ORIGINAL ARTICLE

Dieckol as a Multi-Target Inhibitor of Methicillin-Resistant *Staphylococcus aureus* Virulence and Resistance Proteins: An *In Silico* Molecular Docking Investigation

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant worldwide concern due to resistance to β-lactam and non-β-lactam antibiotics, and its persistence in healthcare and community settings. This requires new approaches focusing on virulence factors rather than bactericidal properties, with marine phlorotannin dieckol, rich in hydroxyl groups, providing multi-target potential through H-bonding and π-interactions. Aim: To evaluate the binding of dieckol to MRSA proteins Sortase A (1T2W, virulence), PBP2a (1VQQ, resistance), and α-hemolysin (4YHD, toxin) by molecular docking. **Methodology:** UCSF Chimera was used for protein preparation, and dieckol (PubChem 3008868) was prepared in AutoDockTools. Docking was performed using PyRx-AutoDock Vina, and results were analyzed in Discovery Studio 2025. **Results:** Molecular docking studies revealed high binding affinities of dieckol to MRSA targets with -9.6 kcal/mol binding energy for PBP2a (PDB: 1VQQ; H-bonds: ARG151, THR165, SER240, THR216; π-cation: HIS293; π-alkyl: VAL256, VAL277), -8.5 kcal/mol for Sortase A (PDB: 1T2W; H-bonds: SER109, ASP111, ASP112, GLU108; π-anion/π-alkyl: ILE65), and -6.6 kcal/mol for α-hemolysin (PDB: 4YHD; H-bonds: LYS58, GLY59, GLY223, SER225; π-cation: LYS37; π-alkyl ILE5, ALA35, VAL149). These non-covalent interactions, namely the hydrogen bonding between the polyhydroxyl groups of dieckol, π-stacking, and hydrophobic interactions, do confirm the presence of stable complexes, thus validating polypharmacology. **Conclusion:** Dieckol does possess polypharmacological potential against the virulence/resistance of MRSA, thus making it at the cutting edge of green, marine-derived one health oriented anti-infectives pending in vitro validation..

Key words: Binding affinity, good health, hydrogen bonding, phlorotannin, polypharmacology, virulence factors, well-being

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is listed as one of the biggest antimicrobial challenges globally due to the remarkably exceptional capability of this microorganism to display resistance to β-lactam antibiotics and other non-β-lactam antibiotics.[1,2] The persistence of MRSA infections within health care facilities, coupled with the community setting, necessitates the need for unconventional therapeutic approaches that are not entirely based on the application of antibiotics.[3] In the recent past, an emerging approach aimed at mitigating the pathogenicity of MRSA through the reduced selective pressure for the development of resistant strains is based on the application of antagonistic small molecules

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that act on the bacterial pathogenicity factors rather than the bacterial viability.[4]

Among the natural product scaffolds, marine-derived polyphenolic compounds have gained considerable interest due to their structural diversity, redox behavior, and ability to bind to biologically relevant macromolecules.[5] Brown seaweed materials are known for their phlorotannin derivatives, which are oligomers of phloroglucinol and are known for their antimicrobial, antioxidant, and anti-inflammatory activities.[6] Dieckol, one of the key hexameric derivatives of phlorotannins, consists of various hydroxyl functionalities and an extended planar framework that are conducive for hydrogen bonding and π-π interactivities with the protein.[7] These chemical functionalities make dieckol one of the potent one-hit inhibitors of the complex bacterial system of MRSA.

Virulence in MRSA is controlled by the major proteins, such as Sortase A, which is involved in the anchoring of surface adhesins to the cell wall, and another protein, α-Hemolysin, a known pore-forming virulence factor accountable for host cell injury and immune system evasion by the pathogen.[8] Meanwhile, resistance in MRSA strains is also catalyzed by major proteins, such as penicillin-binding protein 2a (PBP2a), which has decreased binding activity to penicillin antibiotics, thereby supporting cell wall synthesis even in the presence of such inhibitors.[9] Targeting the virulence factors and the resistance proteins would facilitate a synergistic effect, thereby offering therapeutic advantages for virulence reduction and increased susceptibility.[10]

Molecular docking analysis, being one of the *in silico* studies, plays an important role in the field of chemoinformatics, which can be used to predict the interaction, binding affinity, and molecular interaction at the atomic level between two or more compounds.[11] By performing docking analysis of dieckol and its binding stability toward chosen key MRSA virulence and resistance-associated proteins, insights into the interaction patterns of dieckol, such as its potential as an inhibitor, can be obtained. The purpose of the present study was to investigate the potential of dieckol as a multi-target inhibitor of MRSA infection by analyzing the binding interaction between dieckol and major virulence and resistance-associated proteins using molecular docking.

MATERIALS AND METHODS

Target proteins preparation

The three-dimensional structures of certain MRSA pathogenicity and resistance-associated proteins were obtained from the protein data bank (PDB). The selected proteins included the sortase A, a pathogenicity-associated protein; alpha hemolysin, which is a toxin-associated pathogenicity-associated protein; and the PBP2a is a resistance-associated protein. All selected proteins were processed using UCSF Chimera before performing the docking studies. This software removes the ligands, water, and hetero-atom groups that are included in the proteins during the X-ray crystallography technique. Any missing residues, if included, were corrected, and the proteins were prepared by adding hydrogen atoms. Further, the processed proteins were optimized, and the protein structures were saved in the PDB format for the docking studies.[12]

Ligand preparation

The chemical structure of Dieckol was downloaded from PubChem (ID 3008868) in its SDF format [Figure 1]. The preparation and minimization of the ligand were achieved through the use of Open Babel GUI for the conversion of the format of the ligand. The preparation of the ligand was achieved through the use of AutoDockTools, Version 1.5.7. To prepare the ligand object for use in the docking process, the preparation involved the creation of the rotatable bonds to facilitate the docking. Finally, the saving of the ligand object in its PDBQT format using AutoDock.[13]

Molecular docking

In this regard, molecular docking studies have been conducted to understand the binding mode and affinity between each and every protein-ligand complex. For this purpose, an application named PyRx for virtual screen has been employed, which makes use of the tools of AutoDock Vina in the protein docking process. The protein and respective ligands have been prepared to be transformed into an appropriate format to conduct the molecular docking studies. The receptor site of the protein has been analyzed based on the literature findings and respective structures, to develop a grid space greatly for the protein flexibility. In the case of the molecular docking calculation, the process began by performing the molecular docking calculation for each complex by using the standard settings of the Vina method, which led to the generation of many binding modes for the complexes, followed by the scoring of each binding conformation based on the calculated binding affinity using the kcaL/moL score, leading to the selection of the binding conformation based on the high score.[14]

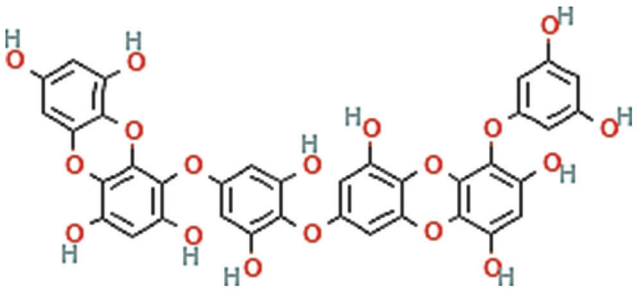

Figure 1: Two-dimensional chemical structure of Dieckol ($C_{36}H_{22}O_{18}$)

Visualization and interaction

The docked forms were further subjected to testing based on ranking and prioritization based on the compound's ranking higher in the study; this involved creating a relationship between the ligand and the binding site. The Discovery Studio 2025 software was utilized in analyzing the interaction between the protein and the ligand. The interaction was analyzed using hydrogen bonding, hydrophobic interactions, π-π stacking interactions, and electrostatic interactions. The interaction was also created in two dimensions to comprehend the snapshot of the interaction sites consisting of the amino acids of the protein. The interaction was also validated using the UCSF Chimera software.[15]

RESULTS

Molecular docking and binding affinity analysis

In molecular docking studies, it was established that dieckol induced significant binding affinities with all the selected MRSA pathogenicity and resistance-related proteins. The receptor-binding affinities of the ligand ranged from −6.6 to −9.6 kcaL/moL, indicating positive complex formation between the ligand-protein complex. Among the targeted MRSA pathogens, the highest binding affinities were found in PBP2a (PDB ID: 1VQQ), followed by Sortase A (PDB ID: 1T2W), while moderate binding affinities were detected with the MRSA α-hemolysin receptor (PDB ID: 4YHD). The negative binding energies of the receptor indicated that dieckol compounds have an exceptionally high inhibitory potential against MRSA pathogens and associated pathogenicity/resistance mechanisms [Table 1].

Interaction study of dieckol with MRSA virulence protein Sortase A (1T2W)

In the catalytic site region, a strong binding interaction was shown by the compound Dieckol [Figure 2a]. It had successfully formed various classical hydrogen bonds with the residues SER109, ASP111, ASP112, and GLU108. Along with this, the π-anion interactions were also formed successfully through the use of the compound dieckol as well as the π-alkyl interaction through the residue ILE65. The various hydrogen bonds formed through its polyhydroxyl residue were sufficient to display a strong binding in the catalytic region [Figure 2a and b].

Interaction analysis of dieckol with MRSA resistance protein PBP2a (1VQQ)

The strongest binding affinity was observed for dieckol when bound to PBP2a, −9.6 kcaL/moL [Figure 2b]. The ligand formed extensive hydrogen bonds with ARG151, THR165, SER240, and THR216 residues, while the contribution of the π-cation interaction to dieckol binding to PBP2a through HIS293, along with the π-Alk interactions through VAL256 and VAL277, collectively implied that dieckol effectively bound to the transpeptidase domain of PBP2a, contributing to cell wall synthesis; hence, inhibiting MRSA's resistance to β-lactam antibiotics [Figure 2c and d].

Interaction analysis of dieckol with MRSA virulence protein α-hemolysin (4YHD)

In the docking procedure, dieckol exhibited moderate binding within the toxin-associated position, hydrogen bonds were found to be stable to LYS58, GLY59, GLY223, and SER225 [Figure 2c]. Moreover, it is clear that the π-cation interaction occurred between dieckol and LYS37, while the π-alkyl interaction occurred between ILE5, ALA35, VAL149, and dieckol. This infers that it is capable of interfering with the processes of pore formation/oligomerization if there is any toxicity of α-hemolysin [Figure 2e and f].

Comparative multi-target binding profile

Comparative analysis of docking scores and interaction patterns confirmed that dieckol represents a consistent

Table 1: Molecular docking results of dieckol against MRSA virulence and resistance proteins

S. No.	Target protein	PDB ID	Functional Role	Binding energy (kcaL/moL)	Key interacting residues	Major interaction types
1	Sortase A	1T2W	Virulence (surface protein anchoring)	−8.5	ILE65, SER109, ASP111, ASP112, GLU108, GLU105	Hydrogen bonding, π–anion, π–alkyl
2	Penicillin-Binding Protein 2a (PBP2a)	1VQQ	Antibiotic resistance (cell wall biosynthesis)	−9.6	ARG151, THR165, SER240, THR216, HIS293, VAL256, VAL277	Hydrogen bonding, π–cation, π–alkyl
3	α-Hemolysin	4YHD	Virulence (pore-forming toxin)	−6.6	LYS37, LYS58, GLY59, GLY223, SER225, VAL149, ILE5, ALA35	Hydrogen bonding, π–cation, π–alkyl

MRSA: Methicillin-resistant *Staphylococcus aureus*

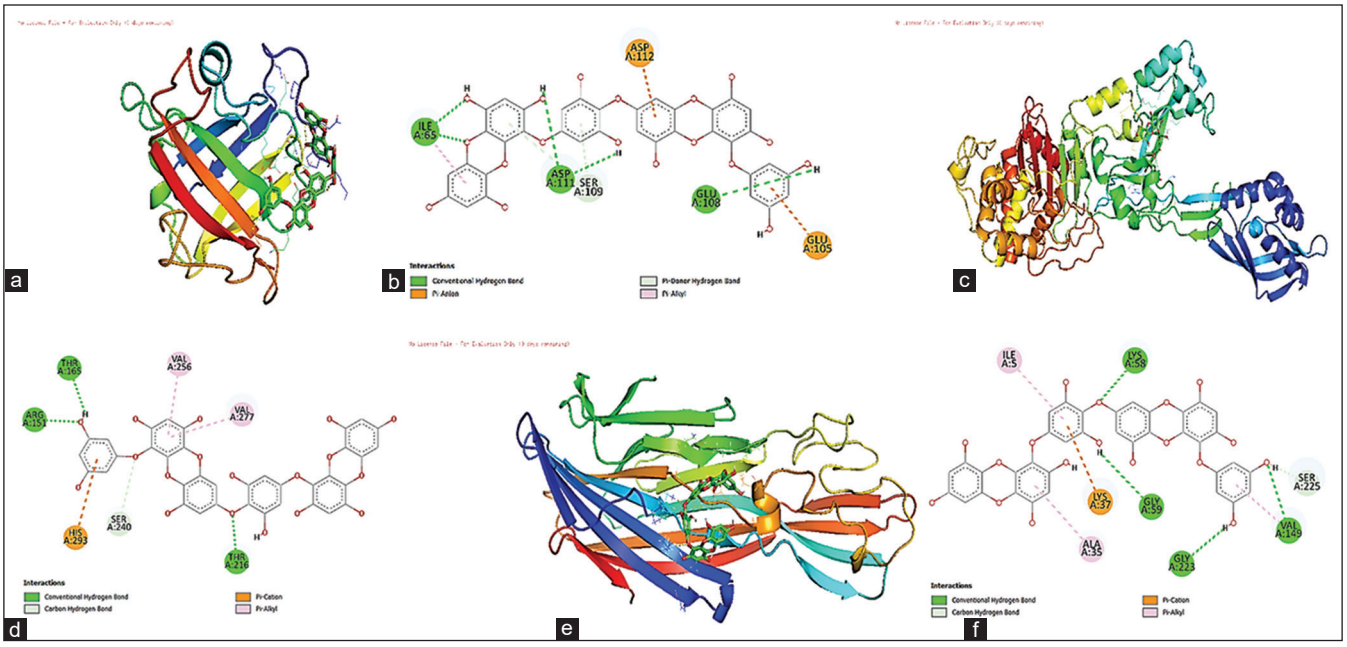

Figure 2: The three-dimensional and two-dimensional interactions of the ligand against target proteins Sortase A (PDB: 1T2W) (a and b), (penicillin-binding protein 2a; PDB: 1VQQ) (c and d), and α-Hemolysin (PDB: 4YHD) (e and f)

and favorable binding profile toward MRSA virulence and resistance targets. Greater binding affinity toward PBP2a, along with intense interactions with Sortase A and α-hemolysin, infers a polypharmacology mode of action. The presence of multiple hydroxyl groups and aromatic rings in dieckol allows for extensive hydrogen bonding, π-cation, and hydrophobic interactions, thus supporting its potential as a lead marine-derived compound for the attenuation of MRSA pathogenicity and resistance.

DISCUSSION

The findings of the present study provide proof that dieckol shows potent and stable binding properties toward major targets related to virulence and resistance factors of major MRSA strain within the body, and thus, the compound satisfies the pre-conditions to become a multi-target compounds with inhibitory properties. The binding energy between this compound and its target molecules (−6.6–−9.6 kcaL/moL), computed through this study, is within and much higher than the required limits of binding, as explicitly computed and observed through a study on the binding and interaction of various polyphenolic compounds and targets related to various types of bacterial infections through the application of a virtual screening system, where all results, however, turned out to be negative against all targets.

Specifically, the strong interaction between dieckol and Sortase A (1T2W) is very noteworthy, as this enzyme is very crucial in anchoring surface proteins, which are very essential for MRSA adhesion, colonization, and immune evasion.[16] The formation of a number of hydrogen bonds with crucial residues, which are responsible for catalysis, that is, SER109, ASP111, and ASP112, indicates that the active site seems to have been perfectly targeted. The suppression of virulence through hydrogen bonding, as observed with phenolic drugs that target Sortase A, results in reduced anchoring and hence reduced bacterial pathogenic effects without necessarily inhibiting the bacterial viability.[17] Anti-virulence strategies are now recognized as promising, especially against the development of resistance.[18]

Dieckol exhibited the highest binding affinity toward (PBP2a; 1VQQ), a key determinant of β-lactam resistance in MRSA. The binding profile showed considerable hydrogen bonding with conserved amino acids crucial for transpeptidase activity, along with stabilizing π–cation and hydrophobic interactions.[19] Literature evidence suggests that effective binding within the active region of PBP2a might disrupt cell wall synthesis, thereby rendering MRSA sensitive to antimicrobial pressure.[20] A high affinity of dieckol toward PBP2a highlights the potential of this natural product to act as a resistance-modulating medication, either solely or in combination with existing antibiotics.[21]

The moderate binding of dieckol to α-hemolysin (4YHD) is beneficial in evaluating the multi-target inhibitory potential of the compound as a potential active molecule. The compound alpha-hemolysin is known to produce holes and induce inflammation in cells of the host by generating cell damage.[22] The compound is a virulence factor in MRSA infection. Various hydrogen bonds, along with the role of π-cation interactions, as they are analyzed for the role of other residues for diekcol-related toxin compounds, manifest a potential inhibitory role of this compound in the oligomerization and contact activity of this compound. Other inhibitory effects of polyphenolic compounds reveal their

influence on the activity of protein toxins against cell toxicity and pathogenicity.[23]

From the chemical side, the hydroxyl-rich aromatic structure of the dieckol core would clearly play a critical role in the versatility of the interaction potential.[24] The ability for multiple hydrogen bonding, along with the aromaticity facilitating π-cation and hydrophobic interaction in distinct protein microenvironments, would clearly indicate the potential for the structure and flexibility of dieckol to explain the universal binding profiles observed toward functionally disparate proteins, and would also be in agreement with previous reports on the privileged nature of the phlorotannins in antimicrobial lead discovery.[25,26]

CONCLUSION

It can, therefore, be conclusively stated that based on the research findings on the docking process and relationship to its profile of interaction and previous research, it is therefore likely that this compound, dieckol, can work through a mechanism of action which is two-step, thus resulting in the reduction and reprogramming of the virulence factors, as well as the antibiotic resistance of MRSA. Although research done utilizing an *in silico* approach is still subject to being confirmed through actual laboratory research, for this research, a potent platform was set up for the study, which can be followed through in subsequent studies on the said drug compound. The multi-target character of binding is what makes this compound, dieckol, an icon for marine-bound polyphenols as green agents in chemical diversity research, which seeks new-generation anti-MRSA drugs.

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