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Original Research Article

COMPARATIVE MOLECULAR DOCKING AND ADMET PREDICTION OF SELECTED PLANT ALKALOIDS AS POTENTIAL INHIBITORS OF *Staphylococcus aureus* NorA EFFLUX PUMP

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ABSTRACT

Efflux pumps are a major mechanism of multidrug resistance (MDR) in *Staphylococcus aureus*. These pumps actively extrude antibiotics, thereby reducing their efficacy. Plants are becoming increasingly recognized as very important sources of medicines due to their diverse phytochemicals, including alkaloids. Alkaloids and other phytochemicals are investigated as potential efflux pump inhibitors (EPIs). EPIs can be used to potentiate the activity of antibiotics via inhibition of the efflux pump through physical blockade of the NorA's anchoring site for substrates (such as antibiotics), thereby preventing the efflux of the administered antibiotics. Currently, there is no known clinically approved efflux pump inhibitor. In this study, ten alkaloids were selected to evaluate their potential as efflux pump inhibitors (EPIs). Docking was performed using AutoDock Vina. Binding affinities among the ten compounds ranged from -8.1 to - 10.8 kcal/mol. Reserpine (a well-established reference inhibitor of *S. aureus* efflux pump), used as a control, exhibited a binding affinity of -9.5 kcal/mol. Three ligands, including toxiferine (the most active alkaloid; -10.8kcal/mol), exhibited a higher binding affinity than reserpine. Docking analysis was guided by key functional residues identified via supervised molecular dynamics (SuMD) of ciprofloxacin to the primary pocket of *S. aureus* NorA. Two-dimensional interaction profiling revealed that high-affinity binding was associated with extensive interaction coverage and formation of strong, specific non-covalent interactions with key functional residues of the NorA substrate-binding pocket. Consequently, toxiferine interacted with all seven of the SuMD-identified hotspot residues, with some of these interactions being conspicuously strong compared with other alkaloids. Conversely, piperine (the least active alkaloid; -8.1 kcal/mol) interacted with only one of the SuMD hotspot residues. ADMET analysis was performed using SwissADME to assess the pharmacokinetic properties of all the tested ligands. The alkaloids exhibited a spectrum of pharmacokinetic properties. Physicochemical and drug-likeness profiling of toxiferine revealed that it violated Lipinski's molecular weight threshold (500 g/mol) and showed very low cLogP (-1.22), which suggests low passive absorption. Remarkably, it maintained low CYP450-mediated metabolic liability. Overall, it shows potential as an inhibitor or lead scaffold for the design of novel EPIs. *In vitro* and *in vivo* assays are required to validate the efficacy and safety of toxiferine and other tested alkaloids.

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Staphylococcus aureus, alkaloids, multi-drug resistance, efflux pump, molecular docking, ADMET

INTRODUCTION

Multidrug resistance (MDR) is a pressing global health concern, driven in part by microbial mechanisms that reduce drug efficacy [1]. Among these, efflux pumps actively expel diverse antimicrobial agents, lowering their intracellular

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concentrations and promoting resistance [2, 11]. Efflux pumps, as the name implies, are channels through which microbes, especially bacteria, actively transport out intracellular substances, including antibiotics. The efflux of these antimicrobial agents significantly reduces the intracellular level of these drugs to a point where their concentration is not enough to exert their toxicity on the bacteria [2, 11]. *Staphylococcus aureus* uses efflux pumps, especially NorA type (among other types), to actively rid itself of antibiotics [3. NorA is a member of the Major Facilitator Superfamily (MFS) of efflux pumps. It is a 12-helix transmembrane protein consisting of 388 amino acids [4]. It is capable of expelling conventional antibiotics such as fluoroquinolones (norfloxacin, ciprofloxacin, etc.) out of the cell [2]. Overexpression of the NorA pump is frequently implicated in clinical isolates of *S. aureus* [2]. The activity of the NorA efflux pump significantly increases the minimum inhibitory concentration (MIC) of antibiotics [3].

Recently, advances in structural biology facilitated the elucidation of the crystal structure of the NorA efflux pump. PDB entry 7LO8 shows NorA in complex with antigen-binding fragments (Fabs) that inhibit NorA by inserting a loop into the substrate-binding pocket [4]. This structural information and previous studies allow a detailed understanding of the key residues and interaction modes that are critical for enhanced inhibition of the NorA efflux pump. Glu222, Asp307, and Arg310 have been identified as critical residues in the binding and inhibition of *S. aureus* NorA efflux pump. Glu222 and Asp307 act as key anchoring points for substrates and inhibitors [4]. The ability of a compound to establish hydrogen bonding with Arg310 is an important indicator of a potent EPI [3]. Therefore, competitive inhibitors bind to these amino acids and occupy the substrate-binding site, thereby blocking access of substrate, including antibiotics [3]. Currently, there is no clinically-approved drug for the inhibition of efflux pumps [5,6].

Plants are increasingly recognized as valuable sources of bioactive compounds with therapeutic potential [7]. This is because natural products are safer for consumption [8]. Plant-derived products such as alkaloids have medicinal properties including antimicrobial, anti-cancer, antioxidant and antipsychotic [9]. The term ‘alkaloid’ (meaning alkali-like) reflects their basic chemical nature, which enables them to exist either as organic acid salts or as free bases. Their names typically feature a fixed ‘-ine’ suffix denoting their amino origin, combined with a variable prefix [10]. Reserpine, an alkaloid, has been tested in the past as a potential EPI. It demonstrated strong inhibition of NorA *in vitro*, but its adoption as a clinical drug attracted enormous scrutiny because of its toxicity profile [2, 11]. However, it remains a widely used reference inhibitor of NorA [3].

Therefore, comparative docking of selected plant alkaloids against the NorA efflux pump promises insight into possible EPIs. This study will help prioritize candidate compounds for further in vitro/in vivo investigation by analyzing their binding affinities, interaction with key residues, interaction (bond) type, and spatial orientation in the substrate-binding pocket.

MATERIALS AND METHODS

Ligand Retrieval and Preparation

The 3D conformation of the ligands was retrieved and prepared as follows. All compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) [12]. For each compound, information about the major plant origin or the plant part(s) from which they are predominantly derived are available on PubChem. Reserpine (PubChem CID: 5770), berberine (PubChem CID: 2353), piperine (PubChem CID: 638024), sanguinarine (PubChem CID: 5154), chelerythrine (PubChem CID: 2703), tetrandrine (PubChem CID: 73078), toxiferine (PubChem CID: 5281411), palmatine ((PubChem CID: 19009), deserpidine ((PubChem CID: 8550), rescinnamine ((PubChem CID: 5280954) were download in SDF format. The ligands were imported into Avogadro (v. 1.2.0) for energy minimization via the MMFF94 force field to devoid them of any geometrical strain. After energy minimization, the ligands were imported into AutoDockTools (ADT) (v. 1.5.7) for the computation of Gasteiger charges as well as the definition of torsion of torsion bonds. After these, the ligands were saved in PDBQT format in preparation for docking. Reserpine was selected as a positive control because of its well-established inhibitory activity against the NorA efflux pump (Zimmermann *et al*., 2019). The 2D structures and natural sources of all the ligands are represented in **Table 1.**

Protein Retrieval and Preparation

The NorA efflux pump protein crystal structure of *Staphylococcus aureus* was obtained from the Protein Data Bank (PDB ID: 7LO8). The structure was processed in BIOVIA Discovery Studio 2025 (Dassault Systèmes) for initial cleaning. Following this step, the protein was exported and prepared in AutoDockTools, where polar hydrogens were introduced, Gasteiger charges were assigned, and the final structure was converted to PDBQT format for docking.

Grid Generation and Molecular Docking

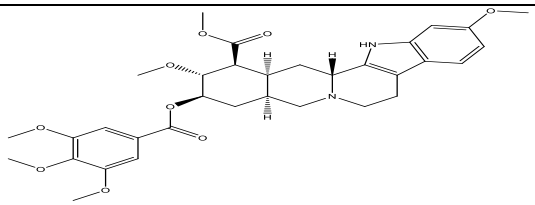
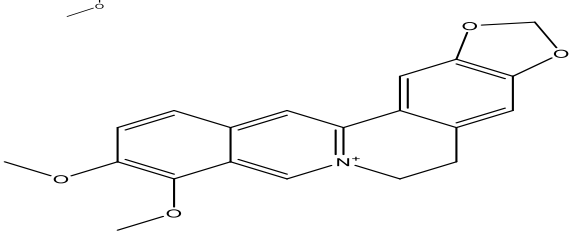
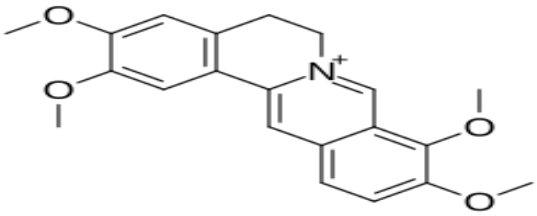
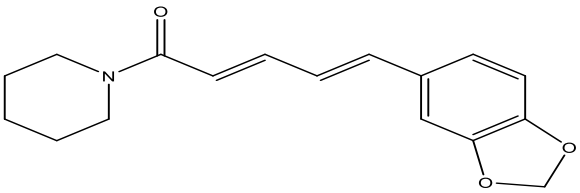
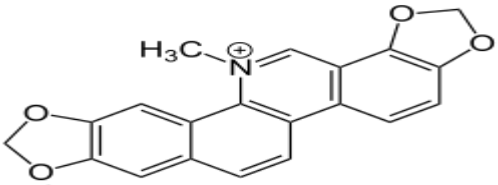
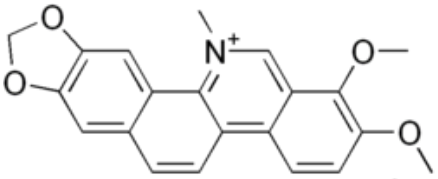
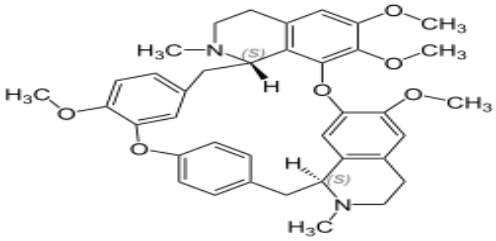
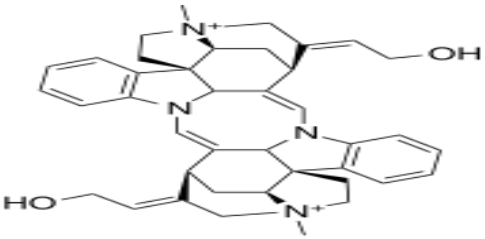
The grid for docking was defined to cover the central binding cavity of the *S. aureus* NorA efflux pump. The grid box was centered on the coordinates of the binding cavity (center_x = 138.033, center_y = 136.349 and center_y = 156.979; size_x = 40, size_y = 40 and size_z = 40).

Molecular docking was performed using AutoDock Vina [13], an open-source docking tool designed to predict the binding orientation and affinity of small molecules (ligands) to a specific target protein (receptor).

ADMET Profiling

The pharmacokinetic properties of all the tested alkaloids will be evaluated using SwissADME (a web-based tool) (http://www.swissadme.ch) [14]. The canonical SMILES of the ligands were retrieved from PubChem. Key pharmacokinetic parameters such as solubility and lipophilicity, drug-likeness, especially Lipinski’s Rule of Five, will be assessed.

Table 1. 2D structure, molecular weight and plant origin of the ligands

Alkaloid	2D Structure	Molecular Weight (g/mol)
Reserpine		608.68
Berberine		336.4
Palmatine		352.4
Piperine		285.34
Sanguinarine		332.3
Chelerythrine		348.4
Tetrandrine		622.7
Toxiferine		614.8

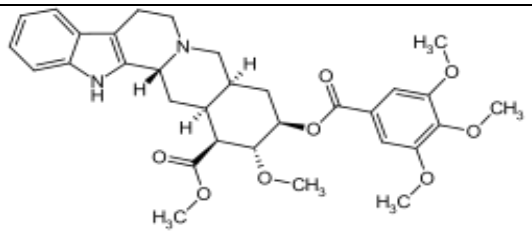
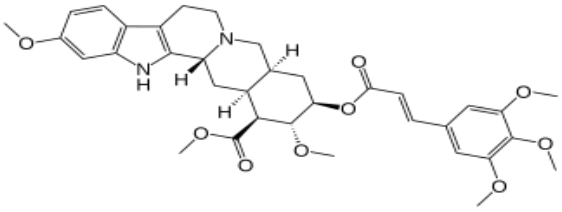
Deserpidine		578.7
Rescinnamine		634.7

Table 2. Summary of the binding affinity and interaction profile of the alkaloids

Alkaloid	Docking Score (kcal/mol)	Interacting Hotspot Residues (I23, F140, E222, Y225, I244, F303, R310)	No. of Contacted SuMD Hotspot Residues
Reserpine	-9.5	F140, E222, I244, F303, and *R310.	5
Toxiferine	-10.8	I23, F140, E222, Y225, I244, F303, and R310.	7
Sanguinarine	-10.5	F140, E222, and *R310.	3
Chelerythrine	-9.9	F140, E222, and *R310.	3
Deserpidine	-9.5	I23, F140, E222, Y225, I244, F303, and R310.	7
Tetrandrine	-9.5	I23, F140, E222, I244, F303, and R310.	6
Rescinnamine	-9.4	I23, F140, E222, F303, and *R310.	5
Berberine	-9.2	F140 and R310.	2
Palmatine	-8.6	F140 and R310.	2
Piperine	-8.1	F140	1

**Conventional Hydrogen Bond*

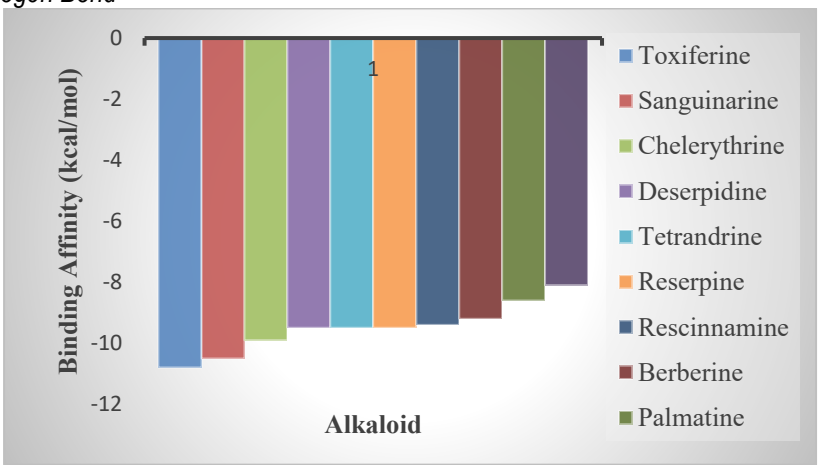


Figure 1. Binding Affinity (kcal/mol) of Alkaloids to the *S. aureus* NorA Efflux Pump.

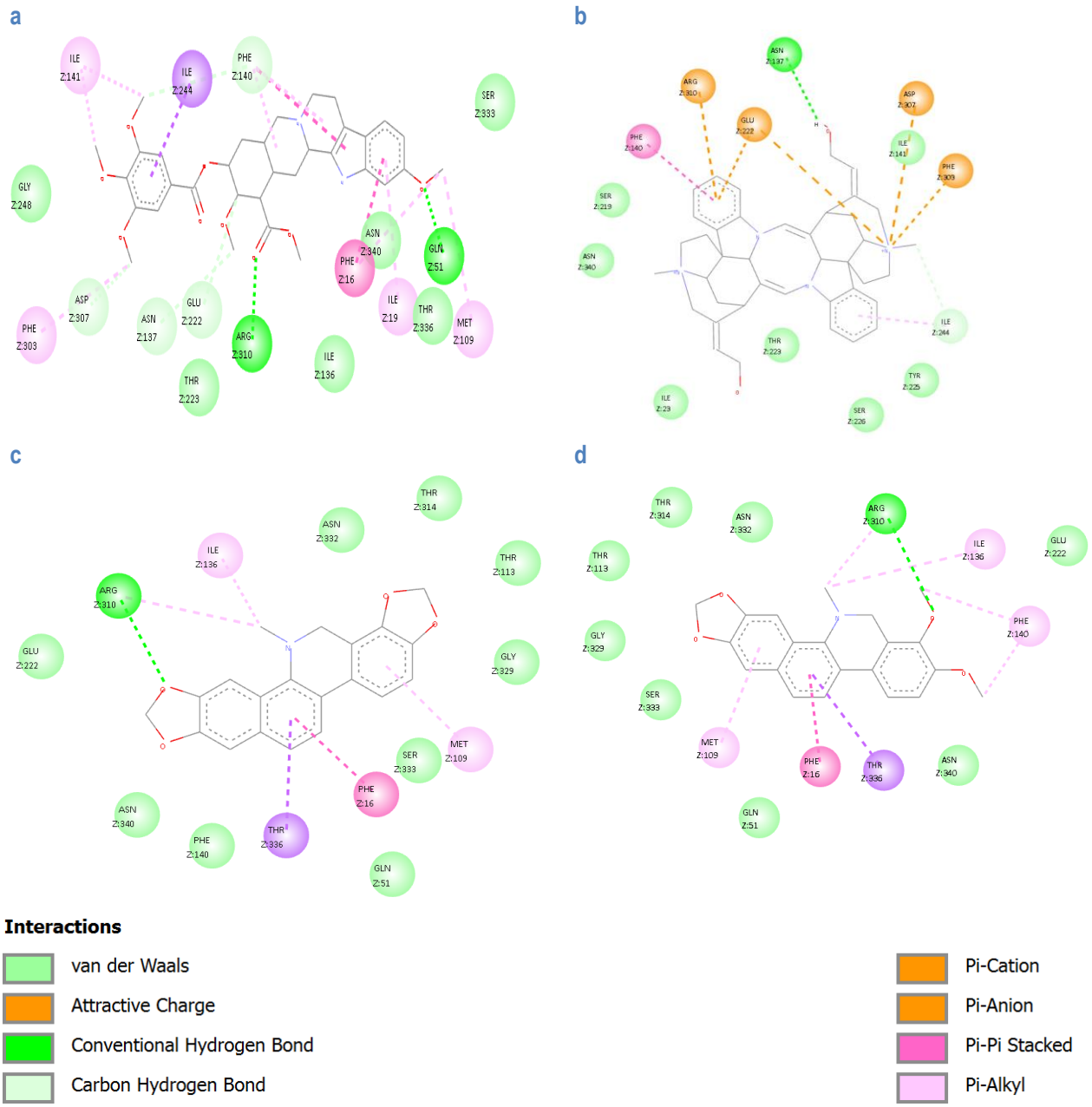


Figure 2. 2D interaction profiles of highest-affinity compounds of NorA. (a) Reserpine (control); (b) Toxiferine (highest binding score); (c) Sanguinarine; (d) Chelerythrine.

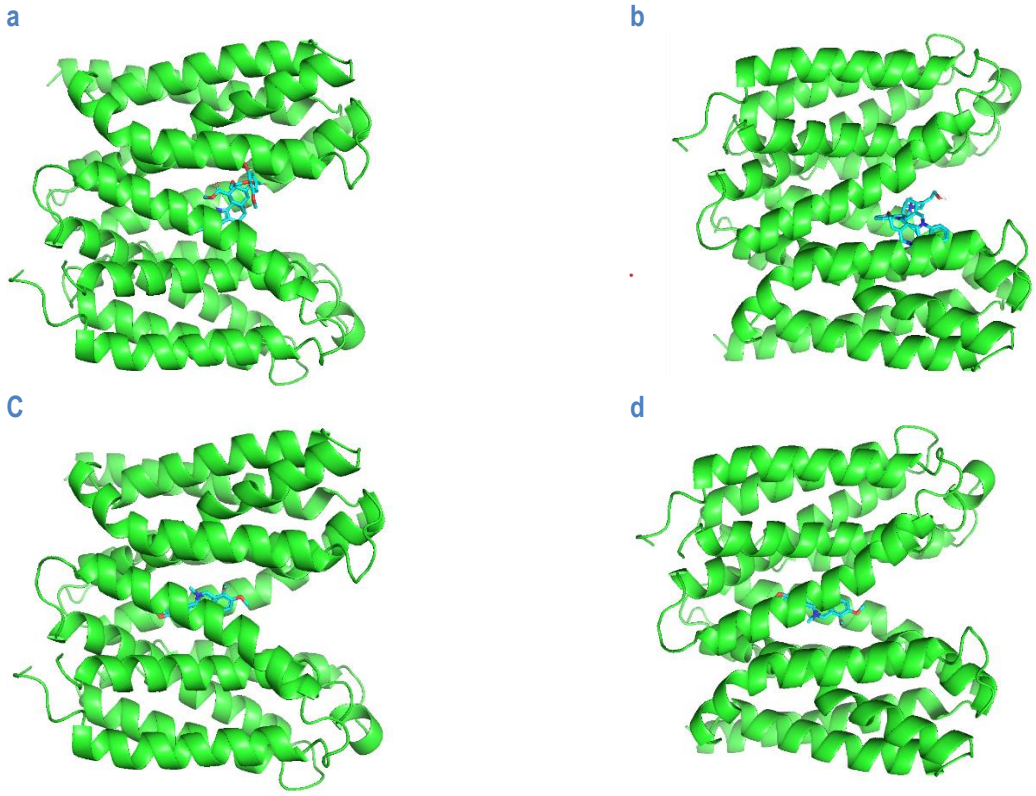


Figure 3. Ribbon representation of ligands bound to the orthosteric site of *S. aureus* NorA efflux pump. (a) Reserpine; (b) Toxiferine; (c) Sanguinarine; (d) Chelerythrine.

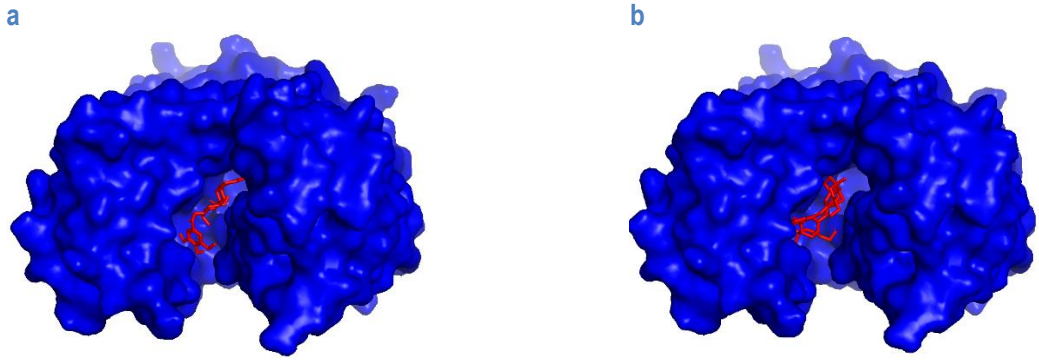


Figure 4. 3D Surface Representation of the Highest Binding Ligand (Toxiferine) and the Control Ligand (Reserpine) in the Orthosteric Site of *S. aureus* Efflux Pump. (a) Reserpine (b) Toxiferine.

Table 3. Pharmacokinetic Properties of Selected Alkaloids Predicted by SwissADME

Alkaloid	MW (g/mol)	cLogP	No. of HA	No. of HD	No. of RB	CYP 450 Inhibition	Lipinski's (Ro5) – Violation
Reserpine	608.68	3.68	10	1	10	No	Yes; 2 Violations: MW>500, NorO>10
Toxiferine	614.8	-1.22	2	2	2	No	Yes; 1 Violation: MW>500
Sanguinarine	332.3	2.88	4	0	0	Yes: CYP1A2, CYP2C19	No
Chelerythrine	348.4	3.02	4	0	2	Yes: CYP1A2, CYP2C19, CYP2C29, CYP3A4	No

Deserpidine	578.65	3.47	9	1	9	Yes: CYP2D6, CYP3A4	Yes; 1 Violation: MW>500
Tetrandrine	622.75	5.49	8	0	4	No	Yes; 1 Violation: MW>500
Rescinnamine	634.72	3.91	10	1	11	No	Yes; 2 Violations: MW>500, NorO>10
Berberine	336.36	2.53	4	0	2	Yes: CYP1A2, CYP2D6, CYP3A4	No
Palmatine	352.40	2.64	4	0	4	Yes: CYP2D6, CYP3A4	No
Piperine	285.34	3.03	3	0	4	Yes: CYP1A2, CYP2C19, CYP2C29	No

Data Analysis

In this study, docking outcomes will be assessed based on binding affinity and capacity to form strong non-covalent interactions with the key residues of the substrate-binding pocket.

RESULTS

Medicinal plants are valuable reservoirs of bioactive compounds that continue to drive drug discovery and development. Among their phytoconstituents, **alkaloids** exhibit wide-ranging pharmacological activities, including antimicrobial, anticancer, antioxidant, and neuroprotective effects [15].

Molecular docking of ten selected plant alkaloids against the *S. aureus* NorA efflux pump was performed using AutoDock Vina [13]. The binding affinities ranged from -8.1 to -10.8 kcal/mol. In docking studies, more negative numerical values indicate a stronger binding affinity [16]. Based on a previous study using supervised molecular dynamics (SuMD) by [17], the dominant cluster of ciprofloxacin is the NorA's primary (orthosteric) site, where ciprofloxacin mostly establishes contacts with Ile23, Phe140, Glu222, Tyr225, Ile244, Arg310. Accordingly, the docking results presented in **Table 2** were interpreted and justified with respect to interactions with these key residues.

Two-dimensional (2D) interaction profiles (**Figure 2**) were generated to comprehensively illustrate the binding interactions of ligands exhibiting stronger binding affinities than reserpine, highlighting their interactions with amino acids necessary for high-affinity binding to the orthosteric pocket of the *S. aureus* efflux pump. The substrate-binding pocket of *S. aureus* NorA comprised mainly of hydrophobic residues (~65%) and aromatic residues arranged in a manner that facilitates its interaction with a broad spectrum of substrates, including various antibiotics [23]. Some of the aromatic residues are Phe16, Phe140, Phe303, and Phe306 [23]. Conserved amino acids such as Asp307 and Glu222 have been identified as crucial residues for the recognition of substrate and the translocation of protons. NorA, a protein comprised of 12 – transmembrane (TM) helices, has a conspicuously large hydrophobic substrate-binding cleft that is structurally supported by eight transmembrane helices [24]. The pocket is lined by non-polar residues such as Val44, Phe47, Gln51, Phe140, Ile244, Gly248, and Phe303, all of which are conserved across efflux pumps in the major facilitator superfamily (MFS) [24]. [23], in a cryo-EM experiment involving NorA and Fab (fragment antigen-binding), identified four ionizable residues that may be crucial for substrate anchoring and proton translocation: Arg98 (TM4), Glu222 (TM7), Asp307(TM10), and Arg310(TM10).

Ribbon representations (**Figure 3**) were generated for ligands exhibiting stronger binding affinities than reserpine to highlight their spatial orientation in the primary binding pocket of *S. aureus* NorA efflux pump.

To further highlight the occupancy and spatial orientation of the ligand in the primary pocket of the NorA efflux pump, a three-dimensional surface representation (**Figure 4**) was generated for the top-scoring ligand and the control ligand.

The SwissADME platform was used to evaluate the oral bioavailability, potential metabolic liability and overall drug-likeness of the ten alkaloid ligands. **Table 3** summarizes the pharmacokinetic properties of the ligands, facilitating their direct comparison as potential efflux pump inhibitors.

DISCUSSION

Docking results indicate that the alkaloids share the same residues as ciprofloxacin in the substrate-binding pocket of *S.aureus* NorA efflux pump. Therefore, alkaloids can be used to potentiate the antimicrobial effects of conventional antibiotics through competitive inhibition. In other words, alkaloids can displace antibiotics by competitively binding to residues required for substrate binding, thereby physically blocking access of the antibiotics [18].

Among the tested alkaloids, toxiferine showed the strongest binding affinity (−10.8 kcal/mol) and contacted all seven SuMD hotspot residues, outperforming the reference inhibitor reserpine (−9.5 kcal/mol). The binding affinity of reserpine is consistent with a previous docking study reporting its interaction with the *S. aureus* NorA efflux pump at −9.4

kcal/mol [5]. The marginal difference of -0.1 kcal/mol may be attributed to differences in docking protocol, including protein and ligand preparation.

Deserpidine, like toxiferine, established contact with all the hotspot residues but with slightly weaker affinity. Sanguarine and chelerythrine exhibited very strong binding affinity compared to reserpine. Notably, only piperine failed to establish an interaction with Arg310. As earlier stated, contact with Arg310, especially through a strong non-covalent bond such as a hydrogen bonding interaction, is an important indicator of a potent inhibitor of the NorA efflux pump [19. Piperine showed inhibitory activity against efflux pumps by reducing the MIC of conventional antibiotics [20,21]. Similarly, berberine and palmatine reduced the MIC of ciprofloxacin on *S. aureus* [28]. Reserpine, berberine and piperine have shown suppressive potentials against NorA, MexXY-OprM, MdeA, and Rv1258c efflux pumps [22]. Structurally, sanguinarine is related to berberine, and sanguinarine has strong antibacterial activity [10]. Significantly, all the ligands established interaction with Phe140 (an aromatic residue), which suggests that it may play a crucial role in anchoring substrates [23].

The high-affinity binding exhibited by these ligands in **Figure 2** is directly related to their ability to form strong, specific interactions with the key residues. The strength of bonding is largely determined by the quantity and quality of the molecular interactions. Key favourable interactions include Conventional Hydrogen Bonds (strong, directional**),** Ionic/Charge Interactions (very strong), and Pi-Pi/Cation/Anion/Alkyl interactions (strong, hydrophobic/electrostatic). Toxiferine (Figure 2b) performed better than other compounds because it engaged favourably with most of the key residues, including Asp307 (which is crucial for anchoring). Asp307 and Glu222 are acidic residues that form a negatively charged patch, which is important for attracting positively charged ligands [23]. Mutation of these residues repealed the resistance of MRSA to norfloxacin. Toxiferine engaged with these residues via very strong non-covalent bonds, such as attractive charge, pi-cation/anion. Salt bridges are a form of attractive charge, which are very strong non-covalent bonds. Notably, Phe303, a crucial (hotspot) residue, engaged with toxiferine via attractive charge interaction. Reserpine (**Figure 2a)** engaged with these residues (Asp307 and Glu222) with much weaker bonds. Consequently, it exhibited low binding affinity compared to toxiferine. Another important point to note is that their interaction with Arg310 via hydrogen bonding (a strong, directional bond) may have compensated for its weak interactions with other important residues [19]. Sanguinarine (Figure 2c) and chelerythrine (Figure 2d) did not engage with Asp307; however, they engaged with Arg310 via a conventional hydrogen bond. Overall, the high-affinity binding of toxiferine compared to reserpine and the other tested compounds can be attributed to its ability to engage all the crucial residues and the presence of a spectrum of strong, exclusive interactions, including hydrophobic contacts.

The results of pharmacokinetic profiling reveal a spectrum of drug-likeness among the alkaloids. Several tested alkaloids (reserpine, toxiferine, deserpidine, tetrandrine, rescinnamine) exceed the 500 Da molecular-weight drug-likeness threshold and are therefore at higher risk of poor passive permeability and oral absorption [25]. Although toxiferine shows the strongest binding affinity to NorA, its physicochemical profile indicates one Lipinski violation (MW > 500 Da) and a low cLogP (−1.22), suggesting poor passive permeability and possible bioavailability limitations despite acceptable hydrogen-bonding and low rotatable-bond counts [25,26]. Toxiferine is very hydrophilic and may require special formulation techniques or a transport-based strategy for oral absorption. However, toxiferine does not exhibit a potential risk of drug-drug interactions (a form of metabolic liability). This is in contrast with sanguinarine, berberine, palmatine, piperine, derspidine, and especially chelerythrine, which inhibit multiple isoforms of CYP 450 enzymes [27].

Compounds with high molecular flexibility (rotatable-bond counts), especially rescinnamine and reserpine, further increase the likelihood of reduced oral bioavailability according to Veber's drug-likeness criteria [26]. The cLogP of 5.49 for tetrandrine suggests low water-solubility and formulation challenges.

CONCLUSION

This study has successfully elucidated the inhibitory potential of alkaloids against the *S. aureus* NorA efflux pump. The docking analysis was essentially guided by functional key residues identified via supervised molecular dynamics (SuMD). The tested alkaloids, especially toxiferine, engaged with key functional residues in the orthosteric pocket of NorA. Interaction with these residues required for the anchoring of antibiotics such as ciprofloxacin is consistent with competitive inhibition. Toxiferine outperformed reserpine (reference inhibitor) by interacting with a broad spectrum of the key functional residues, and via strong and specific molecular interactions, while maintaining a low CYP-mediated metabolic liability. Remarkably, deserpidine engaged all seven key functional residues of SuMD but with much weaker affinity than toxiferine. Sanguinarine and chelerythrine exhibited a stronger binding affinity than reserpine but engaged with fewer key residues.

Toxiferine's molecular weight (>500) and low cLogP of -1.22 may limit passive absorption, high binding affinity and very favourable interaction profile identify it and its structurally related alkaloids as potential inhibitors or scaffold for design of novel efflux pump inhibitors. However, *in vitro and in vivo* assays are required to evaluate the efficacy and safety of toxiferine and the other tested alkaloids.

AUTHORS' CONTRIBUTION

DCI is the sole author of the manuscript.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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