proceedings

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Abstract

Drug-Likeness, Pharmacokinetics, and Toxicity Prediction of Phytotoxic Terpenoids †

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† Presented at the 1st International Electronic Conference on Toxics, 20–22 March 2024; Available online: https://sciforum.net/event/IECTO2024.

Abstract: 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. This study evaluated the drug-likeness of phytotoxic terpenoids obtained from the Toxic Plants–Phytotoxins (TPPT) database via in silico prediction of their pharmacokinetic and toxicity profiles. The TPPT database, comprising 1586 phytotoxins, was filtered to 576 terpenoids. Using Swiss ADME, pkCSM, and ProTox II 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. In total, 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, implying their suitability for transdermal drug delivery. P-glycoprotein was extruded by 29.09% of the compounds and inhibited by 34.45%; 47.27% of the compounds readily crossed the blood–brain barrier, 23.64% penetrated the central nervous system, 56.36% were sensitive to cytochrome p450 isoenzymes, 36.37% inhibited cytochrome p450 isoenzymes, 49.09% resulted in immunotoxicity, 1.82% were toxic to cells, 14.55% would cause cancer, and 21.82% showed high tolerated doses in humans. Most of them showed a high volume of distribution, were free-flowing in plasma, and demonstrated moderate bioavailability, while all had high intestinal absorption and 78.18% demonstrated good water solubility. This 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

Citation: Didigwu, O.K.; Nnadi, C.O. Drug-Likeness, Pharmacokinetics, and Toxicity Prediction of Phytotoxic Terpenoids. *Proceedings* **2024**, *102*, 47. https://doi.org/10.3390/proceedings2024102047

Academic Editor: Youssef Sari

Published: 3 April 2024

Author Contributions: Conceptualization, C.O.N. and O.K.D.; methodology, C.O.N.; software, O.K.D.; validation, O.K.D.; formal analysis, O.K.D.; investigation, C.O.N. and O.K.D.; writing—original draft preparation, O.K.D.; writing—review and editing, C.O.N.; visualization, O.K.D. and C.O.N.; supervision, C.O.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.