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Molecular Dockingon The Metabolites in *Rhoeo discolor* as Antibacterial Agent

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Abstract: Chronic wounds tend to be suffered by people with diabetes mellitus and paralysis, which causes decubitus ulcers. The older the age, low the immunity and the risk of getting infected with the wound become higher. *Staphylococcus aureus, Pseudomonas aeruginosa,* and *methicillin-resistant Staphylococcus aureus* have been reported as the common causes in this case. This has led to reduced quality of life and depression in some patients; even post-amputation surgery sites of the part still have the potential complication of infection. *Rhoeo discolor*, occurs in many tropical countries that are found to have antibacterial properties because of their phenolic contents.Therefore, an in-silico study has occurred using molecular docking to determine which compound potentially has an antibacterial agent in wound infection, which is seen by its binding affinity of each bacterial receptors. The result of molecular docking carried out that one ligand compound has the potential of antibacterial activity to *Staphylococcus aureus*, *Methicillin-resistantStaphylococcus aureus*, *Pseudomonas aeruginosa*, namely as Chlorogenic acid with the binding affinities of each receptor are -8.7, -6.3, -6.3 and -8.2 kcal/mol. However, it needs to be determined by in vivo and in vitro tests for uses of combination effects from all phenolic contents tested on *Rhoeo discolor*.

Keywords: Molecular docking; *Methicillin-resistant Staphylococcus aureus*; *Rhoeo discolor;Pseudomonas aeruginosa*; *Staphylococcus aureus*

I. INTRODUCTION

Chronic wounds tend to be suffered by people with some diseases, like diabetes Mellitus and paralysis, which causes decubitus ulcers.(1) Besides, the older the age, the weaker the immunity and the risk of wound infection becomes higher.(2)*Staphylococcus aureus, Pseudomonas aeruginosa,* and *methicillin-resistant Staphylococcus aureus* have been reported as the common causes in this case.(3,4) This problem has led to reduced life quality and depression in patients;(5) even post-amputation surgery sites of the part still have a potential complication of infection.(6) All treatments can cost up to 25 billion US$ per year,(7) while not all people have access to it. Natural-based medicine can be chosen as an alternative, but the metabolites' function should be ensured. In silico studies using docking is one of the easiest ways to determine bacteria's interaction and effectiveness.

Rhoeo discolor, also called *Tradescantia spathacea*, is a perennial herb that occurs naturally in many tropical countries, including Central America, Mexico, West Indies, China, and Indonesia. It is found to have antibacterial properties due to its phenolic content. This plant is empirically consumed in the form of infusion or used in direct skin contact as a broad-spectrum dermatological anti-inflammatory agent to treat ulcers. Studies describe the benefits mentioned above as due to the secondary metabolite content of the leaves, namely anthocyanin (rhoeonin) and other high phenolic content, like gallic acid, ferulic acid, vanillic acid, p-coumaric acid, and chlorogenic acid. This statement corresponded to HPLC research by García-Varela et al. (2015), which is also indicated by the purple color of the leaves on the epidermis layer.(8–11)

Various models of wound healing have repeatedly demonstrated that complex plant extracts containing active secondary metabolites (polyphenols, flavonoids) and high antioxidants improve wound healing and increase skin collagen deposition while suppressing proinflammatory markers. Research shows that *Rhoeo discolor* leaves have good antioxidant activity and antibacterial effectiveness. The percentage of total flavonoid content studied in the 70% ethanol extract is 1.2426% ± 6.883 x 10-5/1 g extract. Ethanol and chloroform extracts of *Rhoeo discolor* also have antibacterial activity against gram-negative bacteria (*e.g., Escherichia coli, P. aeruginosa, Salmonella enterica*). It is extracted have to antibacterial gram-positive bacteria (*e.g., S. aureus, Bacillus cereus, and Listeria monocytogenes*).(12,13) Therefore, to ensure and invent a new natural medicine for chronic wounds, an in-silico study is done using molecular docking to determine which compound potentially

has an antibacterial agent in wound infection. Furthermore, the other is seen by its binding affinity using each bacterial receptor. The molecular docking process also visualizes the hydrogen bond and amino acid residues.

II. MATERIALS AND METHODS

2.1 Materials

The crystal structure of *Staphylococcus aureus* (PDB ID: 2W9S; 3U2D), *Methicillin-resistantStaphylococcus aureus* (PDB ID: 3VMT), and *Pseudomonas aeruginosa* (PDB ID: 6B8A) were downloaded in PDB format from Protein Data Bank (https://www.rcsb.org/). The ligand compound: vancomycin (control positive), chlorogenic acid, p-coumaric acid, ferulic acid, gallic acid, and vanillic acid were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), while dialkyl carbamoyl chloride (DACC) (control positive) and rhoeonin were drawn using Chemdraw Ultra 12.0 (CambridgeSoft Corporation, USA).

2.2 Instruments

The research instruments were ASUS A416EPO-VIPS554 computer set with Intel CORE i5 processor, 8GB RAM, 512GB SSD storage, Windows 11 (64 bit). The software used is PyRx 0.8, BIOVIA Discovery Studio Visualizer v21.1.0.20298, AutoDockTools-1.5.6, ChemDraw Ultra 12.0, PyMOL 2.5.3 Edu.

2.3 Protein Structure Preparation and Validation Docking Method

The crystal structure of *Staphylococcus aureus* (PDB ID: 2W9S; 3U2D), *Methicillin-resistantStaphylococcus aureus* (PDB ID: 3VMT), and *Pseudomonas aeruginosa* (PDB ID: 6B8A) were downloaded in PDB format from Protein Data Bank (https://www.rcsb.org/). The ligand was separated from the protein, and the water molecules were eliminated in BIOVIA - Discovery Studio Visualizer 2021. The polar hydrogen atoms and Kollman charges were added to the receptors as final prepared files by Autodock Tools 1.5.6 (The Scripps Research Institute Inc.) and saved in PDBQT format for further analysis. The docking method was validated by redocking native ligands (trimethoprim, 08B, LHI, CZG) from co-crystals contained in the receptor with PDB code 2W9S, 3U2D, 3VMT, 6B8A with each of RMSD values are below than 2Å.

2.4 Ligand Collection and Preparation

The ligand compound: vancomycin (control positive), chlorogenic acid, p-coumaric acid, ferulic acid, gallic acid, and vanillic acid were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), while dialkyl carbamoyl chloride (DACC) (control positive) and rhoeonin were drawn using Chemdraw Ultra 12.0 (CambridgeSoft Corporation, USA). All ligand compounds were imported into OpenBabel within the PyRx 0.8 tool and subjected to energy minimization. Existence of the conjugate gradient algorithm, the energy minimization was performed with the universal force field (UFF). The minimized compounds were then transformed into PDBQT format for further analysis.

2.5 Structure-Based Virtual Screening (SBVS)

SBVS using docking simulations was performed on both prepared libraries. The crystal structures were used as receptors and compound libraries as ligands. The binding energies were calculated using Autodock vina within the PyRx 0.8 tool (The Scripps Research Institute Inc.). Afterward, A grid box was set to cover the active site of crystal structures with exhaustiveness to start docking. The result was obtained and analyzed using BIOVIA - Discovery Studio Visualizer Client 2021.

III. RESULTS

Redocking process of natural ligand 2W9S (trimethoprim) obtained grid box with coordinates x = 5.984, y = 0.450, and z = 40,784 with RMSD=0.002, natural ligand 3U2D (08B) obtained grid box with coordinates x = 0.548, y = 2.587, z = 23,462 with RMSD = 1,653, natural ligand 3VMT (LHI) with coordinates x = -25,868, y = 6352, z = -13,956 with RMSD=1,834, natural ligand 6B8A (CZG) obtained grid box with coordinates x = 18,935, y = -24.744, z = 2.1 with an RMSD of 0.813. All natural ligands that underwent a redocking process with the receptor had the appropriate RMSD values so that they could be used to anchor the test compound. The receptors chosen are based on the effectivity of the sensitive antibacterial towards them and how most of the ligands used work in the previous research.

The molecular docking process is carried out using the Autodock vina within PyRx 0.8 tool. Parameters resulting from molecular docking can be seen from the binding affinity (ΔG) and their interaction results viewed on BIOVIA - Discovery Studio Visualizer 2021. The lower the binding affinity value, the stronger bonding between the compound and the receptor. It is because of the stability and strength of the non-covalent interaction between the compound-receptor.[14] The compound-receptor of the whole docking process between eight ligand test compounds and four target receptors, there is one ligand compound that has the best

antibacterial potential for *Staphylococcus aureus*, Methicillin-Resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, namely chlorogenic acid with the binding affinities on each receptor are -8.7, -6.3, -6.3 and -8.2 kcal/mol. The hydrogen bond and amino acid residues of chlorogenic acid are determined, too (Table 1-4).

Table 1. Ligand compounds with *Staphylococcus aureus* (PDB ID: 2W9S)

Ligands	Binding affinity (kcal/mol)	Hydrogen bond	Amino acid residues
Vancomycin (**Control positive**)	-3.4	-	-
Dialkyl carbamoyl chloride (DACC) (**Control positive**)	-3.7	1	1 residue (PHE92)
Chlorogenic acid	-8.7	6	7 residues (ALA7, ILE5, ILE14, GLY15, PHE92, SER49, THR46)
Ferulic acid	-6.5	2	2 residues (ALA7, VAL6)
Gallic acid	-6.0	0	2 residues (ALA7, ILE81)
P-Coumaric acid	-6.1	2	4 residues (ASP27, ILE14, LEU20, THR46)
Rhoeonin	-1.8	-	-
Vanillic acid	-5.9	3	5 residues (ALA7, ILE5, ILE14, LEU20, TYR98)

Table 2. Ligand compounds with *Staphylococcus aureus* (PDB ID: 3U2D)

Ligands	Binding affinity (kcal/mol)	Hydrogen bond	Amino acid residues
Vancomycin (**Control positive**)	-4.4	-	-
Dialkyl carbamoyl chloride (DACC) (**Control positive**)	-3.4	0	3 residues (ARG84, GLU58, GLY85)
Chlorogenic acid	-6.3	5	5 residues (ARG84, ASP57, ASP81, GLU58, GLY85)
Ferulic acid	-5.3	3	5 residues (ARG84, ASP81, GLY85, ILE86, PRO87)
Gallic acid	-6.0	4	4 residues (ASN54, ASP81, GLU58, PRO87)
P-Coumaric acid	-5.2	3	5 residues (ARG84, ASP81, GLY85, ILE86, PRO87)
Rhoeonin	-2.0	-	-
Vanillic acid	-5.4	3	4 residues (GLU58, GLY85, ILE86, THR173)

Table 3. Ligand compounds with *Methicillin-resistantStaphylococcus aureus* (PDB ID: 3VMT)

Ligands	Binding affinity (kcal/mol)	Hydrogen bond	Amino acid residues
Vancomycin (**Control positive**)	-3.5	-	-
Dialkyl carbamoyl chloride (DACC) (**Control positive**)	-3.6	0	1 residue (GLU102)
Chlorogenic acid	-6.3	4	6 residues (ARG103, ARG117, ARG241, ASN224, ASP101, LYS248)
Ferulic acid	-5.9	2	4 residues (ARG117, ASP101, GLU100, GLY130)
Gallic acid	-6.2	8	9 residues (ARG103, ARG117, GLU100, GLU102, GLY114, ILE97, LYS248, MET99, SER98)
P-Coumaric acid	-5.5	3	4 residues (ARG117, GLY131, LYS248, SER98)
Rhoeonin	-2.1	-	-
Vanillic acid	-5.7	2	3 residues (ARG117, GLY130, SER132)

Table 4. Ligand compounds with *Pseudomonas aeruginosa* (PDB ID: 6FTB)

Ligands	Binding affinity (kcal/mol)	Hydrogen bond	Amino acid residues
Vancomycin (**Control positive**)	-3.2	-	-
Dialkyl carbamoyl chloride (DACC) (**Control positive**)	-3.4	1	1 residue (ILE236)
Chlorogenic acid	-8.2	3	6 residues (GLN194, ILE236, ILE263, PRO210, VAL170, VAL211)
Ferulic acid	-6.5	1	6 residues (ALA102, ALA168, ILE149, ILE236, LEU197, PRO238)
Gallic acid	-5.9	5	4 residues (ILE236, LEU197, LEU208, SER196)
P-Coumaric acid	-6.2	2	4 residues (ALA168, ILE236, LEU197, LEU208)
Rhoeonin	-2.1	-	-
Vanillic acid	-5.8	1	3 residues (ILE236, LEU197, LEU208)

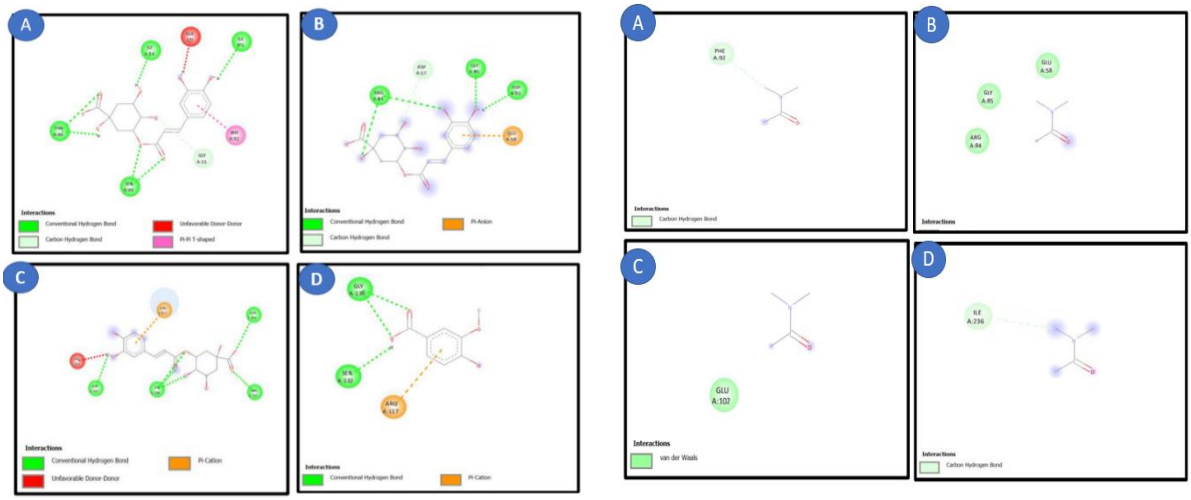

Figure 1. Interaction between chlorogenic acid and *Staphylococcus aureus* (PDB ID: 2W9S) (A), *Staphylococcus aureus* (PDB ID: 3U2D) (B), *Methicillin-Resistant Staphylococcus aureus* (PDB ID: 3VMT) (C), *Pseudomonas aeruginosa* (PDB ID: 6B8A) (D). Interaction between DACC (dialkyl carbamoyl chloride) from cutimedsorbact and *Staphylococcus aureus* (PDB ID: 2W9S) (A), *Staphylococcus aureus* (PDB ID: 3U2D) (B), *Methicillin-Resistant Staphylococcus aureus* (PDB ID: 3VMT) (C), *Pseudomonas aeruginosa* (PDB ID: 6B8A) (D).

IV. DISCUSSION

Chlorogenic acid is an antibacterial substance that works by the permeability of plasma membrane enhancement so that the defense function of bacterial cells will decrease and bacterial cells may disrupt.[15] It is verified in the docking result from its binding towards all receptors. The receptors used are all part of the membrane. The differences are just 2W9S from *S.* aureus targets the dihydrofolate reductase (DHFR) as the only source for THF (tetrahydrofolate) recycling, reducing the NADPH-dependent of dihydrofolate to tetrahydrofolate; 3U2D from *S. aureus* focuses on disrupting the DNA synthesis by DNA gyrase inhibition; 3VMT from MRSA targets bacterial transglycosylase in complex with lipid II, similar to teixobactin that may, in the same way, interacting with the sugar pentapeptide of lipid II;[16] and 6B8A of *P.aureus*, a multiple virulence factor regulator (MVFR) as an essential target to inactivate the virulence genes and disturb the formation and development of antibiotic-tolerant persister (AT/P) cells.[17]

The number of hydrogen bonds possessed by chlorogenic acid significantly enhances ligand-receptor interactions. It enables high-affinity binding of lead compounds, giving them a greater capacity to interact with cellular receptors (Figure 1).[18]

As an antibacterial, it has an apparent inhibitory effect on the growth of both Gram-negative and Gram-positive bacteria. This statement has also proved that the minimum inhibitory concentrations (MICs) are

relatively high. Therefore, the antibacterial activity would not be a reasonable explanation for its treatment of infectious diseases.[19] The work in the MRSA (3VMT) receptor is similar to vancomycin. Vancomycin binds to lipid II by forming five hydrogen bonds between the glycopeptide and the d-Ala-d-Ala end of lipid II, which locks the cell wall precursor in a stable complex so that the entire cycle of peptidoglycan synthesis becomes blocked. However, suppose the MRSA has been resistant to vancomycin. In that case, d-lactate incorporation into the peptidoglycan precursor causes one of the five hydrogens to be lost, decreasing antibiotic activity to 1,000-fold.

In contrast, vancomycin binding to d-Ala-d-Ser termini of lipid II is decreased due to steric hindrance.[20] It means that the MRSA receptor chosen here is still sensitive to vancomycin. Chlorogenic acid might also be ineffective in vancomycin-resistant MRSA because of the similar mechanism of action. However, it can still be tried on another receptor site to find another beneficial mechanism. In *Staphylococcus aureus*, most phenolic contents in the plant fit better in the 2W9S receptor, showing it works more on this site.

The other metabolites, especially rhoeonin, as the most dominant ones. The HPLC study by García-Varela et al. has the least binding affinities. It might fit another site and still need further research. In addition, there is still not much study about this substance. Generally, anthocyanins decompose bacteria and kill them by damaging cell membranes, affecting ATPase, AKP, and SOD, and decreasing pathogen biosynthesis and the TCA cycle.[21] Even if the anthocyanin does not work well, there is still gallic acid as the second dominant content in *Rhoeo discolor* that can increase by heating[22] and be found to be good to affect both gram-positive and negative bacteria by damaging cell membranes to enter the interior of the cell and inhibit DNA synthesis.[23,24] As reported in the previous study, extracts of *Rhoeo discolor* also have ferulic and chlorogenic acid, which targets *Pseudomonas aeruginosa* well by membranes disruption, intracellular potential drainage, and cytoplasmic macromolecules releasing that cause the cell to die.[25–29] Another byproduct of the plant extract is p-coumaric acid which is found to attack MRSA by cell membranes disruption and DNA binding that leads to the death of cells, and vanillic acid that inhibits gram-positive bacteria, such as *S.aureus* with unknown mechanism,[30–32] but was found to work on DHFR enzyme that has been mentioned above which causes damage to cell membranes and death.[33] The higher the extract concentration, the more the metabolite content, hence the effectivity from the amount of each of them towards bacteria, but the collaboration can also affect the result. DACC from cutimedsorbact as a positive control that was stated to have a strong-reducing effect on bacteria even on MRSA[34] is found to have a less binding effect than most of the extract metabolites in this in-silico study because the hydrogen bond is less and mostly are van der Waals. Hydrogen bonds are stronger because they occur between the highly electropositive hydrogen atom of one molecule and the highly electronegative (O, F, N) atom of another molecule and result in a relatively strong relationship in an extreme form of dipole-dipole interaction compared to other intermolecular forces.

Moreover, DACC coated in dressings also works not on releasing antibacterial but binding to bacteria by its hydrophobicity. Nonetheless, there is a limitation that should be noted. Bacteria could adapt to this kind of treatment by changing their surface hydrophobicity, especially bacteria that express a hydrophilic cell surface, like *the S. aureus* strain. Higher inoculum densities, protein, and increasing pH in infected wounds also still have not been well studied on cutimedsorbact (DACC) and stated to decrease the effect of it,[35] while in the *Rhoeo discolor* extract with lower pH (4-5) due to its dominant anthocyanin content can disturb the environment pH of the infected wound that reaches 7.2-8.9 caused by bacteria metabolites which also support their life, thus lowering the pH to decrease the bacteria and helps the wound heal.[36]

V. CONCLUSION

The docking process is carried out between eight ligand test compounds and four target receptors, and there is one ligand compound that has the best potential for the antibacterial activity to *Staphylococcus aureus*, *Methicillin-ResistantStaphylococcus aureus*, *Pseudomonas aeruginosa* namely as Chlorogenic acid with the binding affinities of each receptor are -8.7, -6.3, -6.3 and -8.2 kcal/mol. Chlorogenic acid is an antibacterial substance that works by the permeability of plasma membrane enhancement so that the defense function of bacterial cells will decrease and bacterial cells may disrupt. As an antibacterial, it has an apparent inhibitory effect on the growth of both Gram-negative and Gram-positive bacteria. However, it needs to be determined again by in vivo and in vitro tests for uses of the combination effect from all phenolic contents tested on *Rhoeo discolor*.

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