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Original Article

Molecular Drug Docking of Multi Drug Resistant Antibiotics (Gentamicin, Linezolid and Norfloxacin) with *Staphylococcus aureus* C0673 by Implementing Computational Approach

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ABSTRACT

Background: *Staphylococcus aureus* is an adaptive and versatile microorganism that can cause a wide range of ailments, from intense and short-lived infections to persistent infections that are difficult to cure. Even though *S. aureus* infections could once be treated with ordinary antibiotics, the rise of drug-resistant organisms is currently a major issue. Numerous antibiotics were used to treat *Staphylococcus aureus* infections, but over time, the bacteria eventually developed resistance to multiple drugs. Since then, Methicillin-resistant *Staphylococcus aureus* (MRSA) strain-related nosocomial infections have increased in frequency. Recent advances in bioinformatics and *silico* screening have boosted our rate and chances of discovering medicinal metabolites. **Objectives:** In this study, we understand and analyse the binding efficiency of *Staphylococcus aureus* C0673 with three existing antibiotics employing molecular docking studies. **Materials and Methods:** The genomic sequence of *Staphylococcus aureus* C0673 is retrieved from the Ensemble bacteria database (GCA_00 0638495) and docked with three currently prescribed antibiotics, i.e., Gentamicin, Linezolid and Norfloxacin using HDOCK server. **Results and Discussion:** In the present study Gentamicin, Linezolid and Norfloxacin effectively bind with *Staphylococcus aureus* C0673. Based on the docking score, the efficiency of the compound against the bacterial protein was assessed. Gentamicin shows higher binding affinity when compared to the other two compounds. Hence, Gentamicin can be considered an eligible candidate by combining with novel medicines to treat the Multi-Drug Resistant protein of *Staphylococcus aureus*. **Conclusion:** From this research investigation, we conclude that multidrug resistant antibiotics efficiently bind with *Staphylococcus aureus* C0673. The results obtained from this study play a major role in the field of current bacterial informatics studies.

Keywords: *Staphylococcus aureus* C0673, Gentamicin, Linezolid, Norfloxacin, ModelArchive, HDOCK, Discovery Studio.

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INTRODUCTION

Staphylococcus aureus is a very prevalent invasive bacterial infection that is known to colonize large areas of the human population, resulting in significant morbidity and mortality on a global scale.[1] *S. aureus* is a significant human pathogen that causes an extensive range of infectious diseases in both healthcare and public settings. The Gram-positive pathogen is loaded with a slew of virulence factors that contribute to the formation of infections in hosts.[2]

Staphylococcus aureus is an adaptive and versatile microorganism that can cause a wide range of ailments, from intense and short-lived infections to persistent infections that are difficult to cure.[3] By the late 1960s, Methicillin-Resistant *Staphylococcus aureus* (MRSA) was endemic in hospitals; but, in the 1990s, it quickly and unexpectedly spread to communities and is now widespread globally.[4] In addition to the environment and typical human flora, *S. aureus* can be detected on healthy individual skin and mucous membranes, most commonly in the nose region. On healthy skin, *S. aureus* usually does not cause illness; however, if allowed to penetrate the bloodstream or internal tissues, these germs can cause a variety of potentially serious illnesses.[1]

Multiple antibiotics were administered to treat *S. aureus* infections, but gradually Multidrug resistance of *S. aureus* started to become more common. Since then, nosocomial infections due to Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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strains have become fairly common. Microorganisms undergo mutational changes in their chromosomal DNA or RNA to survive, which confers resistance. One well-known example is *S. aureus* resistance to Methicillin. Multiple resistant strains of *S. aureus* have been developed through evolution.[5]

Multi-Drug Resistance (MDR) is a global issue that is wreaking havoc on health care. Due to constant exposure to antimicrobial medications, bacteria are becoming resistant to antibiotic treatments. Microbial infections have significantly grown during the past ten years, and this has resulted in a surge in resistance.[6] Gentamicin a bactericidal aminoglycoside drug is effective against both gram-positive and gram-negative bacteria, however, it is more useful for treating severe gram-negative infections. Linezolid is a synthetic antibiotic used to treat Gram-positive aerobic bacterial infections. It is bactericidal against most isolates of streptococci and bacteriostatic against staphylococci and enterococci. Norfloxacin is a quinolone monocarboxylic acid that has broad-spectrum anti-bacterial action against most gram-negative and gram-positive bacteria.[7-9]

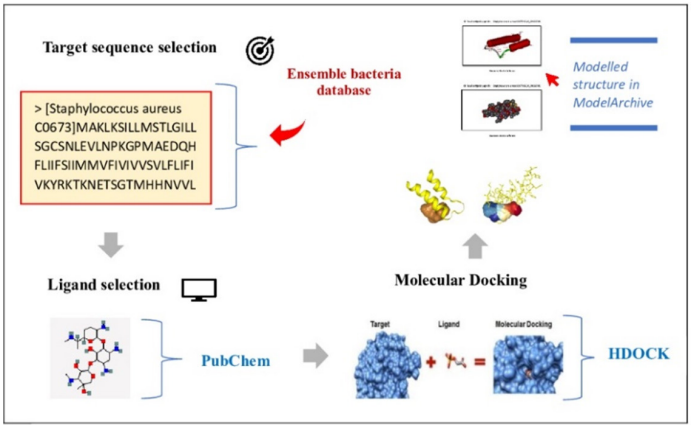
Treatment for *S. aureus* infections is largely dependent on the kind of infection and whether drug-resistant strains are present or not. The type of infection and other factors have a major influence in defining the course and type of treatment when antimicrobial therapy is necessary.[10] *S. aureus* infections are commonly treated by primary care physicians, internists, nurse practitioners, and infectious disease specialists. Identifying and treating drug-resistant strains is the primary goal of treatment. Prevention of *S. aureus* infections remains challenging. Despite their best attempts, scientists have not been able to provide regular vaccination against infections caused by *S. aureus*. As a result, efforts have relied on infection control measures including handwashing practices, hospital decontamination procedures, and MRSA transmission prevention standards.[11]

In fact, millions of compounds may now be virtually screened in a reasonable amount of time owing to *in silico* methods, which also reduce early hit identification costs and raise the likelihood of discovering the intended therapeutic candidates. Drug development efforts can currently be assisted by several molecular modeling techniques, the majority of which can be categorized into structure-based and ligand-based approaches.[12] One of the most well-known and effective structure-based *in silico* techniques for forecasting molecular interactions with biological targets is molecular docking. This is commonly accomplished by first estimating the ligand's molecular orientation within the receptor, and then using a scoring function to determine how complementary the two are.[13]

Antibiotics are required for the management of *Staphylococcus aureus* infections. Most antibiotics used to treat staphylococcal infections aim to interfere with essential bacterial processes, including transcription, translation, DNA synthesis, and cell wall production. However, antibiotic resistance is a growing problem, and ineffective therapies have enormous financial and human implications.[14]

MATERIALS AND METHODS

Step wise methodology of the present study



Micro-organism sequence selection

The genomic sequence of *Staphylococcus aureus* C0673 is retrieved from Ensemble bacteria database.[15] (https://bacteria.ensembl.org / index.html) (GCA_00 0638495) for 3D modelling studies.

Ligand selection

Three chemical compounds (Gentamicin, Linezolid, Norfloxacin) with bactericidal properties were focused for molecular docking studies. Simplified molecular input line entry system (SMILES) format of the selected chemical compounds was retrieved from PubChem.[16] (https://pubchem.ncbi.nlm.nih.gov/). Canonical SMILES (Simplified Molecular Input Line Entry System) of the three chemical compounds were deposited in Online SMILES Translator (https://cactus.nci.nih.gov/translate/) to get the PDB structure.

Molecular drug docking

Molecular docking is one of the most extensively used *in silico* drug discovery tools, investigating the optimum conformations of small molecules during interaction with target molecules. Three different chemical compounds and *Staphylococcus aureus* C0673 were subjected to docking tests.[17] PDB file of the ligand and the receptor sequence (*S. aureus*) were submitted to HDOCK server[18] (http://hdock.phys.hust.edu.cn/) to predicts the interaction between receptor and ligand molecules. HDOCK analysis also revealed data for receptor and ligand surface residues.

3D macromolecular visualization

Following molecular drug docking studies of three chemical compounds- Gentamicin, Linezolid and Norfloxacin with

Staphylococcus aureus C0673, visualization of their 3D structure was done using molecular visualization tool called Discovery Studio.

RESULTS

Gentamicin, Linezolid and Norfloxacin compounds were docked with the modelled *Staphylococcus aureus* C0673 as shown in Table 1 in order to analyse the binding efficiency. Among the top 10 binding models generated by HDOCK server the one with the highest docking score as shown in Table 1 were chosen as it has more Binding affinity towards the Receptor. Docking results clearly shows that Gentamicin compound shows higher binding affinity with docking score of -122.78 *kcal/mol* in comparison to Linezolid and Norfloxacin with docking score of -106.71 *kcal/mol*, -103.85 *kcal/mol* respectively. The score simulates the potential energy change that could occur when the protein and ligand bind. Accordingly, a very negative score indicates a strong binding, whereas a number that is less negative or even positive indicates a weak or non-existent binding.[19]

HDOCK a novel web server of template-based modeling and free docking server was employed in this study for docking Gentamicin, Linezolid and Norfloxacin compounds with the modelled *Staphylococcus aureus* C0673 as seen in Figures 1, 4 and 7 also illustrating drug binding affinities of Ligand and Receptor as seen in Tables 2, 3 and 4. Following the docking study, the 3-Dimensional (3D) structure of the ligand and receptor was viewed in molecular visualization tool called Discovery Studio as seen in Figures 2 and 3 for Gentamicin and *Staphylococcus aureus* C0673, Figures 5 and 6 for Linezolid and *Staphylococcus aureus* C0673, Figures 8 and 9 for Norfloxacin and *Staphylococcus aureus* C0673. Previous studies have proved the efficiency of HDOCK server.[20-25]

DISCUSSION

Gentamicin has bactericidal activity against aerobic gram-negative bacteria, making it a viable treatment choice for a variety of common infections.[26] Gentamicin active transport across the gram-negative membrane is oxygen dependent. Aminoglycosides are inefficient against anaerobic bacteria because they require oxygen to develop.[27] Linezolid inhibits bacterial growth by blocking the first stages of protein synthesis, a method of action unique to this class of medicines. The medication is authorized for the management of specific gram-positive infections, such as drug-resistant forms of pneumococcus, staphylococcus, and enterococcus.[28] Norfloxacin is an antibacterial agent that works by binding to DNA gyrase, an enzyme that allows DNA strands to unwind and duplicate one double helix into two, hence stopping bacterial DNA reproduction. Notably, the medication has a 100-fold higher affinity for bacterial DNA gyrase than for human DNA gyrase.[29]

Table 1: Summary of docking score of ligand and receptor.

Ligand	Receptor	Docking score (ACE)
Gentamicin	*Staphylococcus aureus* C0673	-122.78 kcal/mol
Linezolid	*Staphylococcus aureus* C0673	-106.71 kcal/mol
Norfloxacin	*Staphylococcus aureus* C0673	-103.85 kcal/mol

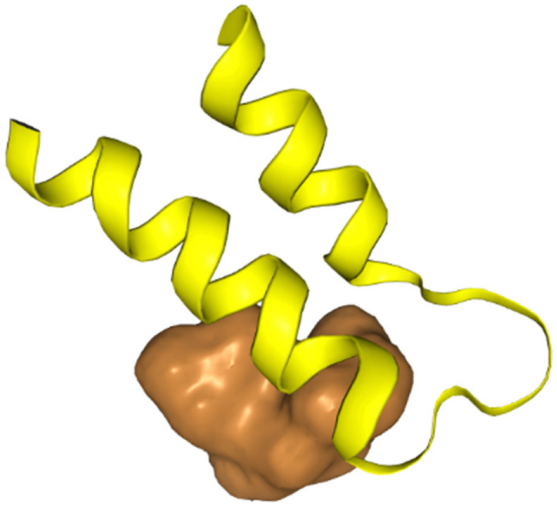


Figure 1: Molecular docking studies of Gentamicin and *Staphylococcus aureus* C0673 illustrating drug binding affinities of Ligand and Receptor. Ligand (Gentamicin) indicated in brown colour surface style and Receptor (*Staphylococcus aureus* C0673) indicated in yellow colour.

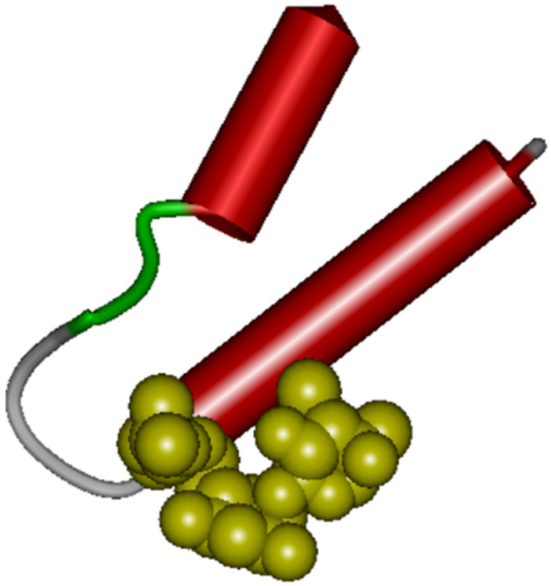


Figure 2: Schematic model view of Gentamycin and *Staphylococcus aureus* C0673 viewed with visualization tool-Discovery studio.

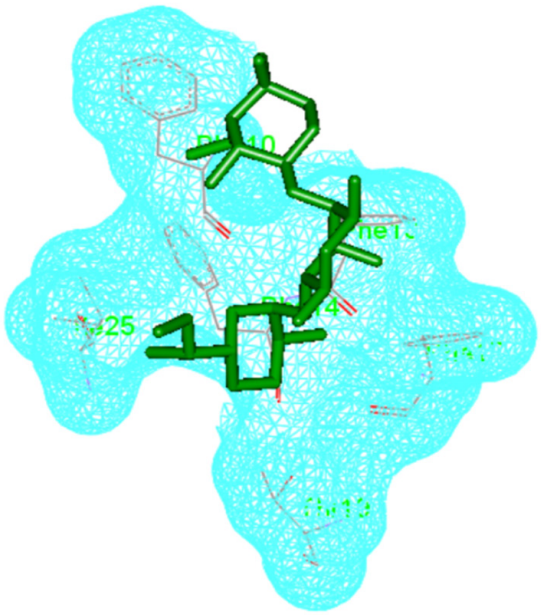


Figure 3: 3D structure of Gentamicin and *Staphylococcus aureus* C0673 illustrating surface around ligand viewed with visualization tool-Discovery studio.

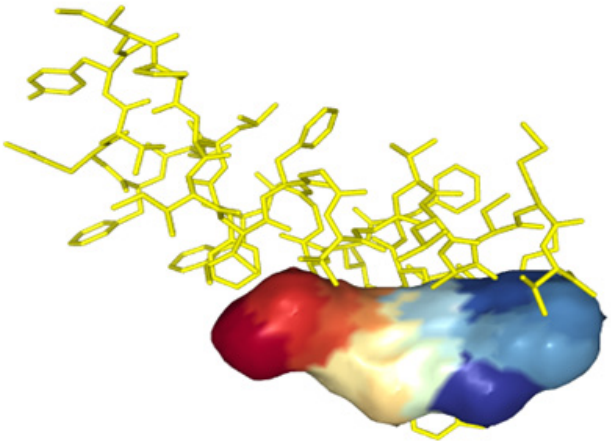


Figure 4: Molecular docking studies of Linezolid and *Staphylococcus aureus* C0673 illustrating drug binding affinities of Ligand and Receptor. Ligand (Linezolid) indicated in rainbow coloured surface style and Receptor (*Staphylococcus aureus* C0673) indicated in yellow colour.

Computational approaches that 'dock' small molecules into the structures of macromolecular targets and 'score' their potential complementarity to binding sites are widely used in hit detection and lead optimization.[13] The subject of *in silico* techniques in computer-aided drug design, which integrates the concepts of molecular biology, biochemistry, and biotechnology, is becoming more and more well-known as a cutting-edge, economical tool for developing drugs for a variety of acute illnesses.[30]

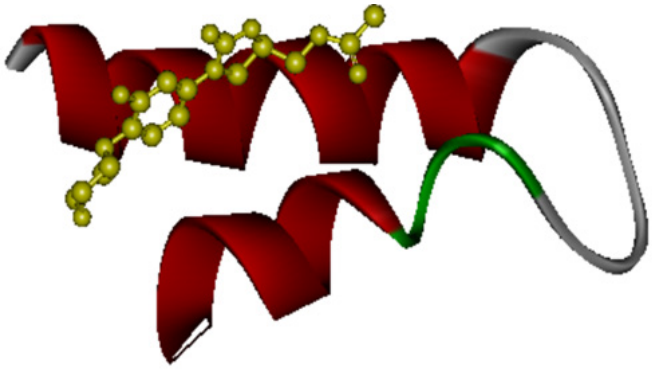


Figure 5: Solid ribbon model view of Linezolid and *Staphylococcus aureus* C0673 viewed with visualization tool-Discovery studio.

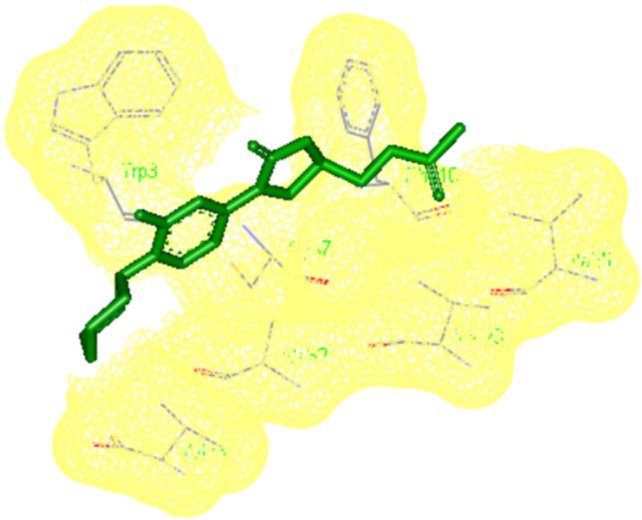


Figure 6: 3D structure of Linezolid and *Staphylococcus aureus* C0673 illustrating surface around ligand viewed with visualization tool-Discovery studio.

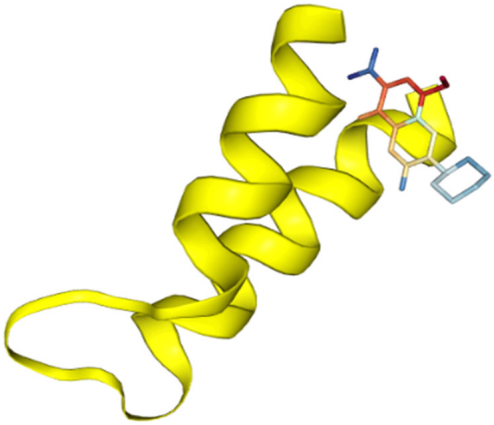


Figure 7: Molecular docking studies of Norfloxacin and *Staphylococcus aureus* C0673 illustrating drug binding affinities of Ligand and Receptor. Ligand (Norfloxacin) indicated in rainbow coloured licorice style and Receptor (*Staphylococcus aureus* C0673) indicated in yellow colour.

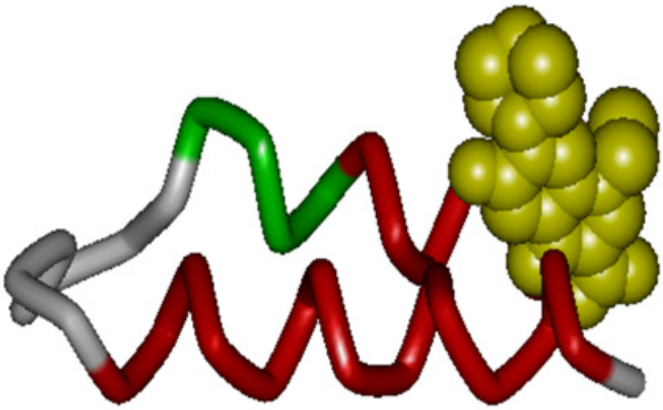


Figure 8: Tube model view of Norfloxacin and *Staphylococcus aureus* C0673 viewed with visualization tool-Discovery studio.

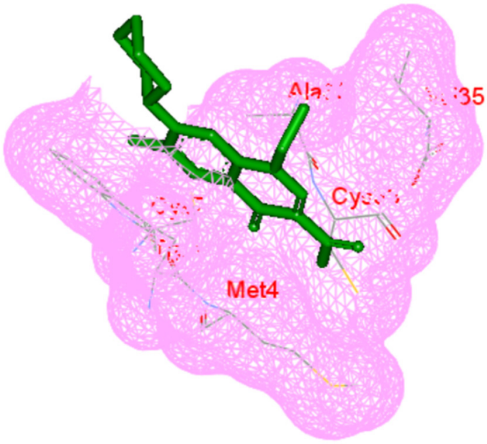


Figure 9: 3D structure of Norfloxacin and *Staphylococcus aureus* C0673 illustrating surface around ligand viewed with visualization tool-Discovery studio.

Table 2: Molecular dynamics (H-bond) Electrostatic interaction between Gentamicin and *Staphylococcus aureus* C0673.

Ligand interface residue(s)	Receptor-ligand interface residue pair(s)
PHE 10A 3.406	0 - 10A 3.406
PHE 13A 2.691	0 - 13A 2.691
PHE 14A 2.531	0 - 14A 2.531
PHE 17A 2.866	0 - 17A 2.866
THR 19A 3.358	0 - 19A 3.358
ILE 24A 4.878	0 - 24A 4.878
ILE 25A 3.401	
Receptor interface residue(s) 0 2.531	

Table 2 shows the Receptor interface residue with Amino acids Phenylalanine, Threonine, Isoleucine on A chain.

Table 3: Molecular dynamics (H-bond) Electrostatic interaction between Linezolid and *Staphylococcus aureus* C0673.

Ligand interface residue(s)	Receptor-ligand interface residue pair(s)
TRP 3A 3.244	0-3A 3.244
MET 4A 4.165	0-4A 4.165
VAL 6A 4.120	0-6A 4.120
CYS 7A 1.751	0-7A 1.751
PHE 10A 2.782	0-10A 2.782
PHE 14A 4.477	0-14A 4.477
ILE 25A 3.006	0-25A 3.006
VAL 28A 3.095	0-28A 3.095
ALA 32A 3.257	0-32A 3.257
CYS 33A 4.936	0-33A 4.936
VAL 35A 2.804	0-35A 2.804
Receptor interface residue(s) 0 1.751	

Table 3 shows the Receptor interface residue with Amino acids Tryptophan, Methionine, Valine, Cysteine, Phenylalanine, Isoleucine, Alanine on A chain.

Table 4: Molecular dynamics (H-bond) Electrostatic interaction between Norfloxacin and *Staphylococcus aureus* C0673.

Ligand interface residue(s)	Receptor-ligand interface residue pair(s)
TRP 3A 2.949	0-3A 2.949
MET 4A 3.129	0-4A 3.129
VAL 6A 4.200	0-6A 4.200
CYS 7A 1.858	0-7A 1.858
PHE 10A 4.827	0-10A 4.827
ALA 32A 2.818	0-32A 2.818
CYS 33A 3.077	0-33A 3.077
MET 34A 4.823	0-34A 4.823
VAL 35A 2.845	0-35A 2.845
Receptor interface residue(s) 0 1.858	

Table 4 shows the Receptor interface residue with Amino acids Tryptophan, Methionine, Valine, Cysteine, Phenylalanine, Isoleucine, Alanine on A chain

Recent discoveries by scientists have fundamentally altered our knowledge of the structure and function of cells. Most significantly, these discoveries have led to the theory that proteins may interact with one another and modify their functions in response to internal situations. Proteins have been shown to assemble into complexes by forming short- or long-term bonds with other proteins or ligands. A protein surface location known as a binding site is where the binding takes place. Protein interactions regulate how proteins operate and ensure their own self-regulation, which is essential for the proper operation of biological systems.[31-33]

Molecular Drug docking studies for Luteolin bioactive compound and Spike glycoprotein of SARS-CoV-2 showed that the intramolecular electrostatic force is based on the binding affinity between the ligand-receptor complexes indicating that the selected drug compound can act as an efficient inhibitor for the target corona virus protein.[34] Protein function depends on binding cavities on protein surfaces since these are often the locations where proteins attach to other biological macromolecules like proteins and nucleic acids or tiny molecules like metabolites and drugs.[35,36]

CONCLUSION

Globally, the threat to public health posed by diverse microbial species resistance to various antibiotics is growing at an alarming rate.[6] The overall results clearly elucidate that the results from docking the drugs (Gentamicin, Linezolid, Norfloxacin) potentially inhibits the hydrophobic regions of the novel predicted structure of the multi-drug resistant target protein of *Staphylococcus aureus*. The modelled structures and docking information have been submitted in ModelArchive. From this research investigation, we conclude that multidrug resistant antibiotics efficiently bind with *Staphylococcus aureus* C0673. The results obtained from this study play a major role in the field of current bacterial informatics studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MRSA: Methicillin-resistant *Staphylococcus aureus*; **SMILES:** Simplified molecular input line entry system; **PDB:** Protein Data Bank; **MDR:** Multi-Drug Resistance.

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