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Screening of Reverse Transcriptase Inhibitor from *Moringa oleifera* Bioactive Compound through In Silico Study Againts HIV-1

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ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) from the retrovirus family can trigger opportunistic diseases of the immune system or AIDS. In these conditions the immune system fails due to infection with bacteria, protozoa, fungi, and other viruses. HIV-1 has several enzymes consisting of reverse transcriptase (RT), integrase (INT), & protease (PR), all of which play an important role in the replication process. Reverse transcriptase plays a role in the formation of HIV-1 cDNA in several stages consisting of lysyl tRNA having a binding site, RT then adds a nucleotide to synthesize cDNA

† Footnotes relating to the title and/or authors should appear here.
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to the non-coding or U5 and R (repeat) region of the viral RNA. RT activity has a crucial role in viral replication and is very likely to be a target in drug design. This study aims to reveal the molecular mechanism of compounds from *Moringa oleifera* to be antiviral for HIV-1 through a bioinformatics approach. Kaempferitrin and β-sitosterol from *Moringa oleifera* are predicted to be HIV-1 antiviral agents. Both compounds can produce more negative binding affinity and weak bond interactions. This indicates the stability of the binding interaction that triggers the inhibitory activity.

Keywords: Bioactive, HIV-1, In Silico, *Moringa oleifera*, Reverse Transcriptase

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) from the retrovirus family can trigger opportunistic diseases of the immune system or AIDS. In these conditions the immune system fails due to infection with bacteria, protozoa, fungi, and other viruses. The identified types of HIV consist of HIV-1 & HIV-2, HIV-1 has a higher infectious nature than HIV-2 because of the genetic drift mechanism[1,2]. Several HIV-1 strains such as A, B, C, D, E, F, G, H, & J were obtained from Africa, Asia, Europe, Australia, and America. HIV-1 has structural genes consisting of env, gag, and pol then essential elements & regulators such as rev, tat, nef, vpr, vpu, and vif that play a role in helping the virus to evade the immune system's response and pathogenesis in host cells[2,4]. Endemic cases of HIV-1 are often found and HIV-2 is very rare, therefore the development of antiretroviral drugs is currently focused on treating HIV-1 infection[5]. Research on HIV-1 vaccines is still in the research phase and some patients are only taking antiretrovirals to survive.

HIV-1 has several enzymes consisting of reverse transcriptase (RT), integrase (INT), & protease (PR), all of which play an important role in the replication process[6,7]. Reverse transcriptase plays a role in the formation of HIV-1 cDNA in several stages consisting of lysyl tRNA having a binding site, RT then adds a nucleotide to synthesize cDNA to the non-coding or U5 and R (repeat) region of the viral RNA[8]. The RT region known as RNAse H degrades U5 and R at the 5' end, then tRNA primers synthesize DNA strands[9,10]. HIV-1 cDNA is carried by integrase to integrate with the host cell genome. RT activity has a crucial role in viral replication and is very likely to be a target in drug design.

Moringa oleifera is a medicinal plant for healthcare that has survived for a long time, WHO has recommended several natural ingredients and medicinal plants to be used as objects of health research[11,12]. Several countries in Africa and Asia use *Moringa oleifera* for HIV antivirals because there are several specific chemical compounds for drug candidates in these plants, the bioactive compounds from *Moringa oleifera* consist of vanillin, kaempferitrin, β-sitosterone, β-sitosterol, & kaempferol, but the molecular mechanism is not yet known[13]. This study aims to reveal the molecular mechanism of compounds from *Moringa oleifera* to be antiviral for HIV-1 through a bioinformatics approach.

METHOD

Ligand-protein preparation

This study used chemical compounds from *Moringa oleifera* consisting of vanillin, kaempferitrin, beta-sitosterone, beta-sitosterol, & kaempferol. Information on the 3D structure, Canonical SMILE, and CID of the target compound was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/)[14]. The HIV-1 reverse transcriptase (RT) protein was used as the target drug design in this study, 3D structure information was obtained from the RCSB PDB database (https://www.rcsb.org/)[15,16].

Structure minimization and water molecule cleaning

The energy minimization process on ligands with file structure data format (sdf) is carried out through OpenBabel v2.3.1 software, it aims to convert sdf files to pdb and increase the flexibility of query ligands[17]. Molecular cleaning is carried out through PyMol v2.5 software with the aim of removing water molecules, ions, and contaminants such as ligands for the effectiveness of the formation of binding energy in the docking simulation[18].

Molecular docking study

The docking in this study aims to identify the binding energy or binding affinity which refers to the inhibitory ability of the ligand of *Moringa oleifera* when interacting with the HIV-1 RT domain[19]. This study uses a blind docking method for screening potential compounds from natural materials and simulations are carried out using PyRx v0.9.9 software[20]. 3D visualization of docking

simulation results is displayed through PyMol v2.5 software with structural selection and coloring methods based on publication standards[21,22].

Chemical interaction

Molecular interactions in the compound complex from *Moringa oleifera* and HIV-1 RT with the strongest binding energy will be shown to determine the type of chemical bond and the position of the interaction[23,24]. This research uses LigPlus v2.2.4 software to identify molecular interactions in the docked molecular complex[25].

RESULT AND DISCUSSION

Revealing of inhibitor molecular mechanism from *Moringa oleifera* compound

Moringa oleifera in people's lives around the world is used for traditional medicine such as anti-inflammatory, antiviral, preventing free radicals, and others[26,27,28]. *Moringa oleifera* was identified to have chemical compounds consisting of Vanillin, Karmpferitrin, β-sitosterone, β-sitosterol, and Kaempferol (Table 1). This study used a chemical compound from *Moringa oleifera* to identify candidate antiviral drugs against HIV-1 by inhibiting the activity of viral reverse transcriptase (RT) by molecular docking simulation with autogrid positions are Center (Å) X:25.084 Y: -22.972 Z: 17.618, Dimensions (Å) X: 106.090 Y: 112.360 Z: 103.725.

Table 1. *Moringa oleifera* chemical compound from PubChem

Compound	CID	Formula	SMILE Canonical
Vanillin	1183	C8H8O3	COC1=C(C=CC(=C1)C=O)O
Kaempferitrin	5486199	C27H30O14	CC1C(C(C(C(O1)OC2=CC(=C3C(=C2)OC(=C(C3=O)OC4C(C(C(C(O4)C)O)O)O)C5=CC=C(C=C5)O)O)O)O)O
β-sitosterone	9801811	C29H48O	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(=O)C4)C)C)C(C)C
β-sitosterol	222284	C29H50O	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
Kaempferol	5280863	C15H10O6	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O

Kaempferitrin and β-sitosterol has a binding affinity of -9.7 kcal/mol more negative than other compounds when it binds to E6 protein (Table 2), Kaempferitrin and β-sitosterol is predicted to inhibit the activity of RT in HIV-1 because it has more negative binding than other compounds. The molecular docking simulation aims to determine the activity of the ligand binding on the protein domain by referring to the binding affinity value[29,30,31,32]. The binding affinity value indicates the inhibitory ability of a ligand on the activity of the target protein. Visualization of docking results is displayed through cartoons structure and sticks with selected coloring (Figure 1).

Table 2. The comparison of compound binding affinity

Compound	Molecular Weight (g/mol)	RCSB Target ID	Minimize Energy (kcal/mol)	Binding Affinity (kcal/mol)
Vanillin	152.15	1REV	+79.78	-5.7
Kaempferitrin	578.5	1REV	+844.04	-9.7
β-sitosterone	412.7	1REV	+579.82	-8.0
β-sitosterol	414.7	1REV	+593.22	-9.7
Kaempferol	286.24	1REV	+357.41	-8.0

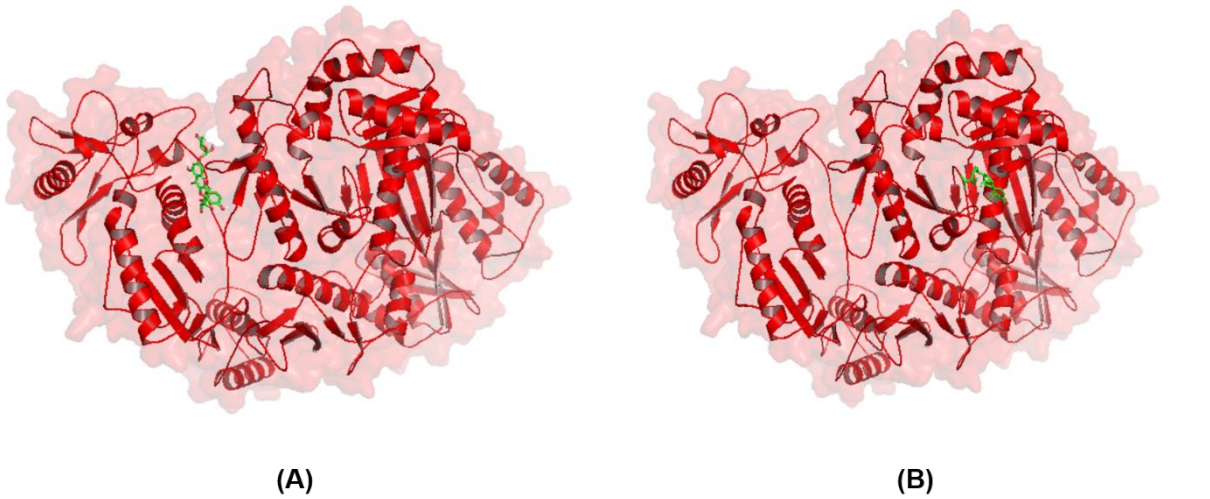

Figure 1. 3D Visualization from the docking results. (A) RT_Kaempferitrin (B) RT_β-sitosterol

Molecular interaction of *Moringa oleifera* compounds at HIV-1 RT

Weak binding interactions of ligand bonds can initiate specific biological activities such as protein inhibitory responses, these interactions are played by hydrogen bonds, hydrophobicity, van der Waals, and pi[33,34,35]. Unfavorable interactions are unstable bonds formed in the molecular complex (ligand-protein) a stable ligand must have at least two unfavorable interactions[36,37,38]. Hydrogen bond interactions have an important role in triggering a specific response to the target protein and are used as an indicator of the effectiveness of a drug's performance, the more types of hydrogen bonding interactions on the target protein, the stronger the effect of the drug[39,40,41,42,43]. Identification of molecular interactions and binding positions on the docked protein-ligand complex (Figure 2) showed that the bonding of kaempferitrin and β-sitosterol compounds in HIV-1 RT resulted in non-covalent bond interactions consisting of Van der Waals, pi, hydrogen, and unfavorable interactions not detected (Table 3). All the weak binding interactions produced by kaempferitrin and β-sitosterol can contribute to the formation of stable ligand-protein complexes and initiate an inhibitory activity response in HIV-1 RT.

Table 3. Molecular interaction on HIV-1 RT pocket binding domain

Compounds	Molecular Interaction
Kaempferitrin	**van der Waals:** Ile142, Glu169, Gly141, Thr165, Pro140, Gln161, Trp88, Glu53 **Hydrogen:** Ser162, Pro52, Lys166, Ile50 **Alkyl:** Lys49, Arg143, Pro52, Lys166
β-sitosterol	**van der Waals:** Lys64, Thr409, Asp186, Gly231, Arg72, Asp110, Gln407, Ala408, Gln373, Lys374, Glu70, Met357, Tyr354 **Alkyl:** Lys65, Val108, Tyr232, Lys66

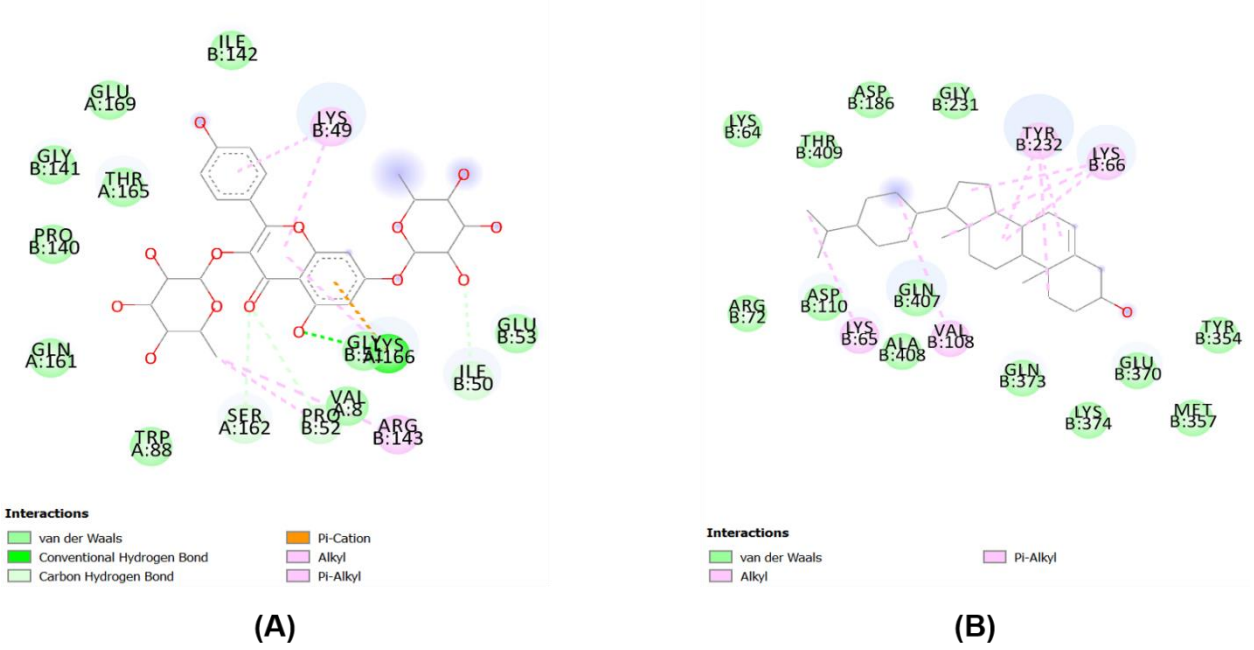

Figure 2. Positions and types of chemical bond interactions. (A) RT_Kaempferitrin (B) RT_β-sitosterol.

CONCLUSION

Kaempferitrin and β-sitosterol from *Moringa oleifera* are predicted to be HIV-1 antiviral agents. Both compounds can produce more negative binding affinity and weak bond interactions. This indicates the stability of the binding interaction that triggers the inhibitory activity. We recommend the RT-HIV-1 binding domain and two potential compounds from Moringa oleifera for further research as a target for HIV-1 drug design and the results of this study are yet to be verified through wet lab testing.

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