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Molecular Docking and *In Vitro* Antibacterial Properties of Several Chalcone Derivatives

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Abstract

Chalcones are flavonoid-derived secondary metabolites known for diverse biological activities, including antibacterial effects. This study investigated the antibacterial properties of two chalcone derivatives i.e. 4-dimethylamino-4-hydroxychalcone (DMAHC) and 6-fluoro-2-chloro-4-hydroxychalcone (FCHC) against *Staphylococcus aureus* and *Escherichia coli* through integrated *in vitro* and *in silico* analyses. Antibacterial activity assessed using the agar diffusion method at concentrations of 1; 5; and 10% (w/v) revealed that DMAHC exhibited dose-dependent inhibition of both bacterial species, whereas FCHC demonstrated activity only against *S. aureus*. Molecular docking was performed using target proteins from *S. aureus* (1MWT) and *E. coli* (7ONW). Both chalcones were capable of binding to the active-site residues of the respective proteins; however, DMAHC showed a more favorable binding affinity toward *E. coli* ($\Delta G = -7.04$ kcal/mol) compared to FCHC ($\Delta G = -6.75$ kcal/mol). Despite its negative binding energy, FCHC failed to inhibit *E. coli in vitro*, likely due to reduced membrane permeability associated with its halogen substituents. Overall, the combined results highlight DMAHC as a more promising antibacterial candidate than FCHC, particularly against Gram-negative bacteria, and underscore the importance of electron-donating substituents in enhancing chalcone bioactivity.

Keywords: flavonoid; chalcone; antibacterial candidate.

Abbreviations: 4-dimethylamino-4-hydroxychalcone (DMAHC); 6-fluoro-2-chloro-4-hydroxychalcone (FCHC).

INTRODUCTION

Antibiotics play a crucial role in preventing bacterial infections by either inhibiting the growth of bacteria or killing disease-causing bacteria. However, excessive use can contribute to the emergence of antibiotic-resistant pathogens. This is due to bacteria's ability to adapt to antibacterial compounds, which can inhibit the effectiveness of these agents. Prestinaci et al. (2015) reported an increase in antibiotic resistance cases involving four major pathogens: *S. aureus*, *K. pneumoniae*, *S. typhi*, and *M. tuberculosis*. This underscores the importance of developing new antibacterial agents.

The development of antibacterial agents can be achieved by adding pharmacophoric substituents to the structure of antibacterial compounds. As demonstrated by Eze et al. (2019), the addition of substituents can enhance antibacterial activity. Another approach involves conducting quantitative structure-activity relationship (QSAR) studies on a compound, generating derivatives, and comparing their pharmacological activities. The relationship between structure and activity can explain the antibacterial mechanism (Dan et al. 2020).

One group of flavonoid compounds reported to have biological and pharmacological activities is chalcones and their derivatives. Several synthesized chalcone derivatives have shown highly beneficial biological activities such as cytotoxic, antimicrobial, antimalarial, and anticancer properties (Ahmed et al. 2011; Bhuiyan et al. 2011; Doan et al. 2011; Syam et al. 2012).

Chalcones are open-chain flavonoids with a reactive α, β-unsaturated carbonyl group. Chalcones continue to attract researchers in the 21st century due to their simple chemical structure, ease of synthesis, and the ability to modify hydrogen groups on the aromatic rings with other groups, such as amino or halogen groups like F and Br, to enhance their biological activity (Xu et al. 2019). Chalcone synthesis has been carried out using various base materials, yielding satisfactory results, as demonstrated by Bathelemy et al. 2016; Susanti et al. 2018; Prabawati et al. 2017; 2022, and Fikroh et al. 2020. However, limited research has been conducted on testing their antibacterial activity both *in vitro* and *in silico*.

Therefore, this study aimsed to evaluate the antibacterial activity of chalcone derivatives, specifically 4-dimethylamino-4-hydroxychalcone (DMAHC) and 6-fluoro-2-chloro-4-hydroxychalcone (FCHC), synthesized by Prabawati et al. 2022. The antibacterial activity will be tested *in vitro* against *Staphylococcus aureus* and *Escherichia coli*. Additionally, the antibacterial activity of these two chalcone compounds will be tested *in silico* using the molecular docking method.

The molecular docking method can analyze the types of interactions between antibacterial compounds and receptor ligands, such as hydrolase enzymes. Active groups in the chalcone structure may enhance the ability of natural hydrolase enzymes to hydrolyze bacterial cell walls. Molecular docking can help identify the active sites in chalcone structures that participate in the hydrolysis process by hydrolase enzymes to destroy bacterial cell walls.

Generally, antibacterial compounds penetrate bacterial cells by damaging the cytoplasmic membrane, leading to the leakage of cellular materials such as nucleic acids and proteins, forming a clear zone as an indicator of interaction between chalcone compounds and bacteria. Conducting *in silico* activity tests is important to identify the active sites of chalcone compounds and their corresponding receptor active sites to ensure the receptor and antibacterial candidate are not antagonistic (Sakkiah et al. 2021).

Thus, this research is expected to inspire the design and exploration of chalcone derivatives as effective antibacterial agents. Furthermore, the results of this study are anticipated to drive the development of chalcone-based drugs that are not only safe and cost-effective but also highly effective against various bacterial infections.

MATERIALS AND METHODS

Chemical and Instrument

The compounds 4-dimethylamino-4-hydroxychalcone (DMAHC) and 6-fluoro-2-chloro-4-hydroxychalcone (FCHC) used in this study were synthesized from 4-hydroxyacetophenone as the starting material, following the procedure previously reported by Prabawati et al., 2022. Other materials used included distilled water, DMSO, amoxicillin, *Staphylococcus aureus*, *Escherichia coli*, and nutrient agar.

The equipment used in this study included an autoclave, petri dishes, aluminum foil, glass stirrers, watch glasses, a Buchner funnel, an incubator, disk paper, and hardware comprising a PC with the following specifications: Intel Core i7 8th Gen processor, 500 GB SSD, 8 GB RAM. The software utilized included the Windows 10 operating system, Autodocks 4.2 (open source), Yasara (licensed), and BIOVIA Discovery Studio 2020 (open source).

Procedures

In Vitro Antibacterial Activity Test

The medium used for the antibacterial test was NA (nutrient agar). A total of 5.75 grams of NA medium was dissolved in 250 mL of distilled water and placed in an Erlenmeyer flask. The medium was covered with cotton and paper secured with a rubber band, then sterilized at 121°C and 1.5 psi pressure for 15 minutes.

Microbial rejuvenation aimed to refresh *Escherichia coli* and *Staphylococcus aureus* bacteria from slant agar into nutrient broth (NB) solution. Prepared NB medium was placed into test tubes and sterilized. Bacteria from the slant agar were taken using a sterile inoculation loop and inoculated into the NB medium. The tubes were covered with cotton and incubated in an incubator at 37°C for 24 hours (Cappuccino and Sherman, 2011). An initial test to observe antibacterial activity was conducted by placing disk papers containing chalcone compounds on NA medium. The NA medium was heated until melted and cooled to 50°C in a water bath, followed by the addition of 1 mL of *S. aureus* bacterial culture. After the medium solidified, disk papers dipped in the test samples (at concentrations of 1%, 5%, and 10% (w/v) in DMSO solvent) were placed on the agar surface. The positive control used was amoxicillin at a concentration of 5 mg/mL, while the negative control was DMSO, used as the sample solvent. The petri dishes were then incubated at 37°C for 24 hours to determine the Minimum Inhibitory Concentration (MIC) and to observe the presence or absence of a clear zone around the disk papers. The test was performed in triplicate for each concentration and also carried out against *Escherichia coli* bacteria.

In Silico Antibacterial Activity Test

Preparation of Enzyme Macromolecules

The study on the antibacterial potential of DMAHC and FCHC compounds was conducted through docking simulations. The crystal structures of the enzyme macromolecules *Staphylococcus aureus* tyrosyl-tRNA synthetase and DNA gyrase topoisomerase II were downloaded from the Protein Data Bank website (https://www.rscb.org/) in PDB format. The proteins were prepared using BIOVIA Discovery Studio 2020 software.

Preparation of Test Ligands

The tested compounds were DMAHC and FCHC, each with five conformational variations. The molecular structures of the primary compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov) in .sdf format and converted to PDB format using Open Babel GUI. The test compounds were prepared by adding polar hydrogen atoms and calculating partial charges. Molecular preparation and conformational adjustments were carried out using BIOVIA Discovery Studio 2020 software, followed by operations in AutoDock 4.2. The

prepared structures were used as input for molecular docking simulations.

Validation of the Docking Method

The docking method was validated on the receptor's active site, which binds to the ligand, by separating the protein from the original ligand attached to the receptor. Redocking was then performed to determine the root mean square deviation (RMSD) and confirm the inhibitor's conformation and binding energy prediction. Subsequently, the docking site's position during the redocking process was determined by adjusting the position and size of the test ligands. The docking grid box was set to a size of 40x40x40 and saved in a .txt file format for docking simulations. The preparation results were saved in PDBQT format.

Ligand-Protein Docking

The prepared ligands and proteins were subjected to the ligand-protein docking process using AutoDock 4.2. The grid box positions of the enzyme, previously saved in the note file, were used for the docking process according to the names of the receptor (protein) and test ligands to be processed. The output files from the docking process were opened using BIOVIA Discovery Studio for 2D and 3D visualization of the types of interactions between the ligands and the proteins.

RESULTS AND DISCUSSION

Result of In Vitro Antibacterial Activity Test

The chalcone derivatives i.e DMAHC and FCHC, were synthesized from the starting material 4-hydroxyacetophenone following a previously reported procedure (Prabawati et al., 2022). The synthesis scheme of the chalcone derivatives is shown in Figure 1. The application of these two chalcone compounds as antibacterial agents was tested against *Staphylococcus aureus* as a Gram-positive bacterium and *Escherichia coli* as a Gram-negative bacterium. The negative control used in this study was DMSO, as DMSO can dissolve both polar and nonpolar compounds and does not exhibit any activity against bacterial or fungal growth. Meanwhile, the positive control used was amoxicillin, since amoxicillin is a broad-spectrum antibiotic effective against bacteria in both humans and animals (Kaur et al., 2011).

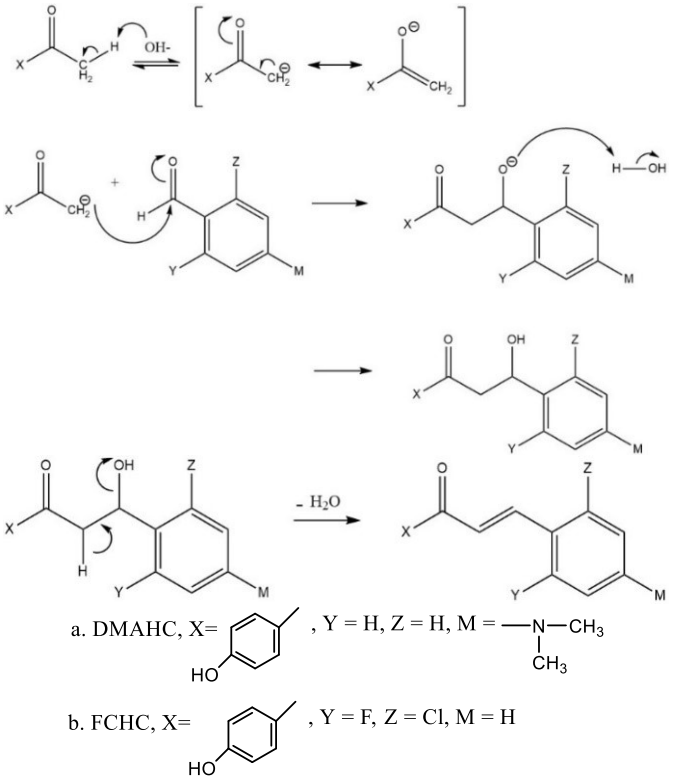


Figure 1. Mechanism in Formation of Chalcone Derivatives.

The results of this study showed that amoxicillin used as a positive control, was able to inhibit the growth of *Staphylococcus aureus* and *Escherichia coli*, with inhibition zone diameters greater than 20 mm. This indicates that both bacteria were sensitive to the amoxicillin disks used in this experiment. Meanwhile, the test results for the negative control, DMSO, showed no inhibition indicating that the use of DMSO did not affect the antibacterial activity results of the DMAHC or FCHC compounds.

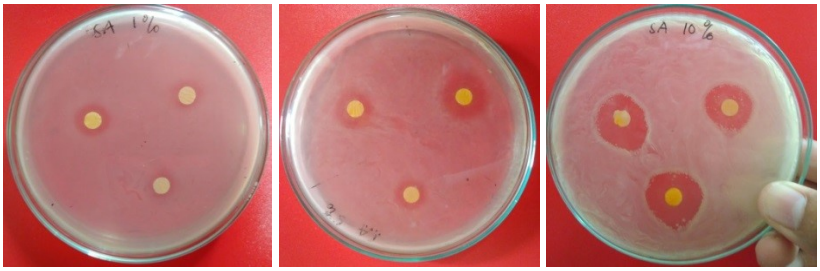
The results of the antibacterial activity test of DMAHC and FCHC compounds against *Staphylococcus aureus* and *Escherichia coli* are presented in Table 1.

Table 1. Results of antibacterial activity tests of chalcone derivatives against *Staphylococcus aureus* and *Escherichia coli* bacteria.

Concentration (%)	Inhibition Zone (mm)			
	DMHAC Compound		FCHC Compound	
	S. aureus	*E.coli*	*S. aureus*	*E.coli*
1	6.60	20.0	3.2	-
5	12.3	21.6	3.7	-
10	16.6	27.3	5.0	-

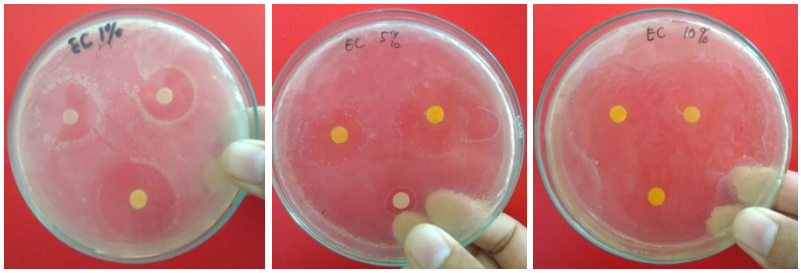
From the data presented in Table 1, it can be observed that the DMAHC compound exhibits antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli*, as indicated by the formation of inhibition zones around the paper discs at concentrations of 1%, 5%, and 10%. The higher the concentration of DMAHC, the larger the diameter of the inhibition zone. Both chalcone derivatives, DMAHC and FCHC, were able to inhibit or kill Staphylococcus aureus (with inhibition zones ranging from 6.6–16.6 mm and 3.2–5.0 mm, respectively). In contrast, against Escherichia coli, the DMAHC compound produced inhibition zones of 20.0–27.3 mm, whereas the FCHC compound showed no antibacterial effect, as no inhibition zone was observed around the disc.

Figure 2-5 shows the results of the antibacterial test of the two chalcone compounds against *Staphylococcus aureus* and *Escherichia coli* bacteria.



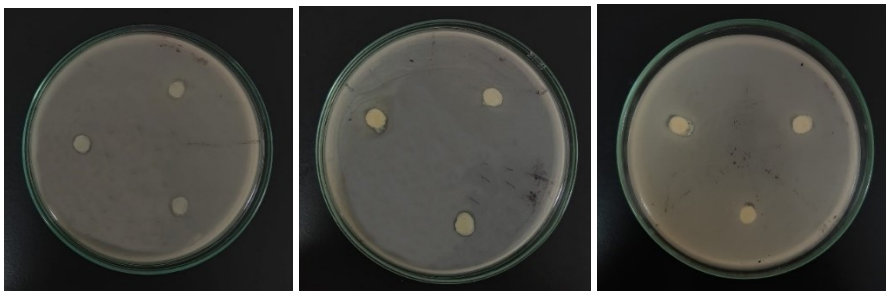
a **b** **c**

Figure 2. Antibacterial test results of DMAHC compound at concentrations of 1% (a), 5% (b), and 10% (c) against *Staphylococcus aureus* bacteria.



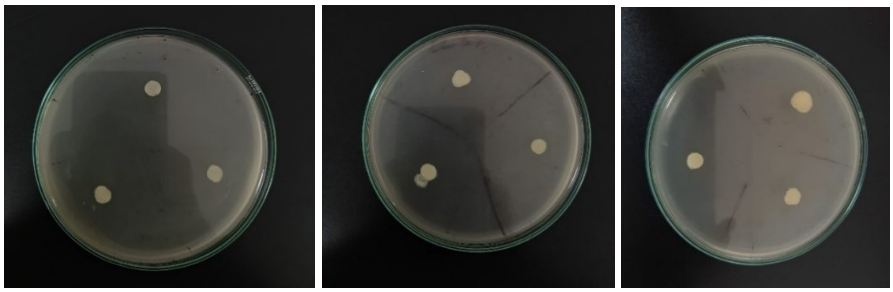
a **b** **c**

Figure 3. Antibacterial test results of DMAHC compound at concentrations of 1% (a), 5% (b), and 10% (c) against *Escherichia coli* bacteria.



a **b** **c**

Figure 4. Antibacterial test results of FCHC compound at concentrations of 1% (a), 5% (b), and 10% (c) against *Staphylococcus aureus* bacteria.



a **b** **c**

Figure 5. Antibacterial test results of FCHC compound at concentrations of 1% (a), 5% (b), and 10% (c) against *Escherichia coli* bacteria**.**

The antibacterial activity tests demonstrated the formation of clear inhibition zones on the agar medium, particularly against *Staphylococcus aureus*. This indicates that both chalcone derivatives, DMAHC and FCHC, were capable of suppressing or killing Gram-positive bacteria. In contrast, only DMAHC produced measurable inhibition zones against *Escherichia coli*, while FCHC showed no detectable inhibitory effect on this organism. These findings are consistent with the known structural differences between Gram-positive and Gram-negative bacteria. As described by Natheer et al. (2012), *E. coli* possesses a more complex cell envelope consisting of an outer membrane, an inner plasma membrane, and a peptidoglycan layer, whereas *S. aureus* contains only a single membrane and a peptidoglycan layer. The outer membrane of *E. coli* acts as a selective permeability barrier that restricts the entry of many antibacterial agents, thereby contributing to its higher resistance to FCHC compared with *S. aureus*.

Evaluating the ability of a compound to inhibit bacterial growth is a fundamental step in antibacterial drug development (Saxena and Gober, 2008). Chalcones are known to possess an α,β-unsaturated ketone moiety (–CO–CH=CH–) that plays a central role in their antibacterial properties. Moreover, the antibacterial activity of chalcone derivatives strongly depends on the nature and position of substituents attached to the aromatic rings (Prasad et al., 2006). In this study, the presence of a dimethylamine group in DMAHC appeared to significantly enhance its inhibitory effect compared with FCHC. As an electron-donating substituent, the amino group increases the electron density and reactivity of the benzene ring, which may improve its interaction with bacterial cellular components and contribute to its superior antibacterial performance.

According to the classification proposed by Davis and Stout (1971), inhibition zones greater than 20 mm indicate very strong antibacterial activity, 10–20 mm indicate strong activity, 5–10 mm moderate activity, and less than 5 mm weak activity. Based on these criteria, DMAHC demonstrated strong inhibitory activity against *S. aureus* (16.6 mm) and very strong activity against *E. coli* (27.3 mm) at the highest concentration tested (10%). In contrast, FCHC exhibited only moderate activity against *S. aureus* (5.0 mm) and no inhibitory effect on *E. coli*. These results clearly highlight the superior antibacterial potential of DMAHC and emphasize the role of electron-donating substituents in enhancing chalcone-based antibacterial efficacy.

In general, antibacterial compounds that penetrate bacterial cells act by damaging the cytoplasmic membrane. Such damage causes the release of intracellular components, including nucleic acids and proteins, resulting in the formation of a clear inhibition zone, which serves as an indicator of the interaction between the chalcone compound and the bacterial cells (Dan and Dai, 2020).

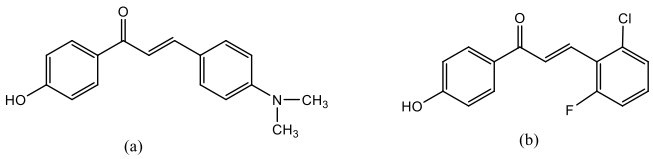


Figure 6. Compound Structure (a) DMAHC and (b) FCHC.

Natheer et al. (2012) explained that the cell wall of *Staphylococcus aureus* consists of a peptidoglycan layer with attached acidic polymers. *S. aureus* possesses only a single plasma membrane; therefore, the antibacterial compounds DMAHC and FCHC can more easily penetrate the bacterial defenses.

Results of in silico Antibacterial Activity Test

Antibacterial activity was also evaluated in silico to observe the interactions between the DMAHC and FCHC compounds (as ligands) and their target proteins. The molecular docking results showed that both chalcone derivatives, DMAHC and FCHC, interacted favourably with the active sites of the target proteins *Staphylococcus aureus* (PDB ID: 1MWT) and *Escherichia coli* (PDB ID: 7ONW). The binding energy of DMAHC with *S. aureus* and *E. coli* was −6.71 kcal/mol and −7.04 kcal/mol, respectively, whereas FCHC showed binding energies of −6.72 kcal/mol and −6.75 kcal/mol for the same proteins. The RMSD values obtained from the redocking process were 2.02 Å and 1.26 Å, confirming that the docking parameters were valid, as they were below the acceptable tolerance limit of 2.5 Å. The small difference in binding energies suggests that both compounds can theoretically bind well to the target proteins; however, the lower (more negative) binding affinity of DMAHC toward *E. coli* indicates a more stable complex conformation

compared to FCHC. These findings support the notion that DMAHC possesses stronger antibacterial potential, particularly against Gram-negative bacteria.

Residue interaction analysis is presented in Figures 7 and 8. The DMAHC compound forms hydrogen bonds with key residues such as SER451, TYR446, and GLU447 in *S. aureus*, as well as THR165 and VAL71 in *E. coli*, all of which are located near the active site of the respective proteins. FCHC also exhibits interactions with polar residues, including LYS406, ASN464, and SER598 in S. aureus; however, these interactions occur away from the catalytic center, resulting in lower complex stability. This difference in binding orientation is influenced by the electronic nature of the substituents on the aromatic ring. The dimethylamino group in DMAHC acts as an electron-donating group, enhancing the compound's polarity and hydrogen-bonding capability, whereas the halogen substituent in FCHC is electronegative and favors weaker hydrophobic interactions. Consequently, DMAHC tends to adopt a more optimal orientation within the protein's active site, while FCHC forms more superficial interactions, making it less effective in inhibiting the target enzymatic activity.

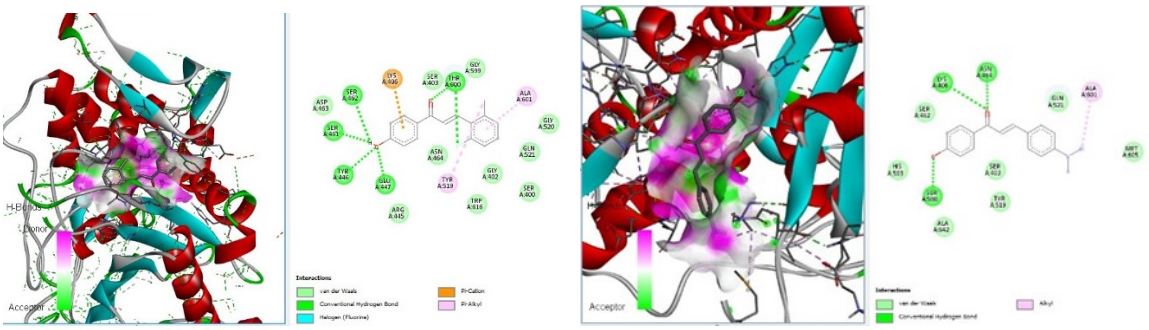


Figure 7. Structure of *S. aureus* amino acid residue binding to FCHC (left) and DMAHC (right) compounds.

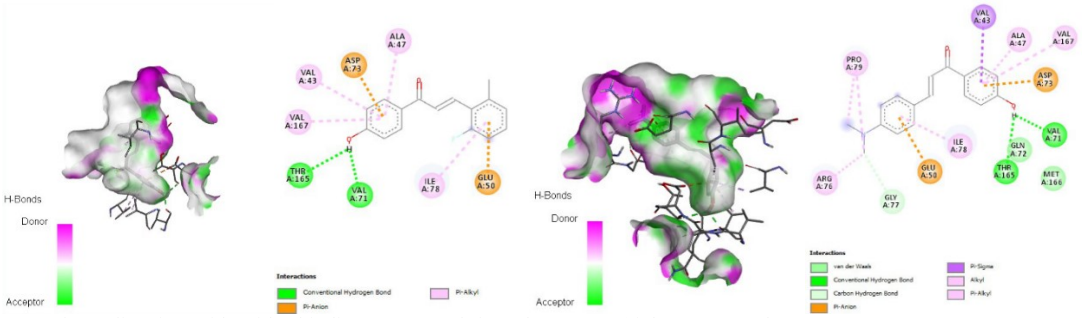


Figure 8. Structure of E. coli amino acid residue binding to FCHC (left) and DMAHC (right) compounds.

Table 2 and Table 3 show the docking scores, which indicate the binding affinity of a compound to the active site of the target protein.

Table 2. Docking scores of test compounds with several commercial antibiotic against the *S. aureus* target protein.

	$\Delta G_{binding}$ (kkal/mol)	Ki (nM) (micromolar)	$\Delta G_{intermolecular}$ (kkal/mol)	$\Delta G_{torsional}$ (kkal/mol)
FCHC	-6.72	11.86	-7.91	+1.19
DMAC	-6.71	12.10	-8.20	+1.49
Amoxilin	-7.63	2.57	-9.71	+2.09
Amphycilin	-7.95	1.48	-9.74	+1.79
Levofloxacin	-6.86	9.32	-7.76	+0.89

Table 3. Docking scores of test compounds with several commercial antibiotic against the *E. coli* target protein.

	$\Delta G_{binding}$ (kkal/mol)	Ki (nM) (micromolar)	$\Delta G_{intermolecular}$ (kkal/mol)	$\Delta G_{torsional}$ (kkal/mol)
FCHC	-6.75	11.29	-8.24	+1.49
DMAC	-7.04	6.96	-8.23	+1.19
Amoxilin	-6.81	10.24	-8.90	+2.09
Amphycilin	-6.58	15.14	-8.37	+1.79
Levofloxacin	-8.28	814.36	-9.18	+0.89

Based on the data presented in Tables 2 and 3, it can be observed that although FCHC exhibited a negative binding energy value against E. coli (−6.75 kcal/mol), the in vitro results showed no inhibition zone for this bacterium. This discrepancy can be scientifically explained by the structural characteristics of the E. coli cell wall, which contains a double layer of lipopolysaccharides that is highly selective and restricts the diffusion of foreign compounds. The halogen substituents present in FCHC increase its hydrophobicity, thereby reducing its solubility and permeability through Gram-negative bacterial membranes. Consequently, although in silico simulations indicate stable interactions at the protein's active site, FCHC likely fails to reach its intracellular target due to the membrane permeability barrier. In contrast, the more polar DMAHC, which contains an electron-donating group, is capable of penetrating the bacterial membrane and forming effective interactions with key residues—resulting in observable antibacterial activity consistent with both experimental and computational findings.

The consistency between the *in vitro* and *in silico* results indicates that DMAHC has greater potential as an antibacterial candidate than FCHC. The lower binding energy and higher number of hydrogen bonds further support the strong interaction of DMAHC with target proteins, which correlates with the larger inhibition zones observed in laboratory assays. In contrast, although FCHC forms several hydrogen bonds, its limited ability to penetrate Gram-negative bacterial membranes results in lower biological activity. The dimethylamino group in DMAHC acts as an electron-donating substituent that enhances the compound's polarity and its capacity to interact with polar residues, whereas the halogen substituents in FCHC are more hydrophobic and less reactive. Therefore, structural modification of chalcone derivatives with electron-donating substituents is considered a promising strategy to enhance antibacterial potential against a broader range of bacterial species.

CONCLUSIONS

Chalcone-based compounds have demonstrated significant potential in medicinal chemistry, particularly as antibacterial agents. Variations in functional groups on the aromatic rings and the presence of α,β-unsaturated carbonyl groups within the chalcone framework play crucial roles in inhibiting bacterial growth. Therefore, the development and structural modification of chalcone derivatives remain important and promising research topics in the field of medicinal chemistry.

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Authors' Contributions: Susy Yunita Prabawati conducted the conceptual study and wrote the manuscript. Priyagung Dhemi Widiakongko processed the data and revised the manuscript. Kurniawan Eka Yuda and Agianti Sugiyati assisted in collecting data in the laboratory. All authors have read and approved the final version of the manuscript.

Competing Interests: The authors of this publication declare that there are no competing interests that might have impacted the research provided in this study.

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