Abstract

When drug-resistant cases of Plasmodium falciparum malaria are on the rise, it becomes an even more pressing public health concern in nations like Indonesia. The enzyme dihydrofolate reductase (DHFR), which is crucial for the production of folate and the survival of malaria parasites, is one of the primary targets for the development of antimalarial prescription drugs. Through the use of molecular docking, molecular dynamics simulations, and ADME-Tox predictions, this study investigated the possibility of five compounds such as Atovaquone, Piperaquine, Pralatrexate, Pyrimethamine, and Tafenoquine that inhibiting DHFR.

According to CB-Dock2, the docking analysis revealed that Piperaquine had the highest value at 11.2 kcal/mol, followed by Pralatrexate at 10.9 kcal/mol, and Atovaquone at 9.9 kcal/mol. Atovaquone appeared to have a more stable interaction with the protein, as confirmed by the lowest average RMSF value (0.967 Å) found in molecular dynamics simulations conducted using CABS-flex. Additionally, piperaquine exhibited strong stability, with an RMSF of 1.010 Å. Thanks to its high bioavailability score (0.85) and lack of infractions of Lipinski's Rule of Five, atovaquone had the best profile in pharmacokinetic analysis conducted utilizing ADME-Tox resources.

When considering potential candidates for DHFR inhibition, Atovaquone and Piperaquine stood out for their strong binding scores, structural stability, and attractive drug-like qualities. Based on these results, further experimental study could be beneficial in the future, and these chemicals could be repurposed to help create new antimalarial drugs.

Keywords: *Plasmodium falciparum*, dihydrofolate reductase (DHFR), molecular docking, in-silico drug discovery, malaria