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Original Article

INTERACTIONS OF GANODERIOL-F WITH ASPARTIC PROTEASES OF HIV AND PLASMEPSIN FOR ANTI-HIV AND ANTI-MALARIA DISCOVERY

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ABSTRACT

Objective: HIV-1 has been a killer disease since two decades ago, while a potential cure has not yet discovered due to the fast mutations of the HIV-1 enzymes,i.e reverse transcriptase, integrase, and protease. Apart of HIV-1, malaria has been the biggest cause of death in human and it is mostly found in the East part of Indonesia. There are some enzymes in the food vacuole of *Plasmodium falciparum* which are the targets of anti-malaria discovery, e.g. plasmepsin I, II, IV, and histo-aspartic protease (HAP). Both plasmepsin and HIV-1 protease are aspartic proteases, therefore a single drug could be designed to inhibit both enzymes. Ganoderiol-F is a triterpenoid isolated from the stem of *Ganodermasinense*which shows inhibition on HIV-1 protease with IC_{50} 20-40 µM.

This project was aimed to study and visualize the interaction of ganoderiol-F with HIV-1 protease and plasmepsin I for anti-HIV and anti-malaria discovery.

Methods: Preparation of the ligand comprises of geometry optimization using MM+ method and Polak-Ribiere (conjugate gradient) algorithm. Molecular docking using AutoDock 4.2 was used to put the ligand into the binding site of both aspartic proteases. Pepstatin-A was used as comparison. The amino acid residues near the drug-target interactions and affinity of the drugs were identified.

Results: The affinity of ganoderiol-F is higher towards HIV-1 protease (binding energy= -11.40kcal/mol and K_i= 4.68nM) than to plasmepsin I (binding energy= -9.96 kcal/mol and K_i= 50.94 nM), meanwhile pepstatin-A has better affinity towards HIV-1 protease (binding energy= -4.52 kcal/mol and K_i= 496.13 µM) than to plasmepsin I (binding energy= -3.07 kcal/mol and K_i= 5.98 mM).

Conclusions: According to the values of binding energy and inhibition constant, ganoderiol-F could be developed further as both anti-HIV and anti-malaria.

Keywords: AIDS, Ganoderiol, HIV-1 protease, Malaria, Molecular docking, Plasmepsin I, *Plasmodium falciparum.*

INTRODUCTION

HIV-1 protease is one of a promising new chemotherapeutics target. HIV-protease inhibitors restrain the viral maturation by preventing the formation of structural and functional proteins and form immature, non-infectious virus. Structurally, HIV-1 protease is a homodimer protein, containing 99 amino acids in each chain, with an active site located in the dimer interface [9]. The protein is composed of three regions, the catalytic core domain (Asp25, Gly27, Ala28, Asp29, and Asp30), flap (Ile47, Gly48, Gly49, and Ile50), and the C-terminal region (Pro81 and Ile84). The amino acid residues of catalytic core are known to be highly conserved residues to which a potent inhibitor may bind strongly [6].

HIV-1 protease and Plasmepsin I enzymes are both aspartic proteases, which catalytic sites contain two aspartic acid residues. They are usually located at the bottom of a cleft in the enzyme surface [11]. Aspartic proteases are inhibited by pepstatin-A, a naturally occurring peptide containing two statins, which replace amino acids [10,13]. The hydroxyl group of the statine binds tightly to the catalytically-active aspartic acid residues in the active site of protease, thereby mimicking the transition state of the peptide cleavage [14]. Plasmepsin Iwhich is found in the food vacuole of *Plasmodiumfalciparum* degrades the hemoglobin directly [1]. The active site of Plasmepsin I contains two important aspartic acid residues, Asp32, and Asp125 [2], both plays a role in the degradation of hemoglobin in the food vacuole of *Plasmodium falciparum.*

Ganoderiol-F is a triterpenoid isolated from the stem of *Ganodermasinense*which inhibits HIV-1 protease with IC_{50} 20-40 µM[12]. Based on this *in vitro* result, an *in silico* approach by molecular docking was interesting to be carried out to study and visualize the interaction of ganoderiol-F with HIV-1 protease and plasmepsin I for anti-HIV and anti-malaria discovery.

MATERIALS AND METHODS

Molecular Modeling Preparation

ASUS U45J operated by Windows 7 Home Premium, Intel® Core™ i5 CPU M450 @ 2.40GHz, 64-bit, harddisk 444 GB, and RAM memory 4.00 GB was used to run molecular docking processes. Softwares installed were (1) ChemBioDraw® Ultra 13.0 free trial supported by Cambridge Soft Corporation (downloaded from www.cambridgesoft.com), to draw the ligand structures in 2D and 3D which are bound to HIV-1 protease and Plasmepsin I (2) Hyperchem Professional 8.0 (10 days usage), with verification code: 0-34733, supported by Hypercube Incorporation (downloaded from www.hyper.com), for geometry optimization and analysis of molecules properties. (3) Swiss-pdbViewer version 4.1 (downloaded from http://spdbv.vital-it.ch), to repair the incomplete crystallized structures and to remove unnecessary receptor chain. (4) Ligand Explorer (available at http://www.pdb.org/pdb/explore), to visualizes the interactions of bound ligands in protein structures. (5) AutoDock 4.2 (downloaded from http://autodock.scrips.edu) for molecular docking process. (6) OpenBabel GUI (downloaded from http://openbabel.org), to convert the molecules format throughout the research. Three dimensions enzyme structures used in this research were HIV-1 protease (PDB code: 1HXW, resolution: 1.8 Å) and Plasmepsin I(PDB code: 3QS1, resolution: 3.1 Å). Three dimensions crystallized ligandwaspepstatin-A (PDB code: 1HDH, resolution: 1.7 Å). The ligand was downloaded from Protein Data Bank (www.pdb.org) database online. Two and three dimensions of ganoderiol-F were drawn using ChemBioDraw® Ultra 13.0 free trial.

Preparation of macromolecules

a. HIV-1 protease (PDB code: 1HXW) and Plasmepsin I(PDB code: 3QS1) were downloaded from Protein Data Bank (www.pdb.org).