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In Silico Study on FtsZ as a Novel Target for Antibacterial Activity

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Abstract

In *silico* molecular docking isusedto predict the binding affinity of a ligand towards the receptor. In this study, the bioactive compounds *of Carissa carandas* plant extractare used as a ligand of the FtsZ receptor. FtsZ is a protein find the bacteria, which is responsible for cell division.Molecular docking is conducted to analyze the potential anti-bacterial compounds found in the *Carissa carandas*. The bioactive constituents of *Carissa carandas* plant extract have been identified through gas chromatography MS analysis. The identified compounds include alkaloids, flavonoids, saponins, and phenolic acids. The pharmacological and nutraceutical profile of *Carissa* species, particularly *Carissa carandas*, has been examined in several areas of research. These studies have identified various bioactive constituents that is a potential inhibitor of FtsZ. The bioactive compounds 4-Bromobenzenesulfono-2-napthamide, 2,6-Dimethyl-7-octyl-1,2,3,4-tetrahydronic and Acetamide found as the best hit of the target, which ranges binding energy between (-9.06 to -6.42 kcal/mol).Thus,the identified inhibitor could serve as a potential inhibitor of FtsZ, further *in vitro* and *in vivo* studies need to validate these results.

Key Words: - Molecular docking, *Carissa carandas*, Antibacterial, Bioactive compounds.

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Introduction

Antimicrobial resistance is a global issue that impacts worldwide and makes it challenging for us to treat common illnesses. Multi-drug resistance, which occurs when bacteria develop resistance to numerous antibiotics, is very concerning and can result in illnesses that cannot be treated with current antibiotics [1].The use of medicinal plants has shown potential in treating multidrug-resistant (MDR) microbes and which makes them a possible alternative source of treatments. A wide variety of secondary metabolites found in medicinal plants, including tannins, terpenoids, alkaloids, and flavonoids, have been *proven in vitro* to possess antibacterial activities [2]. The *Carissa Carandas* Linn. (Karonda) is widely utilised in an autonomous traditional system of medicine and is used as a medicinal herb by tribal people all over the world. In folkloric medicine, all parts of *C. carandas*are used. Traditionally it is used in the treatment of scabies, intestinal worms, pruritus, antiscorbutic, anthelmintic, pain relieving, cancer, and hepatoprotective. However previous studies on *Carissa carandas* also reported its antimicrobial activity [3].Artificial intelligence is now developing at a rapid pace and has a significant impact on the therapeutic field. It is playing a crucial role in the search for new drugs. Molecular docking is an approach used in virtual screening, particularly when the target protein's 3D structure is accessible. This technique was able to predict the structure of the protein-ligand complex as well as the binding affinity between the ligand and protein, which is important knowledge for lead optimisation. Molecular docking has been used for more than three decades, and as a result, various new medications have been developed [4].Plant-based phytochemicals deliver pathogens a desirable, efficient, comprehensive therapeutic activity without an array of side effects. As a result, we are looking at the screening of potential phytochemicals as therapeutic compounds against the FtsZ protein of PDB ID: 5MN4 to evaluate how effective they are against pathogenic bacteria. Using phytochemicals, structure-based drug design may be utilised to streamline the process and lower

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the amount of uncertainty. To address this, the current study focuses on *in silico* docking work on certain phytochemicals of *Carissa carandas* plant extract as lead compounds to examine their binding affinities to modelled FtsZ protein in contrast to approved antimicrobial drugs. The discovery of novel therapeutic targets for pathogenic FtsZ, which is connected to the infection and spread of several infections. FtsZ is the protein that regulates the division of bacterial cells. To divide cells, FtsZ creates filaments that coordinate cell membrane constriction and cell wall [5].

Material and Method

Preparation of Sample:

The *Carissa carandas*were collected from a forest nursery situatedin Jhansi, India. The reference voucher no. 28758 was assigned for *Carissa carandas* by Central Ayurveda Research Institute, Central Council for Research in Ayurvedic Sciences Ministry of Ayush, Govt. of India Gwalior Road, Jhansi (U.P). *Carissa carandas* extract is prepared in methanol by soxhlet apparatus.

Protein target selection and preparation:

The *Carissa carandas* bioactive compounds identified by GC-MS are used as a potential inhibitor of 5MN4, the study has been investigated using molecular docking. Target receptor 5MN4's three-dimensional structures were downloaded in pdb format from Protein Data Bank (https://www.rscb.org).

Ligand selection and preparation:

The Online tool SMILES Translator (https://cactus.nci.nih.gov/translate/) [6], were used to transformligands into 3D structure. The Compounds smile notations were entered into the Online SMILES Translator as input, and PDB was chosen as the output format. PDB was then translated to pdbqt using the Open Babel software [7].

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Molecular docking:

Molecular docking evaluates binding energy, ligand efficiency, van der Waals+ hydrogen + desolvation energy, and hydrogen bond energy of the interaction between 5MN4 and bioactive compounds identified from the GC-MS analysis. (The Scripps Research Institute, La Jolla, San Diego, USA), developed the Auto Dock Vina program used for molecular docking. Although nonpolar hydrogens were incorporated, polar hydrogens were added. The grid map was created using a grid box using AutoGrid. The docking parameters include polar hydrogens were added while nonpolar hydrogens were merged. While AutoGrid was used for the preparation of the grid map using a grid box. The docking parameter includes Lamarckian GA runs of 30, a population size of 150, a maximum number of evaluations of 2500000, a gene mutation rate of 0.02, several generations of 27000, and a cross-over rate of 0.8. Furthermore, all 2D interactions of the docked complexes were illustrated using Discovery Studio visualizer version v19.1.0.18287 (BIOVIA, San Diego, CA, USA) [8], Discovery Studio provides a range of interactions including weak and strong hydrogen bonding interactions between ligands and receptors.

Result and Discussion:

This study aimed to identify potential antimicrobial compounds in the *Carissa carandas* plant using molecular docking. We used Autodock version 4.0 and Chimera 1.8.1 software to simulate the inhibitors bound to target proteins in various poses. Out of the 22 total plant phytochemicals docked to proteins involved in 5MN4, 2 compounds showed the highest binding affinity to the target proteins. The top 2 compounds are 4-Bromobenzenesulfono-2-napthamide, 2,6-Dimethyl-7-octyl-1,2,3,4-tetrahydronic, showing affinity -9.06 and -7.05." Our results suggest that the *Carissa carandas* plant contains several potential antimicrobial compounds that could be further investigated for their therapeutic potential. The compounds 4-Bromobenzenesulfono-2-napthamide, 2,6-Dimethyl-7-octyl-

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1,2,3,4-tetrahydronic in particular, showed high binding affinity to the target proteins and could be promising candidates for further study. Our findings are consistent with previous studies that proved *Carissa carandas* have potential antimicrobial activity [9]. Althogh (Vemula et al 2023) performed the molecular studies and identified1-(((amino(imino)methyl)amino)methyl)-3-(3-(tert-butyl)phenyl)-6,7-dimethoxy isoquinolin-2-ium, and Chlorogenic acid asan inhibitor of Fstz, that inhibit the cell division of bacteria [10]. Moreover, Table 1 shows the molecular docking results of bioactive compounds of *Carissa carandas* towards Antibacterial target 5MN4. Further, the docking images of the top four docked complexes have been provided in (Figure 1). It was observed that the lowest binding energy of-9.06 kcal/mol revealing high binding affinity was obtained by 4-Bromobenzenesulfono-2-napthamide.

Table 1:- Molecular docking Results of Bioactive compounds of *Carissa carandas* towards Antibacterial target 5MN4

S.no	Ligand	Binding Energy (kcal/mol)	Ligand Efficiency	Van der Waals + hydrogen + desolvation energy	Hydrogen Bond
1	1-Phthalanol,1,3,3-trimethyl	-5.76	-0.44	-5.91	2
2	2-(((2-Ethylhexyl)oxy)carbonyl)benzoic acid	-4.69	-0.23	-7.38	3
3	2,6-Dimethyl-7-octyl-1,2,3,4-tetrahydronic	-7.05	-0.35	-9.12	No hydrogen bond
4	2-Benzylidenecyclohexanol	-6.41	-0.46	-6.82	2
5	3-(5-Hydroxy-2,2,6-trimethyl-7-oxa-bic	-5.86	-0.34	-6.85	2
6	4,7-Dimethyl-1-indanone	-5.53	-0.46	-5.38	1
7	4-Bromobenzenesulfono-2-	-9.06	-0.43	-9.8	2

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	napthamide				
8	4-t-Butyl-2-(1-methyl-2-nitroethyl)cyclo	-5.83	-0.34	-6.07	3
9	5,6,6-Trimethyl-5-(3-oxabut-1-enyl)-1-o	-5.58	-0.33	-5.93	4
10	5-heptenoicacid	-5.85	-0.29	-7.69	4
11	6-Ethyl-1,2,3,4-tetrahydronaphthalene	-5.47	-0.46	-5.78	No hydrogen bond
12	Acetamide	-6.46	-0.21	-7.21	2
13	Bis(2-ethylhexyl)	-5.58	-0.47	-6.18	No hydrogen bond
14	Decylhydrogenphthalate	-4.94	-0.22	-7.7	5
15	Napthalene	-5.75	-0.48	-5.75	No hydrogen bond
16	PGH1,methylester	-4.39	-0.17	-8.73	2
17	Phthalic acid, heptyloct-3-yl-ester	-4.32	-0.16	-9.0	
18	Phthalicacid,mono(2-ethylbutyl) ester	-4.97	-0.28	-6.37	4
19	Valtrate	-4.16	-0.14	-7.36	4
20	3-Dodec-7-enyl-2,4,10-trioxa-adamantane	-6.42	-0.29	-9.39	2
21	Diisoocytylphthalate	-4.55	-0.16	-9.34	2
22	Neocurdine	-6.39	-0.38	-6.7	No hydrogen bond

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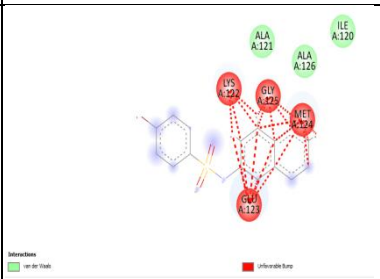
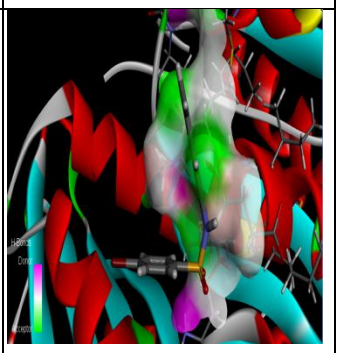
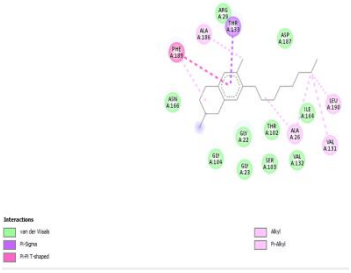
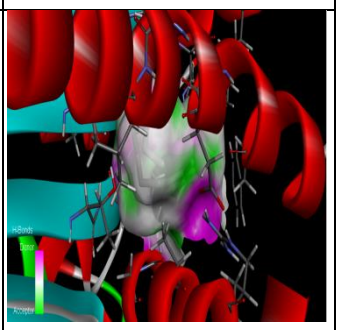
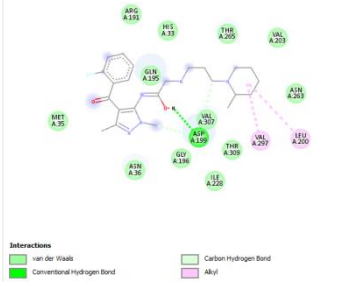
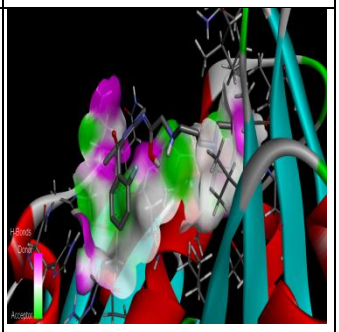
Fig 1:- Top 4, Molecular Docking Images

Sl. No	Ligand	Binding Energy (kcal/mol])	Discovery Studio Images	Hydrogen bond Interaction
1	**4-Bromobenzenesulfono-2-napthamide**	-9.06		
2	**2,6-Dimethyl-7-octyl-1,2,3,4-tetrahydronic**	-7.05		
3	**Acetamide**	-6.46		

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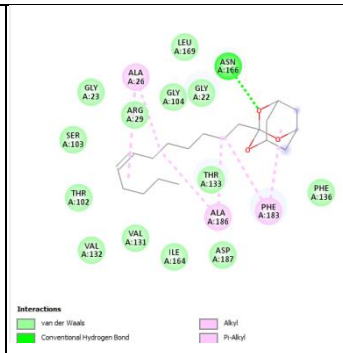
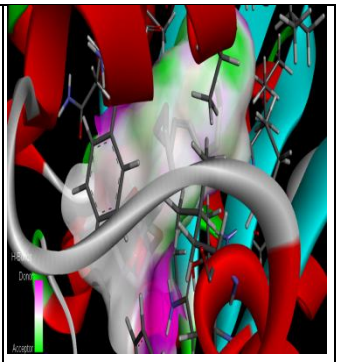
4	**3-Dodec-7-enyl-2,4,10-trioxa-adamantane**	-6.42		

Conclusion:

In conclusion, our study identified several potential antimicrobial compounds in the *Carissa carandas* plant using molecular docking as an inhibitor of the FtsZ target. The virtual screening method selects 22 bioactive compounds and examines drug-likeness properties. Out of these compounds 4-Bromobenzenesulfono-2-napthamide, 2,6-Dimethyl-7-octyl-1,2,3,4-tetrahydronic and Acetamide showed high binding affinity to the target proteins and could be further investigated for their therapeutic potential. Our research contributes to the research about the possible therapeutic applications of plant bioactive compounds.

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