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Computational Study of Triterpenoids of *Ganoderma lucidum* with Aspartic Protease Enzymes for Discovering HIV-1 and Plasmepsin Inhibitors

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Abstract

Rapid resistance development of HIV-1 and *Plasmodium falciparum* parasite requires discovery of more potent new drugs. Aspartic protease enzymes expressed by HIV-1 and *P. falciparum* could be used as important drug targets. The catalytic site is located at the bottom of a cleft in the enzyme surface and consists of triad Asp25, Thr26, Gly27. Important aspartic acids are Asp32 and Asp215. Aspartic proteases are inhibited by pepstatin-A, a naturally occurring peptide containing two statins, which replace the amino acids. The hydroxyl group of the statin binds tightly to the catalytically-active aspartic acid residues in the active site of protease, thereby mimicking the transition state of the peptide cleavage. Previous study proved that ganoderiol-F, a triterpenoid isolated from the stem of *Ganoderma sinense* showed higher affinity towards HIV-1 protease (binding energy= -11.40 kcal/mol and K_i= 4.68 nM) than to plasmepsin I (binding energy= -9.96 kcal/mol and K_i= 50.94 nM). In this paper, computational studies of *G. lucidum* triterpenoids with aspartic protease enzymes of HIV-1 and plasmepsin I, were performed using AutoDock 4.2. Nelfinavir and KNI-10006 were used as the standards for HIV-1 protease and plasmepsin I, respectively. The four triterpenoids are able to interact with both enzymes. Ganoderat acid-B showed the best affinity to HIV-1 protease (binding energy= -7.49 kcal/mol and Ki= 0.001 mM) which is better than nelfinavir. Furthermore, the best affinity to Plasmepsin I is showed by ganodermanondiol (binding energy= -7.14 kcal/mol and Ki= 0.005 mM which is better than KNI-10006. According to the values of binding energy and inhibition constant, triterpenoids of *G. lucidum* could be developed further as both anti-HIV and anti-malaria.

Keywords: Aspartic proteases; HIV-1; Malaria; *Ganoderma lucidum*; Plasmepsin I

1. Introduction

AIDS and malaria are health problems that occur in many parts of the world. According to WHO and UNAIDS, 35 million people are globally living with HIV at the end of 2013. That same year, 2.1 million people became newly infected, and 1.5 million died of AIDS-related causes. Furthermore, in 2012 malaria caused an estimated 627000 deaths (WHO, 2014).

Aspartic proteases play key roles in the biology of malaria parasites and human immunodeficiency virus type 1 (HIV-1). Parikh and colleagues tested the activity of seven HIV-1 protease inhibitors against cultured *P. falciparum*. All compounds inhibited the development of parasites at pharmacologically relevant concentrations. These findings suggest that use of HIV-1 protease inhibitors may offer clinically relevant antimalarial activity (Parikh et al, 2005). This inhibition may occur due to aspartic proteases, e.g. Plasmepsin I (PM I), present in the food vacuole of *P. falciparum.* PM I, II, and IV and histo-aspartic protease encode hemoglobin-degrading food vacuole proteases. Despite having a histidine in place of one of the catalytic aspartic acids conserved in other aspartic proteases, histo-aspartic protease is an active hydrolase. A bioinformatic analysis has demonstrated that *P. falciparum* PM II, which is similar to the secretory aspartic protease 2 of *Candida albicans* (the first nonretroviral microrganism proven to be susceptible to PMs is one of the eukaryotic proteases that most resemble the HIV-1 protease (Baneerje et al, 2002; Savarino et al, 2005).