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ARTICLE

Phytochemical Landscape of *Coleus forskohlii* and Its Role in Countering Staphylococcus Species

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ABSTRACT: Staphylococcal meningitis, a severe infection of the meninges, highlights the urgent need for new strategies to combat *Staphylococcus aureus* (*S. aureus*) infections. In this study, ethanolic leaf extracts of *Coleus forskohlii* were evaluated for their antibacterial potential against clinical *S. aureus* isolates associated with meningitis. Gas chromatography-mass spectrometry (GC-MS) analysis identified 15 phytochemical compounds, two of which—urs-12-en-28-ol (CID 22213452) and petroselaidic acid (CID 5282754) showed promising binding affinities (−7.5 and −5.9 kcal/mol, respectively) against *S. aureus* protein (30S ribosomal subunit) in molecular docking studies. *In vitro* assays confirmed the antibacterial activity of the crude extract, with a minimum inhibitory concentration (MIC) ranging from 62.5 to 125 μg/mL. Disc diffusion and time-kill kinetics further demonstrated concentration-dependent growth inhibition of *S. aureus* strains. These integrated findings suggest that *C. forskohlii*-derived compounds are potential antibacterial candidates worthy of further investigation. However, comprehensive *in vivo* studies are essential to evaluate their efficacy, safety, and therapeutic potential specifically against *S. aureus*-induced meningitis.

KEYWORDS: *Coleus forskohlii*; GC-MS; meningitis; antibacterial; bacteria; virtual screening; ADMET

1 Introduction

Bacterial meningitis is a severe infection that can lead to neuroinflammation of the meninges, posing risks to the central nervous system (CNS), that continues to exact a disproportionate global burden, mostly in low- and middle-income regions and among neonates, children, and immunocompromised adults [1–3]. Among the serious infections caused by such pathogens such as *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*, bacterial meningitis represents a life-threatening condition involving inflammation of the meninges. While *Staphylococcus aureus* is not the most common cause of bacterial meningitis, it remains a significant clinical concern, particularly in postoperative, trauma, or device-related infections [4]. *S. aureus* meningitis, though relatively rare, is associated with high mortality rates ranging from 14% to 77%, underscoring the urgent need for effective therapeutic strategies [5,6].

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The management of staphylococcal meningitis is further complicated by the rising prevalence of antibiotic-resistant strains, which limits treatment options and worsens clinical outcomes [7,8]. This challenge has spurred interest in exploring alternative antibacterial agents, particularly those derived from natural sources such as medicinal plants, which have historically served as reservoirs of bioactive compounds [9–11].

Coleus forskohlii Briq (syn. *Coleus hadiensis* (Forssk.) A. J. Paton), a perennial herb belonging to the Lamiaceae family, is widely recognized in traditional medicine systems across Asia, Africa, and Australia [12,13]. Its leaves have been used in decoctions to treat ailments such as digestive disorders, respiratory infections, and headaches. Modern phytochemical studies have revealed that *C. forskohlii* contains a variety of bioactive compounds, including diterpenoids, phenolics, and flavonoids, which contribute to its documented pharmacological activities such as anti-inflammatory, antioxidant, and antimicrobial effects [14,15]. Previous investigations have reported the antibacterial potential of *C. forskohlii* extracts against pathogens including *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *S. aureus* [16,17]. However, several studies focusing on its activity against clinically relevant *S. aureus* strains, particularly those implicated in invasive infections such as meningitis, remain limited, and its potential in regions such as Saudi Arabia has not been comprehensively explored.

In Saudi Arabia, where *C. forskohlii* grows natively, its phytochemical profile and antibacterial potential warrant further investigation. Advances in computational tools such as molecular docking and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) prediction now enable the virtual screening of plant-derived compounds, offering a rational approach to identifying candidates with desired bioactivity and pharmacokinetic properties prior to costly and time-consuming experimental validation [18,19]. Therefore, this study aimed to investigate the *potential* antibacterial activity of *C. forskohlii* against clinical isolates of *S. aureus* through an integrated *in vitro* and *in silico* approach. Specifically, we (1) profiled the phytochemical composition of an ethanolic leaf extract using GC–MS, (2) evaluated its *in vitro* antibacterial activity against *S. aureus* clinical strains, and (3) performed molecular docking and ADMET analyses to identify promising *virtual hits* with potential antibacterial activity against a relevant *S. aureus* target protein. This work provides a foundational assessment of *C. forskohlii* as a source of antibacterial candidates and highlights compounds warranting further investigation in the context of staphylococcal infections.

2 Materials and Methods

2.1 Plant Material

The fresh leaves of *C. forskohlii* were gotten from Jeddah, Saudi Arabia (coordinates 21.489050, 39.257494) in 2023. The taxonomic verification was provided for the plant specimen by the botany unit at the Department of Biological Sciences, King Abdulaziz University. Before further processing, the *Coleus forskohlii* leaves were rinsed under running tap water. The *C. forskohlii* leaves were shade-dried at room temperature in a dust-free open area for 14 days. Using an electric blender, the dried leaves were ground into a fine powder [20–22].

2.2 Preparation of Crude Ethanolic Extracts

The grounded leaves were subjected to 80% ethanolic extraction using a 48-h maceration period with continuous shaking (150 rpm, room temperature; shaker SHO 1-D). Upon filtration, a rotary evaporator (Buchi Rotavapor R-114) was used to concentrate the extract under reduced pressure at 55°C. The dry-concentrated ethanolic extract was then weighed using a precision balance (ADAM 0.0001 g) to calculate yield before being stored in a dark glass bottle at 4°C [23,24].

2.3 GS-MS Analysis

The ethanolic leaf extracts of *C. forskohlii* samples were analyzed using GC-MS to identify different compounds. The analysis was performed using an Elite-5MS column and a GC Clarus 500 Perkin Elmer instrument. A 2 μL volume of the sample was injected into the GC column, and the machine was run under specific temperature and time parameters. The MS program utilized the NIST library for compound identification. The entire analysis process, including both GC and MS, took a total of 36 min [25].

2.4 Bacterial Strains and Identification

Sixteen clinical isolates of cerebrospinal fluid (CSF) were obtained from the King Fahad Hospital in Madinah, Saudi Arabia. The samples were collected, including phlebotomists and nurses, and then delivered to the microbiology laboratory as pure cultures on a blood agar medium. Isolates were designated KFH1 through KFH16 and were re-identified using colony morphology and culture characteristics. For long-term storage, the isolates were preserved in Brain Heart Infusion (BHI) broth supplemented with glycerol at −80°C. However, for more accuracy in the bacterial taxonomic identification, the clinical isolates were further characterized using the VITEK® 2 COMPACT system (BioMérieux, France) for automated identification.

2.4.1 Antimicrobial Activity

Estimation Minimum Inhibition Concentration (MIC)

Following a micro-broth dilution approach in a 96-well plate, the minimum inhibitory concentration (MIC) of the ethanolic *C. forskohlii* extract was measured. The clinical isolates were exposed to an initial 2-fold serially diluted plant extract. After that, it was followed by incubation, where the metabolism, including viability, was measured by resazurin, an indicator dye. Specially designed control wells were included on all the plates.

Disk Diffusion Method

Disc diffusion on Mueller Hinton Agar (MHA) was carried out to evaluate the antibacterial activity of the extract obtained from *C. forskohlii*. Bacterial lawn preparations were made at a density of 10^6 CFU/mL. Extract-soaked filter discs (7 mm) at concentrations of 125, 250, and 500 μg/mL were applied with oxacillin and sterilized for 30 min, allowing the medicine to diffuse, followed by incubation at 37°C for 24 h. The diameter of distilled water being used as positive and negative controls, respectively. The plates were kept at room temperature, each inhibition zone surrounding the disc was measured in millimeters, and the data was recorded as mean ± standard deviation in triplicate tests [26].

Time-Kill Curve

To determine the time-kill kinetics, Muller Hinton Broth was used, with Augmentin serving as the control. Thus, 125 μg/mL suspensions of *C. forskohlii* extract and 10 μg/mL Augmentin were added to the wells. Each suspension was incubated at 37°C with high aeration. Samples were obtained at predetermined times (0, 2, 4, 6, 8, 10, 12, or 24 h), with each sample utilizing an equal quantity of bacterial suspensions. These samples were plated using blood agar and incubated at 37°C for 24 h before being quantified using the plate counter after counting the colonies that developed during incubation [27].

2.5 Protein Preparation, Refinement and Validation

The molecular docking analysis targeted the *Staphylococcus aureus* 30S ribosomal subunit (PDB ID: 8BH6). This protein was selected because it is essential for bacterial protein synthesis and represents a clinically validated antibacterial target. The PDB format of the 8BH6 structure was retrieved from the UniProtKB database, using the specific identifier Q2FZ25. The obtained PDB structure was refined using GalaxyRefine, resulting in a refined structure with associated RMSD values and an energy score. The ProSAweb server was used to identify potential errors in the three-dimensional structure. Additionally, a Ramachandran plot was employed to visualize and analyze permissible or impermissible regions. To validate the protein, polar and nonpolar hydrogen bond merging was performed, along with the calculation of the Gasteiger charge. The process also involved the removal of metal ions and cofactors, with all steps documented [28].

2.6 Identification of the Active Site of the Protein and Generation of the Receptor Grid

The 8BH6 receptor underwent active site generation by submitting it to the CASRp 3.0 web server. The server generated a document listing the active sites identified based on the solvent-accessible surface. These active sites were visualized using BIOVIA Discovery Studio software [29].

2.7 Molecular Docking Simulation

A molecular docking study was conducted to identify the compound with the highest binding affinity using 15 compounds from *C. forskohlii* and the 8BH6 receptor of *Staphylococcus aureus*. The PyRx program was employed for the molecular docking process. The docking scores were validated, and the interaction between ligands and receptors was examined using the AutoDockVina tools [28].

2.8 ADMET and Toxicity Analysis

The selection of a molecule as a potential therapeutic candidate is primarily guided by its analogues. Careful consideration of chemical properties can help reduce failure rates in both *in vivo* and *In vitro* studies. To identify promising compounds, the web-based system Swiss-ADMET is utilized, which assesses factors such as bioavailability and solubility. Furthermore, the safety profiles of these compounds are thoroughly assessed using computer-aided drug design (CADD) methods. This evaluation plays a pivotal role in determining the potential risks a substance may pose to animals or humans. Rigorous qualitative and quantitative assessments are conducted to evaluate mutagenicity, LD50 value, carcinogenicity, and immunotoxicity. The toxicological profiles are calculated using the ProTox-II web server.

3 Results

3.1 Identification of Bacterial Strain

Table 1 presents the identification results for bacterial isolates obtained from cerebrospinal fluid (CSF) samples. All 16 isolates were collected from CSF specimens at King Fahd Hospital in Medina and identified using the VITEK® 2 system. The isolates comprised: *Pseudomonas aeruginosa* (KFH 1, 6; 97% probability), *Klebsiella pneumoniae* (KFH 2, 7, 8, 11; 99%), *Citrobacter braakii* (KFH 3; 95%), *Staphylococcus aureus* (KFH 4, 5, 12, 16; 94–99%), *Stenotrophomonas maltophilia* (KFH 9, 13; 86–90%), *Sphingomonas paucimobilis* (KFH 10; 96%), *Kocuria kristinae* (KFH 14; 91%), and *Staphylococcus epidermidis* (KFH 15; 97%). Four *S. aureus* isolates (KFH 4, 5, 12, 16) were selected for further evaluation.

Table 1: List of bacteria with their source of isolation, gram staining and identification of bacterial strain using VITEK® 2.

Source	Isolate No.	Code	Gram Positive (+)/ Negative (-)	Identification Using Vitek2	Probability %
King Fahd Hospital in Medina	01	KFH 1	-	*Pseudomonas aeruginosa*	97%
	02	KFH 2	-	*Klebsiella pneumoniae*	99%
	03	KFH 3	-	*Citrobacter braakii*	95%
	04	KFH 4	+	*Staphylococcus aureus*	95%
	05	KFH 5	+	*Staphylococcus aureus*	94%
	06	KFH 6	-	*Pseudomonas aeruginosa*	97%
	07	KFH 7	-	*Klebsiella pneumoniae*	99%
	08	KFH 8	-	*Klebsiella pneumoniae*	99%
	09	KFH 9	-	*Stenotrophomonas maltophilia*	90%
	010	KFH 10	-	*Sphingomonas paucimobilis*	96%
	011	KFH 11	-	*Klebsiella pneumoniae*	99%
	012	KFH 12	-	*Staphylococcus aureus*	99%
	013	KFH 13	+	*Stenotrophomonas maltophilia*	86%
	014	KFH 14	+	*Kocuria kristinae*	91%
	015	KFH 15	+	*Staphylococcus epidermidis*	97%
	016	KFH 16	+	*Staphylococcus aureus*	99%

3.2 Antimicrobial Activity of C. forskohlii

3.2.1 Estimation Minimum Inhibition Concentration (MIC)

The antibacterial potential of *C. forskohlii* ethanolic extract was tested against strains KFH4, KFH5, KFH12, and KFH16 of *S. aureus*. The relative effectiveness of *C. forskohlii* extract compounds against pathogenic strains was evaluated by determining the minimum inhibitory concentration (MIC) and qualitatively assessed using disk diffusion. To observe bacterial growth, the turbidity of the broth was visualized. The recorded MIC of *C. forskohlii* extract against *S. aureus* was between 62.5 µg/mL and 125 µg/mL (Table S1).

3.2.2 Disk Diffusion Method

The disk diffusion test demonstrated that *C. forskohlii* ethanolic extract inhibits the growth of pathogenic *S. aureus* strains. While the highest zone of inhibition was measured from strain KFH 12 (13 mm) when subjected to a 500 µg/mL concentration of *C. forskohlii* ethanolic extract, KFH 4 and KFH 16 displayed the same sensitivity with a 12 mm zone of inhibition. The least zone of inhibition was measured from strain KFH 5 (11 mm). A 1 µg oxacillin (OXC 1) concentration was used as a positive control—with a zone of inhibition between 20.3 and 22.7 mm against the *S. aureus* strains. However, at concentrations of 125 and 250 µg/mL, the zone of inhibition ranged between 9.5 and 11 mm, indicating an average inhibitory effect (Table S2).

3.2.3 Time-Kill Curve

The time-killing curves of *C. forskohlii* extract showed a weaker effect compared to Augmentin against *S. aureus* strains (KFH 4, KFH 5, KFH 12, and KFH 16), as shown in Fig. 1. Following an incubation period of 6 to 24 h, all bacteria were completely eradicated. Without antibacterial treatment, the bacterial density for all strains exhibited a rapid increase, reaching a plateau at 3.6×10^6 CFU/mL. However, when exposed to *C. forskohlii* leaf extract at the minimum inhibitory concentration (MIC), there was an initial decrease in bacterial numbers. After 8 h of incubation, the bacteria were effectively killed, and between 12 and 24 h of incubation, no bacterial outgrowth was observed.

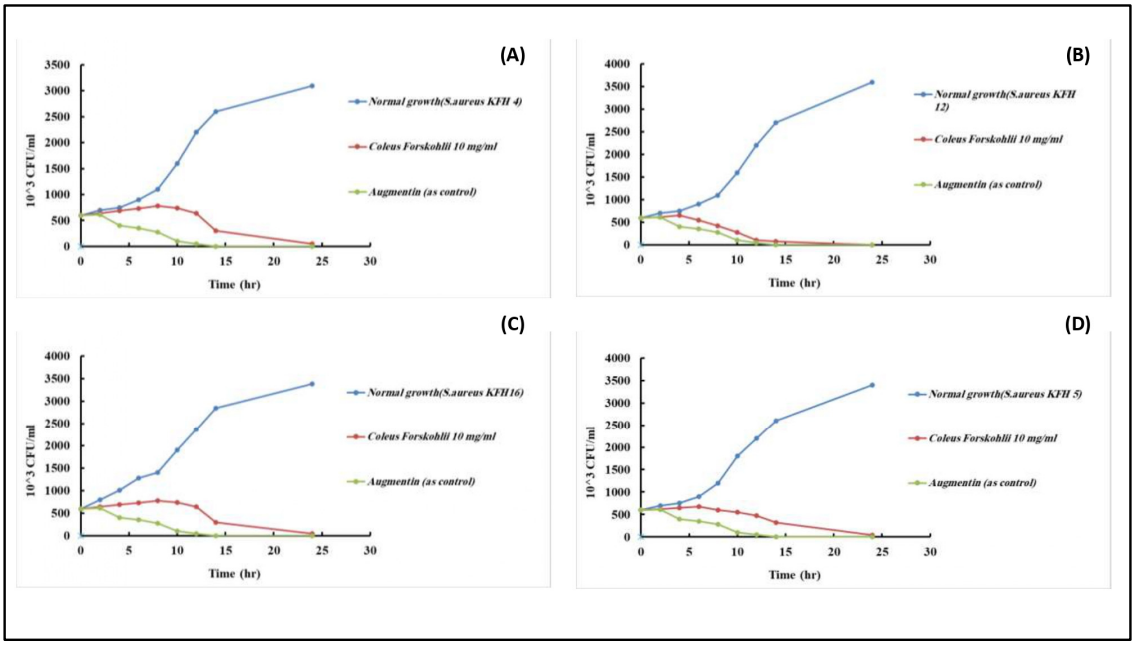

Figure 1: Time–Killing curve for *S. aureus* strins ((**A**): *S. aureus* KFH 4, (**B**): *S. aureus* KFH 12, (**C**): *S. aureus* KFH 16, and (**D**): *S. aureus* KFH 5) of *C. forskolin* leaf extracted by ethanol 80% and MIC of Augmentin as control.

3.3 GC–MS Analysis

The GC-MS screening of *C. forskohlii* identified a total of 15 distinct compounds. The retention time, chemical formula, and peak area of these compounds were recorded within a period of 30 min (Table 2). Notably, most of these biochemical compounds fall between the 17.0–24.0-min marks during the assays (Fig. 2).

Table 2: Small molecules extracted from the *C. forskohlii* through the GC-MS.

SL No.	Peak Time	Area %	Compound Name	CID
1	17.207	0.10	n-Hexadecanoic acid	CID 985
2	18.574	9.54	Methyl 10-trans,12-cis-octadecadienoate	CID 5471014
3	18.627	1.00	9-Octadecenoic acid, methyl ester, (E)-	CID 5280590
4	19.045	1.11	6-Octadecenoic acid	CID 5282754
5	19.414	1.94	Phenol, 4,4′-(1-methylethylidene)bis-	CID 74457
6	20.005	0.83	Palmitoyl chloride	CID 8206
7	21.042	0.83	Sulfurous acid, cyclohexylmethyl pentadecyl ester	CID 6421704
8	21.542	0.57	9,12-Octadecadienoic acid (Z,Z)-, 2,3-dihydroxypropyl ester	CID 5283469
9	21.578	2.14	Oleic anhydride	CID 5369123
10	21.776	1.89	Octadecanoic acid, 2,3-dihydroxypropyl ester	CID 24699
11	23.076	3.24	Terephthalic acid, but-3-enyl heptadecyl ester	CID 91735674
12	23.424	3.41	6-Ethyl-3-trimethylsilyloxydecane	CID 582858
13	23.536	0.97	Urs-12-en-28-ol	CID 22213452
14	23.855	0.65	Sulfurous acid, cyclohexylmethyl pentadecyl ester	CID 6421704
15	24.404	6.12	D:A-Friedooleanan-3-ol, (3.alpha.)-	CID 348029

3.4 Molecular Docking and ADMET

3.4.1 Validation, Refinement and Receptor Preparation

The most optimal three-dimensional protein structure was obtained from the Iterative Threading ASSEmbly Refinement (I-TASSER) server, which generated five predicted models that were evaluated based on their C-scores. Among these, model-1, having the lowest C-score (1.59), was selected and further refined, yielding a 3D-refine score of 37,759.1. The refined model exhibited an estimated Template Modeling score (TM-score) of 0.94 ± 0.05 and a Root-Mean-Square Deviation (RMSD) of 2.5 ± 1.9 Å (Fig. 3). Prior to refinement, the Ramachandran plot showed residues distributed across favorable, allowed, and disallowed regions; however, after refinement, 87.21% of residues were located in the favorable region, 10.24% in the allowed region, and only 2.55% in the disallowed region (Fig. 3A). In addition, the crude model displayed a Z-score of −7.02, indicating acceptable overall structural quality (Fig. 3B).

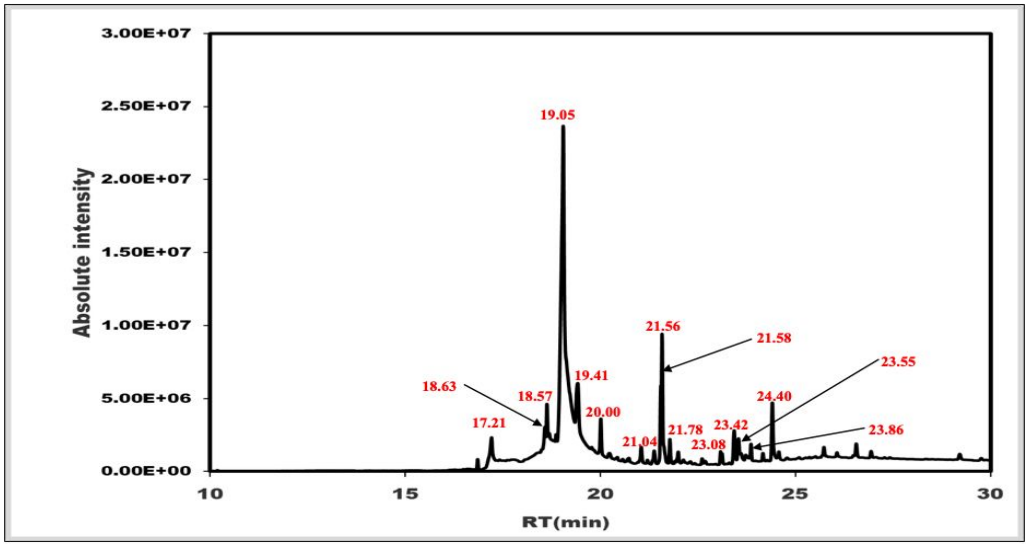

Figure 2: GC-MS chromatogram showing the frequency and intensity of compounds identified in *Coleus forskohlii*.

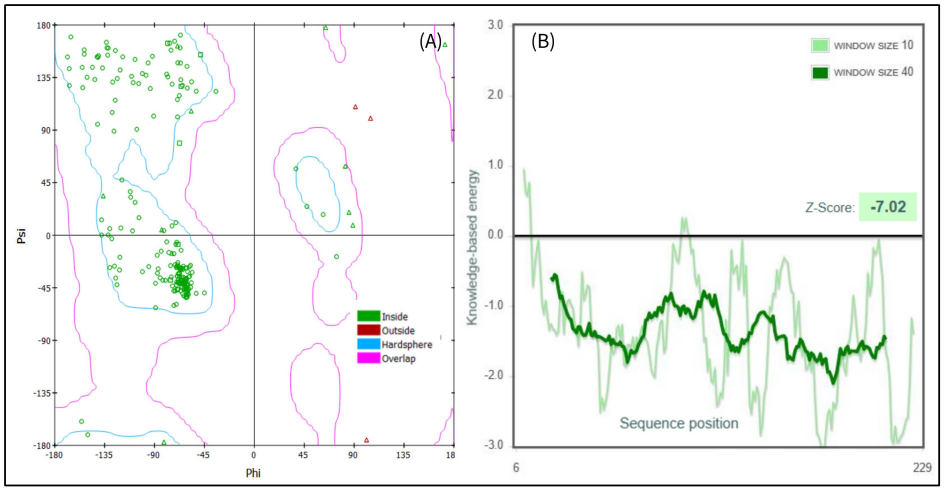

Figure 3: Validation of the 3D 8BH6 protein structure. (**A**) Ramachandran plot showing residues in favored, allowed, and disallowed regions. (**B**) ProSA-web Z-score of the refined 8BH6 model.

3.4.2 Active Sites Searching

The Computed Atlas of Surface Topography of proteins (CASTp) server was utilized to identify the active sites within the protein. The active site of a protein facilitates binding with a chemical substrate, leading to a catalyzed reaction. The stabilization of reaction intermediates occurs at a binding site, which is a specific location on a protein or nucleic acid capable of recognizing a ligand and forming a strong binding interaction with the protein. In this study, CASTp identified 400 active pockets in the 8bh6 structure. Among them, three pockets were selected based on their surface area, and the corresponding amino acid residues were mapped and visualized in Fig. 4. In the process of molecular docking simulation, the binding sites were documented to construct a receptor grid with an angstrom (Å) dimension of X = 38.3066, Y = 42.3265, and Z = 44.1188.

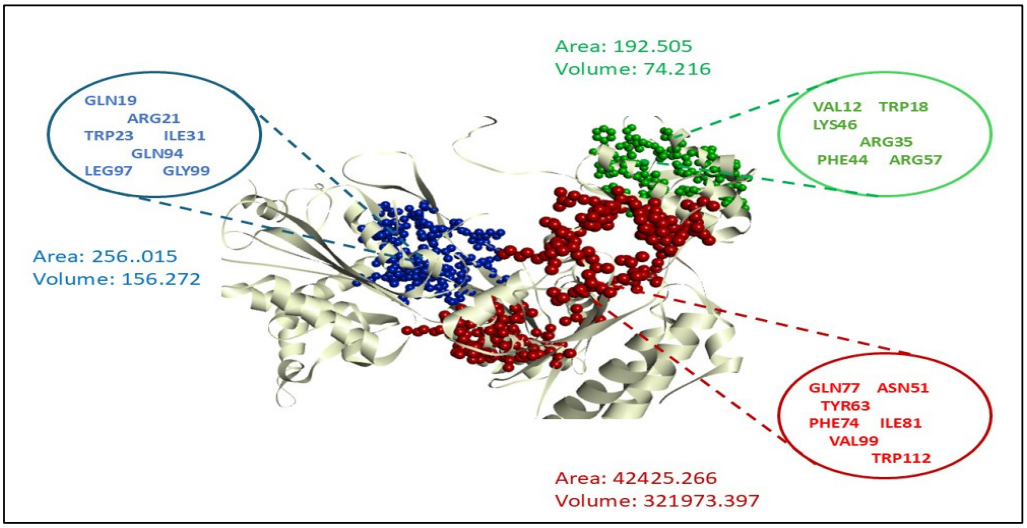

Figure 4: Active and binding sites of 8BH6 protein. The selected pockets are represented as colored spheres (red, blue, and green, respectively), indicating their respective binding site positions.

3.4.3 Molecular Docking Simulation

The molecular docking analysis did not only help to identify potential drug-like small molecule candidates but also allowed for the selection of suitable macromolecule interactions based on intermolecular frameworks. Phytochemical compounds and target proteins were carefully chosen for the study, and 15 phytochemical compounds were screened using the PyRx tool's AutoDock Vina wizard (Table S3). The docking results showed binding affinities spanning from −4 to −7.5 kcal/mol (Table 3). To prioritize the most promising compounds, the top 50% of the phytochemical compounds were selected. Among them, Urs-12-en-28-ol (CID 22213452) and Petroselaidic acid (CID 5282754) emerged as the top 2 compounds, with docking scores of −7.5 kcal/mol and −5.9 kcal/mol. These two compounds were further evaluated using additional screening methods. The selected compounds and their docking scores are presented in Table 3, whereas the docking scores for all compounds can be found in Table S3. To validate the docking scores, a re-docking process was performed by retrieving and re-docking the compounds to the same binding site. The re-docking results revealed that the binding affinities of the compounds remained consistent with the initial docking scores, with minimal upper and lower RMSD values observed.

Table 3: Molecular docking scores (kcal/mol), chemical names, molecular formulas, and PubChem CIDs of the selected compounds.

PubChem ID	Chemical Name	Molecular Weight	Molecular Formula	Binding Affinity (Kcal/mol)
CID 22213452	Urs-12-en-28-ol	426.7 g/mol	C30H50O	−7.5
CID 5282754	Petroselaidic acid	282.5 g/mol	C18H34O2	−5.9

3.4.4 Analysis of the Interaction between the Ligand and Protein

The protein was examined for its interaction with the compounds exhibiting the highest binding scores. These compounds were selected and retrieved to investigate their interaction with the protein. The BIOVIA Discovery Studio Visualizer tool was employed to observe the interactions formed between the two selected ligands and the target protein. The compound CID22213452 formed multiple hydrophobic interactions with the desired protein. Specifically, hydrophobic interactions were identified at the ARG95 and LYS168 positions, as depicted in Fig. 5. The specific types of bonds formed are listed in Table 4. Similarly, the compound CID5282754 was found to form multiple hydrophobic interactions at the residual positions of LEU97, ARG143, and PHE147. Additionally, two conventional hydrogen bonds were observed to form at the positions of ARG143 and ARG143, as illustrated in Fig. 6. Further details about these interactions are provided in Table 4.

Table 4: List of the bonding interactions observed between the selected two phytochemical compounds and the protein.

PubChem CID	Residue	Distance	Type	Category
CID 22213452	ARG95	5.08	Alkyl	Hydrophobic
	LYS168	3.99	Alkyl	Hydrophobic
CID 5282754	ARG143	2.03	Conv-H-Bond	Hydrogen bond
	ARG143	2.86	Conv-H-Bond	Hydrogen bond
	LEU97	5.04	Alkyl	Hydrophobic
	ARG143	4.5	Alkyl	Hydrophobic
	PHE147	5.37	Alkyl	Hydrophobic

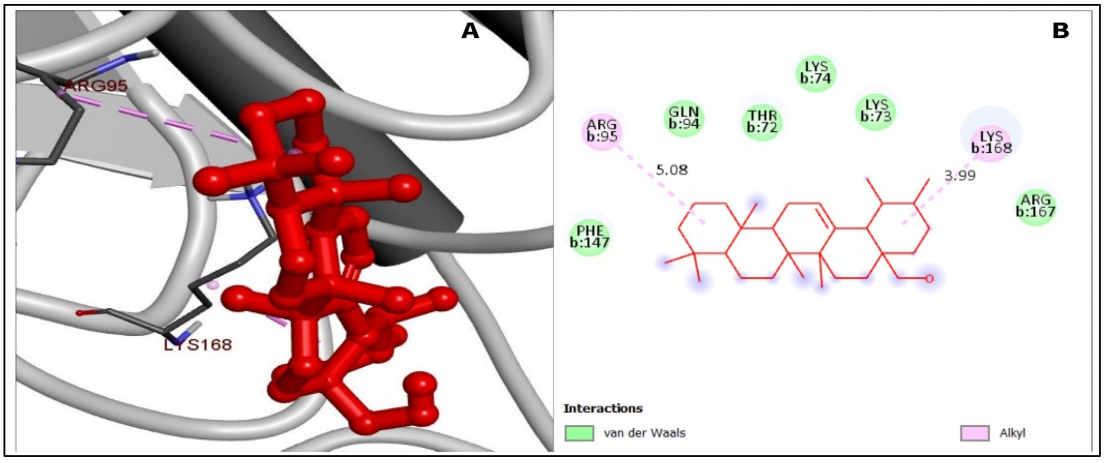

Figure 5: Interaction of compounds CID22213452 with the 8bh6 protein. A-represent 3D interactions; B-represent 2D interactions of the protein-ligand complexes.

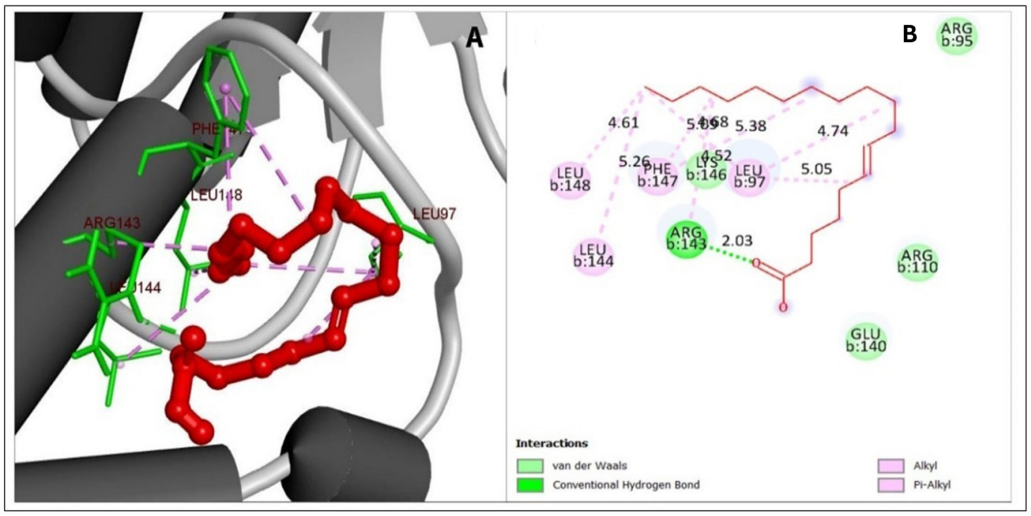

Figure 6: Interaction of compounds CID5282754 with the 8bh6 protein. A-represent 3D interactions; B-represent 2D interactions of the protein-ligand complexes.

3.4.5 ADMET Analysis

For an effective drug design and development process, the pharmacokinetic (PK) properties were assessed and these include the analysis of drug (pharmakon) and movement (kinetikos). The evaluation estimated the ADMET properties, with an emphasis on lipophilicity, water solubility, pharmacokinetics, drug-likeness, and medicinal chemistry parameters. These properties help identify potential hypotheses for selecting optimal drug candidates. Before advancing to preclinical studies, analyzing pharmacophore properties helps determine the compound's regulatory features related to xenobiotic activity. In this study, the SwissADMET server was utilized to assess the pharmacophore properties of our 2 selected drug-like compounds (CID 5282754 and CID 22213452). Although these compounds exhibit slightly promising pharmacokinetic properties, both display a lipophilic nature, enabling their dissolution in fats, oils, and nonpolar solvents. However, CID 5282754 has a marginally better pharmacokinetic profile than CID 22213452 (Table 5).

Table 5: The pharmacokinetics list encompasses the ADMET characteristics of the two selected drugs. Additionally, the list includes a range of physicochemical properties associated with these two substances.

Properties	Parameters	CID 5282754	CID 22213452
	MW (g/mol)	282.5 g/mol	426.7 g/mol
	Heavy atoms	20	31
	Arom. Heavy atoms	0	0
	Rotatable bonds	15	6
	H-bond acceptors	2	1
	H-bond donor	1	1
	Molar refractivity	89.94	135.14
Lipophilicity	Log Po/w	4.25	4.76
Water solubility	Log S (ESOL)	−5.41	−8.06
Pharmakokinetics	GI absorption	Low	Low
Drug likeness	Lipinski, violation	Yes	Yes
Medi. Chemistry	Synth. accessibility	3.07	6.18

3.4.6 Toxicity Prediction

Evaluating the toxicity of compounds is essential to understanding their potential adverse effects on animals, plants, humans, and the environment. As a result, predicting toxicity has become a critical first step in the process of selecting compounds for drug development. Traditional toxicity analysis often relies on animal models, which can be both time-consuming and expensive. Alternatively, computer-based toxicity testing offers a promising approach that eliminates the need for animal models, reduces time requirements, and lowers costs. In the present study, we utilized the popular web servers ADMETSAR 2.0 and ProToxII as *in-silico* toxicity testing platforms to evaluate the toxicity of CID 5282754 and CID 22213452. The servers employed a rat model as the target organism to predict hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity, with the results presented in Table 6.

Table 6: The drug-induced toxicity profile of selected phytochemicals.

PubChem ID	Hepatotoxicity	Immunotoxicity	Carcinogenicity	Cytotoxicity	Mutagenicity
CID 5282754	Inactive	Light active	No	Inactive	Inactive
CID 22213452	Inactive	Inactive	No	Inactive	Inactive

4 Discussion

The growing challenge of antibiotic resistance has renewed interest in natural products as potential sources of novel antibacterial agents. Recent studies have highlighted the efficacy of plant extracts against human pathogenic bacteria, primarily attributed to their diverse bioactive constituents [30–35]. In line with this, the present study investigated the antibacterial potential of *C. forskohlii* against clinical *S. aureus* isolates.

Our GC-MS analysis of the ethanolic leaf extract identified 15 phytochemical compounds, supporting the existing body of evidence on the phytochemical richness of *C. forskohlii* [36]. To rationally prioritize compounds from this complex mixture, we employed computer-aided drug design (CADD) methodologies. CADD offers a cost-effective and efficient strategy for initial compound screening, utilizing techniques such as molecular docking and ADMET analysis to prioritize candidates with favorable predicted biological activity and pharmacokinetic profiles [28,37]. By targeting the *S. aureus* 30S ribosomal subunit protein (PDB: 8BH6) a component essential for bacterial protein synthesis we sought to identify compounds capable of disrupting a fundamental cellular process. Docking simulations ranked urs-12-en-28-ol and petroselaidic acid as the top virtual hits based on their binding affinities. These *in silico* results suggest a potential mechanism of action but must be interpreted as predictive models that generate hypotheses for experimental testing.

Concurrently, our *in vitro* assays confirmed the antibacterial activity of the crude *C. forskohlii* extract, with MIC values (62.5–125 µg/mL) and disk diffusion results demonstrating concentration-dependent inhibition against all four clinical *S. aureus* strains. These findings align with previous reports on the antimicrobial properties of *C. forskohlii* [18,38–40]. For instance, Shanmugam and Pradeep [18] also reported bacteriostatic and bactericidal effects of *C. forskohlii* extracts against *S. aureus*, with MIC ranges comparable to those observed in our study. The consistency in MIC values across studies strengthens the evidence for the reproducible antibacterial activity of *C. forskohlii* extracts against *S. aureus*.

An integrated analysis of the *in silico* and *in vitro* data provides a more comprehensive perspective. While the crude extract showed broad antibacterial activity, the docking study offers insights into specific compounds that may contribute to this effect. However, it is crucial to emphasize that the activity of the

individual compounds, urs-12-en-28-ol and petroselaidic acid, has not been experimentally validated in this study. Their contribution to the observed extract activity remains hypothetical.

Furthermore, the pharmacokinetic (ADMET) and toxicity profiles of the two selected compounds were assessed *in silico*. Although both compounds displayed properties within acceptable ranges for early-stage drug candidates, they showed predicted low gastrointestinal absorption. This preliminary ADMET assessment is valuable for filtering candidates but requires thorough experimental validation in subsequent pharmacological studies [28,37–40]. It is important to acknowledge several limitations of this study. The antibacterial activity and molecular docking results, while encouraging, are derived from *in vitro* and *in silico* models. The specific efficacy against *S. aureus* meningitis has not been established, as central nervous system (CNS) penetration, blood-brain barrier (BBB) permeability, and activity in meningeal infection models remain uninvestigated. Additionally, the molecular docking analysis focused on a single protein target and requires experimental confirmation. Thus, these findings should be viewed as a foundational step for future research.

Despite these limitations, this work provides a valuable platform for further investigation. The identification of urs-12-en-28-ol and petroselaidic acid as virtual hits against a key bacterial target offers a focused starting point. Future studies should involve the isolation and purification of these compounds for direct *in vitro* antibacterial testing, followed by *in vivo* efficacy and safety evaluation in appropriate infection models. Investigating their potential for CNS penetration will be particularly critical for assessing any possible role in treating meningeal infections. Overall, this combined *in vitro* and *in silico* study reinforces the potential of *C. forskohlii* as a source of antibacterial agents and identifies specific compounds for targeted follow-up. The path toward therapeutic application requires a sequential research strategy, moving from virtual screening and extract-level activity to compound-specific validation and comprehensive *in vivo* assessment.

It is important to acknowledge the limitations of this study. While the antibacterial activity and molecular docking results are promising, they originate from *in vitro* and *in silico* models. The specific efficacy against *S. aureus* meningitis has not been established, as central nervous system (CNS) penetration, blood-brain barrier (BBB) permeability, and activity in meningeal infection models remain uninvestigated. Furthermore, the molecular docking analysis focused on a single protein target and lacked comparative docking with known reference inhibitors, which limits the quantitative interpretation of the binding scores. Therefore, these findings should be viewed as a foundational step for future research, and comprehensive *in vivo* pharmacological and toxicological studies are essential before any therapeutic potential for meningitis can be determined.

5 Conclusions

This study investigated the antibacterial potential of an ethanolic extract of *Coleus forskohlii* from Jeddah, Saudi Arabia, against *Staphylococcus aureus* through a combined *in vitro* and *in silico* approach. *In vitro* assays demonstrated that the crude extract exhibited antibacterial activity against clinical *S. aureus* isolates, with MIC values ranging from 62.5 to 125 µg/mL. Computational analyses, including GC–MS profiling, molecular docking, and ADMET prediction, identified two phytocompounds—urs-12-en-28-ol (CID 22213452) and petroselaidic acid (CID 5282754)—as promising virtual hits with favorable binding affinity toward a key *S. aureus* protein target (30S ribosomal subunit). These compounds also displayed acceptable pharmacokinetic and toxicity profiles *in silico*. While these findings highlight *C. forskohlii* as a source of potential antibacterial candidates, it is important to emphasize that the results are preliminary. The activity of the individual compounds has not been validated experimentally, and their efficacy against

S. aureus meningitis remains speculative in the absence of blood-brain barrier permeability and *in vivo* infection model data. Therefore, this work serves as a foundational step for future research. Further studies are necessary to isolate and test the identified compounds *in vitro*, evaluate their *in vivo* efficacy and safety, and assess their potential for central nervous system penetration. Such investigations will be essential to determine the true therapeutic relevance of *C. forskohlii*-derived compounds in countering *S. aureus* infections, including those associated with meningitis.

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Abbreviations

ADMET	Absorption, distribution, metabolism, excretion, and toxicity
BHI	Brain heart infusion
C. forskohlii	*Coleus forskohlii*
CSF	Cerebrospinal fluid
CADD	Computer-aided drug design
GC/MS	Gas chromatography/mass spectrometry
MIC	Minimum inhibitory concentration
OXA	Oxacillin
PK	Pharmacokinetic
PDB	Protein data bank
SDW	Sterile distilled water

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