

ANTIPLASMODIAL ACTIVITY AND MECHANISMS OF ACTION OF *EURYCOMA LONGIFOLIA* JACK ROOT ISOLATED COMPOUNDS

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Abstract. *Eurycoma longifolia* Jack is a medicinal plant had been traditionally used as an antimalarial agent in Indonesia. Antiplasmodial activity and action mechanisms of *E. longifolia* Jack root isolated compounds have not previously been evaluated. In this study we aimed to identify the activity and mechanisms of action of *E. longifolia* Jack against *Plasmodium falciparum* to determine its potential as an antimalarial agent. Five different isolated compounds of the ethyl acetate soluble fraction derived from *E. longifolia* Jack root methanol extract were tested. The antiplasmodial activity against *P. falciparum* FCR3 and D10 strains was tested in vitro. We used a modified fixed-ratio isobologram method to evaluate the activity of each of the 5 isolated compounds against the E64, an epoxide acting as a cysteine protease inhibitor. We used an in vitro Heme Polymerization Inhibition Assay (HPIA) to identify the ability of the isolated compounds to inhibit β -hematin formation of *P. falciparum*. The 50% inhibitory concentration (IC₅₀) values ($\pm$ Standard Deviation (SD)) for the 5 isolated compounds against the *P. falciparum* FCR3 ranged from 2.1 ($\pm$ 0.1) to 808.8 ($\pm$ 26.8) μ g/ml and the IC₅₀ values ($\pm$ SD) against the *P. falciparum* D10 strain ranged from 55.9 ($\pm$ 28.2) to 1151.1 ($\pm$ 122.7) μ g/ml. The selectivity index was in the range of 0.1-66.2. Compounds 4 and 5 had greater antimalarial activity than the other compounds, with an antagonistic and an additive effect, respectively. The activity of Compound 4, interfering with hematin polymerization, and the additive interaction between Compound 5 and E64 corresponding to inhibition of protease enzymes could be possible action mechanisms of Compounds 4 and 5 suggesting them as potential antimalarial drug candidates.

Keywords: *Eurycoma longifolia* Jack root; *in vitro* antiplasmodial activity; selectivity index; protease inhibitor; HPIA.

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