Virtual Screening of Indonesian Herbal Database as HIV-1 Protease Inhibitor

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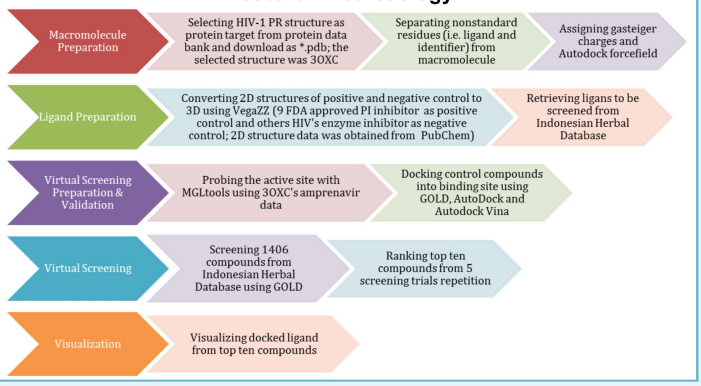
Abstract

HIV-1 (Human immunodeficiency virus type 1)'s infection is considered as one of most harmful disease known by human, the survivability rate of the host reduced significantly when it developed into AIDS. HIV's drug resistance is one of the main problems of its treatment and several drug designs have been done to find new leads compound as the cure. In this study, *in silico* virtual screening approach was used to find lead molecules from the library or database of natural compounds as HIV-1 protease inhibitor. Virtual screening against Indonesian Herbal Database using GOLD, Autodock Vina, and Autodock4 was performed on HIV-1 protease. From the virtual screening using GOLD as relative better approach, top ten compounds obtained were multifloroside, ternatin D; cyanidin 3,5-di-(6-malonylglucoside); cyanidin 3-(6"-malonylglucoside)-5-glucoside; cyanidin 7-(3-glucosyl-6-malonylglucoside)-4'-glucoside; isoscutellarein 4'methylether 8-(2",4"-disulfatoglucoronide); myristin; amaranthine; kaempferol 3-(6"-acetylglucosyl)-(1->3)galactoside; and multiroside.

Background

HIV (Human Immunodeficiency Virus) is a member of retrovirus family which infection could causing AIDS, an epidemic that weakening immune system, upon its infection. AIDS epidemic is on of the most destructive disease and estimated more than 30 million people worldwide have been infected. HIV has high resistance characteristic because of rapid production cycle and high mutation rate, around 5-10 mutation occurred for each cycle. Therefore, research and design of new HIV drug to be used in combination therapy was done in recent decade, especially drug that targeting vital viral enzymes such as reverse transcriptase, protease, and integrase. This research was done to explore new probability of lead compound from natural product in Indonesia, targeting protease as one of HIV vital enzymes. Indonesia are known for it's biodiversity, having more than 40,000 species, ranked second after Brazil, this provides potential discovery of new lead compounds, including HIV protease inhibitor. Virtual screening was employed in this research because the availability of Indonesian Herbal Database from previous research and as a complimentary method virtual screening could cut number of compounds that need to be tested and/or synthetized/isolated.

Research Methodology



Result

Name	GoldScore	SD	CV (%)
Ritonavir*	78.707	3.950	5.019
Lopinavir*	76.490	4.772	6.239
Tipranavir*	74.323	2.628	3.535
Darunavir*	70.095	3.175	4.530
Nelfinavir*	68.604	6.954	10.136
Amprenavir*	67.306	1.760	2.615
Atazanavir*	67.178	1.750	2.604
Saquinavir*	66.717	7.970	11.947
Delavirdine	59.966	0.871	1.453
Rilpivirin	58.864	1.430	2.429
Raltegravir	51.544	3.485	6.762
Etravirine	50.015	3.217	6.433
Nevirapine	37.889	2.415	6.374
Efavirenz	36.345	0.058	0.159

(a)

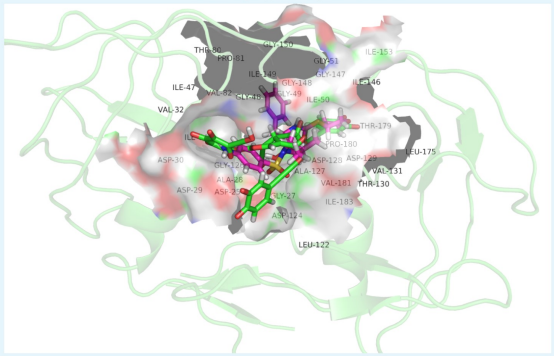
Name	ΔG (Kcal/mol)	SD	CV (%)
Saquinavir*	-11.50	0	0
Nelfinavir*	-10.20	0	0
Lopinavir*	-9.87	0.058	0.585
Tipranavir*	-9.83	0.058	0.587
Ritonavir*	-9.43	0.058	0.612
Darunavir*	-9.33	0.058	0.619
Atazanavir*	-9.03	0.115	1.278
Amprenavir*	-8.60	0.173	2.014
Delavirdine	-8.50	0.100	1.176
Rilpivirin	-8.40	0.100	1.190
Raltegravir	-8.40	0.100	1.190
Etravirine	-7.93	0.058	0.728
Efavirenz	-7.27	0.058	0.795
Nevirapine	-7.20	0	0

(b)

The tables shows the result of previrtual screening docking of 14 control compounds to HIV-1 protease inhibitor, 3OXC, using GOLD (a) and AutoDock Vina (b). The compound ranked based on the higher GoldScore for docking with GOLD or lower ΔG, both obtained from average result of five repetition. Asterisk sign (*) shows positive control.

Rank	Name	Average Gold-Score	SD	CV (%)
1	Multifloroside	91.383	5.3676	5.874
2	Ternatin D	90.345	6.4083	7.093
3	Cyanidin 3.5-di-(6-malonylglucoside)	89.862	5.4561	6.072
4	Cyanidin 3-(6"-malonylglucoside)-5-glucoside	83.795	4.3653	5.271
5	Cyanidin 7-(3-glucosyl-6-malonyl-glucoside)-4'-glucoside	82.811	5.7152	7.104
6	Isoscutellarein 4'-methyl ether 8-(2",4"-disulfatoglucoronide)	80.400	3.9137	4.868
7	Myristin	79.652	4.4704	5.612
8	Amaranthine	79.572	4.0748	5.121
9	Kaempferol 3-(6"-acetylglucosyl)-(1->3)-galactoside	78.225	1.9927	2.547
10	Multiroside	77.597	1.2623	1.627

The table above shows top ten compounds from virtual screening using GOLD with the same configuration as the controls docking



Visualization of docked ligand to HIV-1 PR 3OXC. The position of amprenavir (green) as positive control and multifloroside (magenta) were shown. Residues within 5 angstrom of the docked position were labelled in the picture.

Discussion

In this research, virtual screening of Indonesia Herbal Database with AutoDock, Vina and GOLD to HIV-1 protease. The first step is employ previrtual screening docking of control compounds. The controls 3D data were made by the same steps as the ligand database creation. The configuration and active site were obtained from the protein 3OXC data (HIV PR bound with amprenavir). From the docking, we get the rank of controls based on energy binding for AutoDock and Vina, or GoldScore for GOLD. Out of three software, Vina and GOLD give 1.0 accuracy, it means that all positive controls were ranked first before the negative controls. In other hand, AutoDock docking result only gives 0.5 accuracy which mean out of 8 positive controls, only 4 were ranked first and 4 negative controls shown as false positive. We choose GOLD over Vina because the position of the least ranked positive control and the best ranked negative control were interchangeable in repetition of docking trial (average –8.60 vs –8.50 kcal with SD 0.17 and 0.10 respectively).

The result of virtual screening of HIV-1 PR using GOLD gives compound rank based on GoldScore. Interestingly, nine compounds out of top ten (except myristin) were glycosides. This suggests the potency of glycoside or it aglycones (cyanidin, isoscuttellarein, delphinidin, betanidin) as lead compound in further medicinal chemistry research, especially multifloroside and multiroside that never published in recent research as HIV-1 PR inhibitor or HIV inhibitor in general.

Conclusion

From the docking of 14 control compound, AutoDock Vina and GOLD gives 1 score for accuracy while Autodock only gives 0.5. Top ten compounds from virtual screening of Indonesian Herbal Database using GOLD shows that glycosides appear to be potential HIV-1 PR inhibitor lead compound. We suggest further medicinal chemistry study to optimize the finding of our research, such as QSAR study of glycosides and its aglycones as future potential inhibitor of HIV-1 PR

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