**In silico** approach of antidiabetic compounds from *Caesalpinia crista* seed through docking analysis and ADMET predictions

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**Abstract.** *Caesalpinia crista* (Fabaceae) is one of the herbs traditionally used as a drug for the diabetic. This study aimed to discover bioactivity of the α-caesalpin compound from *Caesalpinia crista* for antidiabetic based on reverse docking studies. Structures of chemical constituents of *Caesalpina crista* (α-caesalpin) was collected from published literature. The water molecule and ligands were removed by using PyMOL v1.7.4.5 Software (Schrödinger). Molecular docking experiments were performed using the PyRx 0.8 software. Prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics and Druglikeness properties of the compounds were predicted using Swissadme. The results showed that α-caesalpin has greater potential as an antidiabetic based on its binding affinity and intermolecular interactions. The binding affinity of α-caesalpin with NOS₃ protein is -7.9, while binding affinity NOS₃ with the control compound β-estradiol is -10.1. AMES Test showed that α-caesalpin is not potential mutagens and not carcinogens. Druglikeness prediction showed that α-caesalpin fulfil the rules of Lipinski, Ghose, Veber, Egan and Muegge with 0.55 Bioavailability Score.

1. Introduction

In 2013, WHO estimated that 422 million people or 6.02% of the 7 billion people of the world suffer from Diabetes Mellitus (DM) and it is predicted that by 2025 it will seek up to 333 million people [1]. International Diabetes Federation (IDF) in 2013 stated that the prevalence of DM in the world was 1.9% and had made DM the seventh leading cause of death in the world [2,3]. Diabetes Mellitus was caused by the presence of insulin resistance and relative insulin deficiency and it was accounted for around 95% of DM presentation [4,5].

Plant-based drugs as an alternative medicine were recommended by the World Health Organization (WHO), because of their perceived effectiveness, with minimal side effects and relatively low costs [6]. *Caesalpinia crista* is one of the herbs traditionally used as a drug for the diabetic [4]. *Caesalpinia crista* is a plant that belongs to the Fabaceae family [7]. These plants generally include South Asia including India, Indonesia and Myanmar [8]. This plant has a height of approximately 10 m and grows wild along mountainous cliffs and broad land [9]. *Caesalpinia crista* has very unique seeds. The seeds of this plant have spines like fine hairs on the entire surface [10]. The seeds are green, big and thick also become the uniqueness of this plant from plants of the same genus [11].

By recent purposes of *Caesalpinia crista* was to use as the conventional herb of some diseases, including diabetic. The seeds of *Caesalpinia crista* are found to contain some chemical constituents, which is consisted by furanoditerpenes-caesalpin-α, caesalpin-γ, caesalpin-δ, caesalpin-ε, caesalpin, and caesalpin-F [12]. In this present study, we discover bioactivity *Caesalpinia crista* for antidiabetic based on Reverse Docking and ADME prediction.
2. Materials and Method

2.1. Ligands Preparation

Structures of the chemical compound of *Caesalpina crista* (α-caesalpin) was collected from published literature. Chemical 3D structure and SMILES of ligand (α-caesalpin) taken from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with number ID: CID 73823459 and Canonical Smile : CC(=O)OC1C2C(CC3=C(C2=C(O)C)C=CO3)C4(C(=O)CCC(C4(C1OC(=O)C)O)(C)=O)C). The two-dimensional (2D) and the three-dimensional (3D) chemical structures of the ligands were sketched using Avogadro and Discovery Studio and were saved in PDB format.

2.2. Target Selection

The protein potential target candidates for docking was prepared using 3 databanks, i.e: Pharmmapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Prediction (www.swisstargetprediction.ch) and validate using Uniport (https://www.uniprot.org). The protein that was collected and validated with PDB (Protein Data Bank https://www.rcsb.org/pdb) than proteins were prepared using clean protein to remove the water molecules from the structure. The water molecule and ligands were removed by using PyMOL v1.7.4.5 Software (Schrödinger). In this study, the target protein used was NOS3 with the SU09 code of PDB, because NOS3 (eNOS) is a compound in the form of an enzyme that plays an essential role in the fidiological and pathophysiological processes of β-pancreatic cells and regulates insulin secretion from β-pancreatic cells [13].

2.3. Molecular Docking

Molecular docking experiments were performed using the PyRx 0.8 software. The reverse docking was carried out using the Vina Wizard feature integrated into PyRx 0.8 software which reacts to the natural compound α-caesalpin, the target protein NOS3 and the control compound (activator compound NOS1). Activator compounds will be a positive control in the docking process. The activator compound of NOS3 is β-estradiol. β-estradiol is a compound that regulates the secretion of NOS3 production in β-pancreatic cells [14].

2.4. Visualization of Molecule and Small Molecule Interaction

The interactions between ligands (α-caesalpin) target protein (NOS3), and known inhibitors of target protein (β-estradiol) visualized and analyzed using PyMol v1.7.4.5 Software (Schrödinger)

2.5. Compound’s Properties and ADMET Predictions

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

3. Results and Discussion

The main compounds found in *Caesalpinia crista* is α-caesalpin. α-caesalpin compounds are known to interact with one type of protein in pancreatic beta cells. Based on Swiss target prediction result which has been found that alpha caesalpin crista has a connection with an enzyme of cell beta pancreatic. One type of protein is Nitric Oxide Synthase 3 (NOS). Nitric Oxide Synthase (NOS) consist of NOS1 (nNOS), NOS2 (iNOS), and NOS3 (eNOS) [2].

Nitric Oxide Synthase (NOS) plays an important role in the fidiological and pathophysiological processes of pancreatic beta cells [2]. NOS1 is an enzyme that regulates insulin secretion from the pancreatic beta and protects cells from apoptosis. The activator compounds of NOS3 is β-estradiol [13]. β-estradiol compounds responsible to regulate secretion from the production of NOS3 in pancreatic beta cells. Beta-estradiol is one of estrogens types which prevent the beta pancreatic cell from apoptosis and insulin deficiency [17].

Structure of natural compounds with control compounds and target proteins, visualized in 3 dimensions (3D) using PyMol (Figure 1). Through reverse docking technique can be known the potential of an α-caesalpin has the potential as antidiabetic. Interaction of α-caesalpin with NOS3
compared to β-estradiol as the control compound. Based on reverse docking results, the binding affinity of NOS3 protein to β-estradiols showed lower binding affinity than NOS3 protein to α-caesalpin.

The number of binding affinities illustrate the potential of a compound or a ligand to interact with its protein (protein target). If the ligand has lower binding affinity, it will be stronger to inherit the protein target [15]. Hence, the lower binding affinity leads the lower energy needed of ligand to interact with the protein target. The NOS3 protein plays a role in the regulatory process of pancreatic beta cells in producing insulin has an interaction with natural compounds from the Caesalpinia crista plant that has been visualized in 3D in PyMol software. The binding affinity of α-caesalpin with NOS3 protein is -7.9, while binding affinity NOS3 with the control compound β-estradiol is -10.1. Based on the result, comparing the strengthen of α-caesalpin with β-estradiol to NOS3 has shown that α-caesalpin has an ability in attaching the protein of beta pancreatic cell.

![Chemical 3D Structure of alpha-caesalpin and Beta Sitosterol](image1)

**Figure 1.** (a) Chemical 3D Structure of alpha-caesalpin and (b) Beta Sitosterol were showed by software PyMol

![Binding Site of α-caesalpin](image2)

**Figure 2.** Binding Site of α-caesalpin (purple), β-estradiol (blue) with NOS3 (green) α-caesalpin

| Ligand           | Binding Affinity |
|------------------|------------------|
| NOS3 and α-caesalpin | -7.9            |
| NOS3 and β-estradiol  | -10.1           |

**Table 1.** The result of Reverse Docking NOS3 with ligand and control activator
Most of the drugs have aimed for treating some chronic diseases. Thus, the concentration of a drug must be consistent [18]. The side effect of the α-caesalpin compound for the body has observed by ADMET predictions which were evaluated and linked to cell permeation, metabolism process and bioavailability. As revealed by the result of this study (AMES Test), the result shows that α-caesalpin is not potential mutagens and not carcinogens. The Ligands is considered to have the potential to enter the cell membrane and be absorbed by the body if they meet Lipinski's rules. The search results show that α-caesalpin fulfills the rules of Lipinski, Ghose, Veber, Egan and Muegge with the Bioavailability Score 0.55.

4. Conclusion
This study proved that α-caesalpin has potential as an antidiabetic based on its binding affinity with -7.9 and intermolecular interactions. Caesalpinia crista contains α-caesalpin which is potential antidiabetic drug according to Lipinski, Ghose, Veber, Egan dan Muegge rule and 0.55 Bioavailability Score.

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