_{16}H_{14}O_4$. UV λ_{max} nm MeOH: 201, 245, 253, 279, 290, 311, 360, 370. IR cm^{-1}: 3434, 2987, 1638, 1263.

2',4'-dihydroxychalcone (2): Yellow needle crystal MS m/z: 241 $C_{15}H_{12}O_3$. UV λ_{max} nm MeOH: 202, 208, 246, 277, 294, 313, 317, 401. IR cm^{-1}: 3433, 1639, 1267.

Liriodenine (3): Yellow needle crystal MS m/z: 275(M^+); UV (EtOH):215, 246, 268, 395, 412 nm; IR (KBr) cm^{-1}:3054, 2685, 1726, 1421, 1265.

Cytotoxic assay: The cytotoxicity assay was determined by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay (Khorshid *et al.*, 2011). Cells were seeded in 96-well microplate at 3×10^5 cells/mL, incubated at 37°C in 5% CO_2 and treated with sample at 2×MFC in Serum Free Medium (SFM) for 240 and 480 min. The culture medium was aspirated, replaced with 0.5 μg mL^{-1} MTT solutions and incubated for 30 min in a CO_2 incubator. The solution was aspirated and added with 1,000 μL DMSO to dissolve the formazan crystals. After 30 min of rotary agitation, the absorbance of the solution was measured at 570 nm using Genesis10 UV-Vis spectrophotometer (Thermo Spectronic, NY, USA). The viable cell number was calculated from the standard curve of cell number by plotting a scattergram of the absorbance value against the known number of cells. IC_{50} values represent the compound's concentration that reduced the mean absorbance at 570 nm to 50% of those in the untreated control wells.

RESULTS AND DISCUSSION

Two chalcones and an alkaloid were isolated from the stem bark of *P. cauliflora* var. *cauliflora*. Both chalcones 1 and 2 have a phenolic OH substituted at position C-2' of A ring and a monosubstituted ring B while the alkaloid is an oxoaporphine type of alkaloid (Fig. 1).

Chalcone 1 (13.4 mg) was isolated as yellow oil. The UV spectrum showed maxima absorption at 201, 245, 253, 279, 290, 311, 344, 360 and 370 nm which are typical of chalcone moiety. The IR spectrum indicated the presence of hydroxyl group at 3434 cm^{-1}, C-H aromatic at 2987 cm^{-1}, C = O at 1638 cm^{-1} and C-O at 1263 cm^{-1}. The mass spectrum showed a molecular ion peak at 270 m/z corresponding to the molecular formula $C_{16}H_{14}O_4$.

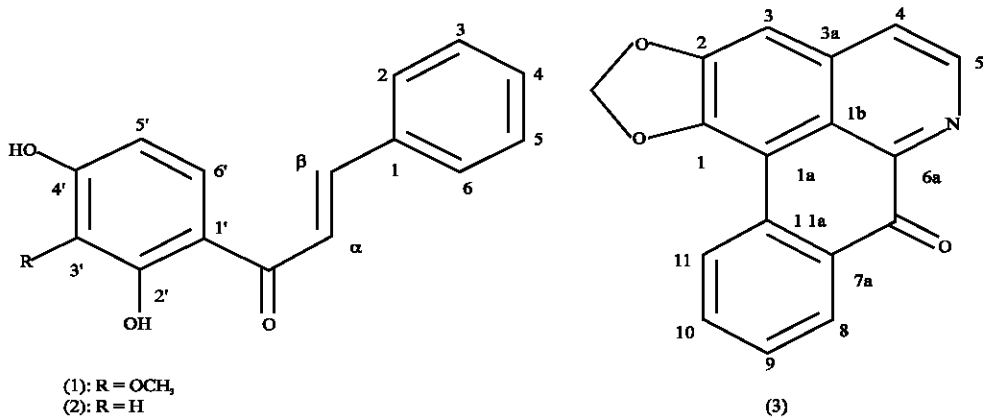

Fig. 1: Chalcones and oxoaporphine isolated from *P. cauliflora* var. *cauliflora*

^{1}H NMR spectrum of 1 showed a mutual pair of doublet at δ 7.92 and δ 7.56 (J = 15.6 Hz) suggesting the presence of *trans* olefin protons H-β and H-α, respectively. A pair of doublets observed at δ 6.59 and δ 7.64 (J = 9.0 Hz) are assignable to ortho-coupled protons at H-5' and H-6', respectively while two multiples at δ 7.46 and δ 7.68 integrated as three and two protons, respectively are characteristic of a monosubstituted ring B. These sets of signal gave clear indication that this compound is a chalcone. A sharp peak at a very downfield region at δ 13.57 is assignable to a phenolic OH chelated to the oxygen of the carbonyl group next to it (Zakaria *et al*., 2010). A signal of methoxy group could be observed at δ 4.05.

The ^{13}C NMR spectrum exhibited 14 signals representing 16 carbons with a carbonyl carbon signal at a very down field region at δ 192.6. Three oxyaryl carbons can be observed at δ 134.3, 155.3 and 157.8 corresponding to C-3', C-4' and C-2', respectively while two quaternary aromatic carbons gave signals at δ 115.0 (C-1') and 134.7 (C-1). Signals at δ 120.2 and 144.7 belong to two olefin sp^2 carbons present in the chalcone nucleus while signals for six aromatic C-H can be observed at δ 106.5 (C-5'), 129.3 (C-6'), 128.6 (C-2/C-6), 129.0 (C-3/C-5) and 130.8 (C-4). Finally a methoxy signal was detected at δ 60.8. These ^{13}C NMR together with ^{1}H NMR data confirmed that this compound is a chalcone with a monosubstituted ring B and a methoxy group located at ring A. Comparison with literature showed close resemblance of this compound with those reported for 2',4'-dihydroxy-3'-methoxychalcone (Svetaz *et al*., 2004).

Chalcone 2 (14.5 mg) was isolated as a yellow needle crystal. The UV spectrum showed the absorption maxima at 202, 208, 246, 277, 294, 313, 317 and 401 nm which are typical of chalcone moiety. The IR spectrum exhibited the presence of OH, C = O and C-O groups at 3433 cm^{-1}, 1639 cm^{-1} and 1267 cm^{-1} respectively. The mass spectral showed a molecular ion peak at m/z 240 suggesting the molecular formula of $C_{15}H_{12}O_3$.

The ^{1}H NMR spectrum (Table 1) exhibited a very downfield signal (singlet) at δ 13.41 indicative of a chelated hydroxyl group at position C-2'. Two multiples observed in the aromatic region at

Table 1: ^{1}H and ^{13}C NMR of compound 1 and 2

	^{1}H NMR (δ ppm)		^{13}C NMR (δ ppm)	
Position	1	2	1	2
1	-		134.7	134.7
2	7.68, m	7.67, m	128.6	128.6
3	7.46, m	7.45, m	129.0	129.0
4	7.46, m	7.45, m	130.8	130.7
5	7.46, m	7.45, m	129.0	129.0
6	7.68 , m	7.67, m	128.6	128.6
1'	-	-	115.0	114.4
2'	-	-	157.8	156.4
3'	-	6.46 (d, J = 2.1 Hz)	134.3	103.8
4'	-	-	155.3	162.9
5'	6.59 (d, J = 9.0 Hz)	6.49 (dd, J = 9.3, 2.1 Hz)	106.5	107.9
6'	7.64 (d, J = 9.0 Hz)	7.85 (d, J = 9.3 Hz)	129.3	132.0
α	7.56 (d, J = 15.6 Hz)	7.59 (d, J = 15.6 Hz)	120.2	120.3
β	7.92 (d, J = 15.6 Hz)	7.91 (d, J = 15.6 Hz)	144.7	144.7
C = O	-	-	192.6	192.0
OCH_3 (C-3')	4.05, s	-	60.8	-
OH (C-2')	13.57, s	13.41, s	-	-

δ 7.45 and δ 7.68 are characteristic of monosubstituted ring B and a pair of doublets at δ 7.59 and δ 7.91 (J = 15.6 Hz) are attributed to α and β protons in trans position. An ABD system could be observed in this structure with the presence of signals at δ 7.85 (d, J = 9.3 Hz), δ 6.49 (dd, J = 9.3, 2.1 Hz) and δ 6.46 (d, J = 2.1 Hz).

The ^{13}C NMR spectrum of 1 showed similar pattern of signals as in compound 2 assignable to chalcone skeleton. An additional signal at δ 103.8 in the spectrum suggests an unsubstitution of C-3' (methine sp^2 carbon). Based on the spectral data and comparison with literature, compound 2 was characterized as 2', 4'-dihydroxychalcone previously reported from the aerial parts of *Galenia africana* (Aizoaceae) (Vries *et al*., 2005). This is the first occurrence of this compound in *Polyalthia* genus.

Compound 3 (1.3 mg) was obtained as yellow needles exhibiting an M^+ at m/z 275, corresponding to molecular weight $C_{17}H_9O_3N$. The UV spectrum showed absorbance bands at 215, 246, 268, 395 and 412 nm suggesting an aporphine moiety. The IR spectrum indicated the presence of C-H aromatic at 3054 cm^{-1}, conjugated C = N group at 2685 cm^{-1}, C = O group at 1726 cm^{-1} and C-O group at 1265 cm^{-1}.

The ^1H NMR spectrum of 3 (Table 2) showed signals of seven aromatic and a methylenedioxy protons. A mutual-coupled protons were observed at δ 6.40 and 7.79 and 8.90 (d, J = 5.1 Hz). Two singlets at δ 6.40 and δ 7.16 were attributed to protons of methylenedioxy and aromatic H-3 respectively. The rest of the signals (δ 6.59, 7.60, 7.64 and 7.92) belong to four methine sp^2 protons in ring D.

The J-mod ^{13}C NMR spectrum of 3 showed the presence of 17 carbons with eight quaternary carbons. One carbonyl carbon appeared at a very downfield region (δ 182.4) while two oxyaryl carbons gave signals at δ 147.9 and 151.7. Signals for six quaternary carbons could be observed at δ 108.2 (C-1b), 131.3 (C-11a), 132.9 (C-7a), 135.7 (C-1a), 145.4 (C-3a) and 146.0 (C-6a) while signal of a methylenedioxy carbon could be seen at δ 102.4. These spectral data suggested compound 3 as an oxoaporphine alkaloid and comparison with the literature confirmed it to be liriodenine (Lavault *et al*., 1981). Compound 3 was reported to display good activity against

Table 2: ^1H and ^{13}C NMR of compound 3

Position	^1H NMR (δ ppm)	^{13}C NMR (δ ppm)
1	-	147.9
1a	-	135.7
1b	-	108.2
2	-	151.7
3	7.16, s	103.3
3a	-	145.4
4	7.79, d (J = 5.1 Hz)	124.2
5	8.90, d (J = 5.1 Hz)	144.9
6a	-	146.0
7	-	182.4
7a	-	132.9
8	8.59, dd (J = 7.8, 1.2 Hz)	128.8
9	7.59, td (J = 7.8, 7.2, 1.5 Hz)	128.6
10	7.76, td (J = 7.2, 1.2 Hz)	133.9
11	8.66, d (J = 7.2 Hz)	127.4
11a	-	131.3
O-CH_2-O	6.4, s	102.4

Table 3: IC_{50} value of compound 1 tested against HeLa, HL-60 and MCF-7 cancer cell lines

Cancer cell lines	Standard (H_2O_2)	IC_{50} (μg mL^{-1})
HeLa	7.02	12.2
HL-60	1.44	5.1
MCF-7	0.36	12.5

*Range of activity (inhibition): <5: Very strong, 5-10: Strong, 10-20: Moderate, 20-100: Weak, >100: Not active (Wibowo *et al*., 2011)

antifungal and cytotoxic (brine shrimp bioassay) (Rahman *et al*., 2005), anticancer against lung cancer cells (Chang *et al*., 2004) and antiparasitic activities (Fernandez *et al*., 2010).

2', 4'-dihydroxy-3'-methoxychalcone (1) was assayed against three cancer cell lines which were HeLa (human servical cancer), HL-60 (human T-promyelocytic leukemia) and MCF-7 (human breast adenocarcinoma cancer) using MTT assay. H_2O_2 was used as standard. Table 3 showed that 2',4'-dihydroxy-3'-methoxychalcone (1) exhibited *in vitro* cytotoxic effect against the three human cancer cell lines. It inhibited strongly the growth of HL-60 cell line with IC_{50} value of 5.1 μg mL^{-1} and moderately HeLa and MCF-7 cell lines with IC_{50} of 12.2 and 12.5 μg mL^{-1}, respectively.

Apoptosis of tumor cells can be triggered by a diversity of extracellular and intracellular factors including cytokines, tumor suppressor genes, oncogenes, radiation and anticancer drugs. The growth inhibition by 2', 4'-dihydroxy-3'-methoxychalcone (1) in the human cell lines may be due to apoptosis as nuclear condensation and fragmentation and DNA ladder formation was observed in all of the cell lines. Like any other chalcones, compound 1 chemically consists of two aromatic rings joined by three carbons, α-β-unsaturated carbonyl system. The reactivity of the carbonyl group and hydroxyl groups at position C-2' and C-4' in 1 is considered to be implicated in the internalization into the cell which in turn leads to interaction with the signal transduction molecules and the proteins involved in mitochondria permeability transition.

Compound 1 has been reported to display an activity against *Phomopsis longiculla* Hobbs CE117 for antifungal assay (Nowakowska, 2007) 2', 4'-dihydroxychalcone (2) also was reported to possess diverse pharmacological activities such as antiprotozoal, antifungal, antiMRSA, antiinflamatory, interleukin-1 and tyrosinase inhibitory, phytoesterogenic, antipyretic, analgesic, antioxidant and anticancer activities (Anto *et al*., 1995; Edenharder and Tang, 1997; Lopez *et al*., 2001; Nerya *et al*., 2004; Uchiumi *et al*., 2003; Wu *et al*., 2003). Thus, compound 2 is expected to display good cytotoxic effect as shown in 1 given that both compounds have hydroxyl group as substituent.

CONCLUSION

In summary, the phytochemical study of *P. cauliflora* var. *cauliflora* has led to the isolation of two chalcone; 2',4'-dihydroxy-3'-methoxychalcone (1) and 2',4'-dihydroxychalcone (2) and one alkaloid; liriodenine (3). *Polyalthia* of Annonaceae is known for its high content of alkaloid but we report here the isolation of chalcones as well. The results from MTT assay showed that chalcone 1, exhibited antiproliferative activity against human leukemia HL60 cells, human cervical cancer HeLa cells and human breast adenocarcinoma MCF-7 cells. Thus, 1 had been shown to induce apoptosis in leukemia cell lines.

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