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Research Article

In Silico Study of Myricetin and Quercetin as Immunomodulator Candidates for Prevent SARS-CoV-2

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Abstract

Background: SARS-CoV-2 virus infection at this time has attacked various countries and becomes a threat that needs to be watched out for, the search for preventive treatment continues to be carried out to significantly prevent it. Antibodies against spikes that neutralize viral infections have potential as a therapy. Purpose of this study was to identify myricetin and quercetin, which were thought to have acted as immunomodulators for prevent SARS-CoV-2 using in silico study.

Material and Methods: Samples of 3D structure compounds from PubChem with the 3D structure of Fab-Antibody protein were docked using AutoDockTools and SwissDock and then validated by performing Molecular Dynamic. The final conformational results were then visualized using the Biovia Discovery studio, analyzed the effectiveness of the docking program, pharmacokinetics, toxicity, and dynamic programming using the Ramachandran plot.

Result: Significant results were obtained where quercetin had good activity at the 7JMO receptor with AutoDockTools and SwissDock where the binding affinity was -7.36 and -8.14. as well as the test compound myricetin, had a significant result having the best activity at the 7KZA receptor with a binding affinity value of -7.36 on AutoDockTools and -8.22 on SwissDock. And validated with the results of Molecular Dynamic having stable binding to the 7KZA receptor on the two test compounds.

Conclusion: From the data presented, it can be concluded that myricetin and quercetin have the potential activity as immunomodulators candidate for prevent SARS-CoV-2.

Keywords: Quercetin; Myricetin; SARS-CoV-2; Immunomodulator; In Silico

Introduction

Until now, even though an emergency vaccine has been found, it has not reduced the anxiety of a protracted pandemic. The existence of several new variants of the SARS-CoV-2 virus according to the World Health Organization (WHO) has motivated researchers from various fields of science to find effective and rapid treatment solutions against the SARS-CoV-2 virus. The weak point in the virus is the antibody, where the improvement of the immune system can be said to be important and become a reference in the treatment process [1,2]. Several studies have shown that flavonoid compounds belonging to the flavonol group, namely quercetin, and myricetin, have activity as immunomodulators. According to Hanifah, Lil, and Kiptiyah Kiptiyah research, flavonoid compounds are known to have potential effects as immunomodulators and antioxidants. Flavonoid compounds such as flavonols, quercetin and myricetin have been shown to inhibit the production of TNF-α and nitric oxide by lipopolysaccharides from activated macrophages. Suppression of TNF-α is suspected to have inhibition through NFκB activation. Inhibition of TNF-α occurs in the post transcription phase while inhibition is induced by nitric oxide synthase in the transcription phase. Myricetin has the potential

to inhibit T-lymphocyte activation in mouse models through anti-CD3 and anti-CD28 bead-immobilized monoclonal antibodies. The study clarified the mechanism of action and reported the suppressive effects of myricetin on T lymphocytes mediated through extracellular. These phenolic compounds were found to inhibit the production of IL-12 induced by lipopolysaccharides in the regulation of nuclear factor Kappa -B (nf-κB) enhancement [3].

Materials and Methods

Materials

The 3-dimensional structural materials of quercetin and myricetin were downloaded from https://pubchem.ncbi.nlm.nih.gov/. The structure of the target protein fragment Fab - Antibody (PDB ID: 6WAQ, 6XC4, 6XCA,7BZ5, 7CJF, 7JMO, 7JMP, 7JMX, 7K3Q, 7KMH, 7KN5 and 7KZA)were downloaded from the PDB website (protein data bank) http://www.rcsb.org/pdb/home/home.do.

Compound 3-dimensional structure optimization

The test compounds were drawn by using Marvin sketch 5.2 software. It was conducted through protonation at pH 7.4 and saved as mrv format. Subsequently, a conformational search was conducted and saved to the file in the form of pdb and mol 2 why is ref 18 just after ref 2. The method used for referencing is incorrect [4].

FAB-antibody protein 3-dimentional structure preparation

Protein preparation was carried out by using the Chimera 1.10.1 program, separated the 3-dimensional structure of the FAB-Antibody protein from its native ligand. Then, the preparation was carried out which separated it from its natural ligand, removed the solvent molecules and increased the hydrogen [4].

Molecular docking method validation

The validation of the molecular docking method was carried out by using the AutoDockTools application (AutoDock 4.2 and Autogrid) by redocking native ligands on Fab-Antibody proteins that had removed their native ligands. The method validation parameter was Root Mean Square Deviation (RMSD). Acceptable RMSD was 2 [4].

Docking test compounds on FAB-antibody protein

The optimized quercetin compound was docked to the Fab-Antibody protein that had removed its native ligand by using the AutoDockTools application with a similar docking procedure as the validation method. The results of the analysis showed the conformation of the compound bonds in proteins with the value of bond energy and hydrogen bonds [4]

Molecular docking data analysis

The analysis of the molecular docking data result was the bond energy and hydrogen bonds formed. The bond energy was used to indicate the bond's strength between compounds and proteins. The lower the bond energy value, the stronger and more stable the bonds were. The type of formed hydrogen bond was used to analyze the interaction mechanism that had formed [4].

Molecular dynamic file preparation

The molecular dynamic simulation file preparation was conducted by optimizing the geometry and minimizing the energy in the complex by using MOE 2009.10 software. The geometry optimization was conducted in the complex by selecting the partial charge option with the use of current forcefield parameter method, MMFF94x. Solvation used were born solvation, RMS gradient 0.05 and other parameters that appropriate with the default and the output file was in MDB format [5].

Molecular dynamic simulation

The parameters used were appropriate with the default in MOE-dynamics, they were the NVT ensemble (N: number of atoms; V: volume; T: temperature) with the Nose-Poincare-Anderson (NPA) algorithm. Molecular dynamics simulation of the ligand complex was conducted at a temperature of 312K which was the human body temperature when infected by the SARS-CoV-2 virus, so, it affected the stability of the drug-receptor complex which was carried out during 2000 ps, with a cooling stage setting for 20 ps. Position, velocity and acceleration results were saved every 0.5 ps. The output of the simulation results was in the form of an mdb format database [6].

Data analysis of molecular dynamic

Analysis of Molecular Dynamic Results Data used a Ramachandran's Plot to see the stability of a protein and to analyze the comparison of active sites during molecular dynamics in order to determine the interaction of ligands with enzyme residues during the simulation period until the end. The observed ligand interactions were residual contact (direct interaction) between the docking residues and molecular dynamic results [7].

Results and Discussion

Results of the docking validation. The validation was conducted before performing the docking simulation by redocking the native ligand on the FAB-Antibody protein that has removed its native ligand. Docking validation was carried out to find out how big the change of the protein-ligand interaction in the crystal structure before and after docking, to determine the deviation value to indicate whether the receptor was valid or not [8]. Docking method validation was done on AutoDockTools software. The results of receptor validation are shown in table 1.

The method validation parameter was Root Mean Square Deviation (RMSD) with an acceptable value of ≤ 2 Å [16]. RMSD as a parameter used to evaluate the similarity of two structures measured based on differences in atomic distances. From 16 receptors that had an RMSD value of ≤ 2 Å, there were only 7 receptors that showed valid values, they were 6WAQ with a value of 1,545, 6XCA with a value of 0.955 Å, 7JMO with a value of 1.727, 7JMP with a value of 1.908, 7KN5 with a value of 1,085 and 7KZA with a value of 1,330. This indicated that the docking method used was valid and the parameter settings met the validation criteria, so that these parameters could be used subsequently for docking test compounds [9].

After that, molecular docking was carried out by using AutoDock Tools software and SwissDock Webservice. The first molecular docking test used AutoDockTools software, the docking

Docking Validation Results				
Receptor	**GRID BOX**			**RMSD**
	X	**Y**	**Z**	**Å**
6WAQ*	28.732	31.728	-36.334	1.545
6XC4	-35.481	-6.088	29.941	3.670
6XCA*	-29.560	-28.716	42.226	0.955
7BZ5	-88.312	-20.943	20.980	5.381
7CJF	8.213	-69.897	8.594	6.694
7JMO*	-73.881	19.962	25.562	1.727
7JMP*	-80.484	19.315	3.008	1.908
7JMX	6.976	-25.200	5.286	10.422
7K3Q	-3.156	-57.375	-6.235	8.280
7KMH	14.160	11.197	24.120	3.703
7KN5*	-26.182	6.788	16.604	1.085
7KZA*	-1.303	33.727	35.976	1.330

Table 1: The results of receptor validation Docking.

Information: *: receptor with valid value.

of the test compound to the receptor that has been validated with the same grid box settings. The purpose of setting this grid box was to direct the ligands of the test compounds to interact within the receptor area [10]. This docking simulation was carried out with 100x running in a flexible ligand position, so it gave a chance to the ligand to make stable structural adjustments when binding to the receptor. The results of docking test compounds with receptors can be seen in table 2.

	Compound	**Receptor**	**Docked structure**	**ΔG (Kcal/ mol)**	**KI (uM)**	**FullFitness (Kcal/mol)**
1	Myricetine	7JMO		-7.36	5.18	
2		7KZA		-8.14	-	-895.44

3	Quercetine	7JMO		-7.66	2.46	
4		7KZA		-8.22	-	-894.63

Table 2: The binding affinity and docked structures of the selected drugs with FAB – Antibody (7JMO & 7KZA) of COVID-19.

The best conformation can be seen through the binding energy (ΔG), where it describes the strength of the bond that occurs between the ligand and the target protein. The bond energy has an inhibition constant relationship, therefore, it can be concluded that the smaller the bond energy, the more favorable the interaction between the ligand and the enzyme [11].

Data show in table 2 show that selected test ligands had the ability to bind to the target protein, the energy values of the native and the tested compounds that have different binding values. From the analysis results, it is known that the compounds with the test ligands had smaller binding energy values than the comparison compound. This indicates test compound could inhibit the target protein well and stably.

In addition, the best compound from docking result were the myricetin test compound from the 7JMO receptor with a binding affinity (ΔG) value of -7.36 and Ki with a value of 5,18 and on the quercetin test compound from the 7JMO receptor with a binding affinity (ΔG) value of -7.66 and Ki with a value of 2.46, and the results of the comparison compound, thalidomide, had the greatest binding affinity value starting from the 6XCA receptor with a binding affinity (ΔG) value of -4.30 and Ki with a value of 1.2. The results of 3D and 2D visualization can be seen in figure 1.

The more interactions between compounds and amino acid residues, it is predicted that the interaction will be better. There are several important amino acids in the receptor with the test

(a)

(b)

Figure 1: Representation of the interacting sites of SARS-CoV-2 FAB-Antibody with receptors 7JMO (AutoDockTools) 7KZA (a) myricetin and (b) quercetin.

compound as an immunomodulator including glutamine (GLN), and arginine (ARG). Two test compounds with 7 receptors as immunomodulators had these residues which could predict their good activity as immunomodulators in the treatment of SARS-CoV-2.

Next is molecular docking by using the SwissDock webservice. Before doing the docking on SwissDock, the downloaded receptor was prepared for adding hydrogen atoms, removing water molecules, and determining partial charge (using the CHARM22 force field) on the UCSF Chimera software. Docking calculations were performed by using SwissDock, an online server that connects ligands to proteins through the EADock DSS20 software. The docking run was conducted by using the ''Accurate'' parameter option, which was the most complete in terms of the number of binding modes sampled. The results of the docking simulation data are shown in table 2.

Table 2 shows the best results for each receptor with referring the result to cluster 0 and the best binding affinity value was provided. Each receptor has a run of 90 - 100 clusters with a different time for each receptor, which ranges from 30 - 60 minutes. The docking results with the lowest binding affinity and FullFitness values on the myricetin test compound were found at the 7JMO receptor, this is similar to the docking results on AutoDockTools although the values are slightly different due to the different systematic docking process. The binding affinity value for the myricetin test compound with the 7JMO receptor was -8.39 and the FullFitnes value was -2041.01. In the quercetin test compound, the best docking results were found at the 7KZA receptor with a binding affinity value of -8.14 and a Fullity value of -894.63. In figure 2, it can be seen the 3D and 2D visualization from the best docking results produced by the myricetin test compound with 7KZA and quercetin with the 7KZA receptor [12].

(a)

(b)

Figure 2: Representation of the interacting sites of SARS-CoV-2 FAB-Antibody with 7KZA (a) myricetin and (b) quercetin.

There was a significant difference between the results of docking from the AutoDockTools software and the SwissDock WebService, where AutoDockTools has the advantage to find out the grid box during the docking process while the SwissDock webservice cannot do that. However, the percentage of "human error" was being a concern in the AutoDockTools software compared to the SwissDock Webservice. SwissDock evaluated the protein-ligand binding energy by using a grading function based on the CHARMM22 force field which required further molecular dynamic testing with Assisted Model Building with Energy Refinement (AMBER). Whereas, on the molecular docking, it was predicted the binding affinity with better correlation with the experimental binding affinity for several proteins by using Lamarckian algorithm force [13].

Next is the dynamic simulation by using MOE.2009.10 software. The purpose of conducting molecular dynamics simulations was to determine the stability of the proteins' interaction with ligands in conditions that are made as close as possible to the physiology of the human body within a certain period. Before doing the molecular dynamics, the molecular dynamic simulation file preparation was performed by optimizing the geometry and minimizing the energy in the complex by selecting the particular charge option with the current forcefield parameter method used. Furthermore, energy minimization was carried out by selecting the minimize energy option with the MMFF94x forcefield parameter. Solvation used in molecular dynamics was different from Molecular docking, where Molecular docking used gas-phase solvation, while in

molecular dynamics, it used born solvation. This kind of solvation is an implicit solvation, where the solvent molecule only acts as a medium and does not involve in the simulation process. It also used RMS gradient 0.05 and other parameters as per default and the output file was in MDB format [13].

As for the parameters, it used MOE-dynamics in accordance with default, they were the NVT ensemble (N: number of atoms; V: volume; T: temperature) with the Nose-Poincare-Anderson (NPA) algorithm. Molecular dynamics simulation of the ligand complex was carried out at a temperature of 312K which was the temperature of the human body when it was infected by the SARS-CoV-2 virus, so, it affected the stability of the drug-receptor complex which was carried out for 2000 ps, with a cooling stage setting for 20 ps. The cooling stage aimed to find the lowest conformational energy of the molecule, this process is also called annealing. Position, velocity, and acceleration results were saved every 0.5 ps. The output of the simulation results was in the form of an MDB format [14].

To analyze and compare the active site during molecular dynamics, the interaction of the ligand with the enzyme residue was observed during the simulation period until the end. The observed ligand interactions included residual contact (direct interaction) between the docking residue and the molecular dynamic result. The results of the simulation analysis can be seen in table 3.

Test Compound	PDB Code	Docking (AutoDock Tools)	Docking (SwissDock)	Molecular Dynamic	Number of Matched Amino Acids
Thalidomide	7JMO	LYS65,MET111, ILE64,LEU163, ILE42,LEU114, TYR113,GLU112, ALA173,ASP174, ALA63,VAL50, LEU86,THR95,ILE109	PRO229,SER232, GLU233,THR250, HSD231,PRO249, LEU251,ILE222, PRO230,GLU252,	ILE64,ALA63, GLY45,ASP174, SER46,LYS158, ALA159,HIS303, GLY116,GLU112, VAL16,LYS65, GLY11,TYR113, LEU114	7
	7KZA	VAL175,PRO173, PHE172,ALA174, SER185,LEU184, SER183,LEU147	THR31,MET2, GLY24,LEU4, ILE34,CYS22, ALA79,PRO53, THR78,ASN77, TYR32,LYS74, GLY54	PHE172,SER185 PRO173,VAL175 LEU184,SER183	6
Myicetine	7JMO	GLU82,LYS65, VAL50,ILE42, LEU114,TYR113, GLU112,LEU163, ALA63,THR95 MET111,ASP174, ALA173,LEU86, GLU82PHE175	GLY117,ILE42, GLY43,ALA63, TYR113,LEU114 LEU163,MET111, THR95,GLU112, GLU82,ALA173, ASP174,ILE109,LYS65	GLY116,LEU114, LYS106,LYS171, LYS158,VAL170, ASP104,THR105	1
Quercetine	7KZA	LEU147,LEU184, SER183,SER185, PHE172,PRO173, VAL175	LYS43,MET40, PRO41,LEU176, VAL175,ALA174, GLU154,THR91, THR116,TYR182, SER89,ALA88	LEU147,LEU184, SER183,SER185, PHE172,PRO173, VAL175	7

Table 3: Differences in Amino Acid Residues from Docking and Molecular Dynamic Simulations.

Based on the analysis and visualization of the data from the in silico study by using molecular dynamics, it is known that the myricetin test compound with the 7JMO receptor had a match on several amino acids from molecular dynamics and molecular docking results, although there was only 1 similarity as can be seen in table 3. When viewed from the docking result from AutoDockTools software and the SwissDock webservice, the myricetin test ligand compound had the best bond with 7JMP protein. When the dynamic simulation was conducted, 7JMP protein only had one amino acid residue in common. Quercetin test compound had also the best dynamics simulation results, it was the 7KZA receptor that had 7 amino acids in common, which means that it can be claimed to be able to bind with the binding site of the enzyme and interact with the catalytic site of the enzyme well until the end of the simulation. It also had some similarities in the number of amino acid residues with the comparison compound which can be predicted that the test compound had acted as an immunomodulatory candidate [15]. In figure 3 below, it can be seen the visualization of molecular dynamic compounds before and after they were conducted.

(a)

(b)

Figure 3: Representation of SARS-CoV-2 interaction site after molecular dynamics validation (a) myricetin and 7JMO (b) Quercetin and 7KZA.

From the results of the dynamics simulation of myricetin and quercetin test compounds with some receptors, there was a change in the type of contact residue at the anchorage area, but, there were some stable residues that still bind well. It indicated the ligand and the receptor had been formed in a complex way at 312°K and run for 2000ps with a cooling stage of 20. Hence, myricetin and quercetin compounds can be predicted to have activity as candidate immunomodulators [17].

There was a change in the type and number of amino acid residues in the anchoring area due to changes in temperature and the presence of solvents in the simulation system, which caused the distance change of atoms that previously interacted being very close to other amino acid residues. However, the test compound still formed complexes with proteins between drug-receptors. In addition, the conformational stability of the protein can be seen based on the number of amino acid residues that can be analyzed by using the Ramachandran plot [18].

Based on the dynamics simulation results of several proteins with myricetin and quercetin test ligands, it can be stated that they still have good stability because they have a disallowed r religion value or unwanted region 15% and have a most favored region value 50% [19], which can be seen in figure 4 and 5.

Figure 4: Results of Ramachandran Plot Quercetin - 7KZA.

Figure 5: Results of Ramachandran Plot Myrisetin - 7JMO.

The number of non-glycine residues in the disallowed region or unwanted region is 0.94%, it can be said that the results of the molecular dynamic protein 7KZA with the quercetin test compound have good quality and the interaction of amino acid residues in the most favored region has a value that more than 50%, which is 87.264%, it can be concluded that the protein structure and the test compound have good stability [20].

It can be seen that the number of non-glycine residues in the region of disallowed religion or unwanted areas is 4.5%, it indicates that the results of molecular dynamic protein 7JMO with the myricetin test compound have good quality and the interaction of amino acid residues in the most favored region has a high value that more than 50%, which is 84.456%. Hence, it can be said that the structure of the protein and the test compound is stable.

Conclusion

The results of the docking simulation showed that myricetin with 7B30 receptor had ΔG -8.39; FF -2041.01 values with SwissDock and ΔG -7.55; Ki 3.01 with AutodockTools. Quercetin with 7KZA receptors obtained ΔG -8.22; FF -894.63 values with SwissDock and ΔG -6.73; Ki 11.58 using AutodockTools, where these results showed the most stable conformational bonds. The results of the molecular dynamics simulation test show that both are able to bind to the binding site of the enzyme and interact with the catalytic site of the enzyme until the end of the simulation.

The suitability of the ligand to the conformation of the catalytic site of the enzyme during the simulation showed that the myricetin ligand had a better suitability and stability in interacting with the catalytic site of the enzyme when compared to quercetin, but from the overall results obtained both mircetin and quercetin had the same potential as immunomodulators in inhibiting SARS. -CoV-2.

Competing Interest

The authors declares that they have no competing interest.

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Data Avaibility

Data for this study will made available upon request

Consent for Publication

All authors have read and approved submission of this research article.

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