**Screening of Multitarget Compounds against Acetaminophen Hepatic Toxicity Using In Silico, In Vitro, and In Vivo Approaches**

**Abstract**

Combination therapy and multitarget drugs have recently attracted much attention as promising tools to fight against many challenging diseases and, thus, represent a new research focus area. The aim of the current project was to screen multitarget compounds and to study their individual and combined effects on acetaminophen-induced liver injury. In this study, 2 of the best hepatoprotective multitargeting compounds were selected from a pool of 40 major compounds present in *Curcuma longa* and *Cinnamomum zeylanicum* by using molecular docking, ADMET profiling, and Pfizer’s rule of five. The two selected compounds, quercetin and curcumin, showed a high binding affinity for the CYP2E1 enzyme, MAPK, and TLR4 receptors that contribute to liver injury. The candidates caused the decreased viability of cancer cell lines (HepG2 and Huh7) but showed no effect on a normal cell line (Vero). Examination of biochemical parameters (ALT, AST, ALP, and bilirubin) showed the hepatoprotective effect of the candidate drugs in comparison with the control group, which was confirmed by histological findings. Taken together, quercetin and curcumin not only satisfied the drug-like assessment criterion and proved to be multitargeting by preventing liver damage but also showed anticancer activities.