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Exploring the Potential of *Calotropis Procera* Ait. (Asclepiadaceae) Phytocompounds against *S. Aureus* TyrRS

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Research Article

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Abstract

In medicinal chemistry the plant-based drugs as an alternative medicine is increasing day by day with realization of toxic effects and health hazards associated with the multiple uses of antibiotics and synthetic drugs and due to the growing resistance of pathogens to conventional antibiotics. *Calotropis procera* is a tropical plant distributed widely in Asia, Africa, and America and native to north Africa. It can produce a wide range of chemical compounds which are biologically active against multidrug resistance bacterial strains (ESKAPE). In this manuscript the docking analysis find out the antimicrobial potential of these plant-derived compounds against S. aureus tyrosyl-tRNA synthetase (PDB ID: 1JIJ). *S. aureus* tyrosyl-tRNA synthetase plays an essential role in protein synthesis by producing charged tRNAs. In this screening of docking score 83 phytocompounds selected compounds which has good binding affinity above -10 which Calotroproceryl acetate A (-10.1), L-rhamnose (-10.2) and Lupeol (-10.4). The interacting analysis showing all the three compounds, Lupeol has highest binding energy which has maximum hydrogen bond interaction with CYS37, HIS47, GLY49, HIS50, THR75, GLN174, ASP177 and GLN190. These residues are important for protein activity and therefore binding at these residues may hamper protein's activity all the three compounds interacted with active site residue of *S. aureus* tyrosyl-tRNA synthetase and therefore it is hypothesized that these compounds are the putative target of the protein activity which enhance bacterial pathogenesis and survival.

Keywords: *Calotropis procera*; *Staphylococcus aureus*; Tyrosyl-tRNA synthetase; Molecular docking

Abbreviations: *C. procera: Calotropis procera*; *S. aureus: Staphylococcus aureus*; TyrRS: Tyrosyl-tRNA synthetase; RO5: Lipinski's Rule of Five; 2D: Two-dimensional; 3D: Three-dimensional.

Introduction

Medicinal plants are the richest source of bioactive phytochemicals which may be responsible for various pharmacological activities including antimicrobial activities [1]. *Calotropis procera* is an indication that the plant, if properly screened using additional solvents, could yield drugs of pharmaceutical significance and can be used in the traditional medicine system to cure various diseases [2]. The whole plant *Calotropis procera* was used to treat common diseases such as fever, rheumatism, indigestion, cold, eczema, and diarrhea, for the treatment of boils, to remove thorn from body and for the treatment of jaundice [3,4]. The antimicrobial effect of ethanol, aqueous and chloroform extracts of leaf and latex of *Calotropis procera* on six bacteria ESKAPE pathogens. Herbal medicines may include whole parts of plant or mostly prepared from leaves, roots, bark, seed and flowers of plants. Medicinal plants are the "backbone" of traditional medicine, which means more

than 3.3 billion people in the less developed countries utilize medicinal plants on a regular basis [5,6]. *C. procera* plant is rich source of polyphenolic agents that might be playing an important role in inhibition of progress of several diseases [7]. The above researches provide a support for the use of *C. procera* in traditional medicine and suggest its further advanced investigation. There is a continuous need of the development of new effective antimicrobial drugs because of the emergence of new infectious diseases and drug resistance [8,9]. *C. procera* was investigated qualitatively and quantitatively by GC-MS. Besides the cardenolides, the other plant-derived given phytochemicals are alkaloids, flavonoids, sterols, saponins, tannins, triterpenes and hydrocarbons coumarins. The reported phytoconstituents contains fatty acids, hydrocarbons, amino acids, proteases, resins and many minerals [10]. The plant is reported for analgesic activity, antimicrobial activity, antioxidant activity, anti-pyretic activity, insecticidal activity, cytotoxicity activity, hepatoprotective activity, pregnancy interceptive properties, purgative properties, procoagulant activity and wound healing activity [11,12]. ESKAPE is an acronym for their names and a reference to their ability to escape the effects of commonly used antibiotics through evolutionarily developed mechanisms [13-17]. Medicinal herbs are more significant to the health of individual and community. In this manuscript author demonstrate the binding form of these compounds in adhesion of the bacterium to the host cell and thus helpful in preventing infection and decreases mortality due to this disease.

Methodology

Molecular Docking: Ligands Preparation

The 2D structures of *Calotropis procera* 83 phytoconstituents were downloaded by PubChem online server which is a freely available. The structures were then converted into Mol 2 format with the help of Chem3D Ultra, and PyRx tool [18].

Target Selection and Preparation

Earlier reported three-dimensional (3D) structure of the Crystal structure of *S. aureus* TyrRS in complex with SB-239629 (PDB ID: 1JIJ) was retrieved from RCSB PDB (https://www.rcsb.org/structure/1JIJ). The water molecules as well as co-crystallized ligands were deleted from the PDB file [19].

Docking Protocol

To determine the binding mode and interaction of the selected compounds and target, docking studies were performed using Auto Dock/vina [20,21]. The pdbqt files of the receptor protein, and *C. procera* compounds along with the grid box getting at the active site of the receptor for compounds binding was done through Auto Dock GUI program. The grid size boundaries along X, Y, and Z axes was scaled at 40 Å with a grid spacing of 1 Å to allow proper binding flexibility at the docked site. The output pdbqt files were written into a configuration (conf) file. The receptor was treated rigid entity whereas ligands were kept flexible to attain the best fitting conformation with respect to the receptor complex. The generated solutions of docking were clustered and those with root mean square deviation (RMSD) value <1.0 Å were considered only. The binding conformation of ligands with the lowest binding affinity was characterized as the most stable conformation of the ligands with respect to the receptor [22,23].

Physiochemical Properties Studies

The Physio-chemical properties of the selected compounds were predicted by freely available online Swiss ADME software. In compound analysis RO5, the molecular weight (M.W.) is >500, number of accepted hydrogen bond (O and N atoms) and number of donor's hydrogen bond (NH and OH) within Lipinski's limits range from 0-10 (H-bond acceptor) and 0-5 (H-bond donor) respectively. Lipophilicity (log P) and Topological Polar Surface Area (TSPA) values are crucial properties for the forecast of oral liability of drug molecules. The ranging of log P from (0-5) our most of the compounds range from 0.94-5.00 (≤5), which is the acceptable limits for drug to penetrate bio-membrane [24-26].

Receptor-Ligand Interaction Analysis

The interaction analysis of the protein-ligand and interaction of the binding sites studied by using the PyMOL The possible dock conformations of the 2D ligand-receptor interactions by using Discovery Studio. Further, binding analysis by using visualization approach was carried out to understand the binding pattern of the drug with proteins [27-30].

Results

Molecular Docking

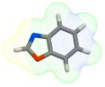
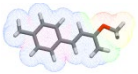
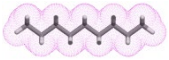
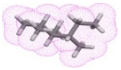
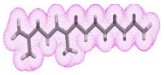
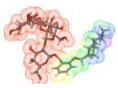
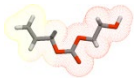
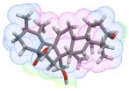
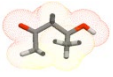
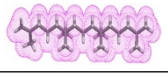
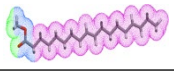
Molecular docking was carried out using the using Auto Dock/vina. The grid box getting at the active site of the receptor for compounds binding was done through Auto Dock GUI program. Grids were generated for the prepared proteins. For *S.aureus* gyrase complex, the grid was generated around SB-239629.

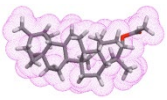
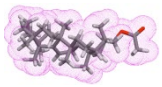
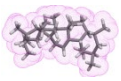
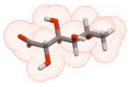
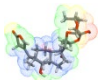
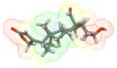
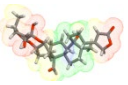
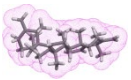
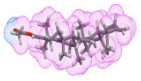
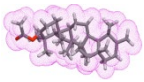
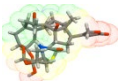
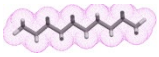
Grid Box Preparation (By using AutoDock Vina).

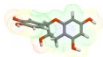
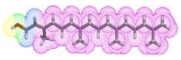
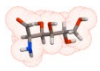
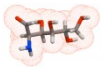
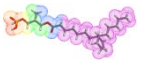
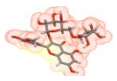
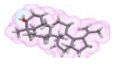
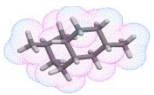
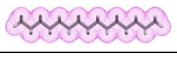
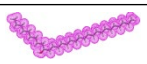
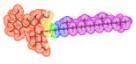
	X	Y	Z
Centre of the grid box	-11.179	11.702	91.461
Dimensions of the grid box	20	22	20

Table 1: Grid Box Preparation (By using AutoDock Vina).

The docked PDB ID: 1JIJ bound ligand SB-239629 had docking score -7.5 kcal/mol. SB-239629 is the (2S)-2-[[(2S)-2-Amino-3-(4-hydroxyphenyl)propanoyl]amino]-2-[(2S,3S,4S,5S)-1,3,4,5-tetrahydroxy-4(hydroxymethyl) piperidin-2-yl]acetic acid Table 2.

S.No.	Compounds	3D structure	DDG
1	(6Z), (9 Z) Pentadecadien 1-ol		-5.8
2	(E)-3-(4-methoxyphenyl-2-O-beta		-6.1
3	(E)-Octadec-7-enoic acid		-5.6
4	1,2-dihexadecanoyl -3-phosphatyl		-6.3
5	1,3,5-Triisopropylbenzene		-6.9
6	2,3,4-trimethylhexane		-4.9
7	2,6 dimethyl tetra-1,5-decaene		-5.7
8	2-H Benzofuranone 5,6,7, 7A		-5.4
9	2-limonenyloxybenzoyl-		-6.4
10	2-propenyl-2-hydroxyethyl		-5.4
11	3,7,11-Trimethyl-2,6,10,12		-6.6
12	3b,27-dihydroxy-urs-18		0.1
13	3b,27-dihydroxy-urs-18-en-	13	-1.3
14	4-hydroxy-4-methylpentan-2-one		-5.0
15	6,10,14-trimethyl, Pentadecanone -2		-6.5
16	9,12,15-Octadecatrienoic acid		-6.2

17	18 H-urs-12, 2 0(30)-dien-3-yl acetate		-6.6
18	a-amyrin acetate		-5.8
19	a-Amyrin		-5.5
20	Acetic acid		-3.5
21	a-rhamnose		-6.0
22	Benzoylisolineolone	22	-3.5
23	Benzoyllineolone	23	-5.4
24	Calactin		-7.8
25	Calotoxin		-7.8
26	Calotropagenin		-7.1
27	Calotropenyl acetate	27	-6.6
28	Calotropin		-5.7
29	Calotroprocerol-A		-6.5
30	Calotroprocerone-A		-0.9
31	Calotroproceryl acetate A		-10.0
32	Calotropursenyl acetate B		-4.6
33	Cardenolide 2-oxovoruscharin		-5.9
34	Choline		-5.8
35	D-arabinose		-6.5
36	Decane		-1.8
37	Diterpene		-3.9

38	Epicatechin		-5.8
39	Ergost-5-en-3-ol		-4.6
40	Farnesol isomer		-6.6
41	Ferulic acid		-8.1
42	Gallic acid		-7.9
43	Glucosamine		-6.0
44	Glucose		-6.8
45	Glyceryl mono-oleolyl-2-phosphate		-7.3
46	Gofruside		-6.2
47	Isorhamnetin-3-O-robinobioside		-6.5
48	Isorhamnetin-3-O-rutinoside		-7.8
49	Isovaleric acid		-8.8
50	L-rhamnose		-10.2
51	Lupeol		-10.4
52	Methyl myrisate		-4.8
53	Multiflorenol		-6.0
54	Naphthalene decahydro2,6 dimethyl		-6.3
55	n-Eicosane		-5.7
56	n-Pentadecane		-1.2
57	p-coumaric acid		-5.7
58	Proceragenin		-5.7
59	Proceranol n-triacontan-10ß-ol		-5.0
60	Procerasesterterpenoyl		-6.4

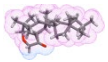
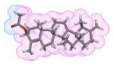
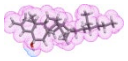
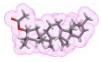
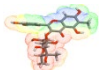
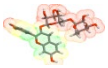
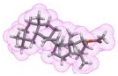
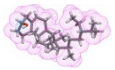
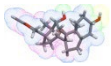
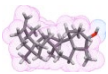
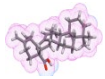
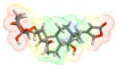
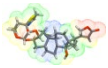
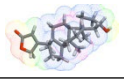
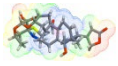
61	Proceraursenolide		-6.1
62	Proceroside		-6.0
63	Procerursenyl acetate		-6.9
64	Procesterol		-6.8
65	Pseudo-taraxasterol acetate		-10.0
66	Quercetagetin-6-methyl ether		-8.0
67	Quercetin-3 rutinoside		-7.9
68	ß-Amyrin acetate		-4.8
69	ß-Amyrin		-8.4
70	ß-Sitosterol		-8.7
71	Stigmasta-5,22-dien-3-ol		-7.9
72	Stigmasterol		-8.7
73	Syriogenin		-9.1
74	Taraxasterol		-6.4
75	Terpenoid glycosides		-8.7
76	Urosolic acid		-5.6
77	urs-19(29)-en-3-yl acetate	77	-6.0
78	Uscharidin		-6.8
79	Uscharin		-4.4
80	Uzarigenin		-6.2
81	Vanillic acid		-7.0
82	Voruscharin a-calotropeol	82	-0.4
83	Voruscharin		-2.0

Table 2: Docking score for the phytoconstituents of *C. procera* with PDB ID: 1JIJ.

In molecular docking the screening of 83 plant-derived compounds produced log files, where the affinity (kcal/mol) obtained and docked poses for discrete compounds analyzed. This log-file screen-out because of the analysis of binding score or docking score.

Physio-chemical Properties

The physiochemical analysis and RO5 analysis shows that all those compound having >500 MW, >10 number of rotatable bonds (nrotb), number of atoms (natoms), hydrogen bond donor and acceptor >5 bonds and logP value is >3 and the parameter of Lipinski's Rule of five unfollow (nVio). Out of these three compounds properties L-rhamnose showing zero nVio which is good for bioavailability of the drug showing in Table 3.

S.No.	MW	miLogP	TPSA	natoms	nON	noHNH	nVio	nrotb
Calotroproceryl acetate A	476.75	8.45	26.30	35	2	0	1	2
L-rhamnose	164.16	-1.64	97.98	11	5	4	0	4
Lupeol	426.73	8.29	20.23	31	1	1	1	1

Table 3: Physio-chemical parameters of the selected phytocompounds of *C. procera* by using SwissADME.

In this screening of docking score 03 phytocompounds which has good binding affinity above -10 which Calotroproceryl acetate A (-10.1), L-rhamnose (-10.2) and Lupeol (-10.4). The interaction analysis of PDB ID: 1JIJ complexes are shown in Figure 1.

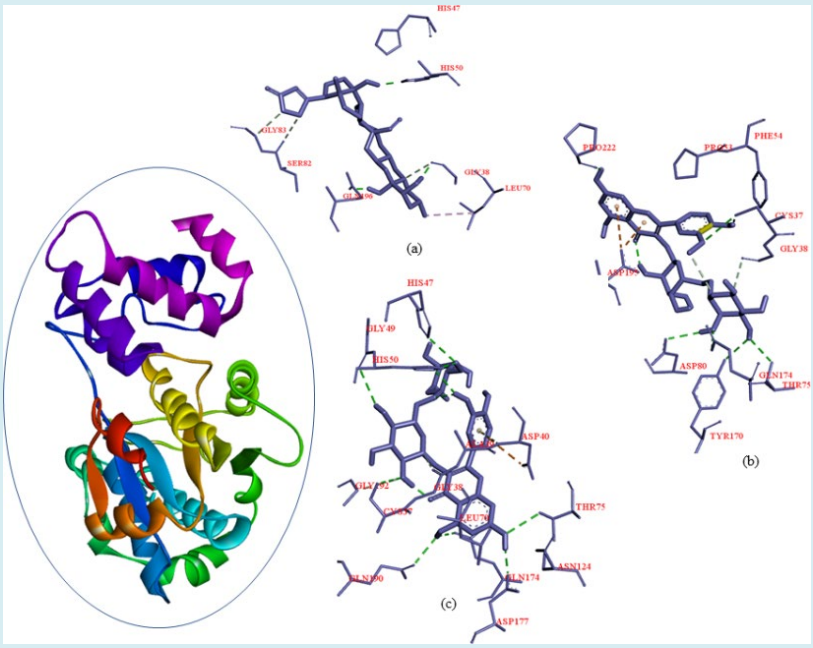


Figure 1: Structure of PDB ID: 1JIJ and the selected top 3 highest biding scores compounds (a-c) Calotroproceryl acetate A, L-rhamnose and Lupeol.

The selected phytocompounds 2D interaction analysis showing involved residues and bonds in Calotroproceryl acetate A, L-rhamnose and Lupeol shows the highly interaction within active site cavity, which is shown in Figures 2-4.

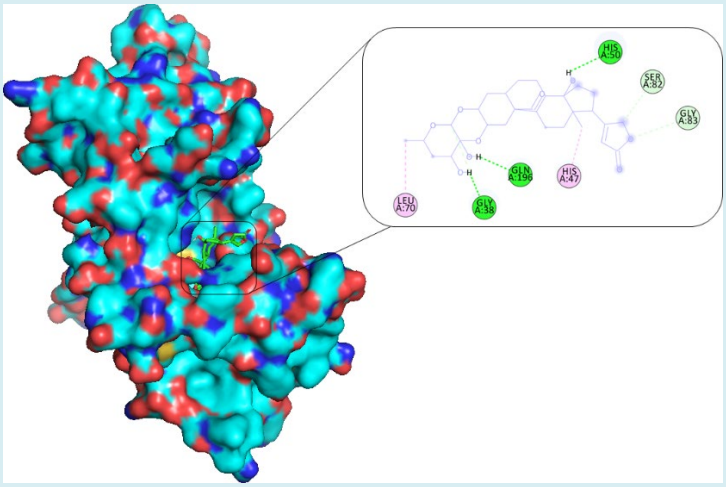


Figure 2: 2D interaction analysis showing involved residues and bonds. The PDB ID: 1JIJ complex with Calotroproceryl acetate A.

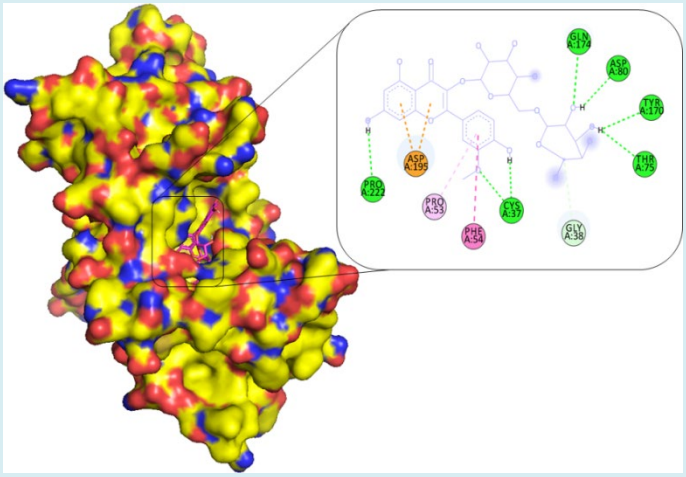


Figure 3: 2D interaction analysis showing involved residues and bonds. The PDB ID: 1JIJ complex with L-rhamnose.

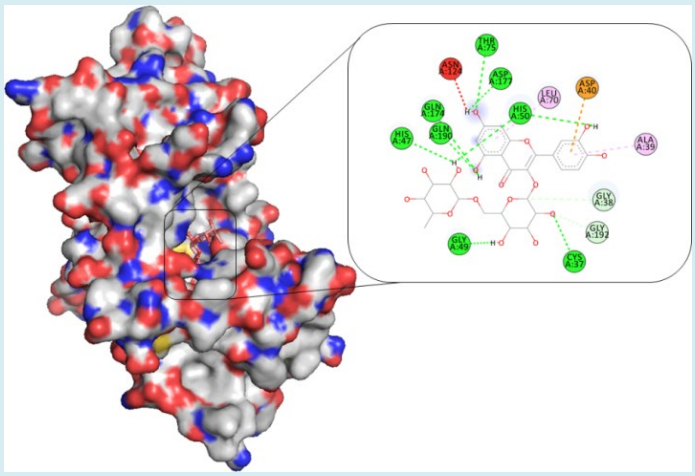


Figure 4: 2D interaction analysis showing involved residues and bonds. The PDB ID: 1JIJ complex with Lupeol.

Receptor-Ligands Interaction Analysis

The receptor-ligands interaction analysis of *S. aureus* TyrRS ternary complexes with plant-derived compounds as the putative inhibitor. In complex file interaction studies showing all these natural compounds closely interacted with active sites /substrate binding domains. The interaction residues of the ternary structure of *S. aureus* TyrRS protein are Cys37, Gly38, Ala39, Asp40, His47, Gly49, His50, Leu70, Thr75, Gln174, Asp177, Gln190, Gly192, Asp195 and Pro222. This interaction study confirmed that there was the involvement of Hydrogen bond (H-bond), Carbon-Hydrogen bond (C-H bond) and Pi-Alkyl bond as shown in Table 4. The interaction study showing the strong interaction between *S. aureus* TyrRS protein with natural compounds Lupeol (-10.4) interactions showing the maximum eight hydrogen bond interaction with CYS37, HIS47, GLY49, HIS50, THR75, GLN174, ASP177 and GLN190 residues which are closely interacted in binding cavity.

S.No.	Ligand	Interacting Residues	Distance (Å)	Category	Type
1	Calotroproceryl acetate A	Gly38	1.58	H-Bond	Conventional
		His47	5.31	Pi-Alkyl	Hydrophobic
		His50	1.99	H-Bond	Conventional
		Leu70	4.09	Pi-Alkyl	Hydrophobic
		Ser82	3.63	Carbon H-Bond	Conventional
		Gly83	3.36	Carbon H-Bond	Conventional
		Gln196	1.83	H-Bond	Conventional
2	L-rhamnose	Cys37	1.99	H-Bond	Conventional
		Gly38	3.58	Carbon H-Bond	Conventional
		Pro53	4.13	Pi-Alkyl	Hydrophobic
		Phe54	5.58	Pi-Alkyl	Hydrophobic
		Thr75	2.82	H-Bond	Conventional
		Asp80	2.67	H-Bond	Conventional
		Tyr170	2.80	H-Bond	Conventional
		Gln174	2.80	H-Bond	Conventional
		Asp195	4.52	Pi-Anion	Hydrophobic
		Pro222	2.54	H-Bond	Conventional
3	Lupeol	Cys37	3.44	H-Bond	Conventional
		Gly38	3.72	H-Bond	Conventional
		Ala39	5.36	Pi-Alkyl	Hydrophobic
		Asp40	4.15	Pi-Anion	Hydrophobic
		His47	2.79	H-Bond	Conventional
		Gly49	3.06	H-Bond	Conventional
		His50	2.38	H-Bond	Conventional
		Leu70	5.41	Pi-Alkyl	Hydrophobic
		Thr75	3.00	H-Bond	Conventional
		Gln174	2.56	H-Bond	Conventional
		Asp177	2.10	H-Bond	Conventional
		Gln190	2.79	H-Bond	Conventional
		Gly192	3.58	H-Bond	Conventional

Table 4: Detailed molecular interactions obtained following the rigid ligand docking.

Discussion

In the present research, we have summarized the current traditional use of medicinal plants *Calotropis procera* Ait. (Asclepiadaceae) phytocompounds against *S. aureus* TyrRS [2,4,10-12]. The data provided here must benefit providing a practical base for further scientific research on these plants and their role in preventing antimicrobial infection [13-15]. Consequently, more plant-derived naturals compounds of *C. procera*, the docking analysis, the 83 natural compounds against *S. aureus* TyrRS having top three good binding affinity scores compounds above -10 which Calotroproceryl acetate A (-10.1), L-rhamnose (-10.2) and Lupeol (-10.4) [10,18-21]. The physiochemical analysis and RO5 analysis shows that all those compound having >500 MW, >10 number of rotatable bonds (RB), hydrogen bond donor and acceptor >5 bonds and

logP value is >3 all the properties showing these compounds are good for bioavailability of the drug [24,25]. The predicted ligand binding site for *S. aureus* TyrRS protein showing pocket residues 36-54, 70-91, 170-196 and 221-241 [22,23]. The receptor-ligands interaction studies against *S. aureus* TyrRS ternary complexes with natural compounds as the putative inhibitor. In complex file interaction studies showing all these natural compounds closely interacted with active sites /substrate binding domains. The interaction analysis of binding residues of the ternary structure of *S. aureus* TyrRS protein are Cys37, Gly38, Ala39, Asp40, His47, Gly49, His50, Leu70, Thr75, Gln174, Asp177, Gln190, Gly192, Asp195 and Pro222. This interaction study confirmed that there was the involvement of Hydrogen bond (H-bond), Carbon-Hydrogen bond (C-H bond) and Pi-Alkyl bond [26,27]. The interaction study showing the strong interaction between *S. aureus* TyrRS protein with compound Lupeol which dock score highest -10.4 and it shows the maximum eight hydrogen bond which is interacted with CYS37, HIS47, GLY49, HIS50, THR75, GLN174, ASP177 and GLN190 residues and all the residues are closely interacted with active sites [28]. The plant-derived compounds of *C. procera* determining the therapeutic target for antimicrobial strains therefore the targeting compounds might be an advantageous step in the direction of therapeutic development.

Conclusion

In the previous studies the ethno-botanical and traditional uses of C. procera plant-derived natural compounds, have gotten a lot of consideration are notable for their adequacy and are generally believed to be harmless for human use. Using plant-derived compounds is the ancient approach for searching the new target molecules which helps in the medication of the various diseases. In previous studies the review of the published literature on *C. procera* shows these phytoconstituents are in the various remedy of ethnic groups, as well as Ayurvedic and traditional uses. Researchers are exploring the therapeutic potential of this plant as it is likely to have more therapeutic properties than are currently known. *C. procera* phytocompounds having higher flavonoids content which is involved in antibacterial and antioxidant profiles. Plant-derived compounds of *C. procera* plant showing the antibacterial activity against an ESKAPE pathogenic strains, as well as an interesting antioxidant profile. These phytocompounds could be considered for its antibacterial potential and could be a valuable source for the design and development of new antibacterial compounds. The potential target studies of *C. procera* phytocompounds using molecular docking which helps to find out the best binding pose of the target protein to elucidate a potential mechanism of action for this compound. As further studies, docking with important target PDB ID:1JIJ, tyrosyl-tRNA synthetase from *S. aureus* were studied as potential targets, and a correlation between the observed inhibitory activity and the *in silico* molecular docking scores was obtained. Moreover, compounds also approved by RO5 drug likeness properties. The possible inhibitors of *S. aureus* tyrosyl-tRNA synthetase protein such as L-rhamnose and Lupeol were selected because of high binding affinities and interactions with catalytic triad residues. *In vitro* work toward this path may give essential information of these proteins that make these proteins magnificent objective for drawing closer for remedial medicine.

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