Exploring the Antibacterial Potential of Xanthorrhizol from Curcuma xanthorrhiza Through Molecular Docking Technology

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ABSTRACT

The escalating threat of antimicrobial resistance (AMR) has emerged as a pressing global health challenge. This study critically assesses the feasibility of targeting UDP-N-acetylenolpyruvoylglucosamine reductase (MurB) as an antibacterial drug target and the pharmacological potential of xanthorrhizol. The latter compound represents the predominant bioactive constituent isolated from the rhizome of Curcuma xanthorrhiza, a plant with established medicinal application. Central to our findings is the observation that MurB occupies an indispensable position within the peptidoglycan assembly pathway of bacteria, a function for which no mammalian counterpart exists an attribute that underscores its exceptional suitability as a selective therapeutic target, providing for a highly selective targeting mechanism with little risk of toxicity to the host. Xanthorrhizol also showed potent bactericidal activity against Gram-negative bacteria by successfully attacking their cellular defenses, preventing biofilm formation, and significantly reducing the count of viable cells. Therefore, xanthorrhizol looks like a very rational candidate for the development of new drugs. In conclusion, xanthorrhizol as an inhibitor of the MurB enzyme is a promising novel strategy in the fight against resistant *Pseudomonas aeruginosa* infections and provides a good theoretical basis that needs further molecular docking simulations and *in vitro* validation.

Keyword: antimicrobial resistance; MurB enzyme; xanthorrhizol; *Curcuma xanthorrhiza; Pseudomonas aeruginosa*

Introduction

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges of the 21st century. The World Health Organization (WHO) defines AMR as "the ability of a microorganism to resist the effects of antimicrobial agents to which it is normally susceptible" [1]. A landmark global study estimated that AMR was directly responsible for 1.27 million deaths in 2019 and contributed to nearly 5 million deaths worldwide [2]. Without effective intervention, projections indicate that AMR could claim up to 10 million lives annually and cause cumulative economic losses approaching USD 100 trillion by 2050 [1].

Among clinically significant pathogens, *Pseudomonas aeruginosa* is particularly concerning due to its intrinsic and acquired resistance to multiple antibiotic classes. The WHO has categorized carbapenem-resistant *P. aeruginosa* as a critical priority pathogen for which new antibiotics are urgently needed [3]. This organism is a leading cause of healthcare-associated infections, including pneumonia, bacteremia, and urinary tract infections, particularly in immunocompromised patients and those with indwelling medical devices. The progressive erosion of therapeutic options against *P. aeruginosa* underscores the urgent need for novel antibacterial strategies with distinct mechanisms of action [4].

Antibacterials exert their effects through interference with vital microbial pathways, including peptidoglycan assembly, protein synthesis, and DNA replication. Bacterial resistance can arise through enzymatic inactivation of drugs, active efflux, target site modification, and decreased membrane permeability [5]. From this perspective, the MurB enzyme (UDP-*N*-acetylenolpyruvoylglucosamine reductase) represents a compelling target for antibacterial drug discovery. MurB catalyzes the NADPH-dependent reduction of UDP-GlcNAc-EP to UDP-MurNAc, a critical step in the early phase of peptidoglycan biosynthesis [6]. This pathway is essential for bacterial cell wall integrity and, importantly, has no mammalian counterpart, making MurB a highly selective target with low potential for host toxicity. Structurally, the MurB active site contains conserved catalytic residues including Arg159, Ser229, and Glu325 in *P. aeruginosa* that are crucial for enzymatic function and serve as logical anchor points for inhibitor design [7].

Natural products have historically been a rich source of antibacterial agents, and *Curcuma xanthorrhiza* Roxb. (Javanese turmeric) exemplifies this potential. This plant contains more than 40 bioactive compounds, predominantly terpenoids and curcuminoids [8]. Xanthorrhizol, its major sesquiterpenoid constituent, has demonstrated broad-spectrum antibacterial activity in vitro. At 4× MIC, xanthorrhizol reduces viable counts of *Bacillus cereus*, *Staphylococcus aureus*, and *Salmonella* spp. by approximately 6–8 log units within 4

hours [8]. It has also shown activity against *P. aeruginosa* and other Gram-negative pathogens, making it a promising candidate for further investigation [9].

Despite these encouraging findings, the specific interaction of xanthorrhizol with the MurB enzyme has not been systematically explored. While previous computational studies have suggested possible interactions with other antibacterial targets such as FabI and MscL [10], the MurB enzyme remains underexplored. Therefore, this study aims to evaluate the binding affinity and interaction profile of xanthorrhizol against the MurB enzyme of *P. aeruginosa* using molecular docking, thereby providing a theoretical foundation for future experimental validation and drug development efforts targeting bacterial cell wall biosynthesis.

Material and Methods Ligand Preparation

The stereochemical coordinates of xanthorrhizol, the main sesquiterpenoid metabolite from *Curcuma xanthorrhiza*, were obtained from the PubChem repository in Structure Data File (SDF) format. The ligand structure was converted to PDB format using Open Babel and then prepared with AutoDockTools (version 1.5.6). Ligand preparation entailed assignment of Gasteiger partial charges, consolidation of nonpolar hydrogens, and automatic enumeration of rotatable bonds to enable conformational adaptability throughout the docking procedure [6].

Protein Target Preparation

The three-dimensional crystallographic structure of the MurB enzyme (UDP-*N*-acetylglucosamine enolpyruvyl reductase) from *Pseudomonas aeruginosa*, solved at a resolution of 2.51 Å, was obtained from the Protein Data Bank under the unique identifier 2Q85.MurB is an attractive target for rational drug discovery of an antimicrobial agent because it plays a vital role in the peptidoglycan biosynthetic pathway of bacteria. The protein structure was prepared for docking by removing the co-crystallized ligand and the crystallographic water molecules, while retaining the protein backbone and catalytic residues. The polar hydrogen atoms were added and Kollman partial charges were assigned. Following preparation, the protein structure was exported and stored in PDBQT format through the AutoDockTools interface. The delineation of the binding pocket was accomplished by referencing the spatial coordinates occupied by the endogenous ligand within the catalytic region of MurB.

Redocking Validation and Molecular Docking

In silico docking studies were carried out using AutoDock Vina software. The center coordinates were fixed at X = 15.164, Y= −7.819, and Z= 10.346 with the spatial dimension of 20 × 20 × 20 Å, and a grid was set up. An exhaustiveness of 16 was used to ensure a thorough

sampling of the conformational space of the ligand and its positions in the active site cavity. The reliability of the docking methodology was subsequently verified through the re-docking procedure applied to the co-crystallized ligand, Naphthyl Tetronic Acid, into the MurB binding pocket under the same docking conditions. We successfully validated the protocol with a threshold of < 2.0 Å root-mean-square deviation (RMSD) between the computationally docked pose and the experimental crystallographic ligand conformation. The redocking process resulted in an RMSD value of 0.932 Å which indicates a good reproducibility of the docking protocol. The native ligand showed a binding affinity of −8.6 kcal/mol which corresponds to an estimated inhibition constant (Ki) of 4.9×10^{-4} mM and formed 10 molecular interactions in the MurB active site [6].

Inhibition Constant (Ki) Calculation

The binding free energy (ΔG) was used to calculate the inhibition constant (Ki) using the thermodynamic relation: via the equation ΔG = -RT ln Ki, with R denoting the universal gas constant (1.987×10^{-3} kcal·mol^{-1}·K^{-1}) and T representing absolute temperature (298.15 K). Ki values were reported in millimolar (mM) units and the lower the Ki values, the more potent the expected inhibitory efficacy against the target protein [7,8].

Results

Redocking of Co-crystallized Ligand Validation and Binding Interaction Analysis

The crystallographic structure of *Pseudomonas aeruginosa* UDP-*N*-acetylglucosamine-enolpyruvate reductase was downloaded directly from the Protein Data Bank with the accession code 2Q85 and was employed as the macromolecular target for the molecular docking studies. The chosen protein structure has a crystallographic resolution of 2.51 Å, which is good enough for computational analysis. Before the docking process, the target protein was prepared in silico by removing the co-crystallized ligand and the crystallographic water molecules, while preserving the native conformation of the catalytic binding pocket. The docking grid was centred at X = 15.164, Y = –7.819 and Z = 10.346 with grid box dimensions of 20 × 20 × 20 Å and the completeness parameter set to 16 to ensure adequate sampling of ligand conformations within the active site.

The native ligand Naphthyl Tetronic Acid was re-docked in the binding pocket of MurB to validate the docking protocol. The authentication process yielded an RMSD value of 0.932 Å, which is below the acceptable limit of 2.0 Å, thus showing that this docking protocol is reliable and can be used to generate binding positions based on crystallography. The native ligand showed binding with an affinity value of −8.6 kcal/mol which is equivalent to an

estimated inhibition constant (Ki) of 4.9 × 10−4 mM. The results indicate that the chosen docking parameters are suitable to investigate the interaction between MurB and the tested compounds.

Analysis of the docking complex showed that the initial ligand formed a reproducible pattern of interactions in the active site of MurB. We identified the catalytic residues Arg159, Ser229, and Glu325 and several surrounding amino acids, totaling 10 molecular interactions in the binding region. The wide interaction pattern indicates that Naphthyl Tetronic Acid efficiently fills the active site and acts as a suitable reference inhibitor to compare with the studied natural compound.

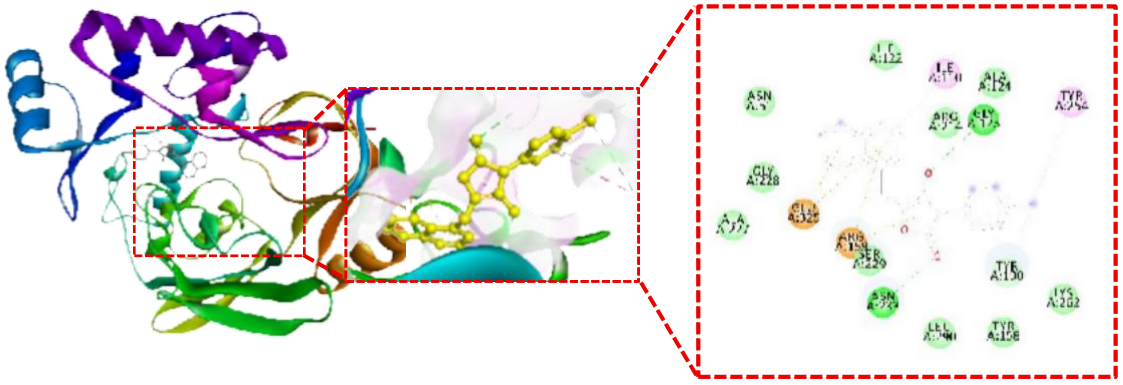

Figure 1. Interaction between Naphthyl Tetronic Acid (co-crystallized ligand) and MurB active site. The figure should show the ligand in stick representation, catalytic residues in ball-and-stick, and hydrogen bonds as dashed lines.

Molecular Interaction Analysis of Xanthorrhizol in MurB

The docking simulation of xanthorrhizol, the main bioactive ingredient found in *Curcuma xanthorrhiza*, showed a binding affinity of -6.2 kcal/mol with an estimated inhibition constant (Ki) of 2.84 × 10^{-2} mM (0.0284 mM). The RMSD value obtained in the verification of the docking configuration was 1.709 Å, which is well below the threshold considered suitable for molecular docking studies. The results show that the binding mode of xanthorrhizol is stable and suitable for further study of the interaction.

Interaction analysis revealed that xanthorrhizol was fitted into the active binding pocket of MurB and interacted with the important catalytic residues Arg159, Ser229 and Glu325. These residues are known to be involved in the catalytic reduction step in peptidoglycan biosynthesis indicating that xanthorrhizol binds within the functional region of the enzyme. Apart from these catalytic contacts, the ligand was surrounded by neighbouring amino acid residues through hydrophobic and non-covalent interactions which helped in stabilization of the ligand-protein complex in the active site.

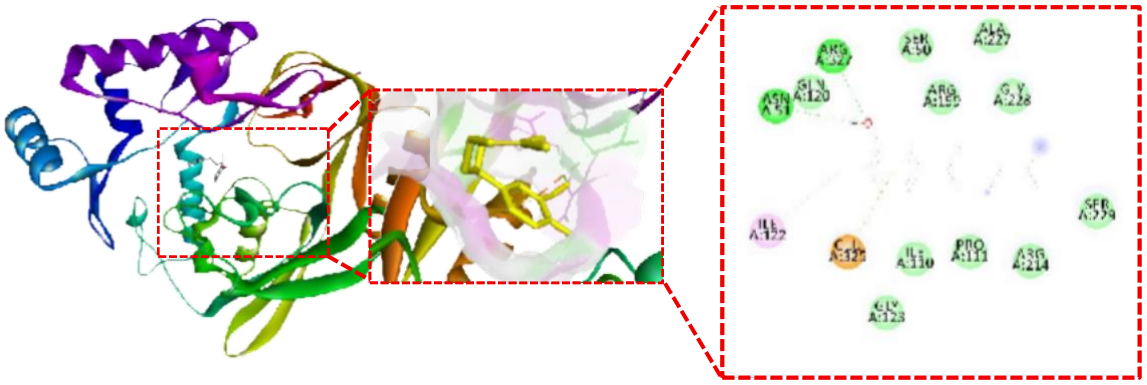

Figure 2. Interaction between xanthorrhizol and MurB active site. The figure should show xanthorrhizol in stick representation, catalytic residues Arg159, Ser229, Glu325 in ball-and-stick, and hydrogen bonds/hydrophobic contacts as dashed lines.

Relative to xanthorrhizol, the native ligand exhibited markedly superior binding parameters, as reflected by its more favorable affinity of (-8.6 kcal/mol) alongside a substantially reduced inhibition constant. However, xanthorrhizol formed interactions with the essential catalytic residues within MurB, despite the relatively low binding energy of (-6.2 kcal/mol). These results suggest that xanthorrhizol can fit into the catalytic pocket and inhibit the enzyme activity needed for bacterial cell wall formation.

Finally, the molecular docking results showed that xanthorrhizol has a high binding affinity for the MurB enzyme of Pseudomonas aeruginosa. The predicted binding strength is not as high as co-crystallized ligand, however, interaction with the catalytic residues Arg159, Ser229 and Glu325 along with acceptable RMSD value suggests that xanthorrhizol is a promising natural candidate for development of new antibacterial drugs. Additional validation using molecular dynamics simulation and experimental tests in vitro is required to prove the stability and efficacy of the xanthorrhizol-MurB complex as an inhibitor.

Discussion

In silico docking simulations showed that Naphthyl Tetronic Acid (used as benchmark ligand) had better binding profile towards MurB enzyme than xanthorrhizol . The binding energy of this reference compound was −8.6 kcal/mol, and the theoretical calculated inhibition constant (Ki) was 4.9 × 10−4 mM. Meanwhile, xanthorrhizol had a binding energy of −6.2 kcal/mol and a predicted Ki value of 2.84 × 10−2 mM. These quantitative assays show that the reference ligand designated is a better inhibitor of MurB activity than xanthorrhizol. Although there was a visible difference in binding efficiency, Xanthorrhizol was still capable of binding to the active site of MurB. It established important interactions with key residues, namely Arg159, Ser229 and Glu325, all of which are involved in the enzymatic process of

peptidoglycan synthesis. The interaction observed here suggest that xanthorrhizol might inhibit bacterial cell wall construction even with its comparatively lower binding strength to the target protein with respect to the co-crystallized reference ligand.

Antimicrobial activity of xanthorrhizol against several pathogenic bacterial species has been repeatedly confirmed in previous studies. The anti-proliferative activity of xanthorrhizol on *Streptococcus mutans, Streptococcus sanguinis, Enterococcus faecalis* and *Bacillus cereus* has been reported [9]. In addition, the compound showed high antibacterial activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The mechanism of this activity was associated with the selective interference with the mechanosensitive channel protein (MscL) that resulted in the release of intracellular components and osmotic lysis of the bacterial cell. In addition, previous computational studies have suggested the possible interactions of xanthorrhizol with other antibacterial targets such as FabI and TadA. The present work, in contrast to these previous studies, aims to investigate a different antibacterial target, UDP-*N*-acetylglucosamine enolpyruvyl reductase (MurB). Thus, the current study offers further proof for the hypothesis that xanthorrhizol might have various molecular targets in its inhibition of bacterial growth [10].

A comparative analysis of binding free energy values explains the difference in binding affinity between the reference ligand and xanthorrhizol. In molecular docking simulations, a more negative binding free energy value corresponds to a more robust and energetically stable interaction between the ligand and the target protein, as the binding event is thermodynamically more favorable. At the same time, the decreased inhibition constant (Ki) value indicates the improved inhibitory potency, according to the theoretical requirement of a lower ligand concentration to decrease the enzymatic activity. Thus, the more negative binding energy (−8.6 kcal/mol) and a lower Ki value of the reference ligand indicate a better affinity of the reference ligand toward the MurB active site than xanthorrhizol. However, the binding affinity of xanthorrhizol (−6.2 kcal/mol) still suggests a favorable interaction with the target protein, supporting its potential as a natural inhibitor of MurB) [11].

The Root Mean Square Deviation (RMSD) values obtained confirmed the robustness of the molecular docking methodology. For validation stage, the RMSD values were obtained as 0.932 Å for benchmark ligand and 1.709 Å for xanthorrhizol. Both calculated values are below the typical acceptability criterion of 2.0 Å, confirming the high accuracy of the computationally generated docking poses in reproducing the experimentally determined crystallographic orientation. RMSD value of 2.0 Å or less is known as a strong evidence for the ability of a docking protocol to predict correctly the inherent conformation of the native

ligand[8]. This value was slightly higher than the reference ligand but was also within the acceptable range for xanthorrhizol. Hence, the docking protocol used in this study was validated and the predicted ligand-protein interactions can be relied upon for further analytical discussions [12].

The computed Root Mean Square Deviation (RMSD) values verified the reliability of the molecular docking approach. Specifically, the RMSD values obtained during validation were 0.932 Å for the standard ligand and 1.709 Å for xanthorrhizol. Both these derived values are below the acceptance threshold of 2.0 Å, which confirms the high accuracy with which the computationally derived docking conformations are representative of the experimentally determined crystallographic arrangement. RMSD values <= 2.0 Å indicate the ability of the docking protocol to reproduce the native ligand's inherent structure correctly [7,12]. The RMSD for xanthorrhizol was slightly higher than that for the benchmark ligand but still within the acceptable range of values.thus confirming the efficiency of the molecular docking approach used in this research project and thereby validating confidence in the accuracy of the predicted ligand-protein binding affinities.

Despite these promising findings, a series of limitations should be carefully taken into account before a potential development of xanthorrhizol as a therapeutic antibacterial agent. The present investigation was based only on in silico molecular docking approaches. These approaches are capable of predicting ligandprotein interactions, but are inherently unable to recapitulate the complex biological milieu of living organisms in their entirety. Moreover, data regarding the pharmacokinetic profile, bioavailability, metabolic fate, toxicological properties and persistent clinical efficacy of xanthorrhizol are surprisingly scant. However, previous studies have shown promising antibacterial properties but more stringent studies are needed to provide conclusive evidence of its therapeutic efficacy and safety [10].

However, with the above limitations in mind, further studies should include molecular dynamics (MD) simulations. These simulations were performed to determine the temporal stability of the complex formed between xanthorrhizol and MurB. Alongside, ADMET predictions should be used for comprehensive assessment of the compound's pharmacokinetic properties and possible toxicological consequences. Additional empirical verification is essential to substantiate the assumed inhibitory profile delineated by this in silico docking simulation. This requires a multi-level experimental approach including enzymatic inhibition assays, in vitro antibacterial susceptibility tests and preclinical in vivo tests. These methodological approaches will together provide more convincing evidence to support the development of xanthorrhizol as a promising candidate compound of natural antibacterial

agent, especially in the direction of bacterial cell wall biosynthesis.

The robustness of the molecular docking methodology was substantiated by the resultant Root Mean Square Deviation (RMSD) metrics. The methodological validation obtained Root Mean Square Deviation (RMSD) metrics of 0.932 Å for the reference control and 1.709 Å for xanthorrhizol. Both these values are well below the standard 2.0 Å cut-off and hence confirm the reliability of the simulated docked conformations as representative of the native crystallographic structure. In computational drug design, an RMSD of ≤ 2.0 Å is a yardstick that validates the accuracy of a docking algorithm to predict real ligand orientation. The binding mode of xanthorrhizol with the target protein is similar to the reported binding mode of the benchmark compound, the RMSD value for the superposition of the binding modes is slightly higher than the benchmark compound but is still within the tolerable limits, thus confirming the validity of the parameters used in this work and the ligand-protein binding affinity calculated [6,12].

The reliability of the molecular docking approach was affirmed through the computed Root Mean Square Deviation (RMSD) measurements. The RMSD values obtained during the validation phase were 0.932 Å and 1.709 Å for the co-crystallized standard and xanthorrhizol, respectively. These figures, meeting the stringent < 2.0 Å cut-off, strongly support the high fidelity of the simulated docking poses in reproducing the true crystallographic architecture. A RMSD below this critical threshold is generally accepted as a clear indication that the docking protocol is able to reproduce the ligand's native spatial arrangement. The structural deviation for xanthorrhizol was marginally above the benchmark molecule but comfortably passed the validation criteria stipulated. The success of this calculation fully justifies the computational framework adopted in this study and gives us great confidence in the predicted ligand-protein binding energies for further theoretical discussion [7,12].

Notwithstanding these encouraging results, a number of constraints warrant careful consideration prior to the potential development of xanthorrhizol as a therapeutic antibacterial agent. The computational docking protocols employed in this research are powerful in estimating molecular interactions, however these in silico frameworks are inherently unable to capture the holistic biochemical complexities present in an intact biological system. Moreover, exhaustive literature regarding the absorption, distribution, metabolism, toxicology and clinical persistence of xanthorrhizol is conspicuously lacking. Thus, although the antimicrobial promise of the compound has been documented previously, subsequent rigorous empirical trials are absolutely essential to substantiate its ultimate therapeutic value and clinical safety [10].

In light of the aforementioned constraints, subsequent investigations ought to incorporate

molecular dynamics (MD) simulations. The objective of these simulations would be to ascertain the temporal stability of the complex formed between xanthorrhizol and MurB. Simultaneously, computational ADMET profiling should be implemented to rigorously analyze the pharmacokinetic behavior of the compound and any possible toxicological liabilities. In parallel direct enzyme inhibition assays, in vitro antimicrobial susceptibility assays and extensive in vivo models are mandatory empirical verifications. The results of these in vitro tests are essential to confirm the predicted inhibition by the present in silico model. Ultimately, the combination of these multi-faceted strategies will provide the definitive empirical data required to transition xanthorrhizol into a promising natural antibiotic targeting the bacterial cell wall assembly pipeline.

Conclusion

The escalating global threat of antimicrobial resistance, particularly among Gram-negative pathogens such as *Pseudomonas aeruginosa*, demands the urgent identification of novel antibacterial agents with distinct mechanisms of action. The MurB enzyme, essential for bacterial peptidoglycan biosynthesis and absent in mammalian systems, represents an attractive and highly selective therapeutic target. In this study, molecular docking analysis demonstrated that xanthorrhizol, the major bioactive constituent of *Curcuma xanthorrhiza*, binds to the MurB active site with a binding affinity of −6.2 kcal/mol and interacts with the critical catalytic residues Arg159, Ser229, and Glu325. Although its binding affinity was lower than that of the co-crystallized ligand, the favorable binding mode and interaction with the catalytic triad suggest that xanthorrhizol has the potential to inhibit MurB enzymatic activity. These findings provide a strong theoretical foundation for further investigation. However, computational predictions must be substantiated through molecular dynamics simulations, enzymatic inhibition assays, and in vitro antibacterial testing. With rigorous experimental validation, xanthorrhizol or its structural derivatives could emerge as a promising lead compound for next-generation antibacterial therapies targeting bacterial cell wall assembly.

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