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Molecular Docking Study on Myricetin Derivates as The Inhibitors of Glucosyl Transferase SI, A Virulence Factor of Streptococcus Mutans in The Causation of Dental Caries

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Abstract

Dental caries is one of the most prevalent infectious diseases in the world. Streptococcus mutans is regarded as a primary microbial agent in the pathogenesis of dental caries. The role of S. mutans in cariogenic activity is its ability to adhere to the initially acquired film, produce acids and synthesize insoluble and soluble glucans that help to maintain plaque by producing glucosyl transferases (Gtfs) which metabolize sucrose into free glucans and fructose. Hence the inhibition of Glucosyl transferases will be an ideal strategy in the prevention of dental caries. The three-dimensional structure of GTF-SI was retrieved from RCSB protein data bank. Its PDB code is 3AIB. A total of 1000 ligands in 2D format were generated from myricetin structure 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 four ligands were selected for the further study. The selected four ligands were then analyzed for drug- relevant properties. On the basis of binding affinity and drug like properties, all these four ligands were taken for further molecular docking study. The ligand 4-(5-hydroxy-8-iodo-1,8a- dihydronaphthalen-2-yl) benzene-1,2-diol is found to have excellent drug likeliness score of 2.2 and a drug score of 0.73. Further the ligand also possesses excellent docking free energy. The results clearly indicate that the ligand should have a good inhibitory property for GTF -SI protein and hence can be a potential drug candidate in the prevention of caries caused by S.mutans.

Keywords: *Streptococcus Mutans, Glucosyl Transferase SI, Myricetin Derivatives, Molecular Docking, Anticaries Activity*

1. Introduction

Dental caries is one of the most prevalent infectious diseases in the world [1]. Streptococcus mutans is regarded as a primary microbial agent in the pathogenesis of dental caries although additional acidogenic microorganisms may be involved [2]. This bacterium synthesizes extracellular glucans from sucrose using glucosyltransferases (GTFs) [3]. Glucans promote the accumulation of cariogenic streptococci and other oral microorganisms on the tooth surface, and are critical for the formation and structural integrity of biofilms [4, 5]. Flavonoids are phenolic plant metabolites that occur ubiquitously in fruit, vegetables, grains, nuts, tea and wine [6, 7]. Up to now, over 6000 different compounds have been identified. Myricetin (3,5,7,3',4',5'-hexahydroxyflavone) (Figure 1) is a major flavonol that is widely distributed in berries, fruit, vegetables, and medicinal herbs [8]. These flavonoids constitute an important group of phytochemicals that gained increased research attention since it was found that they could exert anticarcinogenic, antimutagenic, anti- inflammatory, and antiviral actions [9]. The role of S. mutans in cariogenic activity is its ability to adhere to the initially acquired film, produce acids and synthesize insoluble and soluble glucans that help to maintain plaque by producing glucosyltransferases (Gtfs) which metabolize sucrose into free glucans and fructose [10]. Hence the inhibition of Glucosyltransferases will be an ideal strategy in the prevention of dental caries. In the present study an attempt has been made to produce myrecitin derivatives as the drug candidate in the prevention of dental caries by molecular docking method.

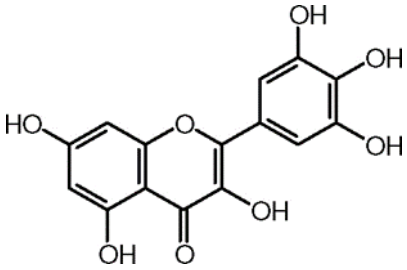

Figure 1: Myricetin

2. Materials And Methods

Protein preparation

The three dimensional structure of GTF-SI was retrieved from RCSB protein data bank. Its PDB code is 3AIB.

Active Site Prediction

The possible binding sites for 3AIB were searched using 3D LIGANDSITE an online tool. The binding sites which are more flexible were selected for this study [11].

Generation and optimization of Ligand

A total of 1000 ligands in 2D format were generated from myricetin structure with the help of software ACD chemsketch.

The ligands were saved in mol 2 format. The OPEN BABEL software (www.vcclab.org/lab/babel/start.html) was used to convert mol format to pdb format. Rapid virtual screenings of these compounds were performed in the docking tool iGEMDOCK v2.0 [13]. A population size of 150 is set with 70 generation and one solution for quick docking. Based on the binding energy a total of four ligands were selected for the further study. The selected four 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 four 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.

3. Results and Discussion

The primary structure of GTF SI in FASTA format is shown in Figure 2. It is made up of 1455 amino acids. The 3D structure of GTF SI is shown Figure 3. 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.

>sp|P13470|GTFC_STRMU Glucosyltransferase-SI OS=Streptococcus mutans serotype c (strain ATCC 700610 / UA159) GN=gtfC PE=1 SV=2
MEKKVRFKLRKVKKRWVTVSVASAVVTLTSLSGSLVKADSTDDRQQAVTESQASLVTTSE
AAKETLTATDTSTATSATSQPTATVTDNVSTTNQSTNTTANTANFDVKPTTTSEQSKTDN
SDKIIATSKAVNRLTATGKFVPANNNTAHSRTVTDKIVPIKPKIGKLKQPSSLSQDDIAA
LGNVKNIRKVNGKYYYYKEDGTLQKNYALNINGKTFFFDETGALSNNTLPSKKGNITNND
NTNSFAQYNQVYSTDAANFEHVDHYLTAESWYRPKYILKDGKTWTQSTEKDFRPLLMTWW
PDQETQRQYVNYMNAQLGIHQTYNTATSPLQLNLAAQTIQTKIEEKITAEKNTNWLRQTI
SAFVKTQSAWNSDSEKPFDDHLQKGALLYSNNSKLTSQANSNYRILNRTPTNQTGKKDPR
YTADRTIGGYEFLLANDVDNSNPVVQAEQLNWLHFLMNFGNIYANDPDANFDSIRVDAVD
NVDADLLQIAGDYLKAAKGIHKNDKAANDHLSILEAWSYNDTPYLHDDGDNMINMDNRLR
LSLLYSLAKPLNQRSGMNPLITNSLVNRTDDNAETAAVPSYSFIRAHDSEVQDLIRNIIR
AEINPNVVGYSFTMEEIKKAFEIYNKDLLATEKKYTHYNTALSYALLLTNKSSVPRVYYG
DMFTDDGQYMAHKTINYEAIETLLKARIKYVSGGQAMRNQQVGNSEIITSVRYGKGALKA
TDTGDRTTRTSGVAVIEGNNPSLRLKASDRVVVNMGAAHKNQAYRPLLLTTDNGIKAYHS
DQEAAGLVRYTNDRGELIFTAADIKGYANPQVSGYLGVWVPVGAAADQDVRVAASTAPST
DGKSVHQNAALDSRVMFEGFSNFQAFATKKEEYTNVVIAKNVDKFAEWGVTDFEMAPQYV
SSTDGSFLDSVIQNGYAFTDRYDLGISKPNKYGTADDLVKAIKALHSKGIKVMADWVPDQ
MYALPEKEVVTATRVDKYGTPVAGSQIKNTLYVVDGKSSGKDQQAKYGGAFLEELQAKYP
ELFARKQISTGVPMDPSVKIKQWSAKYFNGTNILGRGAGYVLKDQATNTYFSLVSDNTFL
PKSLVNPNHGTSSSVTGLVFDGKGYVYYSTSGNQAKNAFISLGNNWYYFDNNGYMVTGAQ
SINGANYYFLSNGIQLRNAIYDNGNKVLSYYGNDGRRYENGYYLFGQQWRYFQNGIMAVG
LTRIHGAVQYFDASGFQAKGQFITTADGKLRYFDRDSGNQISNRFVRNSKGEWFLFDHNG
VAVTGTVTFNGQRLYFKPNGVQAKGEFIRDADGHLRYYDPNSGNEVRNRFVRNSKGEWFL
FDHNGIAVTGTRVVNGQRLYFKSNGVQAKGELITERKGRIKYYDPNSGNEVRNRYVRTSS
GNWYYFGNDGYALIGWHVVEGRRVYFDENGVYRYASHDQRNHWDYDYRRDFGRGSSSAVR
FRHSRNGFFDNFFRF

Figure 2: Primary structure of GTF SI in FASTA format

Figure 3: The 3D structure of GTF SI viewed with Rasmol structure colour scheme

A total of 1000 ligands were generated from myricetin structure using ACD chemsketch software. It was converted to pdb format using OPEN BABEL software. All the 1000 ligands were then subjected to virtual rapid screening with iGEMDOCK software and four compounds were found to have good fit with a low binding energy. The structure and the IUPAC name of the four ligands were shown in the Figure 4. The selected four ligands were then studied for its drug relevant properties.

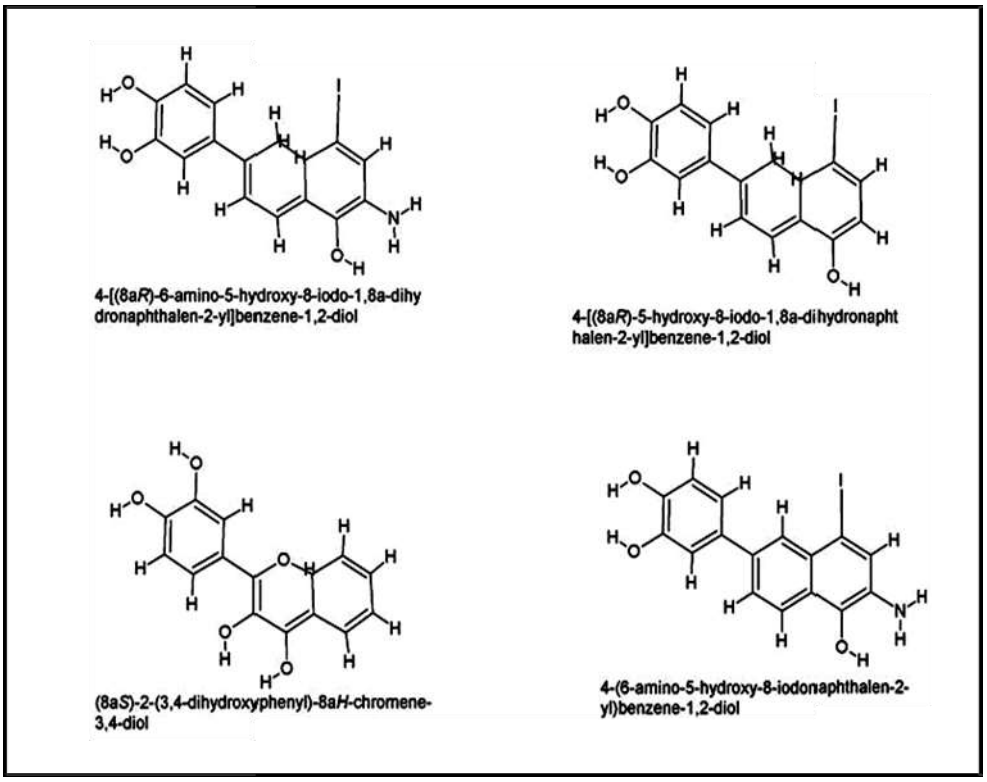

Figure 4: The structure and IUPAC names of the four ligands

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

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

Ligand	Molecular weight	Xlog p	H bond donor	H bond acceptor
2-(3,4-dihydroxyphenyl)-8aH-chromene-3,4-diol	272	1.69	5	4
4-(6-amino-5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	395	2.56	4	5
4-(5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	380	3.69	3	3
4-(6-amino-5-hydroxy-8-iodonaphthalen-2-yl)benzene-1,2-diol	395	2.56	4	5

Table 2: The drug relevant properties of selected four ligan s

Ligand	Drug Likeness	Drug score	Mutagenic	Tumorigenic	Irritant
2-(3,4-dihydroxyphenyl)-8aH-chromene-3,4-diol	1.41	0.83	NO	NO	NO
4-(6-amino-5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	1.13	0.71	NO	NO	NO
4-(5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	2.2	0.73	NO	NO	NO
4-(6-amino-5-hydroxy-8-iodonaphthalen-2-yl)benzene-1,2-diol	1.13	0.71	NO	NO	NO

After the confirmation of ADME properties, the four 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 solutions. The results were projected in the Table 3. From the table it is clear that the ligand 4-(5- hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol is found to have excellent drug likeliness score of 2.2 and a drug score of 0.73. Further the ligand also

posses excellent docking score. Its docking pose was shown in the Figure 3. The results clearly indicate that the ligand should have a good inhibitory property for GTF -SI protein and hence can be a potential drug candidate in the prevention of caries caused by *S.mutans*.

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

IUPAC name	Total energy	Vanderwaals Forces	H-bond	Electrostatic bond
2-(3,4-dihydroxyphenyl)-8aH-chromene-3,4-diol	-89.52	-63.81	-22.14	0
4-(6-amino-5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	-85.95	-57.57	-25.74	0
4-(5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-diol	-83.31	-66.7	-22.83	0
4-(6-amino-5-hydroxy-8-iodonaphthalen- 2-yl)benzene-1,2-diol	-85.58	-67.16	-18.42	0

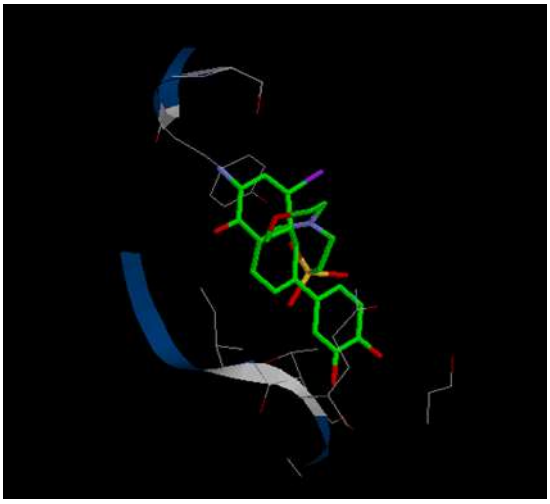

Figure 4: Docking pose of GTF-SI with 4-(5-hydroxy-8-iodo-1,8a-dihydronapthalen-2-yl)benzene-1,2-diol

4. Conclusion

The GTF SI of *S. mutans* is found to be the major virulence factor involved in the causation of dental caries. Hence the inhibitors of the GTF SI can be an effective drug in the prevention and control of dental caries caused by *S. mutans*. In the present study the ligands were generated from myricetin and were studied for its ability to inhibit the GTF SI by molecular docking method. Four ligands with good inhibitory properties were generated among which 4- (5-hydroxy-8-iodo-1,8a-dihydronaphthalen-2-yl)benzene-1,2-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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