IECTO 2024 Conference
The 1st International Electronic Conference on Toxics
20–22 March 2024 | Online

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

Obinna Kenneth Didigwu (obinna.didigwu.241741@unn.edu.ng) *1
Charles Okeke Nnadi (charles.nnadi@unn.edu.ng) 2

[1,2] Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria Nsukka, 410001 Enugu State, Nigeria

INTRODUCTION

Natural products, such as flavonoids, glycosides, alkaloids, terpenoids, quinones, steroids, saponins, and tannins, are secondary metabolites of plants with unique chemical properties and potential for drug discovery and development. Terpenoids and terpenes are particularly noteworthy.

Despite numerous terpenoids from various sources, only a few have been developed into drugs, such as paclitaxel and artemisinin. High attrition rates in drug discovery are due to pharmacokinetic and toxicity issues. Early pharmacokinetic and toxicity profiles are crucial for drug candidates. Considering terpenoids' potential for anticancer and other activities, further optimization, structure modification, or repurposing is necessary.

METHODS

A dataset of 1586 phytotoxins from 844 plant species was analyzed using ACD/ChemSketch v.12.0 software. The compounds were categorized based on secondary metabolites, and the Swiss Institute of Bioinformatics' target protocol was used to predict potential targets. The pharmacokinetic parameters and toxicities of selected compounds were predicted using swissADME and pkCSM web tools.

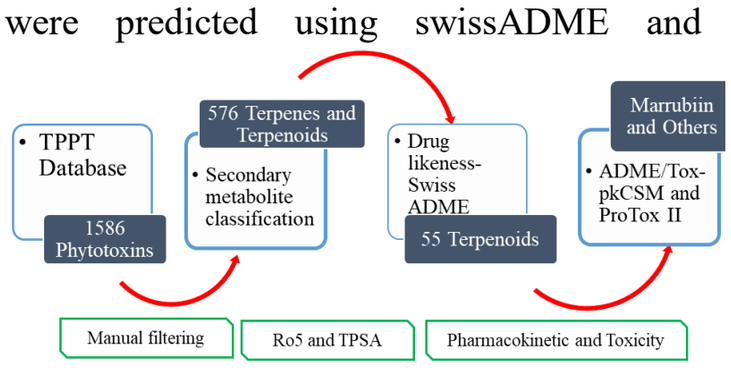

Figure 1. Data pre-treatment and prediction workflow

RESULTS AND DISCUSSION

The study analyzed 1586 phytochemicals in Toxic Plants-Phytotoxins (TPPT) database from 844 plant species, filtering 576 terpenes/terpenoids to create a new chemical dataset. The final dataset included 387 terpenes and 189 terpenoids, with a higher monoterpenoid proportion (30.9%). Drug-likeness properties, pharmacokinetic profiles, and toxicities were also examined.

The distribution of the TPPT into secondary metabolites and terpenoids/terpenes, drug-likeness prediction, pharmacokinetics profile prediction, and toxicity predictions are shown in Figures 2, 3, 4, and 5, respectively.

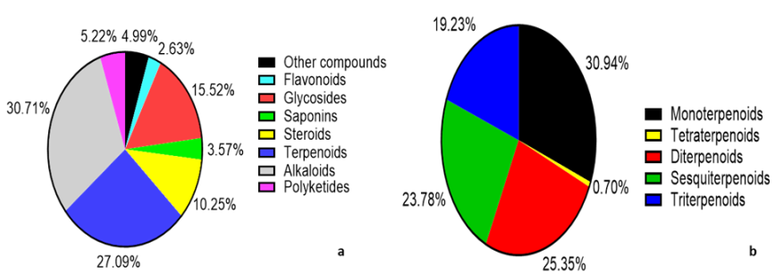

Figure 2. Distribution of TPPTs into (a) secondary metabolites and (b) terpenes/terpenoids

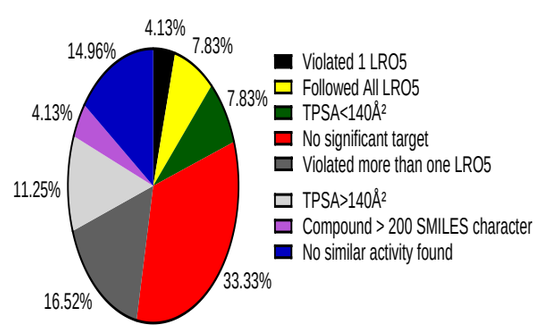

Figure 3. Drug-likeness properties of terpene/terpenoids. The web server could not process compounds with SMILES characters > 200

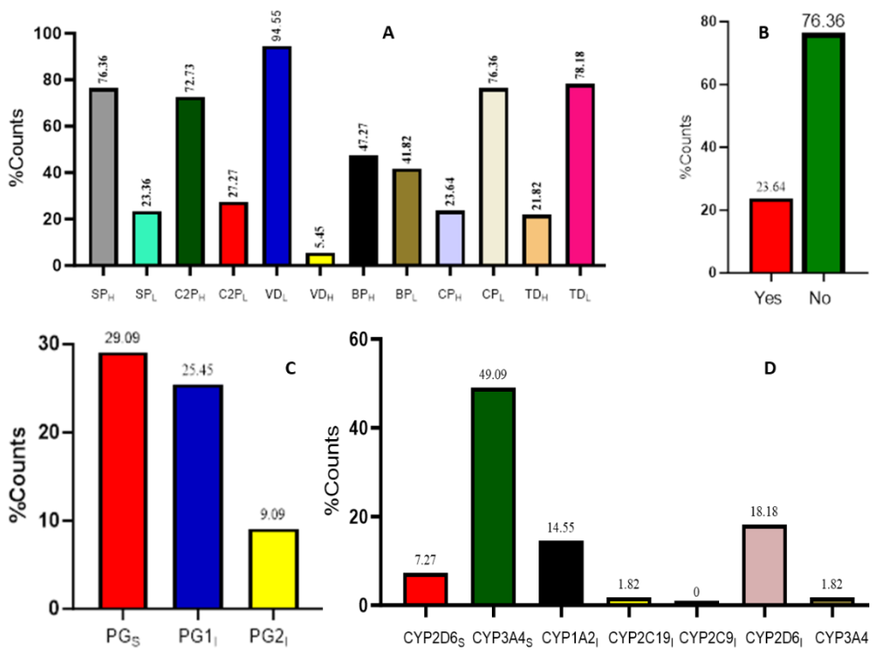

Figure 4. Distribution of (A) ADME (B) p-glycoprotein substrate/inhibitor (C) renal OCT-2 substrate and (D) cytochrome p450 isoenzymes properties of terpene/terpenoids. SP_H-High skin permeability, SP_L-Low skin permeability, $C2P_H$-High Caco-2 permeability, $C2P_L$-Low Caco-2 permeability, VDL-High volume of distribution, VDH-Low volume of distribution, BPH-High blood-brain barrier permeability, BPL-Low blood-brain barrier permeability, CPH-High central nervous system permeability, CPL-Low central nervous system permeability, TDH-High tolerated dose, TDL-Low tolerated dose, PGS-P-glycoprotein substrate, PGI-P-glycoprotein I inhibitor, PGS-P-glycoprotein II inhibitor, CYP2D6S-Cytochrome p450 2D6 substrate, CYP3A4S-Cytochrome p450 3A4 substrate, CYP1A2I-Cytochrome p450 1A2 inhibitor, CYP2C19I-Cytochrome p450 2C19 inhibitor, CYP2C9I-Cytochrome P450 2C9 inhibitor, CYP2D6I-Cytochrome p450 2D6 inhibitor, CYP3A4I-Cytochrome p450 3A4 inhibitor.

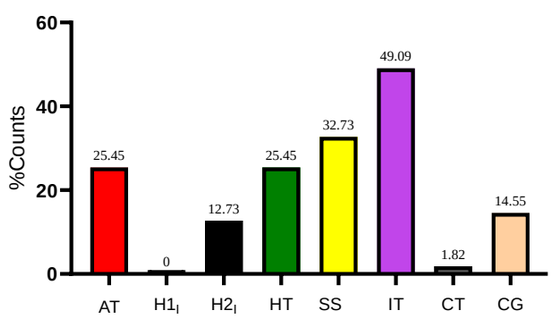

Figure 5. Some toxicological endpoints of terpenes/terpenoids; Ames toxicity (AT), HeRG I inhibitor (H1I-), HeRG II inhibitor (H2I), Hepatotoxicity (HT), Skin sensitization (SS), Immunotoxicity (IT), CT-Cytotoxicity (CT), Carcinogenicity (CG)

CONCLUSION

The study predicts drug-likeness, ADME, and toxicity endpoint properties of 576 phytotoxic terpenes using webserver algorithms, providing a comprehensive tool for drug development and repurposing. Nine terpenes, including marrubiin, were identified as potential lead compounds for optimization and further development.

REFERENCES

C.O. Nnadi, L.U. Ozioko, G.C. Eneje, C.M. Onah, W.O. Obonga. *In-vivo* antitrypanosomal effect and *in silico* prediction of chronic toxicity of N-methylholaphyllamine in rats, Trop. J. Pharm. Res. 19 (2020) 2369-2375, http://dx.doi.org/10.4314/tjpr.v19i11.18

C.A. Lipinski, Lead- and drug-like compounds: The rule-of-five revolution, Drug Discov. Today Technol. 1 (2004) 337–341, https://doi.org/10.1016/j.ddtec.2004.11.007