RESEARCH PAPER

In Silico Molecular Docking and ADMET Assessment of Bioactive Phytocompounds from Murraya koenigii Ethanolic Extract Against Staphylococcus aureus

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ABSTRACT

Background: The growing prevalence of antimicrobial resistance has increased the need for identifying novel bioactive compounds from natural sources. Murraya koenigii is a medicinal plant known for its diverse phytochemicals, particularly carbazole alkaloids, which exhibit potential antimicrobial properties.

Aim: To evaluate the antimicrobial potential and safety profile of selected phytocompounds from Murraya koenigii against the penicillin-binding protein of Staphylococcus aureus using molecular docking and in silico pharmacokinetic analysis.

Materials and Methods: Six phytocompounds—Mahanimbine, Girinimbine, Murrayanine, Koenimbine, (+)-Murrayazoline, and (−)-Caryophyllene—were retrieved from the PubChem database. Molecular docking was performed against the penicillin-binding protein of Staphylococcus aureus (PDB ID: 1VQQ) using AutoDock Vina. ADMET properties were predicted using SwissADME and pkCSM, while toxicity assessment was conducted using the ProTox-II web server.

Results: Docking analysis revealed strong binding interactions for several carbazole alkaloids, with (+)-Murrayazoline showing the highest binding affinity. ADMET predictions indicated favorable pharmacokinetic properties for most compounds, including high gastrointestinal absorption and acceptable drug-likeness. Toxicity prediction suggested generally low organ toxicity, although some compounds showed potential immunotoxicity alerts.

Conclusion: The findings suggest that carbazole alkaloids from Murraya koenigii, particularly (+)-Murrayazoline and Mahanimbine, may serve as promising candidates for antimicrobial drug development. Further experimental studies are required to validate these computational findings.

Key-words: Murraya koenigii, molecular docking, antimicrobial activity, carbazole alkaloids, ADMET prediction, ProTox-II, Staphylococcus aureus,Good Health and Well-Being

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INTRODUCTION

Natural plant-derived compounds have gained considerable attention in recent years as potential alternatives to synthetic antimicrobial agents due to their broad biological activities, improved biocompatibility, and reduced risk of microbial resistance. The increasing prevalence of antibiotic-resistant microorganisms has created an urgent need to explore novel bioactive compounds from natural sources that can effectively inhibit microbial growth while maintaining safety for human tissues.(World Health Organization 2025) Medicinal plants used in traditional systems of medicine represent a valuable reservoir of phytochemicals with diverse pharmacological properties including antimicrobial, antioxidant, anti-inflammatory, and cytoprotective activities. Among these plants, Murraya koenigii (L.) Spreng., commonly known as curry leaf, has attracted scientific interest due to its rich phytochemical profile and therapeutic potential.(Senthil et al. 2025)

Murraya koenigii, belonging to the family Rutaceae, is widely distributed in South Asia and has been traditionally used in Ayurvedic and folk medicine for the treatment of various ailments including infections, inflammation, gastrointestinal disorders, and metabolic diseases.(Senthil et al. 2025) The plant contains several biologically active phytoconstituents such as carbazole alkaloids, flavonoids, terpenoids, and phenolic compounds, which are responsible for its diverse pharmacological effects Phytochemicals such as mahanimbine, girinimbine, murrayanine, and koenimbine have been reported to exhibit significant antimicrobial, antioxidant, and anticancer properties.(Pallavi) Previous studies have demonstrated that extracts of Murraya koenigii, particularly ethanolic extracts, show inhibitory activity against a wide range of pathogenic microorganisms including Staphylococcus aureus, Escherichia coli, and Candida albicans.(Rajeshkumar et al. 2022)

In addition to antimicrobial efficacy, the safety and compatibility of bioactive compounds with human biological systems are crucial for their potential therapeutic applications. Hemocompatibility, which refers to the interaction of substances with blood components such as erythrocytes, platelets, and plasma proteins, is an important parameter when evaluating the safety of natural

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compounds intended for biomedical use.(Vignesh et al. 2024) Plant-derived compounds that demonstrate strong antimicrobial activity but minimal toxicity toward blood cells are considered promising candidates for drug development and biomedical applications.(Patil et al. 2022) Therefore, evaluating both antimicrobial potential and hemocompatibility is essential to identify compounds that are not only effective but also biologically safe.

Recent advances in computational biology and bioinformatics have enabled the use of in silico approaches, particularly molecular docking, to predict the interaction between bioactive compounds and biological target proteins. Molecular docking is a widely used computational technique that helps to estimate binding affinity, interaction patterns, and structural compatibility between ligands and target proteins at the molecular level.(Maheshwaran et al. 2021) These computational methods provide valuable insights into the potential mechanism of action of phytochemicals and allow researchers to screen multiple compounds efficiently before conducting extensive laboratory experiments.(Ganesh et al. 2025)

Although several experimental studies have investigated the antimicrobial properties of Murraya koenigii extracts, limited research has explored the molecular interactions of its phytoconstituents with microbial target proteins using computational approaches.(Danisca et al. 2025) Furthermore, the relationship between the antimicrobial potential of these phytocompounds and their predicted safety or hemocompatibility profiles remains insufficiently investigated. This represents an important gap in the current literature, as understanding the molecular interactions and toxicity profiles of these compounds can help identify promising candidates for further therapeutic development.

Therefore, the present study was undertaken to perform a molecular docking-based in silico assessment of antimicrobial activity and hemocompatibility-related properties of phytocompounds identified in the ethanolic extract of Murraya koenigii. By evaluating ligand–protein interactions and predicting pharmacokinetic and toxicity parameters, this study aims to provide computational evidence supporting the antimicrobial efficacy and biological safety of selected phytoconstituents. The findings of this study may contribute to the identification of potential plant-derived antimicrobial agents with favorable biocompatibility profiles and support future experimental and clinical investigations.

MATERIALS & METHODS

Study Design

The present study employed an in silico molecular docking approach to investigate the antimicrobial potential of phytocompounds identified in the ethanolic extract of Murraya koenigii against Staphylococcus aureus. Molecular docking was used to evaluate the binding interactions between selected phytoconstituents and the bacterial penicillin-binding protein (PBP2a), an essential enzyme involved in bacterial cell wall biosynthesis and antibiotic resistance. In addition, ADMET and toxicity prediction analyses were performed to assess the pharmacokinetic behavior and safety profile of the selected compounds.

Selection and Preparation of Ligands

The phytochemical compounds selected for the docking analysis were reported constituents of Murraya koenigii ethanolic extract. Six major bioactive compounds were included in the study: Mahanimbine (PubChem CID: 167963), Girinimbine (PubChem CID: 96943), Murrayanine (PubChem CID: 96942), Koenimbine (PubChem CID: 97487), (+)-Murrayazoline (PubChem CID: 21770913), and (−)-Caryophyllene (PubChem CID: 5281515). The three-dimensional (3D) structures of these ligands were retrieved from the PubChem database in SDF format. The downloaded structures were imported into PyRx virtual screening software (version 0.8) for further processing. Prior to docking, ligand structures were energy-minimized using the Universal Force Field (UFF) to obtain stable conformations. Hydrogen atoms were added to the molecules to maintain appropriate valency, and the structures were converted to PDBQT format, which is required for docking using AutoDock Vina. Energy minimization was performed to remove steric clashes and to ensure optimal geometry of the ligands before docking simulations.(Ferreira et al. 2015)

Protein Retrieval and Preparation

The crystal structure of the antimicrobial target protein was obtained from the RCSB Protein Data Bank (PDB). The selected protein was the penicillin-binding protein (PBP2a) of Staphylococcus aureus, which plays a critical role in bacterial cell wall synthesis and contributes to methicillin resistance. The protein structure was retrieved with PDB ID: 1VQQ in PDB format. Protein preparation was carried out using AutoDock Tools (ADT). Initially, co-crystallized ligands, water molecules, and heteroatoms present in the protein structure were removed to prevent interference during docking. Polar hydrogen atoms were added to stabilize the protein structure, and Kollman charges were assigned to the protein. The prepared protein structure was then converted into PDBQT format for compatibility with the docking software. This preparation ensured that the receptor structure was optimized for ligand binding analysis.

Molecular Docking Procedure

Molecular docking was performed using AutoDock Vina integrated in PyRx software, which predicts the optimal binding orientation and binding affinity between ligands and target proteins. The prepared protein receptor and ligand molecules were imported into the PyRx docking workspace. A grid box was generated around the active site of the target protein to define the region where docking would occur. The grid box dimensions were adjusted to adequately cover the active binding pocket of the protein, ensuring that potential ligand interactions within the catalytic site were captured. The grid parameters were selected based on the coordinates of the active site residues reported in previous structural studies of PBP2a. AutoDock Vina uses a scoring function that estimates the binding free energy (kcal/mol) between the ligand and receptor. During docking, multiple ligand conformations were generated, and the conformation with the lowest binding energy was considered the most stable and favorable binding pose. Each ligand was docked independently with the target protein, and the resulting docking scores were recorded. Lower binding energy values indicated stronger ligand–protein interactions and greater predicted antimicrobial potential.(Dallakyan and Olson 2015)

Analysis of Ligand–Protein Interactions

The docking results obtained from PyRx were further analyzed using BIOVIA Discovery Studio Visualizer to examine the molecular interactions between the phytocompounds and the protein binding site. Both three-dimensional (3D) and two-dimensional (2D) interaction maps were generated to visualize the binding orientation and key interactions. Specific interactions analyzed included hydrogen bonding, hydrophobic interactions, van der Waals interactions, π–π stacking, and π–alkyl interactions between the ligand molecules and amino acid residues present in the active site of the protein. Identification of these interactions provided insights into the structural compatibility of the phytocompounds with the target protein and helped determine their potential mechanism of antimicrobial action.

ADMET and Toxicity Prediction

To evaluate the pharmacokinetic and safety characteristics of the selected phytocompounds, in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction was performed using publicly available computational tools. The SwissADME online server was used to assess drug-likeness, physicochemical properties, lipophilicity, and gastrointestinal absorption of the compounds. Key parameters evaluated included molecular weight, hydrogen bond donors and acceptors, lipophilicity (LogP), topological polar surface area (TPSA), and Lipinski's rule of five compliance. In addition, pkCSM was employed to predict pharmacokinetic behavior such as intestinal absorption, blood–brain barrier permeability, and metabolic stability. Toxicity prediction was carried out using ProTox-II, which provides estimates of acute toxicity, hepatotoxicity, mutagenicity, and carcinogenic potential of chemical compounds. The integration of molecular docking results with ADMET prediction enabled the identification of phytocompounds that not only demonstrate strong binding affinity toward the antimicrobial target but also possess favorable pharmacokinetic and toxicity profiles.(Türkan et al. 2025)

Data Interpretation

Binding affinities obtained from the docking analysis were expressed in kilocalories per mole (kcal/mol). Compounds exhibiting lower binding energy values and stable molecular interactions with the active site residues of the target protein were considered to have greater predicted antimicrobial potential. The combined evaluation of docking interactions and ADMET predictions provided a comprehensive computational assessment of the therapeutic potential and safety of phytochemicals derived from Murraya koenigii.

RESULTS

The molecular docking analysis assessed the interaction of six phytocompounds identified from the ethanolic extract of Murraya koenigii with the penicillin-binding protein of Staphylococcus aureus (PDB ID: 1VQQ). The docking scores obtained from AutoDock Vina ranged from −6.9 to −9.4 kcal/mol, indicating favorable binding of all tested ligands with the selected target protein.

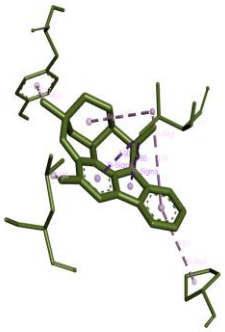

Figure 1: Three-dimensional (3D) representation of the docked complex showing the orientation of (+)-Murrayazoline within the active binding pocket of the protein. The ligand is stabilized within the hydrophobic cavity of the enzyme through multiple non-covalent interactions with surrounding amino acid residues.

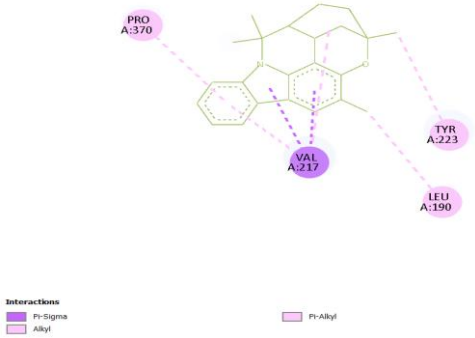

Figure 2: Two-dimensional (2D) interaction diagram illustrating the key residues involved in ligand binding. (+)-Murrayazoline forms π-sigma and π-alkyl hydrophobic interactions with residues VAL217, TYR223, LEU190, and PRO370, contributing to stabilization of the ligand–protein complex within the catalytic region of the penicillin-binding protein.

Among the evaluated compounds, (+)-Murrayazoline showed the strongest binding affinity with a docking score of −9.4 kcal/mol. Its 2D and 3D interaction profiles demonstrated multiple stabilizing interactions within the active site, including π-cation, π-anion, hydrogen bonding, and hydrophobic contacts with residues such as ARG65, ASP304, ILE69, and LYS68 (Figures 1 and 2). These interactions suggest that (+)-Murrayazoline formed the most stable ligand–protein complex among all the tested compounds.

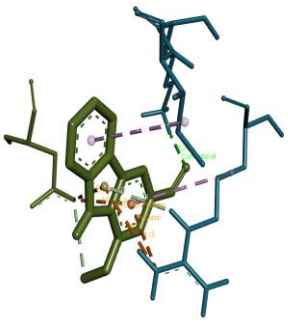

Figure 3: 3D docking conformation of Murrayanine within the PBP2a active site. The compound is stabilized through π-cation and hydrogen bonding interactions, indicating moderate binding stability.

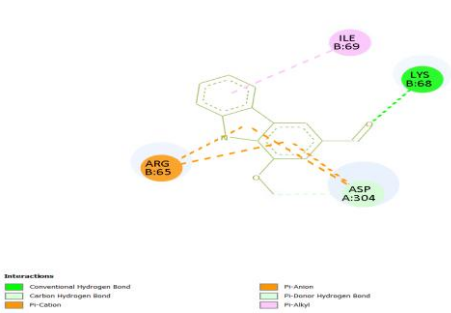

Figure 4: 2D interaction diagram of Murrayanine with PBP2a. The ligand interacts with ARG65, LYS68, and ASP304, forming hydrogen bonding and electrostatic interactions within the protein active pocket.

Murrayanine displayed a moderate docking score of −7.3 kcal/mol. Its 2D interaction profile indicated involvement of ARG65, ASP304, ILE69, and LYS68, mainly through π-cation, π-anion, and hydrophobic interactions (Figure 4), while the 3D image supported its localization within the active region of the receptor (Figure 3). Even though its binding affinity was

lower than that of the carbazole alkaloids, the observed interactions suggest a reasonable degree of inhibitory potential.

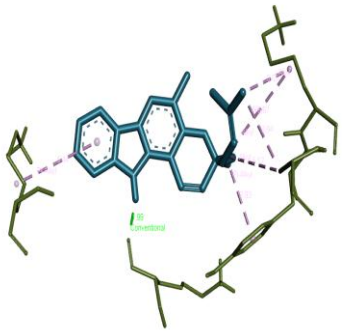

Figure 5: 3D interaction visualization of Mahanimbine with PBP2a. The carbazole core of the compound interacts through hydrophobic and π-alkyl interactions, stabilizing the ligand within the binding site.

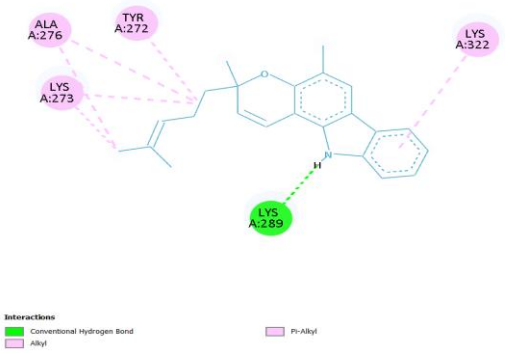

Figure 6: 2D interaction map of Mahanimbine with the target protein. The ligand forms a conventional hydrogen bond with LYS289 and hydrophobic contacts with residues ALA276, TYR272, and LYS273.

Mahanimbine exhibited the next highest binding affinity with a docking score of −8.6 kcal/mol. The 2D interaction diagram showed a conventional hydrogen bond with LYS289 along with alkyl and π-alkyl interactions involving ALA276, TYR272, LYS273, and LYS322 (Figure 6). The 3D interaction image further confirmed proper accommodation of the compound within the hydrophobic pocket of the protein (Figure 5). These findings indicate strong molecular compatibility of Mahanimbine with the binding site of PBP2a.

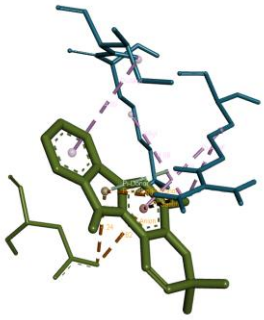

Figure 7: 3D interaction of Girinimbine with PBP2a. The visualization highlights π-π stacking and hydrophobic interactions between the aromatic rings of the ligand and residues located within the enzyme binding cavity.

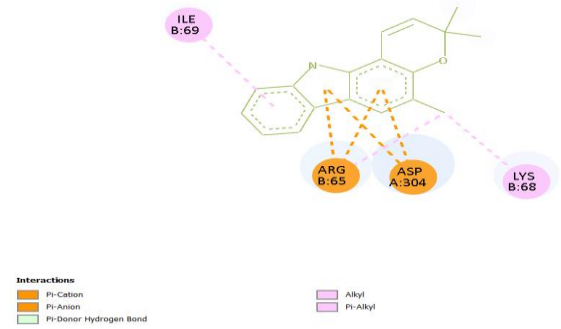

Figure 8: 2D interaction map of Girinimbine with the active site of PBP2a. The compound forms hydrogen bonding with ASP209 along with π-cation and π-sigma interactions with ARG110 and VAL174, suggesting stable ligand–protein interaction.

Girinimbine demonstrated a docking score of −8.5 kcal/mol, suggesting strong binding potential. Its interaction pattern revealed a conventional hydrogen bond with ASP209, π-cation interaction with ARG110, and π–π stacked / π-sigma interactions with PHE211 and VAL174, along with carbon hydrogen bond interactions involving ASN111 and ASN177 (Figures 7 and 8). This mixed interaction profile indicates stable anchorage of Girinimbine within the target pocket.

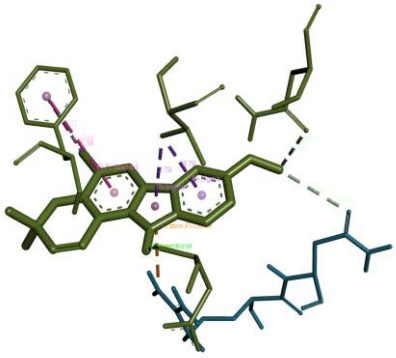

Figure 9: 3D binding interaction of Koenimbine within the active site of the PBP2a protein. The ligand is positioned within the hydrophobic pocket of the protein, showing multiple van der Waals and π-alkyl interactions, which enhance ligand accommodation in the catalytic region.

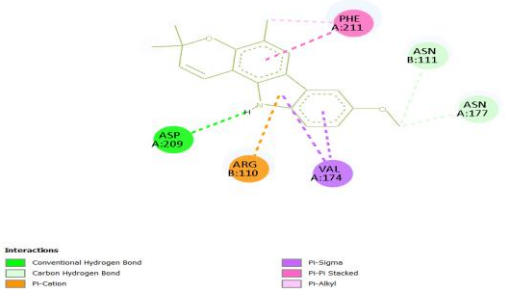

Figure 10: 2D interaction diagram of Koenimbine with Staphylococcus aureus penicillin-binding protein (PDB ID: 1VQQ). The figure illustrates hydrophobic interactions including π-alkyl and π-sigma interactions between Koenimbine and amino acid residues VAL217, TYR223, LEU190, and PRO370, contributing to ligand stabilization within the binding pocket.

Koenimbine showed a binding affinity of −8.4 kcal/mol. The 2D interaction map demonstrated predominantly hydrophobic interactions, including π-alkyl and π-sigma contacts with VAL217, TYR223, LEU190, and PRO370 (Figure 10). The corresponding 3D visualization also confirmed its snug fit within the hydrophobic region of the protein cavity (Figure 11). Although no hydrogen bond was observed, the multiple hydrophobic contacts appear to contribute substantially to ligand stabilization.

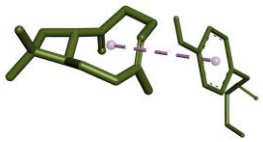

Figure 11: 3D docking conformation of (−)-Caryophyllene within the enzyme pocket. The ligand occupies the hydrophobic cavity of the protein but lacks strong hydrogen bonding interactions, explaining its relatively lower binding affinity.

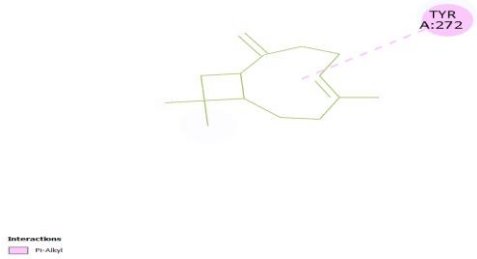

Figure 12: 2D interaction diagram of (−)-Caryophyllene with the PBP2a protein. The interaction is primarily mediated by hydrophobic π-alkyl interactions with TYR272, indicating weaker binding compared with other tested compounds.

Among all the compounds tested, (−)-Caryophyllene exhibited the lowest binding affinity with a docking score of −6.9 kcal/mol. The 2D interaction plot showed only a single π-alkyl interaction with TYR272 (Figure 9), and the 3D conformation confirmed a relatively limited interaction pattern within the active site (Figure 10). The absence of hydrogen bonding and fewer stabilizing interactions may explain its weaker binding compared to the other phytocompounds.

Compound	PubChem CID	Binding affinity (kcal/mol)	Important interacting residues
(+)-Murrayazoline CC1=CC2=C3C4=C1O[C@]5(CC[C@H]([C@@H]4C5)C(N3C6=CC=CC=C62)(C)C)C	21770913	−9.4	ARG65, ASP304, ILE69, LYS68
Mahanimbine CC1=CC2=C(C3=C1OC(C=C3)(C)CCC=C(C)C)NC4=CC=CC=C42	167963	−8.6	LYS289, ALA276, TYR272, LYS273, LYS322
Girinimbine CC1=CC2=C(C3=C1OC(C=C3)(C)C)NC4=CC=CC=C42	96943	−8.5	ASP209, ARG110, PHE211, VAL174, ASN111, ASN177
Koenimbine CC1=CC2=C(C3=C1OC(C=C3)(C)C)NC4=C2C=C(C=C4)OC	97487	−8.4	VAL217, TYR223, LEU190, PRO370
Murrayanine COC1=CC(=CC2=C1NC3=CC=CC=C32)C=O	96942	−7.3	ARG65, ASP304, ILE69, LYS68
(−)-Caryophyllene C/C/1=C\\CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C	5281515	−6.9	TYR272

Table 1: Docking binding energies (kcal/mol) and key interacting amino acid residues of Murraya koenigii phytocompounds with the penicillin-binding protein of Staphylococcus aureus (PDB ID: 1VQQ), indicating the predicted strength and stability of ligand–protein interactions.

The docking results show that all tested phytocompounds were able to bind with the target protein, but their binding strengths differed based on the number and type of interactions formed within the active site. Compounds with lower binding energy values and multiple hydrogen bond, electrostatic, and hydrophobic interactions showed better predicted inhibitory potential. Among them, (+)-Murrayazoline demonstrated the best interaction pattern and the lowest docking score, indicating the most stable complex. Mahanimbine, Girinimbine, and Koenimbine also showed strong and favorable binding, suggesting that these carbazole alkaloids may be the major contributors to the antimicrobial activity of Murraya koenigii. In contrast, (−)-Caryophyllene displayed weaker interaction and a higher docking score, indicating comparatively lower inhibitory potential. Overall, these findings support the possibility that the ethanolic extract of Murraya koenigii contains bioactive phytocompounds capable of interacting effectively with the penicillin-binding protein of Staphylococcus aureus, thereby supporting its potential antimicrobial activity.

Parameter	Mahanimbine	Girinimbine	Murrayanine	Koenimbine	(+)-Murrayazoline	(−)-Caryophyllene
MW (g/mol)	331.45	263.33	225.24	293.36	331.45	204.35
TPSA (Å²)	25.02	25.02	42.09	34.25	14.16	0
Consensus LogP	5.62	4.17	2.69	4.15	4.94	4.24
GI absorption	High	High	High	High	High	Low
BBB permeant	No	Yes	Yes	Yes	No	No
P-gp substrate	Yes	Yes	No	Yes	Yes	No
Lipinski violations	1	0	0	0	1	1
Solubility class	Poorly soluble	Moderately soluble	Soluble	Moderately soluble	Moderately soluble	Soluble
CYP inhibition profile	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4	CYP1A2, CYP2C19, CYP2D6	CYP1A2	CYP1A2, CYP2C19, CYP2C9, CYP2D6	CYP2D6	CYP2C19, CYP2C9
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55
Notable alerts	1 Brenk alert, 1 lead-likeness violation	1 lead-likeness violation	1 Brenk alert, 1 lead-likeness violation	1 lead-likeness violation	1 lead-likeness violation	1 Brenk alert, 2 lead-likeness violations

Table 2: Predicted ADMET and drug-likeness properties of selected phytocompounds from Murraya koenigii

The ADMET analysis indicated that the phytocompounds from Murraya koenigii generally possess favorable pharmacokinetic properties. All compounds showed acceptable molecular weights and high predicted gastrointestinal absorption, except (−)-caryophyllene which exhibited low absorption. Most compounds complied with Lipinski's rule of five, suggesting good drug-likeness. The predicted lipophilicity values were within an acceptable range, with Murrayanine showing the most balanced physicochemical profile. Several compounds demonstrated potential interactions with cytochrome P450 enzymes, indicating possible metabolic considerations. Overall, Murrayanine, Girinimbine, and (+)-Murrayazoline displayed comparatively better ADMET characteristics, suggesting their potential suitability as promising antimicrobial candidates

Parameter	Mahanimbine	Girinimbine	Murrayanine	Koenimbine	(+)-Murrayazoline	(−)-Caryophyllene
Hepatotoxicity	Inactive (0.63)	Inactive (0.63)	Inactive (0.63)	Inactive (0.64)	Inactive (0.80)	Inactive (0.80)
Neurotoxicity	Inactive (0.60)	Inactive (0.60)	Inactive (0.60)	Active (0.52)	Active (0.58)	Inactive (0.51)
Nephrotoxicity	Inactive (0.85)	Inactive (0.85)	Inactive (0.85)	Inactive (0.77)	Inactive (0.87)	Inactive (0.92)
Respiratory toxicity	Active (0.64)	Active (0.64)	Active (0.64)	Active (0.50)	Active (0.74)	Inactive (0.63)
Cardiotoxicity	Inactive (0.86)	Inactive (0.86)	Inactive (0.86)	Inactive (0.85)	Inactive (0.90)	Inactive (0.81)
Carcinogenicity	Inactive (0.68)	Inactive (0.68)	Inactive (0.68)	Active (0.50)	Inactive (0.68)	Inactive (0.70)
Immunotoxicity	Active (0.97)	Active (0.97)	Active (0.97)	Active (0.99)	Active (0.87)	Active (0.54)
Mutagenicity	Inactive (0.68)	Inactive (0.68)	Inactive (0.68)	Active (0.50)	Inactive (0.68)	Inactive (0.95)
Cytotoxicity	Inactive (0.85)	Inactive (0.85)	Inactive (0.85)	Inactive (0.75)	Inactive (0.72)	Inactive (0.75)
BBB-barrier	Active (0.93)	Active (0.93)	Active (0.93)	Active (0.87)	Active (0.95)	Active (0.97)
Ecotoxicity	Active (0.72)	Active (0.72)	Active (0.72)	Active (0.79)	Active (0.79)	Active (0.68)
Clinical toxicity	Inactive (0.64)	Inactive (0.64)	Inactive (0.64)	Inactive (0.56)	Inactive (0.57)	Inactive (0.73)
Nutritional toxicity	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

	(0.52)	(0.52)	(0.52)	(0.55)	(0.73)	(0.63)
GABA receptor (GABAR)	Active (0.50)	Active (0.50)	Active (0.50)	Inactive (0.61)	Active (0.51)	Inactive (0.59)
Pregnane X receptor (PXR)	Active (0.52)	Active (0.52)	Active (0.52)	Active (0.53)	Active (0.50)	Active (0.50)
CYP2C9 activity	Active (0.62)	Active (0.62)	Active (0.62)	Active (0.66)	Inactive (0.58)	Active (0.67)
CYP2C19 activity	Inactive (0.59)	Inactive (0.59)	Inactive (0.59)	Active (0.53)	Inactive (0.74)	Inactive (0.89)
CYP2D6 activity	Inactive (0.55)	Inactive (0.55)	Inactive (0.55)	Active (0.55)	Active (0.62)	Inactive (0.79)
CYP3A4 activity	Inactive (0.65)	Inactive (0.65)	Inactive (0.65)	Inactive (0.53)	Inactive (0.69)	Inactive (0.98)

Table 3: ProTox-II predicted toxicity profile of selected phytocompounds from Murraya koenigii

The ProTox-II toxicity prediction showed that most of the selected phytocompounds had a generally acceptable safety profile, as they were predicted to be non-hepatotoxic, non-nephrotoxic, non-cardiotoxic, and non-cytotoxic. However, immunotoxicity and blood–brain barrier permeability were predicted to be active for most compounds. Among the tested molecules, Koenimbine showed the least favorable toxicity pattern because it was additionally predicted to exhibit neurotoxicity, carcinogenicity, mutagenicity, and multiple CYP-related metabolic liabilities. In contrast, (+)-Murrayazoline and (−)-Caryophyllene showed comparatively safer predicted toxicity profiles, although some alerts related to respiratory toxicity, immunotoxicity, and metabolic interaction potential were still observed.

DISCUSSION

The present in silico study evaluated the antimicrobial potential and predicted safety profile of phytocompounds from Murraya koenigii against the penicillin-binding protein of Staphylococcus aureus using molecular docking, ADMET prediction, and toxicity analysis. The docking results demonstrated that several carbazole alkaloids present in Murraya koenigii exhibited strong binding affinity toward the selected bacterial target protein. These findings are consistent with previous studies reporting the antimicrobial potential of phytochemicals derived from this plant.(Cowan 1999),(Divyashri and Ramesh 2025),(Dineshkumar et al. 2010)

Among the compounds evaluated in the present study, (+)-Murrayazoline showed the strongest binding affinity with the target protein, forming stable interactions within the catalytic binding pocket. The presence of multiple hydrophobic and electrostatic interactions suggests a strong ligand–protein complex, indicating potential inhibitory activity against the bacterial enzyme. Previous phytochemical studies have shown that carbazole alkaloids from Murraya koenigii possess potent antimicrobial activity against various pathogenic microorganisms. Ningappa et al. reported that the biological activity of carbazole alkaloids isolated from Murraya koenigii contributes significantly to its antimicrobial properties due to their ability to interact with bacterial enzymes and disrupt microbial metabolic pathways.(Ningappa et al. 2008)

Mahanimbine also demonstrated strong binding affinity with the target protein in the present docking analysis. Experimental studies have previously reported the antibacterial activity of this compound. Rahman et al. demonstrated that extracts containing carbazole alkaloids such as mahanimbine exhibited inhibitory effects against several bacterial pathogens including Staphylococcus aureus and Escherichia coli.(Rahman and Gray 2005) The strong binding interaction observed in the present docking study supports these experimental findings and suggests that mahanimbine may contribute to the antimicrobial activity of Murraya koenigii by interfering with bacterial cell wall synthesis.

Similarly, Girinimbine showed significant docking interactions with the penicillin-binding protein. The interaction analysis revealed hydrogen bonding and hydrophobic contacts within the protein binding pocket, suggesting stable ligand accommodation. Previous studies have also demonstrated the biological activities of girinimbine. Kumar et al. reported that girinimbine possesses antimicrobial and anti-inflammatory properties due to its ability to inhibit microbial growth and modulate inflammatory signaling pathways.(Kumar and Navaratnam 2013) The results of the present docking study support the antimicrobial potential of girinimbine by demonstrating favorable interactions with an essential bacterial enzyme.

Koenimbine also exhibited strong binding interactions with the bacterial protein. However, toxicity prediction results suggested that this compound may have additional toxicity liabilities compared with other phytochemicals evaluated in this study. Specifically, the ProTox analysis indicated possible neurotoxicity, mutagenicity, and carcinogenicity alerts. Previous studies have highlighted that certain carbazole alkaloids may exhibit biological activity alongside potential toxicity risks depending on their structural characteristics. Gupta et al. emphasized that while carbazole derivatives show promising pharmacological activities, their safety profile should be carefully evaluated before considering them for therapeutic development.(Gupta et al. 2011)

Among the compounds evaluated, Murrayanine showed moderate docking affinity but demonstrated the most balanced pharmacokinetic profile in the ADMET analysis. The compound exhibited acceptable molecular weight, moderate lipophilicity, good gastrointestinal absorption, and minimal predicted toxicity alerts. These properties are important for drug development because compounds with balanced physicochemical characteristics generally exhibit improved pharmacokinetic behavior and bioavailability. Cowan reported that plant-derived antimicrobial compounds often possess favorable safety profiles and improved biological compatibility compared with synthetic antimicrobial agents.(Cowan 1999), (Krishnan et al. 2025) The ADMET profile observed for murrayanine in the present study supports this observation.

In contrast, (−)-Caryophyllene demonstrated comparatively weaker docking interactions with the target protein, although toxicity prediction indicated a relatively safer profile with minimal organ toxicity alerts. Previous studies have also reported that caryophyllene possesses moderate antimicrobial activity but exhibits strong anti-inflammatory and antioxidant effects. Ghasemzadeh et al. reported that caryophyllene-containing plant extracts demonstrate antimicrobial and antioxidant properties while maintaining favorable safety characteristics.(Ghasemzadeh et al. 2010) Thus, although the

docking score observed in the present study suggests relatively weaker antimicrobial binding, the favorable toxicity profile of caryophyllene indicates that it may still contribute to the biological activity of the plant extract.

The ADMET analysis performed in the present study further supported the potential therapeutic relevance of these phytocompounds. Most of the compounds demonstrated high predicted gastrointestinal absorption and acceptable drug-likeness parameters, suggesting potential oral bioavailability. According to Lipinski et al., molecular weight, lipophilicity, and hydrogen bonding characteristics are critical determinants of oral drug absorption.(Lipinski et al. 2012) The majority of the phytochemicals evaluated in the present study satisfied these criteria, indicating promising pharmacokinetic properties.

The toxicity prediction results also indicated that most compounds were predicted to be non-hepatotoxic, non-nephrotoxic, and non-cardiotoxic. Such findings are important in early drug discovery because computational toxicity assessment allows identification of compounds with favorable safety characteristics before experimental validation. Banerjee et al. emphasized that in silico toxicity prediction tools such as ProTox are valuable for early evaluation of chemical safety in drug discovery studies.(Banerjee et al. 2018)

Overall, the combined molecular docking, ADMET, and toxicity analyses suggest that phytochemicals from Murraya koenigii, particularly (+)-Murrayazoline, Mahanimbine, and Girinimbine, exhibit promising antimicrobial potential against Staphylococcus aureus. Among these compounds, (+)-Murrayazoline demonstrated the strongest docking interaction, whereas murrayanine exhibited the most balanced pharmacokinetic profile. These findings support the growing body of literature highlighting the therapeutic potential of carbazole alkaloids derived from Murraya koenigii.

A major strength of the study is the combined computational approach used to evaluate both the binding affinity and safety profile of the compounds. However, the study is limited to in silico analysis and does not include experimental validation. Molecular docking predictions may not completely represent biological interactions in real physiological conditions. Therefore, future studies should include in vitro antimicrobial testing, in vivo toxicity studies, and pharmacological investigations to confirm the predicted activity and further explore the therapeutic potential of these phytocompounds.

CONCLUSION

The present study demonstrated that phytocompounds derived from Murraya koenigii exhibit promising antimicrobial potential against the penicillin-binding protein of Staphylococcus aureus based on molecular docking analysis. Among the evaluated compounds, (+)-Murrayazoline, Mahanimbine, and Girinimbine showed stronger binding interactions with the target protein, suggesting their possible role in inhibiting bacterial activity. The ADMET and ProTox-II predictions further indicated generally acceptable pharmacokinetic and safety profiles for most of the compounds. These findings support the potential of Murraya koenigii phytochemicals as candidates for antimicrobial drug development. However, further in vitro and in vivo studies are necessary to validate these computational predictions and confirm their therapeutic applicability

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