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In Silico Study of Avocado (*Persea Americana* Mill.) Seed Compounds Against PBP2a Receptor on *Staphylococcus aureus*

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ABSTRACT

The nosocomial infection causes 1,4 million mortality every day in the world. *International Nosocomial Infection Control Consortium* (INICC) data shows that 84,4% nosocomial infection is caused by *S. aureus* that can cause skin infection. Avocado (*P. americana*) seed has been reported as an antibacterial agent and used for dermatological applications. This research was aimed to know the potential of antibacterial activity of ethanolic extract of avocado seed in *silico* study. The *in silico* test used *molecular docking* method with PyRx *software* between PBP2a as receptor and phytochemical compounds in avocado seed as a ligand. The result showed that rutin compound had the best potential to bind PBP2a (*binding affinity*: -18,2 kcal/mol). Thus, phytochemical active compounds in avocado seed can be recommended as an antibacterial drug and can increase the number of fibroblast cells caused by *S. aureus*.

Keywords:*In Silico, avocado seed, PBP2a, Staphyloccus aureus*

INTRODUCTION

Study outcome conducted by the International Nosocomial Infection Control Consortium (INICC) from 36 countries in Latin America, Asia, Africa, and Europe report that 84.4% of nosocomial infections caused by *Staphylococcus aureus* [1]. These bacteria cause primary infection of the skin and soft tissue such as folliculitis, furunculosis, and impetigo. National Center for Biotechnology Information (NCBI) data shows that cases of skin and soft tissue infections caused by *S. aureus* amount to 483-537 cases each year from 1991-2002 in France.

Nowadays, *S. aureus* infection is increasing due to its high resistance to various types of antibiotics. This resistance is caused by changing normal PBP2 into PBP2a which has a very low affinity to β-lactam antibiotic [2]. Medicinal plants can be used to treat it because of fewer side effects [3], for example avocado (*Persea americana* Mill.) seeds. The avocado seed contains saponins, tannins, flavonoids, alkaloids and phenol [4], which have antibacterial activity against *S. aureus* in vitro with inhibition zone 30 mm that means the strong category [5]. However, the mechanism of its inhibition is still unknown due to the most active compound of avocado seed that act as an antibacterial agent is still unknown.

This research using in silico study with molecular docking method. This study may be the first step that more effective drug design before in vivo and in vitro studies [6]. The in silico study may demonstrate the potential of ligand and receptor by binding energy score and that activity [7, 8]. The lowest binding energy indicates the great potential for bonding between the ligand and its receptor [9]. Therefore, in silico study also provide bonding information that occurs and can be known the potency of its pharmaceutical drugs.

Avocado seed compounds that have antibacterial activity both gram negative and positive on in vitro such as: chlorogenic acid, catechin, epicatechin, epicatechin gallate, caemferol, rutin, protochatechuic acid, vanillic and linoleic acid [10,11] . This study use molecular docking method between PBP2a (receptor) and active compound of avocado seed (ligand).

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MATERIALS AND METHODS

Preparation

This study used some software PyMOL, Pyrx, and Discovery studio 2016. This study used 3D ligand structures (protocatechuic acid, kaempferol, catechin, vanillic acid, rutin, chlorogenic acid, epicatechin and epicatechin gallate as well as cefixime antibiotics), the 3D structure of PBP2a receptors and quinazolinone protein structure.

Antibacterial Activity Prediction

The SMILE of active compound of avocado seed is downloaded from http://pubchem.ncbi.nlm.nih.gov/ and then analyze Get prediction with PASS software at http: //www.pharmaexpert.ru/passonline.

Ligan Structure Preparation

The 3D structure of ligands from the active compound of avocado seed is downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov) and save in SDF format.

Protein Receptors Preparation

The reference protein that used is quinazolinone, obtained from Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). PBP2a protein sequences downloaded from UniProt (http://uniprot.org/) are modeled on the Swiss Model (http://swissmodel.expasy.org/) and save in PDB format. Separation of proteins from unnecessary molecules using PyMOL software and save in PDB format.

Docking Receptors with Ligands

Docking PBP2a receptors with ligands using Autodock Vina in PyRx software. The separated receptor is inputted and the macromolecule structure is formed. Ligands inputted from sdf format and then the process of docking.

RESULTS AND DISCUSSION

The docking's result of various ligands of the active compound in the avocado seed and the PBP2a receptor (Figure 1) showed that the rutin compound has the lowest binding energy (-18.2 kcal/mol) compared to other compounds.

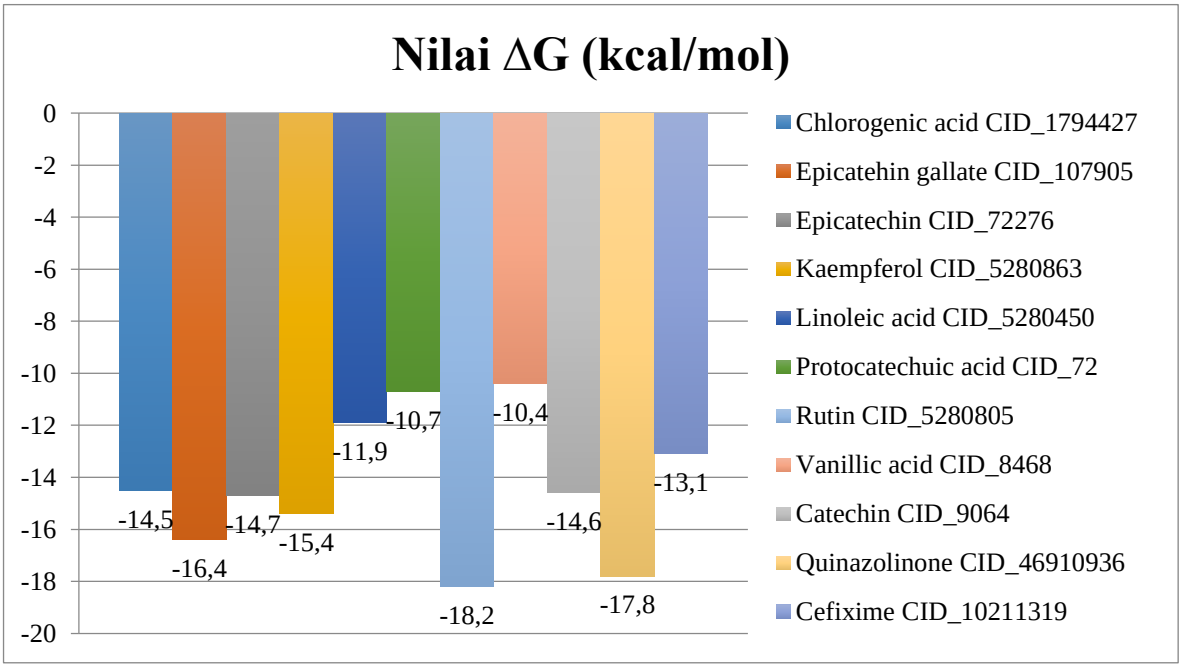

Figure 1. Binding affinity (the result of docking between PBP2a and active compound of *P.americana* Mill.)

The docking's result of various ligands of the active compound in the avocado seed and the PBP2a receptor (Figure 1) showed that the rutin compound has the lowest binding energy (-18.2 kcal/mol) compared to

other compounds. Syahputra et al. [6] suggest that the lower binding affinity (ΔG) lead to more stable ligand interaction with the receptor. Based on these results, stable bonds with PBP2a is a rutin compound (Figure 2). According to Kumar and Pandey [12], rutin compound can bind to the polar groups on the cell membrane, so can increase the membrane rigidity.

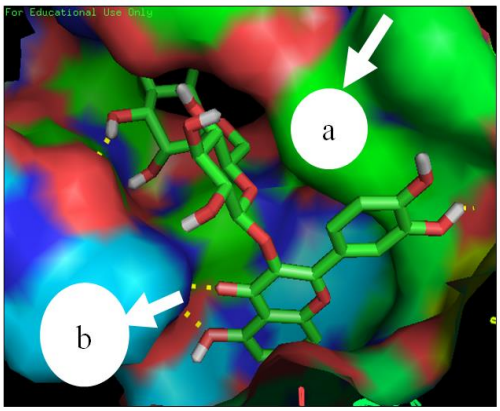

Figure 2. Binding pose rutin compound and PBP2a receptor (a=receptor, b=binding site)

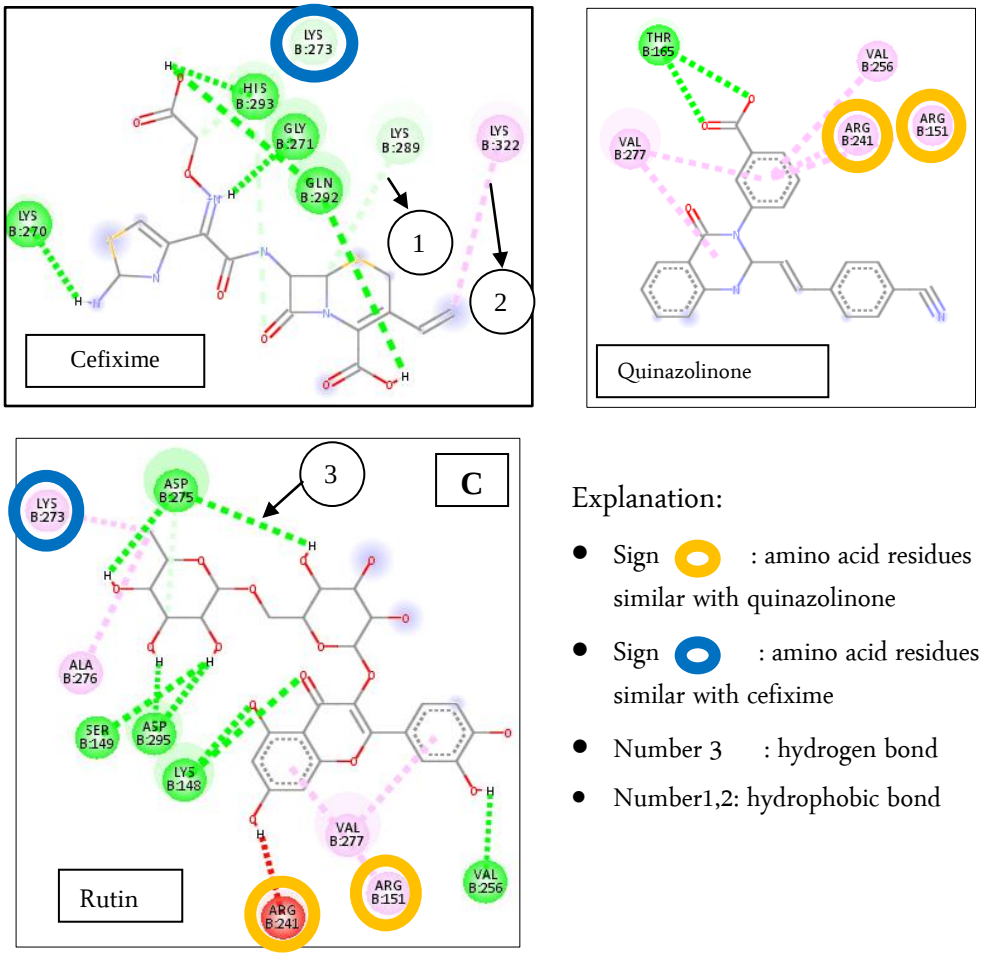

Figure 3. Figures are numbered with Roman numerals and even at the beginning of a sentence

The results of the docking process show the interaction between ligand and protein. Ligands have a binding site with amino acids at the receptor certainly. The visualization of the docking's results (Figure 3) shows the hydrophobic bonds of rutin compounds that have similar amino acid residues with quinazolinone on ARG B: 241, ARG B: 151 and cefixime in the amino acid residue LYS B: 273. Cefixime binds to amino acids number 270-322, while quinazolinone 151-277, rutin bound to amino acids 148-277 so rutin has a similarity of the binding site that to the control comparator (quinazolinone). Thus, rutin compound can be used as a candidate compound that can bind stably with PBP2a and be able to be a candidate for antibacterial drugs. In vitro mechanism shows that rutin compounds can inhibit the dihydrofolate reductase produced by *S. Aureus* [13]. Inhibition of this enzyme causes DNA synthesis and inhibition cell division, so it can cause cell death [14].

CONCLUSION

The active compound in the avocado seed which has potential as an antibacterial drug based on the results of in silico test is a rutin of flavonoid derivatives. Based on in vivo test, ethanolic extract of avocado (*P. americana* Mill.)seed can increase the number of fibroblast cells in mice's skin tissue infected by *S. aureus*.

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