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Original Article

Molecular Docking Studies of Phytochemicals from *Leucas aspera* Targeting *Escherichia coli* and *Bacillus subtilis* Subcellular Proteins

Vivek Jagadeesan Sharavanan, Muthusaravanan Sivaramakrishnan, Ram Kothandan, Shanmugaprakash Muthusamy, Kumaravel Kandaswamy*

ABSTRACT

Objective: Bacterial subcellular proteins play a vital role in cell division, pilus assembly and virulence. In addition, such proteins were perceived as potential antimicrobial targets. Therefore, in this article we attempt to screen for potential phytochemicals that can target those subcellular proteins. **Methods:** A computational screening for phytochemicals from *Leucas aspera* with better bioavailability followed by molecular docking studies for better understanding of interaction between phytochemical and target proteins. **Results:** erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and Leucasperone B from *Leucas aspera* possess great binding affinity (> -100 kcal/mol) towards one or more bacterial subcellular protein targets and possess bioavailability. **Conclusion:** Based on the docking result we claim that erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and Leucasperone B could serve as an effective antimicrobial compounds to treat bacterial infections.

Key words: Docking, Phytochemicals, Antimicrobials, Subcellular proteins, Computational screening.

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INTRODUCTION

Drug resistant bacterial strains pose a serious challenge to physicians as they cause numerous recurrent infections in humans. Bacteral strains such as *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Streptococcus Pyogenes* (*S. Pyogenes*) gained attention for their ability to cause Cystic fibrosis, a chronic lung infection in humans.[1] Urinary Tract Infections,[2] Pharyngitis, respectively.[3] Usage of antibiotics was one of the well-established strategy to mitigate the effects of aforementioned bacterial infections. For instance, antibiotics such as Methicillin, Penicillin, macrolides, fluoroquinolones, sulfonamides, tetracycline and aminoglycosides have been proven to inhibit bacterial cell wall synthesis thereby halting the entire cell division process.[4] However, excessive usage of antibiotics resulted in emergence of drug resistant bacterial strains.[5] Resistance to antibiotic (methicillin) was first demonstrated in the year 1963 using Methicillin Resistant Staphylococcus aureus (MRSA). Subsequently, studies on Antimicrobial Resistance (AMR) was conducted on *S. aureus*, which exhibited abnormal cell division when exposed to antimicrobial peptides.[6] Furthermore, recent studies on AMR clearly shows that during the course of evolution, bacterial species can even gain resistance against antimicrobial peptides.[7-8] Therefore, a novel compound has to be identified to avoid the detrimental effects to drug resistant bacterial strains.

This article describes the use of virtual screening for selection of phytochemicals as a potential antimicrobial agent targeting *Escherichia coli* (*E. coli*) and *Bacillus subtilis* (*B. subtilis*) subcellular proteins. In this article, we confirm the antimicrobial nature of screened phytochemicals by Molecular docking studies. Findings from this study indicates that phytochemicals Leucosperone B, erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol from *Machilus odoratissima, Machilus thunbergii, Leucas aspera, Myristica fragrans* and *Iryanthera ulei* possesses bioavailability and favourable molecular interaction with amino acids present on the active site of selected bacterial subcellular proteins.

MATERIALS AND METHODS

Target selection

Studies have demonstrated that a diverse range of molecules such as proteins,[9-10] lipids[11-12] and DNA[13] are organized at specific locations in and/or around bacterial cell. Such a spatial organization of molecules is crucial in controlling various bacterial developmental programs such as cell wall synthesis, cell

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division and chromosomal segregation.[14-15] For example, FtsZ a cytoskeletal protein localized in a ring-like pattern at the septum of the cell is crucial for correct placement of the cell division site.[16-17] DisA, a checkpoint protein, moves and scans across the cytosol to check for lesions in DNA during chromosomal replication.[18] Penicillin binding protein (Pbp2), which is also co-localized with FtsZ at the septum, plays a major role in cell wall synthesis during cytokinesis. Therefore, in this study we have identified bacterial subcellular proteins such as FtsZ, MreB, MreC, ParM, ZapD and Alp7A (Table 1) from various bacterial species as potential antimicrobial targets.

Selection of subcellular protein targets

MreB is a bacterial cytoskeleton protein that has been identified as an actin homologue.[19] *E. coli* has a single MreB protein[19] and they form helical cables that are responsible for the maintenance of the rod shape of *E.coli*.[20] The membrane-associated MreB filaments coordinate bacterial cell-wall synthesis.[21] The helical structures formed by the MreB are thought to be involved in the spatial organization of penicillin-binding proteins (Pbps),[20] which spatially coordinates the cell wall peptidoglycan synthesis.

Studies in the past infer that antibiotic resistance of bacteria can be compromised by targeting its cytoskeleton proteins such as MreB and MreC.[22] MreC is a cytoskeleton protein that determines the shape of a bacterial cell. Bacterial strains that does not express a functional MreC undergoes significant morphological and growth defects.[23] Furthermore, MreC controls cell viability.[19] MreC forms a complex with MreB. The MreB, C and D proteins in *Escherichia coli* create an essential membrane-bound complex.[24]

ParM is a prokaryotic actin homologue which segregates large DNA plasmids. ParM helps the R1 plasmids (imparting multi-drug antibiotic resistance) to drive to the opposite ends of the cell before cytokinesis.[25-26] Structure of ParM protein shows plasmid segregating spindles.[27] ParM protein exhibits activity to that of ATPases and interacts well with the centromere like ParR- parC complex.[28]

ZapD protein belongs to a group of FtsZ regulatory proteins. It aids in midcell division machinery in *E. coli*.[29] ZapD protein stabilizes FtsZ assembly and forms the Z ring.[30] ZapD protein is a small soluble protein that binds and bundles FtsZ filaments. This Z-ring assembly supports the formation of divisomes and aids in the overall fitness of the cell division process.[31]

FtsZ is a protein which is a prokaryotic homologue to the eukaryotic protein tubulin.[32] FtsZ is a GTPase that is essential for cell division in *B. subtilis*. In *B. subtilis*, FtsZ forms a Z ring at the edge of nascent septum.[33] By targeting FtsZ, cell division of a bacterial cell can be inhibited to a greater extent.[34] The ring pattern of FtsZ is dependent upon SepF, which is a protein conserved in most gram-positive bacteria. This protein is required in later stage of cell division. It has a major role in septum development, hence the name SepF.[35] SepF forms large protein rings that also acts as a membrane anchor for Z-ring.[36] SepF also increases the assembly and bundling of FtsZ filaments.[37]

In addition to the aforementioned proteins, Alp7A an actin-like bacterial cytoskeleton protein present in bacteria such as *B.subtilis*.[38] The main function of Alp7A is to aid plasmid segregation. Alp7A protein also exhibits tread milling and dynamic instability.[39] It segregates low copy plasmid pLS20 in *B.subtilis*.[40]

Table 1: Subcellular protein targets and their localization patterns in Bacillus subtilis and *Escherichia coli*.

S.No	Protein	Bacterial species	Localization pattern	References
1	MreB	*Bacillus subtilis and Escherichia coli*	Helical pattern along the longitudinal axis of the whole cell.	55,56
2	MreC	*Bacillus subtilis and Escherichia coli*	Helical pattern along the longitudinal axis of the whole cell.	57,58
3	FtsZ	*Bacillus subtilis and Escherichia coli*	Assembles into a ring at the future site of the septum of bacterial cell division.	59,60
4	ParM	*Bacillus subtilis and Escherichia coli*	Intaracellular filaments along the length of cell	26
5	ZapD	*Bacillus subtilis and Escherichia coli*	Focal localization at the Mid-Cell at the Septum in a FtsZ dependent manner.	61

Table 2: Phytochemicals with good ADME and Drug likeness score.

Ligands	Mw (g/mol)	Log p (-4.0 to 5.6)	HBA (≤ 10)	HBD (≤ 5)	PSA (0-150) Å2	Drug likeness score
erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	374.17	3.85	6	2	62.05	0.9
Myristargenol B	346.18	4.27	5	3	64.01	0.89
Machilin C	344.16	4.17	5	2	54.34	0.87
Nicotine alkaloid	162.12	0.99	2	0	13.43	0.03
Diisobutylphthalate	278.15	4.41	4	0	42.5	0.07
Catechin	290.08	1.88	6	5	90.45	0.92
Acacetin	284.07	3.41	5	3	63.49	0.52
Chrysoeriol	300.06	3.03	6	3	80.13	0.65
Apigenin	270.05	3.06	5	3	73.57	0.77
epi- α-bisabolol	222.2	4.97	1	1	16.29	0.11
Leucasperone A	478.26	3.21	8	1	91.77	0.55
Leucasperone B	436.25	2.76	7	2	87.52	0.64

Retrieval and Preparation of target protein

Either crystalized or homology modeled structures of the aforementioned biologically important membrane proteins of strains *B. subtilis* and *E. coli* were retrieved from Protein Data Bank (PDB) and Universal Protein (Uniprot) resource database and prepared using protein preparation module of MVD 4.0.[41-42] It assigns missing bonds, bond order, flexible torsions and charges to the input structures during the preparation process and makes them readily available for docking studies.

Retrieval and Preparation of ligands

Previously reported phytochemicals of *Leucas aspera* were listed (Table 2) and its 3-Dimensional structure was retrieved from PubChem and Chemspider databases and prepared for docking studies. Prepare molecule module of MVD 4.0 was used in this study. In MVD, during the preparation process, assigns missing charges, bonds, bond order and hybridization, detects flexible torsions, creates explicit hydrogens and finally energy-minimized structure can be obtained. Based on the structural similarity with known inhibitors 50 phytochemicals of *Leucas aspera*

were selected as ligands and subjected to ADME test, Toxicity risk assessment test, Lipinski, other related Index based filters and Bioavailability.

Molecular Docking

The Molecular docking was performed to understand the inhibitory mechanism and the mode of interaction of selected phytochemicals against receptor protein. The Initial docking analysis was performed using MVD 4.0 package. The Create surface module of MVD creates double colored molecular surface according to the electrostatic property to the receptor protein. The cavity prediction algorithm predicts the cavities present in the receptor protein and display it to the user in green color and finds the potential binding sites of the receptor protein. The parameters were set to molecular surface with extended Van der Waals and number of cavities to five. The Docking was carried out using MolDock simplex evolution search algorithm with grid resolution 30 Å for grid generation and cavity predicted using MVD cavity prediction algorithm.[43] In cavity prediction wizard the number of cavity was restricted to three and the cavity with the large volume was selected as the origin for the binding site. The docking wizard runs with default parameters MolDock SE as a search algorithm, number of runs, maximum population and maximum iteration was limited to 10, 50 and 1500 respectively. The selected phytochemicals were docked against the receptor proteins and best-generated poses were selected based on the MVD docking scores (Figure 1). The Interaction between the ligand and the receptor protein depends on the number of H-bonds, distance and binding energy. Some poses have favorable hydrogen bond interactions with active site amino acid residues of taget bacterial membrane proteins.

Identification of potential ligands

A virtual screening methodology was adopted to identify the potential phytochemicals capable of acting as the drug or lead compound. To identify potential ligand compounds in small time interval Index Based filters were employed. These filters eliminate the compounds with the poor lead likeness. In this study, we use five Index based filters: Lipinski filter, Goose filter, veber filter, Egan Filter and Muegge filter for eliminating poor lead like candidates.[44] Those compounds pass the filters were subjected to Toxicity risk assessment test to identify whether the compound causes any adverse effect on the host system. The phytochemicals with better docking scores were subjected to ADME test using a MOLSOFT.[41] It predicts ADME property of ligands based on their structure, functional groups and molecular properties i.e. Molecular Weight (M W), number of Hydrogen Bond Donors (HBD), number of Hydrogen Bond Acceptors (HBA), Polar Solvent Accessibility (PSA), Octane/water partition coefficient (LogP). Those compounds violate expansion (ADME) test were eliminated since such compounds possess poor ability to cross the biological membranes. The phytochemicals with good ADME and Drug likeness score were selected for further toxicity risk assessment tests. The toxicity risk assessment test was performed using machine learning tools Pred – Skin Web 1.0,[45] Carcinopred – EL,[46] hERG – Pred 4.0 (Figure 2).[47]

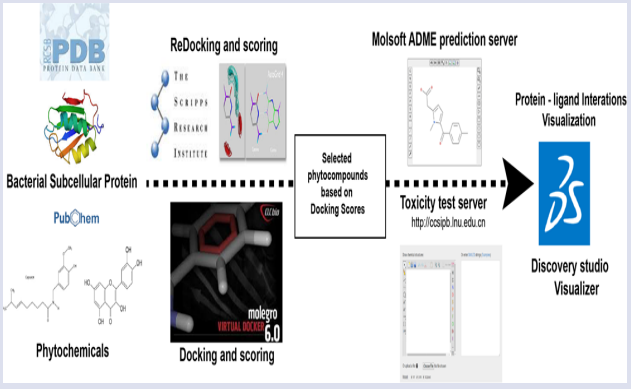


Figure 1: Selection of bacterial sub-cellular protein targets for docking studies

Hardware and Software

Molecular docking studies was performed on Molegro virtual Docker v 4.0. Absorption Distribution Metabolism Excretion (ADME) prediction was performed using using MOLSOFT server and Pred – Skin Web 1.0. The freeware tools Carcinopred – EL and hERG – Pred 4.0 were used for toxicity risk assessment. The workstation used in this study was equipped with AMD A8 processor with 8GB RAM and 1 TB HDD with windows 10 pro as the Operating system.

RESULTS AND DISCUSSION

In total, 50 phytochemicals from *Leucas aspera* have been docked against receptor protein and ligand dataset consists of 20 Terpenes/Terpenoids, 9 Sterols/fatty acids, 5 Glycosides, 7 long chain compounds, 5 flavonoids, 8 lignin and 7 miscellaneous compounds were downloaded from small molecules databases, prepared and 3D geometries were optimized. All collected phytochemicals were evaluated to identify the potential phytochemicals that has a capacity to act as a drug or lead compound. Collected ligands were then subjected to ADME test using a MOLSOFT,[41] which predicts ADME property of ligands based on their structure, functional groups and molecular properties such as molecular weight (MW), number of Hydrogen Bond Donors (HBD), number of Hydrogen Bond Acceptors (HBA), Polar Solvent Accessibility (PSA), Octane/water partition coefficient (LogP). Compounds that violate ADME test were eliminated as those compounds possess poor ability to cross the biological membranes. Only twelve ligands with good ADME and Drug likeness score were selected for further toxicity risk assessment tests and were listed in (Table 2).

The toxicity risk assessment test was performed using machine learning tools Pred – Skin Web 1.0,[45] Carcinopred – EL,[46] hERG – Pred 4.0.[47] No ligands were identified as carcinogen, Binary prediction method of hERG – Pred predicts that ligand Nicotine alkaloid as a hERG pathway blocker. Pred – Skin predicts that only 3 ligands Leucosperone A, Leucosperone B and erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol as nonsensitizers and compiled toxicity results of all selected phytochemicals were listed in Table 3.

The ligands Leucosperone B and erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol passes all five index based filters and so the selected ligands were docked against the receptor proteins and best-generated poses were selected based on the MolDock (Mdock) and Re-rank (Edock) scores. Mdock and Edock scores are scoring function used to explain the binding energy of docked poses.

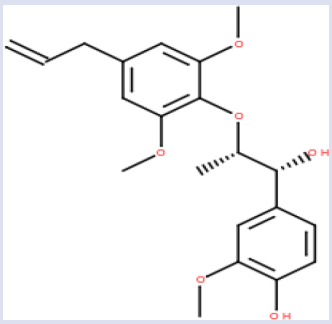
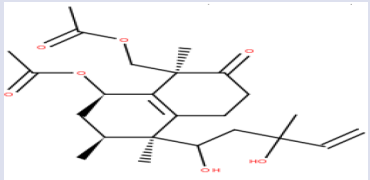
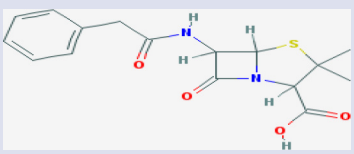
The Interaction between the ligand and the receptor protein depends on the number of H-bonds, distance and binding energy. Some poses have favorable π-π, hydrogen bonding, van der Waals and electrostatic interactions with active site amino acid residues of bacterial membrane proteins.

During Initial stage, the phytochemicals Leucosperone B, erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol were docked against *Escherichia coli* and *Bacillus subtilis* subcellular proteins and their docking scores were compared with commercial antibiotics. The Commercially available antibiotic drug (penicillin) was used as controls in the study. Penicillin belongs to aminoglycosides Beta lactam antibiotic and widely used antimicrobial drug against bacterial infection. Both phytochemicals and control drug were docked against above mentioned subcellular protein receptors (as target) and only the

Table 3: Toxicity prediction of sorted phytochemicals using machine learning tools Pred – Skin Web 1.0, Carcinopred – EL, hERG – Pred 4.0.

Ligands	Carcinopred – EL	hERG – Pred 4.0	Pred – Skin
erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Non- carcinogen	Non- Blocker	Non- Sensitizer
Myristargenol B	Non- carcinogen	Non- Blocker	Sensitizer
Machilin C	Non- carcinogen	Non- Blocker	Sensitizer
Nicotine alkaloid	Non- carcinogen	Blocker	Sensitizer
Diisobutylphthalate	Non- carcinogen	Non- Blocker	Sensitizer
Catechin	Non- carcinogen	Non- Blocker	Sensitizer
Acacetin	Non- carcinogen	Non- Blocker	Sensitizer
Chrysoeriol	Non- carcinogen	Non- Blocker	Sensitizer
Apigenin	Non- carcinogen	Non- Blocker	Sensitizer
epi- α-bisabolol	Non- carcinogen	Non- Blocker	Sensitizer
Leucasperone A	Non- carcinogen	Non- Blocker	Non- Sensitizer
Leucasperone B	Non- carcinogen	Non- Blocker	Non- Sensitizer

Table 4: Molegro docking scores (kcal/mol) for phytochemical ligands with *Escherichia coli* and *Bacillus subtilis* subcellular protein targets.

Compound	Chemical formula	Chemical Structure	Protein Receptors	UNIPROT entry	MolDock Score (M_{dock}) kJ/mol	Rerank score (E_{dock}) kJ/mol
erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	$C_{21}H_{26}O_6$		MreB	P0A9X4	-123.74	-86.029
			MreC	P16926	-114.98	-76.59
			ParM	P11904	-107.87	-33.69
			ZapD	P36680	-107.85	-82.63
			Alp7A	E9RJ95	-132.62	-73.74
			FtsZ	P17865	-129.1	-107.04
			SepF	O31728	-82.0404	-57.454
Leucasperone B	$C_{24}H_{36}O_7$		Mreb	P0A9X4	-100.238	-73.74
			Mrec	P16926	-110.06	-85.48
			ParM	P11904	-91.7836	-76.764
			Zapd	P36680	-104.908	-74.691
			Alp7A	E9RJ95	-112.28	-92.441
			FtsZ	P17865	-103.16	-70.768
			SepF	O31728	-79.62	-62.14
Penicillin	$C_{16}H_{18}N_2O_4S$		MreB	P0A9X4	-115.94	-86.29
			MreC	P16926	-108.64	-87.01
			ParM	P11904	-107.879	-33.692
			Alp7A	E9RJ95	-117.8	-102.9
			FtsZ	P17865	-119.18	-96.96
			SepF	O31728	-75.63	-55.35

phytochemicals with similar or better binding affinity than the control drug were selected. The Binding affinity of phytochemicals and control were evaluated using MVD 4.0 and listed in **Table 4,** during the docking process the cavity with larger volume was preferred as binding pocket site**.**

The control drug, Penicillin shows higher binding affinity against protein FtsZ with MolDock (M_{dock}), re rank (E_{dock}) score, of −119.18 kcal/mol, -96.96 kcal/mol respectively followed by Alp7A (−117.8.62 kcal/mol, -102.9 kcal/mol) and MreB (−115.94 kcal/mol, -86.29kcal/mol). The penicillin with FtsZ form hydrogen bond interactions with amino acid residues such as GLY A:22, GLY A:104, GLY A:107, GLY A:110, GLY A:108, ALA:73, THR A:109, ALA A:71. penicillin form three hydrogen bonds with amino acid residues ARG A:363, SER A:13 with Alp7A. With Mreb protein, penicillin form two hydrogen bonds with amino acid residues GLY A:296, ASA A:21.

MreB shows higher binding affinity with ligands erythro2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and Leucasperone B and have MolDock score -123.74 kcal/mol and -100.238 kcal/mol, respectively (Figure 3). The Lowest-energy docked poses of MreC with ligands erythro2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and Leucasperone B was illustrated in Figure 4.

The *Leucas aspera* (Willd) Linn. belongs to Family: *Lamiaceae*, locally known as 'Thumbai' is spread throughout India from the Himalayas down to southern Kanyakumari. Such plant species has been proven to possess various medicinal properties like antifungal, antioxidant, antimicrobial, antinociceptive and cytotoxic activity. The methanolic fraction and essential oils from *Leucas aspera* possess antibacterial activity against *Staphylococcus aureus, Vibrio cholerae, Salmonella typhi, Klebsiella aerogenes, Escherichia coli, Proteus vulgaris, Pseudomonas pyocyanea*and *Dys. Flexneri.*[48] Leucosperone B is a Diterpene from *Leucas aspera* and its proven to Inhibit Prostaglandin-Induced Contractions and NMR spectrum of the phytochemical was also available in literature[49] and related databases. In this study, the Leucosperone B was docked against *E. coli* and *B. subtilis* subcellular proteins. Docking Leucosperone B with protein targets showed notable docking scores, for instance docking with MreC resuted in dock score, M_{dock} = -110.06 kcal/mol, E_{dock} = - 85.48 kcal/mol. Docking with Alp7A resulted in docking score, Mdock = -112.28

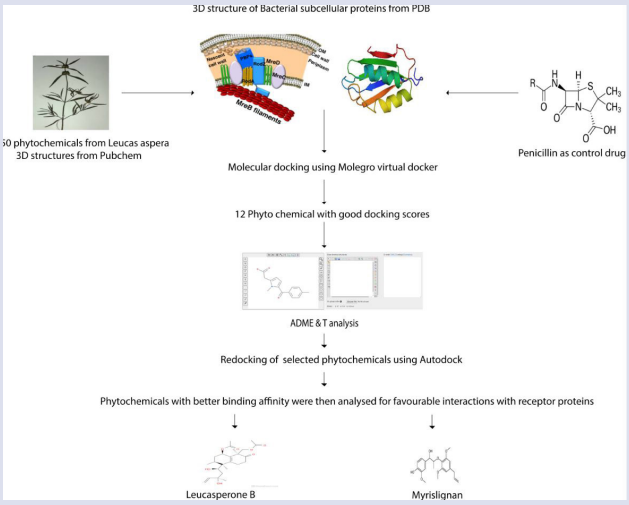


Figure 2: Flowchart explaining the target selection and docking procedure.

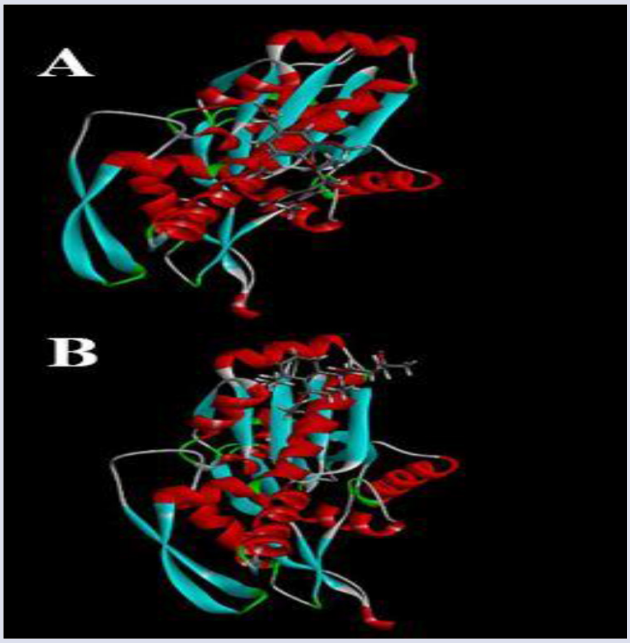


Figure 3: Lowest-energy docked poses of MreB with A) erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and B) Leucasperone B.

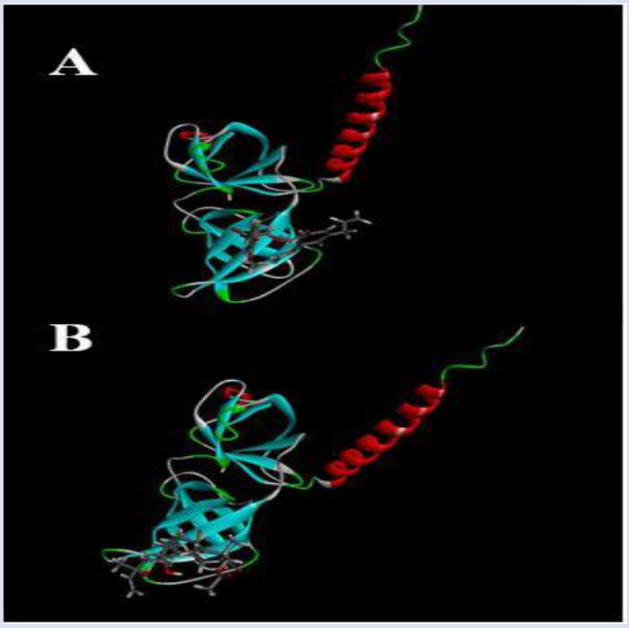


Figure 4: Lowest-energy docked poses of MreC with A) erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and B) Leucasperone B.

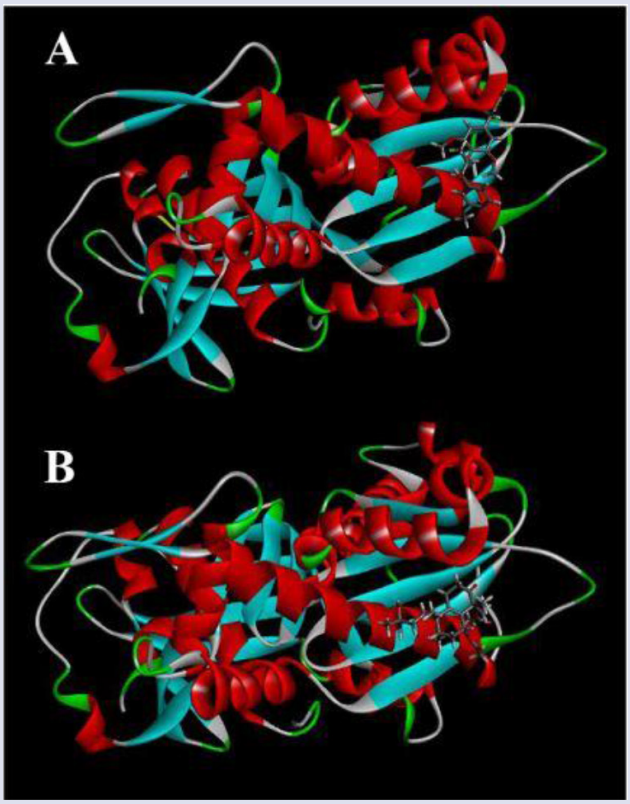


Figure 5: Lowest-energy docked poses of Alp7A with A) erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and B) Leucasperone B.

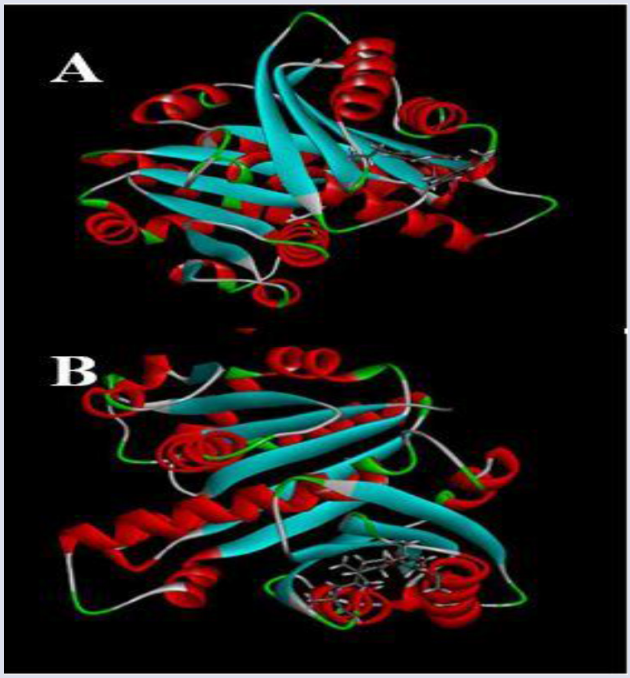


Figure 6: Lowest-energy docked poses of FtsZ with A) erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and B) Leucasperone B.

kcal/mol, E_{dock} = -92.441. Furthermore, Leucosperone B also forms four hydrogen bonds within active site of protein MreC with amino acid residues SER A:153, GLY A:259, TYR A:265, ARG A:103 (Figure 4).

erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol is a neolignan found in plant varieties such as *Machilus odoratissima,*[50] *Machilus thunbergii,*[51] *Leucas aspera,*[52] *Myristica fragrans*[53] and *Iryanthera ulei*.[54] The aforementioned neolignan also showed notable docking profile with protein targets MreC (M_{dock} = -110.06 kcal/mol, E_{dock} = - 85.48 kcal/mol), Alp7A (M_{dock} = -112.28 kcal/mol, E_{dock} = -92.441). In addition, it forms four hydrogen bonds within active site of protein MreC and interacting amino acid residues are SER A:153, GLY A:259, TYR A:265, ARG A:103. erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol when docked to the protein Alp7A at the predicted binding cavity (Figure 5), formed three hydrogen bonds with amino acid residues GLY A:215, GLY A:330, SER A:13.

CONCLUSION

In summary, *in-silico* screening of *Leucas aspera* phytochemicals was performed to identify potential phytochemicals with drug-likeness. We found that phytochemicals erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol and Leucasperone B from *Leucas aspera* possess great binding affinity (> -100 kcal/mol) towards one or more bacterial subcellular protein targets. Both compounds possess favorable interactions with amino acid residues present in the active site pocket of bacterial cell division and cell shape determining proteins such as Mreb, Mrec, Ftsz and Alp7A have valid docking scores (> -100 kcal/mol) Figures (3-6). The sorted phytochemicals were found in common medicinal plants. For example, erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol is a neolignan found in plant varieties such as *Machilus odoratissima,*[50] *Machilus thunbergii,*[51] *Leucas aspera,*[52] *Myristica fragrans*[53] and *Iryanthera ulei*.[54] However, Leucasperone B is found only in *Leucas aspera* sp. We believe that this work will shed light on antibacterial screening and extraction of phytochemicals from *Leucas aspera*. The future studies involves designing of potential structural analogs of identified compounds, chemical synthesis and to evaluate its antibacterial activity *in-vitro*.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADMET: Adsorption, Distribution, Metabolism, Excretion and Toxicity; **MVD:** Molegro Virtual Docker; **Mw:** Molecular weight; **HBD:** Hydrogen Bond Donors; **HBA:** Hydrogen Bond Acceptors; **PSA:** Polar Surface Area.

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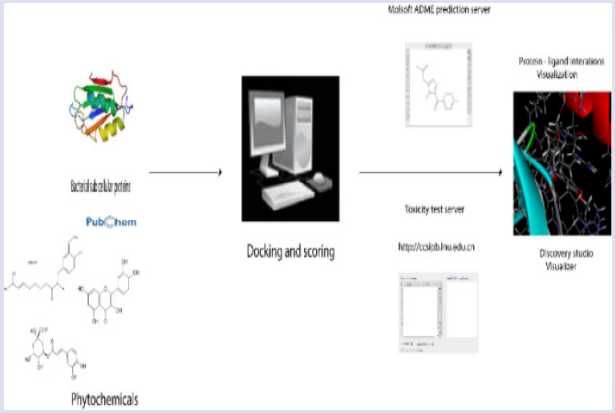
GRAPHICAL ABSTRACT



SUMMARY

- Virtual screening and ADMET studies was performed to screening phytochemicals with drug likeness from Leucas aspera.
- Molecular docking studies of screened phytochemicals against *E coli* and B subtilis subcellular protein was performed using Molegro virtual docker.
- The docking results showed that phytochemicals Leucosperone B, erythro-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol have good inhibition against MreB, MreC, Alp7A proteins.
- We believe that this work will shed light on antibacterial screening and extraction of phytochemicals from Leucas aspera.

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