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Abstract

In Silico Prediction of Drug-Likeness, Pharmacokinetics, and Toxicity of Selected Phytotoxic Pyrrolizidine Alkaloids †

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Pyrrolizidine alkaloids (PAs) are heterocyclic organic compounds of natural origin synthesized by either plants or microorganisms. They are found in species applied in the pharmaceutical industry for their beneficial biological activities to cure disease; thus, a thorough knowledge of their pharmacokinetics and toxicity is of great importance as they are notorious for their acute hepatotoxicity and carcinogenicity in humans and animals. Therefore, this study evaluated the drug-likeness of 15 phytotoxic pyrrolizidine alkaloids that were reportedly isolated from 11 plant species via in silico prediction of their pharmacokinetic and toxicity profiles. Using Swiss ADME, pkCSM, and PreADMET webserver tools, Lipinski's properties and topological polar surface area (TPSA) were predicted for drug-likeness, alongside their pharmacokinetic profiles and toxicity on various organ endpoints. The drug-likeness prediction showed that all the compounds obeyed Lipinski's rule of five (LRo5). None of the compounds inhibited hERG I and hERG II, indicating their non-cardiotoxic nature. In addition, 20% of the compounds elicited AMES toxicity; 53.33% caused liver injury; and none was sensitive to the skin. Furthermore, 13.33% showed high Caco-2 permeability and all displayed good skin permeability, implying their suitability for transdermal drug delivery. Moreover, P-glycoprotein was effluxed by 80% of the compounds and none exhibited inhibition; 86.66% of the compounds readily crossed the blood–brain barrier, 6.66% penetrated the central nervous system, none was a substrate to cytochrome p450 isoenzymes, 6.66% inhibited cytochrome p450 isoenzymes, 53.33% and 26.66% would cause cancer in mice and rats, respectively, and 20% showed high tolerated doses in humans. All demonstrated high intestinal absorption and 46.66% demonstrated good water solubility while a significant number showed a moderate volume of distribution, were free-flowing in plasma, and demonstrated moderate bioavailability. This study identified Jacoline and monocrotaline as drug-like, non-toxic, and highly bioavailable pyrrolizidine alkaloids with strong potential for further assessment, optimization, and development.

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