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Synthesis of C-11 and C-12 oxidized derivatives of3β-[(α-L-arabinopyranosyl)oxy]olean-12-en-28-oic acid and evaluation of their cytotoxic activity in human non-small cell lung cancer (NCI-H292) cells using Sulforhodamine B assay

J. M. J. Jayasundara[1, 2], A. Wickramasinghe[2], D. N. Karunaratne[2], N. S. Wickramaratne[3], S. R. Samarakoon[3] and S. Jayasinghe[2*]

[1]Post Graduate Institute of Science, University of Peradeniya, Sri Lanka
[2] Department of Chemistry, Faculty of Science, University of Peradeniya, Sri Lanka
[3]Institute of Biochemistry, Molecular biology and Biotechnology, University of Colombo, Sri Lanka
susanthij@pdn.ac.lk*

The most common cancer, lung cancer is the foremost reason for cancer deaths in both males and females throughout the world. The two major categories of lung cancer which propagate differently are Non-small cell lung cancer (NSCLC) and Small cell lung cancer (SCLC). Among those NSCLCs are the most prevalent lung cancers, contributing 80% of all lung cancers. Natural products represent the bedrock of drug discovery, providing novel scaffold structures that serve as a starting point for developing novel therapeutic agents. A number of new drugs with improved therapeutic potential have been obtained from natural sources, by functional group modifications or by the synthesis of new compounds, following lead natural compounds as models. The recurrence of cancer due to the drug resistance and undesirable side effects which have limited the use of anticancer drugs, have increased the demand for novel alternative therapeutics with enhanced pharmacological activity and fewer side effects. Hence, the synthesis of natural product derived compound libraries in the discovery of novel drugs is still a key aspect of cancer therapy. 3β-[(α-L-arabinopyranosyl)oxy]olean-12-en-28-oic acid (APOA) is a triterpenoid saponin with the oleanolic acid aglycone linked to arabinopyranose sugar moiety and can be easily isolated from endemic plant extracts of genus *Schumacheria*. This compound exerts potent cytotoxic and apoptotic potential in human NSCLC cells (NCI-H292) with an IC_{50} value of 5.977 μgmL^{-1} while exhibiting a comparable toxicity value (IC_{50} = 5.702 μgmL^{-1}) against normal lung (MRC-5) cells. The objective of this study was to synthesize oxidized structural analogues at C-11 and C-12 positions of the APOA and to evaluate their cytotoxic effect. Sulforhodamine B (SRB) assay is used to evaluate *in-vitro* cytotoxic efficacy of the synthesized analogues on NCI-H292 cells and MRC-5 cells. The methylene group at the C-11 and methine group at C-12 of the ethyl ester of acetylated APOA (Ee-Ac-APOA) was oxidized to afford respective ketones and followed by deacetylation of the afforded analogues resulted in the oxidized analogues with free sugar hydroxyls (Ee-APOA). Chemical structures of the synthesized analogues were confirmed with spectroscopic data and comparative cytotoxic effects of the synthesized analogues were assessed using SRB assay against APOA. GraphPad Prism 7.00 software was used for statistical analysis and the results indicated that the oxidized analogues of Ee-APOA exhibit higher cytotoxicity against NCI-H292 cells than the oxidized derivatives of Ee-Ac-APOA while exhibiting comparable toxicity values against normal lung (MRC-5) cells. However, the α, β-unsaturated derivative of Ee-Ac-APOA exhibited potent cytotoxic activity against NCI-H292 cells while being less toxic to normal MRC-5 cells compared to the parental saponin indicating better activity. These empirical data suggest that the oxidized compounds at C-11 and C-12 of APOA could be a lead to develop promising new anticancer agents.

Keywords: Non-small cell lung cancers, *Schumacheria*, Structural analogues, Oxidized derivatives, Sulforhodamine B assay.

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