Virtual Screening of Natural Compounds for HIV 1 Reverse Transcriptase Inhibitor as Potential Drug’s Candidate

Rizka Elan Fadilah¹, Ahmad Fauzi¹, Arindra Trisna Widiansyah¹, Erna Wijayanti¹

¹Postgraduate of Educational Biology, State University of Malang, Malang, Indonesia

Corresponding author: rizkaelan@gmail.com

Abstract

AIDS is one of major health problem in the world, commonly caused by Human Immunodeficiency virus 1 (HIV-1). Reverse transcriptase is the target of the most widely used treatments for AIDS. One of the problem from treatments is drug resistant. This research aim to discover a new potential drug’s candidate from natural compound to inhibit activity of HIV 1 Reverse Transcriptase. Top ten compounds from Specs Natural Products database as the result of virtual screening by MTIOpenScreen are docked and analyzed using Pyrx 0.8 software. Based on analysis and visualization of 2D and 3D structure using LigPlus and PyMol softwares, known that ZINC57657 (-8 Kcal/mol) and common drug against HIV 1 Reverse Transcriptase, Lamivudine (-5.6 Kcal/mol) equally capable to bind in several amino acids (Thr 131 and Gln 23) located in the active site of HIV 1 Reverse Transcriptase.

Keywords: Drug’s candidate; HIV 1 reverse transcriptase; natural compounds; virtual screening

1. Introduction

Human Immunodeficiency Virus type 1 (HIV1) pandemic is a complex mix of diverse epidemics within and between countries and regions of the world [1]. In 2012, WHO reported there were 2.3 million new infections, 1.6 million AIDS-related deaths, and 35.3 million people living with HIV [2]. Moreover, today, there is no region of the world untouched by this pandemic [3]. Therefore, undoubtedly, HIV-1 is one of virus that causing public health crisis at the present time [1].

Related to its pandemic, AIDS remains a public health challenge until today [2]. But, the problem does not stop here. Another problem arises related to the price of some AIDS drugs [4-6]. The high price of AIDS drugs may be related to the costs incurred in searching and developing these drugs [7]. That problem becomes more serious given that Africa is the region of the world most affected by the HIV/AIDS disease, whereas many countries in this area are quite poor [8,9]. Moreover, a significant number of AIDS infection have become resistant to current AIDS’ drugs [10,11]. There must be an alternative in solving this problems.

Medical plants are commonly used as a alternative medicine [12]. That is because the plants are the source of variety bioactive compounds that have potential as the alternative medicines of various diseases [13,14]. From this perspective, it is possible that plants also contain a variety of natural bioactive compounds that can be used as an alternative treatment for AIDS.

One of natural compounds’ criteria that can be filed as a new drug candidate for AIDS treatment is a compound that can inhibit HIV mechanisms in the taking over the T cells. Takeover mechanisms of T cells by HIV would not have happened if viral RNA can not reverse transcribed into DNA [15]. Therefore, the aim of this study is to find the natural compound from plants that can be used as a potential drug candidate to treat AIDS through inhibiting the activity of HIV 1 Reverse Transcriptase. In silico approach was used in this study.

2. Material and Methods

2.1. Preparation of ligand and receptor 3D Structure

The 3D structure of ligand, Natural compounds were collected from Specs Natural Products database, which downloaded through ZINC database [16], drug control (Lamivudine) was collected from Pubchem and Receptor (HIV 1 Reverse Transcriptase) was obtained from UniProt. To determine the active sites of the protein, we used data from previous study [17].

2.2. Virtual screening and docking

Virtual screening of natural compounds using MtiOpenScreen webserver [18]. Top ten compounds (based on the most negative binding affinity score) and a drug control were docked with HIV 1 Reverse Transcriptase protein. This drug is a commercial synthetic drug that could inhibit HIV 1 reverse transcriptase activity [19]. This process was done using Pyrx 0.8 software [20]. The most negative binding affinity score of natural compound chosen as candidate drug will be analyzed furthermore.

2.3. Visualization of protein-ligand interaction

Docking result were visualized using PyMOL software to show the 3D structure and location of each ligand binding to the protein [21]. In addition, the interaction of ligand and protein was also visualized in 2D using Ligplus software to determine the interaction of intramolecular [22].
3. Results and Discussion

3.1. Preparation of ligand and receptor 3D Structure

1496 Natural compounds were collected from Specs Natural Products database, Lamivudine with PubChem CID 60825 and HIV 1 Reverse Transcriptase with PDB ID: 3DRP has been chosen as a 3D structure [23].

3.2. Virtual Screening and docking

Specs Natural Products database has 1496 natural compounds. The virtual screening results using MTiOpenScreen is shown in Table 1. Table 1 shows top ten results of structure-based virtual screening with HIV 1 Reverse Transcriptase as a protein receptor. Based on this result, the top 10 natural compounds were chosen as the best natural compounds that used for further analysis.

Table 1. Virtual Screening Result Using MTiOpenScreen

<table>
<thead>
<tr>
<th>Compound’s ZINC ID</th>
<th>Binding affinity (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZINC06316369</td>
<td>-12.3</td>
</tr>
<tr>
<td>ZINC04762374</td>
<td>-11.5</td>
</tr>
<tr>
<td>ZINC13334942</td>
<td>-11.3</td>
</tr>
<tr>
<td>ZINC33662878</td>
<td>-11.1</td>
</tr>
<tr>
<td>ZINC03996161</td>
<td>-11.0</td>
</tr>
<tr>
<td>ZINC01658901</td>
<td>-10.9</td>
</tr>
<tr>
<td>ZINC05175910</td>
<td>-10.9</td>
</tr>
<tr>
<td>ZINC00338216</td>
<td>-10.9</td>
</tr>
<tr>
<td>ZINC00057657</td>
<td>-10.9</td>
</tr>
<tr>
<td>ZINC01531449</td>
<td>-10.9</td>
</tr>
</tbody>
</table>

The results of molecular docking between the best natural compound-HIV 1 Reverse Transcriptase and drug control (Lamivudine)-HIV 1 Reverse Transcriptase is shown in Table 2. Based on the binding affinity score, ZINC00057657 was chosen as the best of drug candidate for further analysis.

Table 2. Molecular Docking Result Using PyRx 0.8

<table>
<thead>
<tr>
<th>Name of compound</th>
<th>Binding affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZINC00057657</td>
<td>-8</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>-5.6</td>
</tr>
</tbody>
</table>

3.3. Visualization of Protein-Ligand Interaction

According to the result of 3D visualisation, it is known that ZINC00057657 and drug control have relatively similar binding location on HIV 1 Reverse Transcriptase (Figure 1a). Moreover, 2D visualisation using Ligplus software also shown the similar result. Based on the result known that the intermolecular interaction between HIV 1 Reverse Transcriptase-ZINC00057657 and HIV 1 Reverse Transcriptase-Lamivudine are relatively similar because both of them involve two essential amino acids, Gln 23 and Thr 131. This similarity is shown in Figure 1b and Table 3.

Table 3. The list of Amino Acid Residues using Ligplus

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Lamivudine</th>
<th>ZINC00057657</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asn 137</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Gly 141</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Ser 134</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Arg 143</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Asn 57</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Thr 131</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Gln 23</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Thr 139</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Pro 133</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>
In this study, virtual screening was used as a method to search for a new AIDS drug candidate from natural compound. In principle, this method will search for natural compounds from plants that can be used as a potential inhibitor of HIV 1 Reverse Transcriptase based on drug control that have been chosen. Drug control that has been selected in this study was lamivudine. Lamivudine is a nucleoside analogue reverse transcriptase inhibitor [24]. The mechanism of action this inhibitor is act as a chain terminator of DNA synthesis. Elongation is blocked because the chain terminators lack the 3'-OH functional group essential for incorporation of additional nucleotides [25].

In this study, ZINC00057657 came out as the best potential candidate. ZINC00057657 interact in the same area as the area where lamivudine interact with the HIV 1 Reverse Transcriptase. In this case, ZINC00057657 and lamivudine act as a ligand. Related with that, high-affinity ligand binding results from greater intermolecular force between the ligand and its receptor while low-affinity ligand binding involves less intermolecular force between the ligand and its receptor [26]. The higher the affinity of ligand binding, the lower concentration of a ligand is adequate to occupy maximally a ligand binding site [27]. Related to that, the result of docking showed ZINC00057657 have higher binding affinity (-8 kcal/mol) than lamivudine (-5.6 kcal/mol).

ZINC00057657 is a compound that has a popular name as 7,8-Dihydroxyflavone (7,8-DHF) [16]. This compound is a naturally occurring flavone found in Godmania aesculifolia, Tridax procumbens, and primula tree leaves [28]. G. aesculifolia is a small tree with 15-20 ft high [29]. This plant habitats distributed in the central and south America [30]. T. procumbens is a perennial herb that has a creeping stem which can reach from to 8-30 inches (20-75 cm) long [31]. The plant is native to tropical America, but is widely naturalized in tropical and subtropical areas around the world [31]. The last, primula is a hardy, herbaceous and low-growing perennial that is native to Europe, but many other species are common in Great Britain and Asia in north temperate zones [32]. From this study, 7,8-DHF can act as drug that inhibit HIV 1 Reverse Transcriptase. So, the compound is a recommended compound as a potential drug candidate for AIDS.

4. Conclusion

Based on this study, 7,8-Dihydroxyflavone, natural compound that could be extracted from Godmania aesculifolia, Tridax procumbens, and primula tree leaves, has been predicted as a potential drug candidate for the treatment of AIDS due to its capability to inhibit HIV 1 Reverse Transcriptase activity.

References


Bean, P. New Drug Target for HIV. *Clinical Infection Disease* 2005; 41: S96-S100.


