ANALYSIS OF CYP3A4-HIV-1 PROTEASE DRUGS INTERACTIONS BY COMPUTATIONAL METHODS FOR HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV/AIDS

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HIV infected patients often take at least three anti-HIV drugs together in Highly Active Antiretroviral Therapy (HAART) and/or Ritonavir-Boosted Protease Inhibitor Therapy (PI/r) to suppress the viral replications. The potential drug-drug interactions affect efficacy of anti-HIV treatment and major source of such interaction is competition for the drug metabolizing enzyme, Cytochrome P450 (CYP). CYP3A4 isoform is the enzyme responsible for metabolism of currently available HIV-1 protease drugs. Hence administration of these drugs in HAART or PI/r leads to increased toxicity and reduced efficacy in HIV-treatment. We used computational molecular docking method to predict such interactions by which to compare experimentally measured metabolism of each HIV-1 protease drug. AutoDock 4.0 was used to carry out molecular docking of 10 HIV-protease drugs into CYP3A4 to explore sites of reaction and interaction energies (i.e., binding affinity) of the complexes. Arg105, Arg106, Ser119, Arg212, Ala370, Arg372, and Glu374 are identified as major drug binding residues, and it consistent with previous data of site-directed mutagenesis, crystallography structure, modeling, and docking studies. In addition, our docking results suggested that Phenylalanine clusters and heme are also participated in the binding to mediate drug oxidative metabolism. We have shown that HIV-1 protease drugs such as tipranavir, nelfinavir, lopinavir, and atazanavir differ in their binding modes on each other for metabolic clearance in CYP3A4, whereas ritonavir, amprenavir, indinavir, saquinavir, fosamprenavir, and darunavir share the same binding mode.