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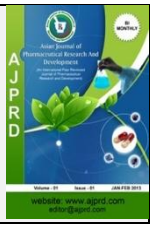

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Research Article

Studi Antiviral *Andrographis Paniculata*, For *Herpes Simplex Virus*tipe 1 (HSV-1) Treatment: In Slico Study

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A B S T R A C T

Herpes simplex virus type 1 (HSV-1) is a lifelong infectious disease. Research and drug development for this disease continues to be developed. Andrographis paniculata or commonly known as Sambiloto is a plant that is commonly used empirically as an HSV-1 drug. Further research is needed to determine the effectiveness of these plants as candidates for HSV-1 treatment. This study will determine several bioactive compounds contained in Sambiloto against the HSV-1 receptor in an insilico study which can be the basis for the discovery of new drugs in the treatment of HSV-1 infection.

Keywords: HSV-1, Andrographis paniculate, N, in silico studies

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INTRODUCTION

WHO published a study in March 2020 that estimated that about 5% of the population had at least one type of herpes. Approximately 491.5 million people are living with Herpes simplex Virus type 2 (HSV-2) infection which is equivalent to 13.2% of the world's population with an age of 15 to 49 years and approximately 3.7 billion people have Herpes simplex Virus type 1 (HSV) infection. -1) equivalent to 66.6% of the world's population aged 0 to 49 years. Herpes is a lifelong infectious disease, so it is estimated that the prevalence will continue to increase with age. Herpes infection affects millions of people around the world and can have health implications. More research is needed in the process of discovery, development and prevention for this type of infectious disease[1].

Research and drug development for HSV-1 infection continues to be developed. Modern medicines have also been found, but these medicines are relatively expensive and sometimes cannot be reached by the small community. Therefore, several natural-based treatments can be alternative treatments for HSV-1 infection[2].Empirically, one of the plants commonly used as HSV-1 treatment is sambiloto (*Andrographis paniculata*, N).The content of secondary metabolites contained therein such as diterpenoid and flavonoid derivatives which can provide pharmacological effects[3].Based on research Andrographis paniculata, N has an effect as anti-inflammatory, anti-

cancer, immunomodulator, anti-infection, anti-hepatotoxic, anti-atherosclerosis, anti hyperglicemic, and anti-oxidant[4]. This study report several bioactive compounds contained in Sambiloto against the HSV-1 receptor in an in-silico study which can be the basis for the discovery of new drugs in the treatment of HSV-1 infection.

MATERIALS DAN METHOD

Materials

Hardware: ASUS laptop with Intel® Core i3-6006U processor specifications CPU @ 2.0 GHz, 4GB DDR3L Random Access Memory (RAM), 500GB HDD, Microsoft Windows 10 operating system

Software: AutodockTools 4.0.1, Discovery Studio Visualizer 3.5, Chem3D Pro 12.0,

Web Server: Protein Databank (https://www.rscb.org), PubChem (https://pubchem.ncbi.nlm.nih.gov/). and Pre ADMET (https://preadmet.bmdrc.kr)

Receptor: 3D HSV-1 protein complex (pdb code is 2KI5)

Ligand: 3D structure of the test ligand (Andrographolide, 14-Deoxy-11,12-didehydroandrographolide, Isoandrographolide, Andrograpanin, Neoandrographolide, 14-Deoxyandrographolide) and control ligand (acyclovir)

Method

The receptors and ligands needed for this study were prepared in advance by adding a charge and hydrogen atoms using the Discovery Studio program and stored in the pdbqt format. Validation was performed by redocking the native ligand to the receptor in Autodock Tools 4.0.1 and the parameters were recorded for use in the docking process of the test and control ligands. Docking was performed on six test ligands and one control ligand with the following parameters: coordinate settings: x = 47.039 y = 84,304 z = 55.082; box sizes x, y, z = 40; walk 100 times. The resulting docking output is in the form of free bond energy (ΔG) and inhibition constant (Ki).

RESULT AND DISCUSSION

The docking process of the test compound from the *Andrographis paniculata*, N plant was carried out after previously validating the native ligand that binds to the 2KI5 receptor, namely Acyclovir to determine whether the 2KI5 receptor can be used. The receptors downloaded on the protein database website can be used during the docking process at the RMSD value generated from the redocking process below 2 Å. The RMSD value resulting from the redocking process of the original ligand (Acyclovir) with the 2KI5 receptor was 1.248 Å. These results indicate that the 2KI5 receptor can be used during the docking process of the test ligand. 3D structure of HSV-1 protein with code 2KI5 can be seen in Figure 1. 2D structure of ligand can be seen in Figure 2.

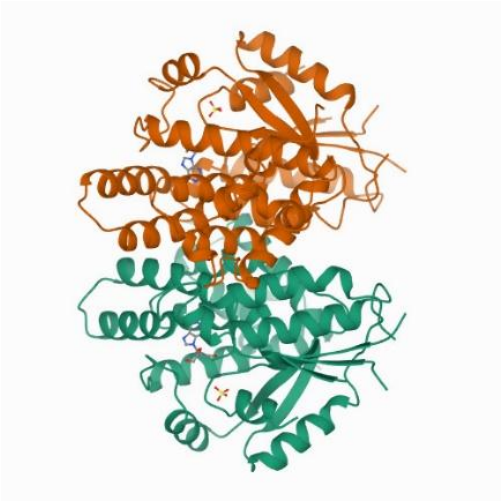
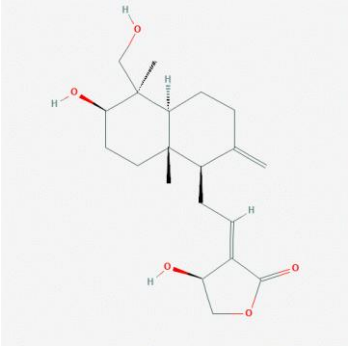
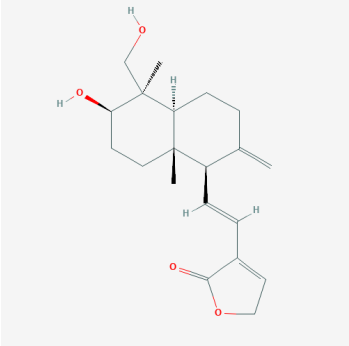


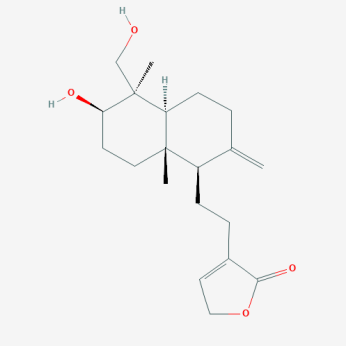
Figure 1: 3D structure of HSV-1 protein with code 2KI5.[5]



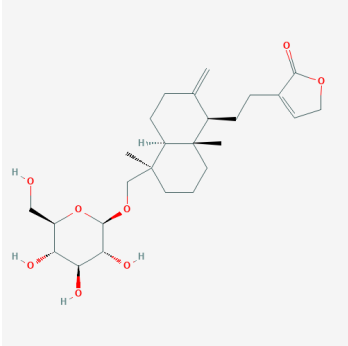
Andrographolide



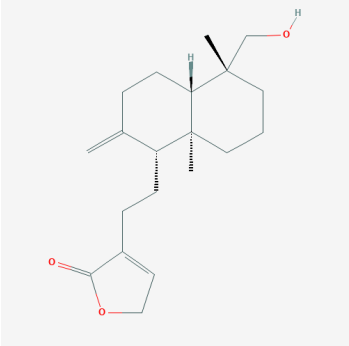
14-Deoxy-11,12-didehydroandrographolide



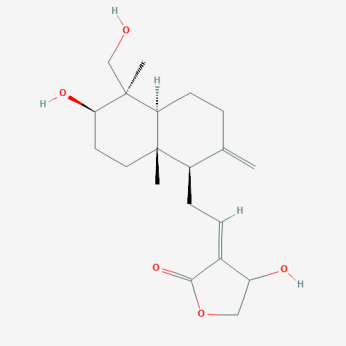
14-Deoxyandrographolide



Neoandrographolide



Andrograpanin



Isoandrographolide

Figure 2: 2D structure of ligand[6]

The molecular docking process was carried out on six test ligands and one control ligand using the same active site as in the validation process. The docking molecular results can be seen in Table 1.

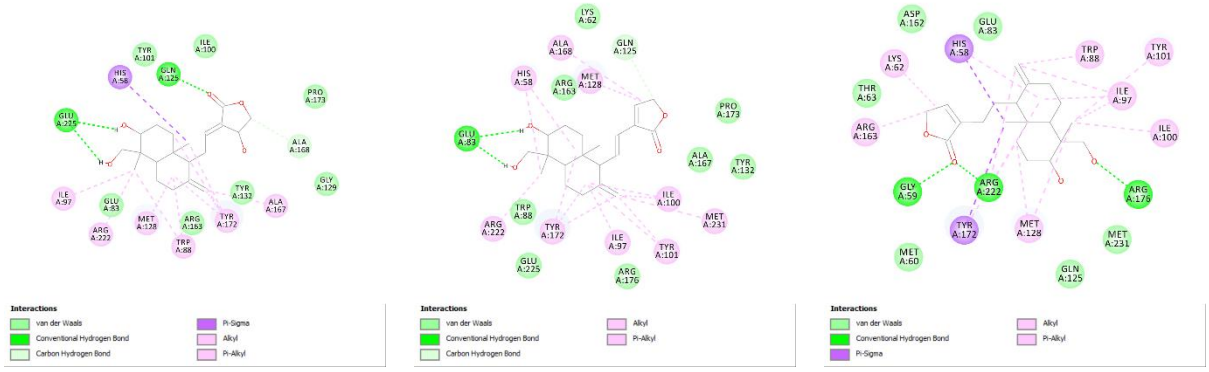
Table 1: Interaction test and control ligands to amino acid residues in 2KI5

Name of ligand	Interaction with amino acid residues	ΔG (kcal/mol)	Ki (μM)
Andrographolide	GLN A:125, GLU A:225 TYR A:101, ILE A:100, PRO A:173, ALA A:168, GLY A:129, TYR A:133, ARG A:163. GLU A:83	-8,97	0,26
14-Deoxy-11,12-didehydroandrographolide	GLU A:83 LYS A:62, ARG A:163, PRO A:173, ALA A:167, TRY A:132, ARG A:176, GLU A:225, TRP A:88	-9,25	0,16
14-Deoxyandrographolide	GLY A:59, ARG A:222, ARG A:176 GLU A:83, ASP A:162, THR A:63, MET A:60, GLN A:125, MET A:231	-9,70	0,07
Neoandrographolide	ALA A:167, ARG A:163, ARG A:222, TYR A:172 GLY A: 125, PRO A:173, ALA A:168, TYR A:132, ARG A:176, GLY A:59, LYS A:62, GLU A:83	-1,63	64370

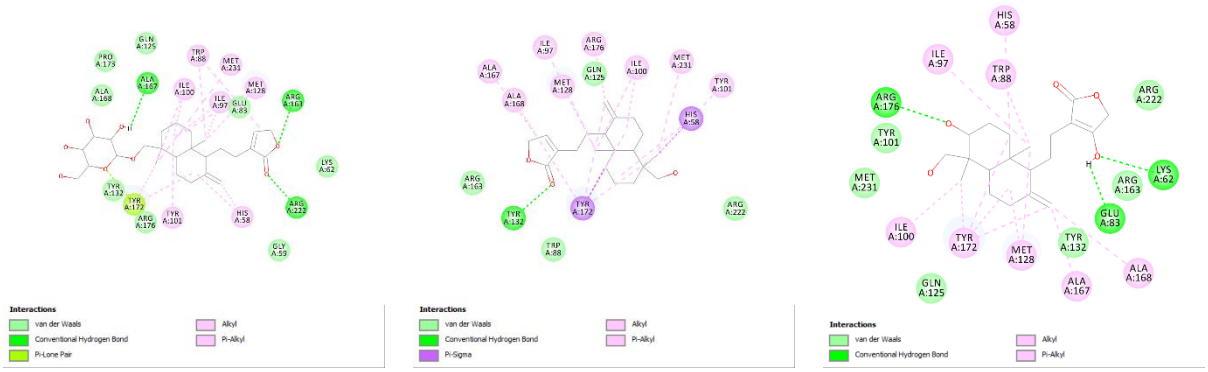
Andrograpanin	GLN A:125 GLN A:125, ARG A:163, TRP A:88, ARG A:222	-6,31	23,83
Isoandrographolide	ARG A:176, LYS A:62, GLU A:83 TYR A:101, MET A:231, GLN A:125, TYR A:132, ARG A:163, ARG A:222	-8,98	0,26
Acyclovir (Control)	GLN A:125, ARG A:176, ARG A:163 MET A:231, TYR A:101, TRP A:88, LYS A:62, GLU A:83	-6,91	8,59

The results of the interaction of the test and control ligands on the 2KI5 receptor produced data in the form of bond types, interactions with amino acid residues, Gibbs free energy (ΔG), and inhibition value constants (Ki). The original Acyclovir ligands form hydrogen bonds with three amino acid residues, namely GLN A: 125, ARG A: 176, and ARG A: 163 and van der Waals bonds with five amino acid residues, namely MET A: 231, TYR A: 101, TRP A : 88, LYS A: 62, and GLU A: 83. Of the six test compounds from *Andrographis paniculata*, N, the ligands 14-Deoxy-11, 12-didehydroandrographolide and Neoandrographolide do not have hydrogen bonds with the same amino acids as the original ligands. The ligands Andrographolide, 14-Deoxyandrographolide, Andrograpanin, and Isoandrographolide have the same hydrogen bonds as the original ligands, namely GLN A: 125, ARG A: 176, GLN A: 125, and ARG A: 176.

The value of free energy gibbs (ΔG) shows the value of the stability of the bond between the receptor and the ligand. A small (negative) free energy value will indicate the better the stability of the bonds formed and also produce a strong bond.[7] The smaller the inhibition constant value, the better the ligand will be used as a drug candidate. Based on the results of the docking that has been done, it is known that all the test ligands have a smaller Ki value than acyclovir except Neoandrographolide and Andrograpanin. The results can be seen in Table 1. The 2D visualization of interaction showed in Figure 3.



Andrographolide 14-Deoxy-11,12-didehydroandrographolide 14-Deoxyandrographolide



Neoandrographolide Andrograpanin Isoandrographolide

Figure 2: The 2D visualization of interaction

All compounds were examined for toxicity and ADME using pre-ADMET prediction. The pharmacokinetic parameters obtained were absorption [(Human Intestinal Absorption) and Caco-2] and distribution (Plasma Protein Binding). In toxicity studies, the parameters used were mutagenic and carcinogenic. The results of the pre-ADMET predictions are shown in Table 2.

Table 2: The results of the pre-ADMET predictions[7]

Compounds	Absorption		Distribution	Mutagenic	Carcinogenic
	HIA (%)	Caco-2 (nm sec^{-1})	PPB (%)		
Andrographolide	89.892	20.414	77.754	-	-
14-Deoxy-11,12-didehydroandrographolide	94.261	20.906	89.479	+	+
14-Deoxyandrographolide	92.833	15.977	92.698	+	+
Neoandrographolide	88.521	18.514	93.716	+	-
Andrograpanin	92.603	19.827	100.000	-	-
Isoandrographolide	94.941	27.175	100.000	+	+

The pre-ADMET study showed that all test ligands had plasma protein bonds above 90% which indicated a strong bond, had moderate permeability to Caco2 cells and were well absorbed in the intestine.

CONCLUSION

Docking against *Andrographis paniculata*, N has been successfully carried out against the 2KI5 receptor as HSV-1. Six compounds contained in Andrographis paniculata, N were compared their interactions with acyclovir. Based on the research that has been done, it is known that the compounds that have the potential to be HSV-1 are Andrographolide, 14-Deoxy-11,12-didehydroandrographolide, 14-Deoxyandrographolide, and Isoandrographolide. The results for Ki and ΔG showed better values than acyclovir and the prediction of pre-ADMET was good despite the risk of carcinogens and mutagens. To get better results, it is necessary to modify the structure.

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