QSAR-driven discovery of novel anticancer derivatives from a natural halogenated scaffold

R. M. R. K. Rathnayaka[1], K. H. Tennekoon[1], D. S. Gunasekara[2]

[1]Institute of Biochemistry, Molecular Biology and Biotechnology, University of Colombo, Sri Lanka

[2]New Frontier Bio,48 Denham Street, Beverly, MA 01915, USA

Natural halogenated compounds have emerged as promising scaffolds for anticancer drug discovery. A previously reported halogenated compound (CMF) from *Mangifera zeylanica*, an endemic plant of Sri Lanka, demonstrated selective cytotoxic activity against triple-negative breast cancer cells (MDA-MB-231; IC50 < 50 µg/mL), with lesser cytotoxicity towards normal breast epithelial cells (MCF-10A; IC50 = > 100µg/mL). However, its moderate potency limited its therapeutic potential. Therefore, the present study aimed to improve the anticancer efficacy of CMF. A quantitative structure–activity relationship (QSAR) model was developed to predict the activity profiles of structurally modified predicted derivatives of CMF. Computational screening revealed several candidate molecules with higher predicted activity compared to the parent compound. Guided by these results, selected derivatives were synthesized using standard synthetic protocols and structurally characterized. *In vitro* cytotoxicity assays demonstrated that these novel derivatives exhibited significantly enhanced activity against MDA-MB-231 cells while maintaining favourable selectivity over MCF-10A cells. These findings validate the predictive power of the QSAR model and highlight the value of integrating computational design with synthetic chemistry to optimize natural product–derived anticancer leads. This study establishes three among ten synthesized halogenated derivatives (Compounds K1, K2, and K3) of CMF, as potential candidates for further development against TNBC, a highly aggressive breast cancer subtype lacking effective targeted therapies.

Keywords: *Mangifera zeylanica, triple-negative breast cancer, QSAR, Natural product derivatives, Drug design*