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Molecular Dynamic Simulation of Wrightiaionoside B from *Wrightia* Genus Against Wild-Type And Quadruple Mutant *Plasmodium falciparum* Dihydrofolate Reductase (pfDHFR)

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Structured Abstract

Background: Malaria is a life-threatening parasitic disease caused by Plasmodium, with Plasmodium falciparum being the deadliest species. Drug-resistant strains of P. falciparum have become a global challenge in malaria control. Antimalarial drugs target essential enzymes like dihydrofolate reductase (DHFR) in the parasite's metabolic pathways.

Methods: The research aims to study specific compounds from the Wrightia genus using molecular dynamics simulation, selected based on their low binding energy and interactions with key catalytic residues. The target protein is the wild-type Plasmodium falciparum dihydrofolate reductase (pfDHFR), a protein associated with malaria. The protein will undergo preparation and optimization steps, including adding missing hydrogens, resolving steric clashes, and minimizing energy using the OPLS3e force field. The protein complex will be solvated, neutralized, and subjected to further minimization. A 100ns MD simulation will be performed under specific conditions. MD simulation results, such as RMSD, RMSF, and interaction analysis, will be examined. The binding free energy of the complexes will be determined using the MM-GBSA analysis with the Prime module v3.1 of the Schrödinger Suite 2018-4.

Results: The result show that the wild type has higher stability with minimal fluctuations and structural integrity throughout the simulation, making it a reliable starting point for further investigations. On the other hand, the quadruple mutant exhibited a higher number of amino acid interactions, suggesting its potential for strong and specific bonding with other molecules. The analysis of ligand torsion angles revealed stable hydrogen bonds with limited rotation, providing an ideal environment for potential interactions. Overall, MD simulations proved to be crucial in understanding the behaviour and potential of the compounds under study.

Conclusion: In conclusion, this study could contribute to the development of novel antimalarial agents and aid in combating drug-resistant malaria, which remains a global health concern. However, it is essential to recognize that this work is part of a broader effort to address the challenges posed by malaria, and further experimental validations will be required to translate these findings into potential clinical applications.

Keywords: Molecular Dynamic, MM-GBSA, Torsion Ligand

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