Strategi pengembangan antimalaria terhadap *Plasmodium falciparum* di Indonesia

ABSTRAK

Malaria masih menjadi masalah kesehatan global yang diperparah dengan terjadinya resistensi parasit malaria terhadap terapi kombinasi berbasis artemisinin (ACTs) yang merupakan antimalaria terbaru dan paling efektif. Penelitian ini bertujuan untuk mengevaluasi aktivitas antiplasmodium dari bahan potensial untuk pengembangan antimalaria baru, yaitu tanaman obat tradisional Indonesia dan senyawa komponen organometalik yang mengandung kompleks emas yang berikatan dengan ligan *NHC*. Selain eksplorasi antimalaria baru, penelitian ini juga bertujuan untuk mengkaji mekanisme resistensi terkait mutasi gen K13 sebagai penanda resistensi artemisinin. Evaluasi aktivitas antiplasmodium tanaman obat tradisional Indonesia dan senyawa sintesis organometalik diujikan pada *P. falciparum* yang resisten terhadap klorokuin. Dari hasil eksplorasi tanaman obat tradisional Indonesia, tujuh dari 25 ekstrak menunjukkan adanya aktivitas antimalaria yang baik (IC_{50} < 5µg/mL) dengan ekstrak dari *Arcangelisia flava* sebagai ekstrak yang paling aktif. Penelitian mendalam terkait senyawa sintesis organometalik menunjukkan bahwa komponen yang paling aktif adalah senyawa kompleks gold(I)-NHC yang bersifat lipofilik dan kationik (IC_{50} 0,32µM). Identifikasi fungsi gen K13 pada resistensi artemisinin dilakukan dengan uji $RSA_{(0\text{-}3h)}$ pada isolat parasit dari pasien malaria di Kamboja dan beberapa galur parasit yang dikembangkan dan dikultur di laboratorium. Hasil uji menunjukkan bahwa parasit yang telah dimodifikasi dengan penyisipan ataupun pengambilan gen mutan K13 memberikan angka ketahanan hidup parasit yang berbeda dan membuktikan terjadinya resistensi artemisinin. Oleh karenanya, dapat disimpulkan bahwa ekstrak tumbuhan *A. flava* dan senyawa kationik kompleks gold(I)-NHC memiliki aktivitas antiplasmodium dan berpotensi untuk dikembangkan menjadi antimalaria baru. Di sisi lain, mutasi gen K13 terbukti berperan dalam kejadian resistensi artemisinin berdasarkan pengujian $RSA_{(0\text{-}3h)}$.

Kata kunci: malaria, *Plasmodium falciparum*, *Arcangelisia flava*, *Pycnarrhena cauliflora* senyawa komplek emas, K13, artemisinin

Strategies for the Development of Antimalarial against *Plasmodium falciparum* in Indonesia

ABSTRACT

Malaria remains a global public health problem and worsening with the resistance of *Plasmodium falciparum* to Artemisinin-based Combination Therapies (ACTs), the latest and most effective antimalarial drugs. This project aimed to evaluate the antiplasmodial activity of possible sources for developing new antimalarial drugs from Indonesian medicinal plants and chemosynthetic organometallic compounds containing gold(I)-NHC complexes. In addition, this research also studied the mechanism of artemisinin resistance related to K13 gene mutation as a molecular marker. Evaluation of antiplasmodial activity from selected Indonesian medicinal plants and gold compound was conducted against *P. falciparum* CQ-resistant-strain. The first part was to look for new antimalarial drugs based on Indonesian ethnobotanical data. Among 25 crude extracts realized on Indonesian traditional medicinal plants, seven showed a good antimalarial activity (IC_{50} < 5µg/mL) with the extracts from *A. flava as* the most active extract. The second part of the study focused on chemosynthetic organometallic compounds. The structure-activity relationships study on organometallic gold(I)-NHC complexes led to a very active compound on *P. falciparum* with an IC_{50} of 320nM. The third part of this work was dedicated to the study of *P. falciparum* resistance to artemisinin and its derivatives. The correlation between *PfK13* polymorphism and artemisinin resistance has been clearly established thanks to reverse genetic with resistant and sensitive laboratory strains and clinical isolates from Cambodia. This resistance was evidenced *in vitro* throughout a parasite survival assay called $RSA_{(0\text{-}3h)}$. In conclusion, *A. flava* and cationic gold(I)-NHC compounds were active against *P. falciparum* and potentially interesting as chemical starting point for new antimalarial drugs. Concerning artemisinin resistance, it has been proved that K13 gene mutation mediated the artemisinin resistance *in vitro* through RSA assay. In fact, any treatment failure or delayed cure with ACTs has yet to be reported in Indonesia. However, because Indonesia is relatively close to the Southeast Asian areas of resistance, the possible occurrence of such cases in Indonesia must be anticipated by determining the variations of *P. falciparum* malaria chemosensitivity and by following *PfK13* polymorphism responsible for artemisinin resistance.

Keywords: malaria, *Plasmodium falciparum*, *A. flava*, *P. cauliflora*, gene K13, artemisinin