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Drug-likeness, pharmacokinetic, and Toxicity Prediction of Phytotoxic Terpenoids

Terpenoids constitute one of the most widespread phytoconstituents with complex chemical structures, a plurality of biological activities, and variable pharmacokinetic profiles. The emerging roles of terpenoids in drug design require an understanding of their ADME/T properties for structure modification and possible repurposing. The study evaluated the drug-likeness of phytotoxic terpenoids obtained from the toxic plants-phytotoxins (TPPT) database by *in silico* prediction of their pharmacokinetic and toxicity profiles. A TPPT database comprising 1586 phytotoxins was filtered to 576 terpenoids. Lipinski's properties and topological polar surface area (TPSA) were predicted for drug-likeness together with their pharmacokinetic profiles and toxicity on various organ endpoints using Swiss ADME, pkCSM, and ProTox II webserver tools. A 9.55% of the terpenoids obeyed Lipinski's rule of five. None of the compounds inhibited hERG I, while 12.73% inhibited hERG II, implying that some were cardiotoxic. In addition, 25.45% of the compounds elicited AMES toxicity; 25.45% caused liver injury and 32.73% caused skin sensitivity. Furthermore, 72.73% showed high Caco-2 permeability and 76.36% displayed good skin permeability- suitable for transdermal drug delivery. A 29.09% of the compounds extruded by p-glycoprotein; 34.45% inhibited p-glycoprotein, 47.27% readily crossed the blood-brain barrier, 23.64% penetrated the central nervous system, 56.36% sensitive to cytochrome p450 isoenzymes, 36.37% inhibited cytochrome p450 isoenzymes, 49.09% resulted in immunotoxicity, 1.82% toxic to cells, 14.55% would cause cancer, 21.82% showed high tolerated dose in human. Most of them showed a high volume of distribution, were free-flowing in the plasma, and demonstrated moderate bioavailability, while all had high intestinal absorption and 78.18% demonstrated good water solubility. The study identified marrubiin as a drug-like, non-toxic, and highly bioavailable terpenoid with strong potential for further optimization, and development.

Keywords: Phytotoxic terpenoids, drug-likeness, pharmacokinetic profiles, toxicity.