Jurnal Penelitian Farmasi Indonesia
p-ISSN : 2302-187X | e-ISSN: 2656-3614
Homepage: https://ejournal.stifar-riau.ac.id/index.php/jpfi/
Vol. 14, No. 1, Hal. 16-22

RESEARCH ARTICLE

MOLECULAR DOCKING OF ASIATIC ACID AND MADECASSIC ACID ON THE TARGET PROTEIN FTSZ IN *Staphylococcus epidermidis* BACTERIA

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Article History

Received:
11 Juni 2025

Accepted:
11 September 2025

Published:
7 November 2025

ABSTRAK

Staphylococcus epidermidis, adalah salah satu bakteri penyebab *acne vulgaris*. Protein FtsZ yang dimiliki oleh *Staphylococcus epidermidis* dapat menjadi target terapi untuk pengobatan *acne vulgaris*. Pegagan merupakan tanaman yang mengandung senyawa asam asiatik dan asam madekasik yang diduga memiliki aktivitas sebagai antibiotik. Penelitian ini, membandingkan efektivitas pengikatan antara ligan uji asam asiatik dan asam madekasik, ligan alami guanosine-5'-diphospate, dan ligan pembanding clindamycin dengan protein FtsZ yang digunakan sebagai target utama penambatan molekuler.Proses docking dilakukan dengan menyiapkan protein FtsZ, yaitu; 4M8I yang diperoleh dari RCSB, kemudian ligan diunduh dari Pubchem. Selanjutnya, Hyperchem 8.0 digunakan untuk preparasi ligan, Molegro Virtual Docker untuk mendapatkan protein hasil preparasi, rerank score, RMSD, dan visualisasi hasil docking protein-ligan.Di antara 4 ligan yang digunakan untuk studi docking; asam asiatik, asam madekasik, guanosine-5'-diphospate, dan clindamycin memiliki skor rerank masing-masing sebesar -63,457 kkal/mol; -86,303 kkal/mol; -129,629 kkal/mol; -110,707 kkal/mol. Kesimpulan: Ligan uji asam madekasik memiliki sifat antibiotik yang lebih baik daripada asam asiatik, tetapi tidak lebih baik dari clindamycin.

Kata kunci: Antimikroba; asam asiatik; asam madekasik

ABSTRACT

Staphylococcus epidermidis, is one of the bacteria that cause acne vulgaris. The FtsZ protein possessed by *Staphylococcus epidermidis* can be a therapeutic target for acne vulgaris treatment. *Centella asiatica*, a plant that contains asiatic acid and madecassic acid compounds that are thought to have antibiotics. Objective: This study, comparing the binding effectiveness between test ligands asiatic acid and madecassic acid, natural ligand guanosine-5'-diphospate, and comparator ligand Clindamycin with FtsZ protein was used as the main target of molecular docking. Methods: The docking process was carried out by preparing the FtsZ protein, namely; 4M8I obtained from RCSB, then the ligand was downloaded from Pubchem. Furthermore, Hyperchem 8.0 was used for ligand preparation, Molegro Virtual Docker to obtain preparation protein, rerank score, RMSD, and visualization of protein-ligand docking results. Results: Among the 4 ligands used for docking study; asiatic acid, madecassic acid, guanosine-5'-diphospate, and clindamycin have rerank score of -63.457 kcal/mol; -86.303 kcal/mol; -129.629 kcal/mol; -110.707 kcal/mol, respectively. Conclusion: The test ligand madecassic acid has better antibiotic properties than asiatic acid, but not better than Clindamycin.

Keywords: Antimicrobial; asiatic acid; madecassic acid

INTRODUCTION

One dermatologic disorder that affects adolescents and adults at an estimated 85% is a chronic inflammatory skin condition called acne vulgaris (Ibrahim *et al*., 2023). Most likely, the inflammation that causes acne vulgaris is caused by the activity of *Staphylococcus epidermidis* bacteria on human epithelium (Claudel *et al*., 2019; Fournière *et al*., 2020). Previous studies reported that methicillin resistant *Staphylococcus epidermidis* (MRSE) (Razavi *et al*., 2018; Tabri, 2017). Methicillin was the first semisynthetic penicillinase-resistant penicillin. It has been withdrawn from the market in the United States due to the high incidence of interstitial nephritis associated with its use. In another report, *Staphylococcus epidermidis* was resistant to erythromycin (65.2%), clindamycin (52.2%), and tetracycline (32.6%) (Sitohang *et al*., 2019).

Acne vulgaris is caused by skin dysbiosis (imbalance in the number of microbes, such as; bacteria) due to opportunistic biofilm formation by *Staphylococcus epidermidis* (Fournière *et al*., 2020).

Filamenting temperature-sensitive mutant Z (FtsZ) is a key cytoskeletal protein in the cytokinesis machinery of bacteria, including *Staphylococcus epidermidis*. This protein forms a ring (Z-ring) under the membrane at the center of the cell, FtsZ forms ring-like structure (Z-ring) takes on the role as a scaffold for the recruitment of multiprotein complex (known as divisome), and may also generate the force that is vital for the viability of the cell (Erickson and Osawa, 2017; Silber *et al*., 2020).

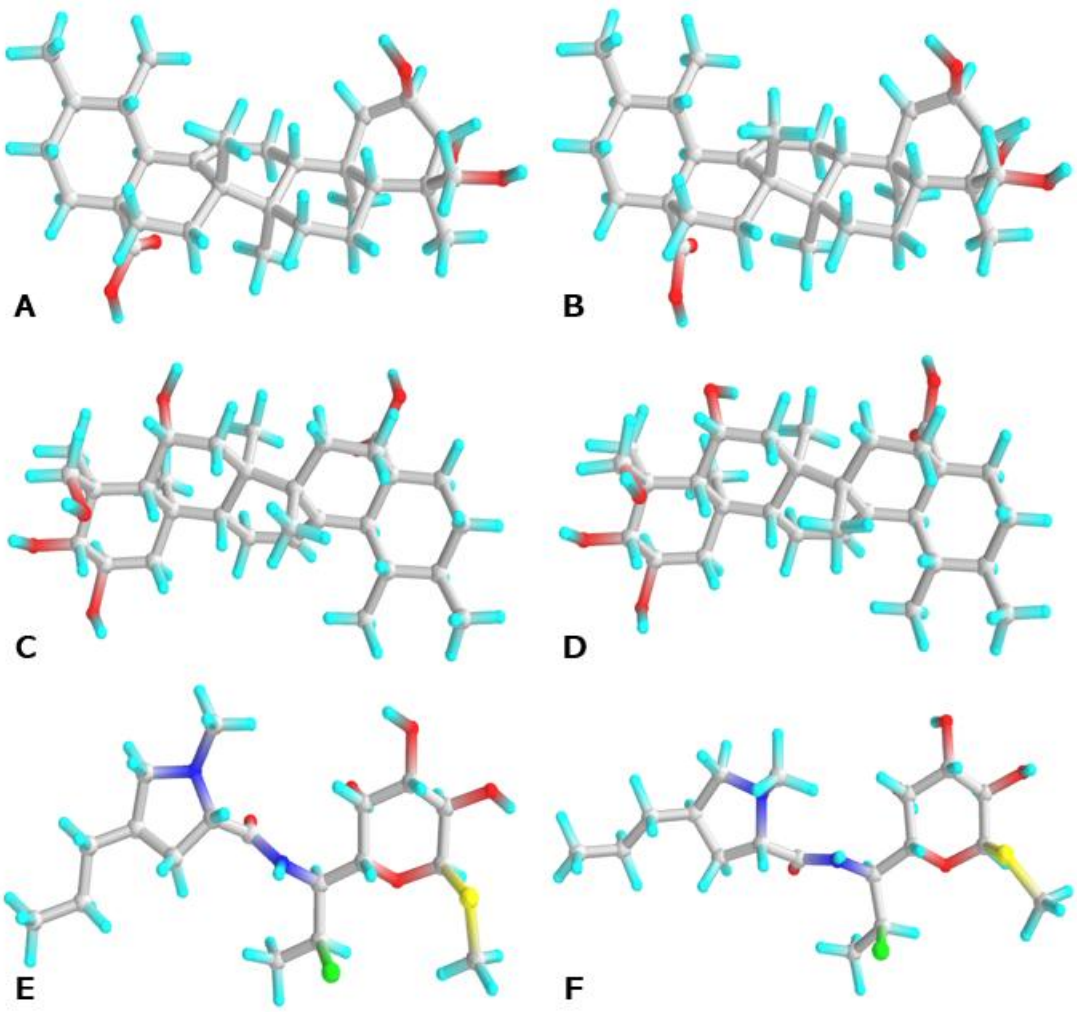

Figure 1. Structure optimization results of asiatic acid single point calculation (A) and geometry optimization (B). Madecassic acid single point calculation (C) and geometry optimization (D). Clindamycin single point calculation (E) and geometry optimization (F)

The discovery of new drugs as antibiotics to disrupt and damage the activity of the FtsZ protein is very important. Clindamycin prevents peptide bond formation, inhibiting protein synthesis by reversibly binding to 50S ribosomal subunits. Depending on the organism, infection site, and drug concentration, clindamycin may be a bacteriostatic or bactericidal antibiotic (Spížek and Řezanka, 2017). Terpenoids are known to have antimicrobial characteristics because they have multiple cellular target sites rather than a single site, including bacteriostatic, inhibiting ATP production, and inhibiting protein synthesis *(Huang et al*., 2022). *Centella asiatica* extracts antimicrobial analysis had successfully inactivated against human pathogenic bacteria such as Bacillus

MATERIAL AND METHODS

Ligand structure optimization

Ligands in the form of test ligands asiatic acid CID 119034, madecassic acid CID 73412, and clindamycin CID 446598 as a comparison ligand were obtained from https://pubchem.ncbi.nlm.nih.gov/. Then, the preparation of each ligand was carried out using

Hyperchem 8.0 software, converting all ligands into MOL format. Settings in Hyperchem 8.0 on the setup menu using Semi-empirical Method selected Austin Model (AM1). Then, on the Compute menu, select Single-point Calculations (record the total energy before geometry optimization). Next, on the Computer menu, select Geometry Optimization, select Polak-Ribiere Algorithm (RMS gradient 0.01 kcal/(Å mol) or 500 cycles, In Vacuo). Record the total energy value after geometry optimization.

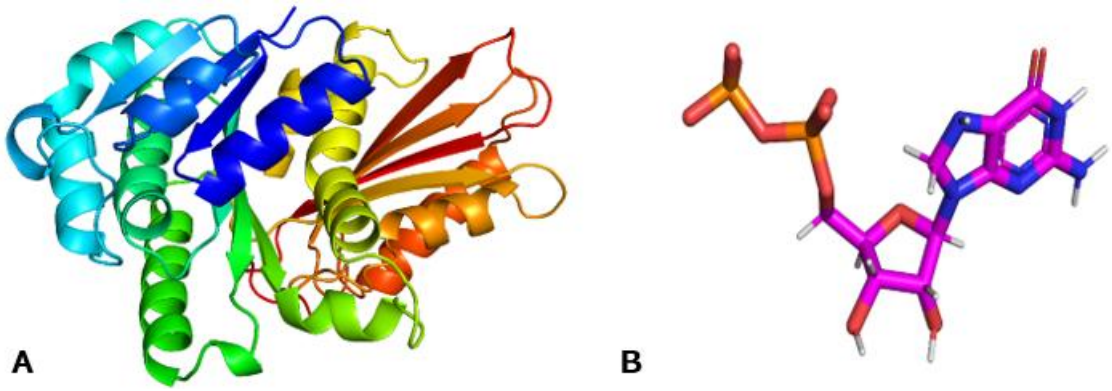

Figure 2. Ftsz protein preparation. (A) Ftsz chain without native ligand RS2, (B) native ligand GDP.

FtsZ protein preparation and validation

The FtsZ ID 4M8I protein obtained from https://www.rcsb.org/ needs to be prepared using Molegro Virtual Docker software by removing cofactors and water molecules, leaving only the native ligand Guanosine-5'-Diphospate (GDP) and the FtsZ protein.

Molecular docking validation

Molecular docking validation was performed by re-docking the native GDP ligand to the prepared FtsZ protein using Molegro Virtual Docker. Binding site box was set and adjusted with x = -18.59 Å; y = -09.82 Å; z = 20.06 Å, grid resolution 0.30 Å, and radius 15. The root mean square deviation (RMSD) value ≤ 2Å indicates the protocol is accepted and the tethering of the test compound on the target protein can be performed.

Test and comparasion ligands docking on FtsZ protein

The optimized test compounds asiatic acid, madecassic acid, and clindamycin were then docked to the prepared FtsZ using Molegro Virtual Dcoker with the same grid box size during the validation step. The result of molecular tethering is binding energy and interaction visualization ((Muslikh *et al*., 2022). The lower the binding energy, the stronger the interaction, indicating the compound's potential as an antimicrobial

Table 1. Rerank score and RMSD of redocking GDP ligand to Ftsz protein

Protein	Ligand	Poses	Rerank score (kcal/mol)	RMSD (Å)	Amino acid residue
FtsZ	GDP	00*	-129.629	0.58	ARG 29
					ARG 143
					ASN 25
					ASN 166
					GLU 139
					GLY 21
					GLY 22
					GLY 108
					GLY 110
					THR 109
					THR 133

*Pose 00 is used as a reference for the RMSD value in the method validation stage.

Table 2. Rerank score and amino acid residues of ligand to Ftsz protein

Protein	Ligand	Rerank score (kcal/mol)	Amino acid residues
FtsZ	Asiatic acid	-63.457	ASN 44
			ASP 46
			ARG 143
			MET 105
			GLU 139
			GLY 21
			GLY 22
			GLY 70
			GLY 104
			THR 45
			THR 109
	Madecassic acid	-86.303	**ARG 143**
			ASN 44
			ASN 166
			MET 105
			GLU 139
			GLY 21
			GLY 70
			GLY 104
			GLY 107
			THR 109
	Clyndamycin	-110.707	ALA 71
			ALA 73
			ARG 143
			GLY 20
			GLY 21
			GLY 22
			GLY 70
			GLY 104
			GLY 107
			GLY 108
			GLY 110
			THR 109

RESULTS

Ligand structure optimization

In the optimization process, single-point calculation and geometry optimization are performed to obtain the most stable asiatic acid and madecassic acid structures with the lowest total energy. The total energy resulting from the single point calculation of asiatic acid, madecassic acid, and clindamycin ligands are -140813.46 kcal/mol, -148206.35 kcal/mol, and -123244.64 kcal/mol, respectively. After geometric optimization, there is a decrease in structural energy to -140853.46 kcal/mol, -148248.20 kcal/mol, and -123281.21 kcal/mol respectively, indicating that stable structures and lower energies were obtained **(Figure 1)**.

FtsZ protein preparation

In this process, the FtsZ protein is separated from the native GDP ligand to provide binding sites for the binding of asiatic acid, madesaccic acid, and clindamycin. This process also aims to obtain the structure of the native GDP ligand used for the method validation process (Figure 2). One protein was chosen to facilitate the determination of the coordinate binding site space where Asiatic acid binds during the docking process. This process applies to madesaccic acid and clindamycin tethered to FtsZ.

Molecular docking validation

Validation was performed by redocking GDP ligand to the FtsZ protein to evaluate the deviation between position or conformation of the original ligand before and after redocking. The minimum deviation can minimize the error in predicting the interaction during the molecular tethering process. The validation process starts with the addition of hydrogen atoms to the FtsZ target protein. This step aims to adjust the pH atmosphere of docking as in the body (Sastry *et al*., 2013).

Coordinates are arranged as the center of the grid and the size of the grid to determine the position of the protein binding site. The redocking process is performed using the semirigid method for macromolecules (Leis and Zacharias, 2012). The redocking process is accepted and valid if the RMSD value ≤ 2 Å. Table 1 shows that conformation three produced the lowest RMSD value (1.00 Å) and met the validation requirements (RMSD ≤ 2.00 Å).

Test and comparasion ligands docking on FtsZ protein

The optimized structures of asiatic acid, madecassic acid, and clindamycin were fitted to the target protein FtsZ using the same binding site box size during validation to ensure the compound was anchored in the active site. Table 2 lowest rerank score value on clindamycin -110.707 kcal/mol.

DISCUSSION

Ligand preparation begins with conversion to MOL format, including asiatic acid and madecassic acid test ligands, clindamycin comparison ligand, so that it can be read by Hyperchem 8.0 (natural ligand energy minimization is carried out at the method validation stage). Single point calculation is carried out to obtain the molecular energy value of the existing geometry, which will then be minimized using geometry

optimization, so that the asiatic acid, madecassic acid, and clindamycin ligands are obtained in a more stable form. The ligand structure is usually optimized by energy minimization to achieve the conformation with the lowest energy that describes its stability (Jász *et al*., 2019; Roy *et al*., 2015).

The crystal structure of the FtsZ protein was obtained from the Protein Data Bank and formed through crystallization experiments using vapor diffusion and sittring drop methods. Hydrogen atoms were assigned to the heavy atoms of the protein and optimized. Water molecules and cofactors were removed (Flachsenberg *et al*., 2024; Qing *et al*., 2022).

Molecular validation uses the parameters rerank score and RMSD. Rerank score is a value that reflects the energy required to form a bond between the ligand and the receptor. Rerank score indicates that the bond between the ligand and the receptor is more stable (Prasetiyo *et al*., 2019). Furthermore, an RMSD value of <2.0 Å is usually used as a criterion for the success of the docking method (Ma'arif *et al*., 2021; Muslikh *et al.*, 2022).

Clindamycin had the lowest rerank score of -110,707 kcal/mol, when tethered to FtsZ protein. Clindamycin and the natural ligand GDP have the same amino acid residues, namely; ARG 143; GLY 21; GLY 22; GLY 108; GLY 110; THR 109. This suggests that Clindamycin is tethered to FtsZ in the same coordinates as the natural ligand GDP in the target protein. Asiatic acid has the same amino acid residues as the natural ligand GDP, including; ARG 143; GLU 139; GLY 21; GLY 22; THR 109. Meanwhile, madecassic acid has similar amino acid residues with natural ligands of GDP, including; ARG 143; ASN 166; GLU 139; GLY 21; THR 109 (see table 2). The test compounds asiatic acid, madecassic acid, and GDP as natural ligands also showed inhibitory activity against FtsZ protein. Using the same method and target protein (FtsZ, PDB ID 4M8I) with a grid size of x = -18.59 Å; y = -09.82 Å; z = 20.06 Å, grid resolution of 0.30 Å, and radius 15 of the native ligand GDP (redocking), the rerank scores of asiatic acid, madecassic acid, and GDP were -63.457 kcal/mol, -86.303 kcal/mol, and -129.629 kcal/mol, respectively.

Based on these results, asiatic acid and madecassic acid are compounds from *Centella asiatica* that exhibit anti-acne antimicrobial activity. However, their effectiveness is inferior to Clindamycin and GDP, as indicated by their higher rerank scores compared to the controls. This finding is further supported by the similarity of their amino acid residue profiles.

Various studies have demonstrated the antimicrobial activity of *Centella asiatica* against several bacterial species, including Staphylococcus aureus, Staphylococcus albus, Escherichia coli, Pseudomonas aeruginosa, Streptococcus pneumoniae, Streptococcus pyogenes, Pseudomonas marginalis, Streptococcus mutans, Streptococcus salivarius, Penicillium expansum, Fusarium oxysporum, Xanthomonas campestris, Lactobacillus acidophilus, Bacillus cereus, Enterobacter aerogenes, Klebsiella pneumoniae, Mycobacterium glutamicum, Proteus vulgaris, Shigella species, Vibrio cholerae, and Pseudomonas marginalis (Harun *et al*., 2019; Sari *et al*., 2023).

Asiatic acid and madecassic acid are triterpenoid compounds found in *Centella asiatica* (Min *et al*., 2024). Terpenoids exhibit antimicrobial activity through several key mechanisms. First, they disrupt bacterial cell membranes by leveraging their lipophilicity to penetrate the phospholipid bilayer, compromising membrane integrity and leading to the loss of essential proteins and enzymes, ultimately exerting bactericidal or bacteriostatic effects. Second, terpenoids inhibit ATP production by causing intracellular and extracellular concentration imbalances, thereby disrupting membrane function and bacterial metabolism. Third, terpenoids act as protein synthesis inhibitors by interfering with various biosynthetic pathways. For instance, cinnamaldehyde has been shown to inhibit FtsZ assembly, disrupt GTP hydrolysis, and impair z-loop dynamics, which collectively contribute to bacterial cell division inhibition (Domadia *et al*., 2007). Additionally, terpenoids can work synergistically with other compounds to enhance their antibacterial efficacy. The mechanisms of action and specific targets of terpenoids in microbial cells have been illustrated in previous studies (Huang *et al*., 2022).

CONCLUSION

Among the ligands tested, madecassic acid has a ranking score of -86,303 kcal/mol which is lower than Asiatic acid -63,457 kcal/mol. Madecassic acid has amino acid residues similar to the natural ligands of GDP, including; ARG 143; ASN 166; GLU 139; GLY 21; THR 109. Asiatic acid and madecassic acid in *Centella asiatica* may be tested in vivo on *Staphylococcus epidermidis* to clarify the findings in this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in writing this article.

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