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# In Silico Evaluation of Physicochemical and ADMET Properties of Bioactive Compounds from *Marchantia paleacea*.

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**ABSTRACT**

*Marchantia paleacea* is a liverwort with diverse secondary metabolites of pharmacological interest. This study aimed to evaluate the physicochemical and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of eighteen bioactive compounds previously identified from *M. paleacea* by GC-MS analysis using an in silico approach. Physicochemical parameters were analyzed using SwissADME, ADMET predictions were performed using pKCSM and ProTox 3.0 for toxicity class analysis. Results showed that most compounds complied with Lipinski's Rule of Five (RO5), demonstrating good oral drug-likeness. All compounds exhibited high human intestinal absorption (86-95%), favorable BBB permeability, and CNS permeability values remained low. Most compounds did not significantly interact with major CYP450 isoenzymes or P-glycoprotein. Toxicity prediction revealed that the majority of compounds were non-mutagenic (Ames-negative), non-hepatotoxic, and did not inhibit the hERG channel, suggesting a relatively safe pharmacological profile. Exceptions included 2-nitro-cyclohexanone (positive Ames test) and thymol (hepatotoxicity). Compounds such as linalool, dodecanoic acid, n-decanoic acid, and bicyclo[2.2.2]hept5-en2-ol demonstrated particularly favorable drug-like characteristics, warranting further experimental validation. These findings provide a computational foundation for prioritizing *M. paleacea* bioactive compounds for future drug development.



## Introduction

The development of novel therapeutics derived from natural products necessitates a thorough understanding of both pharmacokinetic and pharmacochemical properties. Despite significant advancements in pharmaceutical research, the drug discovery and development pipeline remains highly complex, protracted, and capital-intensive, characterized by prohibitive attrition rates during the preclinical phase. A principal contributor to compound failure is unfavorable pharmacokinetic and

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toxicological attributes (Sharma et al., 2018). Although numerous bioactive molecules exhibit potent therapeutic efficacy in vitro, clinical translation is often constrained by suboptimal oral bioavailability, limited membrane permeability, inadequate metabolic stability, or toxic profiles.

The integration of modern analytical techniques, such as gas chromatography (GC-MS), with in silico ADMET screening and pharmochemical profiling has been demonstrated to substantially enhance the success rates of drug development pipelines. In recent years, in silico approaches have emerged as necessary tools in the early stages of drug discovery and lead optimization. Computational methodologies enable the rapid and cost-effective prediction of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties, as well as drug-likeness profiles, prior to experimental validation (Daina et al., 2017). ADMET analysis plays a critical role in identifying compounds with favorable pharmacokinetic characteristics while mitigating the risk of late-stage development failure (Sharma et al., 2018). Parameters estimated to significantly influence molecular efficacy, safety, and metabolism are evaluated across all compounds according to Lipinski's five criteria (Olasupo et al., 2021). Furthermore, molecular physicochemical parameters including molecular weight, lipophilicity, topological polar surface area, hydrogen-bond donors and acceptors, and molecular flexibility are widely recognized as critical determinants of oral bioavailability and membrane permeation, as conceptualized by Lipinski's rule of five and related criteria (Lipinski 2001; Veber et al., 2002). The integration of ADMET prediction and physicochemical profiling provides a robust framework for the rational selection and optimization of potential drug candidates.

Several computational platforms, including SwissADME and ProTox 3.0, have been extensively employed to evaluate the drug-likeness, pharmacokinetic behavior, and toxicity risk profile of bioactive compounds. These computational tools facilitate the efficient screening and prioritization of lead compounds through the systematic analysis of structural and three-dimensional characteristics governing molecular efficacy, safety, and metabolism (Huang et al., 2019). This approach substantially accelerates the drug discovery process while simultaneously reducing the financial burden and experimental demands conventionally associated with pharmacological screening.

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*Marchantia paleacea,* a member of the thalloid liverwort species, is reported to possess diverse pharmacological potential. Prior phytochemical investigations have identified an array of bioactive constituents, including flavonoids, phenolic compounds, terpenoids, saponins, and steroids, which have been associated with a range of biological activities such as immunomodulatory, antibacterial, antifungal, antiviral agents, antidiabetic effects, and cancer (Asakawa, 2017; Purkon et al., 2021). The therapeutic potential of this plant is largely attributed to its terpenoid-rich aromatic compounds and specialized oil bodies. In traditional medicine, several liverwort species have been used to treat burns, bruises, snake bites, pulmonary tuberculosis, neurasthenia, and pneumonia, with terpenoid-driven aromatic compounds and oil bodies playing important roles in these biological activities (Asakawa, 2017).

*M. paleacea* has been reported to exhibit various biological activities, including anticancer potential. A previous study reported by Siregar et al (2026) investigated the anticancer potential of compounds identified through LC-MS/MS analysis using a molecular docking approach against cancer-related protein targets. However, compounds identified through GC-MS analysis from the same species have not been further explored for their potential as drug candidates. Evaluating pharmacokinetic profiles and physicochemical properties is essential for assessing a compound's suitability as a drug candidate through computational approaches. Therefore, this study aims to analyze the pharmacokinetic characteristics and physicochemical properties of GC-MS identified bioactive compounds from *M. paleacea* to evaluate their potential as natural product-based drug candidates. The results are expected to provide a scientific foundation for phytopharmaceutical development and accelerate computational drug discovery.

## Materials and Methods

### Experimental Design

This study was conducted in silico utilizing computational methodologies based on data extracted from previous literature (Siregar et al., 2025).

### Ligand preparation

Bioactive phytocompounds from *M. paleacea* were collected from GC-MS analysis of the methanolic extract in a previous study (Siregar et al., 2025). The Simplified Molecular Input Line Entry System (SMILES) structures of these compounds were retrieved from the PubChem database

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(https://pubchem.ncbi.nlm.nih.gov/) accessed in January 2026.

**Physicochemical Profile of Compound**

Physicochemical profiles of compounds from *M. paleacea* were also analyzed using SwissADME accessed in January 2026 (http://www.swissadme.ch/), which evaluated various physicochemical parameters, including lipophilicity, polarity, solubility, molecular weight (g/mol), number of rotatable bonds, number of hydrogen bond acceptors and donors, and violation of Lipinski's rule of five (Gonzales et al., 2023).

**Prediction of Pharmacokinetic Profiles**

Pharmacokinetic profiles were predicted using a computational approach employing pKCSM pharmacokinetics (https://biosig.lab.uq.edu.au/pkcsm/prediction) encompassing absorption, distribution, metabolism, and excretion (ADME) properties of compounds from *M. paleacea*. Additionally, toxicity analysis was performed using ProTox 3.0 (https://tox.charite.de/protox3/) to determine the toxicity classification levels of the compounds. ProTox 3.0 was an expert at predicting toxicology class using cross-validation on structurally similar compounds in the dataset and classifying compounds based on LD50 values (Banerjee et al., 2024). ProTox 3.0 and pKCSM analysis were accessed in January 2026.

## Results and Discussion

The pharmacological relevance of *M. paleacea* as a source of bioactive metabolites has been substantiated through numerous ethnobotanical and experimental studies documenting its antimicrobial, hepatoprotective, antioxidant, and immunomodulatory properties (Purkon et al., 2022; Fadhilla et al., 2012). These pharmacological activities suggest that the phytochemical constituents of *M. paleacea* warrant further evaluation not only for their biological activity but also for their pharmacokinetic suitability as drug candidates. The bioactive compounds from *M. paleacea* exhibited characteristics supportive of their potential as drug candidates. Among the 18 compounds, several, such as thymol, linalool (3,7-dimethyl-1,6-octadien-3-ol), and fatty acids, including dodecanoic acid, tetradecanoic acid, n-hexadecanoic acid, and n-decanoic acid have been reported to possess antibacterial activity (M ˛aczka et al., 2022; Maser et al., 2022; Yin et al., 2022).

**Physicochemical Profil**

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Physicochemical analysis indicated that the test compounds exhibited a wide range of molecular weight, lipophilicity, and polarity. The parameters analyzed included molecular weight, number of hydrogen bond donors and acceptors, number of rotatable bonds (<9 bonds), molecular polarity based on topological polar surface area (20–130 Å²), and MLOGP (Daina et al., 2017). All hit molecules had molecular weights below 500 g/mol, ranging from 62.07 g/mol (1,2-ethanediol) to 270.45 g/mol (methyl hexadecanoic acid), well within the Lipinski threshold. Drug-likeness prediction was based on Lipinski's Rule of Five (RO5), which includes hydrogen bond donors (no more than 5), hydrogen bond acceptors (no more than 10 ), molecular mass less than 500 Da, and octanol-water partition coefficient (log P) not greater than 5 (Lipinski CA, 2004). This is consistent with findings by Veber et al. (2002), who demonstrated that low molecular weight compounds generally exhibit superior intestinal permeability and absorption. Most molecules showed MlogP values <5, indicating a balanced solubility and permeability profile (Table 1).

Based on the analysis in Table 1, most compounds exhibited physicochemical characteristics consistent with accepted drug-likeness criteria. In addition, nearly all compounds complied with Lipinski's rule of five, except for a few molecules such as pentadecane, (Z)-11-hexadecen-1-ol, 1-tridecene, n-hexadecanoic acid, and methyl hexadecanoic acid, each of which showed one violation. Lipinski's rule stipulates that up to one violation remains acceptable for a candidate to be considered a potential orally active drug (Lipinski et al., 2001). The favorable compliance with Lipinski's Rule of Five suggests that the majority of the identified metabolites possess physicochemical properties compatible with oral drug development. Their relatively small molecular size, moderate lipophilicity, and limited hydrogen-bonding capacity are expected to facilitate passive membrane permeation while maintaining adequate aqueous solubility. Furthermore, oral bioavailability radar plots were predicted to provide an overview of how closely the compounds resemble known drug-like molecules.

**Table 1.** Prediction of physicochemical properties of the compound from *M. paleacea*

| Compounds | Lipinski violations | Molecular Weight (g/mol) | Rotatable Bonds | H- Bond Acceptors | H- Bond Donors | Topological Polar Surface Area (Å²) | MLOGP |
|---|---|---|---|---|---|---|---|
| 1,2-Ethanediol, | 0 | 62.07 | 1 | 2 | 2 | 40.46 | -1.15 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2,4-Hexadiene, | 0 | 82.14 | 1 | 0 | 0 | 0.00 | 2.35 |
| Thymol, | 0 | 150.22 | 1 | 1 | 1 | 20.23 | 2.76 |
| 1-Undecanol, | 0 | 172.31 | 9 | 1 | 1 | 20.23 | 3.13 |
| Tridecan-1-ol, | 0 | 200.36 | 11 | 1 | 1 | 20.23 | 3.68 |
| Pentadecane, | 1 | 212.41 | 12 | 0 | 0 | 00.00 | 6.19 |
| Dodecanoic acid, | 0 | 200.32 | 10 | 2 | 1 | 37.30 | 3.15 |
| (Z)-Tetradecen-9-en-1-ol, | 0 | 212.37 | 11 | 1 | 1 | 20.23 | 3.80 |
| (Z)-11-Hexadecen-1-ol, | 1 | 240.42 | 13 | 1 | 1 | 20.23 | 4.31 |
| 1-Tridecene, | 1 | 182.35 | 10 | 0 | 0 | 00.00 | 5.52 |
| 2-Dodecanone, | 0 | 184.32 | 9 | 1 | 0 | 17.07 | 3.27 |
| Tetradecanoic acid, | 0 | 228.37 | 12 | 2 | 1 | 37.30 | 3.69 |
| n-Hexadecanoic acid, | 1 | 256.42 | 14 | 2 | 1 | 37.30 | 4.19 |
| 3,7-dimethyl-1,6-Octadien-3-ol, | 0 | 154.25 | 4 | 1 | 1 | 20.23 | 2.59 |
| Methyl hexadecanoic acid, | 1 | 270.45 | 15 | 2 | 0 | 26.30 | 4.44 |
| n-Decanoic acid, | 0 | 172.26 | 8 | 2 | 1 | 37.30 | 2.58 |
| Bicyclo[2.2.1]hept-5-en-2-ol, | 0 | 110.15 | 0 | 1 | 1 | 20.23 | 1.35 |
| 2-nitro-Cyclohexanone, | 0 | 253.68 | 2 | 3 | 0 | 62.89 | 1.66 |

The TPSA values ranged from 0.00 Å² (2,4-hexadiene, pentadecane, and 1-tridecene) to 62.89 Å² (2-nitro-cyclohexanone). Compounds with a value below the 130 Å² threshold are associated with poor intestinal absorption. The relatively low TPSA values observed in most compounds indicate limited molecular polarity, which favors passive diffusion through biological membranes and contributes to the high intestinal absorption predicted for these metabolites. This finding is consistent with the concept that compounds with TPSA below 130 Å² generally exhibit favorable oral absorption and membrane permeability (Veber et al., 2002). The radar plots further confirmed the drug-like profiles shown in the polygonal chart, which visualizes the oral bioavailability potential of a chemical compound (Figure 1).

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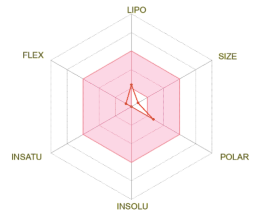
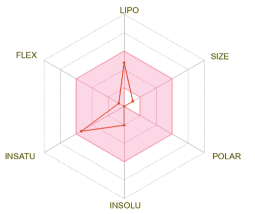
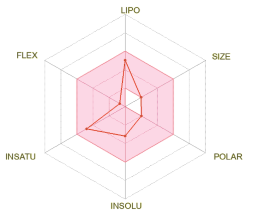


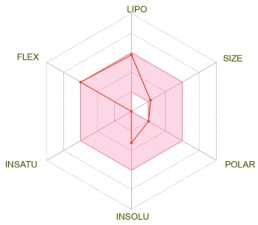
1,2-Ethanediol



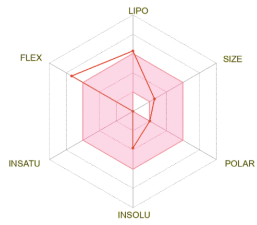
2,4-Hexadiene



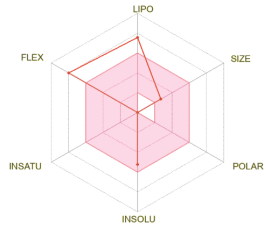
Thymol



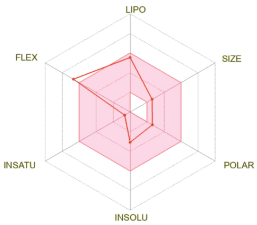
1-Undecanol



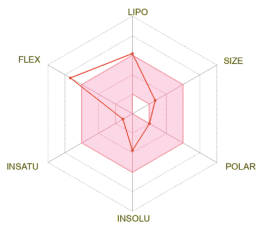
Tridecan-1-ol



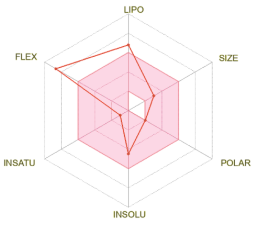
Pentadecane



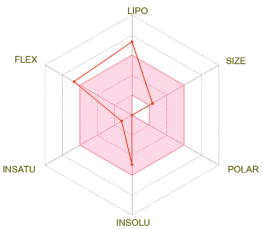
Dodecanoic acid



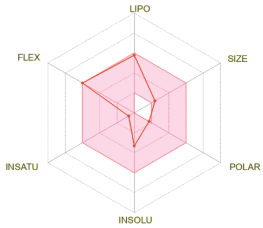
(Z)-Tetradecen-9-en-1-ol



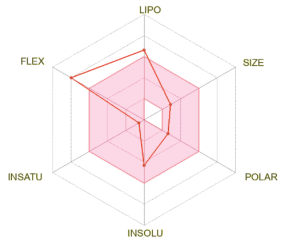
(Z)-11-Hexadecen-1-ol



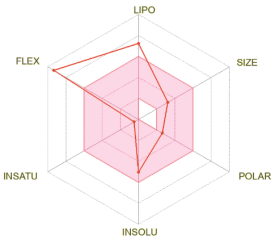
1-Tridecene



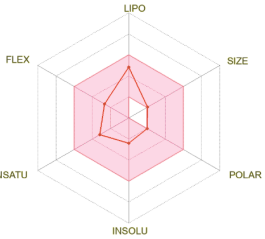
2-Dodecanone



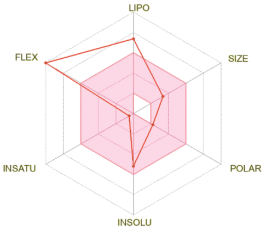
Tetradecanoic acid



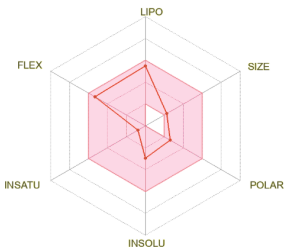
n-Hexadecanoic acid



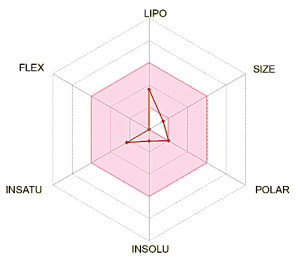
3,7-dimethyl-1,6-Octadien-3-ol



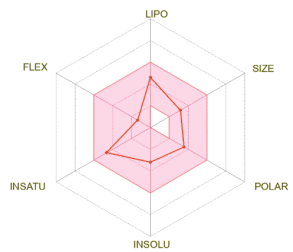
Methyl hexadecanoic acid



n-Decanoic acid



Bicyclo[2.2.1]hept-5-en-2-ol



2-nitro-Cyclohexanone

**Figure 1**. Bioavailability radar of *M. paleacea* extract compounds based on drug-likeness properties.

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Additionally, bioavailability radar analysis provided a rapid evaluation of drug-likeness. This radar plot, a polygonal representation of six parameters: lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), solubility (INSOLU), saturation degree (INSATU), and flexibility (FLEX) assesses a compound's oral bioavailability potential. The present findings indicated that long-chain aliphatic compounds, including tridecan-1-ol, pentadecane, dodecanoic acid, (Z)-tetradec-9-en-1-ol, (Z)-11-hexadecen-1-ol, 1-tridecene, tetradecanoic acid, n-hexadecanoic acid, and methyl hexadecanoic acid, showed minor violations of optimal oral bioavailability criteria. Optimal drug-like compounds exhibit radar plots entirely within the pink area (Daina et al., 2017). Similar to the present findings, Rukmana et al. (2025) reported that compounds satisfying the optimal bioavailability radar criteria generally exhibited favorable oral drug-likeness, supporting the reliability of physicochemical profiling during early-stage drug discovery.

**Pharmacokinetic Profile**

**Absorption**

The pharmacokinetic profiles of 18 bioactive compounds from M. paleacea were analyzed using absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters to evaluate their potential efficacy and safety and to predict a suitable route of administration. ADMET properties are essential criteria, as many molecules fail clinical trials due to suboptimal ADMET profiles (Lagorce et al., 2017). All hit molecules exhibited high human intestinal absorption, ranging 86.376% ( 1,2-ethanediol) to 95.514% (2,4-Hexadiene). Caco-2 cell permeability, a widely used surrogate model for human intestinal permeability, ranged from 1.345 to 1.606 log Papp for all compounds, indicating high permeability. The Caco-2 model is broadly accepted in pharmaceutical research as a predictor of intestinal drug transport (Angelis & Turco, 2011). The compounds also showed good skin permeability and skin permeability values ranging from −4.031 to −1.460 log Kp. Almost all hit molecules were neither substrates nor inhibitors of P-glycoprotein, except bicyclo[2.2.1]hept-5-en-2-ol, which was predicted to be a P-glycoprotein substrate (Table 2).

The absorption profile supported the suitability of *M. paleacea* metabolites for oral administration. All compounds demonstrated high predicted intestinal absorption. Monoterpenoids such as thymol and linalool possess relatively small molecular sizes and moderate lipophilicity,

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characteristics that facilitate passive diffusion across intestinal epithelial membranes. Numerous essential oil constituents are reported to undergo efficient gastrointestinal absorption, which is generally attributed to simple physicochemical structure and capacity to interact with biological membranes (Đorđević et al., 2020; Lammari et al., 2022).

**Table 2.** Absorption profile of the compound from *M. paleacea*

| Compounds | Water solubility (logmol/L) | Caco2permeability (logPappin10cm/s) | Intestinal absorption (human) (% Absorbed) | Skin Permeability (log Kp) | P-glycoprote insubstrate | P-glycoprotein I inhibitor | P-glycoprotein II inhibitor |
|---|---|---|---|---|---|---|---|
| 1,2-Ethanediol, | 1.31 | 1.552 | 86.376 | -4.031 | No | No | No |
| 2,4-Hexadiene, | -2.536 | 1.398 | 95.514 | -1.635 | No | No | No |
| Thymol, | -2.789 | 1.606 | 90.843 | -1.62 | No | No | No |
| 1-Undecanol, | -4.438 | 1.469 | 91.521 | -1.469 | No | No | No |
| Tridecan-1-ol, | -5.557 | 1.467 | 90.834 | -1.829 | No | No | No |
| Pentadecane, | -7.861 | 1.376 | 91.389 | -2.117 | No | No | No |
| Dodecanoic acid, | -4.181 | 1.562 | 93.379 | -2.693 | No | No | No |
| (Z)-Tetradecen-9-en-1-ol, | -5.883 | 1.472 | 90.997 | -1.948 | No | No | No |
| (Z)-11-Hexadecen-1-ol, | -6.76 | 1.471 | 90.31 | -2.379 | No | No | No |
| 1-Tridecene, | -7.001 | 1.378 | 92.552 | -1.576 | No | No | No |
| 2-Dodecanone, | -5.267 | 1.486 | 93.662 | -1.46 | No | No | No |
| Tetradecanoic acid, | -4.952 | 1.56 | 92.691 | -2.705 | No | No | No |
| n-Hexadecanoic acid, | -5.562 | 1.558 | 92.004 | -2.717 | No | No | No |
| 3,7-dimethyl-1,6-Octadien-3-ol, | -2.612 | 1.493 | 93.163 | -1.737 | No | No | No |
| Methyl hexadecanoic acid, | -6.927 | 1.6 | 92.335 | -2.595 | No | No | No |
| n-Decanoic acid, | -3.305 | 1.564 | 94.066 | -2.686 | No | No | No |
| Bicyclo[2.2.1]hept-5-en-2-ol, | -0.906 | 1.474 | 95.311 | -2.843 | Yes | No | No |
| 2-nitro-Cyclohexanone, | -4.056 | 1.345 | 95.284 | -2.535 | No | No | No |

## Distribution and Excretion

The variations in volume of distribution (VDss) and free fraction (Fu) are parameters that reflect the distribution of compounds in body tissues (Smith et al., 2015). In addition, the predicted blood–brain barrier (BBB) permeability and central nervous system partition coefficient (log PS) are important parameters used to determine whether a compound is likely to act on neurological targets and to anticipate potential central nervous system side effects

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(Pardridge, 2012). Compounds with high VDss tend to show extensive tissue distribution. In this study, the VDss values of *M. paleacea* compounds ranged from -0.697 log L/kg (n-decanoic acid) to 0.664 log L/kg (pentadecane). The compound 1,2-ethanediol showed the highest Fu value (0.849), yet exhibited the lowest positive log BB (−0.319). The compounds displayed negative log PS values (Table 3).

Distribution analysis indicated a high volume of distribution for all compounds and good blood-brain barrier (BBB) permeability. In drug discovery, logBB values indicate central nervous system distribution, with categories of high permeability (>0.3) and low permeability (<- 1) reported in experimental pharmacokinetic studies and QSAR modeling (Pajouhesh & Lenz, 2005). In terms of excretion, analysis indicated that (Z)-11-hexadecen-1-ol had the highest total clearance. In addition, none of the compounds were predicted to be substrates of renal organic cation transporter 2 (OCT2) (Table 3). These results align with excretion data, which showed favorable clearance rates for all compounds. The compounds were not substrates for organic cation transporter 2 (OCT2), indicating that their excretion processes are independent of OCT2 and thereby confer a reduced risk of nephrotoxicity interactions.

**Table 3.** Distribution and excretion profile of the compound from *M. paleacea*

| Compounds | Distribution | | | | Excretion | |
|---|---|---|---|---|---|---|
| | VDss (human) (log L/kg) | Fractionunbound (human) (Fu) | BBB permeability (log BB) | CNS permeability (log PS) | Total clearance | Renal OCT2 substrate |
| 1,2-Ethanediol, | -0.359 | 0.849 | -0.319 | -2.916 | 0.625 | No |
| 2,4-Hexadiene, | 0.156 | 0.552 | 0.637 | -1.876 | 0.373 | No |
| Thymol, | 0.512 | 0.203 | 0.407 | -1.664 | 0.211 | No |
| 1-Undecanol, | 0.348 | 0.319 | 0.704 | -2.01 | 1.682 | No |
| Tridecan-1-ol, | 0.424 | 0.221 | 0.742 | -1.901 | 1.76 | No |
| Pentadecane, | 0.664 | 0.074 | 0.92 | -1.471 | 1.811 | No |
| Dodecanoic acid, | -0.631 | 0.26 | 0.057 | -2.034 | 1.623 | No |
| (Z)-Tetradecen-9-en-1-ol, | 0.42 | 0.183 | 0.751 | -1.793 | 1.842 | No |
| (Z)-11-Hexadecen-1-ol, | 0.448 | 0.11 | 0.788 | -1.684 | 1.912 | No |
| 1-Tridecene, | 0.611 | 0.161 | 0.893 | -1.581 | 1.817 | No |
| 2-Dodecanone, | 0.373 | 0.264 | 0.713 | -1.883 | 1.61 | No |
| Tetradecanoic acid, | -0.578 | 0.171 | -0.027 | -1.925 | 1.693 | No |
| n-Hexadecanoic acid, | -0.543 | 0.101 | -0.111 | -1.816 | 1.763 | No |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 3,7-dimethyl-1,6-Octadien-3-ol, | 0.152 | 0.484 | 0.598 | -2.339 | 0.446 | No |
| Methyl hexadecanoic acid, | 0.334 | 0.074 | 0.749 | -1.678 | 1.861 | No |
| n-Decanoic acid, | -0.697 | 0.363 | 0.142 | -2.143 | 1.552 | No |
| Bicyclo[2.2.1]hept-5-en-2-ol, | 0.241 | 0.668 | -0.006 | -2.724 | 0.179 | No |
| 2-nitro-Cyclohexanone, | 0.21 | 0.137 | -0.17 | -1.997 | 0.142 | No |

**Metabolism**

Drug metabolism is a critical determinant of systemic exposure, duration of action, and susceptibility to drug interaction. Most compounds showed metabolic profiles with limited predicted CYP interaction, a favorable finding given that such interactions are frequently associated with pharmacokinetic variability (Zanger & Schwab, 2013). Cytochrome P450 (CYP) enzymes are the major enzyme system studied in phase I drug metabolism, in which CYP isoforms mediate the oxidation of various compounds involved in physiological and pathophysiological drug-related processes (Moroy et al., 2012). Human microsomal P450 enzymes catalyze the metabolism of numerous drugs and xenobiotics. Cytochrome P450 inactivates many drug compounds, whereas others can be bioactivated. C3A4 is one of the major CYP isoforms. In the metabolic profile analysis, most compounds were not predicted to be CYP3A4 substrates, except pentadecane, (Z)-tetradec-9-en-1-ol, (Z)-11-hexadecen-1-ol, n-hexadecanoic acid, and methyl hexadecanoic acid. No compound was predicted to be a substrate of CYP2D6 (Table 4).

**Table 4.** Metabolism profile of the compound from M. paleacea

| Compounds | CYP2D6 substrate | CYP3A4 substrate | CYP1A2 inhibitior | CYP2C19 inhibitior | CYP2C9 inhibitior | CYP2D6 inhibitior | CYP3A4 inhibitior |
|---|---|---|---|---|---|---|---|
| 1,2-Ethanediol, | No | No | No | No | No | No | No |
| 2,4-Hexadiene, | No | No | No | No | No | No | No |
| Thymol, | No | No | Yes | No | No | No | No |
| 1-Undecanol, | No | No | No | No | No | No | No |
| Tridecan-1-ol, | No | No | No | No | No | No | No |
| Pentadecane, | No | Yes | Yes | No | No | No | No |
| Dodecanoic acid, | No | No | No | No | No | No | No |
| (Z)-Tetradecen-9-en-1-ol, | No | Yes | Yes | No | No | No | No |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (Z)-11-Hexadecen-1-ol, | No | Yes | Yes | No | No | No | No |
| 1-Tridecene, | No | No | No | No | No | No | No |
| 2-Dodecanone, | No | No | No | No | No | No | No |
| Tetradecanoic acid, | No | No | No | No | No | No | No |
| n-Hexadecanoic acid, | No | Yes | No | No | No | No | No |
| 3,7-dimethyl-1,6-Octadien-3-ol, | No | No | No | No | No | No | No |
| Methyl hexadecanoic acid, | No | Yes | Yes | No | No | No | No |
| n-Decanoic acid, | No | No | No | No | No | No | No |
| Bicyclo[2.2.1]hept-5-en-2-ol, | No | No | No | No | No | No | No |
| 2-nitro-Cyclohexanone, | No | No | Yes | Yes | No | No | No |

The prediction indicated that only a few compounds were potential CYP1A2 inhibitors, including thymol, pentadecane, (Z)-tetradec-9-en-1-ol, (Z)-11-hexadecen-1-ol, methyl hexadecanoic acid, and 2-nitro-cyclohexanone, which was also predicted to inhibit CYP2C19 (Table 4). This inhibitory tendency toward CYP1A2 is consistent with findings by Pirvu et al. (2025), who reported that hexadecanoic acid an identical compound also identified in the present study was predicted to inhibit both CYP1A2 and CYP2C9 via SwissADME analysis, attributing this behavior to its excessive lipophilicity and high flexibility, which positioned it outside the optimal region of the bioavailability radar.

**Toxicity**

Toxicity prediction indicated that all compounds were non-mutagenic in the Ames test, except for 2-nitro-cyclohexanone, which showed a positive Ames test result. Ames toxicity testing detects substances that cause genetic damage leading to gene mutation (Honma et al., 2019). None of the compounds were predicted to be inhibitors of hERG I or hERG II. With respect to hepatotoxicity, thymol was the only compound predicted to be hepatotoxic, whereas all the compounds were predicted to be non-hepatotoxic. Most compounds also showed potential for skin sensitization, except 1,2-ethanediol, 2,4-hexadiene, and 2-nitro-cyclohexanone. The predicted human maximum tolerated dose ranged from -0.708 to 1.783. The compounds generally exhibit low to moderate acute toxicity, with toxicity classes ranging from 4 to 6. (Z)-Tetradecen-9-en-1-ol and (Z)-11-Hexadecen-1-ol compounds in class 6 are predicted to be safest due to having an LD50 value (Table 5).

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**Table 5.** Toxicity profile of the compound from *M. paleacea*

| Compounds | AMES toxicity | Max. tolerated dose (human) | hERG I inhibitor | hERG II inhibitor | LD50 | LOAEL | Hepato toxicity | Skin Sensitisation | T.P.T | Minnow toxicity | Toxicity Class |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1,2-Ethanediol, | No | 1.783 | No | No | 1.57 | 2.747 | No | No | -2.236 | 3.219 | 5 |
| 2,4-Hexadiene, | No | 0.922 | No | No | 1.78 | 2.177 | No | No | -0.326 | 1.55 | 3 |
| Thymol, | No | 1.007 | No | No | 2.074 | 2.212 | Yes | Yes | 0.387 | 1.213 | 4 |
| 1-Undecanol, | No | 0.402 | No | No | 1.59 | 2.235 | No | Yes | 1.765 | 0.346 | 4 |
| Tridecan-1-ol, | No | 0.23 | No | No | 1.562 | 1.244 | No | Yes | 2.289 | -0.195 | 4 |
| Pentadecane, | No | 0.179 | No | No | 1.52 | 1.342 | No | Yes | 1.989 | -1.168 | 3 |
| Dodecanoic acid, | No | -0.34 | No | No | 1.511 | 2.89 | No | Yes | 0.954 | -0.084 | 4 |
| (Z)-Tetradecen-9-en-1-ol, | No | 0.114 | No | No | 1.528 | 1.225 | No | Yes | 2.345 | -0.32 | 6 |
| (Z)-11-Hexadecen-1-ol, | No | -0.026 | No | No | 1.55 | 1.156 | No | Yes | 2.129 | -0.802 | 6 |
| 1-Tridecene, | No | 0.261 | No | No | 1.501 | 1.394 | No | Yes | 2.053 | -0.595 | 5 |
| 2-Dodecanone, | No | 0.301 | No | No | 1.575 | 1.294 | No | Yes | 1.819 | -0.039 | 5 |
| Tetradecanoic acid, | No | -0.559 | No | No | 1.477 | 3.034 | No | Yes | 0.978 | -0.601 | 4 |
| n-Hexadecanoic acid, | No | -0.708 | No | No | 1.44 | 3.181 | No | Yes | 0.84 | -1.083 | 4 |
| 3,7-dimethyl-1,6-Octadien-3-ol, | No | 0.774 | No | No | 1.704 | 2.024 | No | Yes | 0.515 | 1.277 | 5 |
| Methyl hexadecanoic acid, | No | 0.178 | No | No | 1.635 | 2.998 | No | Yes | 1.935 | -1.373 | 5 |
| n-Decanoic acid, | No | -0.059 | No | No | 1.533 | 2.75 | No | Yes | 0.701 | 0.48 | 4 |
| Bicyclo[2.2.1]hept-5-en-2-ol, | No | 0.991 | No | No | 1.912 | 1.6 | No | Yes | -0.757 | 2.39 | 4 |
| 2-nitro-Cyclohexanone, | Yes | 0.495 | No | No | 2.515 | 1.412 | No | No | 1.699 | 0.561 | 4 |

Toxicity analysis revealed that most *M. paleacea* compounds were non-mutagenic (Ames test negative), except for 2-nitro-cyclohexanone; thus, this compound is not recommended for further testing. Among all test compounds, 2-dodecanone showed the most balanced toxicity profile, its druglikeness, and pharmacokinetic performance were less favorable than linalool, dodecanoic acid, and n-decanoic acid. Although these findings are highly promising, computational studies require experimental validation in wet laboratories, including target validation. These results suggest that the selected hit molecules can proceed to in vitro and in vivo testing, with potential for further structural optimization to develop them as viable drug candidates.

## Conclusions

This in silico study provides a comprehensive physicochemical,

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pharmacokinetic and toxicological evaluation of eighteen bioactive compounds identified from *Marchantia paleacea* by GC-MS analysis. The majority of compounds demonstrated compliance with Lipinski's rule of five and exhibited favorable ADMET profiles, including high human intestinal absorption, good Caco-2 permeability, limited CNS penetration, and negative interaction with CYP450 isoenzymes and P-glycoprotein. Most compounds were predicted to be non-mutagenic, non-hepatotoxic, and devoid of hERG channel inhibition, with a relatively safe pharmacological profile.

The results from this study indicate that bioactive compounds from *M. paleacea,* particularly linalool, bicyclo[2.2.2]hept5-en2-ol, dodecanoic acid, and n-decanoic acid, exhibit promising physicochemical and pharmacokinetic (ADMET) properties, while thymol remains promising but requires dose optimization due to its predicted hepatotoxicity. These findings warrant further validation through in vitro and in vivo studies.

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