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Research Article

Antimicrobial Potential of *Sphaeranthus indicus* Against *Staphylococcus aureus*: A Computational Approach

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ABSTRACT

Sphaeranthus indicus is one of the multipurpose medicinal plants widely used for antimicrobial, wound-healing, anti-arthritics, immunostimulant, immunomodulatory, neuroleptic, etc., activities. Computer-aided drug discovery/design (CADD) methods have been developed to identify promising compounds with advantages over complexity, cost, time consumption, and risk. They may lead to their development as drugs. This study aims to *evaluate the antimicrobial potential of phytochemicals from S. indicus through Molecular docking and ADMET prediction*. In this study, 54 bioactive compounds from *S. indicus* were tested against four bacterial target proteins tyrosyl tRNA synthetase, Dihydrofolate reductase, Gyrase B and sortase A of *Staphylococcus aureus* to determine the potential antimicrobial activity of *S. indicus*. This study is investigated with the help of molecular docking study and ADMET prediction method. About 14 compounds were found as potential inhibitors of *S. aureus* by inhibiting either one or four target proteins. These compounds were found to be safe and have good ADMET properties and showed promising potentials that may lead to their development as drugs target against *S. aureus*.

Keywords: *Sphaeranthus indicus,* Molecular docking, ADMET, Antibacterial, *Staphylococcus aureus, In-silico* drug discovery.

INTRODUCTION

Sphaeranthus indicus, commonly known as "*Gorakhmundi*" and "East Indian Globe Thistle" is one of the multipurpose medicinal plants used in *Ayurvedic* system of medicine and folk medicine. It has been widely used as an antimicrobial,[1,2] wound-healing, anti-arthritics, immunostimulant, immunomodulatory, and neuroleptic activities.[2] Drug discovery entails a complex, costly, time-consuming, and risky process. Various extracts of this plant, including ethanol, methanol, and aqueous extracts, have shown significant inhibitory effects against multiple bacterial and fungal pathogens. Research indicates that its antimicrobial potential is attributed to bioactive compounds such as flavonoids, glycosides, terpenoids, and essential oils, which disrupt microbial cell walls and inhibit growth.

Studies have demonstrated that *S. indicus* is effective against gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*, as well as gram-negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa*. It also exhibits antifungal activity[2] against *Candida albicans*. These findings suggest that *S. indicus* could be a promising source of natural antimicrobial agents against the *S. aureus*.

S. aureus is a gram-positive bacterium commonly found on the skin and mucous membranes but can cause serious infections if it enters internal tissues or the bloodstream.[3-6] The rise of multi-drug-resistant strains, especially MRSA, poses a significant challenge in treatment due to resistance to beta-lactam antibiotics. *S. aureus*[7-10] is responsible for a wide range of infections, including skin infections, pneumonia, and endocarditis. The bacteria evade immune responses through mechanisms like capsule formation and toxin production. Treatment depends on antibiotic susceptibility, with penicillin used for MSSA and vancomycin for MRSA infections.[10,11]

Computer-aided drug discovery/design (CADD) methods such as molecular docking and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction[12,13] have been developed to identify the promising compounds that may lead to their development as drugs.

MATERIAL AND METHOD

The library of 54 phytochemicals from S. indicus were prepared and used for this study. In this study, molecular docking[14,15] and ADMET prediction[13,16] were conducted to predict the bioactive compound from *S. indicus* has inhibitory potential against microorganisms.

Methodology

- Protein preparation (4 Target Protein from *S. aureus*)
- Ligand preparation (54 Phytochemicals Library of *S. indicus*)
- In-silico molecular docking (PyRx Software with Vina Wizard tools)

- Drug likeness properties (Swiss-ADME Test)
- Bioavailability Score and Radar chart preparation (Swiss-ADME Test)
- 2D visualization of interaction (Using Discovery Studio software)

Protein Preparation

Four bacterial receptors of *S. aureus* were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (https://www.rcsb.org/). Protein preparation was done with the help of the "Prepare protein" protocol[17,18] of Discovery Studio 4.0 (DS 4.0). Heteroatoms and water molecules present in the crystal structure were removed.

Removal of water molecules and heteroatoms

Initially, the downloaded PDB structures contained water molecules and heteroatoms (non-receptor atoms such as ions or co-factors). These were removed using the "Prepare Protein" protocol in DS 4.0 to avoid interference with binding site analysis.

Addition of missing atoms/residues

If any residues or atoms were missing from the crystal structure, they were added to ensure structural completeness.

Optimization of protein structure

The protein structure was optimized by correcting bond orders, adding hydrogen atoms, and protonating the titratable groups at a physiological pH. This step ensured the stability of the protein for molecular docking studies.

Energy minimization

To achieve the most energetically favorable protein conformation, energy minimization was carried out using the CHARMm force field in DS 4.0. This step refines the geometry of the protein to eliminate any steric clashes or distortions that could affect ligand binding.

List of four Target protein of *S. aureus*

- *S. aureus* tyrosyl tRNA synthetase (PDB ID: 1JIJ)
- Dihydrofolate reductase (PDB ID: 3FYV)
- *S. aureus* gyrase B (PDB ID: 4URM)
- *S. aureus* sortase A (PDB ID: 2MLM)

Ligands Preparation

Total 54 active phytochemicals were retrieved from the literature. PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) was used for the retrieval of structures in 3D SDF (Three-Dimensional Structure Data File) format. Afterwards, ligand optimization, energy minimization and conversion of retrieved ligands to 3-D PDB format were done with the help of DS 4.0.

Conversion to 3D format

The downloaded ligands were in SDF format, which contains 3D structural information. These structures were converted into 3D PDB (Protein Data Bank) format to make them compatible with the docking software.

Optimization of ligand structures

Before docking, the phytochemicals were optimized to ensure that their conformations were energetically favorable. This involved:

Protonation

Hydrogens were added to the ligand structures, ensuring correct valence for atoms.

Tautomer and isomer selection

The most biologically relevant tautomers and isomers of the ligands were selected.

Geometric optimization

Ligand structures were optimized using a force field to eliminate any conformational strain.

Energy minimization

Energy minimization was performed to achieve the most stable conformation for each ligand. The CHARMm force field was applied, minimizing potential energy to remove any steric hindrance or strain.

Final conversion to PDB format

After optimization and minimization, the ligand structures were saved in 3D PDB format to be used in molecular docking studies.

Molecular Docking with PyRx Software

Molecular docking is a computational technique used to predict the interaction between a ligand (small molecule) and a receptor (protein). PyRx software is a popular tool for performing molecular docking studies due to its user-friendly interface and integration of AutoDock Vina, a widely used docking engine.[15,19-22]

Setting Up the Molecular Docking in PyRx

Selection of docking engine

In PyRx, AutoDock Vina is the default docking engine used for molecular docking simulations.

Grid box configuration

The next step is defining the search space for ligand binding. Identify the active site or binding pocket of the receptor using known information or by visually inspecting the protein structure in PyRx. Create a grid box around the binding site of the receptor to limit the docking search to the active site region. Set the dimensions (x, y, z) of the grid box large enough to encompass the binding pocket.

Running the Docking Simulation

After setting the grid box and docking parameters, run the docking simulation using AutoDock Vina in PyRx.[22] The docking algorithm will attempt to fit the ligand into the binding pocket of the receptor and calculate the binding energy for each pose.

PyRx will display the results, including the binding energy (in kcal/mol) for each pose. The binding energy is a measure of the strength of interaction between the ligand and the receptor, with more negative values indicating stronger binding affinity.

Analysis of Docking Results

Docking poses

After docking, PyRx will display multiple docking poses of the ligand with their respective binding energies. Review the top poses based on binding energy (lowest binding energy values).

Pose visualization

Visualize the best binding pose(s) in PyRx or export them for viewing in other molecular visualization tools such as Discovery Studio. Look for key interactions such as:

- Hydrogen bonds
- Hydrophobic interactions
- Van der Waals interactions
- π-π stacking, etc.

Binding energy interpretation

Analyze the binding energies to determine the most promising ligands with the highest binding affinity to the target protein.

Interaction analysis

Study the molecular interactions between the ligand and the receptor, such as hydrogen bonds, hydrophobic interactions, and π-π stacking, to identify which ligand atoms are involved in binding.

ADMET and Drug-Likeness Prediction

After molecular docking, the top compounds were evaluated for their ADMET properties,[12,13,16] which are crucial for understanding how a compound behaves inside the body. The ADMET predictions helped assess:

Absorption

How well the compound is absorbed into the bloodstream.

Distribution

How the compound spreads through different tissues and organs.

Metabolism

How the compound is metabolized (processed) by the body, primarily in the liver.

Excretion

How the compound is removed from the body (e.g., through urine or feces).

Toxicity

Whether the compound exhibits any toxic effects in the body at therapeutic doses.

Lipinski's rule of five

The drug-likeness of each compound was predicted based on Lipinski's Rule of Five and other properties, such as molecular weight, hydrogen bond donors and acceptors, lipophilicity (logP), and solubility. These parameters helped determine whether the phytochemicals have characteristics similar to approved drugs, making them potential candidates for drug development.[23,24]

Bioavailability and phytochemical characteristics

The selected phytochemicals were also assessed for their bioavailability, which refers to the degree and rate at which an active compound is absorbed and becomes available at the site of action in the body. Bioavailability scores were calculated, reflecting how effectively these compounds could be utilized in the body when taken orally.

RESULTS AND DISCUSSION

Upon molecular docking, a wide range of binding energy was obtained for different targets. For ease of the study, we selected the top ten binding energies among them for further analysis. The Molecular Docking, prediction of ADMET properties and drug-likeness revealed how the best binding compounds may behave inside the body. Different phytochemical has a potential binding affinity with different microorganisms. Binding energy, phytochemical characters and bioavailability score against the respective target are compiled in tabulated format.

Table 1: Docking score of top ranked interaction between phytochemicals from *S. indicus* and 4 target protein from *S. aureus*

S/N	*Name of ligands (Phytochemicals)*	*Target protein of S. aureus*			
		4URM	*3FYV*	*2MLM*	*1JIJ*
1	2,6-Phenanthrenediol, 5,7-dimethoxy (CID_10445823)	-8	-8.4	-6.9	-9.1
2	2-Hydroxycostic acid (CID_13995524)	-7.7	-8.3	-7.3	-7.3
3	5,4'-Dimethoxy-3'-prenylbiochanin A (CID_5487391)	-8.3	-8.8	-7.3	-9.7
4	7-Hydroxyfrullanolide (CID_11983230)	-7.3	-8.4	-7.3	-7.5
5	13-Acetyl-7alpha-hydroxyfrullanolide (CID_101673190)	-8	-8.9	-7.2	-6.9
6	beta-Sitosterol (CID_222284)	-8.3	-9.9	-8.4	-7.2
7	Clionasterol (CID_457801)	-8	-9.7	-8.1	-7.1
8	Isotetrandrine (CID_457825)	-8.2	-7.8	-7.1	-6.6
9	Sphaeranthanolide (CID_14733722)	7.8	-9.2	-7.4	-8.3
10	Phytosterols (CID_12303662)	-8.6	-9.9	-8.2	-7.9
11	Stigmasterol (CID_5280794)	-8.5	-9.8	-8.8	-7.9
12	Stigmasterol glucoside (CID_6440962)	-8.4	-9.4	-7.2	-8.5
13	Telekin (CID_12443309)	-7.2	-8	-7.1	-6.5
14	yadanzioside D aglycone (CASID_99133-00-3)	-8.6	-6.8	-6	-7

Table 2: Test result of drug filter rule of Lipinski rule, Ghose filter, Veber filter, Egan (Pharmacia) filter, and Muegge (Bayer) filter

S. No	*Name of phytochemicals*	*Lipinski*	*Ghose*	*Veber*	*Egan*	*Muegge*
1	2,6-Phenanthrenediol, 5,7-dimethoxy	Yes	Yes	Yes	Yes	Yes
2	2-Hydroxycostic acid	Yes	Yes	Yes	Yes	Yes
3	5,4'-Dimethoxy-3'-prenylbiochanin A	Yes	Yes	Yes	Yes	Yes
4	7-Hydroxyfrullanolide	Yes	Yes	Yes	Yes	Yes
5	13-Acetyl-7alpha-hydroxyfrullanolide	Yes	Yes	Yes	Yes	Yes
6	beta-Sitosterol	Yes	No	Yes	No	No
7	Clionasterol	Yes	No	Yes	No	No
8	Isotetrandrine	Yes	No	Yes	Yes	No
9	Sphaeranthanolide	Yes	No	No	No	Yes
10	Phytosterols	Yes	No	Yes	No	No
11	Stigmasterol	Yes	No	Yes	No	No
12	Stigmasterol glucoside	Yes	No	Yes	Yes	No
13	Telekin	Yes	Yes	Yes	Yes	Yes
14	Yadanzioside D aglycone	Yes	No	No	No	No

Molecular Docking

According to the Molecular Docking Score, 14 Phytochemicals with significant binding energy (Kcal/mol) against target protein were selected for further process and represented here in Table 1. The best-docked compounds from *S. indicus* were taken for drug-likeness test & ADMET profiling with the help of a Swiss-ADME server.

ADMET

Lipinski rule (Lipinski CA. *et al.* 2001) of five is a thumb rule of five, which aids in differentiating between drug-like and non-drug-like molecules by obeying its five parameters. We have also tested the drug filter rule of Ghose filter,[25] Veber (GSK) filter,[26] Egan (Pharmacia) filter,[27] Muegge (Bayer) filter.[28-30] Results of drug likeness rule are compiled in Table 2.

Physiochemical Properties

The physiochemical properties of bioactive compounds are essential for predicting their pharmacokinetic and pharmacodynamic profiles. This section provides a detailed analysis of the selected 14 phytochemicals from *S. indicus*, including their molecular structure, molecular weight (M. Wt.), bioavailability score (BAS), and total polar surface area (TPSA) as shown in Table 3. These properties are crucial in determining the compounds' drug-likeness and bioavailability.

- 2D visualization of different type of interaction between ligands and target site of protein using Discovery studio software: (In color Code)
- Interaction of phytosterol ligand with *S. aureus* gyrase B (PDB ID: 4URM) is represented in Fig.1.
- Interaction of Stigmasterol ligand with *S. aureus* sortase A (PDB ID: 2 mlm)is represented in Fig. 2.
- Interaction of 5,4'-Dimethoxy-3'-prenylbiochanin **A** ligand with *S. aureus* tyrosyl tRNA synthetase (PDB ID: 1JIJ)is represented in Fig. 3.

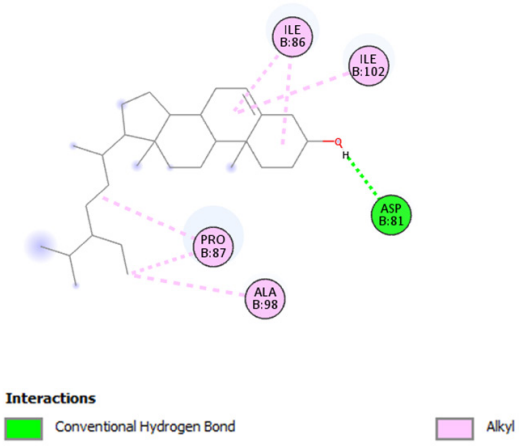


Fig. 1: Protein-ligand interaction diagram of Phytosterol ligand with *S. aureus* gyrase B, where green color indicates conventional hydrogen bond and pink color indicate the Alkyle bond

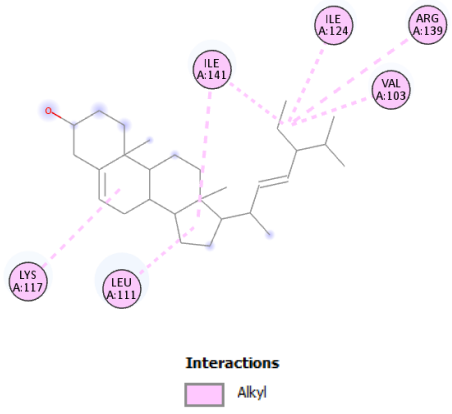
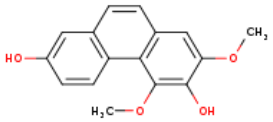
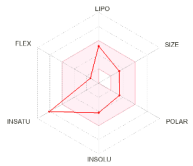
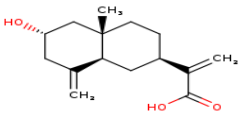
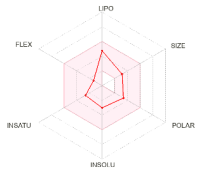
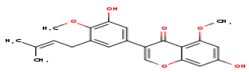
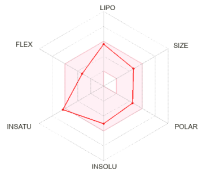
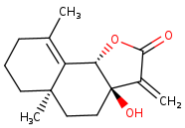
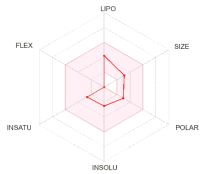
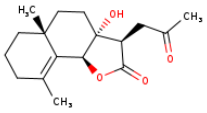
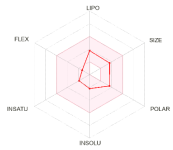
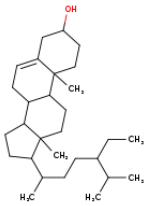
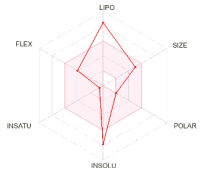
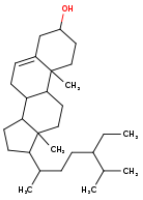
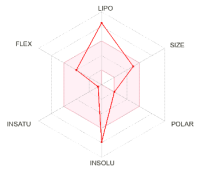
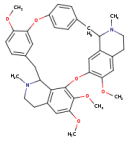
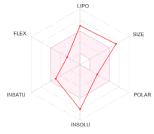
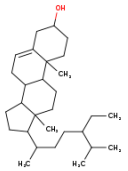
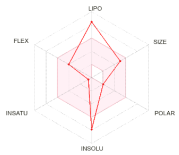
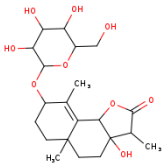
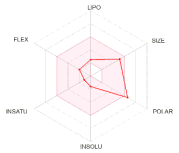
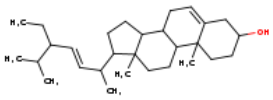
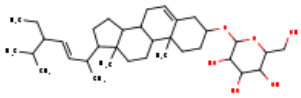
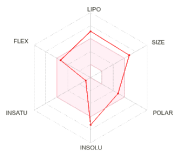
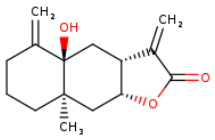
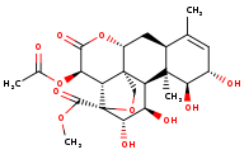
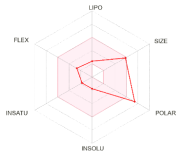


Fig. 2: Protein-ligand interaction diagram of Stigmasterol ligand with *S. aureus* sortase A, where pink color indicate the Alkyle bond

Table 3: Structure, M. Wt. (Molecular Weight), BAS (Bioavailability Score), TPSA (Total Polar Surface Area), and bioavailability radar [16,29] **we selected 14 Phytochemicals from *S. indicus***

S. No.	*Name*	*Structure of the molecules*	*Bioavailability radar*
1	2,6-Phenanthrenediol, 5,7-dimethoxy (CID_10445823) BAS: 0.55 M.Wt.: 270.28 g/mol TPSA: 58.92 Å²		
2	2-Hydroxycostic acid (CID_13995524) BAS: 0.85 M.Wt.: 250.33 g/mol TPSA: 57.53 Å²		
3	5,4'-Dimethoxy-3'-prenylbiochanin A (CID_5487391) BAS: M.Wt.: 382.41 g/mol TPSA: 89.13 Å²		
4	7-Hydroxyfrullanolide (CID_11983230) BAS: M.Wt.: 248.32 g/mol TPSA: 46.53 Å²		
5	13-Acetyl-7alpha-hydroxyfrullanolide (CID_101673190) BAS: M.Wt.: 292.37 g/mol TPSA: 63.60 Å²		
6	beta-Sitosterol (CID_222284) BAS: M.Wt.: 414.71 g/mol TPSA: 20.23 Å²		
7	Clionasterol or GAMMA-SITOSTEROL (CID_457801) BAS: M.Wt.: 414.71 g/mol TPSA: 20.23 Å²		
8	Isotetrandrine (CID_457825) BAS: M.Wt.: 622.75 g/mol TPSA: 61.86 Å		

9	Phytosterols (CID_12303662) BAS: M.Wt.: 414.71 g/mol TPSA: 20.23 Å²		
10	Sphaeranthanolide (CID_14733722) BAS: M.Wt.: 428.47 g/mol TPSA: 145.91 Å²		
11	Stigmasterol (CID_5280794) BAS: M.Wt.: 412.69 g/mol TPSA: 20.23 Å²		
12	Stigmasterol glucoside (CID_6440962) BAS: M.Wt.: 574.83 g/mol TPSA: 99.38 Å²		
13	Telekin (CID_12443309) Formula: C15H20O3 M.Wt.: 248.32 g/mol TPSA: 46.53 Å		
14	yadanzioside D aglycone (CASID_99133-00-3) Formula: C23H30O11 M.Wt.: 482.48 g/mol TPSA: 169.05 Å²		

- Interaction of Phytosterol ligand with *S. aureus* dihydrofolate reductase (PDB ID: 3FYV) is represented in Fig. 4.

The molecular docking and ADMET prediction[13,16,31] studies conducted on the 54 phytochemicals from *S. indicus* against four target proteins of *S. aureus*[5,32-35] revealed valuable insights into their antimicrobial potential. The docking results demonstrated that several compounds exhibited significant binding affinity, as indicated by their binding energies (ranging from -6.0–-9.9 kcal/mol). Among these, 14 phytochemicals were identified as top candidates due to their higher negative binding affinities, which suggest their strong potential to inhibit the growth and function of *S. aureus*. Compounds like beta-sitosterol, stigmasterol, and 5,4'-dimethoxy-3'-prenylbiochanin A were observed to have the highest docking scores, indicating their capacity for stable interaction with bacterial proteins.

The ADMET predictions further validated the drug-like behavior of these compounds. Most of the top 14 phytochemicals satisfied Lipinski's rule of five, a key determinant for assessing oral bioavailability. Additional drug filters such as the Ghose, Veber, Egan,

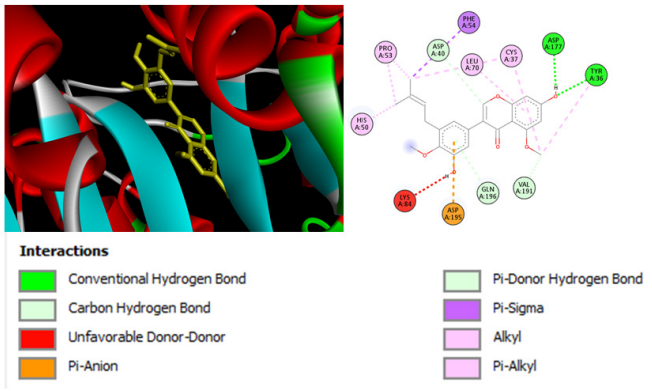


Fig. 3: Docking pose (left) and Protein-ligand interaction diagram(right)of 5,4′-Dimethoxy-3′-prenylbiochanin A ligand with *S. aureus* tyrosyl tRNA synthetase

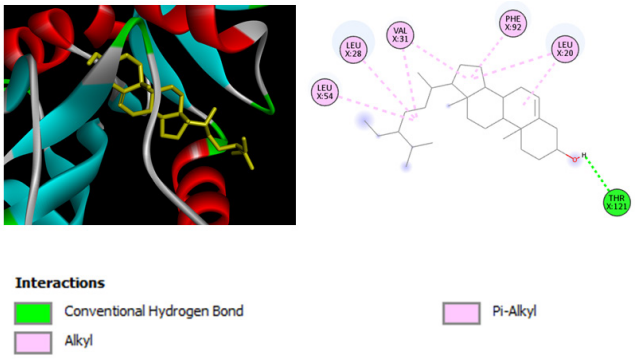


Fig. 4: Docking pose (left) and Protein-ligand interaction diagram (right) of Phytosterol ligand with *S. aureus* dihydrofolate reductase

and Muegge filters were also applied to gauge drug-likeness. While some compounds like beta-sitosterol and stigmasterol failed to meet certain criteria, others like 2,6-phenanthrenediol, 5,7-dimethoxy and Telekin passed all the drug-likeness filters, indicating their potential as lead compounds for drug development.

The bioavailability radar chart (Table 3), generated for each compound, provided a graphical representation of their pharmacokinetic properties, such as lipophilicity, size, polarity, solubility, and flexibility. Compounds that exhibited favorable bioavailability scores are promising candidates for further *in vitro* and *in vivo* investigations.

Overall, this study highlights the potential of *S. indicus* phytochemicals as novel antimicrobial agents against *S. aureus*. While the docking results are promising, further validation through experimental studies is essential to confirm the therapeutic efficacy of these compounds. Additionally, compounds that failed to meet certain ADMET criteria may require structural modifications to enhance their drug-likeness.

CONCLUSION

The current study demonstrates the potential of phytochemicals from *S. indicus* as promising antimicrobial agents through a comprehensive in silico approach. Molecular docking studies revealed strong binding affinities of several phytochemicals with target proteins of *S. aureus*, highlighting their potential to inhibit bacterial activity. The ADMET predictions further confirmed that many of these compounds exhibit favorable drug-like properties, indicating their safety and bioavailability. Some of these phytochemicals not only showed potential against bacteria but may also act as drug candidates against other microorganisms such as viruses.

The use of in silico molecular docking, combined with ADMET profiling, proved to be a valuable tool in understanding the interactions between phytochemicals and pathogen proteins. This approach offers insights into the stability, efficacy, and safety of compounds, streamlining the process of identifying promising candidates for further experimental validation. Ultimately, these findings suggest that phytochemicals from *S. indicus* hold significant potential for future development as therapeutic agents against various microbial infections, with the added advantage of minimizing the need for initial wet-lab screenings.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None.

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