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The Potential of Quercetin as Parkinson's Disease Therapy Assessed From Binding Affinity To Adenosine A2a Receptor Using In-Silico

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ABSTRACT

Parkinson's disease is a degenerative disease that causes impaired mobility and muscle control caused by decreased dopamine production in the brain. Parkinson's disease therapy is dopaminergic therapy using levodopa which works by replacing the reduced dopamine, the use of levodopa has side effects such as dizziness, nausea, and excessive sleepiness. The use of istradefylline with levodopa as a non-dopaminergic therapy in parkinson's reduces side effects and increases therapeutic targets. Quercetin is thought to have activity in improving motor function in parkinson's. The study aimed to look at the potential of quercetin as a parkinson's therapy. Objective: Finding the activity of quercetin as Parkinson's therapy compared with istradefylline using in-silico. Method: The design of this study is in-silico, which is a study using the help of computer calculations, the method used is molecular docking based on the principle of bonding compounds to receptors. Ligand compounds were obtained from PubChem and receptor clusters were obtained from Protein Data Bank. The docking Software used is Pyrex, and Discovery Studio Analizer. Independent variables in this study were quercetin and istradefylline, while the dependent variable was binding affinity ligand to adenosine A2a receptor. In this study, statistical analysis was conducted using an independent sample t-test. Results: In-silico test with molecular docking method showed each 9 ligand position to the receptor, the results of data analysis with the test of independent sample t-test, at the degree of significance $\alpha = 0.05$ obtained statistical results with a significance value of 0.013 which means that the quercetin ligand has stronger potential compared to istradefylline. Quercetin has a binding affinity value of -8.1 kcal/mol, while istradefylline has a binding affinity value of -6.9 kcal / mol. Conclusion: Quercetin has been shown to have potential as an alternative therapy for parkinson's disease.

Keyword : quercetin, parkinson, istradefylline, adenosine A2a receptor, molecular docking

INTRODUCTION

Parkinson's disease (PP) is one of the most common neurodegenerative diseases and ranks second only to alzheimer's disease. It is known that approximately 0.3% of the general population has PP. The degenerative impact on muscle mobility and control can be observed through symptoms known as the three main signs of PP, namely resting tremor, slow movement (bradykinesia), and muscle rigidity, which are caused by decreased dopamine production in the brain (Alia *et al*., 2022). Data on the prevalence of PP in Indonesia is very limited, the data available so far is the result of extrapolation. In this estimate, the incidence of PP is estimated to reach 10 people every year, while the number of sufferers is estimated to range from 200,000 to 400,000 people which is a provisional estimate (Setiarini et al., 2016).

So far, the therapy for PP is dopaminergic therapy using levodopa which works by replacing reduced dopamine, but the use of levodopa has side effects such as dizziness, nausea, and excessive drowsiness (Vasta et al., 2017). Prolonged use of levodopa causes a decrease in the patient's motor skills, which results in a decrease in the patient's quality of life (Oktariza et al., 2019). Combination therapy of levodopa with adenosine A2a antagonists has been shown to reduce levodopa dose requirements.

The discovery of new drugs or so-called novel drugs in PP therapy leads to non-dopaminergic pathways (Jenner et al., 2021). Istradefylline is a novel drug as an adenosine A2a antagonist recognized by the FDA in August 2019 under the brand name "Nourianz" (FDA, 2020), which is the first non-dopaminergic drug for PP therapy along with levodopa. According to a study conducted by (Takahashi et al., 2022), the efficacy of istradefylline in combination with levodopa has increased in 59.8% of patients in Japan. With the high need for the search for potential novel drugs in PP therapy, natural materials have a great potential in developing new drugs, one of the chemical compounds derived from herbal plants that are quite widely recognized for their efficacy is quercetin. Quercetin is a phytochemical compound from the flavonoid group that is found in many fruits and vegetables. In Indonesia, quercetin has been circulated in the form of neutrasetical products with claims of improving the immune system. Quercetin is thought to work with iron-chelating activity that inhibits rotenone induction which causes neuronal degeneration (Boyina *et al*., 2020). The development of quercetin's potential as an adenosine A2a antagonist can be measured through in-silico tests with molecular docking methods.

Molecular docking is one of the biocomputational or in silico methods used to predict the energy interaction between two molecules, namely the ligand and its receptor. The interaction includes protein-protein, protein-drug, protein-DNA, and other protein-molecule bonds. The predicted results from molecular docking can help identify the active side of a protein molecule. (Plewczynski, 2014). Molecular docking is divided into two parts, namely search algorithm and the scoring function. The search algorithm is used to identify the optimal conformation that forms a complex between receptor and ligand. Meanwhile, the scoring function is used to predict the strength of the bond called binding affinity between the receptor and the ligand being docked (Pakpahan *et al*., 2013). Binding affinity refers to the strength of interaction between a ligand/drug and its protein/receptor. The binding affinity value has an inverse relationship with its potency (Salahudeen and Nishtala, 2016). The smaller the binding affinity value is zero or the more negative it is, the stronger the bond and its potency in producing effects on the body (Das et al., 2016). From the above background, an in-silico study was conducted to measure the binding affinity of quercetin to adenosine A2a receptors for further development of alternative non-dopaminergic therapies in Parkinson's disease.

METHOD

The ligands istradefylline and quercetin were prepared and molecular docking procedures were performed on the macromolecular protein adenosine a2a receptor.

RESULT

Binding Affinity

Based on the docking results, quercetin ligand has a binding affinity value of -8.1, while istradefylline ligand has a binding affinity value of -6.8. The docking data shows various binding poses with varied RMSD values, the eligible RMSD data is not more than 2, so there is only 1 pose of two ligands each selected from the data, namely -8.1 (Mode 0) for quercetin and -6.8 (Mode 0) for istradefylline. The data shows that the binding affinity value of quercetin

is higher than the binding affinity of istradefylline, indicating that quercetin has potential as a therapy for Parkinson's disease.

Table. 1 Molecular Docking Results

Ligand Name	Mode	Binding affinity (kkal/mol)
Quercetin	0	-8.1
Quercetin	1	-7.6
Quercetin	2	-7.5
Quercetin	3	-7.5
Quercetin	4	-7.1
Quercetin	5	-7.0
Quercetin	6	-6.9
Quercetin	7	-6.7
Quercetin	8	-6.7
Istradefylline	0	-6.8
Istradefylline	1	-6.4
Istradefylline	2	-6.4
Istradefylline	3	-6.4
Istradefylline	4	-6.3
Istradefylline	5	-6.3
Istradefylline	6	-6.2
Istradefylline	7	-6.1
Istradefylline	8	-6.1

Visualization

The visualization procedure of ligand to protein interaction was performed using Discovery Studio Visualizer software by inputting adenosine A2a receptor protein as macromolecule and ligands consisting of istradefylline and quercetin after the docking process. Interaction visualization is done to see the specific bond between ligand-protein of new drug candidates against the control drug, for further analysis of similar bond types used in seeing the potential of new drugs. The selection of pose mode is based on the pose that has the most similar pocket location between quercetin ligand and istradefylline ligand, researchers chose istradefylline data with mode 0 which has the highest binding affinity as a pivot, and quercetin ligand that is closest to the pivot pocket location is quercetin mode 6 with a binding affinity value of -6.9. The selection of poses with similar pocket locations is carried out to comparing residual bonds between ligands which will be further analyzed, pocket differences can cause interactions between ligands on protein amino acids, significant differences will make it difficult to compare residual bonds to conclude the data.

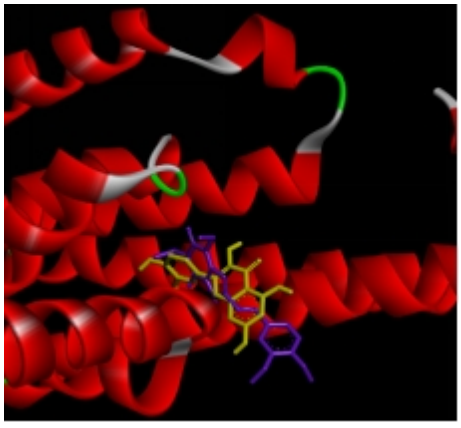

Fig.1 Visualization of Quercetin and Istradefylline Pose against Adenosine A2a receptor

Table 2. Binding of amino-acid quercetin and istradefylline comparison

Ligand	*Hydrophilic Bond*	*Hydrophobic Bond*
Quercetin	LYS A:227, PHE A:295, **ASN A:42**, **THR A:41**, **ARG A:293**, ALA A:231, VAL A:45, **ARG A:291**, **HIS A:230**, TYR A:288, **SER A:234**, ALA A:235, ILE A:98	**ILE A:292**
Istradefylline	GLU A:294, ASN A:39, **ASN A:42**, **THR A:41**, **HIS A:230**, **ARG A:293**, **SER A:234**, **ARG A:291**, ARG A:296	LEU A:37, ALA A:231, LYS A:227, VAL A:45, **ILE A:292**

Based on the visualization of ligand-ligand interactions with macromolecular proteins, the results of quercetin ligand binding to adenosine A2a receptors consisting of 13 amino acid hydrophilic bonds (LYS A: 227, PHE A:295, ASN A:42, THR A:41, ARG A:293, ALA A:231, VAL A:45, ARG A:291, HIS A:230, TYR A:288, SER A:234, ALA A:235, ILE A:98) and also 1 hydrophobic bond (ILE A:292). The binding results of istradefylline ligand to adenosine A2a receptor consist of 9 amino acids (GLU A:294, ASN A:39, ASN A:42, THR A:41, HIS A:230, ARG A:293, SER A:234, ARG A:291, ARG A:296) hydrophilic bonds and 5 amino acids hydrophobic bonds (LEU A:37, ALA A:231, LYS A:227, VAL A:45, ILE A:292).

DISCUSSION

The molecular docking process produces some ligand binding data to the receptor, quercetin ligand has 8 poses of binding models with adenosine A2a receptor, each bond has a binding affinity value of -8.1, -7.6, -7.5, -7.5, -7. 1, -7.0, -6.9, -6.7, -6.7 kcal/mol, while istradefylline ligand has 8 poses of bond model with adenosine A2a receptor, each bond has binding affinity value of -6.8, -6.4, -6.4, -6.4, -6.3, -6.3, -6.2, -6.1, -6.1 kcal/mol. Based on the data obtained, the binding affinity value of the quercetin docking process has a more varied scoring value, this is because quercetin has a higher bond variation compared to istradefylline, while the binding affinity of the istradefylline docking process is relatively more similar, this is because the residue bond in each pose has less variation compared to quercetin. The statement is proven by statistical analysis that shows the standard deviation value of quercetin binding affinity value of 0.47170, the value is greater than the standard deviation of istradefylline binding affinity value of 0.21213.

Assessment of the potential of quercetin as a parkinson's therapy was studied by comparing the binding affinity value of quercetin with the binding affinity of istradefylline to adenosine A2a receptor, binding affinity data from molecular docking was carried out statistical analysis to see the significance value, istradefylline was used as a control or comparison to see the inhibition of adenosine A2a receptor. The statistical analysis method uses an independent t-test based on variables that are not related to each other, it is done to determine whether the existing variables have a significant difference or not, with the assumption that if the candidate drug does not have a significant difference to the control drug, then the candidate drug has the same potential as the control drug. Data analysis shows a significance value of 0.013, this value indicates that 0.013 <0.05, so H-null is rejected and H-1 is accepted, this data indicates that there is a significant difference in the variables, this result is evidenced by quercetin having a more negative binding affinity value than istradefylline. Based on the analysis above, quercetin has potential in the development of Parkinson's therapy. This is supported by in-silico research conducted by Boyina *et al*., 2020 that quercetin has

several potential mechanisms that are neuroprotectors in parkinsonian patients, so this discovery opens further studies on the potential specific mechanisms of quercetin compounds.

The ligand istradefylline has activity as an antiparkinsonian (Takahashi *et al.,* 2022). The results of molecular docking showed that istradefylline has a binding affinity value of -6.8 kcal/mol. Binding affinity quercetin has a value of -8.1 kcal / mol, the data shows that quercetin has a smaller binding affinity value than istradefylline. Smaller or more negative binding values have stronger and more stable strength between ligands and proteins. Similar research conducted by Lakshmi et al., 2023 showed that quercetin has the ability to bind to dopamine receptors compared to levodopa. The data confirmed that quercetin has similar potential as istradefylline in the development of parkinson's disease drugs.

The interaction between ligands and receptors is key in the existence of pharmaceutical activity, based on the results obtained, some data on ligand amino acid binding to proteins were obtained. From several types of bond poses, there are similarities in the amino acid bond interactions of quercetin ligands with adenosine A2a receptor proteins and istradefylline amino acid bond interactions with adenosine A2a receptor proteins, namely the amino acid bond ASN A: 42, THR A: 41, ARG A:293, ARG A:291, HIS A:230, SER A:234 as hydrophilic bonds, and amino acid ILE A:292 as hydrophobic bonds, it shows that quercetin has similar activity with istradefylline against adeosine A2a receptor. In the data obtained, researchers found several types of bonds that have similarities between the two ligands, namely the amino acid bonds ASN, THR, ARG, HIS, SER, and ILE, it is concluded that the bond is one of the keys in the activity of adenosine A2a receptor inhibition. Similar research conducted by (Tian et al., 2017) confirmed that the inhibitory activity of adenosine A2a receptor has amino acid bonds that at least interact with the amino acids ALA, VAL, PRO, LEU, ASN, and ILE. Compared to the research conducted, the ASN and ILE amino acid proteins have similarities to the interaction of quercetin and istradefylline. The quercetin-bonded complex has two bonds that exceed the potential of istradefylline, namely on the amino acid side of VAL and ALA, so that quercetin has a higher potential than istradefylline. The data shows that the docking procedure performed has shown quite clear results on the potential inhibition of adenosine A2a receptor, so quercetin is proven to have a high potential to be further developed in the therapy of Parkinson's disease.

CONCLUSION

Quercetin has potential as an alternative therapy for Parkinson's disease, as seen from the results of in-silico testing using molecular docking method with quercetin binding affinity value of -8.1 kcal/mol.

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