MOLECULAR MODELING STUDIES IN VARIOUS DRUGS

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ABSTRACT

Dental plaque Biofilms are responsible for numerous chronic oral infections and cause a severe health burden further it cannot be eliminated, as the bacteria in the Biofilms are resistant to the host's immune defences and antibiotics. There is a critical need to develop new strategies to control Biofilm-based infections. Biofilm formation in Streptococcus mutansis promoted by major virulence factors known as glucosyltransferases (Gtfs), synthesize adhesive extracellular polysaccharides (EPS). The current study is designed to identify novel molecules that target Gtfs, thereby inhibiting S. mutansbiofilm formation and having the potential to prevent dental caries. Structure-based virtual screening of approximately 150,000 commercially available compounds against the crystal structure of the glucosyltransferase domain of the GtfC protein from S. mutansresulted in the identification of a quinoxaline derivative,2-(methoxyphenyl)-N-(3-{[2-(4 methoxyphenyl)ethyl]imino}-1,4-dihydro-2 quinoxalinylidene)ethanamine, as a potential Gtf inhibitor. The rat model finds that the compound significantly reduced the incidence and severity of smooth and sulcal-surface caries in vivo with a concomitant reduction in the percentage of S. mutants in the animals' dental plaque ($P < 0.05$).

KEYWORD: *Bacteria, biofilms, compounds, molecule .*

INTRODUCTION

Biofilms are the product of a microbial developmental process. The process is summarized by five major stages of Biofilm development namely Initial attachment, Irreversible attachment**,** Maturation I**,** Maturation II**,** Dispersion.

Biofilms are communities of microorganisms that are attached to a surface and play a significant role in the persistence of bacterial infections. Bacteria within a Biofilm are several orders of magnitude more resistant to antibiotics, compared with planktonic bacteria. Thus far, no drugs are in clinical use that specifically target bacterial Biofilms. This is probably because until recently the molecular details of Biofilm formation were poorly understood. Bacteria integrate information from the environment, such as quorum-sensing autoinducers and nutrients, into appropriate Biofilm-related gene expression, and the identity of the key players, such as cyclic dinucleotide second messengers and regulatory RNAs are beginning to be uncovered. Herein, we highlight the current understanding of the processes that lead to Biofilm formation in many bacteria.Several mechanisms have been reported for increased antimicrobial resistance in Biofilm structures. When organized in Biofilms, the micro-organism are less susceptible to anti-microbials and more resistant to immune defense mechanisms.The concentration of an agent which kills planktonis micro-organisms might have to respectively

be increased by 10-1000 times to have the same efficacy on micro-organism in a Biofilm.This relative resistance to anti-microbial agents partly explains why many oral prophylactic predicted to be efficacious in vitro assays show only marginal clinical effects. Retarded or incomplete penetration of the agent into the Biofilm or reduced growth rate of the micro-organism due to nutrients limitations, has been considered a reason for lack of efficacy. Another likely explanation is the fact that micro-organisms.

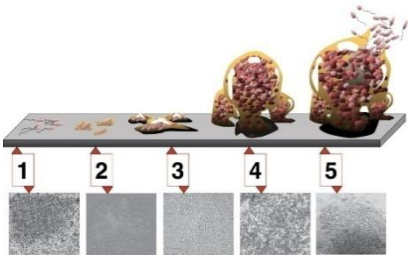

Fig 1.1 Development of oral Biofilms

RELATED WORK

This section overview the different methods for molecular modeling in drug design which have been evaluated by several authors.

1. **Modeling of molecules in drug design by Revecca,C.Vade.**
   It provides a snapshot of the state of the art of molecular modeling in drug design illustrating recent advances and critically discussing important challenges. It deals with virtual screening and pharmacophore modeling, chemoinformatic applications of recent technologies like artificial intelligency and machine learning, molecular dynamic simulation and enhanced sampling to investigate involvement of molecular flexibility to drug receptor interaction, the modeling of drug receptor salvation. It completely shows signposts for future development and computer aided drug design.
2. **Artificial intelligence in drug design by Gerhard Hessler .**
   It finds physiochemical and ADMET properties in quantitative structure property relationship. Combination with synthesis planning and ease of synthesis is feasible and more automated drug discovery by computers is expected in the near future.

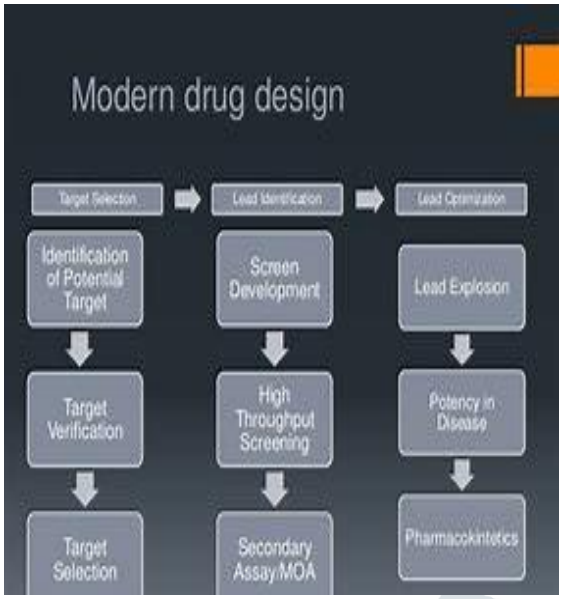

Fig 1.2- Molecular drug design

EXPERIMENT

Two classes of molecules produced by oral bacteria have been implicated as true signals, produced specifically for the purposes of cell-to-cell communication.. There is some debate regarding the status of AI-2 as a true signal because this molecule appears to have a primary role in metabolism in at least some bacteria . Nevertheless, the widespread changes in gene expression induced by AI-2, combined with its apparent activity at extremely low concentrations (in the order often of nanomolars or less), are consistent with a role in signalling. AI-2 and CSPs appear to be involved in intraspecies QS. However, there is accumulating evidence that they are also involved in a variety of interspecies interactions between bacteria. CSPs re short peptides, approximately 17–21amino acids, produced by many streptococci from the proteolytic digestion of the comC gene product.

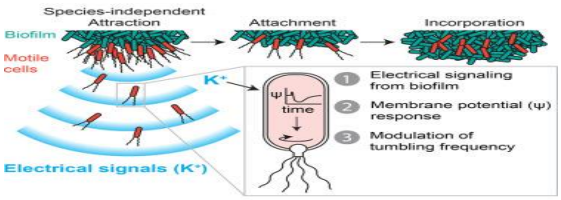

Fig 1.3- Signal transduction System

Two-component signal transduction systems and histidine kinases represent potential prophylactic target. The histidine kinases and response regulators of the two component systems exhibit both conserved and variable domains. This characteristic can be used for the development of inhibitors with species-specific or broad-spectrum activity. The stimulus input domain in the

histidine kinases is the most variable, which reflects the wide variety of stimuli or signal molecules that may be sensed by two-component systems.

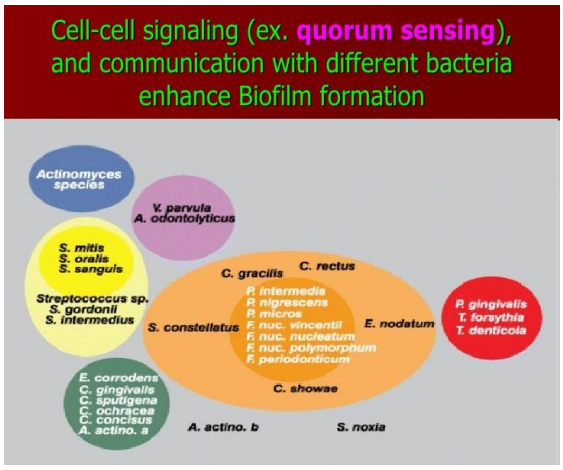

Fig-1.4- Cell Signaling Process

DRUGS

(i) PHYTOCHEMICALS

Phytochemicals are chemical compounds produced by plants, generally to help them thrive or thwart competitors, predators, or pathogens. The name comes from Greek, Modern φυτόν (phyton), meaning 'plant'. Some phytochemicals have been used as poisons and others as traditional medicine.Phytochemical is used to describe plant compounds that are under research with unestablished effects on health and are not scientifically defined as essential nutrients. Phytochemical under research can be classified into major categories ,such as carotenoids and polyphenols,which include phenonic acids,flavonoids and ligands,flavonoids can be divided into group based on their similar chemical structure such as anthocyanins,flavones,flavanones and is flovones and flavanols.Flovanols are classified as catechins,epicatechins and proanthocyanidins.

(ii) FLAVONOIDS

Flavonoids are a group of plant metabolites through to provide health benefits through cell signalling pathway and antioxidant effects. Naturally occurring plant pigments, flavonoids are one of the reasons fruits and vegetables are so good. Flavonoids , like other antioxidants, do their work in the body by corralling cell-damaging free radicals and metallic ions.Food scientist Alyson Mitchell, Ph.D., who studies flavonoids at UC Davis, is optimistic about the salutary power of these compounds: "The current hope of scientists is to discover exactly what flavonoids should be eaten in what amounts to fight specific diseases."

Flavonoids are important antioxidant ,and promote several health effects.Aside from antioxidant activity, these molecules provide the following beneficial effects; a)Anti-viral b)Anti-cancer c)Anti-inflammatory d)Anti-allergic.

MATERIALS AND METHOD

1. NCBI : The National Center for Biotechnology Information (NCBI) is part of the United States National Library of Medicine (NLM), a branch of the National Institutes of Health (NIH).NCBI was established as the government response to the need for more and better information processing method to deals with this challenges

2. PUBMED : PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.

MOLECULAR MODELLING.

Studio is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X- ray reflection data, scripts, and other data .it also provides a rich set of viewers for displaying plot and other graphical representation of data.The application run on window and linux and is a fully integrated desktop environment that provides access to standard operating system features such as the file system, clipboard, and printing services

- **IGEMDOCK**

Structure-based virtual screening and post-screening analysis are emergent tasks in computer-based drug discovery. Combining these two methods to effectively reduce the false positives is considered as a key step to finding the lead compounds. In this study, we have developed a graphical-automatic drug discovery system, called IGEMDOCK, for integrating docking, screening, post-analysis, and visualization. Using IGEMDOCK, the predicted poses generated from the GEMDOCK are able to be directly visualized by a molecular visualization tool and analyzed by post-analysis tool. IGEMDOCK provides the post-analysis tools by using k-means and hierarchical clustering methods based on the docked poses (i.e. protein-ligand interactions) and compound properties .Validation of the protein-ligand docking accuracy and screening accuracies of IGEMDOCK by using a test set with 100 protein-ligand complexes and four targets, respectively, which are thymindine kinase, estrogen for antagonists and agonists, and human DHFR

DOCKING

If the protein ligand output path and parameters, have been set docking can be started by pressing “start docking”. The status of the job will be shown on the screen. During the docking/screening docked posed can be viewed and post analysis of the current job can be carried out .

After docking process is finished the docking result and the poses can be viewed by selecting the “ view docked poses and post- anaylze”, and the predicted poses and energy list of these poses will be saved in to the “best_ pose”, and “fitness.txt” of the output location, respectively. Igemdock provides an anaylsis environment

with visualized tool and post analysis tools for users. 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 term are hydrogen bonding energy and electro statistic energy, respectively.

The data in the post- analysis process will be automatically saved by igemdock into the output directory. The output of igemdock saves in the output directory. The outputs include predicted poses energy list, cluster data and interaction profile. Generally, you may be interest in docked poses and energy table. The lowest energy pose of each ligand is in the folder ”best_pose” and the energy table is result.txt.

CONCLUSION

To conclude there is increasing evidence that the role of oral Biofilm in antibiotic resistance bacteria is significant. The compounds lacking fitness are less likely to be Biofilm, as they after from the common pharmacophore features model for the Biofilm substrate. The two compounds housane and catechol share a very low fitness for the 3IAC and 3TIOC Biofilm abstracted by using igemdock - ing with regards to natural product s, it generally accepted that phytochemicals are less anti infectives than agent of antibiofilm origin, (i.e antibiotic). However, new class of antibiofilm drugs are urgently required and the flavonoids represent a novel set of leads. future optimisation of these compounds through structural alteration may allow the development of a pharmacologically acceptable antibiofilm agent or group of agents. The effect of oral Biofilm need to be considered in the design of future antibiotics and the role of assessed in order to maximize the efficacy of current and future antibiotics. The predicted active residue used as the site for 50 natural flavonoids compounds used for docking studies. The result of the interaction between the active site residues of target s.mutans and 50 flavanoids compound and hesperidin and naringin were found to have the highest total energy of -150 709kcal/mol and -133.142 kcal/mol compared with other compounds which are giving activation energy of <-133. Thus the docking result were analysed and finally reported that among the 50 flavanoid compounds . housane and catechol exhibits the best binding interaction with the s.mutans receptor and further it could be useful for identification and development of new preventive and oral Biofilm drug against gram positive pathogens.

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