International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1704-1716 www.ijprajournal.com ISSN: 2456-4494

Computational ADME Modeling of Selected Terpenoids Using Swiss ADME

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Date of Submission: 10-06-2025 Date of Acceptance: 20-06-2025

ABSTRACT:
Terpenoids, a large and diverse class of naturally occurring organic compounds, have shown significant therapeutic potential, including antimicrobial, anticancer, and anti-inflammatory properties. However, the pharmacokinetic behavior of terpenoids, particularly their absorption, distribution, metabolism, and excretion (ADME) profiles, remains a critical factor in their drug development process. Computational ADME modeling has emerged as a powerful tool for early-stage screening of bioactive compounds, enabling the efficient prediction of pharmacokinetic properties and drug-likeness. This review focuses on the application of SwissADME, a widely used web-based platform, for evaluating the ADME characteristics of selected terpenoids. The tool offers various predictive modules including Lipinski's rule of five, bioavailability radar, gastrointestinal absorption, blood-brain barrier permeability, and cytochrome P450 interactions. By analyzing computational ADME data, this review highlights key pharmacokinetic attributes of terpenoids that influence their drug-likeness and therapeutic potential. Overall, the use of SwissADME in evaluating natural compounds streamlines the selection of promising terpenoid candidates for further experimental and clinical validation, thus accelerating natural product-based drug discovery.

Keywords: Terpenoids, Swiss ADME, Pharmacokinetics, Lipinski's rule, Bioavailability Phytoconstituents.

I. INTRODUCTION:

Terpenoids, also called terpenes or isoprenoids, are natural compounds found in all living things. Over 60,000 types have been discovered, making them one of the largest groups of natural substances. They are a major part of essential oils found in fragrant plants. Substances like turpentine (from tree resin) and cholesterol (in animal cell membranes) are examples. Because of their pleasant smells and flavors, terpenoids are widely used in perfumes, fragrances, and flavoring.[1] They have many biological properties like antioxidant, antimicrobial, anticancer effects, anti-inflammatory, antioxidant, Neuroprotective. They also help in plant growth and development.[2]

In plants, two main pathways are used for the biosynthesis of terpenoids that produce isopentyl diphosphate and dimethylallyl diphosphate. Mevalonic acid pathway, which is also known as MVA pathway, occurs in the cytosol, and methylerythritol phosphate, also known as MEP pathway, occurs in plastids[1]. Plant sources for terpenoids include Taxus plants, Curcuma wenyujin, Citrus sinensis, Cannabis, Perilla frutescens, Artemisia freyniana, Chrysanthemum indicum, Cyclocarya paliurus leaves, liverworts like Radula, and aromatic herbs such as cinnamon, thyme, cumin, fennel, clove, nutmeg, and orange[1,2]. Terpenes can be classified into different classes based on the number of isoprene units (n) in the molecule: Monoterpenoids (C10H16) e.g. linalool and geraniol, Sesquiterpenoids ($C_{15}H_{24}$) bisabolol, bisabolene, and farnesene, Diterpenoids ($C_{20}H_{32}$) gibberellic acid, carnosolic acid and Triterpenoids($C_{30}H_{48}$) betulin, fusidic acid [3].Thymol and carvacrol damage fungal cell membranes by disrupting them and blocking the production of ergosterol, leading to instability. Limonene weakens the fungal cell wall by stopping the production of β-glucan and chitin. Terpenes also harm mitochondria by blocking important enzymes, which lowers ATP (energy) production. In Saccharomyces cerevisiae, triterpenoids and tetraterpenoids reduce the number of mitochondria, affecting ROS levels and energy generation2. Terpenoids prevent fungal cells from adhering and forming biofilms, making them more sensitive to antifungal agents.[4]

II. MATERIALS AND METHODS:

2.1 Swiss ADME:

The Swiss ADME software, developed by the Swiss Institute of Bioinformatics, was accessed through the website www.swissadme.ch. The web

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1704-1716 www.ijprajournal.com ISSN: 2456-4494

server displayed the Submission page of Swiss ADME on Google, which was utilized to estimate the individual ADME behaviors of the compounds derived from medicinal plants. The system requires users to input one molecule per line, using the SMILES format. The results for each molecule are presented in various forms, including tables, charts, and a downloadable spreadsheet.

2.2 Structure and bioavailability radar:

The two-dimensional chemical structure with canonical SMILES is present in the first section to assess the drug-likeness of the molecules of interest. The six different physicochemical properties like lipophilicity. (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), in saturation (INSATU), and flexibility (FLEX) were taken into consideration by the bioavailability radar. The specific criteria for each property are as follows: lipophilicity should have an XLOGP3 value between -0.7 and +5.0, size should have a molecular weight (MW) between 150 and 500 g/mol, polarity should have a topological polar surface area (TPSA) between 20 and 130 0A2, solubility should have alogarithm of the solubility (log S) not exceeding 6, saturation should have a fraction of carbons in sp3 hybridization not less than 0.25, and flexibility should have no more than 9 rotatable bonds.

2.3 Physicochemical properties:

Simple molecular and physicochemical descriptors like molecular weight (MW), molecular refractivity (MR), count of specific atom types and polar surface area (PSA) are compiled in this section. The values are computed with Open Babel, version 2.3.0.[6,7] The PSA is calculated using the fragmental technique called topological polar surface area (TPSA), considering sulfur and phosphorus as polar atoms 25. This has proven a useful descriptor in many models and rules to quickly estimate some ADME properties, especially with regards to biological barrier crossing such as absorption and brain access. [6,7]

2.4 Lipophilicity:

Lipophilicity is considered an important parameter in drug discovery and design.[9]

As it complements the most informative and instructive physicochemical property in medicinal chemistry.[10] It is experimentally demonstrated as partition coefficients (log P) or as distribution coefficients (log D). Log P represents the partition equilibrium of an un-ionized solute between water and an immiscible organic solvent. Higher log P values correspond to greater lipophilicity.[8] To evaluate the lipophilicity of a compound, Swiss ADME provides five freely available models: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. XLOGP3 is an atomistic approach that includes corrective factors and a knowledge-based library.[11] WLOGP is based on a purely atomistic method using a fragmental system.[12] MLOGP is a topological method based on a linear relationship with 13 implemented molecular descriptors.[13,14] SILICOS-IT is a hybrid method based on 27 fragments and 7 topological descriptors. iLOGP is physics based method that relies on the free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model. [6]

2.5 Solubility:

The degree to which a compound dissolves is greatly impacted by the solvent employed, the surrounding temperature, and the pressure. The saturation point indicates the maximum solubility, the stage at which introducing additional solute doesn't lead to a higher concentration in the solution[15]. A drug is deemed highly soluble when the maximum dosage can dissolve in 250 milliliters or less of water-based solution within a pH range of 1 to 7.5. Swiss ADME utilizes two topological techniques to predict water solubility. The initial method involves the use of the ESOL model, which categorizes solubility into classes based on a logarithmic scale (Insoluble<-10, Poorly soluble<-6, Moderately soluble<-4, Soluble<-2, Very soluble<0). Both techniques deviate from the fundamental general solubility equation as they do not account for the melting point factor.[16] Nevertheless, a strong linear correlation exists between the predicted and experimental values (R^2=0.69 and 0.81, respectively). The third predictor in Swiss ADME was developed by SILICOS-IT, which similarly categorizes solubility into classes based on a logarithmic scale (Insoluble<-10, Poorly soluble<-6, Moderately soluble<-4, Soluble<-2, Very soluble<0), with the linear coefficient adjusted by molecular weight (R^2=0.75).[17,18] All predicted values are presented as the decimal logarithm of molar water solubility (log S). Swiss ADME additionally provides solubility values in mol/l and mg/ml, alongside qualitative solubility classes.[19]

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Volume 10, Issue 3 May-June 2025, pp: 1704-1716 www.ijprajournal.com ISSN: 2456-4494

2.6 Pharmacokinetics:

The distinction lies within a region of favorable properties for gastrointestinal (GI) absorption on a graph depicting two computed descriptors: ALOGP versus PSA, respectively. The region that is most populated by molecules that are well absorbed is elliptical in shape and has been named the Egan egg. This egg is utilized to evaluate the predictive capability of the model for passive GI absorption and prediction for brain access through passive diffusion, ultimately resulting in the creation of the BOILED-Egg (Brain or Intestina L Estimate D permeation predictive model). The BOILED-Egg model offers a rapid, spontaneous, efficient, yet robust method for forecasting passive GI absorption, which is beneficial for drug discovery and development.[20] The white region represents the space occupied by molecules with a greater extent of absorption by the GI tract, while the yellow region (yolk) represents the space with the highest probability of permeating to the brain.[6] Cytochrome p450 (CYP) isoenzymes biotransform more than 50-90% of therapeutic molecules through its five major isoforms (CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6). P-gp is widely distributed in the intestinal epithelium and functions to pump xenobiotics back into the intestinal lumen and from the capillary endothelial cells of the brain back into the capillaries.[21,22] Swiss ADME employs the support vector machine algorithm (SVM) for datasets consisting of known substrates/non-substrates or inhibitors/non-inhibitors for binary classification. The resulting molecule will be classified as either "Yes" or "No" depending on whether it is expected to be a substrate for both P-gp and CYP, respectively. The SVM model for P-gp substrate was constructed using 1033 molecules in the training set and tested on 415 molecules in the test set, with a10-fold cross-validation accuracy of 0.72 and an area under the curve (AUC) of 0.77. The external accuracy and AUC=0.94 respectively. The Support Vector Machine (SVM) models for the inhibition of Cytochrome P-450 1A2, 2C19, 2C9, 2D6, and 3A4 molecules were constructed using different training and test sets. For the Cytochrome P-450 1A2 inhibitor molecule, the SVM model was built on a training set of 9145 molecules and tested on 3000 molecules. The 10-fold cross-validation yielded accuracy (ACC) of 0.83 and an area under the curve (AUC) of 0.90. The external validation resulted in an ACC of 0.84 and an AUC of 0.91. Similarly, for the Cytochrome P-450 2C19 inhibitor molecule, the SVM model was constructed using a training set of 9272 molecules and tested on 3000 molecules. The 10-fold cross validation showed an ACC of 0.80 and an AUC of 0.86. The external validation exhibited an ACC of 0.80 and an AUC of 0.87. For the Cytochrome P-450 2C9 inhibitor molecule, the SVM model was developed using a training set of 5940 molecules and tested on 2075 molecules.[23] The 10-fold cross validation yielded an ACC of 0.78 and an AUC of 0.85. The external validation resulted in an ACC of 0.71 and an AUC of 0.81. The SVM model for the Cytochrome P-450 2D6 inhibitor molecule was constructed using a training set of 3664 molecules and tested on 1068 molecules. The 10-fold cross-validation showed an ACC of 0.79 and an AUC of 0.85. The external validation exhibited an ACC of 0.81 and an AUC of 0.87. Lastly, for the Cytochrome P-450 3A4 inhibitor molecule, the SVM model was built on a training set of 7518 molecules and tested on 2579 molecules. The 10-fold cross validation yielded an ACC of 0.77 and an AUC of 0.85. The external validation resulted in an ACC of 0.78 and an AUC of 0.86.

2.7 Medicinal chemistry:

This section intends to aid medicinal chemists in their routine drug discovery efforts. PAINS, also referred to as Pan Assay Interference Compounds or promiscuous compounds, are molecules that consistently yield strong signals in assays, irrespective of the protein targets. These compounds have exhibited activity in a broad spectrum of assays, making them appealing candidates for further investigation. Swiss ADME highlights potential problems if these chemical groups are present in the molecule being examined.[25] In a different strategy, Brenk emphasizes compounds that are smaller and less hydrophobic, departing from the rigid constraints of "Lipinski's rule of 5," to expand the possibilities for drug development. This approach involves excluding compounds containing potentially toxic, chemically reactive, or undesirable groups such as nitro groups, sulfates, phosphates, 2 halo pyridines, and thiols. The Brenk model imposes restrictions on the ClogP/ClogD values, confining them to a range of 0 to 4. Furthermore, the model mandates that the number of hydrogen bond donors should be fewer than 4, while the number of hydrogen bond acceptors must be less than 7. Concerning molecular size, the model requires that compounds possess between 10 and 28 heavy atoms.[26] To be classified as medicinal, compounds must possess a

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Volume 10, Issue 3 May-June 2025, pp: 1704-1716 www.ijprajournal.com ISSN: 2456-4494

simple structure, characterized by fewer than 8 rotatable bonds, fewer than 5 ring systems, and the absence of ring systems with more than 2 fused rings.[27] The concept of lead likeness aims to provide starting points with high affinity in high-throughput screening (HTS), allowing for the exploration of additional interactions during the lead optimization phase. Leads undergo chemical modifications that tend to reduce their size and increase their lipophilicity, making them less hydrophobic than drug-like molecules. Lead optimization is commonly conducted using a rule-based approach, with molecules possessing a molecular weight between 100 and 350 Da and a ClogP between 1 and 3.0 being considered superior to drug-like compounds and thus more lead-like.[28,29]

III. RESULT:

Table 1: General Characteristics of Terpenoid Phytoconstituents:

Sr. No	Phytoconstituents	Pub Chem ID	Molecular Formula	Canonical SMILESS	Molecular Weight (in g/mol)
1	Anethole	637563	C10H12O	C/C=C/C1=CC=C(C=C1)OC	148.2g/mol
2	Thymol	6989	C10H14O	CC1=CC(=C(C=C1)C(C)C)O	150.22g/mol
3	Estragole	8815	C10H12O	COC1=CC=C(C=C1)CC=C	148.2g/mol
4	Eugenol	3314	C10H12O2	COC1=C(C=CC(=C1)CC=C)O	164.2g/mol
5	P-cymene	7463	C10H14	CC1=CC=C(C=C1)C(C)C	134.22g/mol
6	Linalool	6549	C10H18O	CC(=CCCC(C)(C=C)O)C	154.25g/mol
7	Carvone	7439	C10H14O	CC1=CCC(CC1=O)C(=C)C	150.22g/mol
8	Limonene	22311	C10H16	CC1=CCC(CC1)C(=C)C	136.23g/mol
9	Sabinene	18818	C10H16	CC(C)C12CCC(=C)C1C2	136.23g/mol
10	Costunolide	5281437	C15H20O2	C/C/1=C\CC/C(=C/[C@@H]2[C@@H](CC1)C(=C)C(=O)O2)/C	232.32g/mol
11	Citral	638011	C10H16O	CC(=CCC/C(=C/C=O)/C)C	152.23g/mol
12	1,8-cineole	2758	C10H18O	CC1(C2CCC(O1)(CC2)C)C	154.25g/mol
13	Camphor	2537	C10H16O	CC1(C2CCC1(C(=O)C2)C)C	152.23g/mol
14	Citronellol	8842	C10H20O	CC(CCC=C(C)C)CCO	156.26g/mol
15	α- phellandrene	7460	C10H16	CC1=CCC(C=C1)C(C)C	136.23g/mol
16	β-Caryophyllene	5281515	C15H24	C/C/1=C\CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C	204.35g/mol
17	γ- terpinene	7461	C10H16	CC1=CCC(=CC1)C(C)C	136.23g/mol
18	α -pinene	6654	C10H16	CC1=CCC2CC1C2(C)C	136.23g/mol
19	δ- 3- carene	26049	C10H16	CC1=CCC2C(C1)C2(C)C	136.23g/mol
20	β - Pinene	14896	C10H16	CC1=CCC2CC1C2(C)C	136.23g/mol
21	Terpinen -4-ol	11230	C10H18O	CC1=CCC(CC1)(C(C)C)O	154.25g/mol
22	β- phellandrene	11142	C10H16	CC(C)C1CCC(=C)C=C1	136.23g/mol
23	Fenchone	14525	C10H16O	CC1(C2CCC(C2)(C1=O)C)C	152.23g/mol
24	Carvacrol	10364	C10H14O	CC1=C(C=C(C=C1)C(C)C)O	150.22g/mol
25	α- thujone	10931629	C10H16O	CC1[C@H]2C[C@]2(CC1=O)C(C)C	152.23g/mol
26	Camphene	6616	C10H16	CC1(C2CCC(C2)C1=C)C	136.23g/mol
27	Geraniol	637566	C10H18O	CC(=CCC/C(=C/CO)/C)C	154.25g/mol
28	Linalyl acetate	8294	C12H20O2	CC(=CCCC(C)(C=C)OC(=O)C)C	196.29g/mol
29	α-terpineol	17100	C10H18O	CC1=CCC(CC1)C(C)(C)O	154.25g/mol
30	β- myrcene	31253	C10H16	CC(=CCCC(=C)C=C)C	136.23g/mol

Table 2: Lipophilicity of the Terpenoid Phytoconstituents:

Sr. No.	Phytoconstituents	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log *P*0/w
1	Anethole	2.55	3.3	2.62	2.67	2.79	2.79
2	Thymol	2.32	3.3	2.82	2.76	2.79	2.8
3	Estragole	2.47	3.37	2.42	2.67	2.96	2.78

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4	Eugenol	2.37	2.27	2.13	2.01	2.48	2.25
5	P-cymene	2.51	4.1	3.12	4.47	3.29	3.5
6	Linalool	2.7	2.97	2.67	2.59	2.35	2.66
7	Carvone	2.27	2.71	2.49	2.1	2.64	2.44
8	Limonene	2.72	4.57	3.31	3.27	2.97	3.37
9	Sabinene	2.65	3.09	3	4.29	3.23	3.25
10	Costunolide	2.63	2.09	3.55	3.26	3.25	2.96
11	Citral	2.51	3.03	2.88	2.49	2.65	2.71
12	1,8-cineole	2.58	2.74	2.74	2.45	2.86	2.67
13	Camphor	2.12	2.19	2.4	2.3	2.85	2.37
14	Citronellol	2.72	3.91	2.75	2.7	2.51	2.92
15	α- phellandrene	2.64	3.21	3.16	3.27	2.55	2.97
16	β-Caryophyllene	3.25	4.38	4.73	4.63	4.19	4.24
17	γ- terpinene	2.73	4.5	3.31	3.27	2.95	3.35
18	α -pinene	2.63	4.48	3	4.29	2.79	3.44
19	δ- 3- carene	2.63	4.38	3	4.29	2.79	3.42
20	β - Pinene	2.63	4.48	3	4.29	2.79	3.44
21	Terpinen -4-ol	2.51	3.26	2.5	2.3	2.44	2.6
22	β- phellandrene	2.65	3.44	3.16	3.27	2.84	3.07
23	Fenchone	2.21	3.52	2.4	2.3	2.85	2.66
24	Carvacrol	2.24	3.49	2.82	2.76	2.79	2.82
25	α- thujone	2.28	2.27	2.26	2.3	2.63	2.35
26	Camphene	2.58	4.22	3	4.29	3.08	3.43
27	Geraniol	2.52	3.56	2.67	2.59	2.35	2.74
28	Linalyl acetate	3.08	3.93	3.24	2.95	2.98	3.24
29	α-terpineol	2.51	3.39	2.5	2.3	2.17	2.58
30	β- Myrcene	2.89	4.17	3.48	3.56	3.05	3.43

Table 3: Water solubility of the Terpenoid Phytoconstituents:

Phytoconstituents	ESOL				Ali				(SILICOS-IT)			
	LogS (ESOL)	Solubility		Class	LogS (Ali)	Solubility		Class	LogS (SILICOS-IT)	Solubility		Class
		mg/ml	mol/l			mg/ml	mol/l			mg/ml	mol/l	
Anethole	-3.11	1.15e-01	7.77e-04	Soluble	-3.17	1.00e-01	6.77e-04	Soluble	-2.98	1.55e-01	1.04e-03	Soluble
Thymol	-3.19	9.74e-02	6.49e-04	Soluble	-3.4	5.97e-02	3.98e-04	Soluble	-3.01	1.46e-01	9.71e-04	Soluble
Estragole	-3.09	1.21e-01	8.17e-04	Soluble	-3.24	8.49e-02	5.73e-04	Soluble	-3.35	6.54e-02	4.42e-04	Soluble
Eugenol	-2.46	5.69e-01	3.47e-03	Soluble	-2.53	4.90e-01	2.98e-03	Soluble	-2.79	2.65e-01	1.61e-03	Soluble
P-cymene	-3.63	3.12e-02	2.33e-04	Soluble	-3.81	2.10e-02	1.56e-04	Soluble	-3.57	3.58e-02	2.67e-04	Soluble
Linalool	-2.4	6.09e-01	3.95e-03	Soluble	-3.06	1.35e-01	8.75e-04	Soluble	-1.84	2.20e+00	1.43e-02	Soluble
Carvone	-2.41	5.81e-01	3.87e-03	Soluble	-2.72	2.85e-01	1.90e-03	Soluble	-2.16	1.04e+00	6.95e-03	Soluble
Limonene	-3.5	4.33e-02	3.18e-04	Soluble	-4.29	6.93e-03	5.09e-05	Moderately soluble	-2.26	7.54e-01	5.53e-03	Soluble
Sabinene	-2.57	3.71e-01	2.72e-03	Soluble	-2.76	2.38e-01	1.75e-03	Soluble	-2.48	4.55e-01	3.34e-03	Soluble
Costunolide	-2.6	5.88e-01	2.53e-03	Soluble	-2.27	1.24e+00	5.34e-03	Soluble	-3.05	2.06e-01	8.85e-04	Soluble
Citral	-2.43	5.67e-01	3.73e-03	Soluble	-3.05	1.34e-01	8.83e-04	Soluble	-1.96	1.66e+00	1.09e-02	Soluble
1,8-cineole	-2.52	4.63e-01	3.00e-03	Soluble	-2.59	3.98e-01	2.58e-03	Soluble	-2.45	5.45e-01	3.53e-03	Soluble

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Camphor	-2.16	1.04e+00	6.86e-03	Soluble	-2.18	1.00e+00	6.57e-03	Soluble	-2.6	3.83e-01	2.52e-03	Soluble
Citronellol	-2.94	1.79e-01	1.14e-03	Soluble	-4.03	1.45e-02	9.26e-05	Moderately soluble	-2.21	9.64e-01	6.17e-03	Soluble
α-phellandrene	-2.64	3.11e-01	2.29e-03	Soluble	-2.88	1.79e-01	1.31e-03	Soluble	-1.78	2.27e+00	1.67e-02	Soluble
β-Caryophyllene	-3.87	2.78e-02	1.36e-04	Soluble	-4.1	1.64e-02	8.01e-05	Moderately soluble	-3.77	3.49e-02	1.71e-04	Soluble

Phytoconstituents	ESOL				Ali				(SILICOS-IT)			
	LogS (ESOL)	Solubility		Class	LogS (Ali)	Solubility		Class	LogS (SILICOS-IT)	Solubility		Class
		mg/ml	mol/l			mg/ml	mol/l			mg/ml	mol/l	
γ-terpinene	-3.45	4.79e-02	3.52e-04	Soluble	-4.22	8.19e-03	6.01e-05	Moderately soluble	-2.23	8.06e-01	5.92e-03	Soluble
α-pinenes	-3.51	4.24e-02	3.11e-04	Soluble	-4.2	8.59e-03	6.31e-05	Moderately soluble	-2.23	8.06e-01	5.92e-03	Soluble
δ-3-carene	-3.44	4.90e-02	3.60e-04	Soluble	-4.1	1.09e-02	8.01e-05	Moderately soluble	-2.23	8.06e-01	5.92e-03	Soluble
β-Pinene	-3.51	4.24e-02	3.11e-04	Soluble	-4.2	8.59e-03	6.31e-05	Moderately soluble	-2.23	8.06e-01	5.92e-03	Soluble
Terpinen-4-ol	-2.78	2.54e-01	1.64e-03	Soluble	-3.36	6.75e-02	4.38e-04	Soluble	-1.91	1.92e+00	1.24e-02	Soluble
β-phellandrene	-2.79	2.23e-01	1.64e-03	Soluble	-3.12	1.03e-01	7.57e-04	Soluble	-2.03	1.28e+00	9.42e-03	Soluble
Fenchone	-3	1.52e-01	9.97e-04	Soluble	-3.56	4.17e-02	2.74e-04	Soluble	-2.6	3.83e-01	2.52e-03	Soluble
Carvacrol	-3.31	7.40e-02	4.92e-04	Soluble	-3.6	3.79e-02	2.53e-04	Soluble	-3.01	1.46e-01	9.71e-04	Soluble
α-thujone	-2.15	1.08e+00	7.11e-03	Soluble	-2.27	8.27e-01	5.43e-03	Soluble	-2.15	1.08e+00	7.10e-03	Soluble
Camphene	-3.34	6.18e-02	4.54e-04	Soluble	-3.93	1.60e-02	1.17e-04	Soluble	-2.48	4.55e-01	3.34e-03	Soluble
Geraniol	-2.78	2.59e-01	1.68e-03	Soluble	-3.67	3.30e-02	2.14e-04	Soluble	-1.84	2.20e+00	1.43e-02	Soluble
Linalyl acetate	-3.14	1.43e-01	7.30e-04	Soluble	-4.18	1.29e-02	6.58e-05	Moderately soluble	-2.52	5.97e-01	3.04e-03	Soluble
α-terpineol	-2.87	2.10e-01	1.36e-03	Soluble	-3.49	4.95e-02	3.21e-04	Soluble	-1.69	3.17e+00	2.06e-02	Soluble
β-Myrcene	-3.05	1.22e-01	8.96e-04	Soluble	-3.88	1.80e-02	1.32e-04	Soluble	-2.42	5.24e-01	3.85e-03	Soluble

Table 4: Pharmacokinetic Parameters of the Terpenoid Phytoconstituents:

Phytoconstituents	GI absorption	BBB permeant	P-Gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	LogKp (cm/s)
Anethole	High	Yes	No	Yes	No	No	No	No	-4.86
Thymol	High	Yes	No	Yes	No	No	No	No	-4.87
Estragole	High	Yes	No	Yes	No	No	No	No	-4.81
Eugenol	High	Yes	No	Yes	No	No	No	No	-5.69

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P-cymene	Low	Yes	No	No	No	No	Yes	No	-4.21
Linalool	High	Yes	No	No	No	No	No	No	-5.13
Carvone	High	Yes	No	No	No	No	No	No	-5.29
Limonene	Low	Yes	No	No	No	Yes	No	No	-3.89
Sabinene	Low	Yes	No	No	No	No	No	No	-4.94
Costunolide	High	Yes	No	No	No	No	No	No	-6.23
Citral	High	Yes	No	No	No	No	No	No	-5.08
1,8-cineole	High	Yes	No	No	No	No	No	No	-5.3
Camphor	High	Yes	No	No	No	No	No	No	-5.67
Citronellol	High	Yes	No	No	No	No	No	No	-4.48
α-phellandrene	Low	Yes	No	No	No	No	No	No	-4.85
β - Caryophyllene	Low	No	No	No	Yes	Yes	No	No	-4.44
γ- terpinene	Low	Yes	No	No	No	No	No	No	-3.94
α -pinenes	Low	Yes	No	No	No	Yes	No	No	-3.95
δ- 3- carene	Low	Yes	No	No	No	Yes	No	No	-4.02
β - Pinene	Low	Yes	No	No	No	Yes	No	No	-3.95
Terpinen -4-ol	High	Yes	No	No	No	No	No	No	-4.93
β-phellandrene	Low	Yes	No	No	No	No	No	No	-4.69
Fenchone	High	Yes	No	No	No	No	No	No	-4.73
Carvacrol	High	Yes	No	Yes	No	No	No	No	-4.74
α- thujone	High	Yes	No	No	No	No	No	No	-5.62
Camphene	Low	Yes	No	No	No	Yes	No	No	-4.13
Geraniol	High	Yes	No	No	No	No	No	No	-4.71
Linalyl acetate	High	Yes	Yes	No	No	No	No	No	-4.71
α-terpineol	High	Yes	No	No	No	No	No	No	-4.83
β -Myrcene	Low	Yes	No	No	No	No	No	No	-4.17

Table 5: Drug likeness of Terpenoid Phytoconstituents:

Phytoconstituents	**Lipinski**	**Ghose**	**Veber**	**Egan**	**Muegge**	**Bioavailability score**
Anethole	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Thymol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Estragole	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Eugenol	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.55
P-cymene	Yes; 1 violation: MLOGP>4.	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55

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	15					
Linalool	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Carvone	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Limonene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Sabinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Costunolide	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Citral	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
1,8-cineole	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Camphor	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Citronellol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55

Phytoconstituents	**Lipinski**	**Ghose**	**Veber**	**Egan**	**Muegge**	**Bioavailability score**
α-phellandrene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
β - Caryophyllene	Yes; 1 violation: MLOGP>4.15	Yes	Yes	Yes	No; 1 violation: Heteroatoms<2	0.55
γ- terpinene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
α -pinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
δ- 3- carene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
β - Pinene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Terpinen -4-	Yes; 0	No; 1	Yes	Yes	No; 2 violations:	0.55

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ol	violation	violation: MW<160			MW<200, Heteroatoms<2	
β-phellandrene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Fenchone	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Carvacrol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
α- thujone	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Camphene	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Geraniol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
Linalyl acetate	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: MW<200	0.55
α-terpineol	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55
β -Myrcene	Yes; 0 violation	No; 1 violation: MW<160	Yes	Yes	No; 2 violations: MW<200, Heteroatoms<2	0.55

Table 6: Medicinal Chemistry Properties of Terpenoids Phytoconstituent:

Phytoconstituents	PAINS	Brenk	Leadlikeness	Synthetic accessibility
Anethole	0 alert	0 alert	No; 1 violation: MW<250	1.47
Thymol	0 alert	0 alert	No; 1 violation: MW<250	1
Estragole	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	1.28
Eugenol	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	1.58
P-cymene	0 alert	0 alert	No; 2 violations: MW<250, XLOGP3>3.5	1
Linalool	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	2.74
Carvone	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	3.33
Limonene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	3.46
Sabinene	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	2.87
Costunolide	0 alert	2 alerts: isolated_alkene,	No; 1 violation: MW<250	4.29

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		michael_acceptor _1		
Citral	0 alert	3 alerts: aldehyde, isolated_alkene, michael_acceptor _1	No; 1 violation: MW<250	2.49
1,8-cineole	0 alert	0 alert	No; 1 violation: MW<250	3.65
Camphor	0 alert	0 alert	No; 1 violation: MW<250	3.22
Citronellol	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	2.61
α-phellandrene	0 alert	0 alert	No; 1 violation: MW<250	4.15
β-Caryophyllene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3	4.51
Phytoconstituents	**PAINS**	**Brenk**	**Leadlikeness**	**Synthetic accessibility**
γ-terpinene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	3.11
α-pinene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	4.44
Delta -3-carene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	3.84
β –Pinene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	4.44
Terpinen -4-ol	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	3.28
β- phellandrene	0 alert	0 alert	No; 1 violation: MW<250	3.73
Fenchone	0 alert	0 alert	No; 2 violations: MW<250, XLOGP3>3.5	3.22
Carvacrol	0 alert	0 alert	No; 1 violation: MW<250	1
α- thujone	0 alert	0 alert	No; 1 violation: MW<250	2.79
Camphene	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	3.5
Geraniol	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	2.58
Linalyl acetate	0 alert	1 alert: isolated_alkene	No; 2 violations: MW<250, XLOGP3>3.5	2.75
α-terpineol	0 alert	1 alert: isolated_alkene	No; 1 violation: MW<250	3.24
β-myrcene	0 alert	2 alerts: isolated_alkene, polyene	No; 2 violations: MW<250, XLOGP3>3.5	2.85

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IV. DISCUSSION:

Terpenoids are promising natural compounds with diverse biological activities, but their success as drug candidates depends on favorable pharmacokinetic properties. SwissADME provides a simple and effective way to predict ADME parameters such as gastrointestinal absorption, drug-likeness, and metabolic interactions. By analyzing selected terpenoids using SwissADME, compounds with good oral bioavailability and few rule violations can be prioritized for further study. This approach helps streamline the drug discovery process, reducing time and resources needed for experimental screening. Overall, computational ADME modeling is a valuable tool for identifying terpenoids with strong therapeutic potential.

V. CONCLUSION:

The integration of computational tools like SwissADME in natural product research offers a valuable strategy for early assessment of pharmacokinetic properties. This review highlights the effectiveness of SwissADME in predicting the ADME profiles and drug-likeness of selected terpenoids. By identifying compounds with favorable absorption, metabolism, and safety characteristics, SwissADME helps in narrowing down potential drug candidates for further development. While experimental validation remains essential, computational ADME modeling significantly accelerates the screening process and supports the rational selection of terpenoids with promising therapeutic potential.

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