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Insilico Interaction of Selected Phytoalkaloids Against Oral Biofilm (Streptococcus Mutants) Drug Targets

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ABSTRACT

Aim: The aim of this study is to determine the Insilico interaction of selected phytoalkaloids against oral biofilm (streptococcus mutants) drug targets.

Introduction: S. mutans has the ability to metabolize several carbohydrates into organic acids that reduce the pH of dental plaque biofilm, causing. the demineralization of tooth enamel and, consequently, leads to the initiation of dental caries. This bacterium is also a crucial contributor to the formation of a matrix of extracellular polymeric substances (EPS) on dental biofilms.Docking is the computational stimulation of candidate ligand binding to a receptor. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using scoring functions.[14-20]

Materials and methods: Docking of phytoalkaloids of plants against Streptococcus mutants was done by ACD Chemsketch and GOLD protein ligand. ACD/ChemSketch is an advanced chemical drawing tool and is the accepted interface for the industry's best NMR and molecular property predictions, nomenclature, and analytical data handling software. GOLD is a program for calculating the docking modes of small molecules in protein binding sites and is provided as part of the GOLD Suite, a package of programs for structure visualisation and manipulation (Hermes), for protein-ligand docking (GOLD) and for post-processing (GoldMine) and visualisation of docking results. Hermes acts as a hub for many of CCDC's products, for more information please refer to the Hermes product page.

Result: Docking of different active compounds of plants such as Anethole, Ascorbic acid,Kampherol, Nerolidol were compared with Ellagic acid which is taken as a standard gold score using GOLD protein ligand software and their scores are 30.89,
28.29, 22.61, 30.26 respectively with standard gold score of Ellagic acid is 38.11. These scores were done based on the H bond distance between protein and ligand binding.

Conclusion: The compound anethole with GOLD score of 30.89 is most efficient in blocking biofilm formation when compared to other compounds.

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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].

MATERIALS AND METHODS

Docking of Active compounds from Plants against Oral biofilm (Streptococcus mutans)

ACDlabsChemsketch

ACD/ChemSketch is an advanced chemical drawing tool and is the accepted interface for the industry's best NMR and molecular property predictions, nomenclature, and analytical data handling software.

ACD/ChemSketch is also available as freeware, with functionalities that are highly competitive with other popular commercial software packages. The freeware contains tools for 2D structure cleaning, 3D optimization and viewing, InChI generation and conversion, drawing of polymers, organometallics, and Markush structures—capabilities that are not even included in some of the commercial packages from other software producers. Also included is an IUPAC systematic naming capability for molecules with fewer than 50 atoms and 3 rings. The capabilities of ACD/ChemSketch can be further extended and customized by programming.

GOLD - Protein-Ligand Docking

GOLD is a program for calculating the docking modes of small molecules in protein binding sites and is provided as part of the GOLD Suite, a package of programs for structure visualisation and manipulation (Hermes), for protein-ligand docking (GOLD) and for post-processing (GoldMine) and visualisation of docking results. Hermes acts as a hub for many of CCDC's products, for more information please refer to the Hermes product page.

The product of a collaboration between the University of Sheffield, GlaxoSmithKline plc and CCDC, GOLD is very highly regarded within the molecular modelling community for its accuracy and reliability.

GOLD features include:

- A genetic algorithm (GA) for protein-ligand docking
- An easy to use interface with interactive docking set-up via Hermes
- A comprehensive docking set-up wizard
- Full ligand flexibility
- Partial protein flexibility, including protein side chain and backbone flexibility for up to ten user-defined residues
- Energy functions partly based on conformational and non-bonded contact information from the CSD
- A variety of constraint options
- Improved flexible ring handling
- Automatic consideration of cavity bound water molecules
- Improved handling and control of metal coordination geometries
- Improved parameterisation for kinases and heme-containing proteins
- Automatic derivation of GA settings for particular ligands
- A choice of GoldScore, ChemScore, Astex Statistical Potential (ASP) or Piecewise Linear Potential (PLP) scoring functions
- Extensive options for customising or implementing new scoring functions through a Scoring Function Application Programming Interface, allowing users to modify the GOLD scoring-function mechanism in order to either: implement their own scoring function or enhance

existing scoring functions; customise docking output

• A ChemScore Receptor Depth Scaling (RDS) rescore option so that the score attributed to hydrogen bonds is scaled depending on the depth in the binding pocket

• Automatic rescoring with an alternate scoring function at the end of a docking run.

GOLD's genetic algorithm parameters are optimised for virtual screening applications. GOLD is optimised for parallel execution on processor networks; a distributed version of GOLD is available for use on commercial PC GRID systems.

DISCUSSION

Biofilm cells are known to be physiologically distinct from their planktonic counterparts, being surrounded by extracellular polymeric substances (EPS), which have a major role both in biofilm formation and maintenance through nutritive and protective functions. This peculiar form of biofilm development confers on the associated bacteria great resistance to conventional antimicrobial compounds [10] Therefore, the impact of antimicrobials on planktonic S. mutans cannot be compared to the effects on biofilm cells. In fact, biofilm resistance is multi-factorial and several mechanisms have been described, i.e., limited diffusion of antimicrobials through the biofilm matrix, enzyme-mediated resistance, distinct levels of metabolic activity inside the biofilm (from active to dormant state), genetic adaptation, efflux pumps and the presence of persister cells [11]. It is clear that an accurate characterization of the antimicrobial action of a compound should focus cells in both planktonic and sessile states.

In addition to the antibacterial action of these natural compounds, it is very important to understand their cytotoxicity before being used in humans. No obvious cytotoxic effects were detected for the phytochemicals eugenol, citronellol and cinnamic acid. Similarly, Babich & Visioli (2003) using 5 mM of cinnamic acid observed reduced effects on the viability of human gingival GN61 fibroblasts, human gingival S-G epithelial cells and human carcinoma HSG1 cells [12]. In the present work, it was found that fibroblast cells were more sensitive to trans-cinnamaldehyde when compared to other phytochemicals with a cell viability of around 72%. Brari & Thakur (2015) also showed that cinnamaldehyde reduced viability of BV2 (microglia) cell line in a higher extent than citronellol and eugenol. According to ISO 10993-5 (2009), the differences observed were not significant in terms of toxicity, as cytotoxicity is considered when viability is lower than 70% [13]. Therefore, these results showed that citronellol, cinnamic acid and trans-cinnamaldehyde presented antibacterial effects against planktonic and sessile S. mutans, without compromising the viability of fibroblasts cell line L929.

RESULT

Ligand Name	Atom in Ligand	Atom in Protein	H-Bond Distance	Score
ANETHOLE	O10	ASP66:OD2	2.782	30.89
ASCORBIC ACID	O9	GLN864:O	2.752	28.29
	O7	GLN874:N	2.9	
ELLAGIC ACID	O21	GLN864:O	2.981	38.11
	O22	GLN864:O	2.477	
KAMPHEROL	O21	NO H BONDS	2.689	22.61
NEROLIDOL				30.26

CONCLUSION

The standard used in the study is ellagic acid which has the highest GOLD score of 38.11 thereby proving its efficiency in inhibiting the biofilm formation. The compound anethole with GOLD score of 30.89 is most efficient in blocking biofilm formation when compared to other compounds.

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