ABSTRACT

Malaria is a parasitic infection affecting people worldwide, with *P. falciparum* being the most dangerous. Identifying more validated asexual and sexual blood-stage drug targets may be key to malaria eradication and control for a variety of reasons. Gynura divaricata (Lour.) Merr. is an Indonesian medicinal herb that contains various natural compounds with antibacterial and potentially antimalarial properties. This study aims to do an *in-silico* study to evaluate the *G. divaricata* antimalarial property by inhibiting *P. falciparum* asexual and sexual blood-stage proteins. By performing a systematic review, four vital proteins (PfHT1, PfKRS1, PfCDPK1, and PfROM4) were identified as potential targets and docked with fifteen *G. divaricata*-derived compounds from four chemical classes. Proteins and ligands were procured from Phyre2 and the PubChem database (NCBI) respectively, where the modeled proteins demonstrated excellent confidence and coverage. The binding pockets were predicted using the CASTp 3.0 server. Molecular docking was performed within PyRx 0.8 using Autodock Vina, yielding binding affinities ranging from -7.7 to -10.1 kcal/mol, and was validated by i) docking decoy ligands to the proteins; ii) Ramachandran plot and SWISS-MODEL scores. Using BIOVIA Discovery Studio, the interacting residues were visualized in two and three dimensions. Molecular dynamics simulations were done using CABS-flex2. Three proteins (PfHT1, PfKRS1, and PfCDPK1) showed potentially stable interactions with identified ligands from the steroidal and triterpenoid classes. Hence, the natural compounds can be further evaluated for drug compatibility via *in-vitro* and *in-vivo* studies.

Keywords: Malaria, *Plasmodium falciparum*, *Gynura divaricata*, Blood-stage proteins