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In silico evaluation of Catechin derivatives as potential Anti-Quorum-Sensing Agents targeting LasR in Pseudomonas aeruginosa

Nia Karunia [1], **Raudatul Jannah** [1], **Rini Madyastuti Purwono** [2*]

[1] Master Students of Animal Biomedical Sciences, IPB University, Bogor, West Java, Indonesia
[2] Division of Pharmacology and Toxicology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, West Java, Indonesia

Abstract: Quorum sensing (QS) plays an essential role in biofilm production in *Pseudomonas aeruginosa*, a significant cause of nosocomial infections and antibiotic resistance. One herb thought to have antibiofilm activity is green tea (*Camellia sinensis*), which contains catechins and their derivatives. This study aimed to evaluate the molecular interactions between catechin derivatives and LasR, a key quorum-sensing regulator involved in P. aeruginosa biofilm formation, using an in silico approach. Protein and ligand structures are obtained from the Protein Data Bank (RCSB PDB) and PubChem. Molecular docking was simulated with BIOVIA Discovery Studio, AutoDock, and PyMol applications. Visualizations were performed with the LigPlot+ application. Druglikeness was tested based on Lipinski's rule of five and toxicity prediction using ProTox 3.0. Molecular docking studies showed differences in binding affinity and interaction between catechin and its derivatives against protein LasR from *P. aeruginosa*. EGC and EC have higher binding affinity and many similarities in amino acid residues against the natural ligand OHN. Drug-likeness evaluation showed that only the EGCG compound did not meet the criteria of Lipinski's rule of five. Toxicity predictions show that all compounds are in class 4, except for EGC (class 6). Overall, EGC was predicted to be the most promising computational candidate for further investigation as a potential LasR-targeting quorum-sensing inhibitor.

Keywords: Catechin; Derivatives; LasR; Molecular Docking; Drug-likeness

INTRODUCTION

Pseudomonas aeruginosa is a Gram-negative bacterium that is a leading cause of nosocomial infection and can be more severe in immunocompromised patients. *P. aeruginosa* is an opportunistic bacterium that is related to healthcare infections like ventilator-associated pneumonia (VAP), Intensive care unit infection, surgical site infection, and becomes the main cause of urinary tract infections with the number of cases of approximately 10-15% worldwide.[1] *P. aeruginosa* infections have become increasingly difficult to treat due to multiple resistance mechanisms, including biofilm formation, immune evasion, and the production of virulence factors. According to the data from the US Centers for Disease Control and Prevention, it is estimated that about 51.000 infections caused by *P. aeruginosa* occur in the US for several years, with 13% of the infections associated with multidrug-resistant (MDR).[2] The incidence of antimicrobial resistance of *P. aeruginosa* in Indonesia has increased in recent years. Data from the National Hospital, Dr. Cipto Mangun Kusumo, the resistance of *P. aeruginosa* against carbapenem is 21.9%.[3]

Corresponding author.
E--mail address: keyla@apps.ipb.ac.id (Rini Madyastuti Purwono)
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The capacity of *P. aeruginosa* to form biofilm is intimately linked to its resistance. A bacterial community aggregates extracellular matrix components to form a structure known as a biofilm.[4] The biofilm environment is protective, making it challenging to eradicate *P. aeruginosa* infection because bacterial cells are resistant to the immune system, antibiotics, and stress. Quorum sensing, a sort of molecule-mediated communication that requires the release of specific chemicals into the extracellular environment, is a cell-to-cell communication mechanism that regulates biofilm formation and virulence factor production in bacteria.[5] Without these molecules, biofilms cannot obtain the structure of a mature biofilm in the environment, nor can they expand or release planktonic cells as a mature formation. *Acyl-homoserine lactones* (AHL) are crucial molecules for biofilm formation in *P. aeruginosa*, as they facilitate quorum sensing.[6] In *P. aeruginosa*, two QS systems, LasR and Rhl, control the synthesis and perception by the transcription factors LasR and Rhl of the acyl-homoserine lactones (AHL) *N*-(3-oxododecanoyl)-l-homoserine lactone (3-oxo-C12-HSL) and *N*-butanoyl-l-homoserine lactone (C4-HSL), respectively.[7]

Several antibiotic groups, such as carbapenems, sulfonamides, and aminoglycosides, which were previously more effective, have become less effective against certain infections due to the increased drug resistance of organisms.[8] Over the past 25 years, the use of plants in alternative medicine has increased. Rich sources of bioactive compounds, medicinal and aromatic plants (MAPs), can be utilized as drugs while slowing the spread of antibiotic resistance. Green tea (*Camellia sinensis*) is one of these herbal plants. The high catechin concentration of green tea, which accounts for about 15-27% of the dry weight of *Camellia sinensis* leaves, is thought to be responsible for its health benefits. Epicatechin (EC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) are the main catechins in green tea.[9]

Several recent computational studies have explored LasR as a promising target for quorum-sensing inhibition using natural compounds and phytochemicals[10]. Previous studies have demonstrated that catechin compounds possess potential antibacterial and antibiofilm activities[7,11], but systematic comparisons between catechin derivatives and the LasR protein have not been further explored. In particular, earlier docking studies often relied primarily on binding affinity values without integrating residue-level interaction analysis or physicochemical and toxicity-related properties. Meanwhile, research into the antibacterial properties of essential oils continues to grow. Eugenol is an aromatic compound obtained from essential oil plants that has the potential to act as an antimicrobial, antibiofilm, anti-virulence, and anti-QS agent against a variety of bacteria[12]. This study is designed as a confirmatory and comparative in silico analysis to evaluate the binding characteristics of catechin derivatives toward LasR, rather than to propose a novel quorum-sensing inhibitor. Docking validation can provide incremental insight into how structural differences among catechin derivatives influence their predicted interactions with the LasR ligand-binding domain.

MATERIAL AND METHOD

Protein and ligand preparation

The crystallographic structure of *Pseudomonas aeruginosa* LasR was obtained from the Protein Data Bank (IDs 3IX3). Water molecules and co-crystalized ligands were removed by BIOVIA Discovery Studio Visualizer v24.1.0.23298. Proteins are stored in ".pdb" format as "receptors", and native ligands are also in .pdb format. The three-dimensional structures of Epigallocatechin Gallate (EGCG) (PubChem CID = 65064), Epigallocatechin (EGC) (PubChem CID = 72277), Epicatechin gallate (ECG) (PubChem CID = 107905), Epicatechin (EC) (PubChem CID = 72276), and Eugenol (PubChem CID

= 3314) were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) database and used as ligand structures for molecular docking analysis. The structure of the ligand was downloaded in ".SDF" format and converted to a ".pdb" file with software Open Babel 2.4.1. All the ligand structures were generated via AutoDock tools employed for the preparation of a ".pdbqt" file of the receptor by the addition of polar hydrogens, computation with Kollman charges, and ligand with the definition of the number of torsions and the addition of Gasteiger charges. Energy minimization was not performed prior to docking.

Grid box

The grid box was set up to accurately define the binding sites between proteins and ligands. It was also arranged to pinpoint the specific binding site coordinates within the protein. The size of the grid box was adjusted along the x, y, and z axes, using Angstrom (Å) units with a ligand as a center. The grid box center and grid size coordinates from proteins were saved in a Notepad file in .txt format for the next use in molecular docking.

Molecular docking simulations

After preparing the receptor and ligand structures in .pdbqt format, molecular docking was carried out using AutoDock Vina 1.1.2. Prior to the docking process, a configuration file had to be created, which included the receptor and ligand file names, the grid center and size coordinates, the exhaustiveness value was set to 16, the number of modes was 10, as well as the output file name for the docking results. The receptor was treated as rigid, while ligands were allowed full conformational flexibility, and appropriate protonation states were assigned prior to docking. The docking was executed via the command prompt. Docking validation was performed by redocking the native ligand, and the root-mean-square deviation (RMSD) between the docked and crystallographic conformations was calculated after superimposition; values below 2.0 Å were considered acceptable. For each ligand, the top 10 binding poses were generated and ranked based on the Vina scoring function. The docking pose selected for further analysis was determined based on both the binding affinity value and the similarity of binding orientation relative to the native ligand within the LasR binding pocket. This procedure provided the predicted binding affinity and ligand–protein interaction conformations.

Analysis and visualization

Validation of redocking between protein and natural ligand was conducted using PyMOL 3.1.0 and LigPlot+ v.2.2.9 to produce two-dimensional docking representations of all ligands. Two types of interaction were analyzed: hydrogen bond and hydrophobic interaction. The interaction is between an amino acid residue on the target side and the functional group of the ligand side. PyMol was also used to make three-dimensional visualization.

Drug-likeness and Toxicity Prediction

Evaluation of all the compounds' drug-likeness refers to Lipinski's Rule of Five using a web server (https://scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). The analysis is based on five criteria: molecular weight, lipophilicity (LogP), hydrogen bond donor, hydrogen bond acceptor, and molar refraction. In contrast, toxicity prediction uses the ProTox 3.0 web server (https://tox.charite.de) to determine LD50 and toxicity class.

RESULTS AND DISCUSSION

Grid box positioning was based on the crystallographic coordinates of the native ligand-binding pocket of LasR, ensuring that docking simulations were restricted to the biologically relevant quorum-sensing ligand-binding domain.

Gridbox parameters used are listed in Table 1 with a focus on the location of the ligand. Redocking of the native ligand N-(3-oxo-dodecanoyl) homoserine lactone (OHN) into the LasR protein (PDB ID: 3IX3) was performed to validate the docking protocol. Redocking shows an RMSD value of 1.830 Å (Table 2). This result means that the receptor is valid and can be continued for molecular docking studies. Visualization of the native ligand and redocking ligand also shows overlapping positions, as in Figure 1.

Table 1. Gridbox parameters

Macromolecular Code	Gridbox					
	Center			Dimensions (Å)		
	X	Y	Z	X	Y	Z
3IX3	11.003	3.361	21.332	40	40	40

Table 2. Redocking results from the RMSD value

Target Protein Name	Natural Ligands	PDB Code	RMSD (Å)	Condition
LasR	N-(3-oxo-dodecanoyl) homoserine lactone (OHN)	3IX3	1.830	<2.0 Å

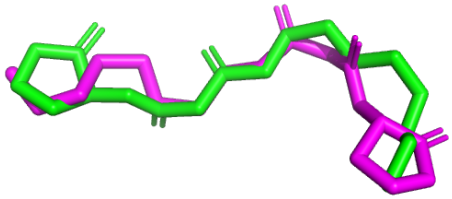
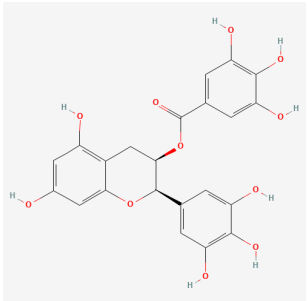
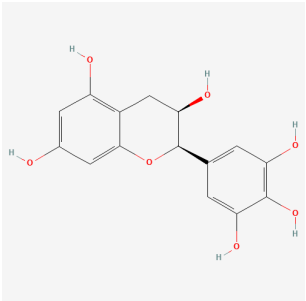


Figure 1. Crystallographic (green) and redocked (magenta) ligand overlay results

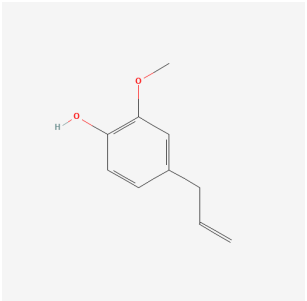
The selected ligands and their chemical structures are shown in figure 2, table 3 shows the calculated binding energies, indicating that most compounds had strong binding affinity for the LasR protein. OHN, as a standard ligand, binds to the LasR protein with a binding affinity of -7.7 kcal/mol. Based on the five selected plant-derived compounds tested, the Epicatechin (EC) compound has the highest binding affinity, which is -10.2 kcal/mol. While the eugenol compound has the lowest binding affinity, which is -6.6 kcal/mol. The binding affinities of the tested compounds were compared with that native ligand under the same docking conditions.



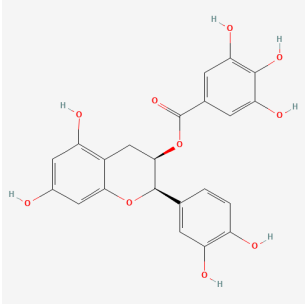
Epigallocatechin Gallate (EGCG)



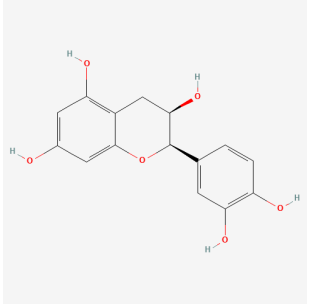
Epigallocatechin (EGC)



Eugenol



Epicatechin gallate (ECG)



Epicatechin (EC)

Figure 2. Chemical structure of major green tea catechins and eugenol

Table 3. Docking results and amino acid residues that bound to the LasR protein

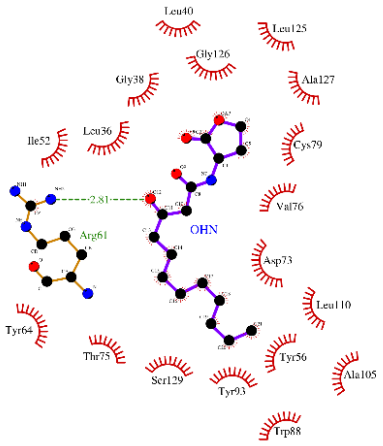
Compound	Amino Acid Residues Hydrogen Bonds	Residue involved in a Hydrophobic interaction	Number of binding sites similar to the standard ligand	Binding affinity (kcal/mol)
OHN (native ligand)	Arg61	Leu40, Leu125, Gly126, Gly38, Ala127, Leu36, Ile52, Cys79, Val76, Asp73, Leu10, Ala105, Tyr56, Trp88, Tyr93, Ser129, Thr75, Tyr64	All	-7.7
EGCG	Glu48, **Tyr56**, Gly54, Ser20, **Ile52**	Asp65, Pro57, **Arg61**, Ala58, Asn55, Val53, Lys16, Ala50, Asn49	3	-7.3
EGC	**Thr75**, **Leu125**, **Tyr64**	**Arg61**, **Tyr56**, **Leu36**, **Trp88**, **Ser129**, **Asp73**, **Ala127**, **Cys79**, **Val76**, **Gly126**, **Leu40**, **Gly38**, Ala50, Leu39, Ala70	15	-10.1
ECG	Glu48, **Tyr56**, Gly54, Ser20, **Ile52**	Asn49, Ala50, **Arg61**, Ala58, Asn55, Val53, Lys16, Asp65	3	-7.5
EC	**Thr75**	**Val76**, **Asp73**, **Ser129**, **Tyr56**, **Leu36**, **Tyr64**, **Arg61**, Ala50, **Gly38**, **Leu40**, Leu39, **Ala127**, **Gly126**, **Leu125**, **Cys79**	14	-10.2
eugenol	Thr115, **Ser129**, **Tyr56**	**Leu36**, **Tyr64**, **Arg61**, Tyr47, **Ile52**, **Asp73**, **Val76**, **Ala127**, **Thr75**	10	-6.6

Figure 3 shows a LigPlot+ image of the LasR protein with some ligands and the 3D visualization. The LasR protein has only one hydrogen bond with its native ligand (OHN) Arg61 and involves 18 amino acid residues in hydrophobic contacts. Each of the tested ligands also successfully formed hydrogen bonds with the LasR protein. Epicatechin (EC) formed one hydrogen bond with Thr75. EGCG formed five H-bonds with Glu48, Tyr56, Gly54, Ser20, Ile52 and ECG also formed five H-bonds with Glu48, Tyr56, Gly54, Ser20, Ile52. Three H-bonds were formed from EGC (Thr75, Leu125, Tyr64) and eugenol (Thr115, Ser129, Tyr56). Several catechin derivatives exhibited interactions with the LasR protein residues also involved in native ligand binding. For example, in the EGCG compound, residues Tyr56, Ile52, and Arg61 overlap with the native ligand residues.

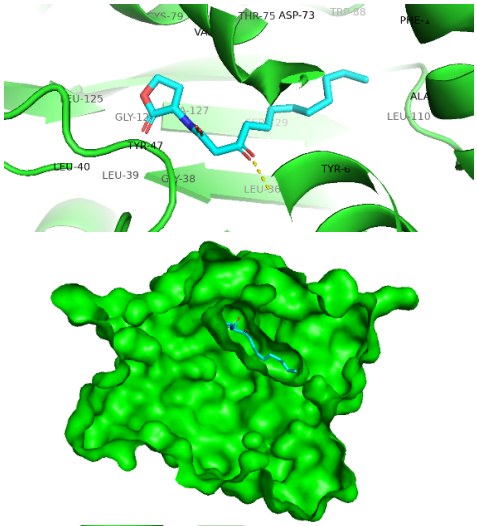
In addition to binding affinity, the similarity of interacting residues with the native ligand provides a more biologically relevant indicator of potential activity. Compounds that share key binding residues with the native ligand are more likely to mimic its binding mode within the ligand-binding domain of LasR. In this study,

EGC showed a higher number of overlapping residues with the native ligand compared to other compounds, suggesting a greater likelihood of competitive interaction with the natural autoinducer. Therefore, residue-level similarity may be considered more informative than binding affinity alone in evaluating potential quorum-sensing inhibitors.

A.



Complex LasR_OHN (native ligand)



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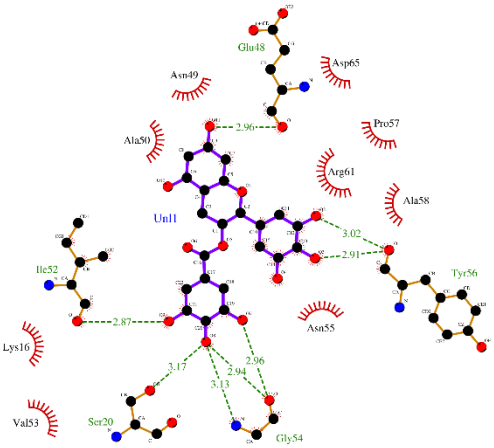
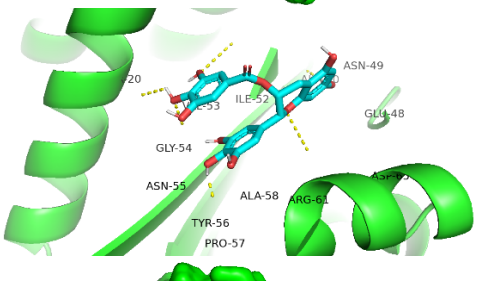
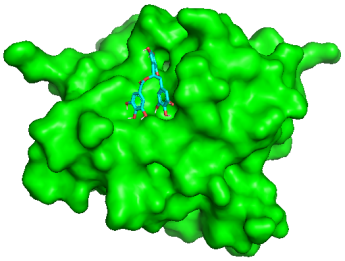
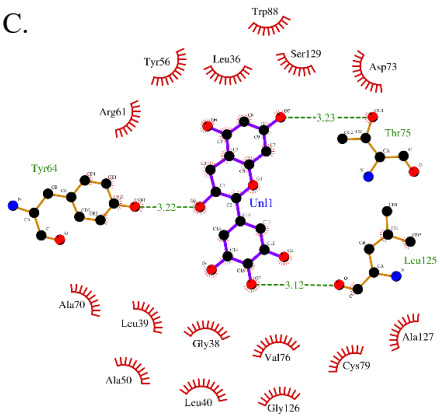


Complex LasR_EGCG

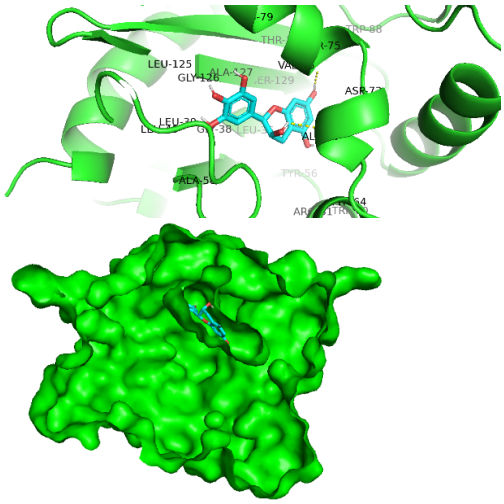




C.



Complex LasR_EGC



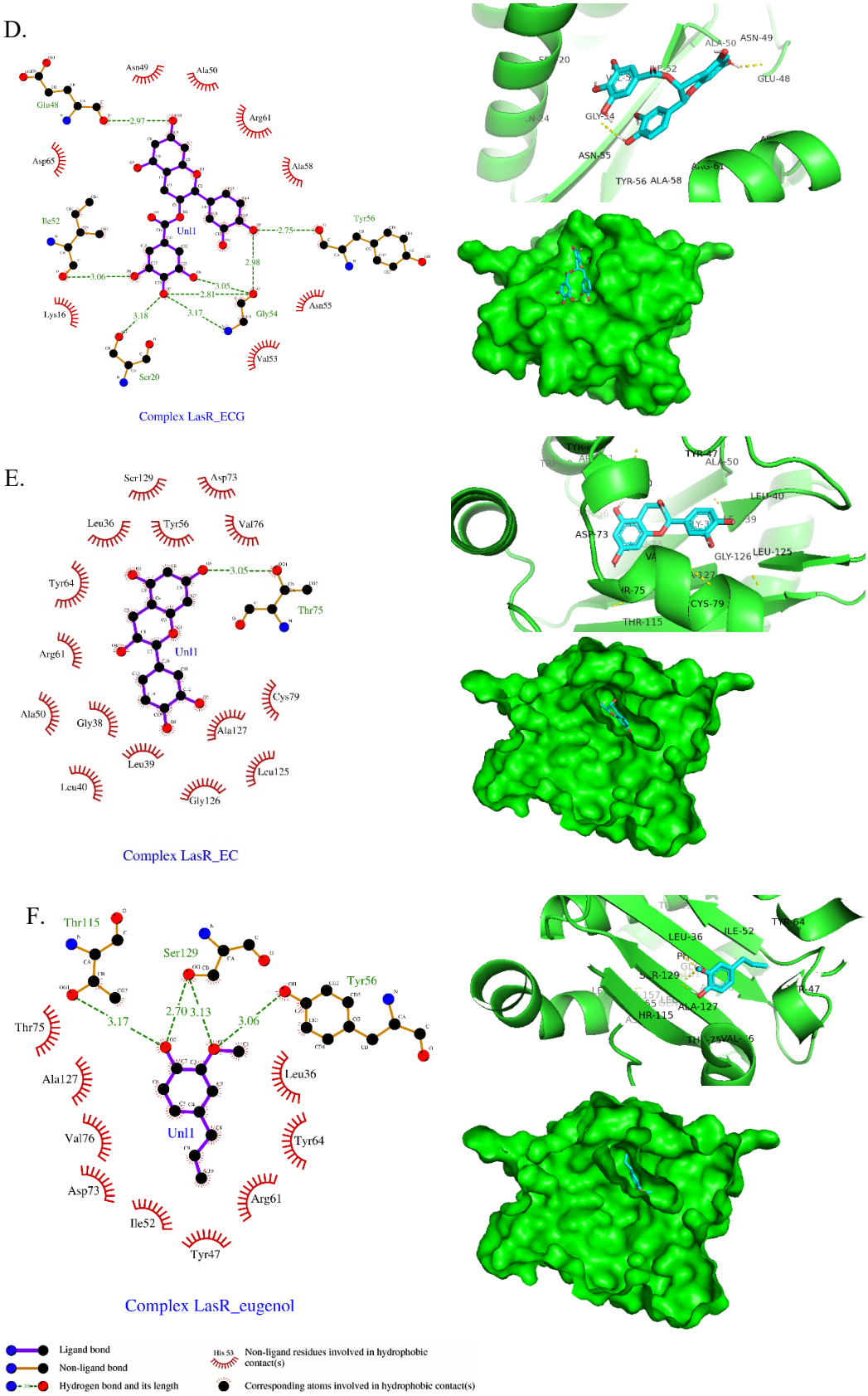


Figure 3. Two-dimensional LigPlot and three-dimensional PyMol image interaction of the Complex LasR protein and ligands. (A) LasR protein and native ligand; (B) LasR protein and EGCG; (C) LasR protein and EGC; (D) LasR protein and ECG; (E) LasR protein and EC; (F) LasR protein and eugenol

Drug-likeness evaluation based on Lipinski's Rule of Five showed that only the EGCG exhibited two violations of Lipinski's Rule of Five and was therefore classified as non-compliant. In contrast, EGC and ECG each showed one violation but were still considered acceptable under Lipinski screening criteria, while EC and eugenol fully complied with all parameters (Table 4). The predictive toxicity outcomes using ProTox 3.0 are presented in Table 5. Most compounds are in class 4, whereas EGC was assigned to class 6 with a higher predicted LD50 value. This result suggests a comparatively lower estimated acute toxicity for EGC within the limitations of computational prediction.

Table 4. Drug-likeness results based on Lipinski's Rule of Five

Compound	Parameter					Number of Violations	Lipinski Assessment
	Mol. Weight (g/mol)	Log *P*	H-Bond Donor	H-Bond Acceptor	Molar Refractivity		
EGCG	458.00	2.23	**8**	**11**	108.92	2	Not compliant
EGC	306.00	1.25	**6**	7	74.28	1	Acceptable (1 violation)
ECG	442.00	2.52	**7**	10	107.25	1	Acceptable (1 violation)
EC	290.00	1.54	5	6	72.62	0	Fully compliant
Eugenol	164.00	2.12	1	2	48.55	0	Fully compliant

Note: Bolded numbers indicate violations in Lipinski's Rule of Five

Table 5. Results of acute toxicity prediction

Compound	Target parameter		
	LD50	Toxicity class	Classification
EGCG	1000 mg/kg	4	harmful if swallowed
EGC	10000 mg/kg	6	Practically non-toxic / low acute toxicity
ECG	1000 mg/kg	4	harmful if swallowed
EC	1000 mg/kg	4	harmful if swallowed
Eugenol	1930 mg/kg	4	harmful if swallowed

Molecular docking is studied to predict interactions between a receptor protein and its ligand. The important components in docking were estimation of binding affinity and binding pose prediction. While a generously broad docking area may generate too many irrelevant binding poses, a small search space may yield an inadequate number of conformations.[13] There are two options for box determination: a single, bigger blind docking run that encompasses the entire protein structure, commonly known as blind docking, or a narrow box focused on a few anticipated binding sites. However, a study shows that with a docking approach focused on areas suspected of being binding sites increases the efficiency and accuracy of ligand-protein docking compared to blind docking.[14] The native ligand is useful as a reference for the ligand to be tested as a comparison for 3D conformation and the type of ligand-protein interaction that occurs, and makes it easier to test the suitability of the parameters used with docking in reality, such as the center of mass and gridbox volume.[15]

The docking was validated by the value of Root Mean Square Deviation (RMSD). An RMSD value less than 2.0 Å means that the calculation results' error is decreasing, making the calculation more accurate. RMSD threshold of less than 2.0 Å was considered acceptable, as it indicates a close reproduction of the crystallographic ligand pose. This criterion is widely used for validating docking protocols involving transcriptional regulators such as LasR, whose ligand-binding domain exhibits limited conformational flexibility. The smaller the RMSD value, the closer the ligand position is to the natural ligand conformation. [16,17]

The target protein may have several pockets or cavities for binding ligands. Some may be buried deep inside the protein, while others may be visible on the surface of the protein.[18] According to the 3D visualization, both EGC and EC ligands occupy the same binding pocket as the native ligand, suggesting that their binding mechanisms are alike. In contrast, EGCG and ECG were observed to bind on the protein surface rather than occupying the native ligand-binding pocket. This binding mode may reduce their plausibility as competitive inhibitors of LasR, as they are less likely to directly interfere with the binding of the natural autoinducer. Surface interactions may still contribute to allosteric effects; however, such mechanisms are generally less predictable and require further validation. This observation further supports the prioritization of EGC, which binds within the canonical ligand-binding domain. Occupation of this pocket by catechin derivatives may competitively interfere with native ligand binding, suggesting a possible mechanism for disrupting quorum-sensing signaling.

Among the five selected phytochemical compounds tested, the binding affinity of EC compound was the highest compared to the other compounds. In addition to binding affinity, the activity of a compound against a protein target can be assessed from the interaction pattern. A substance does not have the best interaction pattern and cannot be said to have the same activity as natural ligands if it has the highest binding affinity value but does not interact with amino acid residues that resemble those of natural ligands.[19] The strongest bonds are hydrogen bonds, which are formed between the protein's amino acids and the ligand's end OH ions. The hydrogen bonds and binding affinity of a ligand increased with the number of hydroxyl groups it contains.[20] Hydrogen bonds and hydrophobic bonds contribute to the mechanical stability of proteins. Although hydrophobic interactions are dominant in the thermodynamic stability of folded proteins, hydrogen bonds are more dominant in providing mechanical resistance.[21]

Based on the bonds formed, the five ligands do not establish hydrogen bonds with the same amino acids. However, several similarities were found in other amino acid residues. For instance, the EC compound only formed one hydrogen bond but has 14 amino acids in common with the native ligand. On the other hand, the EGC compound formed three hydrogen bonds and has 15 amino acid similarities. Therefore, compound prioritization was not based solely on the docking score. Previous studies have suggested that docking scores alone are insufficient for identifying the most relevant ligand-protein interaction because the top-ranked binding pose does not always correspond to the biologically active conformation [16]. Instead, interaction patterns with key amino acid residues and complementary pharmacological properties should also be considered in candidate selection. EGC was selected as the most promising candidate because it demonstrated a more favorable overall interaction profile, including a high binding affinity, the highest number of overlapping residues with the native ligand (15 residues), a greater number of hydrogen bonds (three bonds), and a superior predicted toxicity profile (toxicity class 6). Taken together, these findings suggest that EGC may more closely mimic the native ligand interaction pattern within the LasR binding pocket and therefore represents a more suitable candidate for further investigation as a potential quorum-sensing inhibitor.

Several residues, such as Tyr56, Trp60, Asp73, and Ser129, were particularly crucial in maintaining the binding stability.[22,23] Cys79 in the ligand-binding domain of LasR also appears to be important for ligand recognition and folding of this domain to potentiate DNA binding.[24] Although bonds are not formed with all of these key residues, several residues can still be found separately in the tested compounds. Previous studies have shown that disruption or competitive occupation of the residues impairs LasR-mediated transcriptional activation by interfering with native autoinducer recognition and receptor activation.[25] Although EC exhibited a slightly higher binding affinity than EGC, the prioritization of EGC is based on its more favorable overall interaction profile. EGC formed a greater

number of hydrogen bonds, showed higher similarity to the native ligand-binding residues, and demonstrated a superior predicted toxicity profile. In addition, the EGC component in green tea is more than EC. The largest components of green tea are EGCG (40–69%), followed by EGC (12–23%), ECG (13–21%), and EC (5–9%).[26]

As a comparison, eugenol, which is an essential oil, is also docked. Eugenol was included in this study as a reference compound due to its reported antibacterial and antibiofilm properties. However, it is structurally distinct from catechin derivatives and does not belong to the same chemical class. The docking results showed that eugenol exhibited lower binding affinity and fewer similarities in binding residues compared to catechin compounds. Therefore, its role in this study should be interpreted as a general comparator rather than a directly equivalent ligand, and its mechanism of action may differ from that of catechin-based compounds.

Drug-like and non-drug-like compounds can be distinguished using Lipinski's rule of five. Due to drug resemblance, it forecasts a high likelihood of success or failure for compounds that meet two or more of the following criteria: molecular mass less than 500 daltons, high lipophilicity (expressed as LogP less than 5), less than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors, and molar refractivity should be between 40 and 130.[27] Compounds that adhere to the five principles will have improved pharmacokinetic characteristics and higher bioavailability in the organism's metabolic processes when used orally. The P value is related to the hydrophobicity of a compound; a higher P value indicates increased hydrophobicity. The total quantity of hydrogen-bond donors is derived from adding NH and OH groups. The count of hydrogen bond acceptors is determined by summing the amounts of nitrogens and oxygens. [28,29]

Evaluating the possible toxicity of a compound at an early stage can improve its safety profile. The lethal dose 50 (LD50) refers to the median lethal dose, indicating the amount of a substance required to kill 50% of test subjects upon exposure.[30] LD50 values are given in [mg/kg] and classified as: class I (LD50≤5), class II (5 < LD50 ≤ 50), class III (50 < LD50 ≤ 300), class IV (300 < LD50 ≤ 2000), class V (2000 < LD50 ≤ 5000), and class VI (LD50 > 5000).[31] Taken together, these findings suggest that catechin derivatives may interfere with LasR signaling by occupying the AHL-binding pocket and interacting with key regulatory residues, thereby warranting further experimental validation.

This study is based solely on molecular docking and in silico ADMET prediction, which inherently present several limitations. Molecular docking simulations rely on a static crystallographic structure of the protein and do not fully account for protein conformational flexibility under physiological conditions. In addition, solvent dynamics and explicit water-mediated interactions are not comprehensively modeled in standard docking protocols. Entropic contributions and long-range dynamic effects are also not considered, which may influence the actual binding stability in biological systems. Therefore, the binding affinities and interaction patterns reported in this study represent computational predictions rather than confirmed biological activity. Consequently, experimental validation through in vitro quorum-sensing inhibition assays, biofilm formation studies, and possibly in vivo models is required to confirm the biological relevance of these findings.

CONCLUSION

Based on the present molecular docking and in silico analyses, catechin-derived compounds from green tea show potential interactions with the LasR protein of *P. aeruginosa*. Among the tested compounds, EGC may represent a promising computational candidate for further investigation as a LasR-targeting quorum-sensing inhibitor. However, these findings are limited to computational

predictions and require further experimental validation to confirm their biological relevance.

AUTHORS' CONTRIBUTIONS

Nia Karunia conducted the research and wrote the manuscript, Raudatul Jannah provided resources and wrote the manuscript, and Rini Madyastuti Purwono reviewed the manuscript. All authors have read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The dataset supporting the findings of this research is accessible from the corresponding author upon request.

DISCLOSURE STATEMENT

The author's opinions in this article are their own and do not necessarily align with the policies of their respective affiliated institutions. The data is the result of the author's research and has never been published in other journals.

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