



A Network Biology Investigation of *Amorphophallus Muelleri* as a Promoter of Gut Health in Broiler Chicken

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Abstract. Gut health is influenced by microbiota balance, directly affecting the poultry's nutrient absorption efficiency and overall production performance. Despite the microbial modulation activity of *Amorphophallus muelleri* has been evaluated, the molecular mechanism remains poorly understood. This study investigated the antibacterial potential of bioactive compounds in *A. muelleri* flour, focusing on their interaction with LpxC, a key enzyme in bacterial lipid biosynthesis. Using molecular docking and dynamics simulations, five compounds—glucomannan, mannan, quercetin, orientin, and hyperoside—were assessed for their binding affinity to LpxC's active site, with the native ligand's binding affinity as a reference. Glucomannan, mannan, and quercetin demonstrated the strongest affinities and optimal binding profiles, with glucomannan showing the highest stability through extensive interactions. Molecular dynamics confirmed glucomannan's robust stability, supported by RMSF data, and highlighted its potential as an effective LpxC inhibitor. Mannan and quercetin also displayed significant binding stability, indicating promise as antibacterial agents. The findings suggest that glucomannan's stability, hydrogen bonding capacity, and bioactivity make it particularly effective, while mannan and quercetin offer additional potential. Overall, these results support the feasibility of *A. muelleri* flour as a natural antibacterial resource, providing a foundation for the development of safer, plant-derived antibiotics targeting LpxC to address bacterial infections and resistance.

Keywords: *A. muelleri*, LpxC inhibition, Antibacterial agents, Molecular docking, Glucomannan

1 Introduction

Aviculture remains the most efficient sector of livestock farming, producing 1.63 million metric tons in 2023/2024 relative to 2022/2023 [1] despite rising feed and energy costs [2]. The consumption of chicken has surged by 70% over the past three decades, driven by global food demand and dietary preferences in wealthier nations [3]. Historically, sub-therapeutic antibiotics have been employed as growth promoters

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(AGPs), enhancing gut microbiota, increasing intestinal wall thickness, and improving nutrient absorption. However, their use has also resulted in the emergence of antibiotic-resistant bacteria and environmental contamination [4]. In response to these issues, the EU banned AGPs in 2006, leading to challenges such as elevated feed conversion rates and increased disease incidence among poultry. In Indonesia, the prohibition of AGP (Antibiotic Growth Promoters) use has been established through Law No. 18/2009 juncto Law No. 41/2014 concerning Animal Husbandry and Animal Health, which explicitly bans the inclusion of specific hormones and/or feed-additive AGP in feed. Consequently, research has shifted towards alternatives like probiotics, prebiotics, and microbiome metabolic modulators (MMMs) that promote growth and bolster immune function [5].

Maintaining gut health, regulated by microbiota, is critical for optimal nutrient absorption and overall performance in poultry. Probiotics, such as *Bacillus* and *Lactobacillus*, offer various benefits, including pathogen reduction, enhanced digestion, and immune stimulation. However, their efficacy is influenced by factors such as formulation, age, and environmental conditions [6]. MMMs, including precision biotics (PBs), further optimize gut microbial metabolic pathways, improving nutrient efficiency while mitigating environmental impacts [7]. Various strategies have been implemented to counteract detrimental shifts in gut microbial populations [8,9]. One such approach involves suppressing the growth of pathogenic bacteria by targeting specific proteins, such as LpxC [10]. LpxC plays a crucial role in the survival of Gram-negative bacteria, as lipid A—essential for maintaining membrane integrity and virulence—depends on it [10,11]. Targeting LpxC has been explored as a sustainable alternative to antibiotic growth promoters (AGPs) for supporting gut health, and several phytobiotics have previously been investigated for their antibacterial effects through this mechanism [12].

The production of *Amorphophallus muelleri* (porang) in Indonesia has grown significantly in recent years, driven by rising corm prices and government initiatives to expand cultivation [13]. This plant is valued for its high glucomannan content, which has broad applications in the food industry, medicine, and export markets [13-15]. While glucomannan from related species such as *A. onchophyllus* has been used as a food additive and dietary supplement [16,17], its potential in livestock and poultry feed remains underexplored—particularly from *A. muelleri*. Glucomannan from *A. muelleri* may act as a potent prebiotic that supports gut health, enhances nutrient absorption, and improves broiler growth performance [18,19]. Additionally, its bioactive compounds help strengthen immunity and reduce pathogenic bacteria [20], thereby lowering the need for antibiotics and promoting antibiotic-free poultry farming. Incorporating *A. muelleri* into broiler diets contributes to improved bird health, better meat quality, and more sustainable poultry production.

The evaluation of compounds in *A. muelleri* flour can be conducted computationally using software. Computational methods facilitate the prediction of molecular interactions prior to experimentation, serving as essential tools for validation in both in vitro and in vivo studies. These methodologies are employed to predict ligand-target protein binding, assess energy affinity, and evaluate ligand activity, in addition to modeling 3D molecular interactions and exploring molecular dynamics [21]. Molecu-

lar docking is a specific computational technique utilized to anchor compounds—whether extracted from natural sources or synthesized—to the active sites of target proteins. Its advantages include speed, cost-effectiveness, and immediate data analysis, although it necessitates high computational power and experimental validation. Conversely, molecular dynamics simulations evaluate ligand-protein binding over a defined timeframe, providing insights into the stability of these interactions. This study aimed to evaluate the antibacterial efficacy of bioactive compounds derived from *Amorphophallus muelleri* flour through growth inhibition analysis against pathogenic bacteria.

2 Materials and Methods

2.1 3D Protein Target Structure

The following is the protein structure of LpxC derived from RCSB PDB, prepared by removing water molecules, ions, and other unnecessary components using PyMOL 2.5.4. The 3D structure of the prepared LpxC can be seen in Fig. 1.

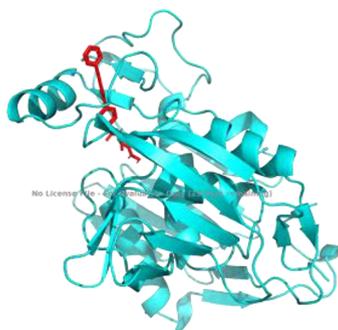


Fig. 1. 3D Structure of the prepared LpxC

2.2 3D Active Compound Structure

The determination of active compounds is conducted through a literature study on the various compositions of *A. muelleri* flour. The identification method for active compounds in the literature must employ chromatography tests. Active compounds are tabulated, and their structures are downloaded from the PubChem database in sdf format.

2.3 Preparation of Target Protein Structure and Active Compounds

The three-dimensional (3D) structure of the target protein was prepared using PyMOL 2.5.4 prior to molecular computational testing. The target protein structure was refined by removing water molecules and unnecessary components, subsequently designating it as a rigid macromolecule [22]. The 3D structure of the active compounds was optimized by minimizing energy using the Universal Force Field (UFF) before being set as ligands with Open Babel [23] in the PyRx 0.8 software [24].

2.4 Binding Site Validation

The binding site position was identified by placing a grid box over the binding site of the native ligand [25]. A run was executed in AutoDock Vina against the native ligand structure to ensure the root mean square deviation (RMSD) was less than 2 Å relative to the conformation of the native ligand prior to molecular docking. This step minimizes deviation values, thereby reducing prediction errors in ligand-protein interactions during computational tests.

2.5 Molecular Docking

AutoDock Vina [26] serves as a plugin within the PyRx 0.8 software for conducting molecular docking. This technique is utilized to screen active compounds based on the lowest binding affinity (< -7 kcal/mol) and the ideal ligand conformation relative to the target protein, including the nature of interactions [27]. The molecular docking procedure involves designating the target protein as a rigid macromolecule while treating the active compounds as flexible ligands within AutoDock Vina. The binding site position was determined using a grid box based on prior validation results. The outcome of molecular docking yielded the most optimal ligand conformations, which were then combined with the target protein in PyMOL 2.5.4 and subsequently visualized in a 2D diagram using Discovery Studio 2019. The data were tabulated and analyzed according to the similarities in interaction types and bindings with the native ligand. The stability of the protein-ligand interactions was also assessed based on the number of hydrogen bonds [28]. The three top-ranking ligands underwent molecular dynamics simulations to evaluate their stability in relation to the target protein.

3 Results

The 3D structure of LpxC was retrieved from the RCSB Protein Data Bank (PDB ID: 3P3E) [18]. This specific LpxC structure was selected due to the presence of the native ligand N-[(1S,2R)-2-hydroxy-1-(hydroxycarbonyl)propyl]-4-(4-phenylbuta-1,3-dien-1-yl)benzamide, which has undergone experimental validation. This compound serves as a control in the study. To determine the binding site, a grid box was defined using AutoDock Vina within the PyRx software, based on the original position of the

native ligand, ensuring a conformation distance of less than 2 Å. The validated binding site yielded a grid box with the parameters as illustrated in Table 1.

Table 1. Gridbox setting for LpxC docking referring to the position and conformation of native ligand

Setting	Position (Å)		
	X	Y	Z
Center	-26.4722	15.8761	-5.2640
Dimension	10.4087	18.7078	15.4433

The conformation distance of the native ligand to its original position prior to validation was measured at 0.610 Å with total of possible mappings: 322486272. This result can be considered valid, as the conformational shift is greater than 2 Å.

The greater the deviation, the higher the risk of errors in predicting interactions between the ligand and protein [21]. This is consistent with the assertion by previous study that docking results are deemed valid if the RMSD value is less than 2 Å [29]. A comparison of the conformation of the native ligand after validation is illustrated in Fig. 2.

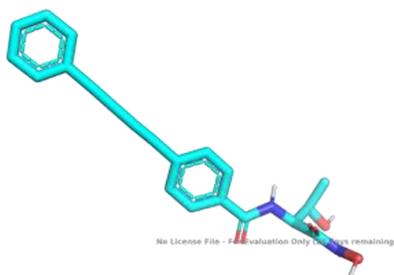


Fig. 2. Validation of Native Ligand LpxC Conformation

Based on the screening results at the LpxC binding site, five compounds exhibited significant interactions with LpxC, as assessed by the lowest binding affinity values (<-7 kcal/mol) and optimal ligand conformations relative to the target protein [27]. The identified active compounds include glucomannan, mannan, quercetin, orientin, and hyperoside. Detailed screening results are presented in Table 2. while the 2D structures of the compounds interacting with LpxC are illustrated in Fig. 2.

Table 2. List of Active Compounds in *A. muelleri* Flour Screened Against LpxC

Active Compound	Binding Affinity
Glucomanan	-5.156
Mannan	-5.883
Quercetin	-7.22
Orientin	-7.122
Hyperoside	-7.402
Native Ligand	-9.322

Based on the molecular docking analysis, Hyperoside exhibited the lowest binding affinity (-7.402 kcal/mol), while Glucomanan had the highest (-5.156 kcal/mol). Nevertheless, the binding affinities of these bioactive compounds remain higher than that of the native ligand (-9.322 kcal/mol). Although there is no universally defined threshold for binding affinity that guarantees potential bioactivity [21], some researchers have chosen -7 kcal/mol as the minimum value needed to achieve a stable protein-ligand complex, which may indicate potential bioactivity [27,30-32]. However, the selection of LpxC inhibitor candidates is determined not only by binding affinity but also by the nature of interactions between the compound structures and amino acid residues in the target protein. The five active compounds were further analyzed for their interaction types with the target protein using Discovery Studio 2019.

The molecular interaction assessment identified three conformations with potential inhibitory effects on LpxC, evaluated based on the number and types of interactions at the binding site with LpxC residues. Among the top three compounds are Glucomanan, Mannan, and Quercetin.

Glucomanan exhibited the highest number of interactions, totaling 14, with no hydrogen bonds, followed by Mannan with 13 hydrogen bonds, and Quercetin with 10 interactions, including 3 hydrogen bonds. Hydrogen bonds are formed between covalently bonded hydrogen atoms and electronegative atoms such as nitrogen and oxygen [20]. The number of hydrogen bonds indicates the stability of the ligand's interaction with LpxC. The 2D interaction graph between the bioactive compounds and LpxC is depicted in Fig. 3.

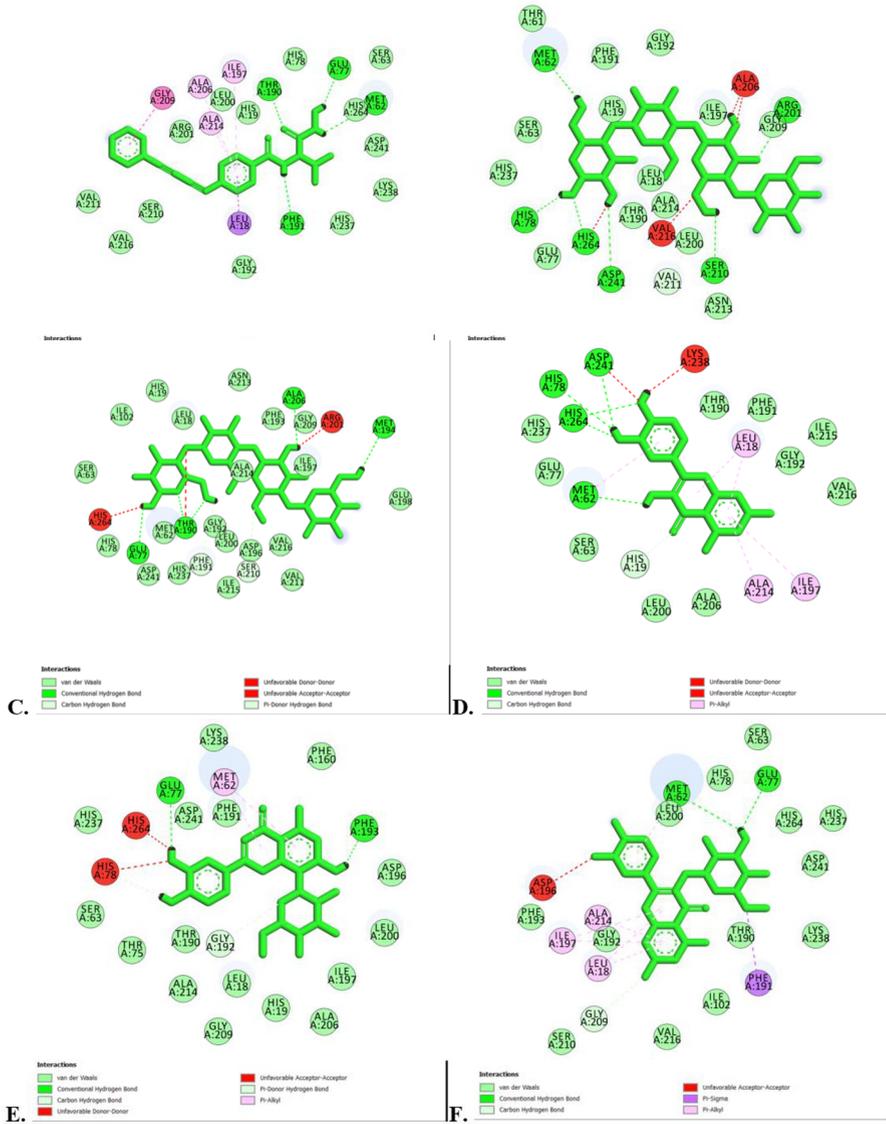


Fig. 3. Interaction Diagram from Molecular Docking with LpxC (A) Native ligand, (B) Glucomannan, (C) Mannan, (D) Quercetin, (E) Orientin, and (F) Hyperoside

4 Discussion

The molecular docking and dynamics analyses reveal that bioactive compounds in *Amorphophallus muelleri* flour, particularly glucomannan, mannan, and quercetin,

exhibit strong binding affinities and stable interactions with LpxC, a key enzyme in lipid A biosynthesis for Gram-negative bacteria [11]. By inhibiting LpxC, these compounds disrupt the structural integrity of bacterial membranes [10], thereby suppressing pathogenic bacteria such as *Escherichia coli* and *Salmonella enterica*, which are detrimental to broiler gut health [33,34]. Glucomannan, with the highest number of interactions, demonstrates potential prolonged inhibitory effects on LpxC. This suppression of pathogenic bacteria emphasizes that reducing pathogenic populations in the gut enhances nutrient absorption efficiency and mucosal immunity [35-37]. Such mechanisms directly translate to improved gut homeostasis in broilers, mitigating dysbiosis and lowering disease incidence—critical factors in antibiotic-free poultry farming.

The stability of these compounds, particularly glucomannan's hydrogen bonding capacity and conformational resilience, suggests sustained bioactivity in the gut environment. Mannan and quercetin, while slightly less stable than glucomannan, still exhibit significant binding through hydrogen bonds and hydrophobic interactions, further contributing to pathogen suppression. This study highlights that a balanced gut microbiota, fostered by reduced pathogen loads, enhances intestinal wall thickness and nutrient utilization—key determinants of broiler growth performance [35,36]. By acting as LpxC inhibitors, these compounds indirectly promote the proliferation of beneficial microbes, such as *Lactobacillus* and *Bacillus*, which compete with pathogens for resources and produce metabolites like short-chain fatty acids [35]. This dual action—pathogen inhibition and prebiotic support—aligns with the study's emphasis on *A. muelleri* as a natural alternative to antibiotic growth promoters (AGPs), addressing both antimicrobial resistance and productivity challenges in poultry farming [16,17].

The broader implications of these findings lie in their potential to revolutionize broiler diets by integrating *A. muelleri* flour as a functional feed additive. The computational validation of glucomannan's efficacy provides a foundation for in vivo studies to confirm its role in enhancing gut health and meat quality. As discussed earlier, replacing AGPs with such natural compounds reduces antibiotic residues in poultry products and environmental contamination, aligning with regulatory bans like Indonesia's Law No. 18/2009. Furthermore, the sustained stability of these compounds ensures long-term gut health benefits, reducing feed conversion ratios and mortality rates in flocks. By leveraging molecular insights to optimize *A. muelleri*'s application, this research supports sustainable poultry production systems that prioritize animal welfare, food safety, and resistance mitigation—a critical step toward meeting global food demands ethically and efficiently.

5 Conclusion

This study underscores the novel potential of *Amorphophallus muelleri* flour as a sustainable, plant-derived alternative to conventional antibiotics in poultry farming, validated through advanced computational methodologies. By identifying glucomannan, mannan, and quercetin as potent LpxC inhibitors with high binding stability, the

research pioneers a pathway toward antibiotic-free strategies that align with global regulatory shifts, such as Indonesia's AGP ban. The integration of molecular docking and dynamics not only highlights the precision of targeting bacterial lipid biosynthesis but also establishes a replicable framework for evaluating natural compounds in agri-health innovations. Future studies should prioritize *in vivo* validation of these compounds' efficacy in enhancing gut health and growth performance, while exploring scalable cultivation and processing techniques for *A. muelleri* to optimize its commercial viability. Additionally, investigating synergistic effects with probiotics or other prebiotics could further advance holistic approaches to poultry nutrition, bridging computational insights with practical, sustainable farming solutions.

Disclosure of Interests. The authors have no competing interests to declare that are relevant to the content of this article.

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