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Original Research Article

Theoretical Drug-likeness, Pharmacokinetic and Toxicities of Phytotoxic Terpenoids from the Toxic Plants-Phytotoxins

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ABSTRACT

Pharmacokinetic and toxicity-related properties are the major causes of attrition in drug development. The emerging roles of terpenes in drug discovery require an understanding of these properties for structure modification and possible repurposing. This study evaluated the drug-likeness, pharmacokinetic, and toxicity profiles of diverse phytotoxic terpenes obtained from the Toxic Plants–Phytotoxins (TPPT) database using different *in silico* algorithms. The database, of 1586 phytotoxins, was filtered to obtain 576 phytotoxic terpenoids (PhytoTerp). The Lipinski parameters, potential targets, pharmacokinetic profiles and toxicity on various organ endpoints were implemented using SwissADME, SwissTargetPrediction, the pkCSM and ProTox II webservers. Drug likeness prediction showed that 9.55% of the PhytoTerp obeyed Lipinski's rule of five. The toxicity profiles showed that none of the compounds inhibited hERG I, while 12.73% inhibited hERG II. In addition, 25.45% of the compounds elicited both AMES and liver toxicities; and 32.73% caused skin sensitivity. Furthermore, 72.73 and 76.36% showed high Caco-2 and skin permeability respectively. The p-glycoprotein was extruded by 29.09% and inhibited by 34.45% of PhytoTerp; 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% were immune-toxic, 1.82% were toxic to cells, 14.55% would cause cancer, and 21.82% showed high tolerated doses in humans. All the PhytoTerp demonstrated high intestinal absorption while a significant number demonstrated moderate bioavailability. This study identified marrubiin and nine other terpenoids as drug-like, non-toxic, and highly bioavailable with potential for further optimization, and development.

Keywords: Drug-likeness, Pharmacokinetic profile, Phytotoxic terpenes, Toxicity.

Introduction

A natural product is a biological substance of natural origin and has pharmacological and biological qualities that serves as templates in the design and development of new drugs. [1] Natural product offer advantages in drug discovery and development, representing chemical novelty and potentially originating lead drug candidates for complex targets compared to other sources. [1,2] They provide the building blocks necessary for the development of early medications and valuable novel treatments for serious illnesses. [3] Most of these natural products are secondary metabolites of plants that occur as flavonoids, glycosides, alkaloids, terpenoids, quinones, steroids, saponins, and tannins. [4-9]Terpenoids represent a highly prevalent class of phytoconstituents, showcasing intricate chemical architectures, a multitude of biological functionalities, and versatile pharmacokinetic attributes. [10] They represent an alternative classification of terpenes that incorporate oxygen molecules as a result of biochemical alterations such as the elimination or introduction of methyl groups. [11] According to the results of various bioassays, terpenoids have the potential to serve as source lead compounds in the treatment of protozoan parasitic diseases such as malaria. [12]

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They have also been reported to elicit antimicrobial activities against both the antibiotic-resistant and antibiotic-susceptible microorganisms. [13] Generally, the utilization of this class of phytochemicals holds immense significance in the treatment of various ailments and has been extensively studied both in controlled laboratory settings and in living organisms. These investigations have demonstrated its potential as an effective tool against cancerous growth, microbial infections, inflammatory responses, oxidative stress, allergic reactions, neural damage, and clotting disorders, as well as for inducing relaxation and relieving pain. The multifaceted therapeutic effects can be attributed to the influence of the number of the isoprene units, and glycoside compounds. [14] Despite countless available terpenes isolated from marine organisms, plants, microbes, endophytes, plant pathogens and animals, only a few terpenes and terpenoids such as the anticancer paclitaxel and antimalarial artemisinin have been developed into drugs. [15] The high attrition rates in drug discovery and development have been significantly attributed to the pharmacokinetic and toxicity issues associated with the potential drug candidates. [16,17] To avert failures at the advanced stage of development, it is imperative to examine the pharmacokinetic and toxicity profiles of potential drug candidates during the early stages of development. Previous data have suggested several important pharmacological activities of terpenes which can be harnessed to develop useful drugs, and typically phytotoxic terpenes have demonstrated stronger potential for anticancer and other activity despite their apparent *in vitro* cytotoxicity. [15] However, this approach to discovering efficacious anticancer chemotherapeutic agents has not been explored to the best of our knowledge. Therefore, these emerging roles of terpenoids in drug discovery and design require that the drug-likeness, pharmacokinetic and toxicological properties be evaluated for further optimization, structure modification or possible repurposing.

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Materials and Methods

Hardware and web servers

A server computer with specifications: processor Intel(R) Dell latitude(R) CPU 847@ 1.10GHz, system type 64-bit OS, RAM 4.00 GB with Windows® 7 was used for the study. The ACD/ChemSketch v.12.0 software (ACD labs, 2021) and freely available web tools such as pkCSM, ProTox II, swissADME and SwissTargetPrediction interfaces were used for the predictions. [18,19] The GraphPad prism v. 10.1.0 was used to analyse the generated data.

Chemical dataset

A data set comprising 1586 freely available phytotoxins obtained from 844 plant species was harvested from the Toxic Plants-Phytotoxins (TPPT) database. [20] The TPPT database is freely available for download from https://www.agroscope.admin.ch/agroscope/en/home/publications/apps/tppt.html. The 2D structure of the compounds was presented using ACD/ChemSketch v.12.0 by inputting their canonical Simplified Molecular Input Line Entry System (SMILES) and stored in mol2 format. The TPPT was clustered into data subsets of secondary metabolites to obtain the phytotoxic terpenes (PhytoTerp).

Prediction of target

The prediction of the target protocol of the Swiss Institute of Bioinformatics′ (SIB) was implemented to identify possible targets of the 576 PhytoTerp. The algorithm involved the identification of the scaffold, and measurement of the fingerprint and shape similarities with known ligands. [18,19,21]

Drug-likeness properties of PhytoTerp

The drug-likeness of the 576 PhytoTerp was predicted by calculating the topological polar surface area (TPSA) and the parameters of the Lipinski's rule of five (Ro5) such as the molecular weight (MW), octanol-water partition coefficient (logPo/w), number of hydrogen bond acceptors (nAcc) and number of hydrogen bond donors (nDon). [22]

Pharmacokinetic profiles of PhytoTerp

The pharmacokinetic parameters (absorption, distribution, metabolism, and excretion, ADME) of selected drug-like PhytoTerp with TPSA < 140 $Å^2$ were predicted using the SIB, swissADME web tool. [23] The pkCSM web tool predicted water solubility, cancer coli-2 (Caco-2) permeability, intestinal absorption, skin permeability, *p*-glycoprotein substrate and inhibitor I/II, volume of distribution in human (VDss) in humans, fraction unbound, blood-brain barrier (BBB) permeability, central nervous system (CNS) permeability, cytochrome p450 enzymes, total clearance, and renal organic cation transporter 2 (OCT-2) substrate. [24]

Toxicity of PhytoTerp

The toxicity of the 55 PhytoTerp that passed Lipinski's Ro5 with TPSA < 140$Å^2$ was predicted using ProTox II and pkCSM web tools. [23,24] The ProTox II web tool predicted hepatotoxicity, immunotoxicity, carcinogenicity, and cytotoxicity. [23] The pkCSM web tool was also used to predict Ames toxicity, maximum recommended tolerated dose (MRTD) in human, cardiotoxic human a-go-go related gene (heRG I/II), oral rat acute toxicity (LD_{50}), oral rat chronic toxicity, hepatotoxicity, and skin sensitization. [24] The analysis workflow is shown in Figure 1.

Results and Discussion

Chemical dataset

The distribution of the TPPTs into different phytochemical classes is shown in Figure 2a. Of the 1586 TPPTs identified in 844 plant species, 576 PhytoTerp were manually filtered in the preliminary investigation to a new chemical dataset. The working dataset comprises 387 terpenes and 189 terpenoids. The distribution of the PhytoTerp into different classes based on the number of isoprene units is shown in Figure 2b, with a significantly higher (30.9%) relative composition of monoterpenoids.

Analysis of drug-likeness of PhytoTerp

The drug-likeness predictions showed that 55 PhytoTerp obeyed all the Lipinski Ro5 and with TPSA < 140 Å. The selected compounds' MW ranged from 150.22 to 496.64 g/mol. The detailed drug-likeness profiles are shown in the supplementary Table S2 while the relative distribution of the compounds' properties is shown in Figure 3. The TPSA of the drug-like PhytoTerp ranged between 17.07- 107.22 $Å^2$ while the drug-likeness prediction showed that 9.55% of the TPPTs conformed with the Lipinski's Ro5 and could be potential lead compounds. A compound is less likely to be employed for drug development if it has a higher MW [10]. The TPSA is a vital parameter used to assess permeability, solubility, and transport characteristics of a compound like intestinal absorption and BBB permeation. The drug-likeness test can be executed by employing various rules such as Lipinski's Ro5, Ghose, Veber, Egan and Muegge's rules, each characteristic criterion for drug-likeness. Nevertheless, Lipinski's Ro5 was used for evaluation due to its extensive utilization and precision. [25] The Lipinski Ro5 specified that MW should fall within the acceptable range of ≤ 500, the nDon ≤ 5, nAcc ≤ 10 and LogP ≤5. [26]

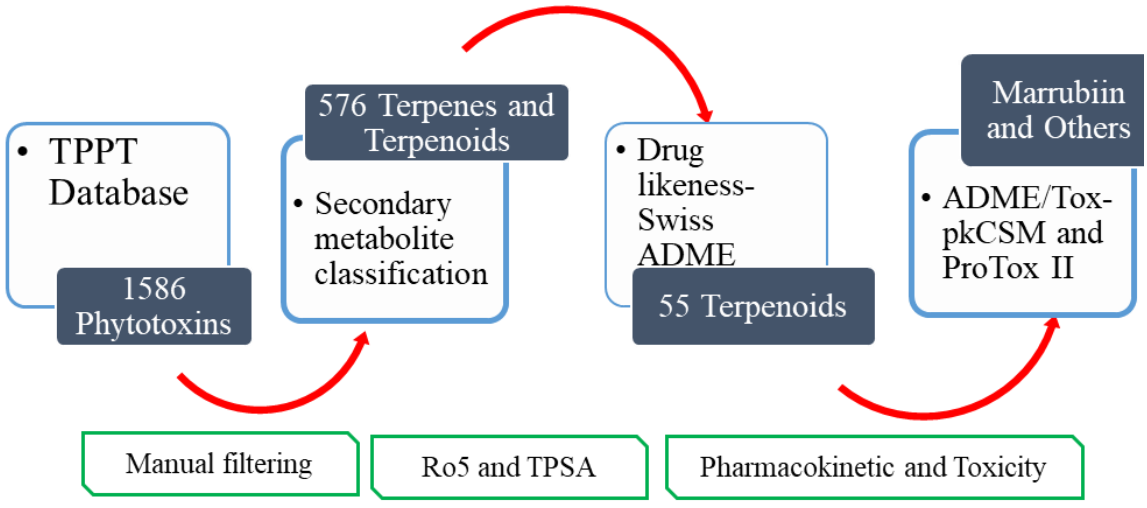

Figure 1. Data pre-treatment and prediction workflow

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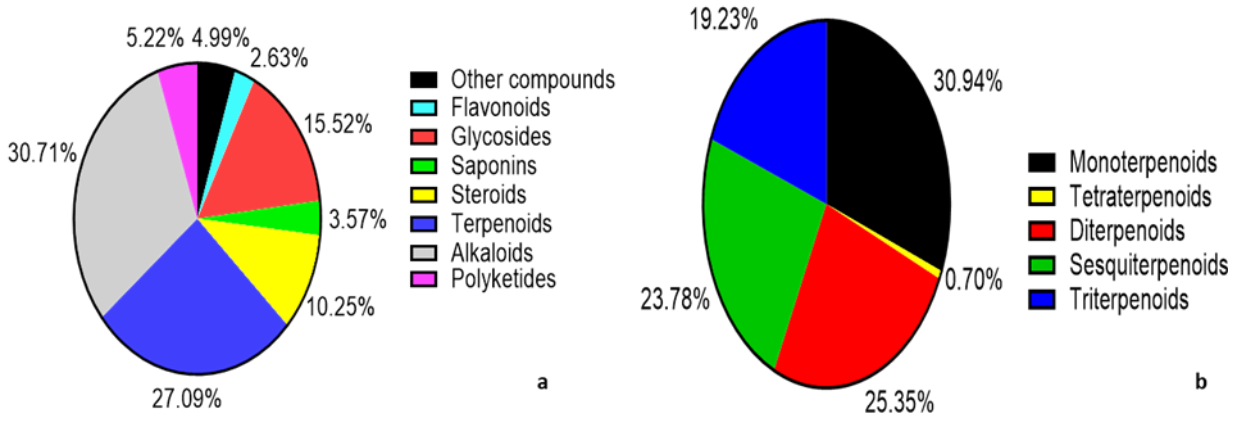

Figure 2: Distribution of TPPTs into (a) secondary metabolites and (b) chemical classes of PhytoTerp

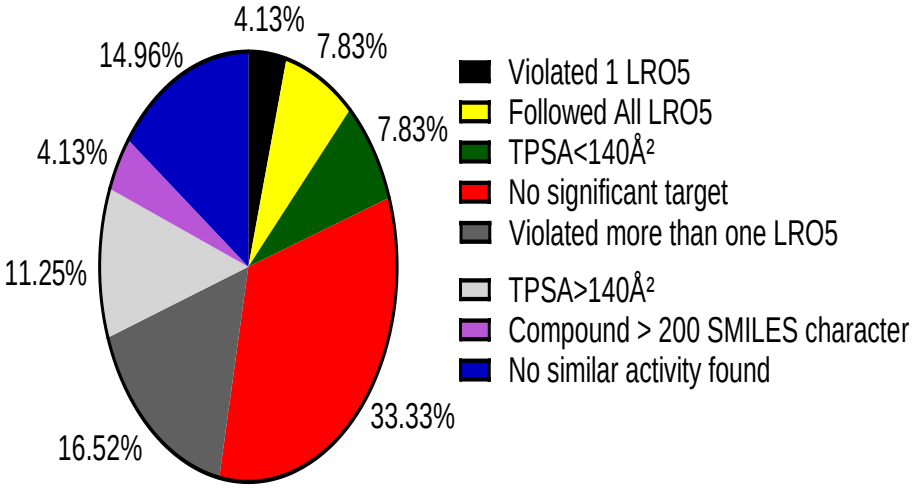

Figure 3: Drug-likeness properties of PhytoTerp. The web server could not process compounds with SMILES characters > 200

Potential PhytoTerp targets

Understanding the interaction of compounds with targets implicated in the pathogenesis of diseases is important in optimizing the pharmacodynamics of drug candidates. The prediction of the target explored different proteins and enzymes that are important in the pathophysiology of many diseases. The PhytoTerp, their possible targets and associated pathological conditions are shown in the Table 1. Common disease conditions implicated in the target prediction analysis included hypertension, attention deficit hyperactive disorder, cancer, neurodegenerative disorders, diabetes and cardiac disorders.

Analysis of pharmacokinetic profiles

The SwissADME and pkCSM prediction of pharmacokinetic profiles are shown in Figure 4. The predicted bioavailability scores showed scores of 0.55 – 0.85 for most of the compounds suggesting moderate to high bioavailability. Bioavailability represents the fraction of an administered drug that reaches the systematic circulation and the site of action. [27]

Water solubility

Aqueous solubility is an important parameter in drug development as both orally and parenterally administered drugs should dissolve in water to effectively release the therapeutic moiety for pharmacological actions. The study revealed that 78.18% of the compounds were soluble while 21.82% were moderately soluble. Here, the decimal logarithm (log S) of the molar solubility in water was adopted by pkCSM for calculating the water solubility of the compounds. [24] The water solubility (logS) of the compounds evaluated ranges from -5.254 to -2.116, which is within the FDA's permitted values. The orally administered drug is absorbed into the portal vein system only if it dissolves in the intestinal fluid. Some drugs in the form of powders need to be reconstituted with water before being administered and thus, the solubility of the powder in water must be ascertained during the pre-formulation studies.

Permeability through barriers

The predicted permeability potential of the compounds through Caco-2, skin, BBB and CNS were analysed. The analysis showed that 72.73, 76.36, 47.27 and 23.64% of the PhytoTerp showed high Caco-2, skin, BBB and CNS permeability (Figure 4A).

The Caco-2 cell line is an *in vitro* model of the human intestinal mucosa used to anticipate the absorption of orally administered molecules. [24] The Caco-2 permeability of potential drug molecules has implications for drug development. It elucidates the biological and biochemical properties underlying the barrier characteristics of the intestinal mucosa as well as insights into the assimilation processes of pharmaceuticals and dietary constituents. [28] The skin permeability is significant in the context of transdermal drug development. In the pkCSM skin permeability model, a compound with a log Kp ≥ -0.25 is considered to possess low skin permeability. [24] The BBB, which can transport molecules that dissolve in both lipids and water, represents a microvasculature of the CNS which shields the brain from exogenous compounds. It also controls the movement of molecules, ions, and cells between the blood and the CNS. [29] In the pkCSM algorithm of BBB, a Log BB ≥ 0.3 suggests efficient permeability, whereas distribution is

inhibited when the Log BB < -1. The ability of a drug to permeate the brain is a significant factor to take into account to potentially reduce any negative effects and toxicities or to potentially enhance the effectiveness of drugs whose pharmacological activity is centred within the brain. This measurement, however, poses some challenges due to some confounding factors. A more accurate assessment is the use of the blood-brain permeability surface area product (logPS) which is derived from *in situ* brain perfusions, wherein the compound of interest is directly administered into the carotid artery. This approach evidenced in the lower number (23.6% CNS vs 47.2% BBB) of PhytoTerp that meets the criterion, eliminates the potential distortions in brain penetration caused by systemic distribution effects. [24]

Table 1: Best drug-like PhytoTerp with associated targets and disease conditions

PhytoTerp	**Ro5**	**Target**	**Associated diseases**
Marrubiin (**17**)	Yes	Kappa Opioid receptor	Major depressive disorder (MDD)
Ascaridole (**20**)	Yes	Nitric oxide synthase, inducible (by homology)	colon, colorectal, gastric, esophageal, and liver cancers
Borneol (**21**)	Yes	Carbonic anhydrase II	osteopetrosis, renal tubular acidosis, and cerebral calcification
Fenchol (**22**)	Yes	Carbonic anhydrase II	osteopetrosis, renal tubular acidosis, and cerebral calcification
Bornyl acetate (**25**)	Yes	Acetylcholinesterase	Alzheimer's disease (AD), Lambert-Eaton myasthenic syndrome (LEMS), and myasthenia gravis (MG), Glaucoma

ADME of PhytoTerp

The bioavailability of orally administered drugs depends on the extent of absorption of solubilized drugs across the permeable intestinal barriers via diffusional processes. The results showed that the compounds have an intestinal absorption range of 62.8 – 100%, which follows the pkCSM algorithm, that oral drugs with absorption > 30% have good intestinal absorption. Distribution is controlled by the volume of distribution (VDss) and fraction of the unbound drug in the plasma. The result of the distribution showed that 80% of the compounds are unbound to plasma protein while 94.5% showed a high VDss. A compound possessing a substantial VDss value signifies that the compound is more extensively distributed throughout the body in comparison to its distribution in the blood plasma. A compound exhibits a diminished VDss if the log VDss < -0.15; and conversely, it shows an elevated volume of distribution if it exceeds 0.45. [24]

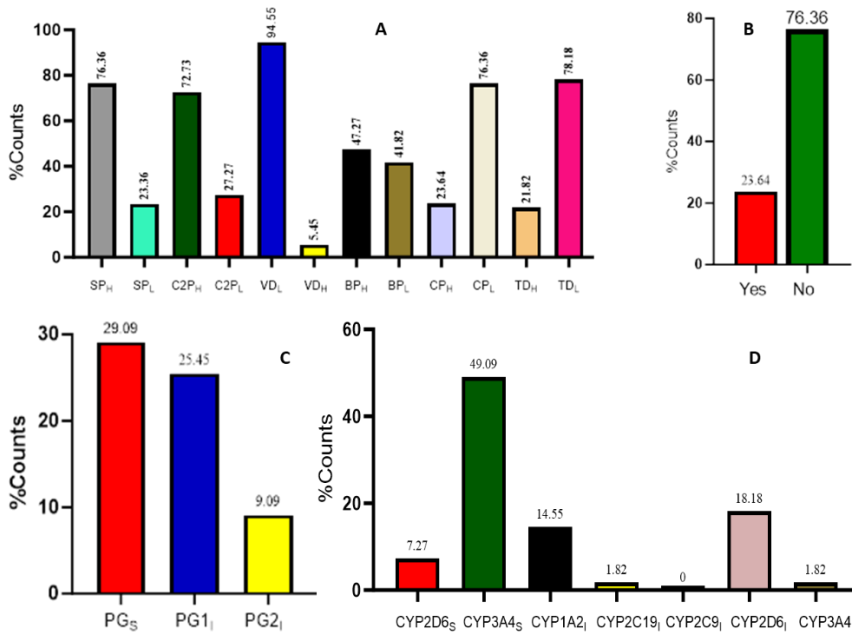

Figure 4: Distribution of (A) ADME (B) p-glycoprotein substrate/inhibitor (C) renal OCT-2 substrate and (D) cytochrome p450 isoenzymes properties of PhytoTerp. SP_H-High skin permeability, SP_L-Low skin permeability, $C2P_H$-High Caco-2 permeability, $C2P_L$-Low Caco-2 permeability, VDL-High volume of 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.

For a drug that commonly binds to a plasma protein, there is a decreased free plasma fraction, prolonged duration of action, and elimination half-life. Thus, less protein-bound compounds penetrate tissue better than those that are highly bound and have a faster excretion rate. Metabolism is the biotransformation of substances in the body and two isoforms of cytochrome p450 enzymes- CYP2D6 and CYP3A4 are responsible (Figure 4D). These enzymes can be inhibited by some substances and can metabolize some substances (substrate). [18] The study showed that 7.27 and 49.09% of the drug-like PhytoTerp are CYP2D6 and CYP3A4 substrates while 14.55, 1.82, 18.18, and 1.82% are CYP1A2, CYP2C19, CYP2D6, and CYP3A4 inhibitors respectively. CYP2C9 was not inhibited by any of the compounds. The elimination profiles were evaluated by the p-glycoprotein, total clearance (CLTOT) and OCT-2 parameters. The study showed that 29.09% of the compounds are p-gp substrates while 25.45 and 9.09% are p-gp I and II inhibitors respectively (Figure 4B). The CLTOT analysis showed that the speed of excretion of the compounds ranged from - 0.048 to 1.365 while 23.6% of the PhytoTerp are substrate to OCT-2 (Figure 4C). P-glycoprotein is an ATP-binding cassette transporter which functions as a biological barrier by extruding toxins out of cells. It is overly expressed in organs like the liver, kidney, pancreas, colon, and adrenal cortex, therefore, maybe be involved in secretion processes in the body. [30,31] The liver, bile and kidneys play vital roles in the process of CLTOT [32]. Total clearance is linked to the bioavailable drug and implies achieving the steady-state concentration. The OCT-2 is a renal transporter that assumes a crucial function in the elimination of drugs and endogenous compounds, thereby influencing their disposition and clearance.

Toxicity of PhytoTerp

Toxicology is the extent to which a compound can cause harm to an organism or its organs, such as the kidneys and liver, and is a major factor contributing to the failure of drug development in later stages [31]. Toxicity predictions encompass a wide spectrum, spanning from prognostications of diverse toxic outcomes such as acute toxicity or carcinogenicity to prognostications of the fundamental mechanisms underlying toxicity, [33] as shown in Figure 5. These mechanisms entail the identification of the targets involved in adverse drug reactions and the associated toxic effects.

Ames toxicity of PhytoTerp

The study showed that 25.45% of the PhytoTerp exhibited Ames toxicity based on the pKCSM algorithm (Figure 5). Ames test is employed to examine the mutagenic potential of a compound using *Salmonella typhimurium*. When exposed to mutagenic substances, these mutant bacterial cells can undergo a reversal of the mutation, thereby allowing the bacteria to thrive in a histidine-deficient environment. [34] A positive test indicates that the compound is mutagenic and therefore may act as a carcinogen. However, only 14.55% of the compounds showed potent carcinogenic activity in the ProTox II algorithm representing their potential to elicit or augment cancer occurrence; either via genotoxicity or non-genotoxicity. [35]

Toxicological endpoints

Other toxicological endpoints were analysed and the results showed that 12.73, 25.45, 49.09, and 1.82% of the compounds could be cardiotoxic (hERG II), hepatotoxic, immunotoxic or cytotoxic (Figure 5). Cardiotoxicity is parametrized by hERG I and II which leads to fatal ventricular arrhythmia via potassium channel inhibition. [36] There was no inhibition of hERG I. Hepatotoxicity affects the pharmacokinetic properties of a drug; it is of great concern during drug development and is one of the leading causes of drug attrition. Therefore, the liver is always vulnerable to ingested drugs that are absorbed from the gastrointestinal tract and transported to the liver. [37] The algorithm modestly categorizes a substance as hepatotoxic, if it possesses at least one pathological or physiological effect of the disruption. [38] Immunotoxicity is characterized as untoward impacts on the operation of both indigenous and general immune systems stemming from encounters with detrimental substances, encompassing chemical warfare agents. This may subsequently break down the immune system, thereby making the body susceptible to infection and tumours. Cytotoxicity measurements serve as a valuable preliminary measure in ascertaining the plausible detrimental effects of the PhytoTerp, and various sources such as chemical agents, interactions with other cellular entities like a natural killer (NK) or T cells, or external factors like exposure to radiation, extreme temperatures, or high-pressure situations. [39]

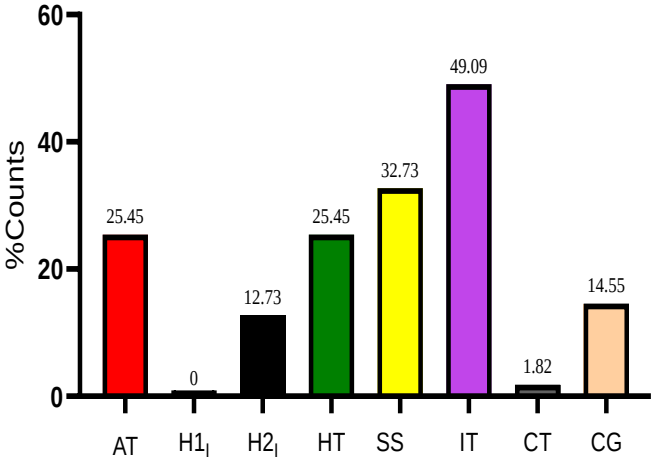

Figure 5: Some toxicological endpoints of terpenes/terpenoids; Ames toxicity (AT), HeRG I inhibitor (H1I-), HeRG II inhibitor (H2I), Hepatotoxicity (HT), Skin sensitization (SS), Immunotoxicity (IT), CT-Cytotoxicity (CT), Carcinogenicity (CG).

Other toxicity indicators

The MRTD represents an estimation of the threshold at which chemicals become toxic to the human body and serves as a valuable tool in determining the appropriate dosage for pharmaceuticals during clinical trials. [24] The MRTD was shown by 21.82% of the compounds. Another toxicity parameter is oral acute toxicity (LD_{50}) with values ranging from 1.568 to 3.139 mol/kg. This prediction is challenging due to its intricate nature, as it relies on the variability exhibited by the biological mechanisms. [40] The oral rat chronic toxicity was designed to examine the outcomes of repeated ingestion, application on the skin, or inhalation of a substance throughout a specified duration. [41] The oral rat chronic toxicity dose ranged from 0.341 to 2.674. this parameter is vital as it is used to determine the MRTD for initiating the initial human studies. [42] Since 76.36% of the compounds were predicted to be permeable to the skin, there are chances of skin sensitization for dermally applied pharmaceutical products. Skin sensitivity was exhibited by 32.73% of the drug-like PhytoTerp. It is a potential adverse effect of these drugs and, therefore, a compound must be evaluated for the potential to induce allergic contact dermatitis when in contact with the skin. This phenomenon is intricately connected to the capacity of a molecule to penetrate the skin, a process that is mainly governed by the physicochemical characteristics of the chemical compound, as well as the physicochemical and biological properties of the skin membrane [31].

Compounds derived from natural sources present a significant advantage in the field of drug discovery and development. [15] It is advisable to conduct experimental profiling of the relevant ADME/T characteristics of these compounds before the identification of potential candidates for further investigation. Nevertheless, this particular procedure is characterized by its lengthy duration and expensive nature. The field of computer-aided drug design (CADD) has produced a profound transformation in the research and development processes involved in the identification of potential drug candidates. This transformation is primarily attributed to the rapid growth in both chemical and biological information. As a result, CADD can be effectively employed in the early assessment of the drug-likeness and ADME/T properties of compounds, effectively reducing the time and

cost associated with screening and testing. This, in turn, facilitates the identification of the most promising candidates for further assessment, while simultaneously eliminating those with a low probability of success or a high attrition rate.

Drug-like terpenes for optimization

The significant roles played by terpenes in the process of discovering and developing drugs necessitate the confirmation of drug-likeness and ADME/Tox properties. In this study, SwissADME, SwissTargetPrediction, ProTox II and pkCSM algorithms were utilized to assess the ADME, potential targets, toxicity and physicochemical properties of the PhytoTerp. Out of the 55 drug-like PhytoTerp that met the basic Lipinski Ro5, only marrubiin (**17**), ascaridole (**20**), borneol (**21**), fenchol (**22**), bornyl acetate (**25**), camphor (**28**), fenchone (**29**), buddledin B (**33**), (+)-isothujone ((+)-β-thujone) (**34**) and cinerin II (**38**) exhibited favorable physicochemical, ADME and toxicity properties (Table 1 and Figure 6).

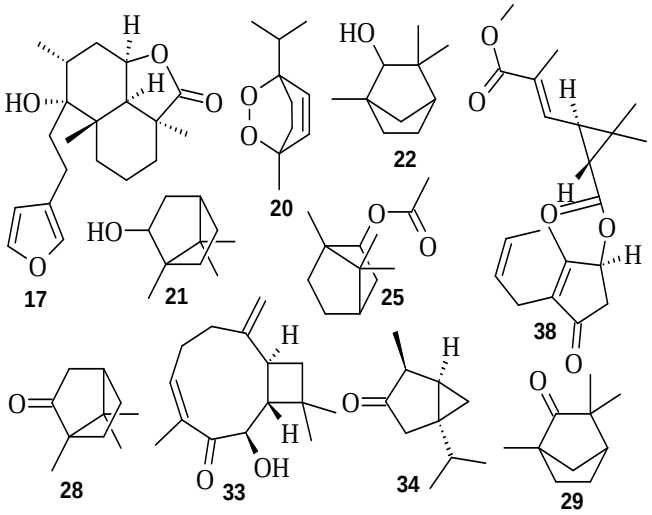

Figure 6. Chemical structures of best drug-like PhytoTerp

Among these, marrubiin derived from *Marrubium vulgare* appeared to be the best lead with high bioavailability and potential for further optimization and development. Consequently, marrubiin can be prioritized for further development based on the computational profiling elucidated in this paper. This investigation proposes that additional experimental analysis be conducted *in vitro* and *in vivo* to authenticate the current prognostication before embarking upon costly clinical trials.

Conclusion

The drug-likeness, ADME and toxicity endpoint properties of 576 phytotoxic terpenes were predicted using different webserver algorithms. This study has provided a comprehensive tool for understanding the roles of terpenes in drug development and further provided evidence for possible repurposing. Furthermore, the study has short-circuited the tortuous journey involved in biological testing protocols to probably arrive at the same goal which SwissADME, SwissTargetPrediction, ProTox II and pKCSM have achieved. Moreover, marrubiin and the other nine terpenes were identified as the potential lead compounds and could be prioritized for optimization and further development based on their drug-likeness, safety, favourable pharmacokinetic properties and the vital enzymes associated with various disease pathophysiology they interacted with in this study.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them. A poster presentation of the abstract of this article can be found in Proceedings of the 1st International Electronic Conference on Toxics (IECC 2024) at https://sciforum.net/paper/view/16994

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