**Abstract**

Adverse effects of first-line drugs used for colorectal cancer (CRC) therapy have been persisting as one of the problems in CRC treatment strategies. Drug repurposing is a method that utilizes approved or investigational drugs that were initially not intended for cancer therapy as an alternative treatment. Simvastatin, a HMG-CoA reductase inhibitor, and ethyl extracts of *Annona muricata* leaves have been extensively investigated for their anti-cancer effects. Hence, it is hypothesized that the combination of these two drugs will yield synergistic cytotoxic effects on cancer cell lines. This study conducted in vitro and in silico analysis which includes cell viability, wound healing and colony formation assays (CFA), and computational simulation using molecular docking. Cell viability assay of simvastatin and EEAM combination resulted in antagonistic effects but CFA results showed that the combination is capable of reducing the clonogenic capacity of HT-29 cells. Molecular docking study demonstrated that simvastatin and various cytotoxic acetogenins may potentially competitively bind to PARP1, caspase-3 and caspase-7 proteins involved in both apoptotic and parthanotic regulated cell death.

Key Words: *Colorectal cancer, simvastatin, Annona muricata, drug combination, cell viability, colony forming assay, molecular docking, apoptosis, parthanatos*