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Insilico Interaction Of Selected Terpenoids Against Oral Biofilm (Streptococcus Mutans) Drug Targets.

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Abstract: Aim: The aim is to analyse the In Silico interaction of selected terpenoids against streptococcus mutans drug targets.
Materials And Methods: • Retrieval of protein using ligand structure.
• Molecular docking using iGemdock.
Results: From this study it is evident that docking is significant in Neptalactone. It has the highest fitness (-48.4), lowest VDW (-32.02), and H bond equal to standard inhibitor (-16.33).
Conclusion: The compound Neptalactone with the highest docking score is most efficient in blocking biofilm formation when compared to other compounds.

Keyword: Insilico, iGemdock, terpenoids.

INTRODUCTION

Streptococcus species are bacteria belonging to the Firmicutes phylum under the order of Lactobacillales and the family of Streptococcaceae [1]. Streptococcus species are found generally in the oral cavity and nasopharynx and forms significant amount of the normal microbiota of human and animals [2,3]. In healthy people, ordinary microbiota are innocuous, be that as it may, they can cause disease under specific conditions, for example, safe compromised state [4]. S. mutans can utilize a few carbohydrates into organic acids that reduces the pH of dental plaque biofilm, causing the demineralization of tooth lacquer and, thus, prompts the commencement of dental caries. This bacterium is likewise a important contributor to the formation of dental framework of extracellular polymeric substances (EPS) on dental biofilms. Besides, S. mutans-determined exopolysaccharides, for the most part glucans, give restricting destinations that advance gathering of different microorganisms on the tooth surface and further formation of cariogenic biofilms [5].

Streptococci have a range of potent virulence factors enabling them to cause such various infections . Adhesins are one such issue as a result of they play a vital role in organization. Adhesins and virulence factors of streptococci are reviewed extensively [6,7]. Carcinogenic capability of S. mutans is essentially obsessed on the ability of the bacterium to adhere and produce acid. S. mutans glucosyltransferases assist within the adhesion method by synthesizing insoluble glucan from

saccharose [8]. The capacity of S. mutans to initiate dental caries via acid production from the metabolism of dietary carbohydrates would be self-destructive if not for its outstanding ability to tolerate acid; signifying an important aspect of its virulence. Inhabitants of plaque expertise rapid, dynamic pH fluctuations that are greatly influenced by carbohydrate intake leading to pH levels that may drop from neutral pH 7.0 to acidic values below pH 3.0 in less than twenty min [9].Antibiotic resistance among pathogens has emerged into a most challenging phenomenon of reversing decades progress of therapeutic success since it causes substantially increased rate of infectious disease morbidity and mortality, as well as huge burden of cumulative socioeconomic costs [10]. The currently employed therapeutic and prophylactic interventions to infectious diseases are limited, however, due to the emergence of resistance to existing therapeutic agents as well as circulation of genetic variants that escape the immune surveillance [11].The scientific approaches of the past are not adequate to address these challenges and consequently there is a need for new research strategies and tactics to minimize these threats and improve global health [12].

MATERIALS AND METHODS

Retrieval of protein and ligand structures

The three dimensional structure of protein was retrieved from PDB database from the website https://www.rcsb.org/, which is a repository of 3D crystal structures of the protein. The structure file can be downloaded as PDB format. The preparation of receptor was done with the help of Discovery Studio Visualizer

tool which involved the removal of bound ligands and water molecules present in the downloaded structure. Once these changes are done the receptor turns into a stable active structure. Similarly, the structures of the five flavanoids chosen were retrieved from the structure databases: https://pubchem.ncbi.nlm.nih.gov/. The structure file was downloaded in .sdf format.
Using Frog2, the .sdf structure was energy minimized and converted to .mol2 format. This structure was used for docking analysis.http://bioserv.rpbs.univ-paris-diderot.fr/services/Frog2/

Molecular docking using iGemdock:
iGEMDOCK is an easy-to-use graphic environment for the docking, virtual screening, and post screening analysis. For post-screening analysis, iGEMDOCKcan enrich the hit rate and provide biological insights by deriving the pharmacological interactions from screening compounds. The pharmacological interactions represent conserved interacting residues that often form binding pockets with specific physico-chemical properties to play the essential functions of the target protein. Experiment results show that the success rate of iGEMDOCK is 78% (root-mean-square derivations below 2.0 angstrom) on 305 protein-compound complexes. iGEMDOCKis useful for understanding the ligand binding mechanisms and discovering lead compounds(Hsu et al. 2011).

Molecular Docking Analysis of The Lead Compounds
Three-dimensional structure of protein
The protein selected was Glucansucrase from *Streptococcusmutans*with PDB ID 3AIC. The crystal structure was determined using X-ray diffraction with a resolution: 3.11 Å. The structure is given in Figure 1.
The sequence length of the protein is 844 containing 8 chains.
The active site was found to be Arg475, Asp477, Glu515, His587, Asp588 and Tyr916 from the earlier researches.(Murugan et al. 2013)

Structure of Ligands
The terpenoids selected were carvone, myrcene, geraniol, nepetalactone and humulene. The standard inhibitor was found to be 2-(4-methoxyphenyl)-N-(3-{[2-(4-methoxyphenyl)ethyl]imino}-1,4-dihydro-2-quinoxalinylidene)ethanamine (Ren et al. 2016) .

Molecular docking Interaction analysis
Fitness is the total energy of a predicted pose in the binding site. The empirical scoring function of iGEMDOCK is estimates as:
Fitness = vdW + Hbond + Elec.
Here, the vdW term is van der Waal energy. Hbond and Elect terms are hydrogen bonding energy and electro statistic energy, respectively.

RESULTS

Table 1: Fitness value and the interaction scores of the ligands.

Ligand	Total Energy	VDW	HBond
Standard inhibitor	-76.6231	-59.7852	-16.838
Carvone	-42.4714	-33.0126	-9.45878
Geraniol	-32.2455	-32.2455	0
Neptalactone	-48.4135	-32.0251	-16.3884
Myrcene	-43.4434	-32.5841	-10.8594
Humulene	-44.5182	-44.5182	0

The highest fitness score was for the compound 1-Pentene, 1,3-diphenyl-1-(trimethylsilyloxy) followed by Benzoic acid, 4-methyl-2-trimethylsilyloxy-,trimethylsilyl ester, 1,3-Dioxolane, 2-(6- heptynyl)-, 2-heptyl 1, 3 Dioxolane and is very low for Tetramethylsilane.Among the five terpenoids chosen, the interaction was highest for Naptalactone. The binding energy was -48.41 for this ligand and it showed hydrogen bond interactions with the side chains of the active site residues.

DISCUSSION

Structure-based drug design is widely used to identify lead compounds with the growing availability of protein structures. Many tools (*e.g.*, GEMDOCK, DOCK, AutoDock, and GOLD) have been developed for virtual screening (VS) and successfully identified lead compounds for some target proteins . *i*GEMDOCK to facilitate steps from preparations of target proteins and ligand libraries toward post-screening analysis. *i*GEMDOCK is especially useful for post-screening analysis and inferring pharmacological interactions from screening compounds. We believe that *i*GEMDOCK is useful for understanding the ligand binding mechanisms and discovering lead compounds.[13].

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