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An *insilico* molecular docking study of myricetin derivatives as inhibitors of SspB, a virulence factor of oral pathogen *Streptococcus gordonii.*

Kannan I*, Priyanka K, Sambandam Cecilia, Jayalakshmi M, Premavathy RK, Shantha S
Department of Microbiology, Tagore Dental College and Hospital, Rathinamangalam, Chennai–600127, India
*E-mail: kannan_iyan@hotmail.com
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Abstract

Streptococcus gordonii is a commensal bacterium which colonizes different sites of human oral cavity. It is strongly believed that *S. gordonii* plays an important role in the development of bacterial communities associated with dental caries, gingivitis, and periodontitis. *S. gordonii* also expresses two cell surface proteins SspA and SspB that belong to the antigen I/II (AgI/I) family of proteins. These proteins are known to have multiple functions, including binding to human salivary agglutinin, collagen, and certain *Actinomyces naeslundii* strains, suggesting that they are important for the development of the plaque community. The three dimensional structure of SspB was retrieved from RCSB database. The possible binding sites of SspB were searched using binding site prediction online tool Q site finder. A total of 500 ligands were generated from myrecitin with the help of software ACD chemsketch. Rapid virtual screenings of these compounds were performed in the docking tool iGEMDOCK v2.0. Based on the binding energy a total of five ligands were selected for the further study. The selected five ligands were then analyzed for drug- relevant properties based on "Lipinski's rule of five" and other drug like properties. The accurate docking of five ligands were performed using docking tool iGEMDOCK v2.0. From the present study, it has been found that2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol, which is a novel compound can act has an inhibitor for the SspB and thus can be a potential drug candidate in the prevention of dental plaque.
Key words: *Streptococcus gordonii*, myrecitin derivatives, dental plaque, molecular docking

Introduction

Streptococcus gordonii is a commensal bacterium which colonizes different sites of human oral cavity. Its interaction properties are important not only for initial adhesion to saliva-coated surfaces but also for interbacterial adhesion and secondary colonization by organisms such as *Porphyromonas gingivalis* [1]. It is strongly believed that *S. gordonii* plays an important role in the development of bacterial communities associated with dental caries, gingivitis, and periodontitis [2]. *S. gordonii* also expresses two cell surface proteins SspA and SspB that belong to the antigen I/II (AgI/I) family of proteins [3].

These proteins are known to have multiple functions, including binding to human salivary agglutinin, collagen, and certain *Actinomyces naeslundii* strains [4,5], suggesting that they are important for the development of the plaque community. SspB is also known to mediate interactions with *Porphyromonas gingivalis* [6]. Thus inhibition of SspB can reduce the formation of dental plaque and thus the dental caries. The effective inhibitor of SspB can be a potential drug in the reduction of dental caries. Myricetin is a major flavonoid found in a number of foods, including onions, berries, grapes and red wine [7]. Its IUPAC name is 3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-1-benzopyran-4-one The studies have shown that myricetin has antioxidant, anti-inflammatory and anti- cancer effects [8,9].

Materials and Methods

Protein preparation

The three dimensional structure of SspB was retrieved from RCSB-PDB data base. Its PDB code is 2WD6.

Active site prediction

The possible binding sites of SspB were searched using binding site prediction an online tool Q site finder [10]. The binding sites which are more flexible were selected for this study.

Generation and optimization of Ligand

The myricetin in sdf format was downloaded from Pubchem database and was converted to mol2 format using OPEN BABEL software (www.vcclab.org/lab/babel/start.html). A total of 500 ligands in 2D format were generated with the help of software ACD chemsketch [11]. The ligands were saved in mol2 format. The OPEN BABEL software was used to convert mol2 format to pdb format. Rapid virtual screenings of these compounds were performed in the docking tool iGEMDOCK v2.0 [12]. A population size of 150 is set with 70 generation and one solution for quick docking. Based on the binding energy a total of five ligands were selected for the further study. The selected five ligands were then analyzed for drug- relevant properties based on "Lipinski's rule of five". Other drug like properties were analysed using OSIRIS Property Explorer (http://www.organicchemistry.org/prog/peo/) and Mol soft, the drug-likeness and molecular property explorer (http://www.molsoft.com/mprop/). On the basis of binding affinity and drug like properties, all these six ligands were taken for further molecular docking study.

Protein-ligand docking

iGEMDOCK is an integrated virtual screening environment from preparations through post-screening analysis with pharmacological interactions . First, iGEMDOCK provides interactive interfaces to prepare both the binding site of the target protein and the screening compound library. Each compound in the library is then docked into the binding site by using the in-house docking tool GEMDOCK. Subsequently, iGEMDOCK generates protein-compound interaction profiles of electrostatic, hydrogen-bonding, and van der Waals interactions. Based on these profiles and compound structures, iGEMDOCK infers the pharmacological interactions and clusters the screening compounds for the post-screening analysis. Finally, iGEMDOCK ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of GEMDOCK. The selected six ligands were subjected accurate docking (very slow docking) by setting population size of 800 is set with 80 generation and 10 solution. After the completion of the docking the post docking analysis was performed to find the docking pose and its energy values.

Results and Discussion

The 3D structure of SspB is shown Figure 1. It is made up of 3072 amino acids. Its 3D structure is viewed as PDB file with Rasmol structure colour scheme. Alpha helices are coloured magenta, beta sheets are coloured yellow, turns are coloured pale blue, and all other residues are coloured white.

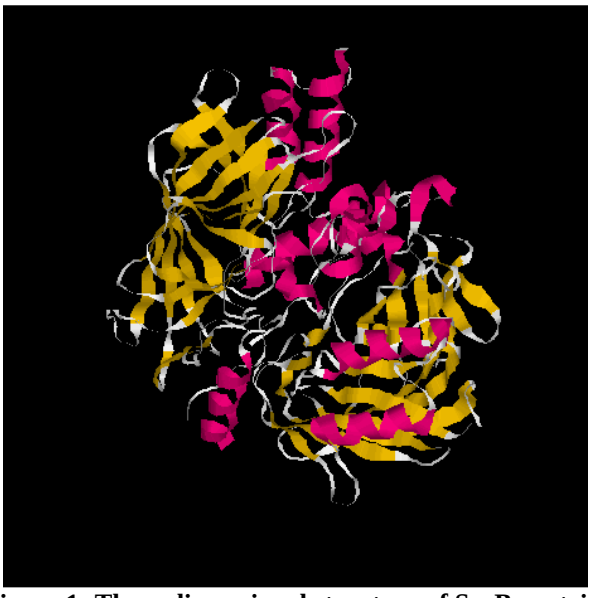

Figure 1: Three dimensional structure of SspB protein

A total of 500 ligands were prepared based on the structure of the SspB protein using ACD chemsketch software. It was converted to pdb format using OPEN BABEL software. All the 500 ligands were then subjected to virtual rapid screening with iGEMDOCK software and five compounds were found to have good fit with a low binding energy. The structure and the IUPAC name of the five ligands were shown in the Figure 2. The selected five ligands were then studied for its drug relevant properties.

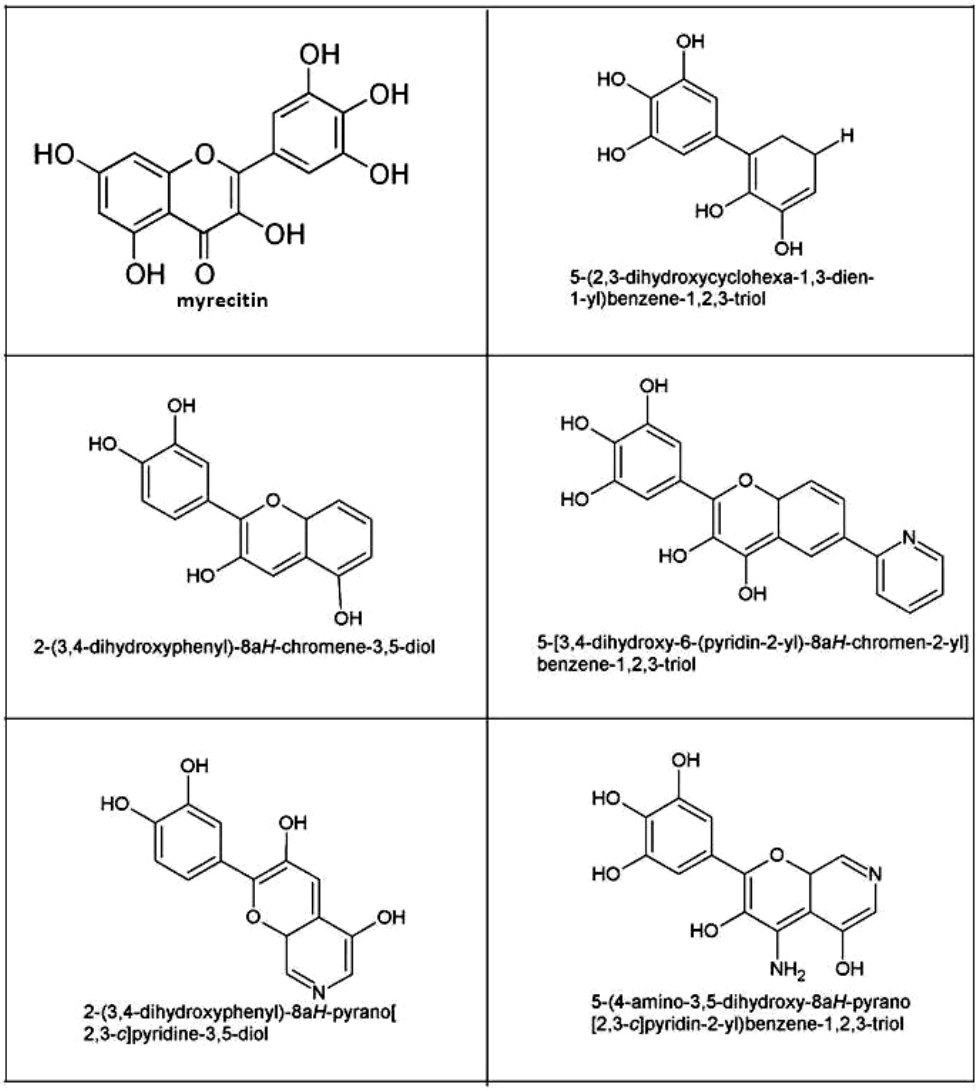

Figure 2: The structure and IUPAC name of the five ligands generated from myrecitin

The Table 1 depicts the values related to the Lipinski's rule of Five. From the table it is evident that all the five selected ligands obey the Lipinski's rule. The Table 2 shows the drug relevant properties of the five ligands. They all possess good drug score and drug likeness.

Table 1: The Lipinski's properties of the selected five ligands

S. No.	Ligand	Molecular weight	Xlog p	H bond donor	H bond acceptor
1.	5-(2,3-dihydroxycyclohexa-1,3-dien-1-yl)benzene-1,2,3-triol	300.31	2.862	4	5
2.	2-(3,4-dihydroxyphenyl)-8a*H*-chromene-3,5-diol	229.11	1.709	4	5
3.	5-[3,4-dihydroxy-6-(pyridin-2-yl)-8a*H*-chromen-2-yl]benzene-1,2,3-triol	365.34	1.564	5	7
4.	2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol	273.24	0.714	4	6
5.	5-(4-amino-3,5-dihydroxy-8a*H*-pyrano[2,3-*c*]pyridin-2-yl)benzene-1,2,3-triol	304.58	- 0.058	5	8

Table 2: The drug relevant properties of selected six ligands

S. No.	Ligand	Drug likeness	Drug score	Mutagenic	Tumorigenic	Irritant
1.	5-(2,3-dihydroxycyclohexa-1,3-dien-1-yl)benzene-1,2,3-triol	1.41	0.83	No	No	No
2.	2-(3,4-dihydroxyphenyl)-8a*H*-chromene-3,5-diol	1.72	0.85	No	No	No
3.	5-[3,4-dihydroxy-6-(pyridin-2-yl)-8a*H*-chromen-2-yl]benzene-1,2,3-triol	1.86	0.82	No	No	No
4.	2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol	2.35	0.89	No	No	No
5.	5-(4-amino-3,5-dihydroxy-8a*H*-pyrano[2,3-*c*]pyridin-2-yl)benzene-1,2,3-triol	1.44	0.84	No	No	No

After the satisfactory results of ADME properties, the five ligands were then subjected to further molecular docking with iGEMDOCK subjecting to accurate docking (very slow docking) by setting population size of 800 with 80 generation and 10 solution. The results were shown in the Table 3. From the table it is evident that all he five ligands have excellent docking energy values. The results clearly indicate that the ligands thus generated should have a good inhibitory property for SspB protein. Among all the ligands generated, the fouth ligand 2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol has very good drug likeliness and drug score of 2.35 and 0.89 respectively. Its docking pose was shown in the Figure 3. Hence this compound can be a potential drug candidate in the prevention of dental plaque as it can prevent the colonisation of *S. gordonii*.

Table 3: The results of iGEMDOCK showing binding energies of five selected ligands

S.No.	Ligand	Total binding Energy (kcal/mol)	Vanderwaals force (kcal/mol)	H Bond (kcal/mol)	Electrostatic bond (kcal/mol)
1.	5-(2,3-dihydroxycyclohexa-1,3-dien-1-yl)benzene-1,2,3-triol	-85.8443	-73.2739	-12.5704	0
2.	2-(3,4-dihydroxyphenyl)-8a*H*-chromene-3,5-diol	-85.2168	-71.2521	-13.9647	0
3.	5-[3,4-dihydroxy-6-(pyridin-2-yl)-8a*H*-chromen-2-yl]benzene-1,2,3-triol	-93.839	-76.331	-17.508	0
4.	2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol	-86.1416	-63.96	-22.1816	0
5.	5-(4-amino-3,5-dihydroxy-8a*H*-pyrano[2,3-*c*]pyridin-2-yl)benzene-1,2,3-triol	-90.3325	-74.8399	-15.4926	0

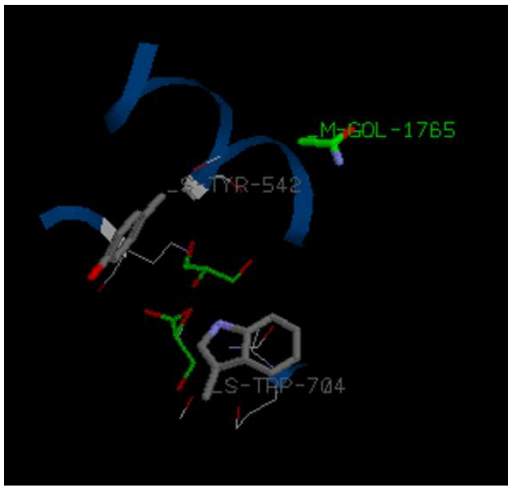

Figure 3: Docking pose of SspB with 2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol

Conclusion

The SspB protein of *S. gordonii* is found to be the major virulence factor involved in the formation of dental caries. Hence the inhibitors of the SspB protein can be an effective drug in the prevention of dental plaque caused by *S. gordonii*. In the present study the ligands were generated and were studied for its ability to inhibit the SspB protein by molecular docking method. Five ligands with good inhibitory properties were generated among which 2-(3,4-dihydroxyphenyl)-8a*H*-pyrano[2,3-*c*]pyridine-3,5-diol, a novel compound is found to be very excellent drug candidate based on the molecular docking studies and its ADME properties.

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