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MOLECULAR DOCKING STUDIES OF NATURAL ANTIMICROBIAL COMPOUND FROM *SARGASSUM WIGHTII* AGAINST SELECTED TARGETS OF PATHOGENS

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ABSTRACT

Sargassum species are distributed worldwide with great ecological and economic importance in marine ecosystems and bioresources. These are nutritious and rich source of bioactive compounds such as vitamins, carotenoids, dietary fibers, proteins, and minerals. Also, many biologically active compounds like terpenoids, flavonoids, sterols, pheophytine sulfated polysaccharides, polyphenols, sargachromenol, sargaquinoic acids, were isolated from *Sargassum* species. Specific targets were selected from pathogens occurs in diabetic foot infection, namely *Pseudomonas aeruginosa, Klebsiella Pneumoniae, Escherichia coli, Staphylococcus aureus and Candida albicans.* Various active compounds were selected from *Sargassum wightii* exibiting antimicrobial activity. Molecular docking studies were performed using Autodock 4.0 server. Among the two compounds each have been screened and docked for binding energy analysis, the potential docked structure confirmed the antimicrobial activity and support our invitro results.

KEYWORDS: *Sargassum wightii*, brown algae, diabetic foot infection.

INTRODUCTION

Foot infections in patients with diabetes cause substantial morbidity and may lead to amputation of a lower extremity. The major predisposing factor to these infections is foot ulceration, which is usually related to peripheral neuropathy Aerobic gram-positive *cocci* are the predominant microorganisms that colonize and acutely infect breaks in the skin. *S.aureus* and the beta - hemolytic *Streptococci* (groups A, C, and G, but especially group B) are the most commonly isolated pathogens. *Sargassum* is a genus of marine macroalgae, belongs to Family *Sargassaceae*, Order *Fucales*, Class of *Phaeophyceae*, Phylum *Ochrophyta*.[1] Research of marine algae has made significant advances in recent years due to its natural products, production of variety of compounds and having biological activity of potential medicinal value.[2,3] Herbal drug development is the one of the most possible way in which the tedious diseases can be overcome. From minerals, medicinal plants, and organic matter many traditional medicines in use are derived.[4] Indian origin plant, herbs and shrubs are having various unknown biological activities but they are hidden. Now a days Diabetic foot infection causes 70% influence on national health. Sudden increase in infection are the most common causes of hospitalization and often resulting in osteomyelitis, amputation, and death.[5, 6] There is an evidence clinically pointing to the higher prevalence of infectious diseases among individuals with diabetes mellitus[7,8] A herbal drug development approach is being carried out by us using brown algae which has tremendous potential to inhibit growth of such bacterial and fungal species. It is different matter that how much potency it has? or what extent it works ? We hypothesised to formulate a new herbal antimicrobial preparation against diabetic foot pathogens. Microbiological studies were performed previously and it is found that, there are certain bioactive compound which having antibacterial activity, to understand more. All the compounds were screened using computational analysis using bioinformatics software's.

METHODS

Preparation of protein structure: Computational chemistry reliable method of drug discovery process. We have selected protein targets from *Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli, Staphylococcus aureus* and *Candida albicans, their* 3D structures were downloaded from database Protein Data Bank (PDB). (PDB: http://www.rcsb.org/ pdb/home/home. do). Pre protein analysis were done by removing all water molecules and hydrogen atoms were added to receptor molecule. Preparation of ligand structure: from the algae we have isolated 2 compounds were selected on the basis of their biological activity reported and molinspiron drawing tool used to draw the 3D structures which were validated. Protein ligand interaction: All the proteins and 2 ligands were subjected to docking studies individually using AUTODOCK 4.0 docking server, is based on the quantum mechanics, it predicts the molecular structures,

active energies, geometry of structure, coordinates of atoms, bond length and bond angle present in their pocket[9]

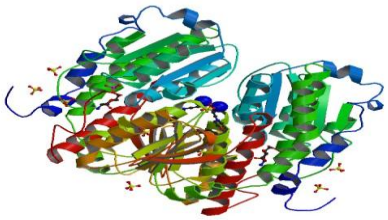
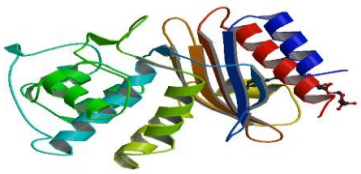
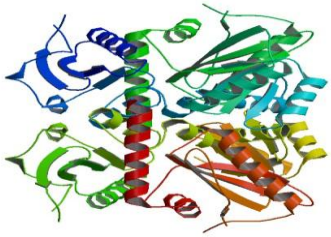
COMPUTATIONAL METHODS

Docking of the selected compounds and target selected were carried out using Autodock.[11,10] Gasteiger partial charges were added to the ligand. Cleaning of the targets and ligand were done using Accelrys Discovery studio visualizer 4.0. Essential hydrogen atoms, Kollman united atom type charges, and salvation parameters were added with the aid of Auto Dock tools maps of 20 Å grid points and 0.375 Å spacing were generated using the Auto grid program automatically. Auto Dock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.[12] Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250,000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied. Also, due to high data output only the best score were selected and bonds were measured.

RESULTS

The receptors are the group of amino acids plays an infective role in bacterial and fungal species. Structures of all proteins of pathogens downloaded from PDB shown in table1. The output of our previous work analysis shows active compounds tested microbiologically against bacterial strains which need to be tested insilico. The 3D structure of the compounds isolated is shown in table 2. Molecular docking was carried out using Lamarckian genetic algorithm (LGA), with Autodock tools, free energy of bindings were recorded for all the compounds with their targets. All docking scores were shown and discussed. There are two compounds docked with the receptors, out of which Trimethyl Teterahydrobenzofuranone shows -6.27kCal/mol and -5.65kcal/mol i.e. good score for binding with receptor by forming strong hydrogen bonding with respective interacting amino acid chains, Table 3.

Table 1 Protein Retrieved from PDB

Sr No	Name of Protein	PDB Id
1	 **Isomerase domain of glucosamine 6-phosphate synthase complexed with glucosamine 6-phosphate**	1MOQ
2	 **Structure of SHV-1 beta-lactamase**	1SHV
3	 **Crystal Structure of the Apo Form of D-Alanine:D-Alanine Ligase (DDl)**	3K3P

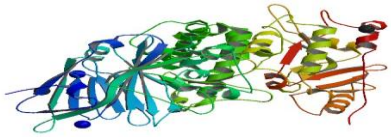
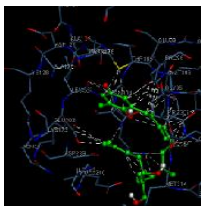
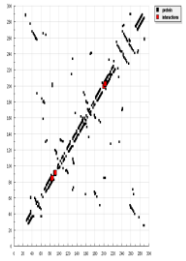
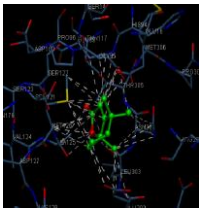
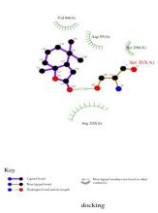
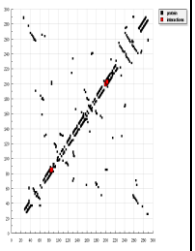
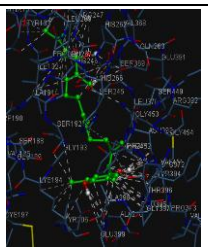
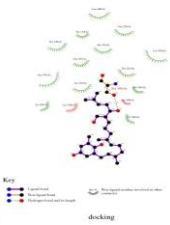
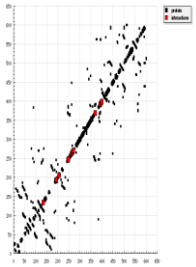
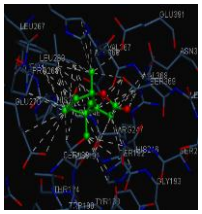
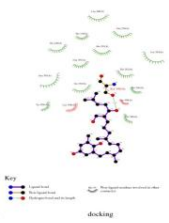
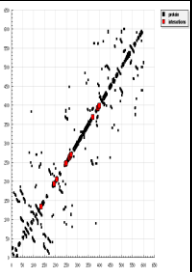
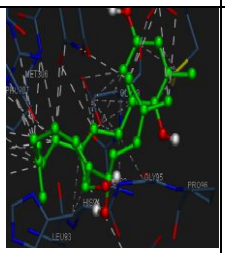
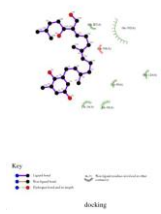
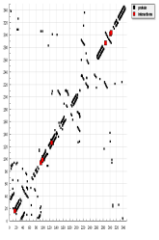
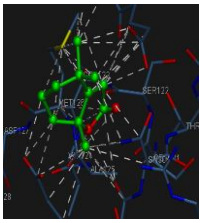
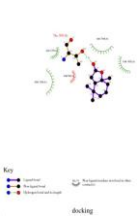
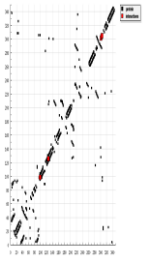
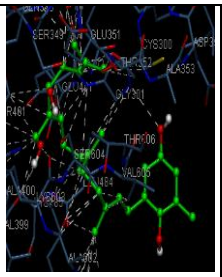
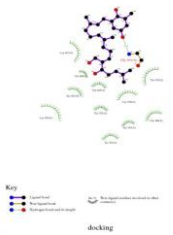
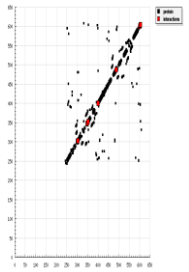
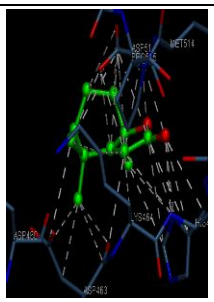
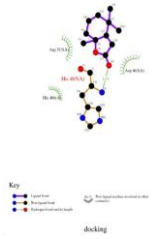
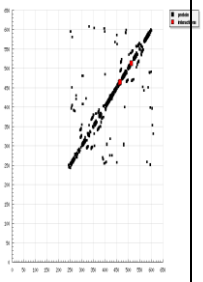
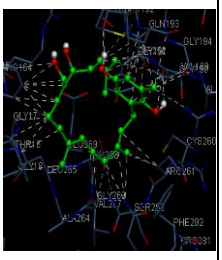
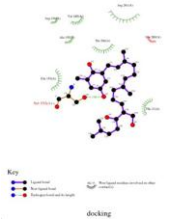
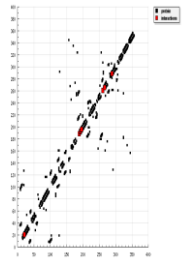
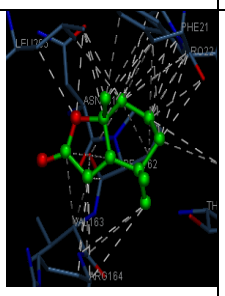
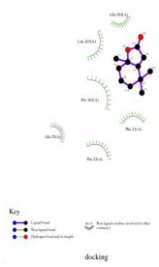
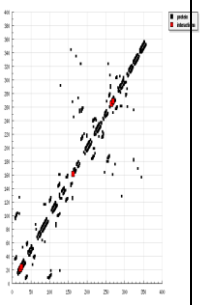
4	 **The 1.9 A crystal structure of Escherichia coli MurG, a membrane-associated glycosyltransferase**	1F0K
5	 **Pseudomonas Aeruginosa Exotoxin A, wild type**	1IKQ

Table 2 Protein Ligand Interaction Docking Scores

Ligands /Protein	1SHV	1MOQ	1IKQ	3K3P	1FOK
FallaQuinone Derivative	+0.23 kcal/mol	+0.30 kcal/mol	-6.27 kcal/mol	-1.87 kcal/mol	-3.71 kcal/mol
Trimethyl Teterahydrobenzofuranone	-3.15 kcal/mol	-3.00 kcal/mol	-5.65 kcal/mol	-5.13 kcal/mol	-5.40 kcal/mol

Table 3 Docking interactions of receptor and ligands

Protein (PDB ID)	Ligand1 (Fallaquinone Derivative)			Ligand 2 (Trimethyl Teterahydro Benzofuranone)		
	docking Target & drug	Interacting chains in pocket	Hydrogen plot	docking Target & drug	Interacting chains in pocket	Hydrogen plot
1SHV						
1IKQ						
3K3P						

1MOQ						
1F0K						

DISCUSSION

There are various literature available in world related to brown algae, but the antibacterial studies against the diabetic foot infection causing pathogen is first time. Primary and secondary metabolites of *Sargassum* may be effective bioactive compounds of interest in the pharmaceutical industry. Various chemically unique compounds of marine origin with various biological activities have been isolated, some isolated compounds are under investigation to develop new pharmaceuticals.[14] Evidence available in the literature saying that the potential protective effects of seaweeds against oxidative stress in target tissues and lipid oxidation in foods.[15,16]

We derived some of the compounds and checked for their antibacterial activity *invitro. Insilico* studies were used to confirm the results and successfully supported. *Candida albicans* was selected pathogen in which Glucosamine 6 Phosphate was selected as target, reported ligand i.e. fallquinone derivative as well as Trimethyl Teterahydrobenzofuranone were docked against it. As results shows there is less docking interaction with compound of fallquinone derivative, where as the -3.00 kcal/mol binding energy noted with one hydrogen bond in case of Trimethyl Teterahydrobenzofuranone which consider as good docking score. This target is having a crucial role in cell wall development or fungal colonization. This can be arrest by docking such a novel compound.

In *Pseudomonas aeruginosa*, Exotoxin A is targeted which exerts its cellular toxicity through ADP-ribosylation of translation elongation factor 2, This finally results into enzyme cleavage activity and binding of cell surface receptor.[13] This can cause toxicity in infected cell, hence the target is important. In current study, docking of the ligand shows very good free binding energy score with both the compounds and formation of hydrogen bonds.

Similarly, *Klebsiella pneumoniae* is also an important organism which plays role in developing foot infection by fermenting sugar and results into pus formation, cause of the issue were targeted here i.e. beta lactamase in *Klebsiella.* It hydrolyse the antibiotics and depress the activity which causes the inactivation of the antimicrobials. Keeping this issue in mind, docking were perfomed. Fallaquinone derivative shows no much interaction hence the score is low but the Trimethyl Teterahydrobenzofuranone results in good interaction with -3.15kcal/mol.

Trimethyl Teterahydrobenzofuranone and Fallaquinone derivative both has great antimicrobial activity and need to be discuss in detail from pharmaceutical point of view in near future. Trimethyl Teterahydrobenzofuranone is the proven as best ligand against *E.coli, S.aureus* by good binding and interaction with amino acids.

CONCLUSION

Herbal drug development is at nascent stage in India like developing countries. Diabetic foot infection is the major concern, antimicrobial resistance is added issue now a days. Hence immediate need to develop a source which overcomes above problems. Computational studies are now a new arena of technology in drug development which ease the discovery of new compounds. In current study an attempt was made to discover a new novel compound using bioinformatic tool. Which supports invitro studies of novel molecules. There are two molecules reported from algae shows antimicrobial activities against diabetic foot pathogen and it is now confirmed that they are having affinity towards receptors of the target organisms. Hence it is clear that both the

molecules shows good docking scores and binding energies towards receptors and in future can act as a potential drug for multi drug resistance microorganisms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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