In Silico Study of Andrographolide as Protease Inhibitors for Antimalarial Drug Discovery

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Abstract:
Malaria parasite encodes several homologues of aspartic proteases such as plasmepsin I, II and IV which are responsible for degradation of host erythrocyte hemoglobin inside the vacuole of parasite food. Hence plasmepsins are novel targets for antimalarial drug discovery. Previous study concluded that *Andrographis paniculata* herbs extract has been proven to exert antimalarial activity. However, the molecular mechanism of this activity was not described. The objectives of this paper were to investigate the interaction between andrographolide, a major constituent of *Andrographis paniculata* with the ligand binding domain of plasmepsin I, II and IV, to find the most favorable binding site as well as to predict the binding mode. Pepstatin, a protease inhibitor, was used as standard. Docking studies showed that pepstatin gave better binding interactions to plasmepsin I, II and IV with binding affinity and inhibition constant of E_i = −10.3 kcal/mol; K_i = 0.02 μM (plasmepsin I), E_i = −8.9 kcal/mol; K_i = 0.3 μM (plasmepsin II), E_i = −9.3 kcal/mol; K_i = 0.15 μM (plasmepsin IV), respectively, while andrographolide showed E_i = −9.8 kcal/mol; K_i = 0.07 μM (plasmepsin I), E_i = −8.7 kcal/mol; K_i = 0.42 μM (plasmepsin II), E_i = −8.8 kcal/mol; K_i = 0.35 μM (plasmepsin IV). According to the result, it was concluded that andrographolide could be developed as protease inhibitor for antimalarial drug.

Key words: *Antimalarial, andrographolide, plasmepsin, protease inhibitor*

Introduction

Hemoglobin metabolism is one of the key metabolic processes for the survival of the parasite in human blood. There are some proteases enzyme involved in the degradation of hemoglobin in the parasite food vacuole. Plasmepsin is an aspartic protease enzyme of the species *P. falciparum* that responsible for the initial cleavage of hemoglobin and is then followed by other protease enzymes [1]. Therefore, plasmepsin can be served as new targets for antimalarial drug discovery [2].

P. falciparum genome sequencing project has identified ten types of protein aspartate protease, where three of them are plasmepsin I, II and IV in charge in the early stages of hemoglobin degradation [3]. Recent studies have shown that effective drugs must be able to interact on more than one type of plasmepsin, this is due to the possibility of parasites can still survive if only one type of plasmepsin are inhibited, and also to avoid drug resistance in malaria treatment [4].

Plasmepsin is an aspartic protease enzyme in which the catalytic of the enzyme contains two aspartic acid residues [5]. Both of these aspartic acid residues act respectively as proton donors and acceptors, as well as a catalyst for the hydrolysis of peptide bonds in proteins [6]. Hemoglobin degradation process begins with the termination of phenylalanine 33 (Phe33) and leucine 34 (Leu34) in the α-globin chains in hemoglobin [7].

Previous studies concluded that the extract of Andrographis paniculata shown to have activity as an antimalarial, but studies of other active compounds and molecular mechanism of action is not described [8, 9, 10, 11].

The main component of *Andrographis paniculata* is diterpenoid compound, named andrographolide [12]. In this study we determined the interaction and affinity of andrographolide against plasmepsin I, II and IV.

Experimental

Hardware and software
Docking calculations were carried out on branded Sony Vaio PC Linux Ubuntu 14.04 LTS as the operating system, with Intel 2.30 GHz Core i5 and 4 GB memory hardware. The softwares used for docking preparation were SPORES, PLANTS 1.2, Open Babel 2.3.2 and python script from Autodock Tools. Meanwhile, PyMOL and AutoDock Vina 1.1 were used for RMSD calculation and binding algorithms. Virtual analysis of docking site was used by AutoDock Tools 1.5.6 and PoseView to generated two-dimensional diagrams of docking poses.

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