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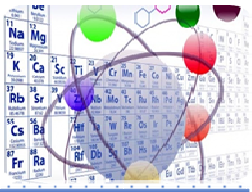

Potential Analysis of Quercetin and Its Derivatives as Inhibitors of Hendra Virus (HeV)

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ABSTRACT

This study aims to determine the inhibitory potential of quercetin and its derivatives on the activity of Hendra virus (HeV) 6BK6 protein with its comparator N-Acetyl-D-[1-13C] Glucosamine. This research was carried out using the molecular docking method in order to obtain information related to binding affinity values, inhibition constants, and amino acid residues in the ligand-receptor hydrogen bonds. It was found that the compound quercetin 3-O-xyloside had the lowest binding affinity among the other compounds, namely -6.92 kcal/mol with an inhibition constant of 8.44 µM. In addition, there are four types of amino acid residues in the ligand-receptor hydrogen bonds including ASP304 (1,90 Å), SER301 (2,47 Å), ARG191 (3,18 Å), and MET188 (4.34 Å). In this case it can be concluded that the compound quercetin 3-O-xyloside has been shown to have the potential to inhibit the activity of the HeV 6BK6 protein.

Keywords: Hendra virus, 6BK6 protein, quercetin.

1. INTRODUCTION

Hendra virus (HeV) cases were first recognized in 1994 in Brisbane, Queensland, Australia where as many as 20 horses were infected with 14 of them dying.[1] With the appearance of the first case of Hendra virus (HeV) it is known to have infected humans which occurred in July 2008, thus resulting in the death of one veterinarian.[2] Under these conditions, horses act as breeding hosts for Hendra Virus as they are the only mammal species known to have been infected directly from bats.[3]

Hendra virus is a single strain RNA virus belonging to the Paramyxiviridae family of the Henipavirus genus. The virus originates from the urine, saliva or mucus of infected fruit-eating Pteropodidae bats. This liquid can contaminate fruit on trees that are to be consumed by mammals such as horses and then infect

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humans. HeV is a pathogen that causes respiratory problems, neurological diseases, urinary incontinence and death in horses when infected with the virus.[4]

HeV infection in humans is commonly encountered with symptoms of headache, nausea, fatigue, high fever, sore throat and dry cough. In addition, severe infections can cause disturbances in the respiratory system, encephalitis, nervous disorders, and lead to death.[5,6,7] The percentage of deaths due to infection with HeV reaches 50-100% in humans, making HeV called the deadliest virus of all time.[8] Judging from the risk of transmission to humans, there is still no vaccine or antiviral drug that is accepted for human use.[9]

Based on these problems, it is known that the compound quercetin is classified as a flavonoid compound that has bioactivity as an antiviral.[10] Therefore, it is necessary to carry out preliminary in silico tests to determine the bioactivity of quercetin compounds and their derivatives against Hendra virus inhibition. Thus, quercetin and its derivatives can be used as an alternative drug solution that can be used in preventing Hendra virus (HeV) infection and inhibiting the spread of Hendra virus in human cells.

2. EXPERIMENTAL

2.1. Chemicals, Equipment, and Instrumentation

The materials used in this study were the structure of the Hendra 6BK6 virus protein as a target molecule downloaded from the RCSB Protein Data Bank as well as the compound quercetin and its five derivatives including Quercetin 3-O-glucoside, Quercetin 3-O-diglucoside, Quercetin 3,4'-diglucoside, Quercetin 3-O-rhamnoside, Quercetin 3-O-xyloside as inhibitory ligands to be tethered to 6BK6 target molecules downloaded from PubChem. In addition, a comparison ligand was used from the compound N-Acetyl-D-[1-13C] Glucosamine with the molecular formula $C_8H_{15}NO_6$ which had previously been used as a HeV inhibitory ligand to validate the value of the binding affinity of the compound quercetin and its derivatives. Also, this research used Ubuntu 20.04.1 and Windows 11 software with computational materials in the form of RCSB Protein Data Bank, PubChem, Autodock 1.5.6, and BIOVIA Discovery Studio 2021 client, while for hardware it uses an 11th Gen Intel® Core™ i5- 1135G7, 8GB RAM.

2.2. Research Procedure

HeV protein and ligan preparation

This preparation aims to separate the residue and water from the target compound so that it does not affect the computational results. The downloaded file is opened using Biovia Discovery Studio 2021, removing chain B (residual compound) and Hetatm (water), so that only chain A and protein groups remain. The file is saved in pdb format. As for the quercetin ligands and their derivatives along with the comparison ligands, it's downloaded in sdf format via PubChem. The downloaded file is opened by show graphic menu using Biovia Discovery Studio 2021. After that, the file is saved in pdb (protein data bank) format.

Docking HeV protein with the ligands

In this process using pdbqt, gpf, and dpf format files from Autodock 1.5.6 which are then computed by Ubuntu 20.04.1 terminal to obtain complex.pdb files and files in dlg format. Those formats contain information on binding affinity, inhibition constants, and amino acid residues in hydrogen bonds.

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Conclusions can be drawn from the acquisition of binding affinity (ΔG), inhibition constant (KI), and visualization of complex shapes that display the bonds that occur in these complex compounds.

3. RESULTS AND DISCUSSION

The process of analyzing the inhibitory activity of quercetin and its derivatives was carried out using the molecular docking method to obtain information on binding affinity values and inhibition constants. The parameters used in the calculations of this study are the binding affinity value (ΔG), the inhibition constant (Ki), and the interaction between the residual amino acids and the ligands that have hydrogen bonds. The type of interaction between the ligand and the receptor which has a hydrogen bond is used as one of the parameters of this study because it has the strongest attraction force among the other interactions. The results of binding affinity, inhibition constants, and residual amino acids in the hydrogen bonding of quercetin compounds and their derivatives on the inhibition of Hendra virus 6BK6 protein activity are shown in the following table 1.

Table 1. The result in ligand-protein 6BK6 docking

Compounds	Binding affinity (kcal/mol)	Inhibition constant (μM)	Amino acid residual in hydrogen bond
Quercetin	-6.88	9.05	MET188, SER301
Quercetin 3-O-glucoside	-4.47	525.83	ILE189, ASP304, SER301, THR192
Quercetin 3-O-diglucoside	-3.53	2.59×10^3	ILE150, ILE189, ASP304, LYS155
Quercetin 3,4'-diglucoside	-6.06	35.89	GLU195, SER301, ILE189, LYS155
Quercetin 3-O-rhamnoside	-6.33	22.81	ASP304, ARG191
Quercetin 3-O-xyloside	-6.92	8.44	ASP304, SER301, MET188, ARG191

It is known that the compound ID 5878729 quercetin 3-O-xyloside has the lowest binding affinity among the other compounds, namely -6.92 kcal/mol with an inhibition constant of 8.44 micro Molar. Binding affinity is the strength of the binding interaction between a single biological macromolecule (protein or DNA) and its ligand or binding partner (inhibitor or drug). Meanwhile, the inhibition constant is obtained through the formula Ki = exp (ΔG/RT), where the Ki value is directly proportional to the binding affinity. The more negative the binding affinity value means the stronger the bonding interaction between the receptor and the ligand, so that the better the inhibition of the ligand against the target macromolecule.[11]

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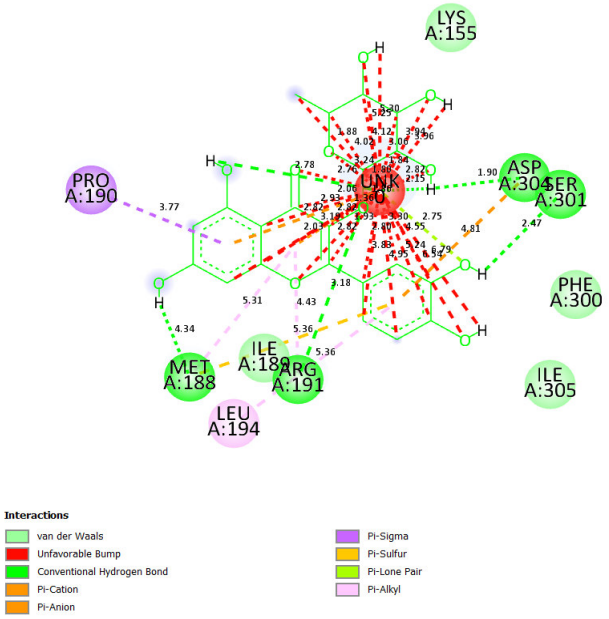

Figure 1. Quercetin 3-O-xyloside with HeV 6BK6 protein interaction

Based on the calculation and visualization results using the BIOVIA Discovery Studio 2021, it is possible to identify the residual amino acids in the ligand-receptor hydrogen bonds and their distances. There are four types of amino acid residues in the ligand-receptor hydrogen bonds shown in Figure 1, namely ASP304 (1.90 Å), SER301 (2.47 Å), ARG191 (3.18 Å), and MET188 (4.34 Å). The more hydrogen bonds formed with amino acid residues, the stronger the ligand-receptor bond, and the lower the energy, thus making the ligand-receptor complex more stable.[12]

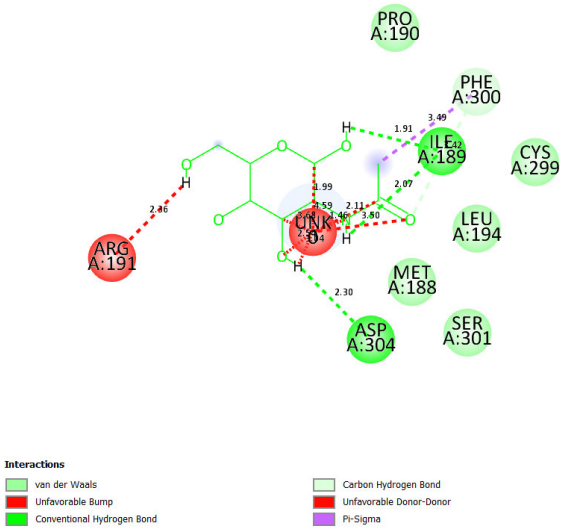

Figure 2. N-Acetyl-D-[1-13C] Glucosamine with HeV 6BK6 protein

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Furthermore, a comparison was made with the reference ligand compound N-Acetyl-D-[1-13C] Glucosamine with the molecular formula $C_8H_{15}NO_6$ which had previously been used as a HeV inhibitory ligand to validate that quercetin 3-O-xyloside is a potential compound in HeV inhibition. Based on the calculations and visualizations carried out in this study, the binding affinity and inhibition constants of the comparator compounds were obtained at -5.04 kcal/mol and 203.68 micro Molar respectively and there were two hydrogen bond interactions formed with amino acid residues, namely ILE189 (1.91 and 2.07 Å) and ASP304 (2.30 Å). This shows that the binding affinity (ΔG) of quercetin 3-O-xyloside as an inhibitory ligand is lower than that of the reference ligand. In addition, the number of hydrogen bond interactions with amino acid residues in the quercetin 3-O-xyloside complex with HeV 6BK6 protein is greater than that of the comparison compound. In order this case the quercetin derivative, namely quercetin 3-O-xyloside, is effective and potential in inhibiting the activity of the HeV 6BK6 protein.

4. CONCLUSION

The quercetin 3-O-xyloside compound has the lowest binding affinity among the other compounds, namely -6.92 kcal/mol with an inhibition constant of 8.44 micro Molar. In addition, there are four types of amino acid residues in the ligand-receptor hydrogen bonds including ASP304 (1.90 Å), SER301 (2.47 Å), ARG191 (3.18 Å), and MET188 (4.34 Å). So that quercetin 3-O-xyloside is effective and potential in inhibiting the activity of HeV 6BK6 protein.

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