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Molecular Dynamics Simulation of Wrightiaionosides A from *Wrightia* Genus against Wild-Type and Quadruple Mutant of *Plasmodium falciparum* Dihydrofolate Reductase (*pf*DHFR).

Nurhidayah Kamarulzaman[a], Syahrul Imran Abu Bakar[a*]

Structured Abstract

Background: *Wrightia* antidysenterica which is an evergreen shrub native to Sri Lanka, has been used for medicinal purposes in India since ancient times. Its leaves treat skin disorders like psoriasis and non-specific dermatitis, while its bark has anti-microbial and anti-inflammatory properties. However, frequent use of antimalarial medications has led to plasmodium parasite mutations, making them more resistant. To achieve WHO targets of reducing malaria cases and mortality rates by 75% and 90% by 2030, new compounds must be discovered. This study focuses on target proteins and evaluates their potential as molecular docking studies and molecular dynamics simulations.

Methods: Compound selection for molecular dynamics simulation involves selecting compounds based on interactions with catalytic residues and lowest binding energies. Protein-ligand complex preparation involves optimizing hydrogen bonds and minimizing restrained energy. System builder step is applied to minimize the protein complex. MD simulation and MM-GBSA analysis are performed to determine binding free energies.

Results: From the findings, it shows that wild type is the most stable compound compared to quadruple mutant as the RMSD analysis shows that the wild type only have minimal fluctuations where the quadruple mutant is having several fluctuations, indicating that the compound is moving too much. In term of interaction, the results shows that wild type is having a strong interaction compared to quadruple mutant as there are more amino acid interaction and the ligand torsion profile also showing that the bond which have amino acid interaction is not moving too much.

Conclusion: This study uses molecular dynamics simulations to study the stability and interactions of Wrightiaionosides A with wild-type and quadruple mutant *Plasmodium falciparum* Dihydrofolate Reductase (*pf*DHFR). Findings suggest wrightiaionosides A as potential antimalarial medications, expanding drug discovery and design possibilities.

Keywords: Molecular Dynamics Simulation, *Wrightia* Genus, *Plasmodium falciparum* Dihydrofolate Reductase (*pf*DHFR).

*Correspondence: syahrulimran@uitm.edu.my

[a]School of Chemistry & Environment, Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia