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Original Article

Virtual Screening of Indonesian Herbal Database as Adenosine A_2A Antagonist using AutoDock and AutoDock Vina

Nabilah Nurtika Salamah, Widya Dwi Aryati, Arry Yanuar*

ABSTRACT

Objective: Previous research found that Adenosine A_2A antagonist allows to reduce motor fluctuations, dyskinesia, protect from neurodegenerative disorder in Parkinson's disease in the human brain which is chronic progressive of losing dopaminergic neurons. The aim of this study is to explore Indonesian herbal compounds as Adenosine A_2A inhibitor using virtual screening method. **Methods:** In this study, virtual screening of Indonesian herbal database as Adenosine A_2A inhibitor was done by AutoDock and AutoDock Vina and was validated by database from A Directory of Useful Decoys: Enhanced (DUD-E). The method was validated by Enrichment Factor (EF) and Area Under Curve (AUC) of Receiver Operating Characteristics (ROC) curve **Results:** Based on the validation results, grid box that was used in virtual screening using AutoDock is 60 × 60 × 60 with EF1% 16.5869 and AUC 0.8406. The two compounds *Chitranone* and *3-O-Methylcalopocarpin* with binding energy -10.19 and -9.55 kcal/mol, respectively showing interaction with Adenosine A_2A active site at residues ALA63, ILE66, ALA81, LEU85, PHE168, GLU169, MET177, TRP246, LEU249, ASN253 and ILE274. **Conclusions:** This study concludes that *Chitranone* and *3-O-Methylcalopocarpin* could be proposed to be developed as Adenosine A_2A antagonists.

Key words: Adenosine A_2A antagonist, Autodock, Autodock vina, Indonesian herbal database, Parkinson's disease, Virtual screening.

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INTRODUCTION

Parkinson's disease is a chronic progressive neurodegenerative disorder. The main feature of Parkinson's disease is the loss of dopaminergic neuron from subtantia nigra pars compacta (SNc) with Lewy body formation. Based on worldwide data analysis, the prevalence of Parkinson's disease is 5.2 million people and high at the age above 40 years with the prevalence of men 1.8 times greater than woman. In Indonesia, as many as 1 in a million people suffer from Parkinson's disease.[1]

The most common therapy for Parkinson's disease is dopamine precursor, L-3, 4-dihydroxyphenylalanine (L-DOPA) with carbidopa as an initial treatment. However, in long term use it can lead to complications such as motor fluctuations,[2] dyskinesia,[3] and cognitive dysfunction.[4] Therefore, a new treatment strategy is needed that aims to provide more effective dopaminergic stimulation to prevent motor complications.[5]

The adenosine A_2A antagonist can provide a new mechanism for treatment of Parkinson's disease because they may exert a neuroprotective effect against deterioration of Parkinson's disease and help to prevent drug induced dyskinesias.[6,7] The adenosine A_2A antagonists inhibit the release of GABA, which enhances motor function. They also modulate release of acetylcholine and can release dopamine from the nigrostriatal tract. Some of the drug compounds of this selective antagonist class of receptors such as Istradefylline, Preladenant, Tozadenant, Vipadenant, ST-1535 and SYN-115 have been carried out clinical trials. Adenosine A_2A antagonists that are non-selective from natural ingredients, namely caffeine and theophylline.[8,9]

Virtual screening is a novel approach to find lead compound in the development of new drugs *in silico*. In virtual screening, the compounds being analyzed are derived from databases of chemical compounds.[10] HerbalDB is a data base developed by the Faculty of Pharmacy Universitas Indonesia which contains three dimensional structure of 1410 medicinal compounds of Indonesia.[11] The virtual screening of the HerbalDB databases as Adenosine A_2A antagonists was performed in this study using AutoDock and AutoDock Vina and validated by using the Directory of Useful Decoys-Enchanced (DUD-E) database to obtain the predicted potentially antagonistic compounds of Adenosine A_2A.

MATERIALS AND METHODS

Materials

Hardware

The first computer was Mac Mini (Apple Inc., USA), Intel® Core™ i5-2450M with CPU (Intel® Core™, USA), GPU Intel Iris 1536 MB (Intel® Core™, USA) and Random Access Memory (RAM), 8 GB DDR3 with × Yosemite 10.10 operating system. The second computer was MacBook Air with Intel® Core™ i5, GPU Intel HD Graphics 6000 1536 MB, RAM 4GB, 1600 MHz DDR3 run with the MacOS High Sierra operating system.

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Software

The software used in this study were OpenBabel (The Blueobelisk Group, USA), PyMOL (Delano Scientific LLC, Italia), AutoDock *Tools* 1.5.6 (The Scripps Research Institute, USA), AutoDock 4.2, AutoDock Vina and PyRx.

Structures of macromolecule target

The three dimensional structure of protein macromolecule target 4EIY (Figure 1) with 1.8Å resolution was downloaded from the Protein Data Bank.[12]

Structures of positive control and negative control compounds

Structures of positive and negative control compounds were downloaded from Directory of Useful Decoys: Enhanced (DUD-E).[13]

Structures of Indonesian herbal database

Structures of Indonesian herbal database were downloaded from HerbalDB and has 1,410 active compounds.[11]

Methods

Preparation of macromolecule 3D structure

The preparation process was consisted of searching and downloading, optimizing, separating of non-standard residues and determining of binding sites. The preparation was performed with AutoDock Tools.

Preparation of ligand 3D structure

There were three types of ligands used for docking in this study, positive control compounds, negative control compounds and herbal database compounds.

Preparation of positive control compounds

Positive control compounds were 844 structures with *mol2 and were converted to *.pdbqt.

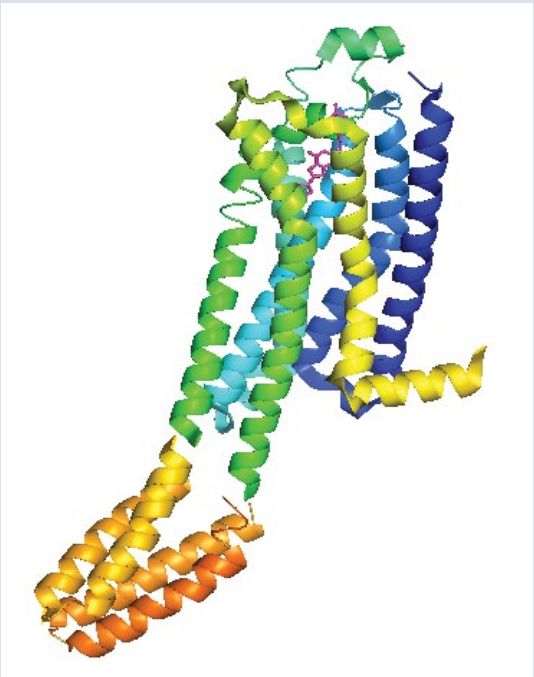

Figure 1: The structure of adenosine A_2A macromolecule with ZMA antagonist ligand.

Preparation of negative control compounds

Negative control compounds were 10,899 stuctures with *mol2 and were converted to *.pdbqt.

Preparation of Indonesian herbal database

Indonesian herbal database were 1,410 structures with *mol2 and were converted to *.pdbqt.

Validation of virtual screening

The validation of virtual screening method was conducted by molecular docking using AutoDock and AutoDock Vina. Validation results optimized by looking at the value of Enrichment Factor (EF) and Receiver Operating Characteristics (ROC).

Virtual screening of adenosine A_2A antagonist compounds from Indonesian herbal database to macromolecule target

In this study, virtual screening was done using parameters obtained from the validation. It was done to 1.410 compounds from Indonesian herbal database (HerbalDB) using AutoDock and AutoDock Vina. Parameters of the results was binding energy, inhibition constant and interactions.

Analysis and visualization of protein-ligand interactions

In this study, the visualization of docking results was performed by PyMOL, Chimera, AutoDock Tools, Marvin Sketch and LigandScout. Visualization was done to see the interactions that occurs between ligand and amino acid residues found in binding sites of the macromolecules target.

RESULTS

Optimization and validation of virtual screening methods using AutoDock and AutoDock Vina

The co-crystalized ligand, ZMA, was redocked to the 4EIY macromolecule using AutoDock and AutoDock Vina. A root mean square deviation (RMSD) calculation was used as a reference to see the results regarding the position similarity between co-crystalized ligand before and after it was redocked to the macromolecule.

Based on the Tables 1 and 2, the RMSD value of redocked co-crystalized ligand with macromolecule target using AutoDock with the size of grid box were 50 × 50 × 50; 60 × 60 × 60; 70 × 70 x70; and 80 x80 × 80, (spaced 0.375 Angstrom per unit) and using AutoDock Vina with the size of grid box were18.75 × 18.75 × 18.75; 22.5 × 22.5 × 22.5; 26.25 × 26.25 × 26.25; and 30 × 30 × 30 (spaced 1 Angstrom per unit).

Parameters used in the validation of virtual screening methods were Enrichment Factor (EF) and Receiver Operating Characteristics (ROC).

Enrichment factor (EF)

EF is the ratio of ligand concentration between docking hits (which have been sequenced) with all the number of ligand docking.[14] EF value that are close to or above the random value (> 1) are categorized as good EF values.[15]

Based on the Table 3, the results of EF by using AutoDock on the 60 × 60 × 60 grid box produced the most active compound although it did not exceeded EF value of previous research 21.8.[13]

Based on the Table 4, the screening results by using AutoDock Vina did not exceeded the EF value of previous research.[13]

Receiver operating characteristic (ROC)

The ROC curve was obtained based on binding energy resulted in molecular docking of positive and negative control compounds. These

binding energies were sorted from the lowest to highest. The ideal value of Area Under Curve of ROC value is above 0.5,[15] which means the ROC line (Figures 2 and 3) are above the random line. Of the overall ROC curve, 60 × 60 x60 grid box was provided the ideal curve shape.

The results of AUC value by using AutoDock in Table 5, showed the four grid boxes above the ideal value (>0.5). The best values found on the 60 × 60 × 60 grid box with the value was 0.8406 and was exceeded the AUC value listed on DUD-E was 0.8339.[13] The 60 × 60 x60 grid box will be used in virtual screening.

The results of AUC value by using AutoDock Vina in Table 6, showed the four grid boxes above the ideal value (>0.5). The best values found on the 22.5 × 22.5 × 22.5 grid box with the value was 0.7973 and did not exceeded the AUC value of the previous research.[13]

Virtual screening by using AutoDock

The screening was performed on 1.410 ligand from Indonesian herbal database (HerbalDB). The best ten virtual screening results were Withanolide, Dehydrodeguelin, Sanggenol O, Cathafiline, Chitranone, Cathaformine, Hinokinin, 3-O-Methylcalopocarpin, Litebamine and 5-Hydroxy-6-oxocoronaridine. The result of binding energy and inhibition constant obtained from virtual screening can be seen in Table 7. Data of physicochemical properties of HerbalDB compounds were listed in Table 8.

Table 1: Binding energy data and RMSD value by using AutoDock.

Grid box (number of points)	Binding Energy/ΔG (kcal/mol)	RMSD (Å)
50 × 50 × 50	-8.69	1.4821
60 × 60 × 60	-8.95	1.3956
70 × 70 × 70	-8.79	1.874
80 × 80 × 80	-8.32	1.9871

Table 2: Binding energy data and RMSD value by using AutoDock Vina.

Grid box (number of points)	Binding energy/ΔG (kcal/mol)	RMSD (Å)
18.75 × 18.75 × 18.75	-9.50	17.699
22.5 × 22.5 × 22.5	-9.50	18.252
26.25 × 26.25 × 26.25	-9.40	18.321
30 × 30 × 30	-9.30	19.255

Table 3: EF calculation results on validation by using AutoDock.

	Grid box	EF1%	EF5%	EF10%	EF20%
This Research	50 × 50 × 50	3.9492	3.2770	3.9936	3.0249
	60 × 60 × 60	16.5869	17.2780	7.8429	4.0390
	70 × 70 × 70	16.5869	11.4528	6.5474	3.0249
	80 × 80 × 80	11.8478	7.5694	7.0446	3.6859
Previous Research [13]	-	21.8	-	-	-

Table 4: EF calculation results on validation by using AutoDock Vina.

	Grid box	EF1%	EF5%	EF10%	EF20%
This Research	18.75 × 18.75 × 18.75	2.3695	3.3482	2.1326	2.0630
	22.5 × 22.5 × 22.5	8.4627	12.2563	7.0446	3.1848
	26.25 × 26.25 × 26.25	8.4627	9.3346	6.0758	3.3482
	30 × 30 × 30	8.4627	8.7116	4.9960	3.2661
Previous Research [13]	-	21.8	-	-	-

Table 5: AUC calculation results on validation by using AutoDock.

	Grid box Unit)	Area Under Curve (AUC)
This Research	50 × 50 × 50	0.6715
	60 × 60 × 60	0.8406
	70 × 70 × 70	0.7892
	80 × 80 × 80	0.7526
Previous Research [13]	-	28.37

Table 6: AUC calculation results on validation by using AutoDock Vina.

	Grid box (Unit)	Area Under Curve (AUC)
This Research	18.75 × 18.75 × 18.75	0.7222
	22.5 × 22.5 × 22.5	0.7973
	26.25 × 26.25 × 26.25	0.7864
	30 × 30 × 30	0.7410
Previous Research [13]	-	28.37

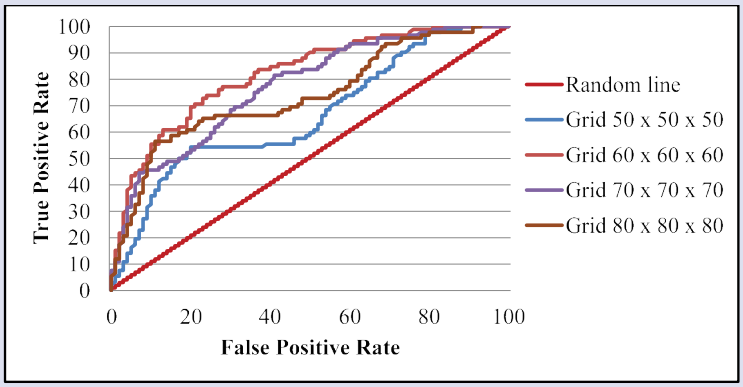

Figure 2: ROC curves of validation results by using AutoDock.

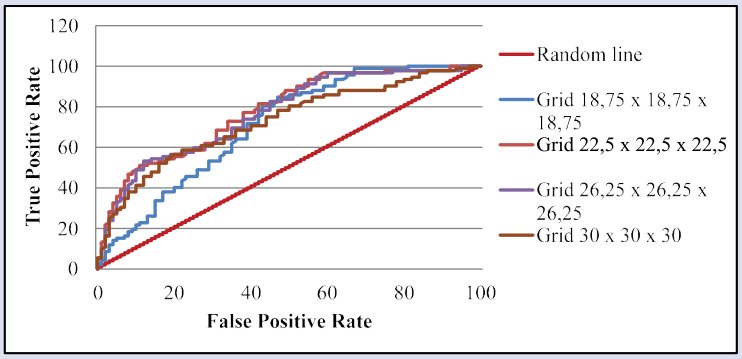

Figure 3: ROC curves of validation results by using AutoDock Vina.

Table 7: The best ten virtual screening results by using AutoDock.

Rank	Compound Name	Binding Energy/ΔG (kcal/mol)	Inhibition Constant (μm)
1	Withanolide	-11.07	7.71
2	Dehydrodeguelin	-10.4	23.8
3	Sanggenol O	-10.36	25.3
4	Cathafiline	-10.21	33.02
5	Chitranone	-10.19	34.06
6	Cathaformine	-10.16	35.43
7	Hinokinin	-9.55	100.72
8	3-O-Methylcalopocarpin	-9.55	99.97
9	Litebamine	-9.37	135.86
10	5-Hydroxy-6-oxocoronaridine	-9.28	158.64

Table 8: Data of physicochemical properties of HerbalDB compounds by using AutoDock.

Compound Name	Molecular Weight (g/mol)	Hydrogen Bonds Donor	Hydrogen Bonds Aceeptor	cLogP	Polar Surface Area (Å²)	Rotatable Bonds
Withanolide	470.606	0	1	3.655	89.950	8
Dehydrodeguelin	392.407	0	2	4.998	70.290	7
Sanggenol O	420.461	3	0	4.289	88.380	8
Cathafiline	369.373	1	2	3.718	85.280	5
Chitranone	374.348	3	2	4.559	89.997	8
Cathaformine	399.399	1	1	3.727	89.510	7
Hinokinin	354.358	0	0	4.594	78.860	4
3-O-Methylcalopocarpin	338.403	1	1	4313	47.920	8
Litebamine	339.391	2	3	3125	62.160	7
5-Hydroxy-6-oxocoronaridine	372.465	1	1	2.997	88.950	8

Analysis and visualization the results of virtual screening

The results of virtual screening by using AutoDock were visualized and interaction analysis were conducted by using PyMOL, LigandScout, Chimera and AutoDock Tools.

In the visualization results of ZMA co-crystal ligand, the interactions of amino acid residues that bind to 4EIY macromolecule by using AutoDock were ALA63, ILE66, ALA81, LEU85, PHE168, GLU169, MET177, TRP246, LEU249, ASN253 and ILE274.[16,17]

Based on Table 9, the visualization results found that in virtual screening by using LigandScout showed two compounds on active site bind to the same amino acid residues as ZMA interactions i.e. *Chitranone* and *3-O-Methylcalopocarpin*.

DISCUSSION

The ZMA ligand (4- (2-[7-amino-2-furan-2-yl [1, 2, 4] triazolo [1, 5-a] [1, 3, 5] triazine-5-yl) amino] ethyl} phenol) bonded to macromolecule 4EIY as Adenosine A_2A antagonist. The structure of 4EIY macromolecule was downloaded from PDB and was optimized using AutoDock Tools. The binding site of the macromolecule was determined using co-crystalized ligand coordinates using AutoDock Tools and was found at × = -0.471; y = 8.935; and z = 17.159.

The validation of molecular docking was conducted by redocking. RMSD value manually calculating using PyMOL. The RMSD value requirement is below 2Å.[18] RMSD value of AutoDock and Vina parameter is shown in Table 1 and Table 2. The optimization results by using AutoDock and Vina showed that the optimal grid box for 4EIY macromolecule was 60 × 60 × 60 showing lowest free binding energy value.

The ten best compounds taken was selected first to qualify for drug compounds that can cross the blood-brain barrier to the central nervous system. Physicochemical properties to be considered in medicinal compounds that may cross the blood-brain barrier include molecular weight <400-600, hydrogen bond donors <3, hydrogen bond acceptor <7, cLogP 2-5, polar surface area <90Å^2 and rotatable bonds <8.[19,20]

In the virtual screening results by using AutoDock showed two compounds have similarity amino acid residues interaction with ZMA co-crystal ligand, which were Chitranone and 3-O Methylcalopocarpin.

Chitranone is a compound from flavonol class. Flavonols are belonging to the class of flavonoids, a large group of polyphenolic compounds having a benzo-γ-pyrone structure and are ubiquitously present in plants. Structure of flavonol (Figure 4) different from many other flavonoids since they have a double bond between position 2 and 3 and an oxygen (a ketone group) in position 4 of the C ring, like flavones from which, however, they differ in the presence of a hydroxyl group at the position 3. Therefore, flavonol skeleton is a **3-hydroxyflavone**.[21,22] This compound can be found in *Plumbago zeylanicia* plant of the family Plumbaginaceae or often called daun encok. This compound has activities as antioxidant activity that reduce the degeneration of neuron and neuroprotective effect. The used part of the plants that was the root, bark and leaf, extracted by reflux method with 90% methanol solvent.[23,24]

3-O-Methylcalopocarpin is a compound from isoflavonoid class. Isoflavonoids are colorless polyphenols belonging to the class of flavonoid. While most structure of flavonoid have B ring attached to position 2 of C ring, structure of isoflavonoid (Figure 5) have a B ring attached to position 3 of C ring.[21] This compound can be found in *Erythrina variegata* plant of the family Fabaceae or often called dadap ayam. This compound has activities as muscle relaxant, anti oxidant, antimicrobial and anti convulsant. The used part of the plants that was the root, bark and leaf, extracted by maceration method with water, ethanol and chloroform solvent.[25,26]

Table 9: Interactions between chitranone and 3-O-Methylcalopocarpin with macromolecule residues.

	Chitranone	3-O-Methylcalopocarpin
AutoDock	ALA59, ALA63, ILE66, ILE80, ALA81, VAL84, LEU85, PHE168, GLU169, MET177, TRP246, LEU249, ILE274, ASN253, TYR271	ALA59, ALA63, ILE66, ALA81, VAL84, LEU85, PHE168, MET177, TRP246, LEU249, TYR271, ILE274, ASN253

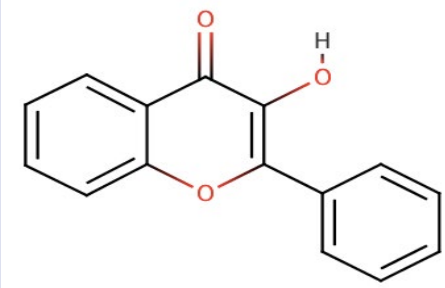

Figure 4: Structure of flavonol.

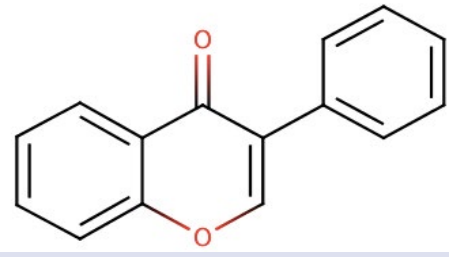

Figure 5: Structure of isoflavonoid.

CONCLUSIONS

The optimum validation parameters was obtained using positive and negative controls from A Directory of Useful Decoys-Enhanced (DUD-E) database using AutoDock with EF 1% value 16.5869 and AUC 0.8406. We also have done virtual screening using the optimized parameters to Indonesian Herbal Database as Adenosine A_2A antagonist. From this virtual screening, we obtained Chitranone and 3-O-Methylcalopocarpin, flavonoid compounds with binding energy -10.19 and -9.55 kcal/mol. These two compounds could be proposed to be developed as Adenosine A_2A antagonist.

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