Cytotoxic properties of the anthraquinone derivatives isolated from the roots of *Rubia philippinensis*

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**Abstract**

**Background:** Cancer is one of the most frequently occurring diseases and is the second leading cause of death worldwide. In this study, anthraquinone derivatives (Compounds 1–5) were evaluated for their anti-cancer potential against various skin and breast cancer cell lines to assess whether these anthraquinone derivatives may serve as a lead for the augmentation of anti-cancer drug.

**Methods:** Anthraquinone derivatives, 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone-3-O-(6′-O-acetyl)-α-rhamnosyl(1→2)-β-glucoside (Comp 1), 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone (Comp 2), and alizarin (Comp 3) were isolated from the dichloromethane fraction of the roots of *Rubia philippinensis*, whereas ethyl acetate fraction yielded xanthopurpurin (Comp 4) and lucidin-ω-methyl ether (Comp 5). Structures of all the isolated compounds were determined by spectral data analysis. All isolated compounds (Comp 1–5) were assessed for cytotoxicity by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay against four different cancer cell lines, i.e. human melanoma (SK-MEL-5), murine melanoma (B16F10), and human breast adenocarcinoma (MCF7 and MDA-MB-231).

**Results:** Significant activity of the compounds 4 and 5 was observed against the breast cancer cell line MDA-MB-231 with IC50 values of 14.65 ± 1.45 and 13.03 ± 0.33 μM, respectively. Encouragingly, IC50 values of 67.89 ± 1.02 and 79.01 ± 0.03 μM against normal kidney epithelial cells (MDCK) were also obtained for compounds 4 and 5, respectively, which indicated very low toxicity and favorable selectivity indices for compounds 4 and 5 in the range of 1.85 to 3.95 and 2.11 to 6.06 against skin cancer cell lines (SK-MEL-5, and B16F10), and breast cancer cell lines (MCF7 and MDA-MB-231), respectively.

**Conclusion:** Our results suggested that the compounds 4 (xanthopurpurin) and 5 (lucidin-ω-methyl ether) showed high selective toxicity towards breast cancer cells at lower concentrations without showing toxicity towards normal cells, thus could be of potential as new lead molecules in cancer treatment.

**Keywords:** *Rubia philippinensis*, Anthraquinone, Cytotoxicity, Breast cancer, Skin cancer

**Background**

Cancer is one of the most frequently occurring diseases and is the second leading cause of death worldwide, while chemotherapy is most extensively used among a wide range of anti-cancer therapies, and its high toxicity, being expensive as well as activating alternative cell signaling pathways are limiting its applications [1]. For centuries to date, being safe, low cost and easily accessible, medicinal herbs are viewed as the main sources of new drugs to treat cancer worldwide while various pharmacological studies continue to validate their uses [1]. Moreover, herbal medicines are widely assumed in complementary and alternative medicine especially in cancer patients with poor socioeconomic condition. Mounting evidences suggest that plants possessing anticancer properties, such as *Soymida fembrifuga*...
(Miliaceae), Tinospora cordifolia (Menispermaceae), Lavana
dula bipinnata (Lamiaceae), Helicteres isora (Sterculiaceae),
Urtica membranacea (Urticaceae), Artenesia monosperma
(Asteraceae), and Orobanum dayi post (Labiatea) etc., are
the source of alternative medicine for cancer therapy in
various regions of the globe [2–4]. However, a large number
of plant species remain to be screened for their therapeutic
potential; consequently, they can be used as a continual
source of new medicines for present and future health
problems of humans, including cancer.

Rubia philippinensis is a rambling and low climbing per-
ennial herb that grows in the Southern part of Vietnam.
Local communities have long utilized this medicinal plant
to treat ordinary ailments such as wounds, inflammation,
and skin infections. Previous investigations of the species
have resulted in the purification of arborine triterpe-
noids, which plays an important role in the pathophysiology of
erosclerosis [5]. Additionally, rubiarbonone C, a popular chemical entity isolated from R. philippi-
nessis, has been shown to inhibit abnormal prolif-
eration and migration of vascular smooth muscle cells,
which plays an important role in the pathophysiology of
erosclerosis. The mechanism by which rubiarbonone C
regulates vascular remodeling was further clarified through
focal adhesion kinase (FAK), MAPK, and STAT3 Tyr705
[6]. In searching for bioactive components from
Rubia philippinensis [6]. In searching for bioactive components from
Rubia philippinensis, in this study, derivatives of anthraquinone were iso-
lated as the major compounds.

Anthraquinones possessing three benzene rings represent
a class of compounds belonging to quinone family. The di-
vergence of the anthraquinone molecules relies on the na-
ture and the setting of the substituents. Anthraquinones
display a number of biological functions, including laxa-
tive [7], diuretic [8], phytoestrogen [9], anti-platelet [10],
anti-fungal [11], anti-viral [12], and anti-cancer properties
[13]. Moreover, they have a significant industrial potential
of being used as textile dyes, food colorants and bugs
repellents.

As a part of continuous attempts to probe the potential
nature-derived drug templates for the treatment of cancer
[5, 14], the current study delineates the isolation and
characterization of five anthraquinone derivatives (com-
pound 1–5) from R. philippinensis. These compounds were
evaluated for their anti-cancer potential against various skin
cancer cells (SK-MEL-5 and B16F10) and breast cancer
cells (MCF7 and MDA-MB-231) to assess whether these
anthraquinone derivatives may serve as a lead for the de-
velopment of anti-cancer drugs.

Methods

Plant materials

Root samples of Rubia philippinensis were procured from
Bidoup–Nui Ba National Park, Lamdong province, Vietnam
and identified by the expert Dr. Phuong Thien Thuong at
the Department of Pharmaceutical Analysis and Herbal
Standardization, NIMM, Hanoi, Vietnam. An authenticated
root voucher sample was deposited at the laboratory of the
NIMM (VDL20140801) and at the Pharmacognosy Labora-
tory, College of Pharmacy, Chungnam National University
(CNU1409), Daejeon, Korea.

Extraction, isolation, and characterization of
anthraquinone derivatives

Anthraquinones were isolated from the root samples of R. philippinensis by chromatographic techniques. In
brief, the ethanol extract of R. philippinensis (150 g) was
suspended in H2O (1.5 L) and sequentially partitioned with
CH2Cl2 (2 L × 3) and EtOAc (2 L × 3) to yield the CH2Cl2
and EtOAc extracts. The CH2Cl2-soluble fraction (50 g)
was loaded into silica gel VLC and eluted with n-hex-
ane-EtOAc (20:1, 10:1, 5:1, 3:1, 2:1) and CHCL3-MeOH
(8:1) to afford six fractions (D-1 → D-6). Fraction D-4
(61 mg) was divided into 10 sub-fractions (D-4-1 → D-4-10)
using MPLC with a step-wise gradient of Acetone-H2O
(60:40, 72:28, 75:25, 95:5, 100:0, each 1.5 L).

Xanthopur-
purin (4) (tR 33.5 min, 28 mg) and lucidin-
ether (5) (tR 36.0 min, 31 mg) were obtained from D-4-4
(320 mg) by HPLC eluting with MeCN-H2O (45.5:45.5,
4 mL/min, UV 360 nm). The EtOAc fraction (14.0 g)
was subjected to silica gel VLC and eluted with n-hexane/
EtOAc/MeOH (2:1:0.2) and CHCl3-MeOH (8:1, 5:1, 3:1,
0:1) to yield five fractions (EA-1 → EA-5). Eight
sub-fractions (EA-1-1 → EA-1-8) were collected from
fraction EA-1 (1.8 g) by utilizing MPLC, eluting with
MeOH-H2O (10:90, 50:50, 67:33, 80:20, 100:0, each
500 mL). Alizarin (3) (tR 44.0 min, 2 mg) was isolated
from EA-1-5 (100 mg) by HPLC eluting with MeCN-H2O
(44.5:55.5, 4 mL/min, UV 360 nm). Two sub-fractions
EA-1-6 and EA-1-7 were combined (EA-1-6-7: yellow powder,
200 mg). Fraction EA-4 (2.6 g) was separated by
MPLC applying mixtures of solvent
MeOH-H2O (23:77, 37:63, 47:53, 52:48, 60:40, 67:33,
100:0, each 400 mL) to yield 11 sub-fractions (EA-4-1 →
EA-4-11). 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone
(2) as orange crystals (200 mg). Fraction EA-4-1 (8.08 (1H, d,
J = 8.4 Hz, H-8), 7.45 (1H, d, J = 2.4 Hz, H-5),
7.40 (1H, s, H-4), 7.20 (1H, dd, J = 8.4, 2.4 Hz, H-7), 5.45
(1H, d, J = 6.9 Hz, Glu-H-1′), 5.28 (1H, d, J = 0.9 Hz,
Rha-H-1′), 2.15 (3H, s, CH3-2), 1.93 (3H, s, OAc-6′), 1.09
The potential cytotoxicity of the isolated anthraquinone derivatives was studied against various cancer cell lines, including SK-MEL-5 (human melanoma), B16F10 (murine melanoma) MCF7 (human breast adenocarcinoma), and MDCK cells. All cell lines were cultured in DMEM medium supplemented with 10% foetal bovine serum (FBS) and streptomycin–penicillin (100 μg/ml each; Hyclone) in a 5% CO₂ humidified incubator. An MTT assay was employed to determine the percentage of the viability of various cancer cells as well as MDCK cells. All cells were first cultured in 96-well plates (1 x 10⁵ cells/ml for all cancerous cells and 5 x 10⁴ cells/ml for MDCK cells) for 24 h, and treated with indicated concentration of isolated compounds (6.25–100 μM for cancerous cells and 6.25–400 μM for MDCK cells). Various dilutions of stock culture were made in the culture medium to get the final concentration of the sample with a 0.1% of DMSO concentration, including the control. After 24 h incubation, MTT reagent was added to each well and the plate was incubated at 37 °C for 1 h. After removing the medium, the plate was washed twice with PBS (pH 7.4). The intracellular insoluble formazan was dissolved in 100% DMSO. A microplate reader was used to measure the absorbance of each cell line at 570 nm, and the percentage of cell viability was calculated. The absorbance value for the average of wells of cells treated with each test sample concentration was expressed as a percentage of this control and the IC₅₀ values for each sample on each cell line were calculated. The anti-cancer drug oxaloplatin was used as a positive control.

Statistical analysis
All the results were presented as the mean ± SD following the analysis of one-way ANOVA. A value of p < 0.05 was recognized as significant for the differences. An SPSS version of Windows (Chicago, Illinois, USA) was performed for all the analyses.

Results
Identification and characterization of anthraquinone derivatives (Fig. 1)
The ¹H NMR data of compound 1 displayed signals of the anthraquinone aglycone, including one aromatic singlet proton δH 7.40 (1H, s, H-4), one ABX ring system δH 8.08 (1H, d, J = 8.4 Hz, H-8), 7.45 (1H, d, J = 2.4 Hz, H-5), 7.20 (1H, dd, J = 8.4, 2.4 Hz, H-7), and one singlet methyl δH 2.15. The glycosidic linkage, meanwhile, contained resonances of two anomeric protons of the sugar moiety at δH 5.45 (glucose), δH 5.28 (rhamnose), one secondary methyl (δH 1.09, rhamnose), and one acetyl group (δH 1.93). The ¹³C NMR data showed 14 signals of a typical anthraquinone, including two ketones (δC 186.3, 181.8), and resonances for glucose (δC 97.3, 76.3, 77.0, 70.0, 74.0, 63.3), acetoxy (δC 170.3, 20.4), and rhamnose (δC 100.2, 70.3, 70.5, 72.0, 68.5, 18.1) moieties. On the basis of NMR spectroscopic data analyses, the compound was identified as 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone-3-O-(6’-O-acetyl)-α-rhamnosiyl-(1→2)-β-glucoside.

Similar to compound 1, compound 2 also showed resonances of one aromatic singlet proton, one ABX ring system and one singlet methyl at δH 7.40 (1H, s, H-4); [δH 8.05 (1H, d, J = 8.4 Hz, H-8); 7.43 (1H, d, J = 2.4 Hz, H-5); 7.20 (1H, dd, J = 8.4, 2.4 Hz, H-7)]; and δH 2.05 (3H, s, CH₃). The skeleton of 14 carbon signals along with two ketonic carbonyls (δC 185.8, 182.0) and one methyl functionality (δC 8.1) was representative of ¹³C NMR data of an
anthraquinone. The 1D NMR of compound 2 resemble closely to those of compound 1, except for the absence of signals belonging to sugar units. In comparison with reference values, compound 2 was determined as 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone. Compound 3, 4, and 5 are also anthraquinone derivatives and their structures were elucidated as alizarin, xanthopurpurin, and lucidin-ω-methyl ether, respectively, based on the NMR data analysis. NMR data of all anthraquinone has been provided in Additional file 1: Figures S1-S5.

Cytotoxicity of anthraquinone derivatives
All compounds were tested for cytotoxicity by MTT assay on cell lines SK-MEL-5, B16F10, MCF7, MDA-MB-231, and MDCK cells as a normal cell line, which showed significant cytotoxicity (Table 1, Additional file 1: Figures S6-S10). Our results showed that the IC<sub>50</sub> values for cancer cell lines treated ranged from 48.68 ± 0.10 to 91.04 ± 1.88 μM for compound 1; 46.75 ± 1.39 to 79.96 ± 1.14 μM for compound 2; 48.64 ± 0.33 to 98.79 ± 2.10 μM for compound 3, 14.65 ± 1.45 to 23.71 ± 1.71 μM for compound 4, and 13.03 ± 0.33 to 42.79 ± 1.32 μM for compound 5. Regarding the normal cell line MDCK cells, the IC<sub>50</sub> values were 192.34 ± 0.49, 168.76 ± 0.61, 199.32 ± 1.88, 67.89 ± 1.02 and 79.01 ± 0.03 μM for compounds 1, 2, 3, 4, and 5, respectively. Interestingly, among all the compounds, compounds 4 and 5 showed strong cytotoxicity towards breast cancer cells (MCF7 and MDA-MB-231) than skin cancer cells (SK-MEL-5 and B16F10) with IC<sub>50</sub> value of 15.75 ± 1.00 and 24.10 ± 1.06 for MCF7 as well as 14.65 ± 1.45 and 13.03 ± 0.33 for MDA-MB-231, respectively.

Table 1 IC<sub>50</sub> values of anthraquinone derivatives (compound 1–5) on various skin cancer cells (SK-MEL5 and B16F10) and breast cancer cells (MCF7 and MBA-MD-231)

| Compounds | IC<sub>50</sub> (μM)<sup>a</sup> |
|-----------|-----------------|
|            | SK-MEL-5 | B16F10 | MCF7 | MDA-MB-231 | MDCK |
| 1          | 91.04 ± 1.88 | 48.68 ± 0.10 | 65.48 ± 1.10 | 49.44 ± 0.78 | 192.34 ± 0.49 |
| 2          | 46.75 ± 1.39 | 77.88 ± 0.34 | 79.96 ± 1.14 | 59.22 ± 0.40 | 168.76 ± 0.61 |
| 3          | 53.08 ± 0.30 | 98.79 ± 2.10 | 49.17 ± 0.85 | 48.64 ± 0.33 | 199.32 ± 1.88 |
| 4          | 21.35 ± 0.99 | 23.71 ± 1.71 | 15.75 ± 1.00 | 14.65 ± 1.45 | 67.89 ± 1.02 |
| 5          | 42.79 ± 1.32 | 29.48 ± 2.61 | 24.10 ± 1.06 | 13.03 ± 0.33 | 79.01 ± 0.03 |
| Oxaloplatin| 14.25 ± 1.02 | 10.51 ± 0.92 | 8.59 ± 1.22 | 7.95 ± 1.92 | 24.02 ± 1.04 |

<sup>a</sup>The values are mean ± standard deviation. IC<sub>50</sub> (concentration inhibiting 50% growth). SK-MEL-5 (human melanoma); B16F10 (murine melanoma); MCF-7 (human breast adenocarcinoma); MDA-MB-231 (human breast adenocarcinoma), MDCK (normal kidney epithelial cells)
In addition, compound 4 and 5 were more cytotoxic to MDA-MB-231 cancer cell line (IC_{50} = 14.65 ± 1.45 and 13.03 ± 0.33 μM, respectively) than to normal cells (IC_{50} = 67.89 ± 1.02 and 79.01 ± 0.03 μM (Table 1), respectively with their respective selectivity indices of 4.63 and 6.06 (Table 2).

Table 2 shows the selectivity indices of the isolated compounds tested against the various cancer cell lines and the non-tumor cell line (MDCK). In the current study, treatments with compound 4 and 5 afforded the highest selectivity indices in breast cancer cell than skin cancer cells. Compound 4 showed the selectivity indices as 4.31 and 4.63 whereas compound 5 showed 3.28 and 6.06 in MCF7 and MDA-MB-231 cells, respectively (Table 2).

**Discussion**

A number of natural compounds have been isolated from different plant sources which have shown enormous biological potential [16–19]. In this study, five anthraquinone derivatives, such as 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone 3-O-(6-O-acetyl)-α-rhamnosyl(1 → 2)-β-glucoside (compound 1), 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone (compound 2), alizarin (compound 3), xanthopurpurin (compound 4), and lucidin-ω-methyl ether (compound 5) were isolated from the root of *Rubia philippinensis*, and were characterized based on the spectral data analysis [16–19].

These anthraquinone derivatives showed significant anticancer potential as confirmed by their cytotoxicity effects against various cancer cell lines, such as cell lines SK-MEL-5, B16F10, MCF7, MDA-MB-231, including normal MDCK cell line. However, according to American National Center Institute, extract/compounds with IC_{50} values lower than 30 μM against experimental cancer cell lines constitute promising anticancer agents for drug development [20]. Therefore, compound 4 and 5 showed IC_{50} values greater than 30 μM against all cell lines tested, and were more cytotoxic to normal line to which the cancer cell lines. Moreover, among the testest compounds, anthraquinone derivatives xanthopurpurin (compound 4), and lucidin-ω-methyl ether (compound 5) showed highest selectivity indices in breast cancer cell than skin cancer cells.

Mounting evidences have considered that a value greater than or equals to 2.0 is an interesting selectivity index [21]. This value means that the compound is more than twice more cytotoxic to the cancer cell line as compared with the normal cell line [21]. These findings demonstrated that compound 4 and 5 can be considered promising lead molecules for the development of anticancer drugs, especially for breast cancer, because they provided indices value greater than 2.

**Conclusions**

It is very important to consider natural compounds as a chemotherapeutic agent for cancer which have minimum or no side effects on normal body cells of patients. To achieve this goal among various ways, one of the way is by employing lower doses of drug at which drug shows highly potent activity as well as exhibits high degree of selectivity. In this study, we presented the cytotoxicity potential of five anthraquinone derivatives isolated from the roots of *Rubia philippinensis*. The results of in vitro studies demonstrate the ability of the compounds 4 (xanthopurpurin) and 5 (lucidin-ω-methyl ether) for high selective toxicity at lower concentrations (Table 1) without showing toxicity towards normal cells, confirming that compounds 4 and 5 may have the potentiality to be developed as anticancer drugs, especially for breast cancer. Further research strategies should investigate cytotoxic potential of compound 4 and 5 against multifactorial drug-resistant cancers for their pharmaceutical formulations.

**Additional file**

**Additional file 1**: Supplementary data contain ten supplementary figures. Among them Figures S1-S5 represent proton and carbon NMR data of the isolated compounds, whereas Figures S6-S10 represent cytotoxic effects of isolated compounds (1–5) against MDCK, SK-MEL-5, B16F10, MCF7, and MDA-MB-231 cell lines. (DOC 899 kb)

**Abbreviations**

ANOVA: Analysis of variance; DMEM: Dulbecco’s Modified Eagle’s Medium; DMIS: Dimethyl sulfoxide; FAK: Focal adhesion kinase; FBS: Foetal bovine serum; HPLC: High-performance liquid chromatography; MAPK: Mitogen-activated protein kinase; MPLC: Medium pressure liquid chromatography; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NMR: Nuclear magnetic resonance; SD: Standard deviation; UV: Ultraviolet; VLC: Vacuum liquid chromatography

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**Availability of data and materials**

All data in combined within the manuscript and additional files.
Authors' contributions
Designed the experiments: VKB, MBA, KTQ, HJC. Performed the experiments: MBA, KTQ, HA, MKJ. Analyzed the data: VKB, MBA, SHL, YKH, MN. Conception and design, analysis and interpretation of data, and contribution of reagents/materials/analysis tools: MKN, SHL. Manuscript preparation and revision: VKB, MBA, YKH, MN. All authors have approved the final draft of the manuscript.

Ethics approval and consent to participate
Not applicable. This study did not involve use of animal or human subjects. The cell line was purchased from American type tissue culture (ATCC).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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