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# In-Silico Test of Activity Apigenin as a Natural Compound in Reducing Uric Acid Level

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# IN-SILICO TEST OF ACTIVITY APIGENIN AS A NATURAL COMPOUND IN REDUCING URIC ACID LEVEL

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This study aims to determine the bioactivity of these compounds apigenin on *Apium graveolens* as a medicine lowering uric acid levels. Chemical structure of compound apigenin contained in *Apium graveolens* taken from the literature. The target protein used is Interleukin 17-A. Water molecules were removed using PyMol v2.5.2 Software. Docking between the target protein and the compound was performed using PyRx-Python Prescription 0.8 Software. The results showed that the apigenin compound has a greater potential for lowering uric acid levels compared to control compounds. The affinity value of Interleukin 17-A with Apigenin is -6.4 while the affinity value of Interleukin 17-A with Allopurinol is -4.8. Compound toxicity test Apigenin The results showed that this compound was not a potential carcinogen.

## 1. Introduction

The cause of gout is high levels of uric acid in the blood and a diet that contains lots of purines[1]. The effect of hyperuricemia on joints, kidneys, and other organs is a sign of gout. If left untreated, it can lead to death[2]. Men have normal uric acid levels of 0.18–0.42 mmol/L (3.0–7.0 mg/dL) and in women the levels are 0.13–0.34 mmol/L (2.2– 5.7 mg/dL)[3]. WHO states that hyperuricemia sufferers are increasing every year, especially in developing countries, including Indonesia[4].

According to WHO, herbal medicines have been used as complementary medicine by Latin countries and support the efficacy and safety of herbal medicines[5]. Celery or *Apium Graveolens* is a plant from the Apiaceae family. *Apium Graveolens* can reduce uric acid levels through boiled water[6]. *Apium Graveolens* lives in man-made habitats[7] Stem herbaceous, smooth, segmented, branched, erect, pale green. Compound thin leaves, young leaves widening or extending from the base, shiny green, at the edges of the leaves are lobed and jagged, alternating leaf arrangement[8]. Flavonoids, saponins, 1% tannin, essential oils, apiin, apigenin, graveobioside A, graveobioside B, choline, asparagines, bitter substances, and vitamin A are the ingredients contained in the celery plant. Apigenin is a compound that can inhibit the formation of uric acid[6].

## 2. Materials and Methods

### *2.1. Ligand Preparation*

The chemical structure of Apigenin was collected from the published literature. The chemical 3D structure and SMILES ligand (apigenin) were taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with ID numbers: CID 5280443 and Canonical SMILEC1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O. The chemical structures of two-dimensional (2D) and three-dimensional (3D) ligands were sketched using Avogadro and saved in PDB format.

2.2. Target Selection

Potential protein target candidates for docking based on published literature. Collected and validated proteins with PDB (Protein Data Bankhttp://rcsb.org/pdb). The protein used is clean protein. Water molecules from the ligands were removed using PyMOL v.2.5 Software. In this study, the target protein used was Interleukin-17A with code 5VB9 from PDB.

*2.3. Molecular Docking*

Molecular docking experiments were carried out using PyRx 0.8 software. The process is carried out using the Vina Wizard feature integrated into the PyRx 0.8 software which reacts to the natural compound apigenin, the target protein Interleukin-17A, and the control compound.

*2.4. Molecular and Small Molecule Interaction Visualization*

The interactions between natural ligands, target proteins, and known control compounds were visualized and analyzed using PyMOL v.2.5 Software.

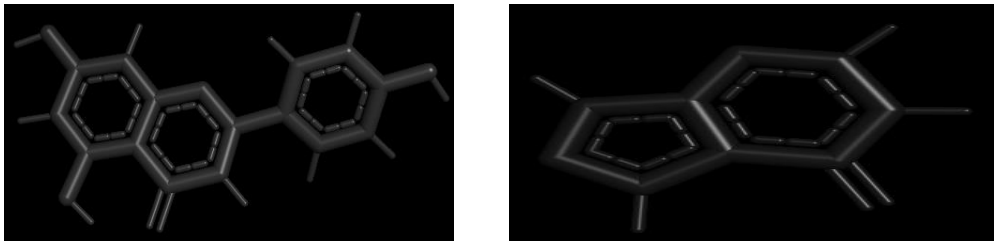
*2.5. Compound Properties and Prediction of ADMET*

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

## 3. Results and Discussion

The main compound found in *Apium Graveolens* is apigenin. Polyphenols which are flavonoids (apigenin) play a dual role in the management of gouty arthritis, namely; the Inhibition of xanthine oxidase thereby reducing uric acid production and acts as an anti-inflammatory agent through inhibition of pro-inflammatory genes involved in canonical inflammatory pathways and apoptosis. The inhibited pathway is the NF-B signaling pathway that leads to transcription of IL-1 and activation of the inflammasome that allows the release of IL-1 into the extracellular space. Interleukin-17A has been implicated in the pathogenesis of gouty arthritis[9].

The structure of natural compounds and control compounds, as well as target proteins, were visualized in three dimensions (3D) using PyMol (Figure 1). Through the reverse docking technique, the potential of apigenin as an antihyperuricemia can be determined. The interaction of apigenin with Interleukin-17A compared to the control compound Allopurinol showed that Apigenin was more bound to Interleukin-17A than Allopurinol. When the affinity of the ligand is low, it will inherit the target protein more strongly. Therefore, the lower the binding affinity, the lower the energy required for the ligand to interact with the target protein[10]. The binding affinity of apigenin with Interleukin-17A is -6.4 while the binding affinity of Allopurinol with Interleukin-17A is -4.8. Based on the results of the study, Apigenin and Allopurinol against Interleukin-17A showed that apigenin could bind to target proteins.



(A) (B)

Figure 1. (a) 3D chemical structure of Apigenin and (b) Allupurinol shown by PyMol software

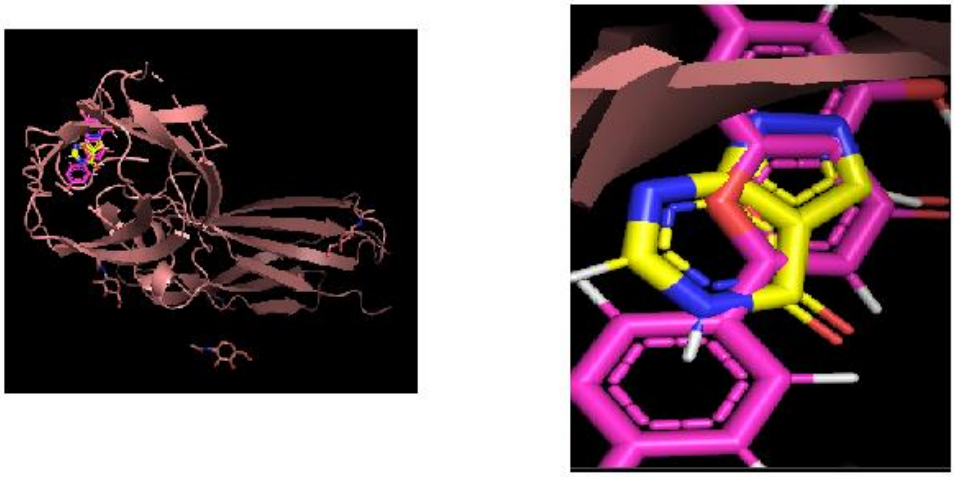


Figure 2. The binding site of Apigenin (purple), Allopurinol (yellow blue) and Interlaukin-17A (band-shaped)

**Table 1.**Results of Interlaukin-17A reverse docking with plant and control ligands

| **Ligand** | **Affinity Binding** |
|---|---|
| Interleukin-17A and apigenin | -6.4 |
| Interleukin-17A and Allopurinol | -4.8 |

Medicines are aimed mostly at treating chronic diseases[10]. The side effects of apigenin compounds with ADMET observations and predictions were evaluated and associated with cell permeation, metabolic processes, and bioavailability, the results showed Apigenin was not a carcinogen. This compound should not be extracted because it is potentially toxic. The search results showed that apigenin complied with the rules of Lipinski, Ghose, Veber, Egan, Muegge, and Bioavailability score 0.55. Meanwhile, the control compound Allopurinol did not meet the Ghose and Muegge rules.

## 4. Conclusion

This study proves that apigenin has potential as anti hyperuricemia based on its binding affinity with -6.4 and intermolecular interactions. *Apium Graveolens* contains apigenin which is a potential antihyperuricemic drug according to the rules of Lipinski, Ghose, Veber, Egan, and Muegge, and a Bioavailability Score of 0.55.

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