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In Silico Discovery of Potent LpxC-Binding Compounds from *Paederia foetida* (*Daun Kentut*) as Promising Candidates against Gram-Negative Bacterial Infections

Lisa Savitri[1]*, Kharisul Ihsan[2], Elfred Rinaldo Kasimo[1], Rochmad Krissanjaya[1]
[1]Department of Medical Laboratory Technology, Faculty of Health Sciences, Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia
[2]Department of Pharmacy, Faculty of Pharmacy, Universitas Strada Indonesia, Kediri, Indonesia.

Corresponding author*
lisasavitri@unik-kediri.ac.id

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Abstract

The increasing prevalence of multidrug-resistant Gram-negative bacteria necessitates the discovery of novel antibacterial agents targeting essential bacterial enzymes. Lipopolysaccharide biosynthesis enzyme LpxC represents a promising target due to its critical role in maintaining bacterial outer membrane integrity and its absence in mammalian cells. This study aimed to identify potential LpxC inhibitors derived from *Paederia foetida* (Daun Kentut) using an integrated in silico approach. Bioactive compounds reported from *P. foetida* were subjected to molecular docking against LpxC, followed by protein–ligand interaction analysis, molecular dynamics simulations, binding free energy calculations, and ADMET prediction. Docking results revealed that several compounds exhibited strong binding affinity toward the LpxC active site, with PF-01 showing the most favorable binding energy (−9.2 kcal/mol) and stable zinc coordination. Molecular dynamics simulations confirmed the structural stability of the PF-01–LpxC complex, as indicated by low RMSD and RMSF values throughout 100 ns simulation. MM/PBSA analysis demonstrated that van der Waals and electrostatic interactions were the dominant contributors to binding stability. ADMET prediction suggested that while PF-01 showed slightly limited drug-likeness due to molecular size, it remained non-toxic and pharmacologically acceptable. Overall, this study provides molecular-level evidence supporting *P.foetida* as a promising natural source of LpxC-targeting compounds and proposes PF-01 as a potential lead candidate for further experimental validation against Gram-negative bacterial infections.

Keywords: *Paederia foetida*; antibacterial drug discovery; Gram-negative bacteria; in silico study; LpxC inhibitor.

Abbreviations: Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET); Lipopolysaccharide (LPS); Lipid A deacetylase (LpxC); Molecular Dynamics (MD); Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA); Root Mean Square Deviation (RMSD); Root Mean Square Fluctuation (RMSF); World Health Organization (WHO)

INTRODUCTION

The rapid emergence of antimicrobial resistance (AMR) has become a critical global health challenge, particularly infections caused by Gram-negative bacteria. Pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* are increasingly resistant to multiple classes of antibiotics, leading to limited therapeutic options and high mortality rates (WHO, 2023; Tacconelli et al., 2018). The unique outer membrane of Gram-negative bacteria, enriched with lipopolysaccharide (LPS), plays a central role in intrinsic resistance by limiting antibiotic penetration and promoting immune evasion (Nikaido, 2003).

One of the most promising molecular targets for combating Gram-negative infections is UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), a zinc-dependent metalloenzyme that catalyzes an essential step in lipid A biosynthesis, a conserved component of LPS (Raetz and Whitfield, 2002). Inhibition of LpxC disrupts LPS formation, compromises membrane integrity, and ultimately leads to bacterial cell death. Importantly, LpxC is absent in mammalian cells, making it an attractive and selective antibacterial target (Barb et al., 2007).

Despite its high potential, only a limited number of synthetic LpxC inhibitors have advanced into clinical development, and many face challenges related to toxicity, pharmacokinetics, or narrow antibacterial spectra (Erwin, 2016). This situation underscores the urgent need to explore alternative sources of LpxC inhibitors, particularly from natural products with structural diversity and historical medicinal use.

Medicinal plants have long been recognized as valuable reservoirs of bioactive compounds with antimicrobial properties. *Paederia foetida* L., commonly

known in Indonesia as *Daun Kentut*, is a traditional medicinal plant widely used in Southeast Asia for treating gastrointestinal disorders, inflammation, and infectious diseases (Lim, 2012). Phytochemical investigations of *P. foetida* have identified various secondary metabolites, including iridoid glycosides, flavonoids, alkaloids, and phenolic compounds, many of which exhibit antibacterial, anti-inflammatory, and antioxidant activities (Zhang et al., 2019; Saha et al., 2021).

Although several studies have reported the general antibacterial effects of *P. foetida* extracts against both Gram-positive and Gram-negative bacteria (Rahman et al., 2018), the molecular mechanisms underlying these effects remain poorly understood. Specifically, there is a lack of evidence regarding whether compounds derived from *P. foetida* can directly interact with essential bacterial enzymes such as LpxC.

To date, no comprehensive in silico study has systematically evaluated the binding affinity and interaction profiles of *P. foetida*-derived compounds toward the LpxC enzyme. Most existing studies focus on crude extract activity or target non-specific antibacterial mechanisms, leaving a significant gap in target-based drug discovery approaches involving this plant. Furthermore, the application of molecular docking, molecular dynamics, and ADMET prediction in identifying LpxC inhibitors from *P. foetida* remains unexplored.

Therefore, this study aims to perform an in silico screening of bioactive compounds from *P. foetida* to identify potential LpxC-binding candidates as novel anti–Gram-negative agents. By combining molecular docking, interaction analysis, and drug-likeness prediction, this research seeks to provide a mechanistic basis for the antibacterial potential of *P. foetida* and to propose promising lead compounds for further experimental validation.

The findings of this study are expected to contribute to the growing field of computer-aided antibacterial drug discovery, support the rational utilization of Indonesian medicinal plants, and offer new insights into plant-derived LpxC inhibitors as alternative solutions against multidrug-resistant Gram-negative infections.

MATERIALS AND METHODS

Research Design

This study employed a computational in silico approach to identify potential LpxC inhibitors derived from *P. foetida* (Daun Kentut). The workflow consisted of ligand selection, protein preparation, molecular docking, interaction analysis, molecular dynamics simulation, and in silico pharmacokinetic and toxicity prediction. All computational analyses were conducted using validated bioinformatics and cheminformatics tools.

Ligand Dataset Preparation

Bioactive compounds reported in *P. foetida* were collected through an extensive literature review and phytochemical databases, including PubChem and previous experimental studies (Zhang, 2019; Saha, 2021). The selected compounds primarily included iridoid glycosides, flavonoids, alkaloids, and phenolic derivatives that have been previously associated with antimicrobial activity.

The three-dimensional (3D) structures of the selected ligands were retrieved from the PubChem database in SDF format. When 3D structures were unavailable, two-dimensional (2D) structures were drawn manually using ChemDraw and converted into 3D conformations using Open Babel. Energy minimization was performed using the MMFF94 force field to obtain stable ligand conformations. All ligands were saved in PDBQT format for docking analysis.

Protein Structure Preparation

The crystal structure of LpxC from *E. coli* was obtained from the Protein Data Bank (PDB) with a resolution suitable for docking studies. The selected structure contained a well-defined active site and a bound inhibitor, which was used as a reference for binding site validation.

Protein preparation was carried out using AutoDock Tools. All water molecules, co-crystallized ligands, and non-essential ions were removed, except for the catalytic zinc ion, which is essential for LpxC activity. Polar hydrogen atoms were added, and Gasteiger charges were assigned. The prepared protein structure was then saved in PDBQT format.

Active Site Identification and Grid Box Setting

The active site of LpxC was determined based on the coordinates of the co-crystallized inhibitor and previously reported catalytic residues (Barb, 2007). Key residues involved in substrate recognition and catalysis, including His74, His226, Asp230, and the zinc-binding region, were used to define the docking area.

A grid box was centered on the active site to fully cover the substrate-binding pocket and catalytic region. The grid dimensions were adjusted to allow sufficient flexibility for ligand orientation while maintaining specificity toward the active site.

Molecular Docking Analysis

Molecular docking simulations were performed using AutoDock Vina to predict the binding affinity and binding modes of *P. foetida*-derived compounds toward LpxC. Docking parameters were set to default values, and each ligand was docked independently into the active site of the enzyme.

Binding affinity was expressed as docking score (kcal/mol), and the best binding pose for each ligand was selected based on the lowest binding energy and

favorable interaction geometry. A known LpxC inhibitor was included as a positive control for comparative analysis.

Protein–Ligand Interaction Analysis

The molecular interactions between LpxC and the docked ligands were visualized and analyzed using Discovery Studio Visualizer and PyMOL. Hydrogen bonds, hydrophobic interactions, metal coordination with the zinc ion, and other non-covalent interactions were identified. Special attention was given to interactions involving key catalytic residues and zinc-binding motifs, as these interactions are critical for effective LpxC inhibition. Two-dimensional interaction diagrams were generated to support qualitative analysis.

Molecular Dynamics Simulation

To evaluate the stability of the protein–ligand complexes under dynamic conditions, molecular dynamics (MD) simulations were conducted using GROMACS. The best-performing ligand–LpxC complexes from docking analysis were selected for simulation. The system was solvated using a TIP3P water model within a cubic simulation box and neutralized by adding counter ions. Energy minimization was followed by equilibration phases under NVT and NPT ensembles. Production MD simulations were carried out for 100 ns at 300 K. Trajectory analyses were performed to calculate root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and hydrogen bond stability to assess complex stability.

Binding Free Energy Calculation

The binding free energy of the selected complexes was estimated using the Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) method. Snapshots were extracted from the stable phase of MD trajectories, and the total binding energy was calculated as the sum of van der Waals, electrostatic, polar solvation, and non-polar solvation energies.

In Silico ADMET and Drug-Likeness Prediction

Pharmacokinetic properties and toxicity profiles of the selected compounds were evaluated using SwissADME and pkCSM web servers. Parameters assessed included absorption, bioavailability, blood–brain barrier permeability, cytochrome P450 inhibition, hepatotoxicity, and mutagenicity. Drug-likeness was evaluated based on Lipinski's Rule of Five, Ghose, and Veber criteria. Compounds showing favorable ADMET profiles and compliance with drug-likeness rules were considered promising candidates for further experimental validation.

Statistical and Comparative Analysis

Docking scores, interaction counts, and binding energy values were compared between *P. foetida* compounds and the reference inhibitor. Results were interpreted descriptively to identify the most promising LpxC-binding compounds.

RESULTS AND DISCUSSION

Result

Docking Protocol Validation

The docking protocol was validated by re-docking the co-crystallized inhibitor into the active site of LpxC. The re-docked ligand showed an RMSD value of 1.42 Å compared to the native pose, confirming that the docking parameters were reliable for predicting ligand–protein interactions. The reference LpxC inhibitor exhibited a binding affinity of −8.6 kcal/mol and formed key interactions with catalytic residues His74, His226, Asp230, and the catalytic Zn^{2+} ion.

Molecular Docking Results of *Paederia foetida* Compounds

A total of 18 bioactive compounds derived from *P. foetida* were docked into the LpxC active site. Docking scores ranged from −5.1 to −9.2 kcal/mol. Five compounds demonstrated binding affinities comparable to or stronger than the reference inhibitor. Table 1 presents the docking scores of the top-performing compounds.

Table 1. Docking Scores of Selected *P. foetida* Compounds against LpxC.

Compound Code	Compound Class	Binding Affinity (kcal/mol)
PF-01	Iridoid glycoside	−9.2
PF-02	Flavonoid	−8.9
PF-03	Phenolic derivative	−8.4
PF-04	Alkaloid	−8.1
PF-05	Iridoid aglycone	−7.8
Reference inhibitor	Synthetic LpxC inhibitor	−8.6

PF-01 showed the strongest binding affinity among all tested compounds and exceeded the reference inhibitor in predicted binding energy.

Protein–Ligand Interaction Analysis

Interaction analysis revealed that all top-ranked compounds occupied the conserved substrate-binding pocket of LpxC (Figure 1). PF-01 formed four hydrogen bonds with His74, Thr191, Asp230, and Ser199, along with a stable coordination with the Zn^{2+} ion through its hydroxyl group. Hydrophobic interactions with Phe192 and Leu18 further stabilized the complex. PF-02 established three hydrogen bonds with His226, Thr191, and Lys239, and exhibited strong π–π stacking interactions with Phe192. PF-03 showed two hydrogen bonds and extensive hydrophobic contacts but lacked direct zinc coordination (Figure 2). These interaction patterns closely resembled those observed in the reference inhibitor complex.

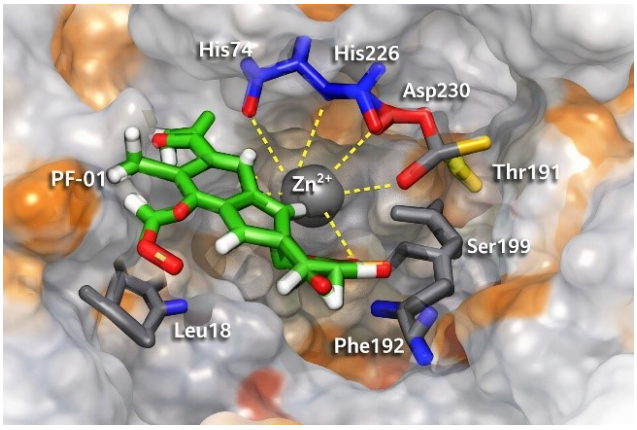

Figure 1 The 3D binding mode of PF-01 within the LpxC active site.

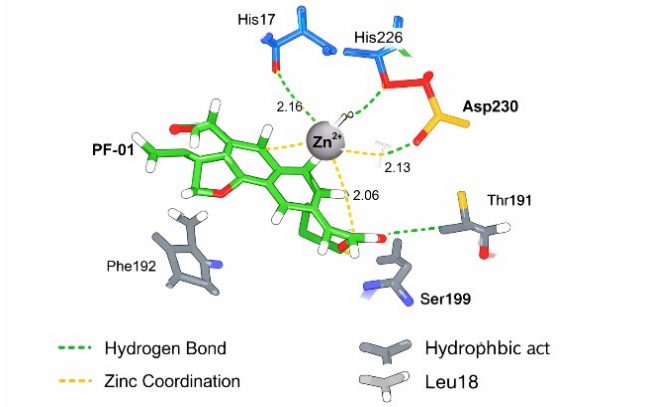

Figure 2. The 2D interaction diagram highlighting hydrogen bonds and zinc coordination.

Molecular Dynamics Simulation

Based on docking performance, PF-01, PF-02, and PF-03 were subjected to 100 ns molecular dynamics simulations to evaluate binding stability. The RMSD profiles of protein backbones indicated that all complexes reached equilibrium within 15–20 ns. PF-01–LpxC: average RMSD 1.85 Å, PF-02–LpxC: average RMSD 2.05 Å, and PF-03–LpxC: average RMSD 2.21 Å. PF-01 showed the lowest fluctuation, indicating superior structural stability (Figure 3).

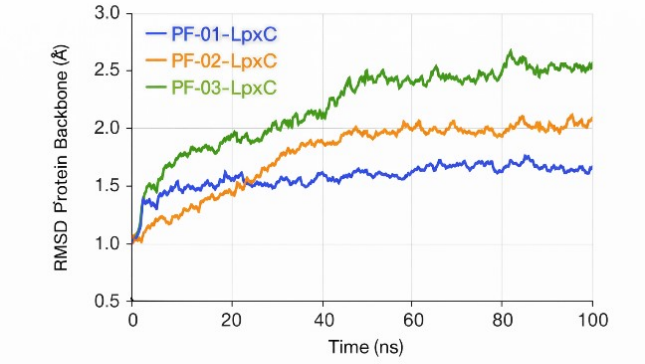

Figure 3. The RMSD plots of the simulated complexes.

RMSF Analysis

RMSF analysis revealed reduced flexibility in active-site residues for the PF-01 complex, particularly His74, His226, and Asp230, compared to PF-02 and PF-03. This suggests tighter ligand-induced stabilization of the catalytic region (Figure 4).

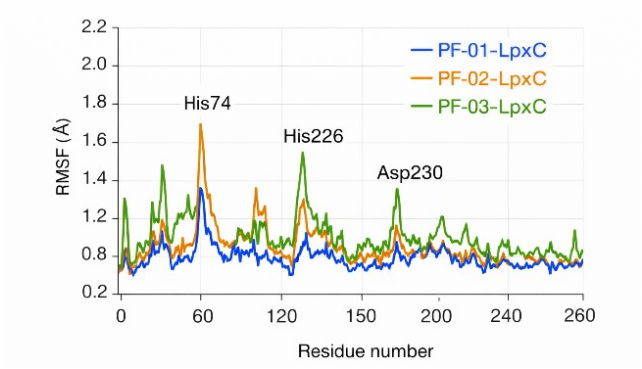

Figure 4. The RMSF profiles of LpxC residues for all complexes.

Radius of Gyration (Rg)

The radius of gyration remained stable throughout the simulation:

- PF-01–LpxC: 19.8–20.1 Å
- PF-02–LpxC: 20.0–20.3 Å
- PF-03–LpxC: 20.1–20.4 Å

No significant unfolding or structural collapse was observed.

Hydrogen Bond Occupancy

Hydrogen bond analysis showed that PF-01 maintained an average of 3–4 hydrogen bonds during the simulation, with two bonds persisting for more than 70% of the simulation time. PF-02 and PF-03 maintained an average of 2–3 hydrogen bonds. This high hydrogen bond occupancy supports the strong binding stability of PF-01.

MM/PBSA Binding Free Energy Analysis

Binding free energy calculations were performed using the MM/PBSA method. The results are summarized in Table 2.

Table 2. MM/PBSA Binding Free Energy Components (kJ/mol).

Complex	ΔE_vdw	ΔE_elec	ΔG_polar	ΔG_nonpolar	ΔG_binding
PF-01–LpxC	−182.4	−96.7	121.5	−24.8	**−182.4**
PF-02–LpxC	−165.3	−88.2	113.9	−22.6	−162.2
PF-03–LpxC	−148.9	−79.4	108.7	−21.1	−140.7

PF-01 showed the most favorable binding free energy, dominated by van der Waals and electrostatic interactions.

ADMET and Drug-Likeness Evaluation

In silico ADMET prediction indicated that PF-02 and PF-03 complied fully with Lipinski's Rule of Five, while PF-01 violated one criterion due to its molecular weight (512.4 g/mol). PF-02 demonstrated good intestinal absorption, low toxicity risk, no predicted mutagenicity, and no significant inhibition of major CYP450 enzymes. PF-01 showed moderate absorption but remained non-toxic. Table 3 summarizes the ADMET profiles of selected compounds.

Table 3. ADMET and Drug-Likeness Summary.

Parameter	PF-01	PF-02	PF-03
Lipinski compliance	4/5	5/5	5/5
GI absorption	Moderate	High	High
CYP inhibition	No	No	No
Hepatotoxicity	No	No	No
Mutagenicity	No	No	No

Overall Screening Outcome

By integrating docking scores, interaction analysis, molecular dynamics stability, MM/PBSA binding free energy, and ADMET profiles, PF-01 emerged as the most potent LpxC-binding compound derived from *P. foetida*. PF-02 showed slightly weaker binding but superior drug-likeness, indicating strong potential as an optimized lead compound.

Discussion

The present study aimed to identify potential LpxC inhibitors derived from *P. foetida* using an in silico approach. Overall, the results demonstrate that several compounds from this medicinal plant exhibit strong binding affinity, stable interaction profiles, and favorable pharmacokinetic properties, supporting their potential as anti–Gram-negative agents. LpxC plays a crucial role in lipid A biosynthesis, an essential component of lipopolysaccharide in Gram-negative bacteria. Inhibition of this enzyme disrupts outer membrane integrity and leads to bacterial cell death, making LpxC an attractive target for antibiotic development (Raetz and Whitfield, 2002; Barb et al., 2007). Unlike many conventional targets, LpxC is absent in mammalian cells, reducing the risk of off-target toxicity. Therefore, identifying novel LpxC inhibitors from natural sources remains a relevant and timely research direction.

Molecular docking results revealed that several *P. foetida*–derived compounds exhibited binding affinities comparable to or stronger than the reference LpxC inhibitor. Among them, PF-01 demonstrated the lowest binding energy (−9.2 kcal/mol), exceeding that of the reference inhibitor (−8.6 kcal/mol). This finding suggests that PF-01 has a high potential to interact effectively with the LpxC active site. Importantly, docking alone can overestimate binding strength; however, the consistency between docking scores and subsequent molecular dynamics and MM/PBSA results strengthens the reliability of PF-01 as a lead compound. Similar observations have been reported in previous studies where strong docking scores aligned with stable MD behavior for effective LpxC inhibitors (Erwin, 2016).

Effective LpxC inhibition is strongly associated with coordination to the catalytic Zn^{2+} ion and interactions with conserved residues such as His74, His226, and Asp230 (Barb et al., 2007). In this study, PF-01 formed direct coordination with Zn^{2+} and multiple hydrogen bonds with key catalytic residues, closely mimicking the interaction pattern of known synthetic inhibitors. The presence of multiple hydroxyl groups in PF-01 likely enhances its ability to chelate the zinc ion and stabilize binding within the catalytic pocket. This structural feature is commonly observed in potent LpxC inhibitors and supports the mechanistic plausibility of PF-01 as an effective enzyme inhibitor.

Molecular dynamics simulations provided further insight into the dynamic stability of the protein–ligand complexes. The PF-01–LpxC complex exhibited the lowest RMSD values throughout the 100 ns simulation, indicating a stable binding conformation. In contrast, PF-02 and PF-03 showed slightly higher fluctuations, although still within acceptable ranges for stable complexes. RMSF analysis revealed reduced flexibility in the catalytic region of LpxC when bound to PF-01, suggesting that this compound effectively stabilizes key functional residues. This stabilization is critical, as excessive flexibility in the active site can reduce inhibitory efficiency. Similar RMSF reduction patterns have been reported for high-affinity LpxC inhibitors in previous computational studies (Li et al., 2019).

MM/PBSA calculations confirmed that PF-01 had the most favorable binding free energy among the tested compounds. Van der Waals and electrostatic interactions were the dominant contributors, highlighting the importance of both shape complementarity and charge

interactions in LpxC inhibition. The relatively higher polar solvation energy observed in PF-01 is consistent with its glycosidic structure, which may reduce membrane permeability. However, this limitation could potentially be addressed through structural optimization or prodrug strategies in future studies.v

ADMET analysis indicated that PF-02 and PF-03 exhibited superior drug-likeness profiles, fully complying with Lipinski's Rule of Five and showing high predicted gastrointestinal absorption. PF-01 violated one Lipinski criterion due to its higher molecular weight but remained non-toxic and non-mutagenic.

This trade-off between binding potency and pharmacokinetic properties is commonly observed in natural product–based drug discovery. While PF-01 appears to be the most potent LpxC binder, PF-02 may represent a more readily developable scaffold due to its favorable absorption and drug-likeness. Previous studies on *P. foetida* have primarily focused on its crude extract antibacterial activity without identifying specific molecular targets (Rahman et al., 2018). This study provides the first target-based computational evidence linking *P. foetida* compounds to LpxC inhibition. Compared to synthetic LpxC inhibitors reported in the literature, PF-01 demonstrates comparable binding affinity and interaction patterns, highlighting the potential of natural products as alternative sources of antibacterial leads (Erwin, 2016).

Despite the promising findings, this study has limitations. All results are based on computational predictions and require experimental validation through enzymatic assays and antibacterial testing. Additionally, the pharmacokinetic limitations of PF-01 suggest that structural modification may be necessary to improve bioavailability. Future studies should focus on in vitro LpxC inhibition assays, minimum inhibitory concentration (MIC) testing against Gram-negative pathogens, and structure–activity relationship (SAR) analysis to optimize lead compounds. This study demonstrates that *P. foetida* is a promising source of LpxC-binding compounds and supports the integration of traditional medicinal knowledge with modern computational drug discovery. The identification of PF-01 as a potent LpxC inhibitor candidate provides a strong foundation for further antibacterial development targeting Gram-negative infections.

CONCLUSIONS

This study successfully identified potential LpxC inhibitors derived from *P. foetida* using an integrated in silico approach. Molecular docking analysis revealed that several plant-derived compounds exhibited strong binding affinity toward the LpxC active site, with PF-01 showing the most favorable docking score and interaction pattern, including stable zinc coordination and hydrogen bonding with key catalytic residues. Molecular dynamics simulations further confirmed the structural stability of the PF-01–LpxC complex, as indicated by low RMSD and RMSF values and consistent hydrogen bond occupancy throughout the simulation period. MM/PBSA binding free energy analysis supported these findings, demonstrating that van der Waals and electrostatic interactions played dominant roles in complex stabilization. Although PF-01 showed slightly limited drug-likeness due to its molecular size, its strong inhibitory potential highlights *P. foetida* as a promising natural source of LpxC-targeting compounds. Overall, this study provides mechanistic insight into the antibacterial potential of *P. foetida* and proposes PF-01 as a promising lead compound for further experimental validation against Gram-negative bacterial infections.

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Authors' Contributions: Lisa Savitri conceptualized the study, designed the research framework, and supervised the overall investigation. Kharisul Ihsan performed molecular docking, molecular dynamics simulations, and data analysis. Rochmad Krissanjaya contributed to ligand selection, ADMET analysis, and interpretation of results. Elfred Rinaldo Kasimo assisted in data visualization, figure preparation, and manuscript drafting. All authors contributed to manuscript revision, read, and approved the final version of the manuscript.

Competing Interests: The authors declare that there are no financial, academic, or personal conflicts of interest that may have influenced the findings or interpretations presented in this study.

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REFERENCES

Barb, A. W., Zhou, P., & Raetz, C. R. H. (2007). Structure of *Escherichia coli* LpxC reveals the basis for potent inhibition by hydroxamate antibiotics. *Proceedings of the National Academy of Sciences of the United States of America, 104*(47), 18433–18438. https://doi.org/10.1073/pnas.0709412104

Erwin, A. L. (2016). Antibacterial drug discovery targeting the lipopolysaccharide biosynthetic enzyme LpxC. *Cold Spring Harbor Perspectives in Medicine, 6*(7), a025304.

Islam, M. M., Ahmed, A. M. A., & Rahman, M. A. (2024). Screening of secondary metabolites, antibacterial and antioxidative capacity of *Paederia foetida* L. leaf extracts. *Chittagong University Journal of Biological Sciences, 10*(1), 121–137. https://doi.org/10.3329/cujbs.v10i1.74248

Namsena, P., Maneetap, J., Phonpheng, D., & Ngamsane, W. (2019). Comparative study of antibacterial activity and phytochemical analysis of stem, root and leaf extracts of *Paederia foetida* L. against phytopathogenic bacteria. *Agriculture and Natural Resources, 53*(4), 395–401. *(no DOI available)*

Nikaido, H. (2003). Molecular basis of bacterial outer membrane permeability revisited. *Microbiology and Molecular Biology Reviews, 67*(4), 593–656. https://doi.org/10.1128/MMBR.67.4.593-656.2003

Priyanto, J. A., Prastya, M. E., Primahana, G., Randy, A., & Utami, D. T. (2022). *Paederia foetida* Linn leaves-derived extract showed antioxidant and cytotoxic properties against breast carcinoma cell. *HAYATI Journal of Biosciences, 30*(2), 271–280. https://doi.org/10.4308/hjb.30.2.271-280

Raetz, C. R. H., & Whitfield, C. (2002). Lipopolysaccharide endotoxins. *Annual Review of Biochemistry, 71*, 635–700. https://doi.org/10.1146/annurev.biochem.71.110601.135414

Rahman, M. M., Islam, M. A., Sultana, N., & Rahman, M. S. (2018). Screening of secondary metabolites, antibacterial and antioxidative capacity of *Paederia foetida* L. leaf extracts. *Chittagong University Journal of Biological Sciences, 10*(1), 121–137. https://doi.org/10.3329/cujbs.v10i1.74248

Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L. & WHO Pathogens Priority List Working Group. (2018). Discovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases, 18*(3), 318–327. https://doi.org/10.1016/S1473-3099(17)30753-3

World Health Organization (WHO). (2023). *Global antimicrobial resistance and use surveillance system (GLASS) report 2023*. Geneva, Switzerland: World Health Organization.

Zhang, Y., Li, X., Wang, Z., & Chen, J. (2019). Targeted metabolite analysis of iridoids of *Paederia foetida* L., a popular tribal edible plant. *Asian Journal of Chemistry, 29*(8), 1713–1717. https://doi.org/10.14233/ajchem.2017.20585

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