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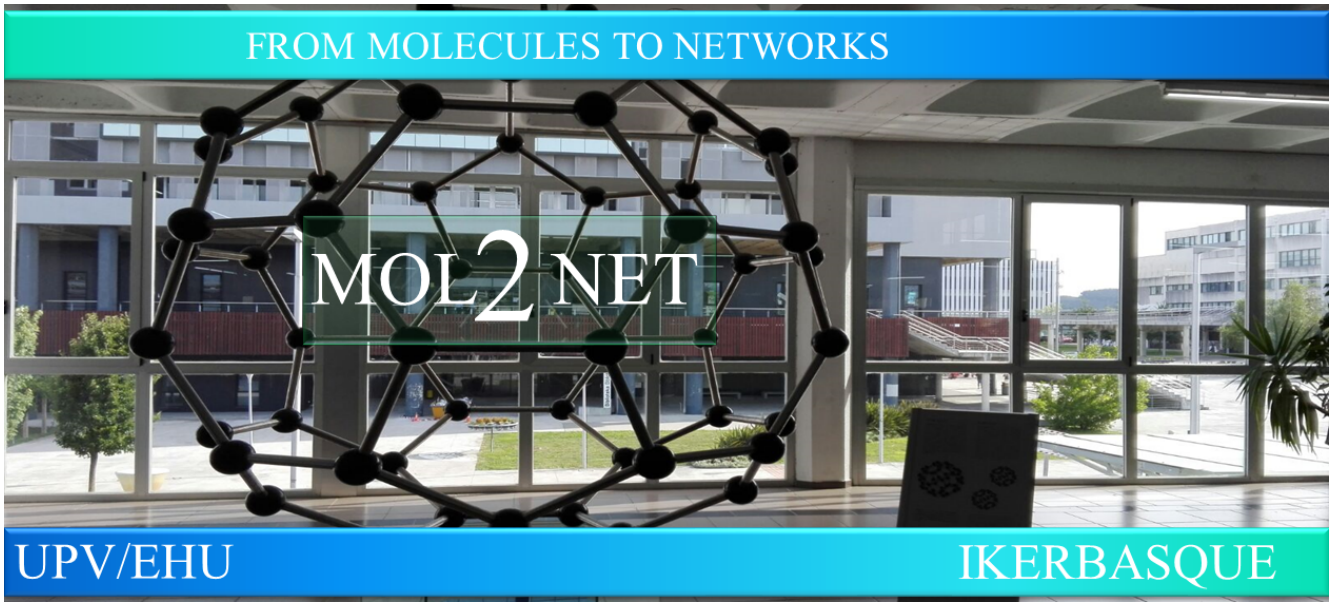

Mini Review: Identification of Arginase Flavonoid Inhibitors against Leishmaniasis and Molecular Docking of Flavonoids

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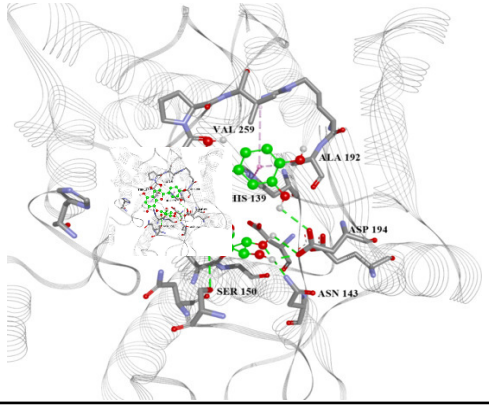
Graphical Abstract



Abstract

This work combines computational approaches, protein modeling, and molecular docking to explore potential targets and drug candidates for leishmaniasis. It contributes to the ongoing efforts to develop effective and accessible treatments for this neglected tropical disease.

Keywords: Flavonoids; leishmaniasis; arginase; leishmanolysin; molecular docking.

Introduction

Leishmaniasis is a significant global health problem caused by parasites transmitted through sandflies[1]. Current treatments have limitations, and the lack of vaccines necessitates the exploration of new therapeutic options. One potential target is a protein called glycoprotein 63 (gp63), found on the surface of Leishmania parasites[2], which plays a role in the parasite's virulence. Computational methods, including molecular docking, can help predict protein structures and interactions with small molecules. This study[3] presents a three-dimensional model of gp63 from *Leishmania panamensis*, validated for reliability. Molecular docking was used to analyze the binding of flavonoid compounds with gp63 from *L. major* and *L. panamensis*, providing insights for potential inhibitors. Another study[4] discusses the importance of arginase, an enzyme involved in the parasite's survival, as a therapeutic target for Leishmania. Arginase inhibitors have shown promise in controlling infection by inducing oxidative stress in the parasite[5]. Natural compounds, particularly flavonoids, have shown promise as arginase inhibitors and potential therapeutic agents against leishmaniasis[6].

Materials and Methods

This study involved the acquisition, processing, and curation of ligand data from the MetIDB database, which contains spectral information on flavonoids. Using a filter based on the Weighted Individualized Ionization Energy (EIIP/AQVN) value, compounds were selected for three-dimensional quantitative structure-activity relationship (3D QSAR) modeling against *Leishmania amazonensis* arginase. GRIND descriptors were calculated, and principal component analysis (PCA) and partial least squares (PLS) models were constructed. Subsequently, molecular docking experiments were conducted to evaluate the interaction of the compounds with Leishmania arginase and human arginase. Furthermore, proteins involved in substance metabolism were used as anti-targets to assess potential interactions with the compounds. The results provided information on the activity of the tested compounds and their interactions with the target and anti-target proteins.

Concurrently, homology modeling of the gp63 protein from *L. panamensis* was performed based on the crystal structure of gp63 from *L. major*. The quality of the model was evaluated using various metrics such as QMEAN, Z-score, Molprobity, ProSA-web, and Verify3D. Subsequently, 200 ns molecular dynamics (MD) simulations were conducted for both modeled proteins using the GROMACS package and the Amber99sb force field. MD trajectories were analyzed using RMSD and RMSF. Additionally, a database containing chalcones, flavonoids, and biflavonoids was prepared and optimized using theoretical density functional calculations. Molecular docking of the compounds with leishmanolysin proteins was performed using AutoDock Vina, and the docking validation was conducted using metrics such as AUC, ROC curve, and enrichment factor (EF1%). A linear correlation analysis was also performed between the antileishmanial activity of the compounds and the calculated affinity. The statistical significance of the models was evaluated through a p-test with a 95% confidence level.

Results and Discussion

In this study, a virtual screening protocol based on sequential filters was used to select candidates for anti-leishmania arginase inhibitors. Virtual screening criteria were established, and QSAR models were constructed based on a training set of 24 anti-leishmania arginase inhibitors. Using these models, 200 flavonoids were selected as candidates for anti-leishmania arginase inhibitors. QSAR analysis revealed the most significant molecular properties for the activity of arginase inhibitors. A PLS model with three latent variables showed a high correlation with experimental activity, indicating that virtual screening based on EIIP/AQVN could be effective in selecting candidates for anti-leishmania arginase inhibitors.

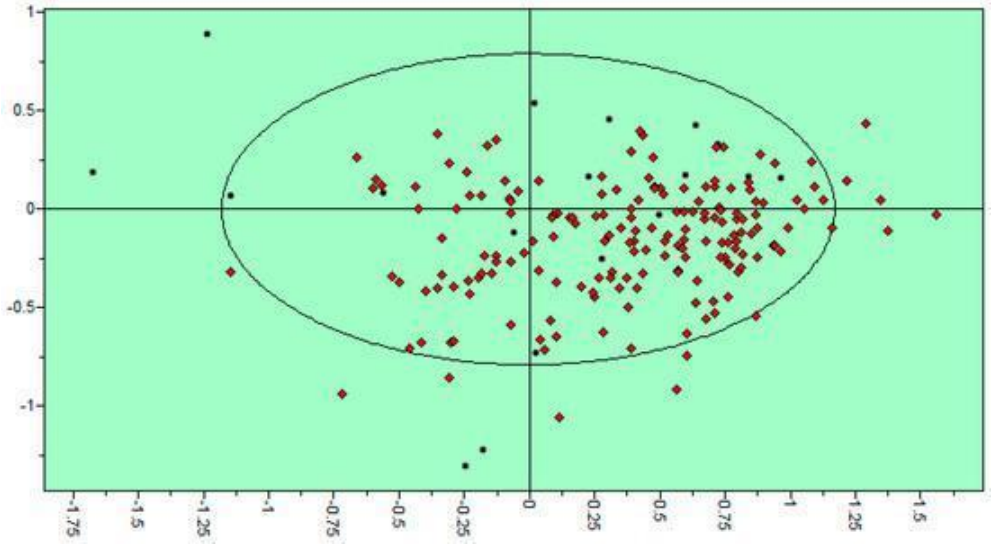


Figure 1. PLS scores of 200 candidates in the Leishmania arginase 3D QSAR model. Red: candidates, black: 18 Leishmania arginase inhibitors.

The results of dynamics simulations demonstrated that the models reached stable states after 200 ns of simulation. Analysis of the trajectories revealed fluctuations in amino acid residues, with the N-terminal and C-terminal regions showing the largest variations. A Ramachandran plot was utilized to assess the conformation of the models, indicating a high percentage of residues in favorable regions. The study also employed molecular docking to investigate the interaction of flavonoid compounds with leishmanolysin. Through molecular docking, favorable interactions between ligands and active sites of the proteins were identified. Lanoraflavone exhibited the highest binding affinity, followed by podocarpusflavone A, amentoflavone, and podocarpusflavone B (figure 2). The interactions primarily occurred through hydrogen bonds, hydrophobic interactions, metal contacts, and π-stacking interactions. In summary, this study constructed structural models of leishmanolysin, validated the stability of the models through molecular dynamics simulations, and identified flavonoid compounds with potential activity against this protein.

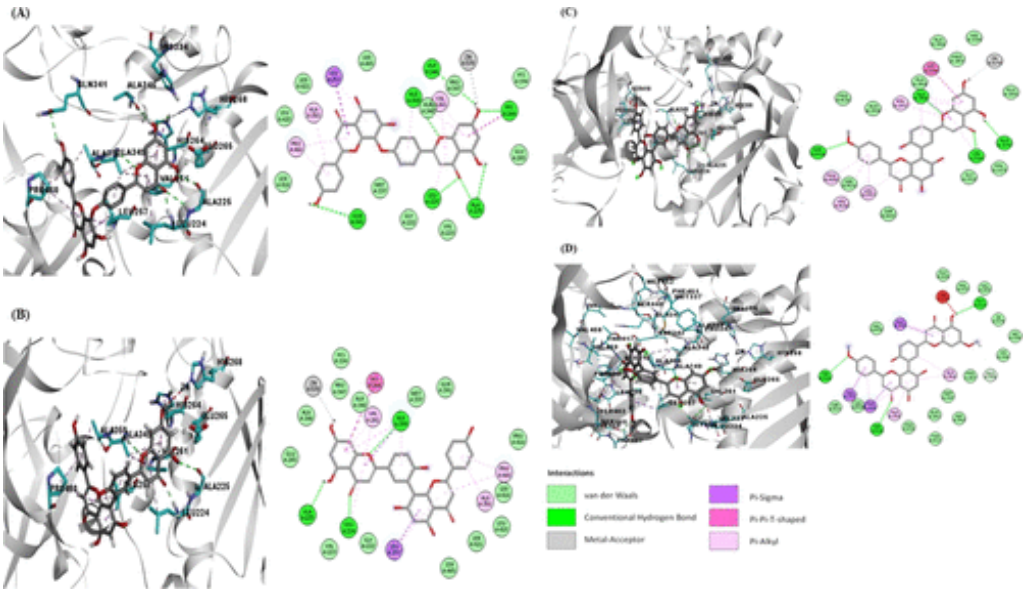


Figure 2. Docking poses of the molecules in the active site of leishmanolysin from *L. panamensis* built by the homology model: (A) lanoraflavone, (B) amentoflavone, (C) podocarpusflavone A, and (D) podocarpusflavone B.

Conclusions

The results showed favorable interaction profiles with arginase and the anti-targets, suggesting that these compounds have the potential for further investigation and may serve as better starting points compared to random screening. Flavonoids, chalcones, and bioflavonoids demonstrated a significant affinity for the leishmanolysin protein from *L. major*. Lanaroflavone, which violated Lipinski's rules, showed the lowest binding energy and exhibited good antileishmanial activity. Overall, the findings of this study suggest that flavonoid derivatives, along with other compounds such as chalcones and biflavonoids, hold promise as natural products for the treatment of leishmaniasis. The favorable interaction profiles observed with both the target protein and the anti-target proteins, as well as the significant affinity demonstrated in the docking studies, indicate the potential effectiveness of these compounds. However, further research is needed to validate and optimize these findings and to explore the therapeutic potential of flavonoid derivatives in treating leishmaniasis.

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