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The anticancer activities of isolated compounds from *Prismatomeris malayana* Ridley against selected cancer cell lines

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Abstract: The methanol crude extracts of the leaves, stems, and roots of *Prismatomeris malayana* were partitioned using petroleum ether, chloroform, and ethyl acetate to produce fractions with different polarity. Form our previous study, compounds in selected fractions were separated using chromatographic techniques. The structural elucidations on these compounds were performed using NMR, IR, and LC-MS/MS and the data produced were compared with the empirical data of known compounds. Twelve compounds were successfully isolated and characterized. Sulphorhodamine-B (SRB) assays were performed on these crude extracts, fractions, and compounds against four different cancer cell lines namely SKOV3, CaOV3, MCF-7, HT-29, and the normal liver cell line; WRL-68. Most of the compounds produced moderate anti-cancer activities with IC_{50} values ranging from 33.6 to 52.2 µg/mL. Compound 1 (a triterpene) was found to be the most active compound against MCF-7, CaOV3, and HT29 cancer cell lines tested (IC_{50} ranged from 5.50 to 15.16 µM) but wasnot active against the normal cell line (IC_{50} > 20 µM).

Keywords: Prismatomeris malayana; anti-cancer, *in vitro*; SRB assay; chemical constituents

INTRODUCTION

Plant-based drugs have a long history in both traditional and modern medicine. Drug discovery from plants still provides important new drugs, many of which are approved or have undergone trials for clinical uses against critical diseases. Diseases that result from either deficient apoptosis or excessive apoptosis causes the largest single cause of death. Therefore, research and development of more effective and less toxic drugs have become necessary. Chemotherapeutic drugs work by impairing mitosis, effectively targeting fast-dividing cells. As these drugs cause damage to cells, they are termed cytotoxic. They prevent mitosis by various mechanisms including damaging DNA and inhibition of the cellular machinery involved in cell division. Currently used drugs,

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however, have a wide range of side effects such as immunosuppression and myelosuppression. antiproliferative screening *in vitro* provides important preliminary data on plants with potential antineoplastic properties for future study. Therefore, research and development of more effective and less toxic drugs that origin from phytochemicals should be intensified. Our previous study on *Prismatomeris tetrandra* reported the isolation and identification of compounds (Nor Hayati, 2014). Their structures were identified from elucidation on spectroscopic data (^{1}HNMR, 1D and 2D, IR and mass) and by comparing the data with the literature values. The objective of this study is to evaluate the anticancer effects *in vitro* of the extracts and compounds of *P. malayana* towards MCF7 (breast CCL), CaOV3 (ovarian CCL), SKOV3 (ovarian CCL), and HT-29 (colorectal CCL).

MATERIALS AND METHODS

In vitro antiproliferative assay: Cancer cells (including ovarian, breast, colorectal, and skin) and normal cell lines were purchased from the American Type Culture Collections (ATCC), USA and were cultured in 96-well plate at a density of 4 × 104 – 6 × 104 cells/ mL following method. The cells will then be treated with the extracts of the leaves, roots, and stems at different concentrations (eg. 0, 1, 5, 25, 125, 625 µg/ mL). The reactions were then stopped using SRB assay (Skehan et al. 1990) after 72 hr and the results were measured at OD of 492nm with ELISA plate reader. The percentage of cells viability was then calculated: (OD492nm of treated cells/ OD492nm of non-treated cells) × 100. The IC_{50} values were then analyzed from the results. The analysis was performed from three triplicate wells.

RESULTS AND DISCUSSION

The methanol extracts of roots, stems, and leaves were fractionated successively by using the solvent-solvent partitioning method starting with non-polar followed by the polar solvents: petroleum ether, chloroform, and ethyl acetate to give petroleum ether, chloroform, ethyl acetate, and water fractions. All fractions were subjected to further fractionation and compound isolation, followed by purification to identify the chemical constituents of this species. Eighteen compounds were successfully isolated from this plant (Nor Hayati, 2014). However, only 12 compounds were selected to be evaluated for their cytotoxicity test due to insufficient quantity (Figure 1). The selected 12 compounds were pentacyclic triterpenes (1-4), anthraquinones (7-12), and iridoids (5,6) isolated from three different plant parts. Besides, the methanol extract was also tested for cytotoxicity to identify the potential therapeutic value of this species as an anticancer remedy. The results are expressed by mean of IC_{50} (Figure 1) values which enables the identification of the potential of an extract having active (hit) compounds. Crude extracts that can kill 50% of the cancer cells at the concentration of less than 20 µg/mL are strongly cytotoxicity (Boik 1996). However, the extracts of towards MCF7, CaOV3, SKOV3, HT-29, and normal liver cell line (WRL-68) (Figure 1). They only killed the cancer cells (more than 50%) at a very high concentration (50 to more 100 µg/ mL). Compound 1 was found to be the most active in inhibiting the proliferation of HT-29, MCF-7, and CaOV-3. Whereas, the other compounds had moderate anticancer activities (46.84 to 55.60 µg/ mL). However compound 1 was not active against normal cell line which makes it has a potential anti-cancer candidate. It was more active than tamoxifen (positive control) in MCF7, CaOV3, and HT-29 but less active compared to paclitaxel (positive control).

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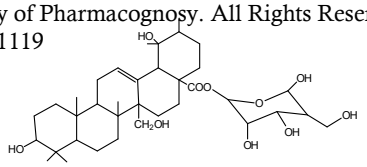
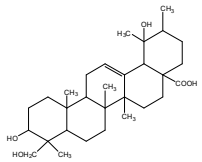
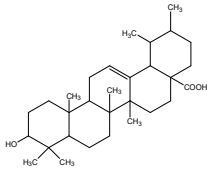


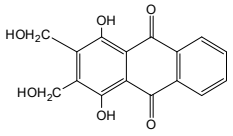
(2) PMLEA 294 28-O-β-glucopyranosyl-3α,19α,24-trihydroxyurs-12-en-28-oic acid



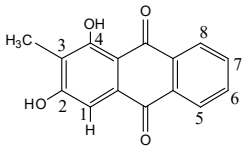
(3) PMLC1643b Barbinervic acid



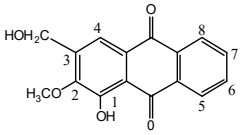
(1) PMLC36 Ursolic acid



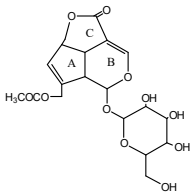
(7) PMREAII81



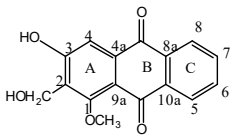
(9) PMREAII5b Rubiadin



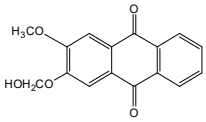
(12) PMREAII72 Lucidin-3-methyl ether



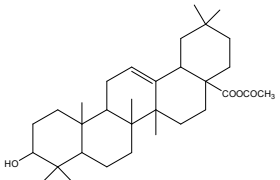
(6) PMSW10 Asperuloside



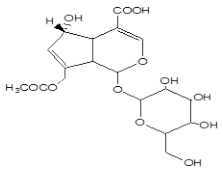
(8) PMREAII87 Damnacanthol



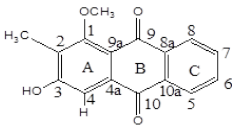
(11) PMREAII86 2-oxyhydroxymethyl-3-methoxy-9,10-anthraquinone



(4) PMREAII3 3β-acetylolean-12-en-28-oic acid



(5) PMLW846 Asperulosidic acid



(10) PMREAII755 Rubiadin-1-methyl ether

Figure 1: Isolated compounds

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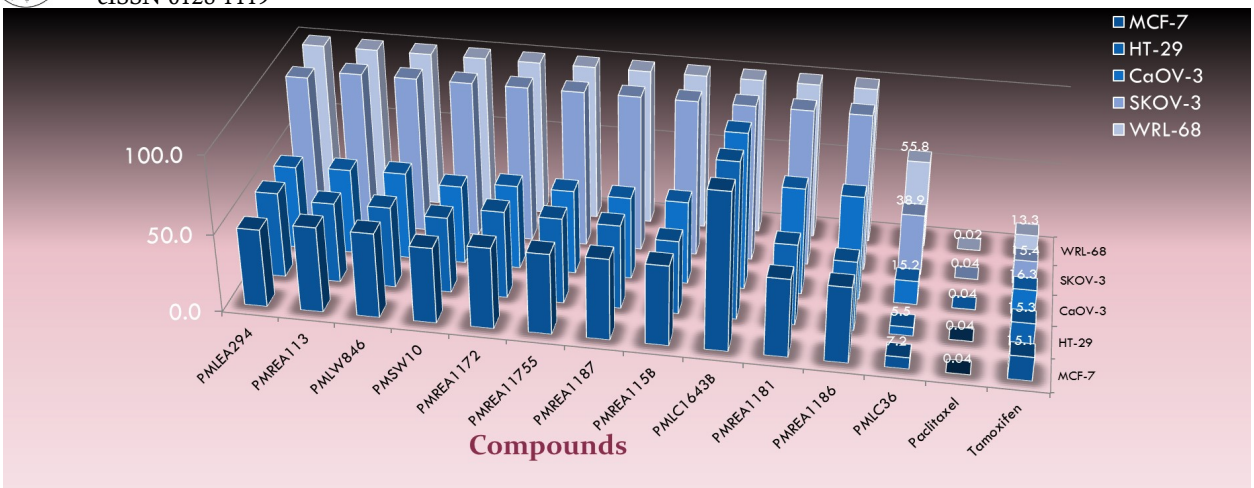

Figure 2. IC_{50} values of chemical compounds isolated from P. malayana against selected cancer cell lines: MCF-7 (breast cancer), HT-29 (colorectal cancer); CaOV-3 and SKOV-3 (ovarian cancer) and normal cell line: WRL-68.

Compound 2 showed moderate activity probably because of the presence of glucose moiety while compound 3 and 4 due to the presence of extra OH group and re-arrangement of the methyl group from geminal into a vicinal arrangement, respectively, that make the compound loss their activity. The iridoids (5-6) and anthraquinones (7-12) showed moderate activity towards MCF7, CaOV3, HT-29 cancer cell lines but not active towards SKOV3 and normal cell line, HT-29.

ACKNOWLEDGMENT

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DECLARATION OF CONFLICT OF INTEREST

No conflict of interest to declare.

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