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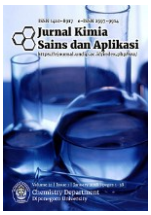

Comparative Docking of Laccase Enzyme Isoforms on Quinolone Pollutants

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Abstract

A molecular study employed molecular docking simulations to investigate potential interactions between the laccase enzyme and the quinolone compound. Quinolones, a class of synthetic antimicrobial agents that are also environmental pollutants, were tested for their interactions with the laccase enzyme, known for degrading various organic compounds. This study investigated the binding affinity and stability of the laccase-quinolone complex, with and without water, using both rigid and flexible docking methods. The docking result suggests feasible recognition/binding of quinolones by the laccase active site regions, with binding energies ranging from -6.879 to -8.633 kcal·mol^{-1} in the absence of water and from -5.543 to -6.547 kcal·mol^{-1} in the presence of water. The RMSD values for the laccase-quinolone complex varied between 0.7519 and 1.655, indicating a stable interaction, particularly with nalidixic acid as the ligand. A comparison study was conducted with other laccase enzymes, implying valuable insight into the potential use of *T. hirsuta* laccase for quinolone degradation, offering a promising biotechnological approach for environmental applications. The MD simulations also demonstrated similar results, which enzyme-quinolone complex had a comparatively low RMSF, indicating that the laccase enzyme facilitated the degradation of the quinolone.

1. Introduction

Antibiotics are a type of medicine frequently used to treat symptoms of bacterial infections. They are used in various fields, such as cattle and aquaculture, to prevent disease outbreaks and boost food production yields. Constant use can leave residues in the resulting food products, and antibiotics can be discharged into the environment via soil, water, or sediment [1, 2, 3]. Concerns about antibiotics in the environment arise because they can promote the development of antibiotic-resistant bacteria, with serious consequences for human health.

A previous study [4] has found that antibiotic levels in Jakarta's waterways range from 17 to 1489 ng/L. Furthermore, antibiotic use in Indonesia, especially in animal sectors such as livestock and aquaculture, is expected to increase substantially, forecast to more than quadruple by 2030 [5]. Around 30–90% of the antibiotics are released into the environment via soil, water, or sediment. Antibiotic contamination in the environment continues to increase, perhaps supporting the emergence of antibiotic-resistant microorganisms. Bacterial resistance lowers the efficacy of therapies and treatments [2]. For example, almost 70% of *S. aureus* isolates developed erythromycin resistance 6 months after the initial therapy [6]. Approximately 81% of *E. coli* isolates from water samples in China carry tetracycline resistance genes [7]. This condition can be fatal if the harmful bacteria cause a life-threatening disease.

One potential approach to this problem is to use conventional wastewater treatment plants (WWTPs). However, this approach is ineffective and generates additional issues, such as the accumulation of pollutants,

providing a breeding ground for resistant, harmful bacteria [3, 8, 9]. Bacterial and enzymatic degradation may be a feasible alternative to conventional WWTPs because they can effectively break down antibiotics and produce ecologically benign intermediate products or residues. This procedure is less expensive than other procedures [10].

Trametes hirsuta D7 is a novel variety in Indonesia that produces oxidoreductase enzymes, including laccase [11]. Laccase is a copper-containing oxidoreductase enzyme that is widely generated by white-root fungi. It can catalyze or degrade molecules containing phenol, diamine, methoxy, aniline, aromatic thiol, and other organic substituents commonly found in antibiotic compounds [8, 12]. Laccase can also be used in multipurpose applications, such as the degradation of dye compounds [13] and pharmaceuticals [14], biofuel production [15, 16], and antibiotics [1]. However, its potential to degrade antibiotics remains underexplored. Antibiotics such as quinolones are widely used, leading to their accumulation in the environment, especially in water bodies, where they account for 61.19% of antibiotic pollutants in China [17]. This study employs an in silico approach using QSAR and conformational sampling to evaluate the potential interaction between laccase and quinolones.

2. Experimental

This study used in silico methods to simulate the interactions of the laccase enzyme with quinolone antibiotic compounds. Preliminary studies were first conducted using QSAR analysis to observe the potential biological action against the laccase inhibitor. Next, molecular docking was performed, followed by molecular dynamics.

2.1. Quantitative Structure Analysis Relationship (QSAR) Analysis

The PASSONLINE web-based server (www.way2drug.com) was used to conduct QSAR research on the target quinolone molecular compounds prior to molecular docking. The web-based server receives the structure of the target molecular compound in SMILES format. The potential biological activity of the target chemical compounds against laccase inhibitors is indicated by the P_a (probability of activity) and P_i (probability of inactivity) values from the QSAR data.

2.2. Molecular Docking Simulation using Molecular Operating Environment Software

Before molecular docking, structural data of the antibiotics and laccase enzyme were prepared. The laccase structure was obtained from the Protein Data Bank (PDB ID: 3FPX) via www.rcsb.org [18]. The quinolone compound was obtained from http://pubchem.ncbi.nlm.nih.gov/. The quinolone compounds and their IDs are displayed in Table 1. All structures and ligands of the laccase enzyme were stripped, leaving only the initial sequence and Cu ion. The LigX method was then used for protonation with a strength of 100000 and an energy minimization gradient of 0.05 kcal·mol^{-1}.A^{-2}. The final structure was saved in .moe format. The enzyme active site was identified using Site Finder, with Phe463 selected as the reference site [19].

Molecular docking was performed using the Molecular Operating Environment (MOE 2014.09) with both rigid and flexible docking methods. For rigid docking, the MMFF94X force field was used. Before molecular docking, the downloaded compounds underwent several steps: washing, partial charge, and energy minimization. The quinolones force field was then adjusted to the MMFF94X force field and saved in the .mdb format. The protein and quinolones structure solutions were adjusted to the gas phase. The top 10, top 30, and top 100 poses were analyzed to assess pose convergence and ranking stability. The conformations with the lowest Gibbs free energy ($\Delta G_{binding}$) and a root mean square deviation (RMSD) value of < 2 Å were chosen for further study using the flexible docking approach [2, 20]. Furthermore, the AMBER10 force field was used for flexible docking. The top five poses with the lowest $\Delta G_{binding}$ and RMSD values < 2 Å were identified using molecular docking by utilizing 100 poses [2, 21].

Results of molecular docking of the laccase enzyme 3FPX against other laccase enzymes. This comparison of the laccase enzyme is broken into two parts: homology modeling and molecular docking. SwissModel (https://swissmodel.expasy.org/), a web server-based homology modeling tool, was used. The laccase enzyme structure with ID 3FPX was uploaded in.pdb format, followed by a template search. The homology modeling result with high sequence identity and similarity was applied to molecular docking following the same approach as before.

2.3. Molecular Dynamics Analysis using CABSFLEX 3.0

The CABSFLEX 3.0 web server (https://lcbio.pl/cabsflex3/) enabled MD simulations of the laccase-quinolones complex. This tool enables rapid simulation of protein structural flexibility using coarse-grained protein modeling. Both the laccase enzyme and the laccase enzyme-quinolones structure files in.pdb format were transferred to the CABSFLEX 3.0 server using the SS2 mode, with the protein residues set to semirigid. This MD simulation was performed at 1.4 K across 50 cycles, with the trajectory frames changed to 50 for each cycle [22, 23, 24].

Table 1. The quinolone compounds and their identification numbers

No	Compound	PubChem ID
1	Cinoxacin	2672
2	Flumequine	3374
3	Nalidixic acid	4421
4	Nemonoxacin	11993740
5	Oxolinic acid	4628
6	Pipemidic acid	4831
7	Piromidic acid	4855
8	Rosaxacin	6537204

3. Results and Discussion

3.1. QSAR Analysis

QSAR testing is used to determine whether a structure has biological activity against a protein/enzyme whose structure has been statistically examined. Table 2 shows the result of the QSAR analysis of the target chemicals [25]. Among the quinolone antibiotics examined, only nalidixic acid had biological action against laccase inhibitors. The $P_a > P_i$ values indicated the activity is more probable than inactive, but Pa < 0.5 indicates low confidence and requires caution. The remaining quinolone compounds lacked biological activity, or no QSAR analysis was conducted on those molecules [26]. These results served as a preliminary screening for binding propensity, providing an introduction to molecular docking simulations.

Table 2. QSAR result of quinolones toward laccase inhibitor activity

No	Compound	Laccase Inhibitor	
		P_a	P_i
1	Cinoxacin	-	-
2	Flumequine	-	-
3	Nalidixic acid	0.16	0.075
4	Nemonoxacin	-	-
5	Oxolinic acid	-	-
6	Pipemidic acid	-	-
7	Piromidic acid	-	-
8	Rosaxacin	-	-

3.2. Molecular Docking Result and Analysis

In molecular docking, we examined the influence of water on the structural stability of the enzyme-ligand complex. This analysis was performed to derive more accurate and representative findings for the system with water as the solvent. Flexible docking, which employs an induced-fit paradigm, affords greater adaptability in forecasting the binding conformations of interactions, such as those in protein-ligand complexes. Unlike rigid docking, this approach evaluates the potential of ligands to elicit modifications or reorientations in the side-chain residues situated at the active binding site of the target [2, 27, 28]. In this simulation, the $\Delta G_{binding}$ and RMSD values for the laccase-ligand complex were calculated under both conditions with and without water. The results of the molecular docking simulation are illustrated in Table 3.

The binding energies for both rigid and flexible docking in the presence of water were determined to range from -3.9997 to -4.6221 kcal·mol^{-1} and from -5.6083 to -6.5472 kcal·mol^{-1}, respectively. In the absence of water, the corresponding binding energies for these docking methods decreased slightly, from -6.644 to -8.583 kcal·mol^{-1} and from -6.879 to -8.633 kcal·mol^{-1}, respectively, indicating a stronger affinity between the ligand and laccase. The inclusion of water was observed to hinder the ligand-enzyme interaction, thereby reducing the binding affinity [29, 30]. When a water molecule binds to an enzyme/receptor, it experiences a loss of rigid-body translational and rotational freedom. This loss of flexibility corresponds to an increase in $\Delta G_{binding}$ [30]. The laccase-nalidixic acid complex exhibited the lowest binding energy across both simulation scenarios. This observation aligns with the QSAR analysis, which indicates that nalidixic acid alone is expected to demonstrate biological activity toward the laccase enzyme. As a result, nalidixic acid was selected for subsequent MD simulations employing CABSFLEX 3.0.

Table 3. The molecular docking results of laccase enzyme-quinolones

Compound	Flexible docking with water		Rigid docking with water		Flexible docking without water		Rigid docking without water	
	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD
Cinoxacin	-6.996	1.002	-4.349	1.904	-7.515	1.501	-5.871	1.813
Flumequine	-6.644	2.639	-3.999	1.716	-7.536	0.755	-5.608	1.683
Nalidixic acid	-8.583	1.859	-4.622	1.604	-8.633	1.655	-6.547	1.675
Nemonoxacin	-7.007	2.504	-4.425	1.316	-6.879	1.497	-5.543	0.804
Oxolinic acid	-7.694	2.150	-4.511	1.519	-7.538	1.504	-5.962	1.742
Pipemidic acid	-8.308	1.145	-4.153	1.937	-7.992	1.564	-6.322	2.106
Piromidic acid	-7.320	0.862	-4.219	1.450	-7.346	0.777	-5.769	0.868
Rosaxacin	-7.318	1.197	-4.465	1.970	-7.924	1.237	-6.031	3.048

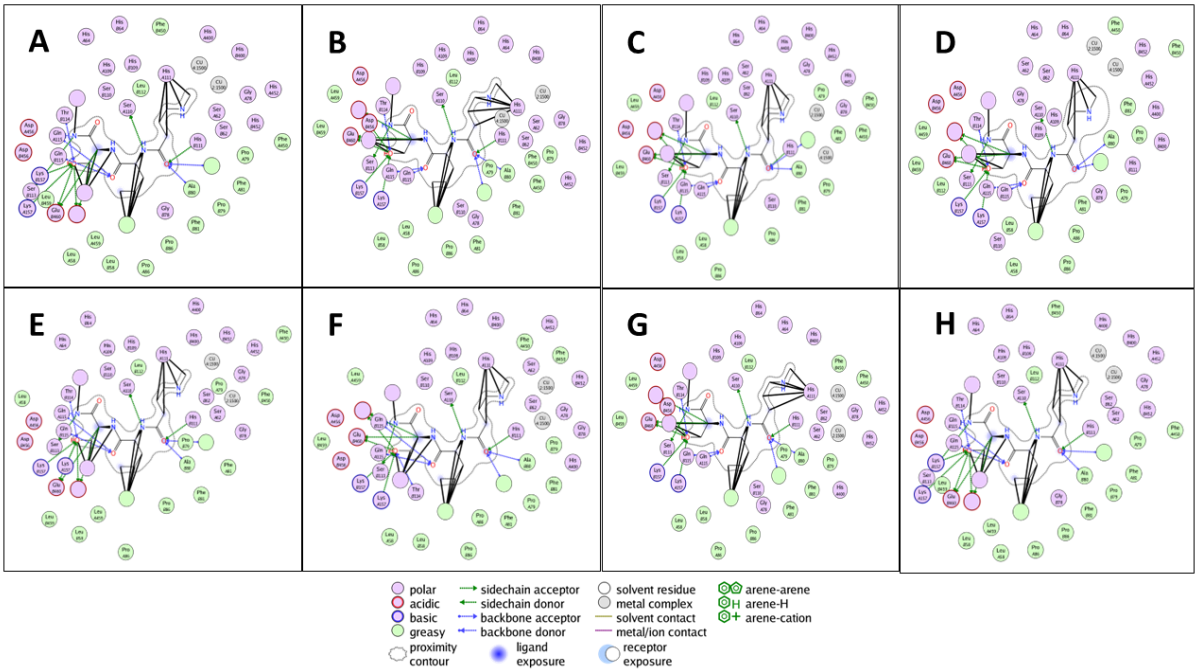

Figure 1. Visualization of the interaction between quinolone and laccase. (a) cinoxacin, (b) flumequine, (c) nalidixic acid, (d) nemonoxacin, (e) oxolinic acid, (f) Pipemidic acid, (g) piromidic acid, and (h) rosaxacin

Table 4. Homology modeling results of laccase enzyme 3FPX

Laccase ID	Microorganism	Active site	Reference	Sequence identity	Sequence similarity
3DIV	*Trametes trogii*	His455, Cys456, His457	[31]	94.99	0.61
1KYA	*Trametes versicolor*	Asp206, His396	[32]	88.15	0.59
5NQ8	*Trametes sanguinea*	Phe114, Ile115, and His477	[33]	84.68	0.58

The RMSD value is a parameter that shows the stability and flexibility of a protein or enzyme, as well as the distance between the backbone and protein atoms [20, 34, 35]. The low RMSD value suggested that the formation of the laccase-chloramphenicol complex was stable [36, 37]. The RMSD values of both rigid and flexible docking in the presence of water ranged from 1.3163 to 1.9706 and 0.8043 to 3.0481, respectively. The RMSD values for both methods without water were 0.862–2.639 and 0.7519–3.3824, with nalidixic acid having the lowest.

Figure 1 shows the interaction between the laccase-quinolone complex. All quinolone antibiotics interact with the side residue chain of laccase enzyme, indicating that they can be biodegraded. Although some quinolones lack phenolic, aromatic, or amide groups, laccase enzymes can nevertheless break down or interact because of their strong oxidation capabilities. Based on the free binding energy values between laccase and ligands, nalidixic acid has the lowest value, which is due to its more open N group (NH_3), allowing it to interact easily with the laccase enzyme [27].

3.3. Comparison with Other Laccase Enzymes

SWISS-MODEL is a fully automated protein structure homology modeling server that predicts three-dimensional protein structures based on the amino acid sequence similarity to the experimentally determined template structures. This study analyzed structural conservation among Trametes laccase enzymes and developed models for laccase variants lacking experimental structures. The amino acid sequences of the target laccase enzymes were uploaded in .pdb format to the SWISS-MODEL web-based server. The automated template search used BLAST and HHblits algorithms to find structurally comparable proteins in the SWISS-MODEL Template Library (SMTL), which is based on the PDB [38]. The template selection was based on the sequence identity, coverage, and resolution of the available crystal structures.

The homology modeling results for the 3FPX enzyme structure [19] are shown in Table 4. The 3DIV [39], 1KYA [32], and 5NQ8 [33] enzyme structures were chosen because they have high sequence identity and similarity values, and will be used for molecular docking to investigate their interactions with quinolone molecules. Compared with 3FPX, as shown in Table 5, these three enzymes had higher binding energies, indicating weaker interactions with quinolones. This result shows that the 3FPX enzyme has a higher potential to interact with and degrade quinolone molecules than these enzymes.

Table 5. Molecular docking result of other laccase enzymes

Compound	3DIV		1KYA		5NQ8		3FPX	
	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD	$\Delta G_{binding}$ (kcal·mol^{-1})	RMSD
Cinoxacin	-5.931	1.266	-6.720	1.334	-6.958	1.543	-7.515	1.501
Flumequine	-5.972	1.887	-6.505	1.108	-5.729	2.255	-7.536	0.755
Nalidixic acid	-8.499	4.887	-6.465	0.951	-8.454	1.286	-8.633	1.655
Nemonoxacin	-6.083	1.006	-6.042	0.951	-6.353	1.412	-6.879	1.497
Oxolinic acid	-6.015	2.642	-5.868	1.632	-6.867	1.782	-7.538	1.504
Pipemidic acid	-7.342	1.192	-5.724	1.817	-7.936	1.667	-7.992	1.564
Piromidic acid	-6.861	1.102	-8.218	1.164	-7.503	1.055	-7.346	0.777
Rosaxacin	-7.012	1.327	-7.794	1.593	-7.709	2.001	-7.924	1.237

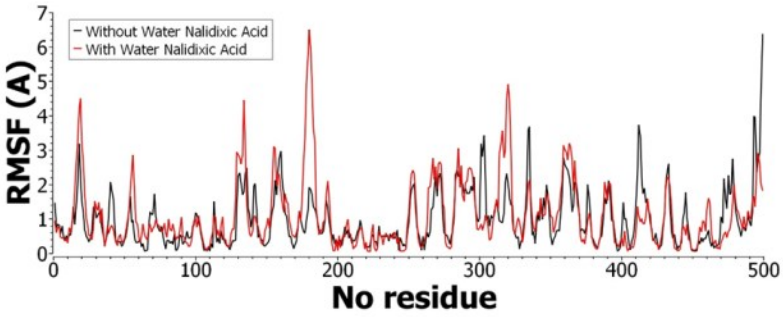

Figure 2. RMSF results of the laccase-nalidixic acid complex with and without water treatment

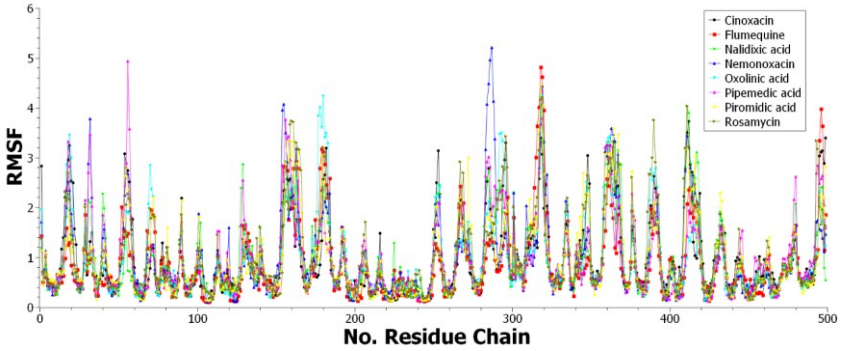

Figure 3. RMSF results of the laccase-quinolones complex without water treatment

Quinolones mostly have aromatic groups, which interact well with enzymes that have hydrophobic active sites or pockets. The 3FPX laccase enzyme has a more hydrophobic active site than other laccase enzymes, allowing for $\pi-\pi$ stacking interactions with quinolones. This is indicated by the lowest binding energy compared to other enzymes. Meanwhile, all three enzymes have active groups that are generally polar. In the active group Asp206, 1KYA has an active site that is less optimal for binding quinolones due to its limited hydrogen-bonding capacity [40]. Meanwhile, the active group in 3DIV exhibits severe steric hindrance, limiting substrate location. This results in a weaker binding or interaction with quinolones than with 3FPX [41]. The active site of 5NQ8 contains a chain of residues that can form hydrogen bonds but are less suitable for hydrophobic interactions with quinolones. This is because the size of the active group Histidine (five-membered aromatic ring) provides a smaller surface area, reducing its ability to bind the substrate via $\pi-\pi$ stacking compared to phenylalanine in 3FPX [42].

3.4. Molecular Dynamics Result and Analysis

MD simulation is a method for simulating the protein-ligand complex over a specified time period, enabling the examination of protein-ligand complex stability and the characterization of conformational changes. In this study, we used CABSFLEX 3.0 to perform MD simulations and investigate the conformational change of the laccase-quinolone complex [23]. The simulation was performed on nalidixic acid, which has the most stable complex with the laccase enzyme.

Figure 2 shows the RMSF values for the laccase enzyme and laccase-quinolone. The complex maintained a more flexible conformation in the absence of water than in the presence of the laccase enzyme. Laccase binding to the ligand results in the presence of water system in a significant rise in RMSF value (up to 6.51 Å) in a specific residue location (around residue 180), indicating a shift from stiffness to flexibility [43].

Figure 3 shows the molecular dynamics results for the laccase enzyme complex with quinolone antibiotics, calculated using CABSFLEX 3.0. All quinolone compounds revealed relatively low RMSF values near the residue chain bound to laccse enzyme [44]. The lower RMSF values indicate a stronger binding interaction between the protein and a ligand. This suggests that the quinolone molecules bind strongly to the residu chain of the enzyme, resulting in a hard complex conformation after the laccase enzyme binds to the quinolones.

4. Conclusion

The molecular simulations revealed that laccase enzymes have the potential to degrade quinolone, with binding energies ranging from 6.844 to -8.711 kcal·mol^{-1} in the absence of water and -5.543 to -6.547 kcal·mol^{-1} in the presence of water. The RMSD values for the laccase-quinolone complex ranged from 0.7519 to 3.3824, with lower values indicating higher stability. Docking to 3FPX and related fungal laccases suggests feasible recognition of several quinolones (notably nalidixic acid) within laccase binding pockets. Coarse-grained simulations indicate local flexibility changes upon binding. These results motivate targeted biochemical assays to determine whether these quinolones are true laccase substrates (with or without mediators) and to quantify any oxidative transformation. A comparison study was performed, including homology modeling and molecular docking. The comparison result showed that the 3FPX structure enzyme has good recognition of quinolone molecules. This finding is supported by the molecular dynamics results, which show that the RMSF of the enzyme-quinolone complex is relatively low compared to the RMSF of the laccase enzyme, indicating that the conformation of the laccase enzyme's flexibility facilitates catalysis towards quinolones.

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