IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 20, Issue 2 Ser. 2 (Mar. – Apr. 2025), PP 05-11
www.Iosrjournals.Org

In Silico Method For Screening Major Compounds Of Essential Oil From Syzygium Aromaticum Against Methicillin-Resistant Staphylococcus Aureus

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Abstract:
Background*: Methicillin-resistant Staphylococcus aureus (MRSA) is a major health concern due to its resistance to many antibiotics. This resistance is linked to penicillin-binding protein 2a (PBP2a), which blocks β-lactam antibiotics. Eugenol and carvacrol, compounds found in clove oil, have antimicrobial properties. This study explores their potential to inhibit PBP2a using molecular docking techniques.*
Materials and Methods*: Molecular docking was used to evaluate eugenol and carvacrol interactions with PBP2a. Two PBP2a structures were obtained from a database. DockThor was used for docking simulations, and PoseView analyzed the results. Key interactions, including hydrogen bonds and hydrophobic contacts, were assessed.*
Results*: Both eugenol and carvacrol showed strong binding to PBP2a, with eugenol having a higher affinity. They formed hydrogen bonds and hydrophobic interactions with key amino acids, suggesting they might interfere with PBP2a function and help restore β-lactam antibiotic effectiveness.*
Conclusion: *Eugenol and carvacrol show promise as antimicrobial agents against MRSA by targeting PBP2a. Computational tools proved useful in this analysis, but further laboratory and clinical studies are needed to confirm their effectiveness. This research opens new possibilities for combating bacterial resistance in veterinary and medical fields.*
Key Word: *Intrathecal; MRSA. Eugenol. Carvacrol. Docking.*

Date of Submission: 25-03-2025 Date of Acceptance: 05-04-2025

I. Introduction

Staphylococcus aureus is one of the primary agents of infections in livestock, particularly in dairy herds, where it is associated with cases of bovine mastitis. This bacterium has the ability to produce β-lactamase enzymes, encoded by the *blaZ* gene, which degrade β-lactam antibiotics, such as penicillins, rendering them ineffective[1, 2]. This resistance mechanism complicates treatment and can lead to significant economic losses, as mastitis affects both the quality and quantity of milk produced. Furthermore, studies indicate that different species of staphylococci can be isolated from raw milk, many of which exhibit virulence factors and resistance to β-lactam antibiotics, underscoring the need for constant monitoring and the development of new therapeutic strategies in the agricultural sector[3, 4].

The spread of resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA), has further exacerbated challenges in both veterinary medicine and public health. MRSA resistance is associated with the *mec*A gene, which encodes the PBP2a (Penicillin-Binding Protein 2a), capable of preventing the action of β-lactam antibiotics[5, 6]. Although this variant was initially identified in hospitals, cases of MRSA have increasingly been reported in livestock, raising concerns about the potential for transmission between humans and animals. As herds can act as reservoirs for this pathogen, stringent biosecurity measures and health surveillance are essential to contain the spread of these resistant bacteria[7, 8].

In light of the rising bacterial resistance, computational tools such as molecular modeling and docking techniques have been widely employed in the search for new antimicrobials. These approaches allow for the simulation of interactions between molecules and bacterial targets, aiding in the identification of compounds with therapeutic potential before laboratory testing[9,10]. By predicting how a substance binds to essential proteins for bacterial survival, these methods help select promising candidates for drug development. Thus, the use of computational simulations accelerates the drug discovery process and reduces costs, making the search for effective alternatives against infections more efficient and accessible [11, 12].

One natural source that has garnered attention for its antimicrobial potential is *Syzygium aromaticum*, commonly known as clove. Its essential oil, rich in compounds such as eugenol and carvacrol, exhibits potent antibacterial activity against various pathogenic species, including bacteria resistant to conventional antibiotics. Studies show that eugenol possesses antibacterial and anti-biofilm properties, making it a promising alternative in combating infections caused by resistant pathogens[13, 14, 15]. Research utilizing molecular docking techniques has been crucial in understanding how compounds interact with essential bacterial proteins, such as PBP2a, involved in MRSA resistance[16,17]. These analyses suggest that both compounds can bind to the active site of this protein, potentially inhibiting its function and restoring the efficacy of β-lactam antibiotics. These findings point to the possible use of these natural substances in combined therapies, paving the way for new strategies in combating bacterial resistance [18, 19].

This study aims to analyze, through molecular docking techniques, how eugenol and carvacrol interact with the PBP2a protein responsible for MRSA resistance. The goal is to verify and understand the interaction of these substances with PBP2a using the DockThor and PoseView servers.

II. Material And Methods

Acquisition of PBP2a Receptor Protein

The penicillin-binding proteins 2a (PBP2a) of MRSA were researched in the RCSB PDB database. Two PBP2a structures, namely 6Q9N with a resolution of 2.50 Å in complex with Piperacillin (JPP) and Quinazolinone (QNL), and 1MWT with a resolution of 2.45 Å in complex with Penicillin G (PNMa and PNMb), were downloaded as PDB files[20, 21].

Physicochemical Properties of PBP2a

The Pepstats database[22] and the ProtParam tool from the ExPASy database[23] were used to predict the physicochemical properties of PBP2a.

Preparation of PBP2a Protein as Receptor

The preparation of PBP2a proteins was performed using PyMOL software. During this step, all water molecules were removed to avoid solvent-mediated salt bridge interactions between the ligands and the active and allosteric sites of the protein. Subsequently, interaction sites were defined based on the position of the ligands, using the commands “select ligand, resn XXX” to select the ligand and “create site_ligand, ligand around 5” to create an interaction site within a 5 Å region around the ligand. After this definition, the coordinates of the interaction site were determined with the help of the AutoDock Vina plugin in PyMOL, adjusting the search box to encompass the identified region. These coordinates were recorded for later use in the molecular docking step[24].

Acquisition of Ligands and Preparation for Docking

The three-dimensional structure of the compounds eugenol and carvacrol was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). For each compound, the search was conducted using its name or identification number in the database. The 3D structures of the ligands were then downloaded in SDF (Structure Data File) format, ensuring the preservation of the spatial information of the molecules. These structures will be subsequently converted and prepared for molecular docking analyses.

Molecular Docking

The molecular docking step was performed using the DockThor server (https://dockthor.lncc.br/), which allows for the prediction of interactions between proteins and ligands based on a flexible docking model.

PBP2a without water molecules and without its co-crystallized ligands were first loaded. The ligands of interest, eugenol and carvacrol, were converted to MOL2 format using PyMOL software. This conversion ensured the correct parameterization of the ligands for submission to DockThor. The grid box definition was carried out considering the coordinates of the previously identified interaction site, ensuring that the active region of the protein was explored by the docking algorithm. Finally, the docking process was executed, and the resulting protein-ligand complexes were analyzed based on binding energy and the molecular interactions formed. The most stable models were selected for subsequent structural and biochemical interpretation[25].

Ligand Interactions with Amino Acid Residues

The analysis of molecular interactions between the protein and the ligands was conducted using the PoseView server (https://poseview.zbh.uni-hamburg.de/), which generates two-dimensional (2D) representations of the interactions between the compounds. The three-dimensional structure of the protein was prepared and saved in PDB format, ensuring that only the polypeptide chain was included. Similarly, the ligands in their respective coordinates were converted to PDB format before being loaded onto the server. The protein and ligand files were uploaded, allowing for the automatic generation of interaction maps. The 2D representations provided by the server highlight different types of molecular interactions, such as hydrogen bonds, hydrophobic interactions, and ionic bonds, facilitating the interpretation of the formed complexes. The results were analyzed to identify the main protein residues involved in interactions with the ligands, allowing for a better understanding of the affinity and stability of the studied complexes[26].

III. Result

3D Structure and Physicochemical Properties of Proteins 6Q9N and 1MWT

The functional PBP2a is a protein composed of two chains. Chain A of the 6Q9N protein has 638 amino acid residues, a charge of 6.5, and an isoelectric point of 8.4704. In turn, chain B of 6Q9N contains 637 amino acid residues, with a charge of 7.5 and an isoelectric point of 8.7234. Regarding the 1MWT protein, chain A has 635 amino acid residues, a charge of 5.5, and an isoelectric point of 8.0589. Chain B of 1MWT, on the other hand, has 626 amino acid residues, a charge of 3.5, and an isoelectric point of 7.2441. The different chains of the proteins are highlighted in distinct colors in the PyMol software, as illustrated in Figures 1A and 1B.

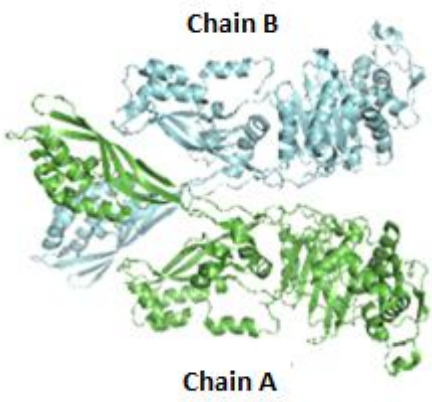
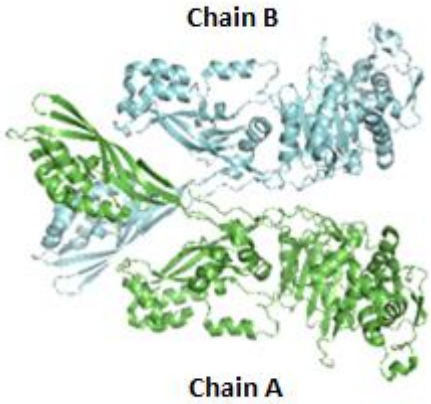
Figure 1A. 3D structure of 6Q9N	**Figure 1B**. 3D structure of 1MWT
	

Table no 1 presents the physicochemical properties of the 6Q9N and 1MWT proteins. The aliphatic index of a protein, which represents the relative volume occupied by aliphatic side chains (such as alanine, isoleucine, leucine, and valine), is 79.10 for 6Q9N and 78.76 for 1MWT. These values indicate the thermostability of both PBP2a proteins. Furthermore, the instability index, which considers values below 40 as indicative of stability, presents results of 31.03 for 6Q9N and 31.22 for 1MWT, confirming that both proteins are stable. Finally, the Grand Average of Hydropathy (GRAVY) value of a protein is calculated by the sum of the hydropathy values of all residues, divided by the total number of amino acids in the sequence. The predicted GRAVY values for the proteins under study are -0.798 and -0.799, which indicates that both are hydrophilic.

Table no 1: Physicochemical Properties of Penicillin-Binding Protein 2a 6Q9N and 1MWT.

	A6Q9N	1MWT
Sequence Length	642	626
Molecular Weight	73180.77	73670.36
Isoelectric Point	8.27	8.25
Aliphatic Index	79.10	78.76
Molecular Formula	$C_{3246}H_{5150}N_{870}O_{1019}S_{16}$	$C_{3266}H_{5185}N_{875}O_{1026}S_{17}$
Total Number of Atoms	10301	10369
GRAVY	-0.798	-0.799
Instability Index	31.03	31.22

Identified Sites in 6Q9N and 1MWT for Docking

The grid box definition for molecular docking simulations was performed considering the coordinates of the interaction sites previously identified in proteins 6Q9N and 1MWT. To ensure that the active region of each protein was correctly explored by the docking algorithm, the coordinates of the co-crystallized ligands were used as a reference. For protein 6Q9N, two interaction sites were established, corresponding to the ligands JPP (X = -5.54, Y = -13.48, Z = 45.44) and QNL (X = -5.34, Y = -13.43, Z = 46.04). In protein 1MWT, the interaction sites were identified based on the location of the co-crystallized penicillins; in Chain A (X = 17.92, Y = 29.49, Z = 52.25) and in Chain B (X = -8.39, Y = 46.56, Z = 44.13).

Docking Results Using the DockThor Server

Table no 2 presents the results generated by DockThor, showing, unanimously, low values of van der Waals Energy (vdW), Electrostatic Energy (Elec. Energy) and Affinity. The highest Affinity values were observed in the 6Q9N protein for the carvacrol ligand, with -5.858 in both binding sites tested. The lowest Affinity values were recorded in the 1MWT protein, with -7,580 for eugenol and -7,530 for carvacrol, in the A chain sites. The lowest value for van der Waals Energy was also observed in this protein, with -16,164 for eugenol and -14,083 for carvacrol, also in the A chain. Regarding Electrostatic Energy, the lowest values were recorded in the 6Q9N protein for the eugenol ligand, being -17,492 in the QNL site and -16,435 in the JPP site. More negative values suggest stronger interactions.

Table no 2: Docking Results of Proteins 6Q9N and 1MWT with Eugenol and Carvacrol.

Protein	Site	Compound	Affinity	Total Energy	vdW Energy	Elect. Energy
6Q9N	JPP	Eugenol	-7.003	18.706	-11.594	-16.435
		Carvacrol	-5.858	14.093	-10.351	-14.548
	QNL	Eugenol	-7.000	18.623	-10.705	-17.492
		Carvacrol	-5.858	14.050	-9.922	-14.942
1MWT	PNMa	Eugenol	-7.580	21.918	-16.164	-6.810
		Carvacrol	-7.530	17.181	-14.083	-7.463
	PNMb	Eugenol	-7.158	23.815	-14.075	-7.023
		Carvacrol	-7.447	17.799	-13.708	-7.444

Ligand Interactions with Amino Acid Residues

The results of the analyses of intermolecular interactions between the ligands and the amino acid residues of proteins 6Q9N and 1MWT demonstrate the formation of hydrogen bonds and hydrophobic interactions at different binding sites. In protein 6Q9N, the JPP site showed interactions of eugenol through hydrogen bonds with residues Asp297B and Lys127B (Figure 2A), while carvacrol established a hydrogen bond only with residue Asp297B (Figure 2B). At the QNL site, eugenol interacted through hydrogen bonds with residues Asp297B and Lys127B and exhibited a hydrophobic interaction with Asp297A (Figure 2C). Carvacrol, at this same site, formed a hydrogen bond with residue Asp297B (Figure 2D).

For protein 1MWT, at the PNMa site, eugenol established hydrogen bonds with residue Leu365A and hydrophobic interactions with Lys25A (Figure 2E), while carvacrol formed hydrogen bonds with residues His225A and Asn367A (Figure 2F). At the PNMb site, eugenol presented hydrogen bonds with residue His221B (Figure 2G), and carvacrol formed hydrogen bonds with residues Asn363B and His221B (Figure 2H).

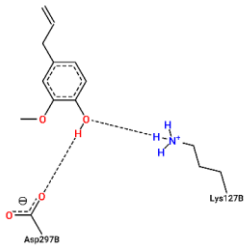


Figure 2A

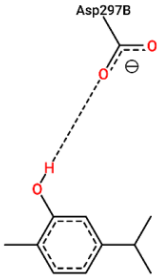


Figure 2B

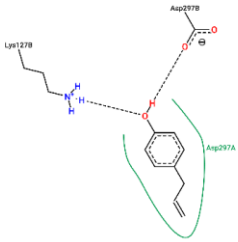


Figure 2C

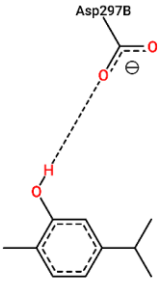


Figure 2D

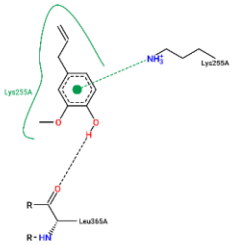


Figure 2E

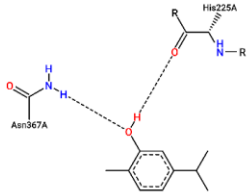


Figure 2F

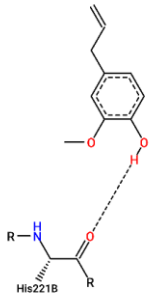


Figure 2G

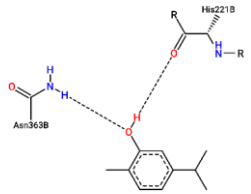


Figure 2H

IV. Discussion

The resistance mechanism of MRSA strains is largely attributed to specific structural characteristics of the PBP2a protein, particularly in its active site, which interferes with the binding and acylation of β-lactam antibiotics. One of the most critical residues in PBP2a is Ser403, which acts as the nucleophilic site for acylation. However, compared to penicillins, PBP2a performs this reaction at a significantly slower rate, reducing the effectiveness of the antibiotics. Additionally, alterations in adjacent amino acids, such as the substitution of proline for leucine at position 458 (P458L), may influence resistance levels, affecting the overall

structure and interaction dynamics of the protein. These modifications collectively contribute to MRSA's ability to resist treatment with β-lactams[27, 28, 29].

The variations in residues involved in interactions with phenolic compounds, such as eugenol and carvacrol, can be explained by the structural differences between the analyzed proteins (6Q9N and 1MWT). Resistance to β-lactams in PBP2a is associated with specific modifications in the active site, such as Ser403 and P458L. In contrast, the interactions of eugenol and carvacrol occur in distinct regions of the proteins, where factors such as local conformation and ligand accessibility influence the participating residues. Thus, the differences in the amino acids involved reflect not only the distinct function of these proteins but also the selectivity of phenolic compounds for their respective binding sites[30, 31].

The molecular docking results obtained through the DockThor server indicate that both eugenol and carvacrol exhibit significant binding affinities with PBP2a proteins. The more negative affinity values observed for eugenol and carvacrol in protein 1MWT suggest stronger interactions, which is desirable in drug design. The analysis of interaction energies, including contributions from van der Waals forces and electrostatic interactions, reveals that these forces play a crucial role in the stability of the protein-ligand complexes. Furthermore, the overall flexibility and conformational changes of PBP2a are critical for its function. When exposed to β-lactams, the protein undergoes structural rearrangements that help maintain its catalytic role in cross-linking peptidoglycans. These adaptations may hinder effective drug binding and acylation, further increasing the resistance profile of MRSA strains. Understanding these structural and functional aspects of PBP2a is essential for developing new strategies to combat resistance to β-lactams[32, 33, 34].

The parameters obtained from molecular docking simulations are fundamental for understanding the compatibility between the ligands and the binding site of PBP2a. Binding affinity, which indicates the strength of the interaction, is an important criterion for drug design, with more negative values suggesting stronger interactions. Interaction energies, which include forces such as van der Waals, electrostatic interactions, and hydrogen bonds, allow for the identification of which contributions are most relevant to the total binding. Additionally, the analysis of conformational states provides insights into the flexibility of both the ligand and the receptor, influencing the effectiveness of binding. Ligands with higher affinity are more likely to act as effective inhibitors or modulators of the target protein, while the analysis of energy contributions enables adjustments to optimize ligand efficacy[35, 36, 37.]

V. Conclusion

This study demonstrated that the compounds eugenol and carvacrol, present in the essential oil of *S. aromaticum*, interact promisingly with the PBP2a protein of MRSA, potentially inhibiting its function and restoring the efficacy of β-lactam antibiotics. Molecular modeling and docking techniques proved to be valuable tools in identifying significant interactions between the ligands and the target protein. These findings pave the way for the development of new therapeutic strategies in combating bacterial resistance. Future research should evaluate the antimicrobial efficacy of eugenol and carvacrol in in vitro and in vivo assays, as well as explore their potential in combined therapies with conventional antibiotics. Additionally, analyzing other bioactive compounds present in *S. aromaticum* and medicinal plants may expand therapeutic alternatives against resistant microorganisms. Understanding the molecular interactions of these compounds under different physiological conditions can provide relevant information to optimize their application in both veterinary and human medicine.

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