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In-Silico Test Against Sinensetin Activity as One of the Flavoid Natural Compounds of Orthosiphon Stamineus in Crushing Kidney Stones

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In-Silico Test Against Sinensetin Activity As One Of The Flavoid Natural Compounds Of *Orthosiphon stamineus* in Crushing Kidney Stones

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Abstract. *Orthosiphon stamineus* is a type of herbal plant that contains many active chemical compounds, one of which is sinensetin which can be used as a drug in destroying kidney stones. This research The aim of this study was to determine the bioactivity of the sinensetin compound *in destroying* kidney stonesbased on reverse docking studies. The structure of the chemical constituents of sinensetin collected from the published literature. Water molecules and ligands are removed using PyMOL v1.7.4.5 (Schrödinger) software. Test Molecular docking was performed using PyRx 0.8 software. Prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of compounds were predicted using Swissadme. Research result showed that sinensetin had greater potency in destroy kidney stones based on their binding affinity and interactions between the molecules. Sinensetin binding affinity to proteinP-Glycoprotein (P-GP) is -8.6, while the binding affinity P-Glycoprotein (P-Gp) with the control compound of tamsulosin was -9.5. The AMES test shows that sinensetin is neither a potential mutagen nor a carcinogen.

1. Introduction

In Indonesia, there are about 50 thousand patients with kidney failure. Of this number, only 4,000 people are able to perform dialysis. Of course, the cause is the high cost of treatment. Therefore, it is necessary to find other alternatives for the treatment of kidney stones, one of which can be done with the Kumis Kucing herbal plant (Fery, 2021).

Tezuka et al. (2000); Hossain and Rahman (2011) stated that six flavonoid compounds isolated from O . leaves. *stamina* Based on their structure they are known as eupatorin, sinensetin, salvigenin, 5-hydroxy-6,7,3',4'-tetramethoxyflavone, 6-hydroxy-5,7,4'-trimethoxyflavone and 5,6,7,3'-tetramethoxy-4'-hydroxy-8-C-prenylflavone. Sinensetin is a compound that does not show toxicity properties.

Tamsulosin belongs to the class of alpha blockers (*alpha blocker*). This drug works by relaxing the muscles in the prostate gland and bladder, so urine can flow more smoothly. Please note that tamsulosin cannot cure or shrink the size of an already enlarged prostate (Guo, 2020). Side effects that may appear after taking tamsulosin include:dizzyor dizziness, runny or stuffy nose, impaired ejaculation anddrowsiness (Pattanaik, 2019).

When compared with tamsulosin as a chemical drug in destroying kidney stones, the bioactive compound sinensetin from herbs *O. stamina has better effectiveness.* In this study, we found the bioactivity of *O. stamina* to destroy kidney stones based on Reverse Docking and ADME predictions.

2. Materials And Methods

2.1 Ligand Preparation

Chemical compound structure *O. stamineus* (sinensetin) collected from the published literature. The 3D chemical structure and SMILES ligand (sinensetin) were taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with ID number: CID145659 and Canonical Smiles: COC1=C(C=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC)OC)OC)OC. Two dimensional (2D) and three dimensional (3D) ligand chemical structures were sketched using Avogadro and Discovery Studio and saved in PDB format.

2.2 Target Selection

Potential protein target candidates for docking were prepared using 3 data banks, namely: Pharmmapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Prediction (www.swisstargetprediction). .ch) and validation using Uniport (https://www.uniprot.org). Proteins were collected and validated with PDB (Protein Data Bank https:///www.rcsb.org/pdb) then protein was prepared using protein cleaner to remove water molecules from the structure. Water molecules and ligands were removed using PyMOL v1.7.4.5 (Schrödinger) Software (Sulfahri et al., 2019). In this study, the target protein used wasP-Glycoprotein (P-Gp) with the code 6C0V of PDB, because P-Glycoprotein (P-Gp) is a compound that acts as a diuretic for kidney stones.

2.3 Docking Molecules

Molecular docking experiments were carried out using PyRx 0.8 software. The docking process is carried out using the Vina Wizard feature integrated into the PyRx 0.8 software (Sulfahri et al., 2019) which reacts to the natural compound sinensetin, the target protein P-Glycoprotein (P-Gp) and the control compound (activator of the P-Glycoprotein compound (P-Glycoprotein). P-GP)). The activator compound will be a positive control in the docking process. The P-Glycoprotein (P-Gp) activator compound is Tamsulosin.

2.4 Molecular Visualization Interaction and Small Molecules

The interactions between the ligand (sinensetin) of the target protein (P-Glycoprotein (P-Gp)), and the known inhibitory target protein (Tamsulosin) were visualized and analyzed using PyMol Software v1.7.4.5 (Schrödinger).

2.5 Compound's Properties and ADMET Predictions

Swissadme (http://www.swissadme.ch) and admetSAR (lmmd.ecust.edu.cn: 8000) were used to predict and significant descriptors of the Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds.

3. Results and Discussion

The leaves of the cat's whiskers are efficacious as urine laxative (diuretic), anti-inflammatory (anti-inflammatory), remove heat and moisture, and destroy bladder stones (Dalimartha 2000). The results of research conducted in various Asian countries on the efficacy of cat whiskers prove that 40% of patients from 23 patients with kidney stones experienced a decrease in the size of kidney stones by up to 0.5 cm after consuming this herb regularly (Fery, 2021).

The structure of natural compounds with control compounds and target proteins, visualized in 3 dimensions (3D) using PyMol (Figures 1 and 2). Through the reverse docking technique, it can be seen that sinensetin has the potential to destroy kidney stones. The interaction of sinensetin with P-Glycoprotein (P-Gp) was compared with tamsulosin as a control compound. Based on the results of reverse docking, the binding affinity of P-Glycoprotein (P-Gp) to tamsulosin showed a lower binding affinity than P-Glycoprotein (P-Gp) with sinensetin.

The number of binding affinities describes the potential of a compound or ligand to interact with its protein (target protein). If the ligand has a lower binding affinity, it will be stronger to inherit the target protein (Baker et. al. 2007). Therefore, the lower the binding affinity, the lower the energy required for the ligand to interact with the target protein.

P-Glycoprotein (P-Gp) which acts as a diuretic to destroy kidney stones has an interaction with natural compounds from herbs *O.stamineus* which has been visualized in 3D in the PyMol software. The binding affinity of sinensetin with P-Gp was -8.6, while the binding affinity of P-Gp with the control compound tamsulosin was -9.5. Based on the results of the study, comparing the strengthening of sinensetin with tamsulosin against P-Gp has shown that sinensetin has the ability to destroy kidney stones.

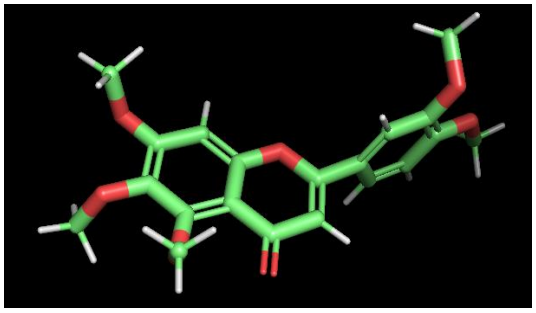

Figure 1. 3D chemical structure of Sinensetin Using PyMol software

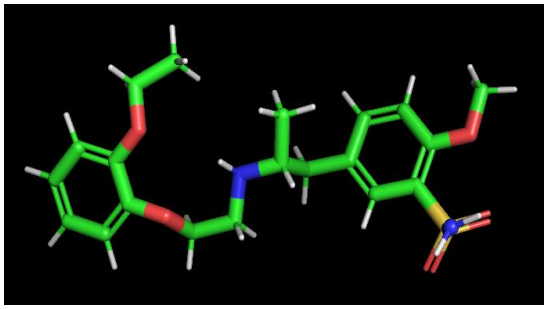

Figure 2. 3D chemical structure ofTamsulosin Using PyMol software

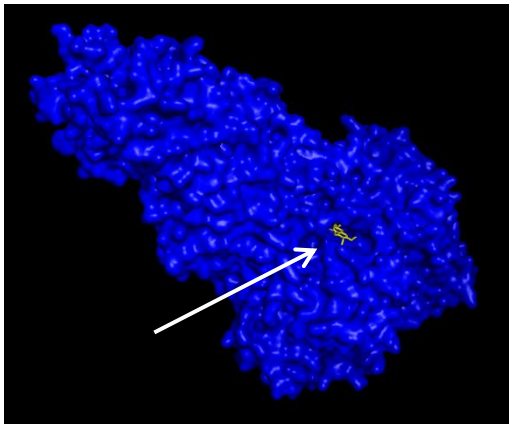

Figure 3. Binding of Plant Ligands (Sinensetin) and Target Proteins (P-Glycoprotein (P-Gp))

Table 1. Results of Docking P-Glycoprotein (P-Gp) with Ligands and Control Activators

Origin of Compound	Ligand	Binding affinity (kcal/mol)
Orthosiphon stamineus	Sinensetin	-8.6
Control	Tamsulosin	-9.5

Most drugs are intended to treat several chronic diseases. Thus, the concentration of a drug must be consistent (Doogue MP., 2013). The results of this study indicate that sinensetin from*O.stamineus* not a potential mutagen and not a carcinogen. Ligands are considered to have the potential to enter the cell membrane and be absorbed by the body if they meet Lipinski's rules.

4. Conclusion

From the result of pFrom this research, it can be concluded that sinensetin which is the active compound of the herbal Orthosiphon stamineus has the potential as a drug in destroying kidney stones based on its binding affinity with intermolecular interactions, namely -8.6.

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