Molecular docking studies of *Staphylococcal clumping* factor A inhibitors from *Elettaria cardamomum* and *Acacia nilotica*

Rosy Kumari and Ratish Chandra Mishra

Department of Genetics,
Maharshi Dayanand University,
Rohtak-124001, Haryana, India
Email: rosyaryanature@gmail.com
Email: rcmishra0001@gmail.com

Shivani Yadav

Department of Computer Science and Application,
Maharshi Dayanand University,
Rohtak 124001, Haryana, India
Email: shivaniyadav17@gmail.com

Jaya Parkash Yadav*

Department of Genetics,
Maharshi Dayanand University,
Rohtak-124001, Haryana, India
Email: yadav1964@rediffmail.com
*Corresponding author

Abstract: Clumping factor A (ClfA) is a cell wall adhesin protein of methicillin-resistant *Staphylococcus aureus* (MRSA) which plays an important role in interaction with host. In the present study, virtual screening of potential inhibitors from *Elettaria cardamomum* and *Acacia nilotica* was carried out against ClfA using autodock 4.0. Top score phytoligands were further subjected to absorption, distribution, metabolism, excretion (ADME) analysis. Among ninety nine phytochemicals screened, santalol, stigmasterol, undecylenic acid, β-sitosterol, bergamotol, geraniol showed high dock score against ClfA. In addition undecylenic acid, β-sitosterol and geraniol follows Lipinski rule and does not inhibit the metabolic enzyme cytochrome p450. Therefore, these compounds can be the potential source of drug development against MRSA.

Keywords: MRSA; clfA; *Elettaria cardamomum*; *Acacia nilotica*; phytoligands; molecular docking; druglikness; ADME; absorption, distribution, metabolism, excretion; MBE; minimum binding energies; PDB; protein data bank.

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Biographical notes: Rosy Kumari is a PhD scholar at the Department of Genetics, M. D. University, Rohtak, Haryana, India. She obtained her BSc (Hons) in Biochemistry and MSc in Plant Molecular Biology and Biotechnology from the University of Delhi, India. Her research interests include natural products research, *In silico* drug design and nanoscience.

Ratish Chandra Mishra is a research scholar at the Department of Genetics, M. D. University, Rohtak, Haryana, India. He obtained his BSc in Lifesciences from the University of Delhi and MSc in Biosciences, from Jamia Millia Islamia, Delhi, India. His research interests include medicinal plant research, bioactive compound isolation, molecular docking and nanomedicine.

Shivani Yadav is a PhD scholar at the Department of Computer Science and Application, M. D. University, Rohtak, Haryana, India. She obtained her BTech Computer Science and Engineering from Kurukshetra University, Kurukshetra and MTech Computer Science and Engineering from Maharshi Dayanand University, Rohtak. Her research interests include software engineering and computational drug design.

Jaya Parkash Yadav is Dean Faculty of Life Sciences and Professor at the Department of Genetics, M. D. University, Rohtak, Haryana, India. He has supervised 25 PhD scholars and more than 50 MSc disserties. He has published about 200 research articles in peer reviewed journals. His research interests include ethanomedicine, microbial and plant genetics, recombinant DNA technology, nanosciences and pharmacological studies.

1 Introduction

As a major cause of bacterial disease, Methicillin Resistant *Staphylococcus aureus* (MRSA) has appeared worldwide since 1960s (Lee et al., 2018). On breach of the skin or mucosal barriers, it causes a wide range of infections from superficial to life-threatening invasive diseases. *S. aureus* cause many human ailments including skin and soft tissue lesions, inflammation, gingivitis (Abbas et al., 2017); toxic shock (Tong et al., 2015); bone infection in children (Hardgrib et al., 2016); necrotising pneumonia and medical devices related infections (Wen et al., 2018). The virulence nature of *S. aureus* is multi-factorial and depend on a number of staphylococcal exotoxins, biofilm formation, immune evasion by secreting proteases and various adhesion molecules such as fibronectin-binding protein (FnBP), protein A, clumping factor (Otto, 2012; Hodille et al., 2017). Cell wall adhesion protein clumping factor A (ClfA) is a significant bacterial adhesion protein that helps to infect human fibrinogen by adhering to it (Zecconi and Scali, 2013; Herman-Bausier et al., 2018). ClfA plays an important role in the molecular pathogenesis of various diseases such as endocarditis, septic arthritis, renal abscesses and septicemia (Flick et al., 2013). ClfA contains 933 amino acids, cross-connections to fibrinogen essential for platelet aggregation and clumping (Siboo et al., 2001; Ashraf et al., 2017). The significant virulence factor responsible for clumping pathogen in blood plasma is Clumping factor A (ClfA). The factor helps in evading immune system by inhibiting phagocytosis (Higgins et al., 2006). It also promotes the attachment of *S. aureus* to biomaterial surfaces (Vaudaux et al., 1995). ClfA were predicted to be non human homologues by BLASTp tool (Deodurg et al., 2016). Medicinal plants are at great attention to the researchers as they are the rich source of

therapeutic compounds. Methanol extract of *Elettaria cardamomum* seed pod and *Acacia nilotica* twig extract exhibited highest activity against *S. aureus* in our previous studies. GC-MS analysis revealed various phytochemicals in *A. nilotica* extract which may possess antimicrobial potential (Kumari et al., 2019). *Acacia nilotica* (L.) is imperative nitrogen fixing leguminous multipurpose plant. It is used for dysentery, bleeding piles, leprosy leucoderma, tuberculosis, smallpox and HIV (Jame, 2018). In different regions of Chhattisgarh (India) it is used by traditional healers in treatment of various cancer types of mouth, bone and skin (Ali et al., 2012). *Elettaria cardamomum* known as small cardamom or chhoti elaichi belongs to the Zingiberaceae and also called as "Queen of Spices". From ancient times its seeds are used to cure muscle, asthma, constipation, colic, diarrhea, breath freshener, hypertension, epilepsy and skin care (Ghosh et al., 2015; Asakawa et al., 2017).

Molecular-docking-based screening is an economic viable tool in drug discovery driven by rapidly improving computational platforms (De Ruyck et al., 2016). Using this approach, large database of possible chemical compounds can be screened before proceeding to experimental research. Autodock4.0 software has been widely used for precise molecular docking predictions (Froufe et al., 2011; Ferreira et al., 2015). The aim of this study is to determine molecular docking to find out the phytochemicals which exhibit high binding affinity against clumping factor A of *S. aureus.*

2 Materials and methods

2.1 Protein preparation

The ClfA structure (PDB ID 1N67) was downloaded in PDB format (https://www.rcsb.org/structure/1N67) from Research Collaboratory for Structural Bioinformatics (RCSB). Before proceeding to molecular docking analysis extra groups including water molecules and other heteroatoms were removed.

2.2 Ligands preparation

The structure of ligands were identified from Pubchem, drawn in Chemsketch and saved as 2D mol file 2000. All files were converted into PDB format using Open Babel 2.3.2.

2.3 Molecular docking

Docking of various ligands to the clumping factor A of *S. aureus* was performed. Autodock 4.0 version 1.5 6rC3 docking software was used to create grid maps (Mishra et al., 2020). The grid box size was generated for asparginine (Asn) A 267 coordinates: 14.803, 83.081 and 80.245 for *x*, *y* and *z* respectively, covering all the residues of amino acids in the active ligand binding pocket. Lamarckian genetic algorithm was used to select the best conformers. A maximum of 10 conformers (run) were generated for each compound during the docking phase.

2.4 ADME analysis

The freely accessible SwissADME web tool (http://www.swissadme.ch) was used for calculating ADME properties (Daina et al., 2017).

3 Results and discussion

Many scientists have studied the ClfA protein as a prospective target due to its virulence nature. Recombinant ClfA vaccine protects against *S. aureus* infection. In the present undergoing clinical trials ClfA has also been used as an antigen in production of several multivalent vaccines against *S. aureus* (Anderson et al., 2016). The structure of ClfA protein elucidated using X-ray diffraction (Deivanayagam et al., 2002) has been shown in Figure 1. The present docking studies revealed the interactions of ClfA of *S. aureus* with the ninety-nine ligands from *Elettaria cardamomum* and *A. nilotica* twig extract by Autodock 4, with respect to binding energy, number of hydrogen bonds and amino acids involved in bond formation. Minimum binding energies (MBE) of the selected ligands against the ClfA are shown in Tables 1 and 2. Among 99 molecules, β-santalol, stigmasterol, undecylenic acid, β-sitosterol, bergamotol and geraniol showed lower MBE with ClfA (Figure 2 and Table 3). More negative the binding energy, better the binding affinity of ligand with protein and also selected as lead compound in this study. In our previous gas chromatography-mass spectrometry (GCMS) based studies we found percentage area of these lead compounds i.e., 1.14%, 0.33%, 0.46%, 0.97%, 0.46% and 0.46% respectively (Kumari et al., 2019). These compounds were well known for their antimicrobial activity e.g., santalol against *S. aureus* (Hire and Dhale, 2012) and influenza virus A (H3N2) at concentration of 100 µg/mL (Paulpandi et al., 2012). According to report shown by Adnan et al, stigmasterol inhibits the growth of MRSA by blocking its protein synthesis and it has been proven to be a non-toxic to human cells (Adnan et al., 2017). A fatty acid undecylenic acid showed the significant docking score in our study. This compound is used as a topical agent for the treatment of fungal infections (Mionić Ebersold et al., 2018). β-Sitosterol which is a known secondary metabolite present in oil producing parts of natural products; fruits, seeds etc. exhibits various biological properties including antimicrobial activity against *S. aureus* with Minimum Inhibitory Concentration (MIC) value of 25 µg/mL (Odiba et al., 2014), anti-diabetic (Sujatha et al., 2010), anti-cancer (Iyer and Patil, 2012). Geraniol demonstrated anti-biofilm and anti-inflammatory efficacy against *Staphylococcus epidermidis* infections (Arunachalam et al., 2018). Geraniol enhanced the kanamycin and cefotaxime antibiotic effect against MRSA (Melo Coutinho et al., 2015; Kannappan et al., 2019).

Figure 1 Structure of ClfA protein (see online version for colours)

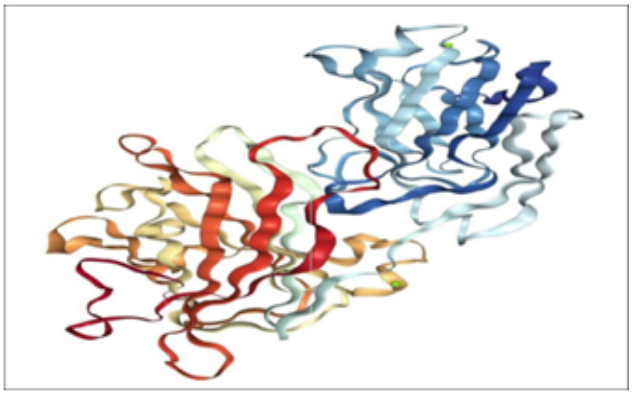


Figure 2 Structures of lead molecules with minimum binding energy (MBE) in kcal/mol

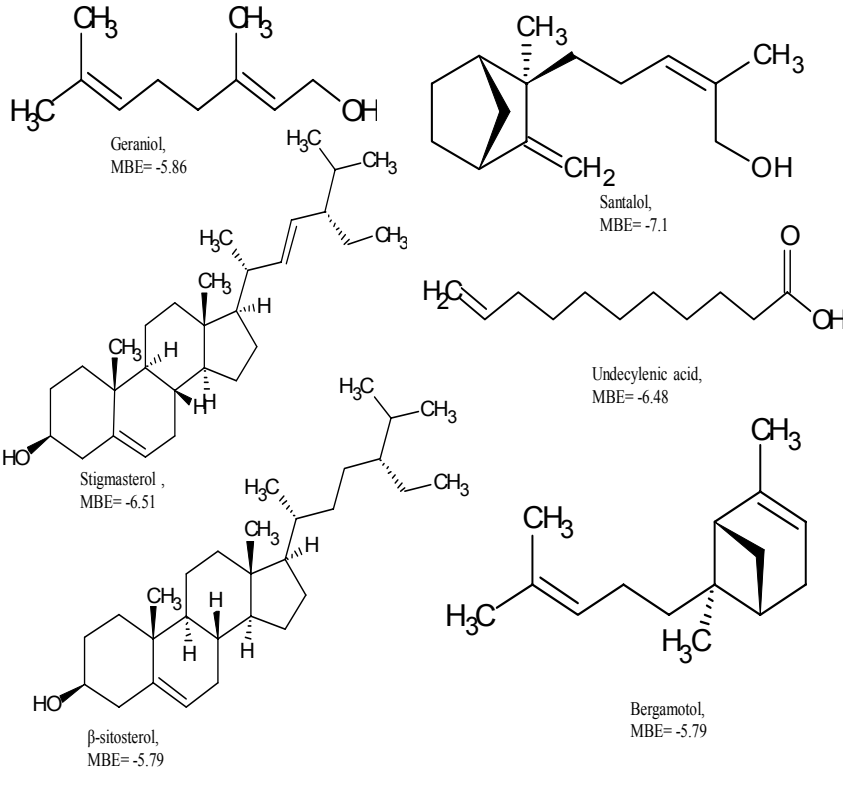


Table 1 Binding energy of *Acacia nilotica* compound with ClfA

S. No.	*Compounds*	*MBE in (kcal/mol) against ClfA*
1	1,3,5,7-Tetroxane	–2.52
2	1,8,11-Heptadecatriene	–4.3
3	1, E–6, Z–11-Hexadecatriene	–3.97
4	2,2'-Oxybis[Ethanol]	–3.94
5	3-Tetradecyn–1-ol	–3.28
6	6-(P-Tolyl)–2-methyl–2-heptenol, trans-	–5.16
7	9,12-Octadecadienoic acid	–4.36
8	9,12-Octadecadienoicacid(z, z)-, methylester	–4.82
9	9,12-Octadecadienoylchloride	–3.21
10	9-Octadecenamide	–3.52
11	9-Octadecenoic acid	–4.18
12	12-Hydroxy–9-octadecenoic acid	–4.9
13	13-Hexyloxacyclotridec–10-en–2-one	–4.91
14	14-Methyl–8-hexadecyn–1-ol	–4.19

Table 1 Binding energy of *Acacia nilotica* compound with ClfA (continued)

S. No.	*Compounds*	*MBE in (kcal/mol) against ClfA*
15	Alanine	–2.77
16	Bergamotol, z-.alpha.-trans	–5.79
17	Beta.-Santalol	–7.1
18	Cis – Lanceol	–5.51
19	Limonene	–4.05
20	Neophytadiene	–4.05
21	N-Hexadecanoic acid	–3.98
22	Oct–2-ynoic acid	–3.09
23	Octadecanoic acid	–4.6
24	Stigmast–5-en–3-ol, (3.beta.)-	–6.48
25	Stigmast–5-en–3-yl (9Z)–9-octadecenoate	–5.63
26	Stigmasterol	–6.51
27	Undecylenic acid	–6.48

Table 2 Binding energy of *Elettaria cardamomum* compound with ClfA

S. No.	*Compounds*	*MBE in (kcal/mol) against ClfA*
1	2-Furanmethanol	–4.33
2	2-Propanone, 1-(acetyloxy)-	–3.54
3	Cyclopent–4-ene–1.3-dione	–4.77
4	2(3h)-Furanone, dihydro-	–5.10
5	2H-Pyran–2-one, tetrahydro–6-methyl-	–4.99
6	Cyclohexanone	–4.55
7	2,4-Dihydroxy–2.5-dimethyl–3(2h)-furan–3-one	–3.89
8	(1,3-Dimethyl–2-methylenecyclopentyl)methanol	–4.32
9	2-Hydroxy-gamma-butyrolactone	–4.42
10	Benzeneacetaldehyde	–4.56
11	2,5-Anhydro–1.6-dideoxyhexo–3.4-diulose	–3.92
12	Phenol, 2-methoxy-	–4.04
13	1,6-Octadien–3-ol, 3,7-dimethyl-	–4.61
14	2-Acetyl–2-hydroxy-.gamma.-butyrolactone	–3.75
15	4H-Pyran–4-one,2,3-dihydro–3.5-dihydroxy–6-methyl-	–4.09
16	P-Mentha–1.5-dien–8-ol	–4.38
17	1-Isopropyl–4-methyl–3-cyclohexen–1-ol	–5.05
18	Benzenemethanol, alpha–4-trimethyl-	–4.48
19	(+)-Alpha-terpineol (p-menth–1-en–8-ol)	–4.43
20	2,3-Dihydro-benzofurane	–4.01

Table 2 Binding energy of *Elettaria cardamomum* compound with ClfA (continued)

S. No.	*Compounds*	*MBE in (kcal/mol) against ClfA*
21	2,6-Octadien–1-ol, 3,7-dimethyl-, (e)-	–5.86
22	Azepan–2-one	–4.45
23	1,2-Benzenediol, 4-methyl-	–4.13
24	Cyclohexene,3-acetoxy–4-(1-hydroxy–1-methylethyl)–1-methyl-	–4.13
25	2-Methoxy–4-vinylphenol	–4.24
26	2h-Pyran–3-ol, 6-ethenyltetrahydro–2.2,6-trimethyl-	–4.45
27	2H-Pyran, tetrahydro–4-methyl–2-(2-methyl–1-propenyl)-	–4.30
28	Cyclohexanemethanol, 4-hydroxyalpha–4-trimethyl-	–4.65
29	Beta-Pinene, 3-(acetylmethyl)-	–3.79
30	3-Cyclohexene–1-methanol, alpha–4-trimethyl-	–4.43
31	1,2-Cyclohexanediol, 1-methyl–4-(1-methylethenyl)-	–4.89
32	Phenol, 2-methoxy–4-(2-propenyl)-	–4.47
33	4H–1.2,4-Triazole–3-thiol, 5-amino–4-cyclohexyl-	–5.18
34	2-Isopropylidene–5-methylhex–4-enal	–4.52
35	3-Cyclohexene–1-methanol, 5-hydroxy-alpha–4-trimethyl-	–4.43
36	Benzaldehyde, 4-hydroxy–3-methoxy-	–4.37
37	1,3,3-Trimethyl–2-oxabicyclo[2.2.2]octane–6.7- endo-diol	–4.56
38	2-((1R,4R)–4-Hydroxy–4-methylcyclohex–2-enyl)propan–2-yl acetate	–5.18
39	Limonene dioxide 4	–4.67
40	1-Methyl–4-(1-acetoxy–1-methylethyl)-cyclohex–2-enol	–5.40
41	Undecylenic acid	–3.56
42	7-Methyl–3-methylenehexahydrobenzofuran–2-one	–4.87
43	2H-Pyran–3-ol, 6-ethenyltetrahydro–2.2,6-trimethyl	–4.45
44	Methyl-alpha-[4-methylpentyl]oxiranmethanol	–4.57
45	(1S,2S,4S)-Trihydroxy-p-menthane	–4.97
46	2-Oxabicyclo[2.2.2]octan–6-ol, 1,3,3-trimethyl-	–4.92
47	Hydroxy-alpha-terpenyl acetate	–5.49
48	2(3H)-Furanone, dihydro–5.5-dimethyl–4-(3-oxobutyl)-	–5.57
49	Hydroxy-alpha-terpenyl acetate	–4.47
50	Acetic acid, 1-methyl–1-(4-methyl–5-oxo-cyclohex–3-enyl)ethyl ester	–4.85
51	Cis-Limonene oxide	–4.90
52	Hydroxy-alpha-terpenyl acetate	–4.47
53	2-Oxabicyclo[2.2.2]octan–6-ol, 1,3,3-trimethyl-, acetate	–4.64
54	2-Oxabicyclo[2.2.2]octan–6-ol, 1,3,3-trimethyl-, acetate	–4.67

Table 2 Binding energy of *Elettaria cardamomum* compound with ClfA (continued)

S. No.	*Compounds*	*MBE in (kcal/mol) against ClfA*
55	10,11-Dihydroxy–3.7,11-trimethyl–2.6 dodecyl	–4.63
56	2-((2-(2-Methoxyethoxy)ethoxy)carbonyl)benzoic acid	–5.39
57	N-Hexadecanoic acid	–3.82
58	13-Hexyloxacyclotridec–10-en–2-one	–4.86
59	9,12-Octadecadienoic acid, methyl ester	–4.97
60	9-Octadecenoic acid (Z)-	–5.69
61	10,12-Hexadecadien–1-ol	–5.29
62	Cyclopropaneoctanoic acid	–5.22
63	Cyclopropaneoctanoic acid	–5.22
64	2-Oxabicyclo[2.2.2]octan–6-ol, 1,3,3-trimethyl-	–4.47
65	Carbonic acid, 2-dimethylaminoethyl ethyl ester	–3.48
66	3-Cyclopentylpropionic acid, 2-dimethylaminoethyl ester	–5.00
67	9,12-Octadecadienoyl chloride, (Z, Z)-	–3.39
68	Benzedrex	–4.33
69	9-Octadecenamide, n-butyl-	–2.66
70	Fumaric acid, 2-dimethylaminoethyl octadecyl ester	–2.74
71	10-Undecenoyl chloride	–4.25
72	Oxazole,2-butyl–5-ethyl–4-methyl-	–3.67

Lead phytoligands form hydrogen bonding with active site of receptor Clumping factor A, at Ser268, Val265 and Val329 amino acids (Figure 3 and Table 3). Among 6 lead molecules stigmasterol, undecylenic acid, β-sitosterol interact with ClfA via hydrobhobic interaction while β-santalol, bergamotol, geraniol interaction take place with both H-bond and hydrobhobic. The fibrinogen binding region of clumping factor has been identified which includes amino acids of ClfA gamma chain at 221–550 (Zong et al., 2005). Even calcium ion (Ca^{2+}) binds to an inhibitory site within ClfA at residues 310–321 and induces a conformational change that is incompatible with binding to the fibrinogen (O'Connell et al., 1998). Antibiotic tefibazumab inhibit the ClfA (at amino acid 229–545) binding with Fg (Ganesh et al., 2016). Therefore region of amino acid residues 220 to 550 were taken for molecular docking studies. Some natural compounds from neem such as salanin, astragalin, azadiradione, catechin, epicatechin and epoxyazdiradione showed the high dock score against ClfA (Gunamalai and Vanila, 2014). The mint-derived compound acetylated abietane quinone showed the excellent binding affinity to ClfA protein (Wadapurkar et al., 2018). ADME analysis of top 6 effective compounds was done (Table 4). Lipinski's rule of five state that there should not be more than one breach of the requirement necessary for screening medicine with pharmacological activity i.e., molecular weight < 500Da, amount of donor H-bonds < 5, no. of acceptor H-bonds < 10, and xlog P < 5 are important (Nogara et al., 2015).

The metabolising enzymes CYP 450 contribute significantly to elimination pathways of new chemical entities (Di, 2014).

Table 3 Effective phytochemicals hydrogen bonding with ClfA

Compounds Name	*Area %*	*Source plant*	*Gibbs free energy* (kcal/mol)	*No. of H-bond*	*Amino acid*	*Bond length* (in Å)
Beta-Santalol	1.14	*A. nilotica*	–7.1	2	Val329, Val265	2.734,2.757
Stigmasterol	0.33	*A. nilotica*	–6.51	0	0	0
Undecylenic acid	0.46	*A. nilotica*	–6.48	0	0	0
β-Sitosterol	0.97	*A. nilotica*	–6.48	0	0	0
Bergamotol	0.46	*A. nilotica*	–5.79	2	Ser268	2.908, 3.151
Geraniol	0.46	*E. cardamomum*	–5.86	3	Val329, Val265	2.68,3.46,2.63

Figure 3 Binding view of lead compounds such as: (a**)** bergamotol; (b) β-santalol; (c) geraniol; (d) β-sitosterol; (e) stigmasterol and (f) undecylenic acid with active site of ClfA (see online version for colours)

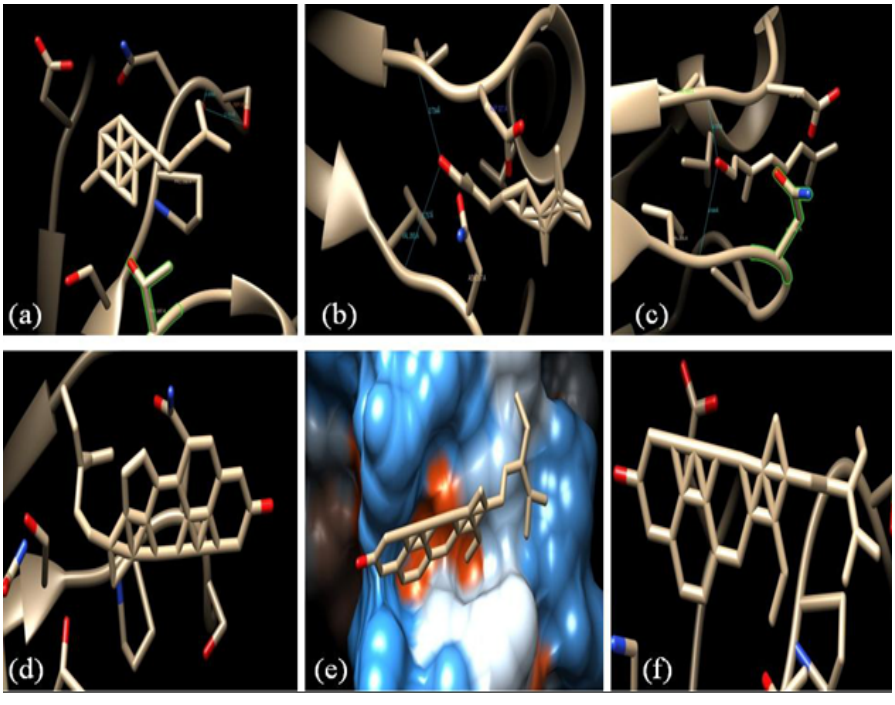
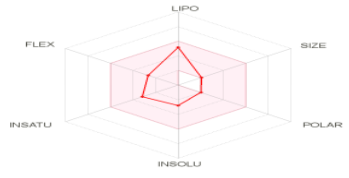
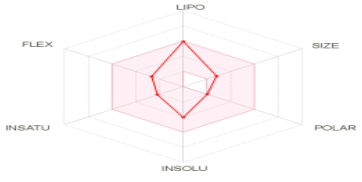
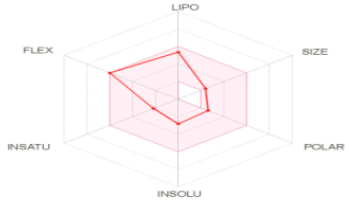
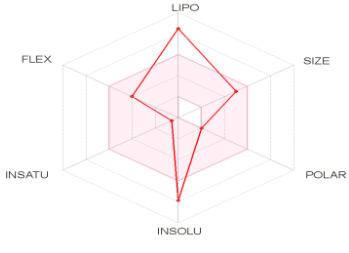
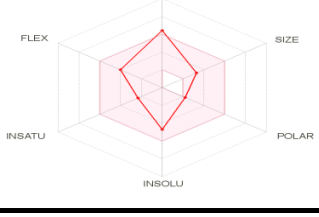


Table 4 ADME properties analysis (see online version for colours)

Compound name	*Druglikeness*	*GI absorption*	*Lipinski's rule*	*CYP 450 inhibitor*
Geraniol		High	Yes	No
Beta-Santalol		High	Yes	Yes
Stigmasterol		Low	Yes	Yes
Undecylenic acid		High	Yes	No
β-Sitosterol		Low	Yes	No
Bergamotol		High	Yes	Yes

4 Conclusion

Natural products are sources of novel biochemical diversity as well as part of the pharmaceutical compendium. Geraniol, β-sitosterol and undecylenic acid showed the optimal condition for drug likeliness, follows the Lipinski rule and does not inhibit metabolic enzyme cytochrome p450. Therefore, comprehensive study of function and mechanisms of specific inhibitors could open the way to develop novel therapies for diseases caused by *Staphylococcus aureus*.

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Conflicts of interest

The authors declare that there was no conflict of interest.

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