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Molecular Docking Study of HIV-1 Antiretroviral Candidate via Reverse Transcriptase Inhibitor from Zingiber officinale var. Roscoe

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ABSTRACT
HIV-1 is a member of the Retrovirus and the virus causes AIDS in humans. AIDS affects the dynamics of the immune system leading to fatal opportunistic infections. Reverse transcriptase plays an important role as a functional enzyme in the viral replication process, the enzyme works to carry out the transcription process of ssRNA into cDNA and then initiates the viral integration process of the genome into the nucleus. Currently many use of HIV-1 NNRTIs, the nevirapine type, with a molecular mechanism that can bind to the active site of the HIV-1 reverse transcriptase enzyme to inhibit its activation. A new problem arises because the reverse transcriptase in HIV-1 undergoes a cross mutation and causes nevirapine resistance. Previous research using an in vitro approach showed the ability to inhibit the process of replication, attachment, and internalization of the virus shown by Zingiber officinale var. Roscoe, then another ability is that these herbal plants can trigger cell stimulation for interferon-β secretion. This study aims to screen the chemical compounds of Zingiber officinale var Roscoe for the discovery of new antiretrovirals through computational study. Zingiber officinale var. Roscoe is predicted to act as an antiretroviral agent through with a mechanism of HIV-1 reverse transcriptase activity inhibition at Pro95, Tyr181, Val179, Leu100, Tyr188, Val106, Leu234, Phe227, Tyr318, Asn103, Gly99 residues, β-sitosterol is predicted to act as a drug-like molecule, the antiretroviral potential of Zingiber officinale var. Roscoe must undergo further analysis to provide strong scientific evidence.

Keywords: Antiretroviral, Bioinformatics, HIV-1, Zingiber officinale

INTRODUCTION

HIV-1 is a member of the Retrovirus and the virus causes AIDS in humans. AIDS affects the dynamics of the immune system leading to fatal opportunistic infections[1]. AIDS is a worldwide public health problem in modern times, this disease first appeared in 1981 and was isolated in 1983[2]. The

† Footnotes relating to the title and/or authors should appear here.

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HIV-1 virion has a spherical shape with a diameter of 80-100 nm, an ssRNA genome, has glycoproteins like gp41 & gp120, and three types of enzymes that consists of reverse transcriptase, integrase, and protease[3]. Reverse transcriptase plays an important role as a functional enzyme in the viral replication process, the enzyme works to carry out the transcription process of ssRNA into cDNA and then initiates the viral integration process of the genome into the nucleus[4].

The role of reverse transcriptase in HIV-1 is crucial and according to previous studies it can be used as a target for antiretroviral drug design[5]. HIV-1 reverse transcriptase inhibitors have been identified by the FDA and are categorized into three NRTIs, NtRTIs, and NNRTIs[6]. Currently many use of HIV-1 NNRTIs, the nevirapine type, with a molecular mechanism that can bind to the active site of the HIV-1 reverse transcriptase enzyme to inhibit its activation[7]. A new problem arises because the reverse transcriptase in HIV-1 undergoes a cross mutation and causes nevirapine resistance. Nevirapine resistance is caused by mutations in the amino acid residue of the reverse transcriptase active site in Y181C and K103N, these cases must be treated immediately as well as the discovery of new antiretrovirals[8].

The use of ginger has become a tradition in various parts of the world, besides being used for cooking spices, ginger can be used as a mixture in herbal ingredients[9]. Previous research using an in vitro approach showed the ability to inhibit the process of replication, attachment, and internalization of the virus shown by *Zingiber officinale* var. Roscoe, then another ability is that these herbal plants can trigger cell stimulation for interferon-β secretion[10]. This study aims to screen the chemical compounds of *Zingiber officinale* var Roscoe for the discovery of new antiretrovirals through computational study.

METHODS

Sample retrieval

The bioactive compound *Zingiber officinale* var. Roscoe consists of 10-Gingerol, Cyclosativene, Zingiberene, β-sitosterol, and Hexahydrocurcumin obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). This study used reverse transcriptase of HIV-1 (GDP ID: 3LP1) obtained from the protein databank (https://www.rcsb.org/). The ligand conversion process from *sdf* format to *pdb* was carried out using PyRx 0.9.9 version software and PyMol 2.5 version is used to remove water molecules in proteins[10].

Docking Simulation

This simulation is to identify the ability of molecular interaction between ligand-protein and refers to the value of binding affinity. This study used a docking screening method to determine potential domains in proteins for ligand binding targets[11]. PyRx 0.9.9 version software was used in this study to simulate the docking of *Zingiber officinale* var. Roscoe compound with reverse transcriptase. The position of the docking grid in this study was set to cover the entire protein surface[12].

Molecular Interaction

Weak bonds play a role in ligands to produce an activity response to proteins. The ligand-protein interactions formed are weak bonds, weak bonds such as hydrogen, electrostatic, alkyl, van der Waals, and hydrophobic[13]. The Discovery Studio 2016 software version was used in this study to identify the weak bonds formed in molecular complexes.

3D Visualization

Molecular visualization of the ligand-protein complex was carried out using PyMol 2.3 version software through staining and structural selection methods. The 3D structure shown consists of cartoons, surfaces, and sticks, staining is done on the protein constituent chains[14].

Druglikeness and Bioactivity Prediction

Prediction of drug-like molecules on candidate ligands of antiviral agents from *Zingiber officinale* var. Roscoe was carried out in this study via the server http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp by following at least one of the five Lipinski rules. The parameters used in the Lipinski Rule of Five are molecular mass, LogP, hydrogen acceptors, donors, and molar refractivity. Prediction of bioactivity as anti-inflammatory was performed via PASSOnline (http://way2drug.com/PassOnline/)[15]

RESULT AND DISCUSSION

Binding affinity of *Zingiber officinale* var. Roscoe compounds

Molecular interaction simulation through 3D structure with bioinformatics approach is molecular docking[16]. This simulation aims to identify the chemical bonding activity of ligands in protein-specific domains[17]. This study used ligands consisting of Cyclosativene, Zingiberene, β-sitosterol, 10-Gingerol and Hexahydrocurcumin and reverse transcriptase as targets. The docking results showed that β-sitosterol had the most negative binding affinity then Nevirapine in the grid docking at center (Å) X: 9.7 Y: 16.0 Z: 18.2 and dimensions (Å) X: 25.0 Y: 25.0 Z: 25.0 (Table 3). 3D visualization of the two compounds was carried out through cartoon structures, surfaces, and sticks (Figure 1). Thus, β-sitosterol compounds from *Zingiber officinale* var. Roscoe are predicted to act as potential inhibitors of reverse transcriptase activity because they have a more negative binding affinity.

Table 1. Binding affinity from docking simulation

Compounds	CID	Molecular Weight (g/mol)	Target	Binding Affinity (kcal/mol)
Nevirapine (Control)	4463	266.3	Reverse Transcriptase	-8.8
Cyclosativene	519960	204.35	Reverse Transcriptase	-8.7
Zingiberene	92776	204.35	Reverse Transcriptase	-8.2
β-sitosterol	222284	414.7	Reverse Transcriptase	-9.9
Hexahydrocurcumin	5318039	374.4	Reverse Transcriptase	-8.1
10-Gingerol	168115	350.5	Reverse Transcriptase	-7.9

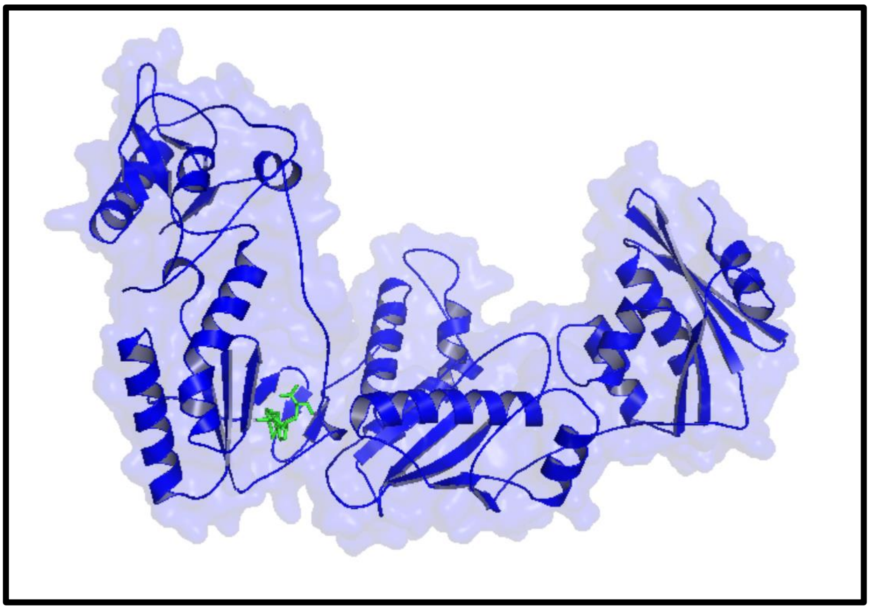

Figure 1. 3D structure of molecular docking β-sitosterol_Reverse Transcriptase through PyMol software visualization. The cartoons structure in blue is Reverse Transcriptase and β-sitosterol is a green stick.

Molecular interaction on HIV-1 reverse transcriptase domain

Chemical bond interactions in molecular complexes are identified to determine the type of bond and position. β-sitosterol have interaction position Pro95, Tyr181, Val179, Leu100, Tyr188, Val106, Leu234, Phe227, Tyr318, Asn103, & Gly99, this position allows them to act as potential domains to lead inhibitory activity at reverse transcriptase (Table 2). Weak bond interactions such as hydrogen and alkyl are also formed in all ligands, β-sitosterol has more chemical interactions than other compounds and this can strengthen the prediction that β-sitosterol can act as a good drug candidate. Weak bond interactions consisting of van der Waals and alkyl can play a role in triggering the response of biological activity on the target protein. The number of van der Waals interaction can be used as an indicator of the stability of a drug candidate molecule[18]. Thus, β-sitosterol is predicted to become a drug molecule because it can affect the activity of reverse transcriptase protein through weak bonds and has the highest number of hydrogen bonds. the visual results of molecular interactions in this study are displayed with a 2D structure (Figure 2).

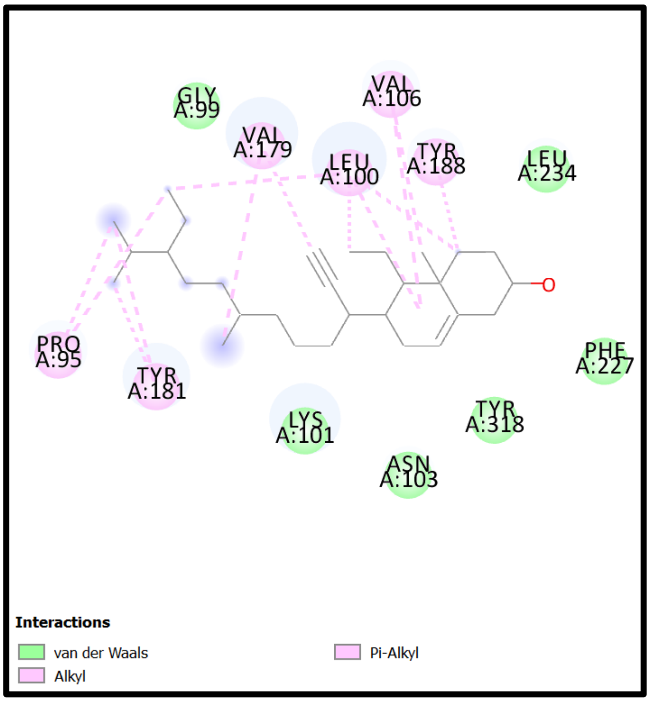

Figure 2. Chemical bond and interaction position on the β-sitosterol_Reverse Transcriptase complex.

The potency of β-sitosterol as drug-like molecule

Prediction of β-sitosterol bioactivity was carried out through PASS Online to validate its potential as an anti-inflammatory in general. The prediction process is done by entering SMILE Canonical on the web server. Prediction results are categorized as proven to be potential in computational and wet labs if they have an activation probability value[19]. Prediction with probability (Pa) > 0.7 is accuracy > 80%, prediction result shows β-sitosterol has Pa>0.7 as antiviral through inhibition of reverse transcriptase activity. Lipinski's rule can be used to identify drug-like molecules in candidate compounds. This method can predict the properties of drug candidate compounds with parameters of molecular weight, LOGP, hydrogen bond acceptor, donor, and molar refractivity[20]. Lipinski's analysis results show that β-sitosterol compounds with more negative binding affinity values are predicted to have potential as drugs because they meet Lipinski's five rules, so β-sitosterol from *Zingiber officinale* var. Roscoe can act as a drug like molecule for anti-inflammatory agents.

CONCLUSION

Zingiber officinale var. Roscoe is predicted to act as an antiretroviral agent through with a mechanism of HIV-1 reverse transcriptase activity inhibition at Pro95, Tyr181, Val179, Leu100, Tyr188, Val106, Leu234, Phe227, Tyr318, Asn103, Gly99 residues, β-sitosterol is predicted to act as a drug-like molecule, the antiretroviral potential of *Zingiber officinale* var. Roscoe must undergo further analysis to provide strong scientific evidence.

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