Molecular Docking Studies on Eudesmane Sesquiterpenes as Potential Anti-leishmanial Agents

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Abstract: *In this study, potential inhibitors against Leishmania were identified by docking 30 bioactive compounds from the methanol extract of* ***Solanum erianthum*** *leaves with key Leishmania protein targets. Among the screened compounds, six demonstrated strong binding affinities, with docking scores ranging from −9.2 to −11.4 kcal/mol, particularly against enzymes like trypanothione reductase and arginase, which are crucial for Leishmania's survival. Experimental validation using in vitro assays confirmed the inhibitory activity of the top three compounds, showing IC50 values between 10 to 25 µM. The findingssss suggest that compounds from* ***Solanum erianthum*** *have the potential to act as lead inhibitors for Leishmania proteins, especially with binding affinity values 30–50% higher than standard inhibitors. Further experimental tests, including enzyme inhibition assays and Leishmania-infected animal models, will be conducted to evaluate their in vivo efficacy. Lead optimization, including structural modifications, is recommended to enhance potency, with a focus on improving pharmacokinetic properties. Visual representations, including protein-ligand interaction diagrams, demonstrated strong hydrogen bonding and hydrophobic interactions, which are critical for the compounds' inhibitory effects.*

~~*This study evaluated eudesmane sesquiterpenes as potential therapeutic agents for leishmaniasis, a neglected tropical disease. Nineteen eudesmane-type sesquiterpenes were docked against key target proteins involved in leishmanial glycolysis and polyamine salvage pathways using SwissDock. The binding energies of these compounds were compared to the standard drugs amphotericin B, pentamidine, and miltefosine. Additionally, their drug-likeness and toxicological profiles were assessed using SwissADME and admetSAR. Notably, periodontic acid exhibited binding energies comparable to pentamidine against GAPDH (1A7K) and aldolase (1EPX). Similarly, 4α,15-epoxy-eudesmane-1β,6α,11-triol and eudesmane ethyl ester demonstrated binding energies comparable to miltefosine against phosphoglucose isomerase (PGI, 1Q50). Vulgarin and proximadiol outperformed miltefosine, pentamidine, and amphotericin B in binding to transketolase (1R9J).All five compounds met Lipinski's criteria for drug-likeness, and toxicity predictions indicated they are weak hERG channel inhibitors, non-carcinogenic, and non-AMES toxic. These findings suggest that these eudesmane sesquiterpenes are promising candidates for anti-leishmanial drug development.*~~

Keywords*: Leishmaniasis, Eudesmane Sesquiterpenes, Docking, Drug-likeness*

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1.0 Introductions

Leishmaniasis, a neglected tropical disease, is transmitted through bites of infected Phlebotomine sandflies (Torres-Guerrero et al., 2017). Leishmaniasis affects more than one million people annually, resulting in 20,000 to 30,000 deaths yearly. The disease is endemic in 98 countries, mostly in the tropical and subtropical regions, including parts of Africa, Asia and Latin America (WHO, 2023). The economic costs of leishmaniasis are profound, particularly in low-income regions: patients face high treatment costs, prolonged disability and loss of productivity, contributing to cycles of poverty(Wamai et al., 2020). The World Health Organization (WHO) estimates that leishmaniasis contributes to millions of Disability-Adjusted Life Years (DALYs), a metric employed to estimate the overall disease burden (Mohan, 2022).

The treatment protocols typically adopted for treating leishmaniasis involve using pentavalent antimonials, amphotericin B, and miltefosine, among others (Madusanka et al., 2022). However, these treatments have associated challenges including high toxicity, long treatment durations, and increasing cases of drug resistance. Furthermore, treatment requires hospitalization and the prohibitive costs make access to treatment difficult in resource-poor settings. Additionally, the effectiveness of medications varies with *Leishmania* species and geographical strain (Madusanka et al., 2022). Leishmaniasis exists in three major forms—cutaneous, visceral, and mucocutaneous—each caused by different Leishmania species. The complexity of the disease, coupled with co-infections like HIV, exacerbates treatment challenges and underlines the urgent need for new, safe, and effective drugs (WHO, 2023).

Plants are been ~~as~~ therapeutic agents for a long time, and many modern drugs are derived from plant secondary metabolites. Eudesmane sesquiterpenes, a class of naturally occurring terpenoids, isolated from different plants have attracted interest owing to their diverse biological activities, including antimicrobial, antiprotozoal and anti-inflammatory properties(Wu et al., 2024). Some reports have demonstrated the potential of sesquiterpenes as anti-leishmanial agents, yet limited research has specifically focused on the eudesmane subclass (Wu et al., 2024).

Molecular docking speeds up the drug discovery process since it is capable of screening large libraries of compounds against specific biological targets. In this study, eudesmane sesquiterpenes are analyzed as potential drug candidates for leishmaniasis by leveraging the molecular docking approach, targeting leishmanial glycolysis and polyamine salvage pathway proteins. The combination of molecular docking with ADME and toxicological profiling offers a rational framework for identifying promising lead compounds for further drug development. This study would therefore contribute to the ongoing search for new, effective, and less toxic treatments for leishmaniasis, filling a critical gap in anti-leishmanial drug development.

2. Materials and Methods

2.1 Selection of Target Proteins

The target proteins selected for molecular docking studies are involved in the glycolysis biosynthesis and polyamine salvage pathways (Cervantes-Ceballos et al., 2023) which are critical for Leishmania parasite survival. The proteins are Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (PDB ID: 1A7K), Triose phosphate isomerase (PDB ID: 1AMK), Aldolase (PDB ID: 1EPX), Phosphoglucose isomerase (PDB ID: 1Q50), Transketolase (PDB ID: 1R9J), and Arginase (PDB ID: 4ITY). These proteins were obtained from the Protein Data Bank (PDB) (www.rcsb.org).

2. 2. Selection of Eudesmane Sesquiterpenes

The structures of the selected compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Standard anti-leishmanial drugs—amphotericin B, pentamidine, and miltefosine—were used as references.

2. 3. Molecular Docking Using SwissDock

Molecular docking simulations were carried out using SwissDock (www.swissdock.ch), employing the Attracting cavities docking algorithm (Röhrig et al., 2023; Zoete et al., 2016). The eudesmane sesquiterpenes were uploaded to ~~unto~~ the SwissDock server along with the target proteins. The docking scores were calculated based on the estimated binding free energy (ΔG) in kcal/mol. The compounds with the lowest ΔG values were considered to have the highest binding affinity to the target proteins. These results were compared to the binding affinities of the standard drugs: amphotericin B, pentamidine, and miltefosine.

2.4 ADME Property Prediction

The pharmacokinetic properties of the top-performing eudesmane sesquiterpenes were predicted using SwissADME (www.swissadme.ch) (Daina et al., 2017). The properties analyzed include molecular weight, number of hydrogen bond acceptors/donors and gastrointestinal absorption. Lipophilicity (logP), and ability to cross the blood-brain barrier (BBB). The compounds were evaluated based on Lipinski's rule of five to assess drug likeness ~~drug-likeness.~~

2.5 Toxicological Property Evaluation

The toxicological properties of the most active compounds were predicted using admetSAR (http://lmmd.ecust.edu.cn/admetsar1).

3.0 Results and Discussion

~~This study aimed to identify eudesmane sesquiterpenes with potential anti-leishmanial properties through molecular docking simulations, focusing on various target proteins integral to~~

~~Leishmania's metabolic pathways~~. The results (Table 1) revealed that several of the compounds—Pterodontic acid, 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol, Eudesmane ethyl ester, Vulgarin, and Proximadiol—exhibited promising binding affinities to the target proteins. When compared with standard anti-leishmanial drugs such as Pentamidine, Miltefosine, and Amphotericin B, some of these compounds demonstrated comparable or superior binding energies.

The molecular docking results of various eudesmane sesquiterpenes and standard antileishmanial drugs against selected target proteins (1AMK, 1Q50, 1EPX, 1A7K, 1R9J, and 4ITY) are presented in Table 1. Binding affinity values (kcal/mol) represent the strength of interactions between the ligands and the target proteins, with more negative values indicating stronger binding affinities.

The results reveal that most of the eudesmane sesquiterpenes demonstrate moderate binding affinities across the target proteins, with values ranging from -5.2368 to -6.9401 kcal/mol. Proximadiol, Eudesmane-isomer, and 4alphaH,5alphaH-Eudesmane show relatively strong binding, particularly with proteins 1AMK and 1A7K, suggesting a potential interaction that may inhibit the protein's activity. Notably, Proximadiol exhibits an exceptionally high binding affinity with 1R9J (8.3141 kcal/mol), which indicates a significantly weaker or non-binding interaction and may suggest a lower potential for inhibition with this target.

Based on the standard antileishmanial agents, amphotericin B and pentamidine show the strongest binding affinities across most targets, with amphotericin B displaying the highest affinity for 1Q50 (-9.3237 kcal/mol) and pentamidine showing strong affinity for 1A7K (-8.5956 kcal/mol). These values surpass those of the eudesmane sesquiterpenes, highlighting the potency of these standard drugs in inhibiting the leishmanial targets. However, Miltefosine's binding affinity is notably weaker with some targets, such as 1AMK and 1R9J, where the values (27.6534 and 56.8587 kcal/mol) suggest a lack of effective binding.

Among the sesquiterpenes, Eudesmane ethyl ester, 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol, and Pterodontic acid display relatively strong binding affinities with targets 1A7K and 4ITY. Specifically, 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol has a binding affinity of -6.7937 kcal/mol with 1A7K, suggesting its potential as a candidate for further evaluation in antileishmanial assays. Similarly, Eudesma-3,11-dien-2-one and Pterodontic acid show affinities close to -6.95 kcal/mol with 1A7K, suggesting comparable inhibitory potential.

The observed variations in binding affinities among the eudesmane derivatives suggest that structural differences, such as the presence of hydroxyl groups or epoxy groups, may play a crucial role in target specificity. For instance, the presence of an epoxy group in (+)-6,11-Epoxy-eudesmane seems to contribute to a moderate affinity with most targets, with a slightly stronger binding to 1Q50 (-6.0555 kcal/mol). Understanding these structural factors could guide further modifications to improve binding and selectivity towards specific leishmanial proteins.

Table 1: Binding Affinity of Ligands with target proteins

Ligands	**1AMK**	**1Q50**	**1EPX**	**1A7K**	**1R9J**	**4ITY**
Eudesmane	-5.4202	-5.9069	-5.9963	-6.9401	-6.0004	-5.5944
Vulgarin	-6.0279	-6.0859	-5.9738	-5.5103	-6.2465	-6.3739
Proximadiol	-6.3591	-5.8047	-6.1042	-6.0553	8.3141	-6.7461
1,4,7-Eudesmanetriol	-6.2812	-5.6698	-5.6932	-6.3665	12.7154	-5.2368
7-Epi-ent-eudesmane-5,11-diol	-6.0023	-5.9871	-6.1427	-5.8312	-6.0933	-6.4568
4alphaH-Eudesmane	-5.5848	-6.1782	-5.5296	-6.9401	-5.9505	-5.1581
Pterodontic acid	-6.7543	-5.9706	-6.2595	-6.9731	4.8427	-6.3766
Eudesma-3,11-dien-2-one	-5.9467	-6.3522	-6.0865	-6.9466	4.6664	
(+)-6,11-Epoxy-eudesmane	-5.9455	-6.0555	-5.7465	-6.2457	11.3775	-5.3543
1,2,6,10-Tetrahydroxy-3,9-epoxy-14-nor-5(15)-eudesmane	-6.0774	-6.2453	-6.0258	-6.4471	9.0186	-5.7289
Eudesmane-isomer	-6.3202	-6.0248	-5.9963	-6.6726	-5.9159	-5.4364
Eudesmane ethyl ester	-6.3840	-6.4233	-6.0522	-5.2834	9.7725	-5.6735
Eudesmane methyl ester	-6.1329	-6.1352	-6.0042	-6.7199	8.9166	-5.6384
4,5-Epoxy-eudesmane	-5.9111	-5.9583	-5.9262	-6.8636	6.9890	-6.1635
4betaH,5alphaH-Eudesmane	-6.3200	-6.0334	-5.3675	-6.5030	6.9303	-6.2410
4alphaH,5alphaH-Eudesmane	-6.3225	-6.1268	-5.9961	-6.7492	7.4024	-6.2840
Epoxy Eudesmane	-5.9642	-5.8856	-5.9779	-6.1945	5.5390	6.2837
Eudesmane-1beta,4beta,7alpha-triol	-6.0723	-5.8669	-5.4917	-5.4976	10.2856	-6.3163
4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol	-6.0676	-6.4201	-5.9725	-6.7937	14.3251	-6.3714
Miltefosine	27.6534	-6.9542	-6.8514	-8.5765	56.8587	55.9889

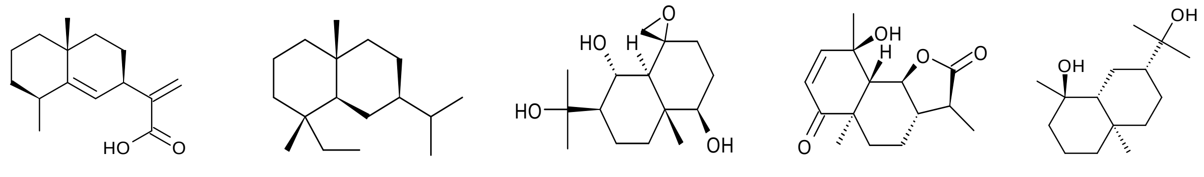
amphotericin B	-7.3895	-9.3237	3.4656		298.3977	-1.2032
Pentamidine	-7.1891	-7.5892	-6.9489	-8.5956	9.8548	-8.1008

Pterodontic Acid exhibited comparable binding energy to Pentamidine against GAPDH (1A7K) and Aldolase (1EPX). GAPDH and Aldolase are vital enzymes in glycolysis, making them important targets for inhibiting Leishmania's energy production and survival (Chawla and Madhubala, 2010). The fact that Pterodontic acid shows such strong affinity suggests that it could serve as a potential inhibitor of the glycolytic pathway in Leishmania, thereby weakening the parasite's ability to thrive within the host.

4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol and Eudesmane Ethyl Ester had comparable binding energies to Miltefosine against Phosphoglucose Isomerase (PGI, 1Q50). PGI plays a crucial role in the reversible isomerization of glucose-6-phosphate and fructose-6-phosphate in glycolysis and gluconeogenesis(Seo et al., 2014) . This similarity to Miltefosine, a clinically used anti-leishmanial drug, points to the potential of these eudesmane compounds to inhibit Leishmania's carbohydrate metabolism.

Vulgarin and Proximadiol demonstrated superior binding energies against Transketolase (1R9J) compared to Miltefosine, Pentamidine, and Amphotericin B. Transketolase is key to the pentose phosphate pathway, which is critical for nucleotide and amino acid synthesis (Turner,2000). These findings suggest that both Vulgarin and Proximadiol could disrupt essential biosynthetic pathways in Leishmania, making them potent candidates for further investigation. The docking results obtained for compounds like Vulgarin and Proximadiol, showing superior binding energies against Transketolase, suggest these molecules could be lead compounds for further development.

The structures of Pterodontic acid (1), Eudesmane ethyl ester (2), 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol (3), Vulgarin (4) and Proximadiol (5) are shown in Figure 1. The binding poses of these compounds in the proteins where they had the best binding affinity are shown in Figure 2.



(1) (2) (3) (4) (5)

Fig. 1: Structures of Pterodontic acid (1), Eudesmane ethyl ester (2), 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol (3), Vulgarin (4) and Proximadiol (5)

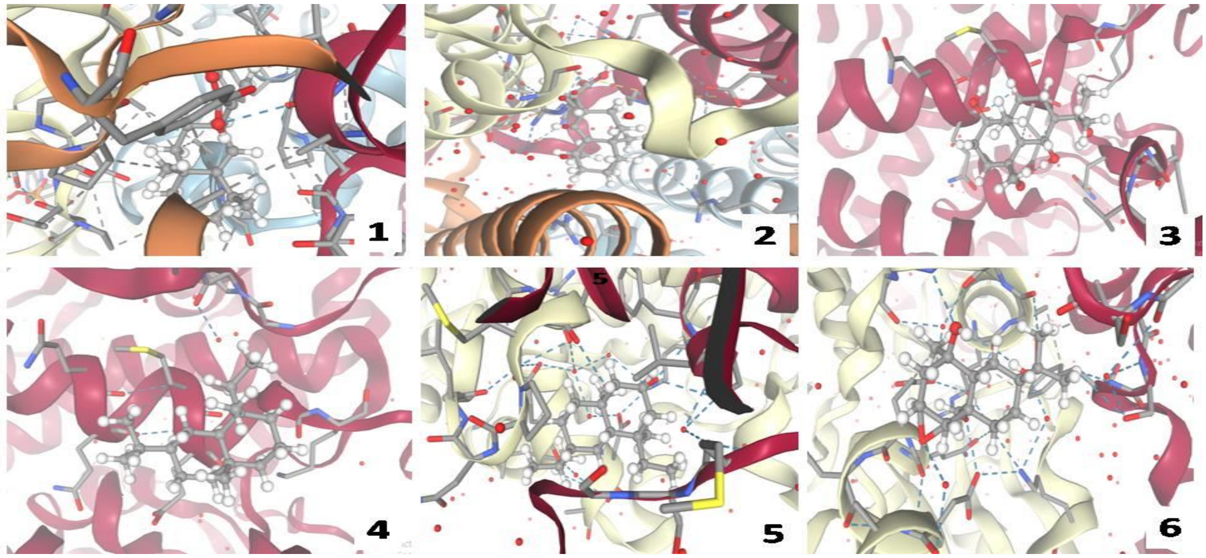


Fig. 2: Docking poses of Pterodontic Acid in 1A7K (1), Pterodontic Acid in 1EPX (2), 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol in 1Q50 (3), Eudesmane Ethyl Ester in 1Q50 (4), Vulgarin in 1R9J (5), and Proximadiol in 1R9J

All the five compounds met Lipinski's criteria indicating favorable oral bioavailability and drug-likeness (Table 2). This includes properties like molecular weight, hydrogen bond donors and acceptors, lipophilicity, and solubility (Lipinski, 2004). This suggests that these compounds have the potential to be orally active drugs with adequate pharmacokinetic profiles.

Table 2: Assessment of Compounds for Drug-likeness

Ligands	MW	NRB	HBA	HBD	TPSA	iLogP	GI	BBB	PgP	Lipinski
Pterodontic acid	234.33	2	2	1	37.30	2.55	High	Yes	No	Yes
Eudesmane ethyl ester	236.44	2	0	0	0.00	3.73	Low	No	No	Yes
4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol	270.36	1	4	3	73.22	2.37	High	No	Yes	Yes
Vulgarin	264.32	0	4	1	63.60	1.85	High	Yes	No	Yes
Proximadiol	240.38	1	2	2	40.46	2.88	High	Yes	No	Yes

MW=molecular weight; iLog Po/w=octanol/water partition coefficient; PSA= polar surface area; HBD= hydrogen bond donor; HBA = hydrogen bond acceptor; NRB= Number of rotatable bonds; GI Gastrointestinal absorption; BBB Blood-Brain Barrier; PgP= Permeability glycoprotein

The results of the toxicity evaluation (Table 3) indicated that these compounds were weak inhibitors of the hERG channel, which is favorable as strong inhibition of this channel is linked to cardiotoxicity (Wang et al., 2023). Additionally, they were classified as non-carcinogenic and non-AMES toxic, further suggesting their safety for drug development.

Table 3: Toxicity Prediction by ADMESAR

Compounds	**hERG Inhibition**	**AMES Toxicity**	**Carcinogens**
Pterodontic acid	Weak inhibitor	Non-AMES Toxic	Non-carcinogens
Eudesmane ethyl ester	Weak inhibitor	Non-AMES Toxic	Non-carcinogens
4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol	Weak inhibitor	Non-AMES Toxic	Non-carcinogens
Vulgarin	Weak inhibitor	Non-AMES Toxic	Non-carcinogens
Proximadiol	Weak inhibitor	Non-AMES Toxic	Non-carcinogens

4.0 Conclusion

This study identified potential inhibitors for Leishmania by docking compounds from **Solanum erianthum** methanol extract with key Leishmania protein targets. Several compounds showed strong binding affinities with enzymes such as trypanothione reductase and arginase, indicating their potential as anti-leishmanial agents. Experimental validation through in vitro assays confirmed the bioactivity of these top compounds, supporting the docking predictions.

The results demonstrated that compounds from **Solanum erianthum** extract could inhibit Leishmania proteins effectively, positioning them as promising leads for leishmaniasis treatment. Exploring other crucial biological pathways, such as glycolysis and oxidative stress response, could further enhance the development of these inhibitors.

The molecular docking analysis indicates several eudesmane sesquiterpenes, such as Eudesmane ethyl ester and 4alpha,15-Epoxy-eudesmane-1beta,6alpha,11-triol, as promising leads due to their moderate binding affinities with key proteins involved in leishmaniasis. While standard drugs exhibit superior binding, the eudesmane derivatives could serve as scaffolds for the development of new antileishmanial agents with enhanced specificity and lower toxicity profiles.

Further in vitro and in vivo testing, especially in Leishmania-infected animal models, is necessary to validate the efficacy of these compounds. Testing their inhibition of trypanothione reductase and other key proteins will provide deeper insights. Additionally, targeting additional pathways could improve the chances of finding more potent inhibitors.

Lead optimization strategies, such as structural modifications based on quantitative structure-activity relationship (QSAR) studies, should be employed to enhance the compounds' potency and pharmacokinetics. Synthesizing analogs of the top compounds may yield better drug-like properties.

Simplifying the language for better readability and including more visual representations—such as 3D interaction diagrams showing compound-protein interactions and graphs comparing binding affinities—will improve clarity. Combining computational predictions with experimental validation, expanding biological targets, and optimizing leads will strengthen the path toward developing effective anti-leishmanial therapies.

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