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Quercetin from Miana Leaf (Coleus Scutellarioides) Extract as Inhibitor of Dengue Virus NS5 Protein

Alfani Maring Datu, Syahrijuita Kadir and Sulfahri Sulfahri

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Alfani Maring Datu[1], Syahrijuita Kadir[2], Sulfahri[3]

[1] Master Program of Biomedical Science, Graduate School Hasanuddin University, Makassar, South Sulawesi, Indonesia
[2] Departement of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[3] Departement of Biology, Faculty of Mathematic and Natural Science Hasanuddin University, Makassar, South Sulawesi, Indonesia

Email: alfanimaringdatu@gmail.com

Abstract

This study aimed to examine the Quercetin compound from Miana (*Coleus Scutellarioides*) leaf extract as an inhibitor of Non Structural Protein (NS5) Dengue virus. This study was conducted by molecular docking by using Pyrx 0.8 application. The structure of target protein (NS5) was obtained from Protein Data Bank site (https://www.rcsb.org), and then the water molecules on target protein were removed by using the Pymol software application. After the docking process completed, then interaction of the ligand and the target protein visualized in the Pymol software. The value of binding affinity from molecular docking between Quercetin and NS5 Protein was -7.6 kcal/mol, and between control ligand (Ribavirin) and NS5 Protein is -5.8 kcal/mol. Results analysis of Quercetin compounds using Swissadme and AdmetSAR showed that Quercetin did not have a toxic effect and did not carcinogenic. Quercetin compounds also meet all the parameters in Lipinski's rule.

KEYWORDS : *Quercetin, Ribavirin, NS5 Protein, Dengue, Docking.*

Introduction

Dengue is an infectious disease caused by the dengue virus which is transmitted by Aedes aegypti and Aedes albopictus mosquitoes. The dengue virus belongs to Flavivirus group. Dengue virus was a single-stranded RNA virus, the size about 50 nm. The virion consists of a nucleocapsid with a cubic symmetry that is enclosed in a lipoprotein envelope [17]. Genome structure of the dengue virus is 11644 nucleotides in length and it's composed of three structural gene proteins encoding the nucleocaprid or core protein (C), Premembrane/membrane (PrM/M), envelope protein (E), and seven non-structural gene proteins (NS).): NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5. The protein is flanked by the 5'Untranslated region (5'-UTR) and 3'Untranslated Region (3UTR) [1]. 5'-UTR consists of 95-101 nucleotide sequences in four serotypes dengue virus (Serotype 1-4), whereas 3'UTR has various lengths on each virus serotype [8]. Structural proteins and non-structural proteins from dengue virus plays different roles in the biological structure of the virus. The structural proteins are the components of the virus and non-structural proteins have various enzymatic activities that play a role in

viral RNA replication [4]. Non-structural proteins, namely NS3 and NS5, have a role in the viral RNA replication process. NS2B is a serine protease enzyme from viruses, these NS proteins together with NS1, NS2A, NS4 and NS4B proteins play various roles in viral replication, formation, and release [8].

Miana leaf (*Coleus scutellarioides*) is an ornamental plant from the Lamiaceae family that easy to find in various regions in Indonesia, more over people in one area in South Sulawesi consume miana leaves as medicine and vegetables. Asian people in general also use the leaves for various treatments, for example asthma, skin rashes, bronchitis, insomnia, and scorpio bite [15]. According to the research by Ridwan et al. In 2006 about extract from miana leaf, it was found that the most dominant secondary metabolites in miana leaves were flavonoids and tannins. Miana leaves have various variants. The results of the study on four variants of miana leaves, the deep purple, greenish purple, green, reddish purple variants showed that the highest flavonoid content was in the greenish purple variant [10,11].

Molecular docking is a beneficial instrument in finding a potent and effective compound to be used as a drug. The principal method in molecular docking is ligand-based drug design [9]. Molecular docking on the activity of several compounds, one of which is from the flavonoid group that will be used as a candidate inhibitor against Chikungunya virus, this research was conducted by Faqih et al. in 2019 showed that quercetin compounds from the flavonoid group had a fairly good binding affinity against Chikungunya virus inhibition. According to this research outcome, then underlies this research on how the effect of quercetin from Miana extract (*Coleus scutellarioides*) on the inhibition of Dengue virus [3]

Method

1. Ligands Preparation

   Structures 3D of chemical compound Quercetin was taken from Pubchem compound database (https://pubchem.ncbi.nlm.nih.gov/). Pubchem CID was 5280343 and Canonical Smile C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O. The 3D structure of Quercetin was sketch using Pymol software [14].
2. Protein Target

   Protein target as Non Structural Protein 5 (NS5) from dengue virus. The structure of protein target was collected from Protein Data Bank (https://www.rcsb.org/), then water molecul were removed by Pymol software [14].
3. Molecular Docking

   Ligand ang macromolecul (protein target) were convert to suitable format for docking in Autodock vina on Pyrx app (PDB format) [2]. Ligand from natural compound and ligand control; and macromolecule add to Pyrx. Vina Wizard was chosen as docking algoritm [12].
4. Visualization of the interaction between Ligand and Makromolekul

   The interactions between ligands (Quercetin) and target protein (NS5), visualized and analyzed using PyMol Software (Schrödinger) [14].
5. Compound's Properties and ADMET Predictions

   Swissadme (http://www.swissadme.ch) and admetSAR (lmmd.ecust.edu.cn:8000) is used to predict the prediction and significant descriptors of

Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds [14].

Results

1. Protein Target Before and After Water Molecule removed

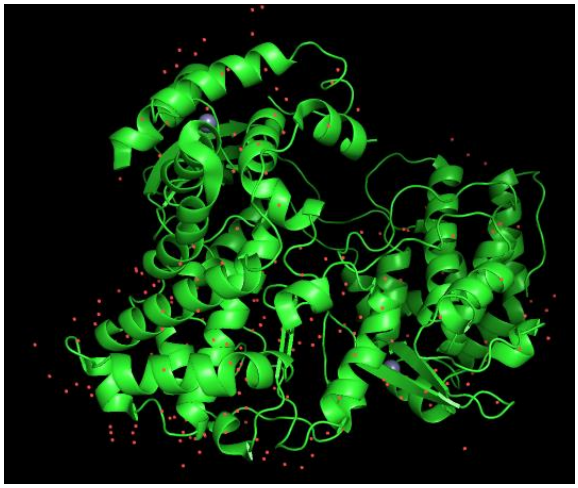

Figure 1. NS5 Before water removed

Figure 2. NS5 After water removed

2. Structure of Quercetin and Ribavirin
   Quercetin as a ligand from Coleus scutellarioides and ribavirin as ligand kontrol

Figure 3. Quercetin (L) and Ribavirin (R)

3. Molecular Docking Protein Target (NS5) and Ligand Quercetin

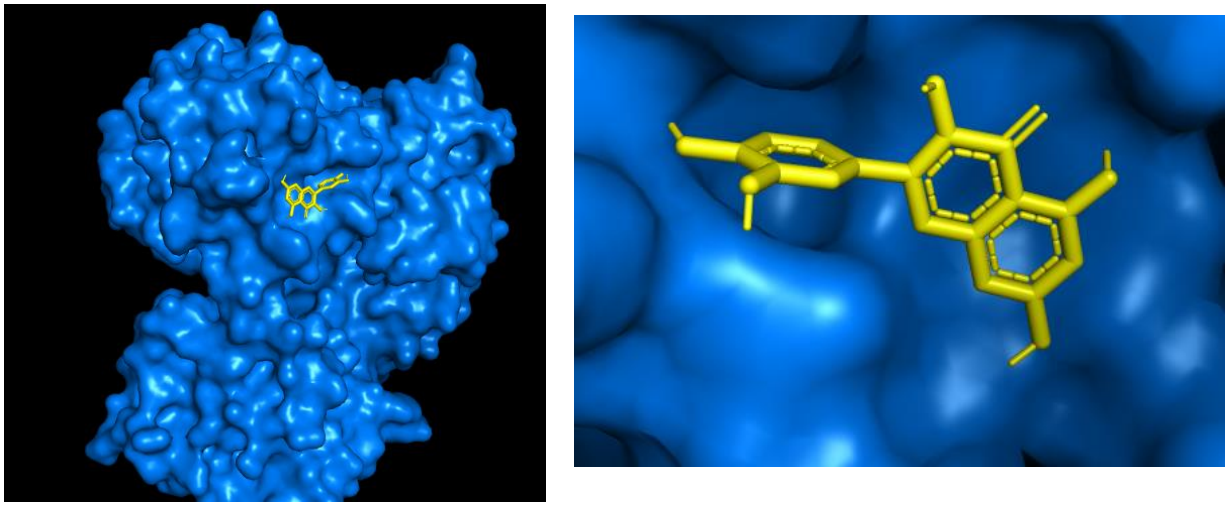

Figure 4. Molecular Docking NS5 and Ligand Quercetin

Table 1. Binding Affinity Quercetin-NS5 Protein and Ribavirin-NS5 Protein

Ligand	Binding Affinity (kcal/mol)
Quercetin	-7.6
Ribavirin	-5.8

4. Compound's Properties and ADMET Predictions

Table 2. Compound's Properties and ADMET Predictions of Quercetin

AMES Toxicity	Non AMES toxic	0.7220
Carcinogens	Non-carcinogens	0.9450

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Discussion

Treatments and vaccines against dengue are still being developed. In this study, molecular docking was carried out on the Quercetin ligand which is one of the type from flavonoid compound. Various studies have conducted on miana leaves (*Coleus scutellarioides*) showed that this plant has a fairly high content of flavonoid compound [5,10,11]. The ligand control is ribavirin. From the literature it is stated that ribavirin can be used as an antiviral compound. Prediction about the potential of compounds to be used as drugs can be done by using molecular docking. The molecular docking results show the strength of the interaction between the ligand compound and the target protein [7].

Docking molecular studies are used to examine the interaction between two molecules to find the best orientation of the ligand. The best output will show in a complex with minimum binding energy [13]. The result of molecular docking between Quercetin and NS5 Protein has a binding affinity value of -7.6 kcal/mol, the binding affinity value between control ligand (Ribavirin) and NS5 Protein is -5.8 kcal/mol. This result shows that Quercetin has a better value than Ribavirin.

There are four parameters that have to be fulfilled by a compound related to solubility and permeability so that compound can be used as a drug ingredient. According to Lipinski, there is a rule known as "the Rule of 5", which must be met, including the number of hydrogen donors < 5 (expressed as the sum of OH and NH), Molecular Weight (MWT) < 5, Log P < 5, bond acceptors –H < 10 [6]. The body will give its respond according to the new chemicals compound that enter the body. It will identify that material as a poison or foreign object, so that the body will involve various organs to respond against these chemicals. This response can be in the form of inhibition of absorption, restriction of distribution, metabolism of chemicals into forms

that are easy to secrete. The development of chemical compounds into drugs needs to validate the assessment of the body's absorption, distribution, metabolism, and excretion (ADME) against these chemical compounds to reduce the occurrence of failures in further clinical development. There are many things that need to be considered in the development of a chemical compound as a drug candidate, including toxicity effects and carcinogenic effects to the body. Computational techniques can help in the early stages of chemical development studies to find drug candidates [16]. The results of the analysis of Quercetin compounds using Swissadme and AdmetSAR showed that Quercetin compounds did not have a toxic effect and were not carcinogenic. Quercetin compounds also meet all the parameters in Lipinski's rule.

Conclusion

Quercetin has a good enough potential to be a candidate as a dengue virus NS5 protein inhibitor by looking at the binding affinity value of -7.6 kcal/mol; has no toxic effect and is not carcinogenic; and meets all the parameters in Lipinski's rule.

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