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In Silico Molecular Docking of Plant-Derived Compounds Targeting PBP2a to Combat MRSA Antibiotic Resistance

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Abstract

Background: The escalating threat of antibiotic resistance, particularly in Methicillin-Resistant *Staphylococcus aureus* (MRSA), underscores the urgent need for novel therapeutic strategies. The PBP2a protein, encoded by the *mecA* gene, is a primary driver of MRSA resistance to beta-lactam antibiotics. This *in silico* study aims to identify plant-derived compounds with potential to inhibit PBP2a, offering alternatives to conventional antibiotics.

Materials and Methods:
Using a descriptive-analytical approach, molecular docking was performed with Molegro Virtual Docker 6.0 and Molegro Molecular Viewer 2.5. The 3D structure of PBP2a was retrieved from the Protein Data Bank (PDB), and seven phytochemical ligands—Allicin, Carvacrol, Thymol, Curcumin, Eugenol, Quercetin, and Terpinen-4-ol—were sourced from PubChem. Docking simulations evaluated ligand binding affinity to PBP2a's active site.

Results and Conclusion:
Curcumin (PubChem ID: 969516) exhibited the highest binding affinity with a MolDock score of -281.131 kJ/mol, indicating strong interaction with PBP2a's active site. Quercetin (PubChem ID: 5280343) followed closely with a score of -279.218 kJ/mol, positioning both as promising candidates. Conclusion: Curcumin and Quercetin demonstrate significant potential as PBP2a inhibitors, warranting further *in vitro* and *in vivo* studies to validate their efficacy against MRSA infections. These findings highlight the value of phytochemicals in addressing antibiotic resistance.

What is "already known":	• Methicillin-Resistant *Staphylococcus aureus* underscores the urgent need for novel therapeutic strategies. • The PBP2a protein, encoded by the *mecA* gene, is a primary driver of MRSA resistance to beta-lactam antibiotics.
What this article adds:	• *In silico* studies identified new plant-based compounds such as curcumin and quercetin capable of binding and inhibiting the PBP2a protein of MRSA. • Curcumin exhibited the highest binding affinity, indicating strong interaction with PBP2a's active site. • Quercetin followed curcumin in having one of the highest binding affinities, interacting strongly with PBP2a's active site. • Curcumin's ability to form central hydrogen bonds and hydrophobic contact with critical amino acid residues of the active site is the main cause of the stability of its protein complex. • Investigations on the antimicrobial effects of plant-derived compounds such as curcumin and quercetin have mostly been *in vitro* studies. This is the first *in silico* study that demonstrates inhibition of the PBB2a by curcumin and quercetin

1. Introduction

Staphylococcus aureus, a Gram-positive coccus forming grape-like clusters, is a prevalent human pathogen and part of the normal skin and nasal flora. It causes a spectrum of infections, ranging from minor skin conditions like abscesses to severe diseases such as pneumonia and septicemia. Its adaptability and production of virulence factors, including toxins and enzymes, enhance its pathogenicity [1-3]Antimicrobial resistance (AMR) has also been recognized as one of the largest public health threats in the current century. This is due to bacteria and other microbes changing, and the drugs that can treat their infections no longer are effective. Infections become harder to treat, and disease transmission, serious disease, and ultimate death become inevitable. *S. aureus* is a established example of this problem as its drug-resistant strains, specifically Methicillin-Resistant *Staphylococcus aureus* (MRSA), are able to resist major antibiotics like beta-lactams [4-7]. Bacteria have evolved various advanced mechanisms to achieve antibiotic resistance (Table 1). Such protections involve enzymatic inactivation, whereby the bacterium produces enzymes (like beta-lactamases) that break down and neutralize the antibiotic. Target modification is one of the key mechanisms by which the bacterium alters the conformation of the protein onto which the antibiotic would otherwise bind, rendering the drug ineffective. Bacteria also employ efflux pumps to actively export antibiotics out of the cell, or they can reduce the permeability of their cell membrane so that entry of the drug is blocked [8-10].

Table 1. Mechanisms of microbial resistance to antibiotics

Mechanism	Description
Enzymatic Inactivation	Bacteria produce enzymes (like beta-lactamases) that break down and neutralize antibiotics.
Target Modification	The bacterium changes the shape of the protein that the antibiotic would normally bind to, making the drug ineffective.
Efflux Pumps	Bacteria actively pump antibiotics out of the cell.
Reduced Permeability	The bacterium's cell membrane becomes less permeable, which blocks the entry of the antibiotic.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) beta-lactam antibiotic resistance is the quintessential example of target modification. The rationale underlying such resistance is essentially due to the presence of the *mecA* gene, instructing the bacterium to produce a new protein, Penicillin-Binding Protein 2a (PBP2a). The host PBPs found in drug-sensitive bacteria are the proteins that build the cell wall and serve as targets for beta-lactam drugs, while PBP2a has a different conformation. This difference gives it an exceptionally low binding affinity to common beta-lactam antibiotics like Methicillin. This means that even when the antibiotic is present, PBP2a is still functional, allowing the bacterium to build its cell wall and survive. PBP2a is thus a prime drug target for the discovery of new drugs that can bypass this resistance [7,11-13] . With the urgent need for new anti-MRSA drugs, computational methods like molecular docking can be used as powerful and efficient tools for identifying promising drug candidates. This method allows researchers to simulate the interaction of thousands of potential molecules with the active site of the target protein and predict their binding affinity. This research has used this method to search among natural compounds. The focus has been on plant-based compounds like quercetin, curcumin, eugenol, carvacrol, thymol, terpinen-4-ol, and allicin to

investigate their potential for inhibiting the PBP2a protein and providing new solutions against antibiotic resistance [14-20]. The plant-based compounds investigated in this research, include allicin, carvacrol, thymol, curcumin, eugenol, quercetin, and terpinen-4-ol, each of which possess unique medicinal properties (Table 2). Allicin and carvacrol act through their strong antibiotic and antimicrobial properties, respectively, notably by dama-ging bacterial cell membranes. Thymol is also recognized as an effective antibacterial and antifungal agent. On the other hand, curcumin and quercetin exhibit prominent anti-inflammatory and antioxidant properties, with quercetin being particularly active against *S. aureus*. Finally, eugenol is known for its antimicrobial and local anesthetic proper-ties, and terpinen-4-ol for its antibacterial and antifungal qualities, making them important candidates in pharmaceutical research. These diverse properties make these compounds attractive options for investigating a solution to antibiotic resistance [15-20]. The main goal of the article is to use molecular docking to find plant-based compounds that can serve as an alternative to antibiotics and help overcome MRSA bacterial resistance.

Table 2. List of Plant-based compounds, their sources and key antimicrobial properties.

Compound	Plant Source	Key Properties
Allicin	Garlic, onion, and other plants of the Allium family	Possesses strong antibiotic and antifungal properties, and is active against both Gram-positive and Gram-negative bacteria.
Carvacrol	Thyme, oregano, marjoram	A powerful antimicrobial compound that damages bacterial cell membranes.
Thymol	Thyme and oregano	An antibacterial, antifungal, and antiseptic agent.
Curcumin	Turmeric	Possesses prominent anti-inflammatory, antioxidant, and antimicrobial properties.
Eugenol	Clove, cinnamon, basil	Has antimicrobial and local anesthetic properties.
Quercetin	Onion, apple, grape, cabbage	A flavonoid with antioxidant and anti-inflammatory properties that is active against bacteria.
Terpinen-4-ol	Tea tree	The main active component of tea tree oil with antibacterial and antifungal properties.

2. Materials and Methods

2.1. General Principles of This Research: The study was conducted by means of a descriptive-analytical method. Initially, eight compounds were investigated. Then, 3D structures of the compounds were downloaded in SDF formats from the PubChem database of chemical compounds. Lastly, the crystallographic structure of the drug receptor protein (the PBP2a protein) was downloaded from the protein database (www.rcsb.org).

2.2. Protein and Ligand Preparation: The 3D structure of PBP2a protein was downloaded from the Protein Data Bank (PDB). In the process of preparing the protein for docking, water molecules and unwanted ligands were removed, hydrogen atoms were added, and atomic charges were automatically determined and assigned using the Molegro Virtual Docker (MVD) software.

A set of natural compounds, namely allicin (65036), carvacrol (10364), thymol (6989), curcumin (969516), eugenol (3314), quercetin (5280343), and terpinen-4-ol (11230), were downloaded from the PubChem database. For preparation, each of them was loaded individually into the MVD software and

their structures were prepared for optimization of atomic charge and rotatable bonds.

2.3. Docking Simulation: Molecular docking was performed using the Molegro Virtual Docker (MVD) software to analyze the interactions between PBP2a and the compounds. The highest-scoring molecular cavities in the active site of the protein were identified. Docking was performed by employing the MVD (Molegro Virtual Docker) method and the MolDock SE algorithm. The runs of the interaction were 10, and the docking scores were calculated as the MolDock score. Visualization of the ligand binding to the protein was done at the completion of the docking procedures with the help of the Molegro Molecular Viewer software.

3. Results and Discussion

Seven varied plant-based ligands were docked in this study to the target protein PBP2a (Figs. 1 and 2). The most important feature of assessment was the MolDock score, which is an indication of the binding stability of the ligand with the active site of the protein. The more negative the score, the higher the binding affinity.

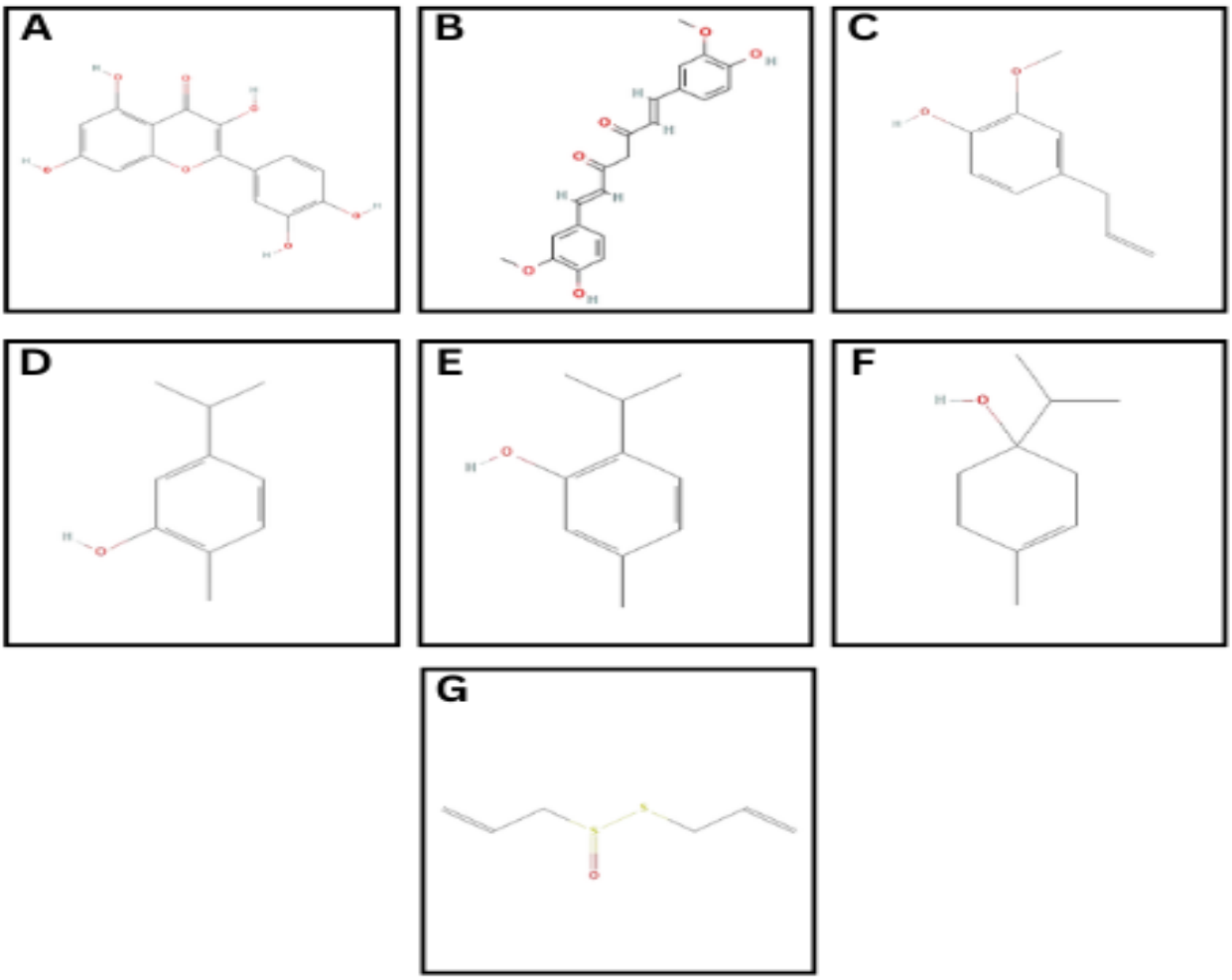

Figure 1: This figure illustrates the chemical structures of seven bioactive compounds. Quercetin (A), Curcumin (B), and Eugenol (C) are shown alongside Carvacrol (D) and Thymol (E). The figure also includes Terpinen-4-ol (F) and Allicin (G).

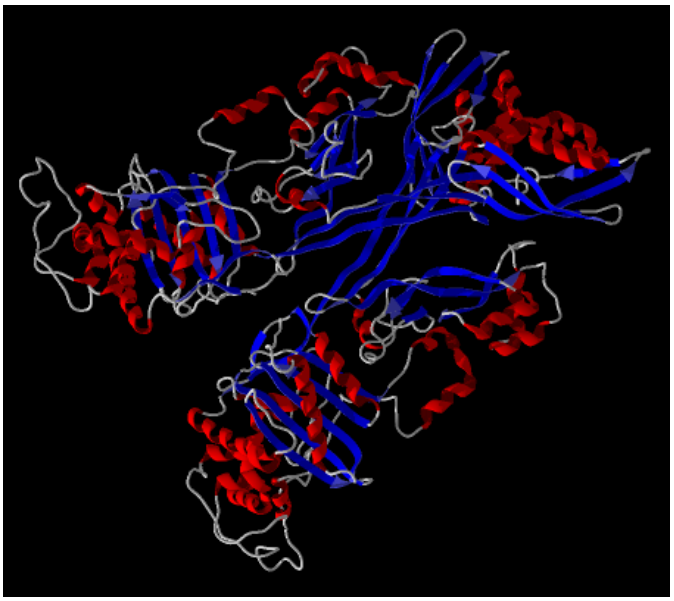

Figure 2: This image shows the secondary structure of PBP2a, a critical enzyme known for its role in methicillin resistance in *Staphylococcus aureus*. The red helices represent alpha helices and the blue arrows represent beta sheets, which are common secondary structural elements of proteins. The overall white ribbon outlines the protein backbone, revealing its complex folded structure.

3.1. Molecular Docking Analysis

The results from the molecular docking are summarized in Table 3. As seen from the table, the ligand curcumin (ID 969516) was identified as the best candidate with a score of -281.131 kJ/mol. This score is significantly better than other compounds and indicates the highest binding affinity and strongest interaction with the active site of the PBP2a protein among the compounds studied. Quercetin also showed a strong score, making it the second most promising candidate.

Table 3. Results of the molecular docking analysis.

Ligand Name	Ligand ID	Best MolDock Score (kJ/mol)	Corresponding Run	Status
Curcumin	969516	-281.131	Run ۲	Top Candidate
Quercetin	5280343	-279.218	Run 8	Strong Candidate
Eugenol	3314	-155.959	Run 1	Moderate
Carvacrol	10364	-148.647	Run 1	Moderate
Thymol	6989	-147.575	Run 1	Moderate
Terpinen-4-ol	11230	-136.561	Run 3	Weak
Allicin	65036	-98.1925	Run 1	Weak

The results from the molecular docking simulation are helpful in interpreting the inhibition potential of the selected natural compounds against the PBP2a protein. Of particular interest in this section is the MolDock score interpretation and analysis of molecular interactions in the protein active site.

3.2. Interpretation of Docking Score

As presented in the results, the compound curcumin (ID 969516) gave the best performance with a score of-281.131 kJ/mol. This score, which represents the highest binding free energy, is a clear indicator that this compound is forms a stable complex and has a higher affinity for the active site of the protein compared to all other ligands. The significant difference in this score from the scores of the other compounds clearly illustrates the structural and chemical superiority of this molecule to bind with PBP2a. This finding places curcumin as the top candidate for further development. Quercetin (ID 5280343), with its score of -279.218 kJ/mol, also remains a very strong candidate (Table 3).

3.3. Molecular Interaction Analysis of the Top Ligand

The overall analysis of the interactions of the top ligand at the active site gives an understanding of its mechanism of binding. As seen from the results in the software, this ligand is positioned perfectly inside the binding pocket. This high stability is due to the presence of two significant types of molecular interactions:

Hydrogen Bonds: The top ligand forms some crucial hydrogen bonds with significant amino acid residues at the active site of the protein. These bonds account for the anchoring and stabilization of the ligand within the protein cavity.

Hydrophobic Interactions: The hydrophobic regions of the ligand are also positioned along with the nonpolar residues of the amino acids of the protein. These interactions account for the greater stability of the complex.

All these findings collectively indicate that curcumin is structurally complementary to the active site of PBP2a.

4. Conclusion

This "*in silico*" model-based research predicted with high accuracy the ligands that show high inhibitory action against the Methicillin-Resistant *Staphylococcus aureus* (MRSA) PBP2a protein. In accordance with the updated molecular docking results, the compound curcumin is among the best options. It is selected on the basis of its molecular docking results, having the highest binding energy and best protein-molecule interaction at the active site of the protein. Its higher score is an indication of perfect structural complementarity and optimal stability at the binding site.

As indicated from the data, this compound's ability to form central hydrogen bonds and hydrophobic contact with critical amino acid residues of the active site is the main cause of the stability of its protein complex. The results not only provide evidence for our hypothesis that this compound holds the promise to inhibit PBP2a effectively but also for our understanding of its likely mechanism of action.

However, it must be understood that these results are a lead to drug design. For this "*in silico*" lead compound to be made into an effective drug that can be accessed by people, "*in vitro*" tests need to be performed to determine biological compatibility and determine its antimicrobial character in the lab. In subsequent steps, "*in vivo* studies on animal models need to be conducted to study its efficacy, safety, and potential toxicity. Last, the work provides an avenue for subsequent studies and introduces curcumin and quercetin as an optimal platform for molecular

optimization and synthesis to construct a new generation of anti-MRSA compounds.

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6. Conflict of Interest

The authors declare no conflict of interest.

7. Authors Contributions

Designate each author's contribution using their initials.
Conceptualization, RN and PS; methodology, RN; software, RN.; validation, RN& PS.; formal analysis, RN; investigation, RN & PS; resources, RN & PS; data curation, RN; writing-original draft preparation, RN & PS; writing-review and editing, PS.; visualization, RN & PS; supervision, PS; project administration, PS.

8. Using Artificial Intelligent chatbots: No AI chatbots or tools were used in this research

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