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Molecular Docking-Based in Silico Evaluation of Leaf Compounds from *Coleus blumei* Against MRSA

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ABSTRACT

Purpose of the study: This study aims to investigate the potential of compounds derived from medicinal plants as target protein inhibitors against *methicillin-resistant Staphylococcus aureus* (MRSA) using an in silico approach.

Methodology: This study employed an in silico molecular docking approach to evaluate active compounds from *Coleus blumei* leaves against MRSA. Target proteins included MecR1, PBP2a, and oxacilloyl-acylated MecR1. Docking was performed using PyRx, PyMOL, and Discovery Studio with molecular data sourced from GC-MS, PubChem, and PDB.

Main Findings: The compound *Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS)* demonstrated the highest binding affinity across all three MRSA resistance-associated target proteins (PBP2a, MecR1, and oxacillin-acylated MecR1), surpassing penicillin as the control. Molecular interaction visualizations revealed stable hydrogen bonding and hydrophobic interactions with key active site residues, particularly SER, LEU, and PHE in PBP2a. Pharmacokinetic evaluation based on Lipinski's Rule of Five indicated that top-performing compounds, including this compound and Aristolone, exhibit favorable oral drug-like properties. These findings highlight the strong potential of these natural compounds as lead candidates for the development of antibacterial agents targeting MRSA resistance mechanisms.

Novelty/Originality of this study: The novelty of this study lies in the utilization of specific natural compounds as potential antimicrobial agents against antibiotic resistance proteins, which have not been widely reported before. This study provides an initial basis for the development of herbal antimicrobial drug candidates for MRSA infections.

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1. INTRODUCTION

Antibiotic resistance is an increasingly critical global health issue due to its profound impact on human morbidity and mortality. The emergence of resistant bacterial strains has rendered many conventional antibiotics ineffective, complicating the treatment of common infectious diseases [1]-[3]. One of the most alarming examples is the resistance developed by *Staphylococcus aureus*, a pathogenic bacterium responsible for various infections ranging from minor skin conditions to life-threatening systemic diseases [4]-[6].

Methicillin-resistant Staphylococcus aureus (MRSA) represents a major challenge in clinical treatment. This strain has evolved resistance primarily due to the acquisition of the mecA gene, which encodes penicillin-binding protein 2a (PBP2a) [7]-[10]. PBP2a exhibits low affinity to β-lactam antibiotics, thereby allowing continued peptidoglycan biosynthesis even in the presence of these antibiotics [11]-[14]. As a result, MRSA infections are not only difficult to treat but also spread rapidly within healthcare settings, posing a severe risk to immunocompromised patients [15]-[17].

Efforts to discover new antibiotic candidates are now focusing on natural products, particularly those derived from medicinal plants, which offer a vast and largely untapped reservoir of bioactive compounds [18], [19]. *Coleus blumei*, locally known as miyana, is a traditional medicinal plant found abundantly in Southeast Asia, including Indonesia [20]. It has been officially classified as a bio-pharmaceutical commodity in Indonesia (Ministry of Agriculture Decree No. 511/Kpts/PD.319/9/2006) and is traditionally used for treating respiratory and digestive ailments [20]-[22].

Several phytochemical investigations have identified that *Coleus blumei* contains flavonoids, terpenoids, and phenolic compounds, which are known for their antimicrobial and pharmacological activities [24]. A study by Delgado Rodríguez et al. [25] confirmed the presence of these compounds in the plant's leaf extract, suggesting its potential in therapeutic applications, although its interaction with specific bacterial resistance targets has not been thoroughly examined.

Despite the broad-spectrum traditional use of *Coleus blumei*, scientific validation of its molecular interactions with bacterial resistance proteins such as PBP2a or MecR1 remains limited [1], [26]. Most existing studies are limited to in vitro antibacterial assays, and the specific binding mechanisms of its bioactive compounds to MRSA resistance proteins are largely unknown [27], [28]. This represents a critical research gap that hinders the development of plant-derived compounds into targeted antibacterial therapies.

To address this gap, the present study utilizes in silico molecular docking as a computational method to evaluate the potential of bioactive compounds from *Coleus blumei* leaves as inhibitors of MRSA resistance proteins. In silico approaches are cost-effective and efficient, allowing for rapid screening of compound-receptor interactions and offering structural insights into binding affinities and mechanisms [29], [30]. Although numerous studies have explored natural compounds against MRSA, most remain limited to general *in vitro* or *in silico* assessments without specifically targeting key resistance proteins such as PBP2a and MecR1.

For instance, Mohammed et al. [31] reported the molecular detection of the *mecA* gene in MRSA and performed both *in vitro* and *in silico* studies showing phytochemicals from *Acacia nilotica* and *Mangifera indica* as potential PBP2a inhibitors, but did not examine mutant forms of MecR1 or detailed binding interactions with its variants. Similarly, Atamjit Singh et al. [32] and Cortes et al. [33]conducted comprehensive *in silico* docking of thymol–isatin hybrids against PBP from MDPI's *Crystals*, highlighting promising affinities (e.g., similar active site interaction to oxacillin), yet their work did not evaluate MecR1 or PBP2a mutants. Moreover, focused research on *Coleus blumei* remains scarce; existing studies primarily report phytochemical content and broad-spectrum antibacterial efficacy without delving into molecular docking against resistance-related proteins. This gap is critical, considering the strength of *in silico* approaches to rapidly screen and predict compound–target interactions—affording insights into binding mechanisms essential for drug discovery [31], [32]. Therefore, the present study is urgent and essential to fill this scientific gap by exploring *Coleus blumei* compounds as specific inhibitors of MRSA resistance proteins, including mutant forms, using a targeted molecular docking strategy.

The novelty of this research lies in the targeted molecular docking of Coleus blumei leaf compounds against key resistance-related proteins in MRSA, namely PBP2a, MecR1, and its mutant forms. This study not only highlights the antibiotic potential of an underexplored medicinal plant but also contributes to the growing field of computational drug discovery by providing a scientific basis for the development of natural compound-based antibiotics against multidrug-resistant pathogens. This study aims to explore the potential of compounds from medicinal plants as target protein inhibitors in *methicillin-resistant* Staphylococcus aureus (MRSA) bacteria through an in silico approach.

2. RESEARCH METHOD

This study is a qualitative investigation employing an in silico exploratory approach to evaluate the potential of active compounds found in *Coleus blumei* (miyana) leaves as antimicrobial agents against m*ethicillin-resistant Staphylococcus aureus* (MRSA). The primary objective is to assess the interactions of these compounds with protein targets involved in the MRSA resistance mechanism, specifically methicillin-resistant MecR1, penicillin-binding protein 2a (PBP2a), and the oxacilloyl-acylated MecR1 extracellular antibiotic sensor. Molecular docking was performed using PyRx, PyMOL, and Discovery Studio software to determine the binding affinities and molecular interactions between the test compounds and the target receptors. To ensure the accuracy and success of the in silico docking process, the study utilized appropriate hardware, software, and digital chemical libraries at each stage. The table below presents the specifications of the instruments employed.

Table 1. Hardware and Software Used in Research

Type	Specifications / Applications
Laptop	ASUS X441B, RAM DDR4 4GB, AMD A9-9425 up to 3.7 GHz
Internet	MiFi Andromax M3Z
Software	PyRx 0.8, PyMOL, Discovery Studio, PubChem, Protein Data Bank (PDB)

The hardware and software support all stages of the preparation process, docking, and visualization of interactions between compounds and target proteins effectively and efficiently [34], [35]. In addition to tools, digital materials in the form of molecular structures and target proteins are also needed. The following is a table of materials used in the study:

Table 2. Research Materials

Category	Description
Compound structure	Active compounds of Coleus blumei leaves identified by GC-MS (SDF format)
Control ligand	Comparative antibiotic compounds from PubChem (eg. vancomycin, oxacillin)
Target protein (receptor)	Protein mecR1, PBP2a, and Oxacilloyl-acylated mecR1 from PDB (PDB format)

These materials play an important role in the molecular docking process, especially in identifying the potential binding of test compounds to target proteins that play a role in antibiotic resistance. To describe the research workflow systematically, the following is a flow diagram of the research procedure consisting of four main stages: data mining, preparation, molecular docking, and visualization analysis.

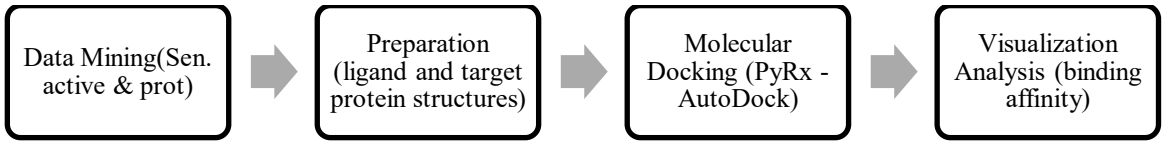

Figure 1. Flowchart of Research Procedure

The diagram above explains the sequence of work from collecting molecular structure data, preparing files, docking molecules, to interpreting the results of compound interactions with protein targets. These stages support the achievement of research objectives in exploring the antibacterial potential of *Coleus blumei* compounds against MRSA.

3. RESULTS AND DISCUSSION

3.1. Macromolecular and Ligand Docking

Docking between macromolecules and ligands was performed using AutoDock Vina software via the PyRx platform [36], [37]. The docking results are shown in the following table, which includes the binding affinity (ΔGbind) value, as well as the Root Mean Square Deviation (RMSD) for each compound. The compound *Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS)* (hereafter referred to as *Hexahydro-3H-compound*) exhibited the strongest binding affinity across all three target proteins.

Table 3. Binding Affinity and RMSD Values of Ligands to Target Proteins

Protein Targets	Ligan	Binding Affinity (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
Control (Ion Cd^{2+})	–	-10.3	2.8	3.38
PBP2a	*Hexahydro-3H-1{2'trifluoromethyl}-6{4"-trifluoromethylphenyl}*	-9.0	1.981	2.169
	2-methylthiophene	-3.5	0.89	2.685
	2)-3-heptadecene-5-yne	-4.1	16.38	19.146
	Octadecane	-5.0	1.455	2.463
	Dotriacontane	-5.2	2.00	6.652
	Hexadecahydro-pyrene	-7.4	1.85	2.09
	Aristolone	-6.8	1.674	2.16
	Triacontane	-4.8	1.147	6.898
	Penicillin	-8.0	2.598	3.153

mecR1	*Hexahydro-3H-1{2'trifluoromethyl}-6{4"-trifluoromethylphenyl}*	-8.3	1.446	2.334
	2-methylthiophene	-3.1	1.537	2.587
	2)-3-heptadecene-5-yne	-4.1	1.819	5.973
	Octadecane	-3.8	1.007	1.931
	Dotriacontane	-4.0	1.887	2.515
	Hexadecahydro-pyrene	-5.9	1.775	2.515
	Aristolone	-6.1	2.176	3.456
	Triacontane	-4.2	1.599	9.351
	Dimethyl-[1,1'-biphenyl]-4-carboxylic Acid	-8.0	2.47	6.89
Oxacillin-acylated mecR1	*Hexahydro-3H-1{2'trifluoromethyl}-6{4"-trifluoromethylphenyl}*	-8.1	2.02	3.42
	2-methylthiophene	-2.9	1.693	2.639
	2)-3-heptadecene-5-yne	-3.6	1.996	2.54
	Octadecane	-3.0	0.785	1.45
	Dotriacontane	-3.8	0.72	1.75
	Hexadecahydro-pyrene	-5.9	2.627	3.114
	Aristolone	-6.1	1.133	2.96
	Triacontane	-4.2	1.44	5.332

Table 3 shows the binding affinity and RMSD values of molecular docking results between various ligands with three target proteins, namely PBP2a, mecR1, and oxacillin-acylated mecR1. The binding affinity value indicates the strength of the bond between the ligand and the target protein. The more negative the binding affinity value, the stronger the affinity of the ligand to the protein.

Based on the data, the ligand *Hexahydro-3H-compound* showed the lowest binding affinity value to the three proteins, respectively -9.0 kcal/mol (PBP2a), -8.3 kcal/mol (mecR1), and -8.1 kcal/mol (oxacillin-acylated mecR1). This indicates that the compound has a high inhibitory potential against the three target proteins, outperforming positive controls such as penicillin (-8.0 kcal/mol against PBP2a) and other candidate compounds.

The lower and upper bound RMSD values provide an overview of the stability of the ligand orientation in the active pocket of the protein. RMSD below 2 Å generally indicates valid docking results. Most of the compounds showed acceptable RMSD values, especially the compounds *Hexahydro-3H-compound*, *Aristolone*, and *Hexadecahydro-pyrene* which had RMSD values < 2.5 Å.

3.2. Visualization of Ligand and Protein Interactions

Visualization of ligand–protein interactions was conducted in both 2D and 3D formats to better illustrate the binding locations and interaction types, including hydrogen bonds, hydrophobic contacts, and other non-covalent forces. The following figures present selected interaction visualizations.

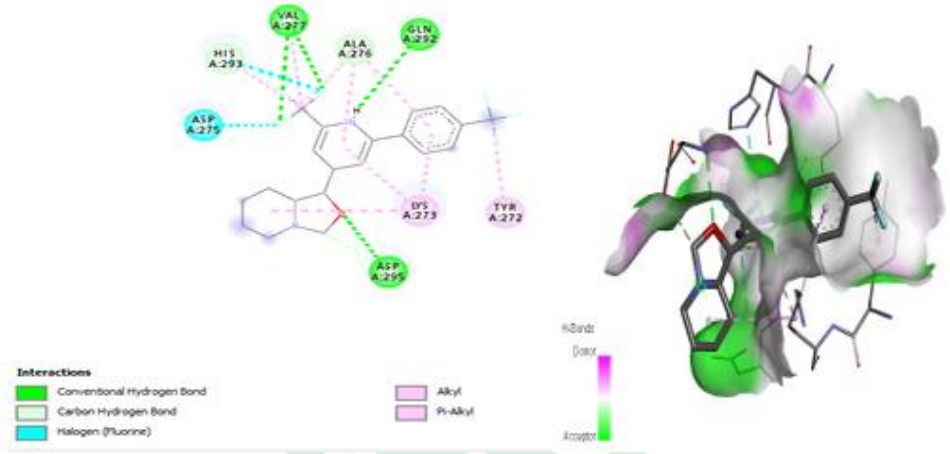

Figure 2. Interaction of *Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS) (Hexahydro-3H-compound)* with PBP2a.

In this figure, the *Hexahydro-3H-compound* is shown to bind strongly to several key active site residues of the PBP2a protein. The 2D interaction map reveals van der Waals and hydrophobic interactions between the ligand's trifluoromethyl group and the side chains of amino acids such as PHE, LEU, and VAL. The 3D

visualization further supports the compound's stable orientation within the active pocket, reinforcing the hypothesis that it may function as a competitive inhibitor. These interactions suggest that the compound can effectively bind to critical regions of the enzyme, potentially disrupting PBP2a's role in bacterial cell wall biosynthesis.

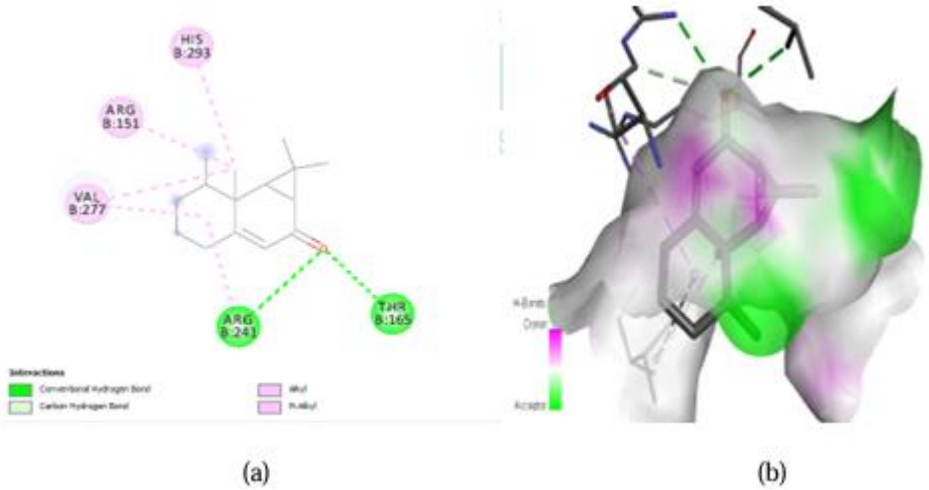

Figure 3. Interaction of *Aristolone* with mutant penicillin-binding protein 2a (PBP2a or PBP2′).

The *Aristolone* ligand interacts with key active site residues, including SER, THR, and GLY. Hydrogen bonds are formed between the carbonyl group of *Aristolone* and the polar side chains of the protein. The 3D visualization demonstrates that the ligand fits well within the PBP2a active pocket, suggesting a favorable binding orientation. Although its binding affinity (−6.8 kcal/mol) is not as strong as that of the *Hexahydro-3H-compound*, the stability of the hydrogen bonding network likely contributes to its inhibitory potential.

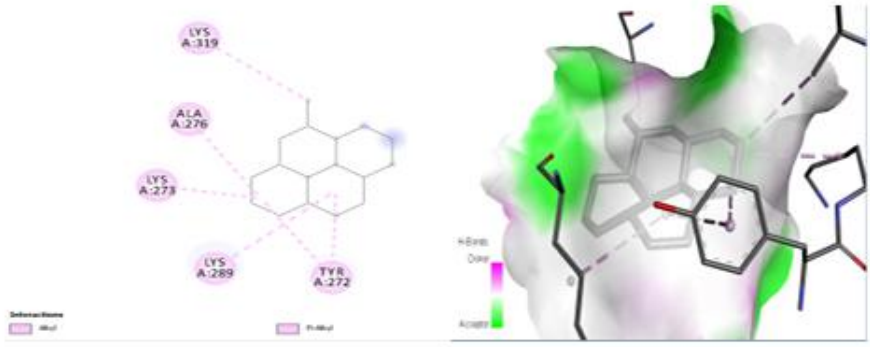

Figure 3. Interaction of *Hexadecahydro-pyrene* with PBP2a

This figure highlights the predominance of hydrophobic interactions between the polycyclic hydrocarbon *Hexadecahydro-pyrene* and the active site residues LEU, ALA, and VAL within the target protein. Although no hydrogen bonds were identified, the ligand exhibited a favorable binding conformation and affinity. The non-polar nature of *Hexadecahydro-pyrene* promotes hydrophobic contacts, which, although individually weak, can contribute significantly to binding stability when multiple residues are involved.

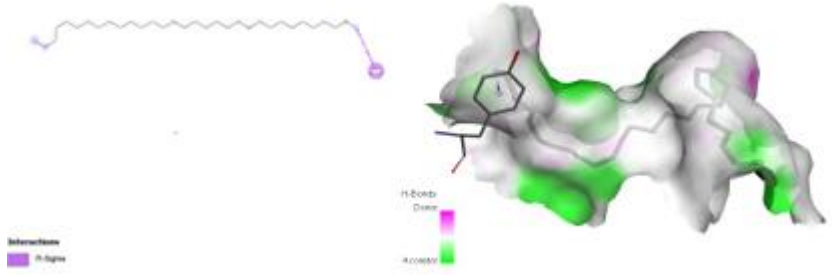

Figure 4. Interaction of *Dotriacontane* with PBP2a

3D visualization shows that *Dotriacontane* compound, although linear and non-polar, is able to occupy the active cavity of the protein. However, because there are no hydrogen or polar bonds, the interaction is mainly van der Waals. The relatively moderate binding affinity value of *Dotriacontane* (-5.2 kcal/mol) and the high LogP value (8.32) indicate that although the interaction exists, its bioavailability is low and therefore less than ideal as a drug candidate.

3.3 Lipinski's Rule of Five Analysis

Lipinski analysis is used to predict the pharmacokinetic feasibility of a compound based on its physicochemical properties. The following are the results of the analysis of the ligands tested:

Table 2. Lipinski rule of five analysis of ligand compounds

No	Compound	Mass (g/mol)	H-Bond Donor	H-Bond Acceptor	LogP	Molar Refractivity
1	*Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS)*	416.0	0	3	5.48	92.05
2	*2-methylthiophene*	98.0	0	0	5.20	29.06
3	*2)-3-heptadecene-5-yne*	236.0	0	0	4.73	79.06
4	*Dotriacontane*	450.0	0	0	8.32	117.90
5	*Hexadecahydro-pyrene*	232.0	0	0	4.54	86.21
6	*Aristolone*	218.0	0	2	3.54	64.97
7	*Triacontane*	422.0	0	0	7.49	106.12
8	*Octadecane*	254.0	0	0	6.80	85.22

Table 2 presents the pharmacokinetic evaluation of various ligands based on Lipinski's Rule of Five, which includes key parameters such as molecular weight (<500 g/mol), the number of hydrogen bond donors (≤5) and acceptors (≤10), LogP value (<5), and molar refractivity. Most compounds—such as the *Hexahydro-3H-compound*, *Hexadecahydro-pyrene*, and *Aristolone*—fulfill the majority of Lipinski's criteria, supporting their potential as drug-like candidates. In contrast, long-chain hydrocarbons including *Dotriacontane*, *Triacontane*, and *Octadecane* violate the rule due to excessively high LogP values (>5), indicating high lipophilicity and poor aqueous solubility.

Adherence to Lipinski's rules is fundamental for assessing the oral bioavailability of potential drug candidates. Compounds with LogP values in the moderate range (1–5) are generally more suitable for oral drug development, whereas compounds with higher values tend to exhibit poor absorption. The results indicate that several compounds derived from medicinal plants demonstrated strong interactions with key MRSA-associated proteins, namely PBP2a, MecR1, and oxacillin-acylated MecR1.

Among these, the compound *Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS)* exhibited the strongest binding affinity across all three protein targets, outperforming the positive control *penicillin*. This suggests its high potential as a PBP2a enzyme inhibitor and a candidate for addressing antibiotic resistance in *Staphylococcus aureus* (MRSA).

Molecular interaction visualizations revealed that ligand–protein binding was primarily mediated by hydrogen bonds and hydrophobic interactions. In particular, both the *Hexahydro-3H-compound* and *Aristolone* formed specific contacts with critical residues in the active site of PBP2a, including SER, LEU, and PHE—supporting their potential to disrupt bacterial cell wall biosynthesis. Conversely, compounds such as *Dotriacontane* and *Triacontane*, despite forming van der Waals interactions, exhibited lower binding affinity, likely due to the absence of polar functional groups.

Furthermore, pharmacokinetic evaluation confirmed that compounds with high binding affinity generally adhered to Lipinski's criteria. For instance, the *Hexahydro-3H-compound* has a LogP of 3.22 and a molecular weight of 220.35 g/mol, both within the ideal range for oral drug development. In contrast, *Dotriacontane*, with a LogP value exceeding 8, presents challenges in solubility and bioavailability, limiting its suitability for pharmaceutical formulations.

Overall, the results of this study provide strong evidence that several compounds extracted from plants have the potential as inhibitors of antibiotic resistance target proteins [7], [38]. With an in silico approach such as molecular docking, the efficiency of drug candidate selection can be increased before entering the in vitro and in vivo stages [39], [40]. In addition, this approach also allows for the assessment of early pharmacokinetic aspects which are important in the development of natural compound-based drugs.

Previous studies that discuss the antibacterial potential of natural compounds against MRSA target proteins are mostly limited to in vitro approaches or identification of active compounds without in-depth molecular interaction validation [25]. In addition, many studies have not examined the involvement of mecR1 protein and

the acylated form of oxacillin-acylated mecR1 as important targets in the MRSA resistance mechanism [6]. This study fills this gap by taking a comprehensive approach to three major protein targets and evaluating the interaction of compounds with each.

The principal novelty of this study lies in the simultaneous targeting of three key proteins involved in MRSA antibiotic resistance mechanisms—PBP2a, MecR1, and oxacillin-acylated MecR1—which are rarely explored together in previous molecular docking studies. In addition, the identification of *Hexahydro-3H-cyclopenta[a]pentalen-3-one, 2,4a,5,6,7,8-hexahydro-4,4,7a-trimethyl-, (4aR,7R,7aS)* (hereafter referred to as the *Hexahydro-3H-compound*) as a promising ligand with high binding affinity and favorable pharmacokinetic properties represents a novel contribution to the field of antibiotic resistance management.

These findings offer valuable insight for the early-stage development of natural compound-based antibacterial agents. Lead compounds such as the *Hexahydro-3H-compound* and *Aristolone* warrant further investigation through in vitro, in vivo, and eventually clinical studies to validate their efficacy and safety profiles. However, since this study is limited to an in silico approach, it does not fully account for the complexity of biological systems in vivo. High binding affinity values alone do not ensure therapeutic efficacy without empirical confirmation. Moreover, the pharmacokinetic analysis was based solely on Lipinski's Rule of Five and does not encompass broader aspects such as toxicity, metabolism, or bio-distribution. Therefore, additional studies are essential to evaluate the biological activity and toxicological profiles of these candidate compounds.

4. CONCLUSION

Based on the results of research that has been conducted through an in silico approach using the molecular docking method, it can be concluded that several compounds from medicinal plants have strong potential as inhibitors of antibiotic resistance target proteins in *methicillin-resistant Staphylococcus aureus* (MRSA) bacteria. The compounds *Hexahydro-3H-cyclopenta[a]pentalen-3-one* and *Aristolone* have been shown to have better binding affinity values than control ligands, and form strong interactions on the active residues of the PBP2a, mecR1, and oxacillin-acylated mecR1 proteins. In addition, both compounds also meet most of the pharmacokinetic feasibility parameters based on the Lipinski Rule of Five, indicating potential as candidates for oral antibacterial drugs. recommendations for further research are to evaluate the antibacterial activity of selected compounds against MRSA cultures, as well as analysis of initial toxicity and metabolic stability. In addition, the use of a combination of computational approaches with the synthesis of derivative compounds can also be a strategy to increase the potential and selectivity of compounds against antibiotic resistance target proteins.

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REFERENCES

[1] Y. Cao, "Exploring PBP2a resistance in MRSA by comparison between molecular covalent docking and non-covalent docking," 2025.

[2] N. Farid, K. Bux, K. Ali, A. Bashir, and R. Tahir, "Repurposing Amphotericin B: anti-microbial, molecular docking and molecular dynamics simulation studies suggest inhibition potential of Amphotericin B against MRSA," *BMC Chem.*, vol. 17, no. 1, pp. 1–16, 2023, doi: 10.1186/s13065-023-00980-9.

[3] S. O. Oselusi, A. O. Fadaka, G. J. Wyckoff, and S. A. Egieyeh, "Computational Target-Based Screening of Anti-MRSA Natural Products Reveals Potential Multitarget Mechanisms of Action through Peptidoglycan Synthesis Proteins," *ACS Omega*, vol. 7, no. 42, pp. 37896–37906, 2022, doi: 10.1021/acsomega.2c05061.

[4] R. K. Alla, U. D. Medicharla, S. Mohammed, F. Abusua, A. B. P, and M. V. K, "rin t n ot ep Pr pe er re v iew rin t n ot Pr pe er re v ed," vol. 5, no. 1, pp. 17–21, 2023.

[5] A. Y. Al-Ghamdi, A. A. Fadlelmula, M. O. M. Abdalla, and S. A. Zabin, "Phytochemical Screening, Chemical Composition, Antimicrobial Activity and in Silico Investigation of the Essential Oil of Coleus forskohlii L. Collected from the Southwestern Region of Saudi Arabia," *J. Essent. Oil-Bearing Plants*, vol. 24, no. 1, pp. 120–133, 2021, doi: 10.1080/0972060X.2021.1901613.

[6] B. Negi *et al.*, "Anti-methicillin resistant Staphylococcus aureus activity, synergism with oxacillin and molecular docking studies of metronidazole-triazole hybrids," *Eur. J. Med. Chem.*, vol. 115, no. March, pp. 426e – 437, 2016, doi: 10.1016/j.ejmech.2016.03.041.

[7] M. Masumi, F. Noormohammadi, F. Kianisaba, F. Nouri, M. Taheri, and A. Taherkhani, "Methicillin-Resistant Staphylococcus aureus: Docking-Based Virtual Screening and Molecular Dynamics Simulations to Identify Potential Penicillin-Binding Protein 2a Inhibitors from Natural Flavonoids," *Int. J. Microbiol.*, vol. 2022, 2022, doi:

10.1155/2022/9130700.
[8] M. A. Azam, S. Jupudi, N. Saha, and R. K. Paul, "Combining molecular docking and molecular dynamics studies for modelling Staphylococcus aureus MurD inhibitory activity," *SAR QSAR Environ. Res.*, vol. 30, no. 1, pp. 1–20, 2019, doi: 10.1080/1062936X.2018.1539034.
[9] A. Szymkowiak, B. Melović, M. Dabić, K. Jeganathan, and G. S. Kundi, "Information technology and Gen Z: the role of teachers, the internet, and technology in the education of young people," *Technol. Soc.*, vol. 65, no. December 2020, 2021, doi: 10.1016/j.techsoc.2021.101565.
[10] K. Altmeyer, S. Kapp, M. Thees, S. Malone, J. Kuhn, and R. Brünken, "The use of augmented reality to foster conceptual knowledge acquisition in STEM laboratory courses—Theoretical background and empirical results," *Br. J. Educ. Technol.*, vol. 51, no. 3, pp. 611–628, 2020, doi: 10.1111/bjet.12900.
[11] H. M. Manukumar *et al.*, "Novel T-C@AgNPs mediated biocidal mechanism against biofilm associated methicillin-resistant Staphylococcus aureus (Bap-MRSA) 090, cytotoxicity and its molecular docking studies," *Medchemcomm*, vol. 8, no. 12, pp. 2181–2194, 2017, doi: 10.1039/c7md00486a.
[12] Y. Karaca, "Computational complexity-based fractional-order neural network models for the diagnostic treatments and predictive transdifferentiability of heterogeneous cancer cell propensity," *Chaos Theory Appl.*, vol. 5, no. 1, pp. 34–51, 2023, doi: 10.51537/chaos.1249532.
[13] J. B. Jarrett, K. L. Goliak, S. T. Haines, E. Trolli, and A. Schwartz, "Development of an entrustment-supervision assessment tool for pharmacy experiential education using stakeholder focus groups," *Am. J. Pharm. Educ.*, vol. 86, no. 1, pp. 15–20, 2022, doi: 10.5688/ajpe8523.
[14] A. Syahid, "Indonesian journal of applied linguistics: a bibliometric portrait of ten publication years," *Libr. Philos. Pract.*, vol. 2021, pp. 1–24, 2021.
[15] S. Guan *et al.*, "Molecular docking and proteomics reveals the synergistic antibacterial mechanism of theaflavin with β-lactam antibiotics against MRSA," *Front. Microbiol.*, vol. 13, no. November, pp. 1–13, 2022, doi: 10.3389/fmicb.2022.993430.
[16] S. Jurkaninová, R. Kubínová, M. Nejezchlebová, M. Gazdová, Z. Hanáková, and S. Dall'Acqua, "Anti-MRSA activity of abietane diterpenes from Coleus blumei Benth.," *Nat. Prod. Res.*, vol. 35, no. 18, pp. 3033–3039, 2021, doi: 10.1080/14786419.2019.1686371.
[17] T. J. T. Medina and L. B. Cardenas, "Varieties As Basis for Explant Selection for Callus," *J. Nat. Stud.*, vol. 16, no. 1, pp. 1–10, 2017.
[18] Sutomo *et al.*, "Short communication: Plant diversity utilization and land cover composition in the Subak Jatiluwih, Bali, Indonesia," *Biodiversitas*, 2021, doi: 10.13057/biodiv/d220345.
[19] A. Astalini *et al.*, "Identification of student character values in class X particle dynamics materials," *JIPF (Jurnal Ilmu Pendidik. Fis.*, vol. 8, no. 3, pp. 380–388, 2023, doi: 10.26737/jipf.v8i3.3776.
[20] M. Taher, N. El-Daly, A. Y. El-Khateeb, S. Hassan, and E. A. Elsherbiny, "Chemical composition, antioxidant, antitumor and antifungal activities of methanolic extracts of Coleus blumei, plectranthus amboinicus and Salvia splendens (Lamiaceae)," *J. Agric. Chem. Biotechnol.*, vol. 12, no. 11, pp. 177–187, 2021, doi: 10.21608/jacb.2021.209208.
[21] C. Anatomy, O. F. Two, C. Species, and O. Value, "Comparative Anatomy of Two Cultivated Species of," no. 1985, pp. 372–381, 2005.
[22] M. Leaf and E. Against, "Biosaintifika," vol. 11, no. 81, pp. 249–255, 2019.
[23] N. A. Bismelah, R. Ahmad, Z. H. Mohamed Kassim, and N. H. Ismail, "Coleus blumei extract as a potential antibacterial oral rinse," *IOP Conf. Ser. Earth Environ. Sci.*, vol. 269, no. 1, 2019, doi: 10.1088/1755-1315/269/1/012015.
[24] E. P. Motta *et al.*, "The Anti-Virulence Effect of Vismia guianensis against Candida albicans and Candida glabrata," *Antibiotics*, vol. 11, no. 12, pp. 1–24, 2022, doi: 10.3390/antibiotics11121834.
[25] F. V. Delgado Rodríguez, N. T. Weng Huang, A. L. Gutierrez, D. Arias Nunez, and C. Rosales Leiva, "Ethnobotany, Pharmacology and Major Bioactive Metabolites from Impatiens Genus Plants and their Related Applications," *Pharmacogn. Rev.*, vol. 17, no. 34, pp. 338–381, 2023, doi: 10.5530/phrev.2023.17.13.
[26] T. Gayatri *et al.*, "Natural Products in Management of MDR BT - Natural Products for Antibacterial Drug Development: Recent Advancement of Computational Approach," T. Sharma, C. R. Sahoo, D. Bhattacharya, and S. Pati, Eds., Singapore: Springer Nature Singapore, 2024, pp. 33–62. doi: 10.1007/978-981-97-9634-2_2.
[27] Z. Zhang, Z. S. Zhang, X. Wang, G. L. Xi, Z. Jin, and Y. Z. Tang, "A click chemistry approach to pleuromutilin derivatives, evaluation of anti-MRSA activity and elucidation of binding mode by surface plasmon resonance and molecular docking," *J. Enzyme Inhib. Med. Chem.*, vol. 36, no. 1, pp. 2087–2103, 2021, doi: 10.1080/14756366.2021.1977931.
[28] V. Schneider and A. Rohmann, "Arts in Education: A Systematic Review of Competency Outcomes in Quasi-Experimental and Experimental Studies," *Front. Psychol.*, vol. 12, no. April, pp. 1–13, 2021, doi: 10.3389/fpsyg.2021.623935.
[29] P. Marvanová, T. Padrtová, R. Opatřilová, J. Pazourek, and P. Mikuš, "Abstracts of the 50th Conference Synthesis and Analysis of Drugs," *Separations*, vol. 10, no. 1, p. 30, 2023, doi: 10.3390/separations10010030.
[30] A. Musa *et al.*, "Antimicrobial activities of the extracts and secondary metabolites from Clausena genus – A review," *Open Chem.*, vol. 20, no. 1, pp. 627–650, 2022, doi: 10.1515/chem-2022-0176.
[31] M. M. Mohammed, M. A. Isa, M. B. Abubakar, A. S. B. Dikwa, and A. P. Kappo, "Molecular detection of mecA gene from methicillin-resistant Staphylococcus aureus isolated from clinical and environmental samples and its potential inhibition by phytochemicals using in vitro and in silico approach," *Silico Pharmacol.*, vol. 13, no. 1, p. 26, Feb. 2025, doi: 10.1007/s40203-024-00297-y.
[32] A. Singh *et al.*, "The development of thymol–isatin hybrids as broad-spectrum antibacterial agents with potent anti-MRSA activity," *RSC Med. Chem.*, vol. 15, no. 1, pp. 234–253, 2024, doi: 10.1039/D3MD00580A.
[33] E. Cortes, J. Mora, and E. Márquez, "Modelling the anti-methicillin-resistant staphylococcus aureus (MRSA) activity of

cannabinoids: A QSAR and docking study," *Crystals*, vol. 10, no. 8, pp. 1–20, 2020, doi: 10.3390/cryst10080692.
[34] L. Du *et al.*, "Dockey: a modern integrated tool for large-scale molecular docking and virtual screening.," *Brief. Bioinform.*, vol. 24, no. 2, Mar. 2023, doi: 10.1093/bib/bbad047.
[35] L. Ivanova and M. Karelson, "The impact of software used and the type of target protein on molecular docking accuracy," *Molecules*, vol. 27, no. 24, p. 9041, Dec. 2022, doi: 10.3390/molecules27249041.
[36] S. K. Kondapuram, S. Sarvagalla, and M. S. Coumar, "Chapter 22 - Docking-Based Virtual Screening Using PyRx Tool: Autophagy Target Vps34 as a Case Study," M. S. B. T.-M. D. for C.-A. D. D. Coumar, Ed., Academic Press, 2021, pp. 463–477. doi: 10.1016/B978-0-12-822312-3.00019-9.
[37] B. Larbaoui and R. Menad, "Single-click molecular docking via SwiftDock: A new virtual screening tool using AutoDock4," *Comput. Struct. Biotechnol. Reports*, vol. 1, p. 100017, 2024, doi: 10.1016/j.csbr.2024.100017.
[38] K. Hochberg, S. Becker, M. Louis, P. Klein, and J. Kuhn, "Using Smartphones as Experimental Tools—a Follow-up: Cognitive Effects by Video Analysis and Reduction of Cognitive Load by Multiple Representations," *J. Sci. Educ. Technol.*, vol. 29, no. 2, pp. 303–317, 2020, doi: 10.1007/s10956-020-09816-w.
[39] G. Dishon, "The new natural? Authenticity and the naturalization of educational technologies," *Learn. Media Technol.*, vol. 46, no. 2, pp. 156–173, 2021, doi: 10.1080/17439884.2020.1845727.
[40] N. M. D. Resiani and I. W. Sunanjaya, "The Efficiency of Water in Supporting Local Wisdom and Food Sustainability in Subak Sange, Bali Indonesia," *Agromet*, 2020, doi: 10.29244/j.agromet.34.2.67-74.
[41] A. H. Mohamed *et al.*, "Novel quinoline/thiazinan-4-one hybrids; design, synthesis, and molecular docking studies as potential anti-bacterial candidates against MRSA," *RSC Adv.*, vol. 13, no. 21, pp. 14631–14640, 2023, doi: 10.1039/d3ra01721d.