Computer Aided Drug Discovery Utilization in Conservative Dentistry

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Abstract

Computer aided drugs discovery or in silico design is bioinformatics' contribution that supports pharmacy, medical and dentistry fields. It creates innovation in the search, design and optimization of new drug candidates.

The method minimizes the use of animal models and in vitro assay laboratory work, which are very time and resources consuming processes. Even though it has big advantages, it has not been utilized frequently in conservative dentistry fields. Researches using CADD approaches in conservative dentistry shown in the reviews, used Structure-based design and Ligand-based design, both are two methods to predict compound-protein interaction. Utilized as genome identification of Streptococcus mutans, CADD can differ the genome from other bacteria and gives confirmation to polymerase chain reaction examination. CADD also beneficial to predict pharmacokinetics of drug candidates.

This method exhibits great prediction in screening active compounds that have inhibition action in bacterial growth and adhesion on dental plaque. CADD approach has been used in conservative dentistry and showed great predictions to minimize numbers of trials in laboratory works. Expansion of application might boost drugs design projects in conservative dentistry.

Review (J Int Dent Med Res 2022; 15(2): 899-903)

Keywords: Computer aided drugs discovery, in silico, conservative dentistry, life expectancy.

Received date: 15 January 2022 **Accept date:** 02 March 2022

Introduction

Bioinformatic defines as computational and informatic sciences application on biology field that enable scientists to manage, process and analyze genomic and molecular data. Computer aided drug discovery, as bioinformatic product, boosts progress in pharmacy, medical and dentistry sciences, by using data to identify pathway of diseases, prediction of reliable treatment approaches and accelerate drug discovery process.[1] It shorten the time needed to develop new drugs.

In early days, development of a new drug would take 12 to 15 years. The process including years of basic research, lead discovery, preclinical development, clinical development and Food and Drug Administration filing. Failure in each step might prolonged the process.[2,3,4] Computer aided drugs discovery (CADD) assists target identification, validation, optimal hits selection and help the hit to lead step. Hit is term used to define molecule that has desired activity in compound screen and the activity confirmed upon retesting. CADD works based on molecular data, biomolecular knowledge and appropriate computational method to analyze the complex combination.[4]

There are two methods in CADD, they are structure-based drug design (SBDD) and ligand-based drug design (LBDD). SBDD is used when the structure of the target protein is known. Structure of target protein is beneficial to identify key sites and interaction that impact on biological function of the protein. LBDD is used when the ligands which binds to the desired target site is known. Physicochemical properties of the ligands is used to predict structure activity relationship, as in this method assumed similar structure of compound will have similar biological action and interaction with target protein. [5,6]

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Review

CADD gives advantages in researches based on medical and dentistry sciences. This approach is also known in conservative dentistry, but not yet popular in these past 10 years (Table 1). Conservative dentistry comprise preventive, operative and endodontic scopes. The main objective is to conserve the teeth in oral cavity. Complexity to be aware, is that oral cavity has the second largest and diverse microbiome after the gut.[6,7,8] Any alteration in oral cavity will have impact on the harmony and the teeth as well.

CADD utilization purposes	Known structure protein (p), ligands (l), bacteria (b), monomer (m)	Unknown structure protein (p), ligands (l), bacteria (b)	Prediction
Bioactivity[7,8]	Peptide of casein (p)		bioactivity, toxicity, allergenicity
	C-phycocyanin of microalgae (p)		Sucrose sequestration
Antimicrobial[9–16]	Phosphoglucosamine mutase and pyruvate kinase (p)	Candidate compound SM001-SM010 (l)	inhibit growth in dental pluque
	Molecules (in Morin) (l)	antigen I/II (p)	inhibit adhesion
	Capsaicin, genistein, glychirrizin (l)	*Streptococcus mutans*, *Enterococcus faecalis*, *Porphyromonas gingivalis*, *Treponema denticola* and *Tanerella forsythia* (b)	virulence properties
	Niconitrile, thienopyridines (l)	COX-2 (p)	biofilm inhibitor
	Ocimum americanum, *Ocimum basilicum L.* (l)	MurA enzyme (p) of *S. mutans, S. sanguinis, E.faecalis*	binding affinity
Genome Identification [17,18]	*Streptococcus mutans* (b)		differ from PCR
	Streptococcus mutans and *Streptococcus sanguinis* (b)		similar proportion genes
Pharmacokinetic (ADME, toxicity) [10,19,20]	Molecule (in Morin) (l)	Antigen I/II (p)	inhibit adhesion
	Phosphotransferase *S mutans*		No natural ligands
	Henicosa-1,3-dyn10 from *Acmella calva (l)*	Peroxidase resistant gene and glucan binding protein β (p)	
Toxicity[21]	MMA, HEMA, TEGDMA, UDMA (m)		neurotoxic
Antivirus[22]	Chlorhexidine (l)	SARS-CoV-2 (p)	

Table 1. CADD utilization in Conservative Dentistry

To prevent the caries, micro-organisms harmony in oral cavity needs to be maintained. Casein and microalgae are proteins that had been analyzed using CADD approaches. 70 peptides identified from casein hydrolysates were predicted to have no toxicity, no allergenic activity and 15 among others were predicted to have several bioactivity, such as ACE activity, antioxidative activity, anti-inflammatory, immunomodulating and antithrombic activity.[9] C-phycocyanin, pigment of microalgae, was predicted to have antimicrobial activity. Study showed C-phycocyanin had low binding energy to sucrose and potential to sequester the sucrose. It predicted to decrease caries-causing bacteria.[10]

Studies were also conducted to sort compound candidates that have ability to inhibit *S. mutans*, as target in reducing caries.[25] Structure-based method were used in these studies. To evaluate *S. mutans* inhibition in dental plaque, phosphoglucosamine mutase and pyruvate kinase were used as protein target. Candidates of compound were selected from ZINC database and labeled as SM001-SM010. Protein ligand interaction was analyzed using AutoDock Vina. Conclusion of the research was those compounds were predicted to have better affinity against molecular target than triclosan, which is known as inhibitor of the glycolysis pathway. [11]To evaluate compounds with potential inhibition of *S. mutans* adhesion, Antigen I/II used as protein target. There are two natural products that show ability as inhibitor, they are curcuma and Morin. Morin show the same IC50 as couple molecules that were evaluated in the research.[12]

In separate researches, capsaicin, genistein and glychirrizin antimicrobial potential were predicted. The bacteria targets were *S. mutans*, *Enterococcus faecalis*, *Porphyromonas gingivalis*, *Treponema denticola* and *Tanerella forsythia*. Ligand-based drug design approach were used in the studies. Sequence protein were taken from STITCH data base, functional class that interact with ligand was obtain from VICMpred server. Virulence properties of interacting protein was predicted using VirulentPred tool, epitope was predicted by BepiPred 2.0 server, and PSORTb V.3.0 was used to predict protein localization. Researchers concluded that each compound has potent antimicrobial factor to all bacteria understudy. [14-17]

Novel compound of COX-2 and biofilm inhibitor had been reported. Research to obtained these compounds and revealed the mechanism inhibition was done by collaboration of *in vitro* and *in silico* analysis. CADD approach that had been done in the research amplified the *in vitro* result. Niconitrile showed to have better

binding to protein target, COX-2, than Celecoxib, the drug of choice. All the ligands, niconitrile and thienopyridines, fulfilled the Lipinski rule and considered as drug like.[17]

The same protein target, MurA enzyme, of *S. mutans*, *Streptococcus sanguinis* and *E. faecalis* were analyzed in two studies. One study using *Ocimum americanum*, while the other study using *Ocimum basilicum L*. Compound that was evaluated achieved from *in vitro* research and *in silico* tools was used to determine the binding affinity of ligands and MurA enzyme (PDB). *In silico* prediction was established using PyRx 0.8. CADD analysis showed the investigated compound has low binding affinity, and revealed the hydrogen bond and hydrophobic interaction of compound and protein target.[17,18]

Genome identification using CADD approaches were done in two studies. The first one using *in silico* as confirmation of the *S. mutans* genome from saliva that had been collected in a population study. *In silico* analysis was conducted with Primer-BLAST tool. The study concluded that *S. mutans* genome obtain by PCR was not 100% identic to *S. mutans* primer.[19] Another study has predicted differences metabolic pathway of *S. mutans* and *S. sanguinis*. Genome were obtained from database. Metabolic pathway that had been evaluated were pyruvate and glutathione pathway. The study show that the two bacteria have similar proportion of genes in each category, but strain-specific gene variants possibly determined fitness factor under selective condition.[20]

Pharmacokinetic properties of the compounds including their absorption, distribution, metabolism and excretion (ADME) could be predicted using CADD. ADME of the compounds that had been analyzed interaction against Ag I/II, were predicted using SwissADME tools.[12] There are other tools that could predict ADME, such as QuikProp and PreADME. QuikProp was used in research that using three phosphotransferase proteins of *S. mutans* as protein target, which shown to have no natural ligands. Although several compounds that had been screened has pharmacophoric motifs.[21] PreADME was used in research that using henicosa-1,3-dyn10 from *Acmella calva* as ligand. Ligand-based drug design was applied. Protein target of *S. mutans* that impacted were peroxidase resistant gene and glucan binding protein β. ADME prediction showed the compound as a potent compound with no capacity to cross blood brain barrier. The toxicity was predicted using ProTox.[22]

CADD approach also useful to predict toxicity of restorative material. Previous study using ligand-based drug design to evaluate toxicity resin monomers after they pass across the blood brain barrier (BBB). Monomers were selected based on *in vitro* research. The prediction of ligand passage through BBB was carried out using ACD/Percepta software. The method showed passive transport of monomers through BBB and act as neurotoxic substances.[23]

Corresponding to pandemic era, chlorhexidine utilization as mouthwash before dentistry procedure was predicted using CADD. Crystal structure and FASTA code of SARS-CoV-2 proteins were obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank. Eight compounds were selected from PubChem and molecular docking was done by AutoDock Vina and visualized on UCSF Chimera. Chlorhexidine showed to have most active compound to reduce Sars-CoV-2.[24,25]

Discussion

CADD or *in silico* study serves prediction of bioactivity, antimicrobial, genome identification, pharmacokinetics, toxicity and antiviral in previous researches in conservative dentistry. It works altogether with *in vitro* and *in vivo* laboratory work. Bioactivity study of peptides from hydrolysate casein based on application Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) as caries prevention method. CPP-ACP forms calcium and phosphate reservoir, thereby reducing demineralization and enhancing remineralization.[26] *In silico* approach amplified *in vitro* and *in vivo* finding by showing bioactivity, non-allergenic and non-toxicity potential of peptides from hydrolysate casein. The study predicted safety and multi-bioactivity of hydrolysate casein.[7] This approach also amplified chlorhexidine application to minimize SARS-CoV-2.[24] As the result is in line to *in vivo* finding. [27]

Antimicrobial activity of capsaicin, genistein and glychyrrizin were evaluated on *S. mutans*, *Enterococcus faecalis*, *Porphyromonas gingivalis*, *Treponema denticola* and *Tanerella forsythia*. *S.*

mutans is known on its role in caries induction, while *E. faecalis* is linked to endodontic treatment failure. *T. forsythia* is also found in the same case although not as dominant as *E. faecalis*. [28] Ligands that were analyzed are active compounds of nature sources, they are capsaicum, soy and *Glychyrriza glabra*.[11–13]

To overcome the antibiotics resistance, studies of infectious diseases treatment is done sustainably. Biofilm is identified as trigger of severe human infections. *In silico* research to evaluated biofilm inhibitor and anti-inflammation candidates were done. *S. mutans*, *Escerichia coli* and *Staphylococcus aureus* were the bacteria targets. These bacterias cause severe inflammation by forming biofilm to adhere. The *in silico* design predicted the novel compounds, niconitrile and thienopyridines, have biofilm inhibition and anti-inflammation ability by binding to COX-2. [14]

The study also predicted the absorption, distribution, metabolisms, excretion and toxicity (ADMET) properties of the compounds by analyzing whether they meet the Lipinski's rule or not. Lipinski's rules, also known as Rule of Five, is a filter of drug likeness. It distinguishes whether a molecule is absorbed well or not, according to molecular weight, octanol/water partition coefficient, number of hydrogen bond donors and number of hydrogen bond acceptors. However, ADMET prediction by computational could be done in several ways, for instance by calculate the ADMET score. [29] Previous studies showed many tools that could be used to predict ADMET of the small molecules. [10,19,20]

In conservative dentistry, composite resin become material of choice to restore dental cavities. Composite resin is consisted of monomers that will be polymerized to polymer matrix. Studies concern to monomers toxicity had been done.[30] CADD could be use as toxicity prediction tools as showed in previous study.[21] The toxicity of monomers also induced research to find the safe monomers to use as dental restorative materials. [31]

CADD approach shown as preferable method in numbers of steps in drugs discovery. Both LBDD and SBDD predict protein-ligand interaction. Binding affinity is a measure how strong interaction between ligand and protein target; and an indicator of potential drug. It can be obtained experimentally and computationally. *In silico* predicts binding affinity at a low cost, accurate and precise results. [32,33] CADD was also used as confirmation of *S. mutans* genome that obtained from PCR.[17] The result showed that PCR has probability of false result as shown in other study.[34,35]

CADD approach gives advantage in research in conservative dentistry research, and there are many possibilities to be explored. Knowledge of the users become the base of CADD utilization. Things to be considered is there are many options of databases and tools that support CADD. Selection of the proper method, trustworthy databases and appropriate tools will affect the reliability of the prediction result. Competence to interpret the results is also the key. CADD applies as prediction that need to be confirmed by *in vitro* and or *in vivo* research. It also can become confirmation or amplification of *in vitro* result.

Conclusion

CADD approach has been used in conservative dentistry and showed great predictions to minimize numbers of trials in laboratory works. Expansion of application might boost drugs design projects in conservative dentistry

Acknowledgements

All authors would like to thank Faculty of Dental Medicine, Universitas Airlangga for support to this research.

Declaration of Interest

The authors report no conflict of interest.

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