Molecular Docking of Catechin from *Uncaria gambir* as a Potential Inhibitor of MurB Enzyme for Antibacterial Drug Development

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ABSTRACT

The increasing prevalence of antibiotic-resistant *Pseudomonas aeruginosa* highlights the need for novel antibacterial agents targeting essential enzymes such as MurB, a key enzyme in peptidoglycan biosynthesis. This study aimed to evaluate the inhibitory potential of catechin against MurB (PDB ID: 7ORZ) using molecular docking. Docking validation was performed through redocking of the co-crystallized ligand, yielding an RMSD of 0.962 Å, confirming the reliability of the method. Catechin exhibited a stronger binding affinity (−7.9 kcal/mol) compared to the reference ligand (−5.2 kcal/mol), with a significantly lower inhibition constant (Ki = 1.63 μM vs. 153 μM), indicating approximately 100-fold higher inhibitory potential. Interaction analysis revealed that catechin forms multiple hydrogen bonds, electrostatic interactions, and hydrophobic contacts with key catalytic residues, including Arg166, Ser239, and Glu335. These interactions suggest that catechin effectively occupies the active site and may interfere with the NADPH-dependent catalytic mechanism of MurB. In conclusion, catechin demonstrates promising potential as a MurB inhibitor and may serve as a lead compound for the development of antibacterial agents against *P. aeruginosa*. Further experimental validation is required to confirm its biological activity.

Keyword : MurB enzyme; antibacterial agents; catechin; enzyme inhibition molecular docking; peptidoglycan biosynthesis*; Pseudomonas aeruginosa*

Introduction

Antimicrobial resistance (AMR) has emerged as one of the most pressing global public health challenges of the 21st century, threatening the efficacy of antibiotic therapy worldwide [1]. The overuse of conventional antibiotics in human health, veterinary medicine, and agriculture has accelerated the evolution and spread of resistant bacteria. Multidrug-resistant (MDR) pathogens are becoming leading causes of death globally, imposing major hurdles to drug discovery programs [2]. The drying pipeline of new antibiotics has raised concerns about a return to the pre-antibiotic era, making the search for alternative therapeutic strategies an urgent necessity. The challenge extends across diverse clinical settings, including MDR periodontal pathogens (*Porphyromonas gingivalis*, *Fusobacterium nucleatum*) and uropathogenic *Escherichia coli* and *Pseudomonas aeruginosa* [3,4]. The World Health Organization has classified *Acinetobacter baumannii* and other resistant bacteria as critical priority pathogens.

In this context, plant-derived bioactive compounds have emerged as promising reservoirs for antibacterial drug discovery [5]. Plants are rich sources of secondary metabolites such as alkaloids, flavonoids, and polyphenols, many of which possess antibacterial activity [6]. Polyphenolic compounds are especially promising due to their ability to disrupt bacterial membranes, inhibit efflux pumps, and interfere with quorum-sensing and biofilm maturation [3]. Targeting novel bacterial enzymes that are essential for survival but absent in mammalian cells represents a particularly attractive strategy to reduce host toxicity. The bacterial cell wall is an ideal target, and among peptidoglycan biosynthesis enzymes, MurB (UDP-N-acetylenolpyruvoylglucosamine reductase) plays a crucial early role [7]. MurB catalyzes the NADPH-dependent reduction of UDP-GlcNAc-EP to UDP-MurNAc, an essential precursor for peptidoglycan synthesis. MurB is a flavoprotein, and its absence in mammalian systems makes it a highly selective target. Inhibition of MurB blocks cell wall synthesis, leading to bacterial lysis. Structural studies have identified conserved catalytic residues (e.g., Arg160, Ser230, Glu326 in *E. coli*) that are critical for inhibitor design [8].

Uncaria gambir Roxb (gambir), a plant widely distributed in Southeast Asia, contains catechin as a major bioactive flavonoid [9,10]. Catechin (flavan-3-ol) exhibits broad-spectrum antibacterial activity against pathogens including *Campylobacter jejuni*, *E. coli*, *Streptococcus mutans*, and methicillin-resistant *Staphylococcus aereus* (MRSA) [11,12]. Its antibacterial mechanisms include membrane disruption, efflux pump inhibition, and oxidative stress [1]. Catechin also possesses potent antioxidant activity due to its multiple hydroxyl groups. Despite these known activities, research specifically investigating

catechin's interaction with MurB is limited. However, in silico studies have shown that catechin binds MurA (another cell wall synthesis enzyme) with good affinity, suggesting potential against the Mur pathway [9].

Molecular docking is a well-established computational tool for predicting ligand-receptor interactions and guiding experimental validation [13]. Given the availability of MurB crystal structures (e.g., PDB ID: 7ORZ for *P. aeruginosa*, 1HSK for *S. aureus*, 2Q85 for *E. coli*) and catechin's structural features multiple hydroxyl groups and aromatic rings suitable for hydrogen bonding and hydrophobic interactions docking can provide valuable insights into binding affinity and mode. Previous docking studies have shown that active MurB inhibitors typically form hydrogen bonds with key residues such as Ser229 [14]. Therefore, the present study aims to investigate the potential of catechin from *Uncaria gambir* Roxb. as a MurB inhibitor using molecular docking. Specifically, we seek to: (1) evaluate the binding affinity of catechin to the MurB active site; (2) identify key molecular interactions with catalytic residues (Arg166, Ser239, Glu335); (3) characterize the binding mode within the MurB pocket; and (4) assess catechin's potential as a lead compound for novel antibacterial agents targeting peptidoglycan biosynthesis. This integrative approach provides a foundation for future experimental validation of catechin-based MurB inhibitors.

Material and Methods

Ligand Preparation

The three-dimensional (3D) structure of catechin (CID: 9064) was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The ligand structure was energy-minimized using the MMFF94 force field with conjugate gradient algorithm to achieve a stable conformation. The minimized structure was then converted to PDBQT format using AutoDockTools (version 1.5.6), with assignment of Gasteiger partial charges and merging of non-polar hydrogens. Rotatable bonds were defined automatically by the software[15].

Protein Target Preparation

The crystal structure of MurB enzyme from *P. aeruginosa* was obtained from the Protein Data Bank (PDB ID: 7ORZ; resolution: 1.850 Å). This structure was selected due to its high resolution and the presence of the FAD cofactor and bound substrate analog. The protein preparation involved: (1) removal of water molecules and heteroatoms not relevant to the binding site, (2) addition of polar hydrogens, (3) assignment of Kollman partial charges, and (4) energy minimization using the CHARMM force field. The prepared protein was saved in PDBQT format using AutoDockTools[16].

Active Site Identification

The binding pocket of MurB was identified based on the location of the FAD cofactor and previously reported catalytic residues (Arg160, Ser230, Glu326 in *P.aeruginosa* numbering). The grid box was centered at coordinates x = -45.892, y = 5.757, z = 4.470 (Å), with dimensions of 16 × 18 × 16 Å³ and a grid spacing of 1.0 Å. This grid box was designed to encompass the co-crystallized ligan to substrate-binding region including all key catalytic residues.

Molecular Docking Procedure

Molecular docking was performed using AutoDock Vina. The exhaustiveness parameter was set to 32 to ensure thorough sampling of ligand conformations. The maximum number of binding modes generated was set to 20. Other parameters were kept at default values. The docking protocol was validated by re-docking the native co-crystallized ligand 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid as MurB inhibitor to ensure reproducibility of the binding pose (RMSD < 2.0 Å)[17].

Analysis of Docking Results

The binding affinity (kcal/mol) of catechin to MurB was recorded from the docking output. The best docking pose was selected based on the lowest binding energy and clustering analysis. Visualization and analysis of intermolecular interactions (hydrogen bonds, hydrophobic interactions, π-π stacking, and electrostatic interactions) were performed using Biovia Discovery Studio Visualizer (version 2021) and Chimera. Specific attention was given to interactions with key catalytic residues: Arg160, Ser230, and Glu326 (homologous to Arg166, Ser239, Glu335 in other MurB sequence numbering systems).

Inhibition Constant (Ki) Calculation

Following the molecular docking simulation, the inhibition constant (Ki) was calculated for the best-docked pose of catechin against the MurB enzyme. The Ki value, which represents the concentration of inhibitor required to occupy 50% of the enzyme's active site, was derived from the predicted binding free energy (ΔG, in kcal/mol) obtained from AutoDock Vina. The calculation was performed using the standard thermodynamic equation that relates free energy to the equilibrium constant at a given temperature--.

The formula used is as follows:

$$\mathbf{\Delta G = -RT \ln Ki}$$

Where: **ΔG** = Binding free energy (kcal/mol);

R = Universal gas constant (1.98719×10^{-3} kcal·mol^{-1}·K^{-1}, or 1.98719 cal·mol^{-1}·K^{-1})-

T = Absolute temperature (298.15 K, which corresponds to 25°C), a standard physiological temperature for in silico assays.

The conversion factor of 1000 is used to align the energy units (kcal/mol) with the gas constant (cal/mol·K). The resulting Ki value is expressed in micromolar (μM) units, with smaller values indicating stronger inhibitory potential[18,19].

For comparative analysis, the Ki of a positive control (a known MurB inhibitor) was calculated using the same protocol. The binding energies and Ki values for catechin and the control were tabulated to quantify and benchmark the predicted inhibitory activity.

Control and Comparative Analysis

To benchmark the binding affinity of catechin, a positive control (a known MurB inhibitor, 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid as co-crystallized ligand) was docked under identical conditions. Additionally, docking was performed using a decoy molecule (a non-active flavonoid) to confirm the specificity of catechin binding.

Results

Redocking Validation and Binding Interaction Analysis

Redocking of the co-crystallized ligand, 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid, into the active site of MurB enzyme (PDB ID: 7ORZ) from *Pseudomonas aeruginosa* was conducted to validate the docking protocol. The obtained binding affinity was −5.2 kcal/mol with an RMSD value of 0.962 Å, indicating high reliability of the docking method, as an RMSD below 2.0 Å confirms accurate reproduction of the native binding pose. Based on the binding free energy, the inhibition constant (Ki) was estimated to be approximately 1.53×10^{-4} M (153 μM), reflecting a moderate binding affinity typical of reference ligands used in validation procedures in **Figure 1**.

Interaction analysis demonstrated that the ligand is well accommodated within the MurB binding pocket and interacts with key catalytic residues. Notably, Arg166, Ser239, and Glu335 recognized as essential residues in the catalytic mechanism were directly involved in ligand stabilization. A conventional hydrogen bond was observed with Ser239, supported by additional hydrogen bonding interaction with Gly130, contributing to proper ligand anchoring. Electrostatic (attractive charge) interactions were identified with Arg166 and Arg224, highlighting the role of positively charged residues in stabilizing the negatively charged carboxylate group of the ligand. Furthermore, hydrophobic interactions were observed with Ile117, Ile129, and Ala131 through π-alkyl interactions, as well as with Leu228 via π-sigma interaction and Val301 through van der Waals contacts, collectively enhancing binding stability. The trifluoromethyl moiety also contributed through halogen

interactions with Ala237, Ser239, and Glu335, further reinforcing ligand positioning within the active site in **Figure 1**.

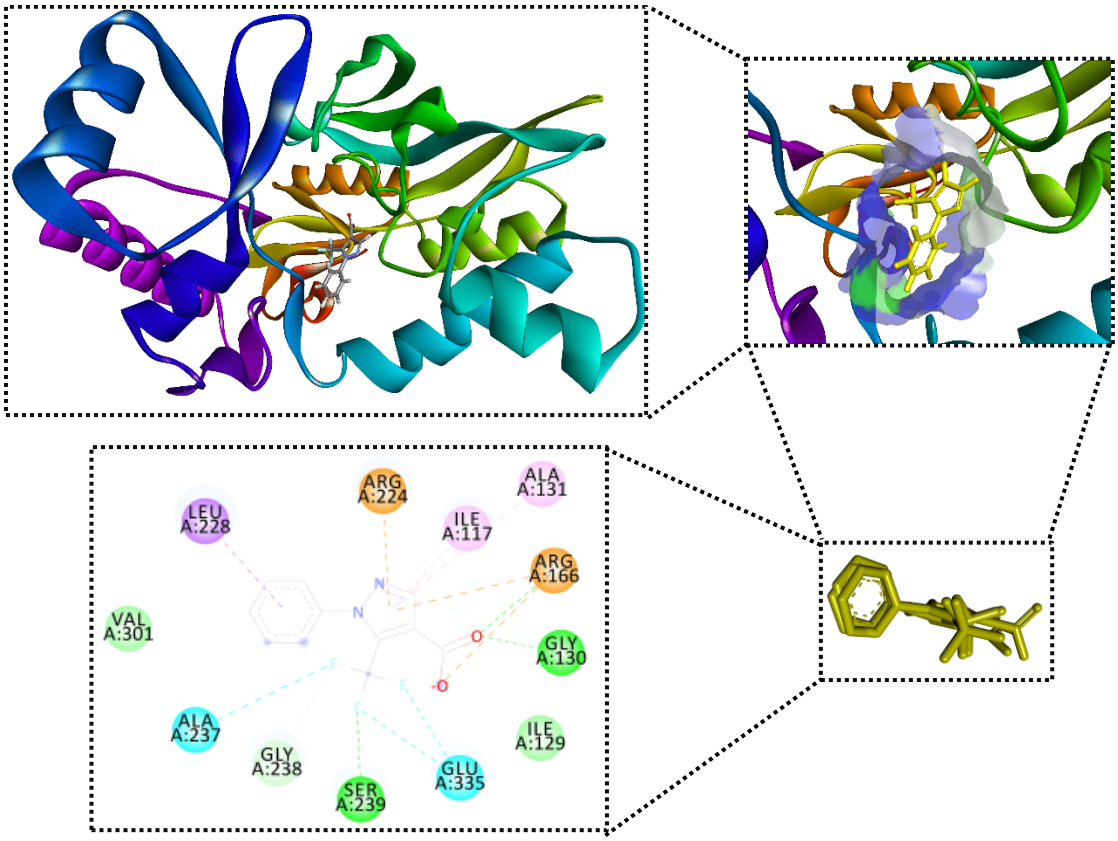

Figure 1. Redocking co-crytallized ligand to MurB as validation docking parameters

The presence of multiple interaction types, including hydrogen bonding, electrostatic, hydrophobic, and halogen interactions, indicates a stable and well-defined binding mode. Importantly, the ligand maintains interactions with all key catalytic residues (Arg166, Ser239, and Glu335), confirming that the docking protocol successfully reproduces biologically relevant interactions. These findings, supported by the low RMSD value and consistent interaction profile, validate the reliability of the docking setup and justify its application for subsequent virtual screening and structure-based drug design targeting MurB inhibition in *P. aeruginosa*.

Interaction of Catechin to MurB

Docking analysis of the test ligand catechin against MurB enzyme (PDB ID: 7ORZ) from *Pseudomonas aeruginosa* demonstrated a strong binding affinity with a calculated binding energy of −7.9 kcal/mol and an RMSD value of 1.426 Å. The RMSD value, being below 2.0 Å, indicates that the docking pose is reliable and structurally consistent. Based on the binding free energy, the estimated inhibition constant (Ki) was approximately 1.63×10^{-6} M (1.63 µM), suggesting a significantly higher binding affinity compared to the reference

ligand, and indicating the potential of catechin as a promising MurB inhibitor in **Figure 2**.

Interaction analysis revealed that catechin is well accommodated within the active site and forms multiple stabilizing interactions with both catalytic and surrounding residues. Importantly, catechin directly interacts with key catalytic residues, particularly Arg166 and Glu335, confirming its ability to occupy the functional binding pocket. A conventional hydrogen bond was observed between catechin and Arg166, while additional hydrogen bonding interactions were formed with Tyr165 and Phe241, contributing to strong ligand anchoring within the binding site. Furthermore, π-cation interactions were identified with Arg224, and π-anion interaction with Glu335, indicating favorable electrostatic complementarity between the ligand's aromatic system and charged amino acid residues.

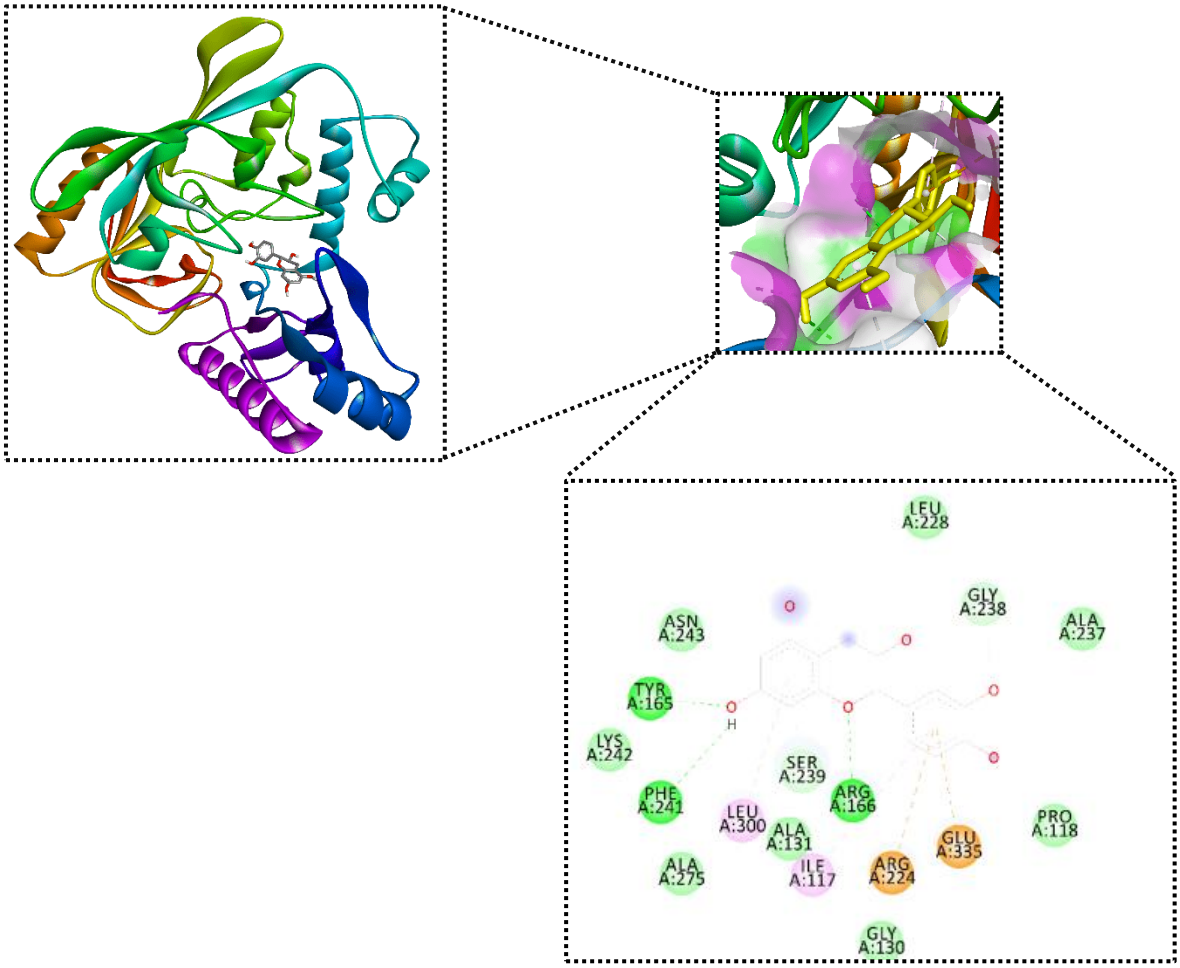

Figure 2. Visualization of catechin interaction binding to MurB Enzyme

Hydrophobic interactions also played a crucial role in stabilizing the ligand-receptor complex. π-alkyl interactions were observed with Ile117 and Leu300, while van der Waals interactions involved residues such as Leu228, Ala131, Gly130, Pro118, Ala237, Gly238, Asn243, Lys242, and Ala275, forming a supportive hydrophobic environment around the ligand. Additionally, a π-donor hydrogen bond interaction was identified with Gly238, further enhancing binding stability. The interaction profile of catechin demonstrates a well-

balanced combination of hydrogen bonding, electrostatic, and hydrophobic interactions. The ability of catechin to engage key catalytic residues, particularly Arg166 and Glu335, along with its low binding energy and micromolar Ki value, suggests a strong inhibitory potential against MurB. These findings indicate that catechin may serve as a promising lead compound for further development of antibacterial agents targeting *P. aeruginosa*, especially through inhibition of peptidoglycan biosynthesis via MurB enzyme interference.

Discussion

The reliability and accuracy of the molecular docking protocol were first validated through redocking of the co-crystallized ligand, 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid, into the active site of MurB enzyme from *Pseudomonas aeruginosa* (PDB ID: 7ORZ). The redocking procedure yielded a root mean square deviation (RMSD) value of 0.962 Å, which is well below the commonly accepted threshold of 2.0 Å, confirming the validity of the docking methodology [10,20]. This low RMSD indicates that the docking protocol successfully reproduced the crystallographic binding pose, thereby ensuring the reliability of subsequent docking simulations involving catechin [1,6]. Such validation is essential to confirm that the docking algorithm can accurately predict ligand orientation and interactions within the enzyme active site [2,16].

Comparative molecular docking analysis revealed that catechin exhibits significantly stronger binding affinity toward MurB compared to the co-crystallized reference ligand. The reference ligand showed a binding energy of −5.2 kcal/mol with an estimated inhibition constant (Ki) of 153 μM, whereas catechin demonstrated a more favorable binding energy of −7.9 kcal/mol and a markedly lower Ki of 1.63 μM, corresponding to an approximately 94–100-fold increase in predicted inhibitory potency. These values fall within the range reported for effective MurB inhibitors (−5.73 to −12.33 kcal/mol), indicating that catechin possesses competitive binding characteristics [21,22]. Furthermore, the lower binding energy reflects a more thermodynamically stable ligand-protein complex, which is typically associated with stronger inhibitory activity [7,15]. Similar trends have been reported for flavonoid compounds, where low micromolar Ki values correlate with significant enzyme inhibition [18,23].

From an interaction perspective, both ligands occupy the same catalytic pocket; however, catechin demonstrates a substantially more extensive and diverse interaction network. The co-crystallized ligand primarily stabilizes through limited hydrogen bonding and electrostatic interactions involving residues such as Arg166 and Arg224, with moderate contribution from its carboxylic acid and trifluoromethyl groups [24,25]. In contrast, catechin

forms multiple conventional hydrogen bonds with key residues, including Arg166, Ser239, Tyr165, and Phe241, significantly enhancing binding specificity and stability [26,27]. The interaction with Ser239 is particularly important, as this residue plays a critical role in MurB catalytic activity and substrate binding [28,29]. Additionally, catechin establishes π-cation and π-anion interactions with Arg224 and Glu335, respectively, further strengthening electrostatic complementarity within the active site [14,30].

The superior binding performance of catechin can be attributed to its polyphenolic structure, which provides multiple hydroxyl groups capable of forming an extensive hydrogen bonding network. These hydroxyl groups act as both donors and acceptors, enabling strong interactions with polar and charged residues, including Arg166, Ser239, and Glu335 [8,31]. In addition, the aromatic rings of catechin facilitate π-based interactions such as π-cation, π-anion, and π-alkyl contacts, contributing to stabilization within the hydrophobic regions of the binding pocket [32]. Compared to the control ligand, which possesses limited hydrogen bonding capacity, catechin's multi-functional structure enables a more balanced hydrophilic–hydrophobic interaction profile, resulting in improved binding affinity [33].

Importantly, catechin maintains direct interactions with key catalytic residues, particularly Arg166, Ser239, and Glu335, which are essential for MurB enzymatic function. MurB catalyzes the NADPH-dependent reduction of UDP-N-acetylglucosamine enolpyruvate to UDP-N-acetylmuramic acid, a crucial step in bacterial peptidoglycan biosynthesis [34]. The interaction with Arg166 is associated with substrate stabilization, while Glu335 plays a critical role in proton transfer during the catalytic cycle [35]. The ability of catechin to simultaneously interact with these residues suggests a potential inhibitory mechanism involving disruption of substrate binding and interference with the catalytic proton transfer process [36,37].

Furthermore, catechin's binding mode suggests potential competition with both the natural substrate and the NADPH cofactor. Its aromatic structure may overlap with regions involved in cofactor binding, thereby interfering with electron transfer processes required for MurB activity [38]. This multi-target interaction mechanism is consistent with previous reports indicating that effective MurB inhibitors often disrupt multiple stages of the catalytic process [39]. The broader interaction coverage of catechin across the binding pocket further contributes to its enhanced stability. In addition to catalytic residues, catechin interacts with surrounding amino acids such as Ile117, Leu228, Gly130, Ala131, and Pro118 through hydrophobic and van der Waals interactions, creating a tightly bound ligand–protein complex [9]. This extensive interaction network contrasts with the more limited binding profile

of the control ligand and explains the observed difference in binding energies.

From a structure activity relationship perspective, key features contributing to catechin's activity include the catechol moiety on the B-ring, hydroxyl groups at positions C-5, C-7, and C-3, and the flexible flavan-3-ol scaffold, all of which enhance hydrogen bonding and conformational adaptability within the active site [40]. These characteristics are consistent with previous findings that polyphenolic compounds exhibit strong enzyme inhibitory activity due to their high density of functional groups.

Inhibition of MurB by catechin is expected to disrupt peptidoglycan biosynthesis, leading to impaired bacterial cell wall formation and eventual cell. Given that MurB is absent in mammalian cells, it represents an attractive target for selective antibacterial therapy with minimal host toxicity. The predicted inhibitory activity of catechin is also consistent with its previously reported antibacterial properties against both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. Despite these promising findings, this study is limited to molecular docking analysis, which represents a static model of ligand–protein interactions. Therefore, further validation through molecular dynamics simulations, in vitro enzyme inhibition assays, and antibacterial studies is necessary to confirm the predicted activity and stability of the catechin-MurB complex [41]. In conclusion, catechin demonstrates significantly stronger binding affinity and inhibitory potential against MurB enzyme compared to the co-crystallized reference ligand. Its ability to form extensive interactions with key catalytic residues, combined with favorable binding energy and Ki values, highlights its potential as a promising lead compound for the development of novel antibacterial agents targeting *Pseudomonas aeruginosa*.

Conclusion

This study demonstrated that catechin exhibits significantly stronger binding affinity toward the MurB enzyme (PDB ID: 7ORZ) from *Pseudomonas aeruginosa* compared to the co-crystallized reference ligand, 1-phenyl-5-(trifluoromethyl)pyrazole-4-carboxylic acid. The lower binding energy (−7.9 kcal/mol) and markedly reduced inhibition constant (Ki = 1.63 μM) indicate a substantially higher predicted inhibitory potency, approximately 100-fold greater than the reference ligand. Mechanistically, catechin is predicted to inhibit MurB by interfering with substrate binding and disrupting the NADPH-dependent catalytic process required for peptidoglycan biosynthesis. The presence of multiple hydroxyl groups and aromatic rings in its polyphenolic structure enables multi-modal interactions, contributing to enhanced binding stability and specificity within the enzyme active site. These findings highlight catechin as a promising natural lead compound for the development of novel

antibacterial agents targeting bacterial cell wall synthesis, particularly against *Pseudomonas aeruginosa*. However, as this study is limited to in silico molecular docking analysis, further validation through molecular dynamics simulations, in vitro enzyme inhibition assays, and antibacterial activity testing is required to confirm its therapeutic potential.

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