Molecular docking of active compounds from caulerpa lentillifera targeting Cutibacterium acnes lipase as anti-acne candidates

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Received: February 9, 2026
Accepted: Mei 20, 2026

DOI: 10.1980/jses.v1i1.3

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Abstract: *The growing concerns about antibacterial resistance in Cutibacterium acnes (C. acnes) have encouraged the development of alternative acne therapies, including the use of natural bioactive agents. In this study, ten bioactive compounds from Caulerpa lentillifera (C. lentillifera) were docked against C. acnes lipase (PDB: 6KHM) using YASARA Structure and further analyzed with Discovery Studio. Method validation showed a redocking RMSD value of 1.6482 Å, with heptane-1,1-diol serving as the native ligand. Two compounds, isoquercetin and catechin, demonstrated direct interactions with both the catalytic triad and lid-domain residues, while rutin primarily interacted with the lipase lid domain. All three compounds exhibited lower ΔG binding than the native ligand, at −7,3772; −7,3750; and -7,2977 kcal/mol respectively, indicating more stable binding affinities. These findings highlight the potential of isoquercetin, catechin, and rutin as natural lipase inhibitors and support the use of C. lentillifera as a promising source of anti-acne agents*

Keywords: *Cutibacterium acnes, Caulerpa lentillifera, Docking Molecule, Antibacterial.*

Introduction

Acne vulgaris (AV) is a chronic inflammatory disorder of the pilosebaceous unit that commonly affects adolescents and occurs in up to 90% of the global teenage population [1]. One of the major contributing factors in AV pathogenesis is the activity of Cutibacterium acnes (C. acnes). This bacterium is known to trigger inflammation and cytotoxicity by inducing pro-inflammatory cytokines and producing several enzymes, including lipase, hyaluronidase, and protease. Among these virulence factors, C. acnes lipase (CALipase) plays a central role by hydrolyzing sebum triglycerides into free fatty acids, which irritate the follicle and promote the formation of inflammatory lesions [2].

Current treatments targeting C. acnes rely largely on antibiotics such as erythromycin, clindamycin, and tetracycline [3]. However, the extensive and prolonged use of these agents has led to concerns over rising antibiotic resistance [3], [4]. In parallel, phytochemicals have a long history of use in traditional medicine for the management of various conditions, including bacterial infections [5]. These secondary metabolites are widely distributed across plant species and are associated with antibacterial, anti-inflammatory, and antioxidant activities. Several have also been shown to suppress C. acnes growth or interfere with its virulence mechanisms [3]

Caulerpa lentillifera (C. lentillifera) is a green alga known to contain a variety of phytochemicals, particularly phenols and flavonoids [6]. Its secondary metabolites have been reported to exhibit antimicrobial and anti-inflammatory activities [7], [8]. This species is abundant in tropical marine environments, including the Indonesian coastline, which is characterized by exceptional marine biodiversity[9]. Its availability and diverse metabolic profile provide a compelling rationale to explore C. lentillifera as a natural source of compounds capable of interacting with biological targets associated with C. acnes, particularly CALipase. Despite its potential, molecular-level investigations examining interactions between metabolites of this alga and CALipase remain limited.

Therefore, this study aims to assess the ability of bioactive compounds from C. lentillifera to interact with CALipase using a molecular docking approach. This work contributes to the identification of natural inhibitor candidates targeting a key virulence enzyme of C. acnes and provides new molecular insight that may support the development of safer, plant-based anti-acne strategies.

Methodology

The structural data of *Cutibacterium acnes* lipase (CALipase) (PDB ID: 6KHM) were retrieved from the Protein Data Bank [10]. The protein structure was prepared in YASARA Structure by removing non-essential water molecules and ions. Only chain A was retained, as it contains the catalytic site within the core domain of the enzyme [11]. The native ligand, heptane-1,1-diol, was preserved as a reference, and a simulation box was generated by extending 5.0 Å in the X, Y, and Z directions from the outermost atoms of the ligand. Docking was performed in YASARA Structure using a flexible–rigid docking protocol and a force-field–based scoring function. To assess the reliability of the docking workflow, the native ligand was redocked using the built-in YASARA docking module, and the predicted pose was compared with the crystallographic pose to ensure parameter consistency.

Ten bioactive compounds from *Caulerpa lentillifera* (**Table 1**) were selected as test ligands. The molecular structures of these compounds were obtained from PubChem and subjected to energy minimization in YASARA Structure to generate stable conformations and reduce steric strain [12]. All compounds were subsequently docked into the CALipase active site using the same simulation box parameters applied during the validation step to maintain consistency across docking results [12].

The primary device used in this study was a computer equipped with an Intel Core i5-4460 processor and 4 GB of RAM, operating on Windows 10 Home Single Language 64-bit. The main software packages included YASARA Structure version 24.4.10 [12] and Discovery Studio Visualizer (DSV) version 25.1.0.24284. All software settings were maintained at their default configurations. The material used in this study consisted of the crystallographic structure of Cutibacterium acnes lipase (CALipase) with PDB ID: 6KHM [10].

Result and Discussion

Molecular docking is a computational approach used to model the structural complexes formed between two or more interacting molecules. Its primary objective is to predict the three-dimensional configuration of a target–ligand complex, making it a key technique in modern drug discovery. Molecular docking provides essential tools for drug design and analysis, including the prediction of molecular interactions and convenient access to structural databases widely used in medicinal chemistry [13].

In this study, the selected target was Cutibacterium acnes lipase (CALipase). Structurally, CALipase consists of two functional domains. The first is the core domain, which contains the catalytic triad Ser114, Asp252, and His285 and is responsible for the hydrolysis of sebum triglycerides. The second is the hydrophobic lid domain, which is dominated by bulky aromatic residues such as Phe176, Phe179, Phe211, and Trp192 [14]. This domain functions as a dynamic gate that regulates substrate access to the active site. Because of this gating role, ligand interactions in either the core or lid domain may influence the overall enzymatic activity [2]. These structural features are represented in the crystallographic model of CALipase (PDB ID: 6KHM) [10]. Previous studies have also shown that the catalytic triad can act as a potential binding region for inhibitory molecules [15], which supports its relevance as a key interaction site in the present analysis.

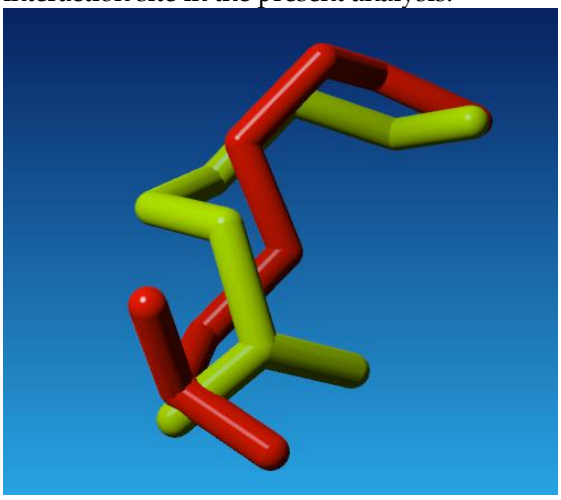

Figure 1. Superposition of the crystallographic pose of the native ligand (red) and the redocked pose (green) within the CALipase binding site (PDB ID: 6KHM). The RMSD value of 1.6482 Å supports the validity of the docking protocol.

The selection of an appropriate PDB structure from the RCSB Protein Data Bank must follow key criteria to ensure reliable docking performance. The protein model should be an X-ray crystal structure with adequate resolution, preferably below 2 Å and acceptable up to 3 Å, to provide accurate atomic coordinates. The selected entry must represent the wild-type (non-mutated) form of the protein and retain all essential residues within the active site. Whenever possible, structures containing a native (co-crystallized) ligand are

preferred, as they facilitate validation of the docking protocol through redocking.

Table 1. Binding energies and interacting receptor residues identified from the docking simulations.

Ligand	Binding energy (Kcal/mol)	Contacting receptor residues
Tridecyne [17]	-5,0846	**Trp 192**, Phe 146, Leu 223, His 285, **Phe 179**, **Phe 176**, Val 140, Ala 254, Leu 38
Thiazole [17]	-2,0760	Trp 192, Ala 180
Rutin [8]	-7,2977	Leu 138, Pro 189, Ala 213, His 203, **Trp 192, Phe 176**, **Phe 211**, Gly 39
Oleamide [8]	-6,2395	His 203, His 285, **Phe 211, Phe 176, Phe 179**, Phe 146, Leu 38, Leu 223, Val 193, Ser 114, Gly 37, **Trp 192**, Ala 254
Isoquercetin [8]	-7,3750	His 285, His 203, **Phe 176, Trp 192,** Leu 38, Gly 39, Ala 213, Asn 209, **Phe 211**
Hexadecanoic acid [17]	-5,6643	Phe 146, Val 140, Ala 254, Leu 223, His 285, **Phe 176,** Leu 38, **Phe 179, Trp 192**
Catechin [8]	-7,3772	Ala 213, **Phe 211**, **Ser 114,** Glu 286, His 203, Leu 38, **Phe 176**
Alpha-pinene [17]	-5.0138	Val 140, His 285, Phe 146, **Phe 179, Trp 192,** Leu 38, **Phe 176**, Leu 223
2-Methylbutanoic anhydride [17]	-5,4072	Leu 38, Trp 115, His 203, Val 193, **Trp 192, Phe 176, Phe 179**
1-Methyl-4-(1-methylethenyl)cyclohexane [17]	-5,3224	Phe 146, **Phe 176,** Met 118, Val 140, His 285, Leu 38, **Trp 192,** His 203
Native Ligand	-4.3831	**His 285**, Trp 115, Met 118, **Phe 176**, **Phe 179**, Phe 146, Val 140, **Trp 192**, Ala 254

Note: Bolded residues indicate key CALipase residues involved in ligand binding.

Before the docking process was performed, the method was validated through redocking of the native ligand. The validation parameter used was the Root Mean Square Deviation (RMSD), where an RMSD value of ≤ 2 Å is generally considered indicative of acceptable accuracy [16]. In this study, the native ligand produced a redocked pose with an RMSD of 1.6482 Å, which falls within the acceptable range. Therefore, the docking procedure was deemed reliable for evaluating the ligands (Figure 1).

Once the docking protocol was validated, all selected metabolites from Caulerpa lentillifera were docked into the CALipase binding site. The native ligand was included as a positive control to provide a reference for comparing both binding affinity and interaction patterns. The analysis focused on the predicted free binding energy (ΔGbinding) and the specific amino acid residues involved in ligand–protein interactions. Docking poses were ranked according to their ΔG binding values, with lower energies indicating more stable and favorable binding [16].

As shown in Table 1, the native ligand formed a single hydrogen bond with His285 of the catalytic triad, while additional hydrophobic contacts with Phe176, Phe179, and Trp192 within the lid domain contributed to complex stability. This interaction profile demonstrates that the native ligand engages key structural regions of CALipase, with the aromatic residues of the lid domain playing a central role in stabilizing the binding pose.

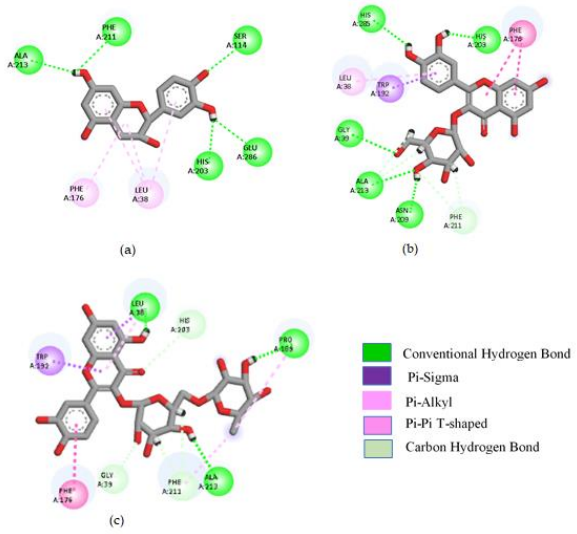

Figure 2. (a) Interaction profile of catechin with CALipase (PDB ID: 6KHM); (b) Interaction profile of isoquercetin with CALipase (PDB ID: 6KHM); (c) Interaction profile of rutin with (PDB ID: 6KHM CALipase).

The docking analysis revealed notable differences in both the binding affinities and the residue interaction profiles of the tested compounds toward CALipase (Table 1). Most of the compounds were able to interact with key residues located either in the catalytic core domain or within the lid domain. Among the

ten evaluated ligands, two compounds, isoquercetin and catechin, displayed the most prominent interaction patterns, as they engaged both the catalytic triad and the aromatic residues of the lid domain.

Isoquercetin formed a hydrogen bond with His285, one of the catalytic triad residues, in addition to hydrophobic contacts with Phe176, Phe211, and Trp192. Catechin, on the other hand, established a hydrogen bond with Ser114 in the core domain and also interacted hydrophobically with Phe211 and Phe176 in the lid domain (**Figure 2**). The remaining seven compounds primarily interacted with residues within the lid domain, most frequently Trp192, Phe176, and Phe179, but did not reach the catalytic triad (**Table 1**).

The binding affinity analysis showed that most of the ligand exhibited lower ΔG binding than the native ligand, with variations across the molecules reflecting differences in their ability to stabilize the CALipase–ligand complex. Catechin displayed the strongest affinity, followed by isoquercetin and rutin, with binding energies of −7.3772, −7.3750, and −7.2977 kcal/mol, respectively. The negative ΔG binding indicate a spontaneous binding process and the formation of a thermodynamically stable complex [16]. The combined interaction profiles and binding stability indicate that these three compounds may act as promising CALipase inhibitors and hold potential as lead candidates for the development of nature-derived anti-acne agents.

These findings strengthen the role of Caulerpa lentillifera phytochemicals as a source of bioactive compounds with antibacterial potential, particularly against C. acnes. The ability of several metabolites to interact directly with the catalytic triad as well as with residues on the lid domain suggests two possible inhibition mechanisms: restricting substrate access to the active site or directly impairing the catalytic residues themselves. Both inhibitory modes are biologically relevant, as CALipase mediates the hydrolysis of sebum triglycerides into pro-inflammatory free fatty acids. Thus, the formation of stable ligand–protein complexes may reduce enzymatic activity and ultimately diminish the production of free fatty acids that drive inflammatory responses in acne vulgaris.

Conclusion

This study identified two compounds, isoquercetin and catechin, that interact directly with the catalytic triad as well as key residues within the lid domain of CALipase, while rutin predominantly engages residues in the lid domain. All three ligands exhibited lower free binding energies than the native ligand (−7,3772; −7,3750; and -7,2977 kcal/mol, respectively), indicating stronger and more stable predicted interactions. These findings suggest that the bioactive metabolites of Caulerpa lentillifera may serve as promising candidates for anti-acne therapy through CALipase inhibition. Nevertheless, these conclusions are preliminary. Further validation, including molecular dynamics simulations to assess binding stability over time, as well as in vitro and in vivo studies to confirm lipase inhibition and biological activity, is required before these compounds can be considered viable therapeutic leads

Author Contributions

Conceptualization, A.D.A. and S.A.I.M.; methodology, A.D.A.; software, F.P.R.; validation, A.D.A., S.A.I.M., and F.P.R.; formal analysis, F.P.R.; investigation, F.P.R.; resources, A.D.A.; data curation, F.P.R.; writing—original draft preparation, F.P.R.; writing—review and editing, A.D.A. and S.A.I.M.; visualization, F.P.R.; supervision, A.D.A.; project administration, A.D.A.; funding acquisition, A.D.A. All authors have read and agreed to the published version of the manuscrip

Funding

Please this research received no external funding.

Conflicts of Interest

"The authors declare no conflict of interest."

References

[1] Y. B. Lee, E. J. Byun, and H. S. Kim, "Potential role of the microbiome in acne: A comprehensive review," Jul. 01, 2019, *MDPI*. doi: 10.3390/jcm8070987.

[2] M. Pengsawang, B. Toviwek, W. Sangthong, A. Boonmee, P. Chairatana, and P. Pongprayoon, "The binding modes of brazilin and hematein from Caesalpinia sappan L. to Cutibacterium acnes lipase: Simulation studies," *PLoS One*, vol. 20, no. 3 March, Mar. 2025, doi: 10.1371/journal.pone.0318706.

[3] C. Sun, Y. Na, Z. Wang, T. Zhu, and X. Liu, "Phytochemicals, promising strategies combating Cutibacterium

acnes," 2024, *Frontiers Media SA*. doi: 10.3389/fphar.2024.1476670.

[4] G. Condrò, M. Guerini, M. Castello, and P. Perugini, "Acne Vulgaris, Atopic Dermatitis and Rosacea: The Role of the Skin Microbiota—A Review," Oct. 01, 2022, *MDPI*. doi: 10.3390/biomedicines10102523.

[5] M. Liang *et al.*, "Phytochemicals with activity against methicillin-resistant Staphylococcus aureus," *Phytomedicine*, vol. 100, p. 154073, Jun. 2022, doi: 10.1016/j.phymed.2022.154073.

[6] W. F. Yap, V. Tay, S. H. Tan, Y. Y. Yow, and J. Chew, "Decoding antioxidant and antibacterial potentials of Malaysian green seaweeds: Caulerpa racemosa and caulerpa lentillifera," *Antibiotics*, vol. 8, no. 3, Sep. 2019, doi: 10.3390/antibiotics8030152.

[7] A. U. Saputri, L. Purnamayati, and A. D. Anggo, "Aktivitas Antibakteri Anggur Laut (Caulerpa lentillifera) TERHADAP Staphylococcus aureus dan Escherichia coli," *Jurnal Ilmu dan Teknologi Perikanan*, vol. 1, no. 1, pp. 15–20, Jun. 2019, doi: 10.14710/jitpi.2019.5240.

[8] S. Yoojam, A. Ontawong, N. Lailerd, K. Mengamphan, and D. Amornlerdpison, "The enhancing immune response and anti-inflammatory effects of caulerpa lentillifera extract in raw 264.7 cells," *Molecules*, vol. 26, no. 19, Oct. 2021, doi: 10.3390/molecules26195734.

[9] N. Syakilla *et al.*, "A Review on Nutrients, Phytochemicals, and Health Benefits of Green Seaweed, Caulerpa lentillifera," Sep. 01, 2022, *MDPI*. doi: 10.3390/foods11182832.

[10] H. J. Kim, B.-J. Lee, and A.-R. Kwon, "The grease trap: uncovering the mechanism of the hydrophobic lid in Cutibacterium acnes lipase," *J Lipid Res*, vol. 61, no. 5, pp. 722–733, May 2020, doi: 10.1194/jlr.RA119000279.

[11] A. P. Singh, H. Arya, V. Singh, P. Kumar, and H. K. Gautam, "Identification of natural inhibitors to inhibit C. acnes lipase through docking and simulation studies," *J Mol Model*, vol. 28, no. 9, p. 281, Sep. 2022, doi: 10.1007/s00894-022-05289-3.

[12] A. D. Ananto, H. D. Pranowo, W. Haryadi, and N. Prasetyo, "Flavonoid Compound of Red Fruit Papua and It Derivatives Against Sars-cov-2 mpro: An In Silico Approach," *J Appl Pharm Sci*, vol. 14, no. 12, pp. 90–97, 2024, doi: 10.7324/JAPS.2024.177392.

[13] N. More, D. Wagh, C. Chavan, R. L. Navasare, and D. H. Rajput, "A Review on Molecular Docking," *INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES*, vol. 2, no. 12, 2024, doi: 10.5281/zenodo.14274558.

[14] M. Lin, L. He, G. Ye, and X. Zhao, "Computational methodology and molecular dynamics analysis of andrographolide bioactivity against Cutibacterium acnes," *Front Chem*, vol. 13, 2025, doi: 10.3389/fchem.2025.1627758.

[15] A. C. Y. Yu, G. Volkers, S. A. K. Jongkees, L. J. Worrall, S. G. Withers, and N. C. J. Strynadka, "Crystal structure of the *Propionibacterium acnes* surface sialidase, a drug target for *P. acnes* -associated diseases," *Glycobiology*, vol. 32, no. 2, pp. 162–170, Mar. 2022, doi: 10.1093/glycob/cwab094.

[16] R. G. Putri, M. Safithri, H. Husnawati, and R. Kurniasih, "Penambatan Molekuler Senyawa Aktif Sirih Merah (Piper crocatum) pada Butirilkolinesterase sebagai Kandidat Antialzheimer," *ALCHEMY Jurnal Penelitian Kimia*, vol. 19, no. 1, p. 68, Mar. 2023, doi: 10.20961/alchemy.19.1.59676.68-85.

[17] R. Rajasegaran, A. Elengoe, S. Pin Woo, M. A. Abd Hamd, N. Yahaya, and S. Hamid, "Analysis of Volatile Compounds in Caulerpa lentillifera for Anti-Proliferative Studies in HEPG2 Liver Cancer Cells and in silico Comparison," *Pharmacognosy Res*, vol. 16, no. 4, pp. 854–860, Nov. 2024, doi: 10.5530/pres.16.4.97.