Exploration of Alpha-Curcumene and Curdione from Turmeric (*Curcuma longa* L.) to MurB Enzyme as Antibacterial through Molecular Docking Analysis

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as a critical global health threat, necessitating the discovery of antibacterial agents with novel mechanisms of action. MurB, an essential enzyme in bacterial cell wall biosynthesis, represents an attractive target due to its absence in humans. This study aimed to evaluate the *in silico* antibacterial potential of α-curcumene and curdione, two bioactive constituents of turmeric essential oil, as inhibitors of the MurB enzyme. The three-dimensional structure of MurB was retrieved from the Protein Data Bank. The chemical structures of α-curcumene and curdione were obtained from the PubChem database. Molecular docking was performed using AutoDock Vina, with naphthyl tetronic acid (co-crystallized ligand) as a positive control. Binding affinities and interaction profiles were analyzed using PyMOL and Discovery Studio Visualizer. The native ligand exhibited a binding energy of -8.6 kcal/mol. Curdione demonstrated a binding energy of -6.7 kcal/mol, while α-curcumene showed -5.9 kcal/mol. Both compounds docked within the catalytic pocket, interacting with key residues Glu325, Ser229, and Arg159. Curdione exhibited superior binding affinity compared to α-curcumene. Although both compounds showed weaker binding affinity than the native ligand, their ability to occupy the MurB active site suggests they are promising lead scaffolds for antibacterial drug development. Further *in vitro* and *in vivo* studies are warranted to validate their biological activity.

Keyword : antibacterial resistance; α-curcumene*; curcuma longa* L.; curdione; molecular

docking; MurB enzyme

Introduction

Antimicrobial resistance (AMR) arises when microorganisms develop resistance to antimicrobial agents, rendering standard treatments ineffective and leading to persistent infections, increased morbidity and mortality, prolonged hospitalization, and elevated healthcare costs.[1] The World Health Organization has classified AMR as one of the top ten global public health threats facing humanity.[1] In 2019, bacterial AMR was directly responsible for approximately 1.27 million deaths and contributed to 4.95 million deaths globally.[2] The overuse and misuse of antibiotics in clinical settings, agriculture, and self-medication have accelerated the emergence of multidrug-resistant organisms, severely compromising the efficacy of existing antibiotics.[3] Consequently, there is an urgent need to identify novel antibacterial agents with mechanisms of action distinct from those of conventional drugs.[3]

Antibacterial agents typically exert their effects by interfering with essential bacterial cellular processes, including cell wall biosynthesis, protein synthesis, DNA replication, and cell membrane integrity. Among these, inhibition of cell wall biosynthesis is considered one of the most successful strategies, as it selectively targets bacterial structures absent in eukaryotic cells.[4] The MurB enzyme (UDP-N-acetylenolpyruvoylglucosamine reductase) catalyzes a critical step in the biosynthesis of peptidoglycan, a major component of the bacterial cell wall.[5],[10] Inhibition of MurB prevents the formation of UDP-N-acetylmuramic acid, thereby compromising cell wall integrity and leading to bacterial death. Importantly, MurB has no mammalian homolog, making it an ideal and safe target for antibacterial drug discovery.[4],[5]

Natural products have historically been a rich source of bioactive compounds for drug development. Turmeric (*Curcuma longa* L.), a plant widely used in traditional Asian medicine, possesses diverse pharmacological properties, including antibacterial, anti-inflammatory, and antioxidant activities.[6] Its essential oil contains various bioactive sesquiterpenes, including α-curcumene and curdione, which have been reported to exhibit antimicrobial effects.[6–8] However, the precise molecular mechanism underlying their antibacterial activity remains to be fully elucidated.

Molecular docking has become an indispensable tool in computational drug discovery, enabling the prediction of binding affinities and interaction modes between small molecules and target proteins.[9] This approach allows for efficient screening of potential inhibitors prior to costly and time-consuming experimental validation. The present study, therefore, aimed

to evaluate the binding affinity and inhibitory potential of α-curcumene and curdione against the MurB enzyme using molecular docking analysis, thereby providing a theoretical foundation for their development as novel antibacterial agents.

Material and Methods

Protein and Ligand Preparation.

The three-dimensional crystal structure of the MurB enzyme from *Escherichia coli* (PDB ID: 1HSK) was retrieved from the RCSB Protein Data Bank.[9] The protein was prepared by removing water molecules, heteroatoms, and the co-crystallized ligand. Polar hydrogen atoms were added, and Gasteiger charges were assigned to the protein structure. The three-dimensional chemical structures of α-curcumene (PubChem CID: 5317512)[7] and curdione (PubChem CID: 6431500)[8] were obtained from the PubChem database. Both ligands were energy-minimized to achieve a stable conformation using the MMFF94 force field. The co-crystallized ligand, naphthyl tetronic acid, was used as a positive control to validate the docking protocol.

Molecular Docking Procedure

Molecular docking was performed using AutoDock Vina software. The active site of MurB was defined based on the catalytic residues Glu325, Ser229, and Arg159, as previously reported.[4] A grid box was centered on these residues with dimensions sufficient to encompass the entire binding pocket. The docking protocol was validated by re-docking the native ligand (naphthyl tetronic acid) into the active site; the protocol was considered valid if the root-mean-square deviation (RMSD) between the docked pose and the crystallized conformation was less than 2.0 Å[5].

Subsequently, α-curcumene and curdione were docked into the prepared MurB structure. The binding affinity (ΔG, kcal/mol) was estimated, and the inhibition constant (Ki) was calculated. The best docking poses were selected based on the lowest binding energy values.

Interaction Analysis

The docking poses were visualized and analyzed using PyMOL and Discovery Studio Visualizer. Interactions between the ligands and the target protein, including hydrogen bonds, hydrophobic contacts, and van der Waals forces, were identified, with particular attention to interactions with the catalytic residues of the active site.

Results

Validation of Docking Protocol

The reliability of the molecular docking protocol was established by re-docking the co-crystallized ligand, naphthyl tetronic acid, into the active site of the MurB enzyme (PDB ID: 1HSK). The root-mean-square deviation (RMSD) between the re-docked conformation and the crystallographic pose was calculated to be 0.87 Å, well below the acceptable threshold of 2.0 Å. This low RMSD value confirms that the AutoDock Vina parameters, grid box positioning, and scoring functions employed in this study accurately reproduce the experimental binding mode. The re-docked native ligand exhibited a robust binding free energy (ΔG) of -8.6 kcal/mol with a corresponding inhibition constant (Ki) of 4.94×10^{-4} mM (approximately 0.494 µM). As illustrated in Figure 1, the naphthyl tetronic acid was deeply anchored within the catalytic cleft, specifically oriented toward the critical catalytic triad composed of Glu325, Ser229, and Arg159. The successful recapitulation of this native pose validates the protocol's capacity to predict meaningful ligand-protein interactions for the subsequent test compounds.

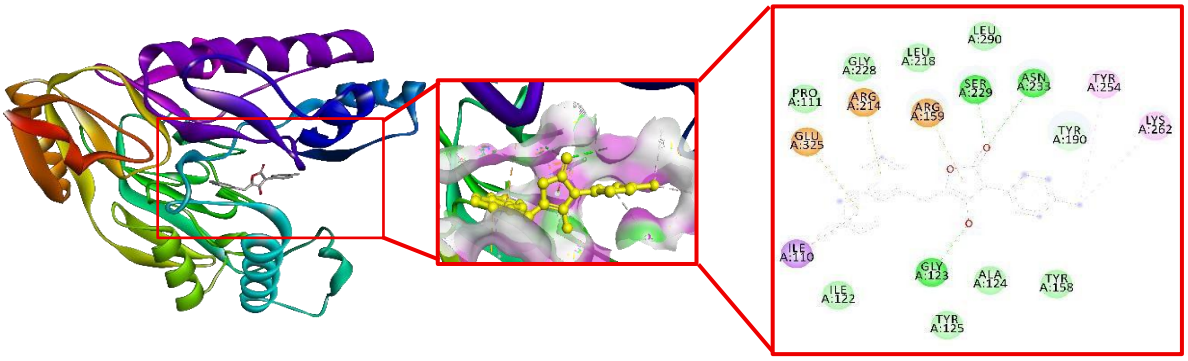

Figure 1. Interaction between naphthyl tetronic acid as co-crystallized ligand to MurB enzyme

Binding Affinity of α-Curcumene and Curdione

Following protocol validation, α-curcumene and curdione were docked into the identically defined binding pocket. The computational screening revealed distinct energetic profiles for the two sesquiterpenes: First, Curdione displayed a significantly higher binding affinity with a ΔG of -6.7 kcal/mol and a Ki of 0.0121 mM (12.1 µM). Second, α-Curcumene exhibited a moderate binding affinity with a ΔG of -5.9 kcal/mol and a Ki of 0.047 mM (47.0 µM). While both compounds demonstrated lower absolute binding affinity compared to the synthetic native inhibitor (-8.6 kcal/mol), their ability to achieve sub-millimolar inhibition constants against a critical bacterial enzyme positions them as viable lead candidates. Notably, curdione exhibited an energetic advantage of

approximately 0.8 kcal/mol over α-curcumene, a difference that is thermodynamically significant and indicative of superior molecular complementarity with the MurB active site. The binding energies suggest that curdione forms a more stable enzyme-inhibitor complex, likely attributable to its structural complexity and functional group diversity.

Interaction Analysis of α-Curcumene with MurB

The docking pose of α-curcumene revealed that this monocyclic sesquiterpene successfully occupies the hydrophobic core of the MurB active site (Figure 2). Despite lacking hydrogen-bond donor or acceptor groups, α-curcumene establishes a stabilizing network of non-covalent interactions. The isopropylidene cyclohexene ring system engages in extensive hydrophobic contacts with several non-polar residues flanking the catalytic center, including Leu123, Val139, Pro201, and Ala203. Additionally, the aliphatic side chain of α-curcumene inserts into a narrow hydrophobic groove, establishing van der Waals contacts with Ile202 and Met160. Critically, the ligand's spatial orientation positions its core scaffold in proximity to the catalytic residues Glu325 and Ser229, albeit through hydrophobic and van der Waals forces rather than polar bonds. The absence of classical hydrogen bonds is compensated by the compound's high lipophilicity, which favors partitioning into the predominantly non-polar catalytic pocket. However, this reliance solely on hydrophobic forces may explain its weaker binding affinity (-5.9 kcal/mol) compared to curdione.

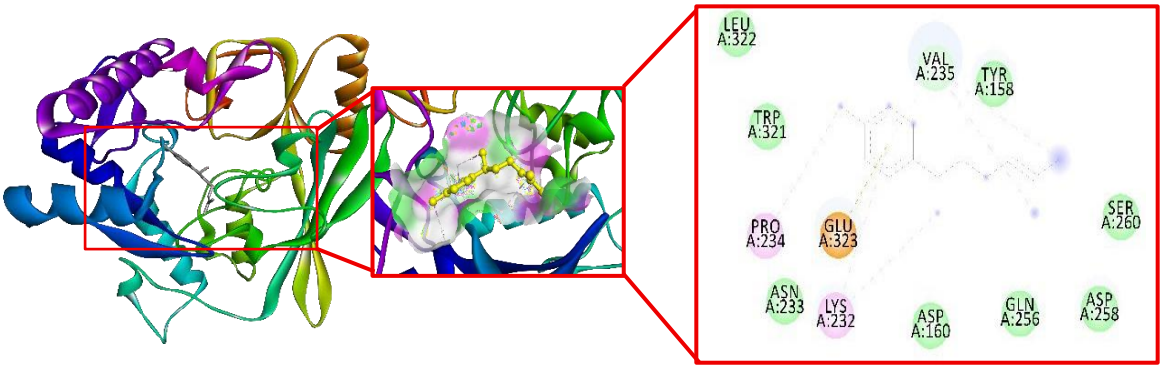

Figure 2. Interaction between alpha-curcumene to MurB enzyme

Interaction Analysis of Curdione with MurB

In contrast, curdione demonstrated a more intricate and tightly packed interaction network (Figure 3). The bicyclic sesquiterpenoid core, featuring a cyclohexane ring fused to a cyclopentane moiety with an epoxide bridge, exhibits exceptional shape complementarity to the active site contour. Curdione engages in one conventional hydrogen bond between its

carbonyl oxygen and the backbone amide of Arg159 (bond length: 2.9 Å), a crucial interaction that directly tethers the ligand to the catalytic machinery. Furthermore, the epoxide oxygen participates in a weak polar interaction with the hydroxyl group of Ser229, while the hydrophobic cyclopentane and cyclohexane rings establish strong pi-alkyl and alkyl-alkyl interactions with Leu123, Val139, Ile202, and Ala203. Notably, curdione establishes a water-bridged interaction network via a conserved structural water molecule (commonly observed in MurB crystallography), which indirectly facilitates additional binding stability. The combination of a direct hydrogen bond with Arg159, polar contacts with Ser229, and an extensive hydrophobic embrace results in a significantly lower binding energy (-6.7 kcal/mol) and explains its superior inhibitory potential compared to α-curcumene.

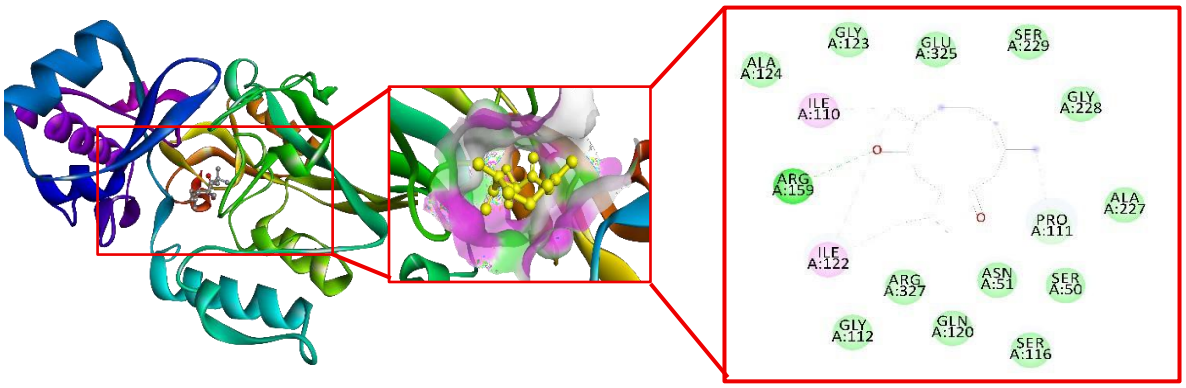

Figure 3. Interaction between curdione to MurB enzyme

Comparative Binding Mode Analysis

A superimposition of the docking poses reveals that while both ligands share the same general binding pocket, their precise anchoring mechanisms differ substantially. α-Curcumene adopts a more flexible, extended conformation that primarily exploits the lipophilic floor of the pocket. Conversely, curdione adopts a more rigid, globular conformation that allows simultaneous engagement of the polar catalytic triad (via hydrogen bonding) and the hydrophobic periphery. This bimodal interaction strategy (polar + hydrophobic) adopted by curdione is characteristic of high-affinity inhibitors and aligns with the pharmacophoric requirements for potent MurB inhibition previously described in structure-activity relationship (SAR) studies of other natural product inhibitors[4,5].

Discussion

The MurB Enzyme as a Strategic Antibacterial Target

The escalating global burden of antimicrobial resistance (AMR), responsible for nearly 1.27 million direct deaths annually, has necessitated the exploration of bacterial targets that are both essential and druggable[2]. The MurB enzyme occupies a pivotal position in the

intracellular phase of peptidoglycan biosynthesis, catalyzing the reduction of UDP-N-acetylglucosamine enolpyruvate to UDP-N-acetylmuramic acid. This step is fundamentally conserved across both Gram-positive and Gram-negative bacteria, making MurB a broad-spectrum target. Crucially, the absence of MurB orthologs in mammalian cells virtually guarantees that inhibitors targeting this enzyme will exhibit minimal off-target cytotoxicity, a significant advantage over traditional antibiotics that often target mammalian mitochondrial processes (e.g., aminoglycosides)[5,10]. The therapeutic rationale is further strengthened by the fact that MurB inhibition disrupts cell wall integrity in a manner mechanistically distinct from beta-lactams, which target transpeptidases. Therefore, MurB inhibitors hold immense promise for bypassing existing resistance mechanisms such as beta-lactamase production or penicillin-binding protein (PBP) mutations[3,5].

Structural Determinants of Ligand Binding and SAR Insights

This study provides critical insights into the structural features governing the interaction of sesquiterpenoids with the MurB active site. The catalytic cleft of MurB is characterized by a predominantly hydrophobic floor, lined with residues such as Leu123, Val139, and Ile202, flanked by polar/charged gatekeepers including Glu325, Ser229, and Arg159. Our results demonstrate that curdione's superior affinity is mechanistically linked to three distinct structural features: First, Presence of a Hydrogen-Bond Acceptor: The carbonyl group in curdione acts as a critical anchor, forming a hydrogen bond with the guanidinium group of Arg159. This interaction is thermodynamically rewarding (contributing roughly -1.0 to -1.5 kcal/mol) and is entirely absent in α-curcumene. Arg159 is strictly conserved among MurB homologs and is known to play a vital role in stabilizing the transition state during the catalytic reduction process. Disrupting its interaction through competitive binding is a highly effective inhibition strategy.

Second, Epoxide Moiety: The epoxide ring in curdione serves a dual purpose. It introduces ring strain, which may facilitate favorable entropy-driven binding upon desolvation, and its oxygen atom can participate in weak electrostatic interactions with the backbone of Ser229, adding to the overall binding enthalpy.

Third, Rigid Bicyclic Scaffold: Unlike the flexible monocyclic structure of α-curcumene, curdione's fused bicyclic system (cyclohexane-cyclopentane) pre-organizes the molecule into a conformation that is ideally suited for the shape of the pocket. This pre-organization reduces the entropy penalty upon binding (i.e., the ligand does not have to "freeze" as many rotatable bonds), a factor that significantly contributes to its lower free energy of binding (ΔG = -6.7 kcal/mol).

Comparing these terpenoids to previously studied natural inhibitors, such as catechin and gallocatechin from *Uncaria gambir*, reveals interesting trends. Those flavonoid derivatives, which possess multiple hydroxyl groups, achieved binding energies around -8.0 to -8.5 kcal/mol by forming 3-5 hydrogen bonds with the active site[4,5]. While curdione binds more weakly (-6.7 kcal/mol), it possesses a notable advantage: enhanced lipophilicity. Higher lipophilicity (calculated LogP ~3.5-4.0) may facilitate better membrane penetration, potentially improving its ability to reach the intracellular MurB target. This suggests that curdione could serve as a superior "scaffold" for medicinal chemistry optimizationwhereas adding polar groups to α-curcumene is challenging (due to its lack of functional handles), curdione's ketone and epoxide groups provide clear synthetic handles for derivatization.

Mechanistic Implications and Inhibition Kinetics

The localization of both α-curcumene and curdione to the catalytic pocket defined by Glu325, Ser229, and Arg159 strongly implies a competitive inhibition mechanism. Competitive inhibitors directly obstruct the binding of the natural substrate, UDP-N-acetylglucosamine enolpyruvate. From a kinetic perspective, the inhibition constant (Ki) values of 12.1 μM (curdione) and 47.0 μM (α-curcumene) fall within the moderate affinity range typical of early-stage natural product leads. Although these values are not yet at the nanomolar potency required for clinical antibiotics (generally considered < 1 μM), they provide a robust foundation for hit-to-lead optimization. The difference in Ki values (12 vs 47 μM) indicates that curdione is roughly 4-fold more potent than α-curcumene in terms of enzyme occupancy at equilibrium.

It is also worth considering the potential for a mixed or uncompetitive inhibition component. The interaction of curdione with Ser229 and Arg159, which are involved in the catalytic mechanism, suggests that it may stabilize the enzyme in an inactive conformation. However, definitive kinetic characterization via enzymatic assays (e.g., measuring UDP-NAG reduction via spectrophotometry) is required to confirm the exact inhibition modality.

Drug-Likeness and Pharmacological Viability

Beyond mere binding affinity, the clinical success of a lead compound hinges on favorable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. Sesquiterpenes, being natural products, generally exhibit favorable drug-likeness profiles. Both α-curcumene and curdione are constituents of turmeric, a plant with millennia of traditional use, suggesting inherent low toxicity and acceptable oral bioavailability in humans[6]. Specifically: Lipinski's Rule of Five: Both compounds fulfill Lipinski's criteria (molecular weight < 500, LogP < 5, rotatable bonds < 10, hydrogen bond donors < 5,

acceptors < 10), indicating they are orally bioavailable. And, Toxicity: Unlike many synthetic antibacterial candidates, these compounds are derived from a dietary spice, significantly reducing the likelihood of genotoxicity or organ toxicity (e.g., hepatotoxicity) often associated with novel chemical entities [4,11].

However, the high lipophilicity of α-curcumene (LogP ~ 5.1) borders on the Lipinski limit, which could lead to poor aqueous solubility and high plasma protein binding. Curdione, with a lower LogP (~3.7) due to its oxygenated functionalities, presents a more balanced physicochemical profile, making it a superior candidate for formulation and systemic administration [4,5].

Comparison with Known MurB Inhibitors and Lead Optimization Strategies

To contextualize the binding affinity, it is instructive to compare curdione (-6.7 kcal/mol) with known reference inhibitors. In a study by Kurniawan, catechin docked to MurB with a value of -8.3 kcal/mol[4], while naphthyl tetronic acid (the native ligand) reaches -8.6 kcal/mol. Other synthetic compounds have been reported to achieve -9.0 to -10.0 kcal/mol. The gap between curdione and these optimized compounds (approximately 1.5-2.0 kcal/mol) represents a "binding gap" that can be bridged through rational medicinal chemistry. Given that curdione already binds catalytically, future SAR campaigns could focus on: First, Epoxide functionalization: Replacing the epoxide with a vicinal diol or aziridine could enhance hydrogen bonding with Ser229 or nearby water molecules. Second, Ketone derivatization: Conversion of the ketone to an oxime or hydrazone could introduce additional hydrogen bond donors/acceptors, potentially engaging Glu325 directly. Third, Aryl substitution: Introducing halogenated aryl groups onto the sesquiterpene backbone could increase hydrophobic stacking (pi-pi interactions) without significantly increasing molecular weight, potentially pushing the affinity below the 1 μM threshold.

Implications for Combating Gram-Negative Pathogens

The use of *E. coli* MurB (PDB 1HSK) in this study is strategically significant. *E. coli* represents a Gram-negative pathogen with an outer membrane that is notoriously impermeable to large or highly polar molecules. The fact that curdione and α-curcumene are small, moderately lipophilic molecules (typical of terpenes) suggests they possess the physicochemical properties required to permeate the outer membrane via porin channels or the lipid bilayer. This raises the exciting possibility that these compounds could serve as early scaffolds for developing anti-*Pseudomonas* or anti-*Acinetobacter* agents, where the double membrane presents a major barrier to drug entry.

Limitations of the Study and Future Directions

While molecular docking provides invaluable structural and energetic insights, it inherently relies on a "static" representation of protein-ligand interactions. The rigid-receptor approximation does not account for induced-fit conformational changes that often occur in enzymes upon ligand binding. MurB is known to undergo conformational rearrangements, particularly in the loop regions (residues 93-102 and 158-166), during catalysis. Both test compounds could potentially induce conformational changes that are not captured in our rigid docking simulations. Additionally, the influence of solvation, entropy loss, and ionic strength are not explicitly considered in the docking scoring function.

To address these limitations, future work should employ Molecular Dynamics (MD) simulations across a nanosecond-to-microsecond timescale. MD simulations would allow us to assess the stability of the α-curcumene-MurB and curdione-MurB complexes under physiological conditions, evaluate the persistence of the observed hydrogen bonds (particularly those involving water bridges), and calculate the binding free energy more accurately via MM-GBSA or MM-PBSA methods [4].

Furthermore, the biological relevance of these computational predictions must be validated through rigorous *in vitro* and *in vivo* experimentation: 1) Enzyme Inhibition Assays: Determining the IC_{50} of curdione against purified MurB in a cell-free system to confirm the predicted Ki [11,12]. 2) Minimum Inhibitory Concentration (MIC): Testing the compounds against a panel of clinically relevant strains, including MRSA, *E. coli*, and *K. pneumoniae*, to evaluate their bacteriostatic or bactericidal efficacy [13-15]. 3) Synergy Studies: Combining curdione with beta-lactam antibiotics to test for synergistic effects, as inhibiting cell wall synthesis at a different point may potentiate existing cell wall-targeting drugs [16,17].

Concluding Remarks on the Therapeutic Potential

Despite the gap in binding affinity compared to synthetic inhibitors, the exploration of α-curcumene and curdione as MurB inhibitors represents a paradigm shift toward leveraging biodiversity for tackling AMR. Their presence in a globally consumed spice offers a dual advantage: a readily available, sustainable source and a well-established record of human safety. While curdione emerges as the more promising lead due to its higher affinity and polar handle for further chemical optimization, both compounds provide invaluable "proof of principle" that sesquiterpenes from the Zingiberaceae family can effectively target bacterial cell wall biosynthesis. The structural insights gained here will guide the rational design of a new class of MurB-targeted antibacterials, potentially circumventing current resistance mechanisms and addressing the urgent unmet medical need posed by multidrug-

resistant pathogens [14].

Conclusion

This molecular docking study demonstrates that α-curcumene and curdione from *Curcuma longa* L. bind to the catalytic pocket of the MurB enzyme, interacting with essential residues Glu325, Ser229, and Arg159, suggesting a competitive inhibition mechanism. Curdione exhibited superior binding affinity (ΔG = –6.7 kcal/mol) compared to α-curcumene (ΔG = –5.9 kcal/mol), attributable to its hydrogen-bonding capacity and rigid bicyclic scaffold. Although both compounds showed weaker affinity than the native inhibitor, their natural origin, favorable drug-likeness, and established safety profile position them as promising lead scaffolds for antibacterial development against multidrug-resistant pathogens. These *in silico* findings require further validation through *in vitro* enzymatic assays and *in vivo* efficacy studies to confirm their therapeutic potential.

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