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IN SILICO STUDY TO ASSESS ANTIBACTERIAL ACTIVITY FROM *Cladophora Sp.* ON PEPTIDE DEFORMYLASE: MOLECULAR DOCKING APPROACH

Yoni Rina Bintari*

Rio Risandiansyah

Universitas Islam Malang, Malang, East Java, Indonesia

email: yonirinabintari@unisma.ac.id

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Abstract

Increasing antibiotic-resistant pathogenic bacteria is a severe problem in the world. Therefore, there is a need to identify new drugs from natural products and also new drug targets. Cladophora sp. is a marine organism which is known to have bioactive compounds and a potential antibacterial. On the other hand, Peptide Deformylase (PDf) may prove to be a novel drug target since it is crucial for native peptide functioning in most pathogenic bacteria. This study screens for PDf inhibition activity of compounds from Cladophora sp. using molecular docking approach and screening the binding affinity of bioactive compounds against the peptide receptor PDf using Pyrex Autodock Vina software. Docking results were stored and visualized using Biovia Discovery Studio and PyMOL ligand. Ligands were obtained from previous literature in PubChem, and receptor peptide PDf from pathogenic bacteria: Pseudomonas aeruginosa (PDB ID:1N5N), Escherichia coli (PDB ID:1BSK), Enterococcus faecium (PDB ID:3G6N) and Staphylococcus aureus (PDB ID:1LQW), was obtained from the peptide data bank. The results of this screening show with ligand the highest binding affinity against PDf of P. aeruginosa, E. coli, E. faecium, and S. aureus is stearic acid (-5.9 kcal/mol), eicosapentaenoic acid (-6.6 kcal/mol), stearic acid (-5.8 kcal/mol), and stearic acid (-6.2 kcal/mol) respectively. The binding of natural compounds from Cladophora sp. with PDf models may provide a new drug with a different drug target for antibacterial potential..

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INTRODUCTION

Antibacterial resistance is one of the big problems in the world of health. The Centers for Disease Control and Prevention (2013) reports that in 2025 it is predicted that around 23,000 people will die from infectious diseases with antibacterial resistance. Antibacterial resistance can occur through changes in the molecular structure of antibiotics; decreased antibiotic penetration and efflux pumps; side active changes from antibiotics and cell adaptation due to antibiotic exposure (Munita & Arias, 2016). To overcome this, searching of new antibiotics from nature and design antibiotics with new targets.

This study aims to design antibiotics that work on new target peptides. *Cladophora Sp*. is a marine green algae that is widely spread in Tamban Malang ocean. Ethanolic extract of *Cladophora Sp*. has potential as an antibacterial compound (Saadatmand *et al*., 2011). The active compound contained in *Cladophora Sp*. including linoleic acid, linolenic acid, palmitic acid, palmitoleic acid, eikosapentanota, and oleic acid. Peptide Deformylase (PDf) is a metaloenzyme that plays a role in protein maturation by catalyzing the formation of formyl from terminal N residues on methionine (Fieulaine *et al*., 2016; Gupta & Sahu, 2016; Apfel *et al*., 2001).

PDf has the potential to become a new target protein in finding new antibiotic drugs. Inhibition of PDf target proteins is predicted to inhibit protein maturation, so that it can inhibit growth of bacteria (Rampogu *et al*., 2018). This study aims to predict the ability of the active compounds of methanol extract *Cladophora Sp*. inhibits PDf from pathogenic bacteria. Pathogenic bacterial PDf becomes the target protein for analysis from *Pseudomonas aeruginosa, Escherichia coli, Enterococcus faecium*, and *Staphylococcus aureus* (Snow-Snetzer *et al*., 2016; Agarwal *et al*., 2014). Prediction of the inhibition ability of active compounds with PDf using a molecular docking approach *in silico*.

MATERIAL AND METHODS

Ligands Preparation

The active compound of *Cladophora Sp*. extract obtained from GC-MS from our previous study. The structure of 3D active ingredient and control compounds (anonine and amoxicilline) was downloaded from the PubChem server (https://pubchem.ncbi.nlm.nih.gov). The CID of each active compound is recorded. The 3D structure of each ligand is downloaded in the .sdf format.

Receptors Preparation

Protein receptors (PDf) from bacteria *Pseudomonas aeruginosa, Escherichia coli, Enterococcus faecium, Leptospira interrogans, Streptococcus mutans, Vibrio cholera*, and *Staphylococcus aureus* was downloaded from the server Protein Data Bank (https://www.rcsb.org/). The protein obtained was downloaded and stored in the .pdb format.

Molecular Docking

The docking process is carried out using the AutoDock Vina with PyRx program. It was performed by adjusting appropriate parameters such as coordinate of grid box center: X= 170.754; Y= 146.896; Z= 118.8194 and grid box size: X= 55.1016; Y= 54.5187; and Z= 40.435 Å. The ligand from the docking process (ligand validation) was stored and a comparison with the control ligand to see the value of root-mean-square deviation (RMSD). Docking software is preferred to predict results from experimental positions with RMSD no more than 2.0 Å (Pratama & Suhartono, 2018). The docking results are then visualized using the PyMol program. To see the interaction between receptors and ligands using the Biovia Discovery Studio program.

The results of affinity binding are chosen from the most negative values. Negative values indicate ligand conformation with the most stable receptors (Pratama & Pratomo, 2017). Withdrawal of conclusions was obtained from the binding affinity value that was more negative than the counter and more amino acids were bound by the same hydrogen bond as the control (Snow-Snetzer *et al*., 2016; Agarwal *et al*., 2014). The efficiency of a ligand complex with a protein receptor can be seen from the bonding energy between the ligand and the minimum protein, and the ligand interaction with the active side of the receptor protein (Pratama *et al*., 2018).

RESULTS AND DISCUSSION

Previous literature studies have shown that the bond between thiazide derivatives and receptor protein is a potential drug model for diseases caused by antibacterial resistance (Agarwal *et al*., 2014). The result of in silico study *Cladophora Sp*. metabolites to PDf are shown in Table 1. From the results of docking of *Cladophora Sp*. metabolites for PDf, the most negative affinity value is eicosapentanoic acid against *E. coli* with the binding affinity of -6.6 kcal/mol.

Table 1. Inhibiting potency of *Cladophora Sp*. metabolites against PDf Receptor from pathogen bacteria

Compounds	CID	Receptor	Binding Affinity (kcal/mol)
linoleic acid	5280450	*E. faecium*	-5
linolenic acid	5280934	*E. faecium*	-5.5
palmitic acid	985	*E. faecium*	-4.6
palmitoleic acid	445638	*E. faecium*	-4.5
eicosapentanoic	446284	*E. faecium*	-5.4
oleic acid	445639	*E. faecium*	-4.7
stearic acid	5281	*E. faecium*	-5.9
linoleic acid	5280450	*E. coli*	-5.2
linolenic acid	5280934	*E. coli*	-5.6
palmitic acid	985	*E. coli*	-5
palmitoleic acid	445638	*E. coli*	-5.5
eicosapentanoic	446284	*E. coli*	-6.6
oleic acid	445639	*E. coli*	-5.5
stearic acid	5281	*E. coli*	-5.9
linoleic acid	5280450	*P. aeruginosa*	-4.6
linolenic acid	5280934	*P. aeruginosa*	-4.7
palmitic acid	985	*P. aeruginosa*	-3.7
palmitoleic acid	445638	*P. aeruginosa*	-4.4
eicosapentanoic	446284	*P. aeruginosa*	-5.2
oleic acid	445639	*P. aeruginosa*	-4.4
stearic acid	5281	*P. aeruginosa*	-5.8
linoleic acid	5280450	*S. aureus*	-5.2
linolenic acid	5280934	*S. aureus*	-5.7
palmitic acid	985	*S. aureus*	-4.3
palmitoleic acid	445638	*S. aureus*	-5.6
eicosapentanoic	446284	*S. aureus*	-5.5
oleic acid	445639	*S. aureus*	-4.7
stearic acid	5281	*S. aureus*	-6.2

The affinity binding value of eicosapentanoic acid on E. coli bacteria has a more negative value compared to the control of actinonine and amoxiciline as shown in Table 2.

Table 2. Binding Affinity of reference ligands actinonin and amoxicilin

Compounds	Binding Affinity (Kcal/ Mol)			
	E. Faecium	*E. Coli*	*P. aeruginosa*	*S. aureus*
Actinonine	-6.2	-6.4	-6	-6.9
Amoxicilline	-6.3	-6.5	-6.5	-7.1

Comparison of the similarity of amino acids is shown in the percentage of amino acids that interact with the results of test ligand docking compared to ligand references (Pratama *et al*., 2018). Whereas ligands that have similar hydrogen bonds with controls are stearic acid. Stearic acid has a similarity with control of 50%. Table 3 shows that the same amino acid residues bound by both the control and stearic acid are valine in position 72.

Table 3. Binding Affinity of reference ligands actinonin and amoxicilin

Receptor	Actinonine	Amoxicillin	Stearic Acid
1 N5N	71-Arg; **72-Val**; **115-Arg**	**72-Val**; **115-Arg**; 122-Glu; 158-Lys	91-Gly

Electrostatic interaction between hydrogen atoms that is attached to an electronegative atom with another electronegative atom is hydrogen bonding. In medicine, hydrogen bond strength is under the covalent bond, but its presence is very important. The presence contributes to molecule structures and characteristics. Hydrogen bond plays a role in studying the design and interaction between drug molecules and metabolic system in the body (Damayanti *et al*., 2016). The visualization of interaction between the ligand and protein receptor of PDf from *P. aeruginosa* is shown in Figure 1.

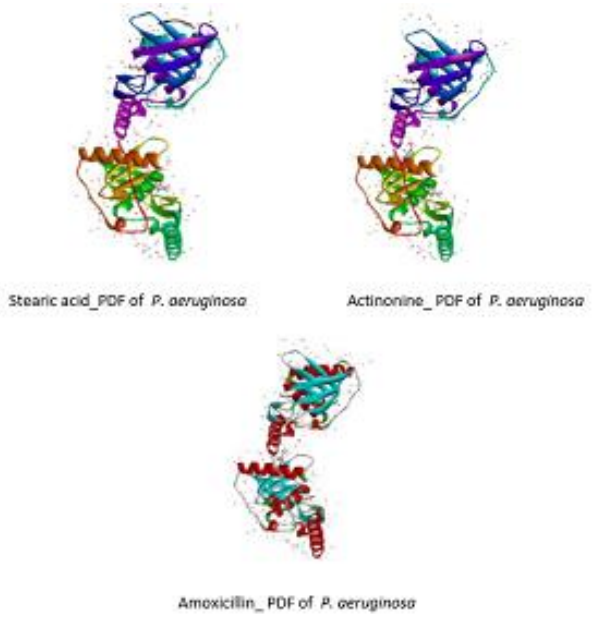

Figure 1. Interaction between ligand and receptor in PDf of *P. aeruginosa*

CONCLUSION

The results of this screening shows with ligand the highest binding affinity against PDf of *P. aeruginosa*, *E. coli, E. faecium*, and *S. aureus* are stearic acid (-5.9 kcal/mol), eicosapentanoic acid (-6.6 kcal/mol), stearic acid (-5.8 kcal/mol), and stearic acid (-6.2 kcal/mol), respectively. Stearic acid from *Cladophora Sp.* Had similar binding interaction of 50% amino acid residue compare to the control antibiotics actininone and amoxicillin, which is valine in position number 72. The binding of natural compounds from *Cladophora sp*. with PDf models may provide a new drug with a different drug target for antibacterial potential

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