Screening of Common Potential Inhibitors against Periodontitis and Alzheimer's Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Authors MK and SK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors ML, HAA, SH, MK and SM managed the analyses of the study. Authors SK and ML managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Introduction: As the amyloid precursor protein performs a remarkable part in chronic periodontitis and the progression of Alzheimer's disease growth, discoveryof novelactive inhibitors of this protein can be of great standing in the treatment of periodontitis. Chronic periodontitis is one of the causative factors and metabolic stressor for diabetes control. In chronic periodontitis and Alzheimer's disease, some molecules have been proposed to inhibit proteins in past.
Methods: This study was planned to find present potent inhibitors,A library of KDM compounds was obtained from Chem Div Database. Here, all complexes with goodglide score were short listed

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for analysis of protein-ligand interaction. Calculations were carried out to estimate the interaction of the ligands selected in complex with the beta amyloid protein.

Results: Five top hits were found considering Curcuminas reference. Five small molecules have been proposed as possible inhibitors of this protein. Here in this study, we have focused on small molecule lead inhibitors for identification of Chronic Periodontitis and Alzheimer's disease.

1. INTRODUCTION

It is important to note that individualshaving periodontitis have an elevated risk of developing Alzheimer's disease (Chen et al., 2017), and people with Alzheimer's disease or dementia have records of poor oral health, and are more disposed to developing chronic oral diseases, including periodontitis, tooth loss and mucosal damagedue to a mental waning, (Tada et al., 2006). Studies have also depicted connections of periodontal disease to an augmentedbuild-up of beta-amyloid in the brain - a neurological symbol of Alzheimer's disease. The involvement of periodontitis as a factor for a number of chronic diseases is widely proposed and there is rising different hypothesis-based indication for a relationof periodontitis with AD. Recent epidemiological, microbiological, and inflammatory reports support this connotation, demonstrating that periodontal pathogens may contribute to neural soreness and AD.This study is based on the established relationship between periodontal diseases and AD [1-3,4,5,6,7]. Periodontitis is a progressive anddisparagingstate that distresses the gum tissue, periodontal ligament, and alveolar bone due to lingeringcomplex inflammatory alterations in periodontal tissues resulting from the host's response to periodontal pathogens [1]. Over 400 microbial species colonize the periodontal expanse [2]. The commonmost bacterial societiesare Gram-negative bacteria which invade tissue.The response to these pathogens is dependent on host's gene polymorphisms, predominantly those that code IL-1 and TNF-α [7,8,9,10]. In addition, the lifestyle factors such as tobacco chewing and smoking, and stress, are related with host's response, which are also associated with an increased risk of AD [11]. A number ofof lifestyle factors including nutritional habits are thought to affect gene expression. Epidemiological studies in the United States and United Kingdom have shown increase in incidences of severe periodontitis affectinga large number of the population along with the increasedprevalence of AD, with the growing aging population [12,13]. More than 38% of American adults aged 30 and over had various degree of periodontitis, where as,it encompasses 64%people aged 65 and over [13]. Periodontitis is a regularcause of chronic systemic infection [14,15,16]. The non-keratinized periodontal areas and adjacent epithelium, particularly the ulcerated ones, serve as a gateway for microbes and their endotoxins entry into the systemic circulation [15,17,18,19]. These microbes in the circulatory system stimulate systemic immunomodulation, as host's retort to periodontal pathogens [13,20,21]. Alzheimer's disease is a neurodegenerative disease that progressively hampers cognitive ability and memory and is usuallyassociatedwith disorientation, mood swings, and sometimes delirium and dementia. Dementia is coupled with a set of signs that like memory loss, mood swings, communication problems, and loss of reasoning [22]. The reduced intellectual ability results in hampered ordinary daily activities in spite of intact consciousness [23]. It was estimated that over 35 million people worldwide had AD in year 2010, and around 496,000 people in the UK alone were affected in 2013 [22]. AD is not essentially the result of aging, [24] but its frequency roughly doubles every 5 years above age 65, [25] the odds of being diagnosed with AD at over 85 exceed 1: 3 [26]. With the increasing population ages, the frequency of people with AD in creasestheatrically. The characteristic feature of AD is the loss of neuron and the occurrence of senile plaques, containing β-amyloid (Aβ) protein and neurofibrillary tangles of hyper-phosphorylated tau protein [27]. However, plaque build-up has been correlated with loss of cognitive ability [28]. On the contrary, the soluble forms of Aβ and tau are proposed to promote the disruption of synaptic function and neurodegenerative processes [29,30]. An association has been shown between AD and the Chronic inflammation of brains and inflammation-related proteins stimulate the formation of Aβ, andgeneration of tangles [6,7].It is also believed that several potentially modifiable risk factors have a

collectiveadversative effect on the brain throughout life. Among the risk factors are the cerebrovascular diseases, infectious mediators, host immune response, [31] low cognitive reserve (i.e., intellect, profession, and education), [32] reduced physical activity, [33] alcohol consumption, [34] deprivation in childhood, tooth decay, [31] age, [35] head trauma, [36] and female sex [37]. Inflammation in the brain, which, once started, continues, and causes neurodegeneration [38] in senile plaques and neurofibrillary tangles, in a cycle that is certainly perpetuated [39] the primary cause of AD is Chronic inflammation is, but is a secondary consequence.This study attempts to determine common therapeutic Ligands that may act as potent drugs against both periodontitis and AD.

2. MATERIALS AND METHODS

2.1 Computer Aided Drug Designing (CADD)

Computer Aided Drug Design is a widely used and widely used computer program for virtual screening and molecular docking. The discovery and development of a new drug is generally considered to be a very complex process that takes a lot of time and resources. Therefore, computer aided drug design approaches are widely used to increase the efficiency of the drug discovery and development process.

2.2 Virtual Screening

Virtual screening is the computational approach for screening biological databases. It is used to rate, classify, and filter a set of structures using one or more computational notation of biological molecules.

2.3 Molecular Docking

Molecular docking is an essential tool in structural molecular biology and in computer-aided drug design. The purpose of protein-ligand docking is to predict the predominant binding mode (s) of a ligand with a known three-dimensional structural protein [40,41]. Successful anchor methods efficiently find large spaces and use a notation function that correctly ranks candidate anchors.

2.3.1 Aim of potential research.

As it remains to be determined whether periodontitis is a risk factor for Alzheimer's disease and whether effective treatment of periodontitis will delay the progression of AD.

Such research will be particularly difficult due to the multifactorial aetiology and chronic nature of periodontitis and AD [42]. The specific needs and disabilities of those with AD will also pose unique challenges.

2.3.2 Selection of target protein structure

Human beta-amyloid peptide fibrils (Abeta) are most important drugs target for therapeutic drugs. Here we usedstructure of beta amyloid (PDB ID: 1Z0Q). Whilepreparation of the receptor, all water molecules have been removed andthe missing hydrogen atoms were added and prepared viaSchrödinger, maestro.

2.3.3 Preparation of ligand library

A library of KDM compounds was obtained fromChemDiv Database (http://www.chemdiv.com/cns-bbblibrary/). The KDM ChemDiv Database Compound is known as Antioxidant and Anti-Inflammatory Neuroinflammation, and the 2D structures in Sdf format were downloaded from the ChemDivDatabase.

2.4 Virtual Screening

Here in this study, we used the KDM library from the ChemDiv database and tracked a cut-off for virtual screening like HTVS-30%, SP-20%, and XP-10%, respectively. The fast and accurate prediction of aligand that binds tightly and specifically to a target protein is acrucial step for computer virtual screening.

2.5 ADMET Properties

The predicted ADMET properties showed that these compoundscould be a potent and effective inhibitor against the protein ligandinteraction. The ADMET properties of the ligands were predicted using Qik-Prop the compounds prepared were subjected todrug-likenessfiltered.

2.5.1 Docked protein-ligand

All docking calculations were performed using the optionPrecision Extra Mode (XP)" via Schrodinger SuiteGlide. A scale factor of 0.8 and a partial atomic charge less than0.15 was applied to the atoms of the two proteins for van der Waalsrays.

3. RESULTS

The focus of present study is to identify Chronic Periodontitis and Alzheimer's drugs for the treatment of AD as well as Periodontitis. KDM

library of ChemDiv Database small leads were screened via virtual screening here in this study,and after using molecular docking. The top hit leads have docking score was observed in the range of −3.81 to −3.34.

3.1 Post Virtual Screening Analysis

Virtual screening options for HTVS (High Throughput Virtual Screening), SP (Standard Precision), and Glide XP (Additional Precision) docking have all been verified to be executed. The best scoring ligand obtained from the Glide XP docking was the known ligands in five numbers. Then, a total of 50 SP ligands and 250 HTVS anchor ligands were obtained.

3.1.1 Glide XP docking for known inhibitor curcumin

Docking was performed for Curcumin ligand. The glide energy obtained was -30.6 with a Glide score (K cal mol-1 was -3.30 (Fig. 1). There were four hydrogen bond interactions with Val12, Phe19,20 and Asp23.

3.1.2 Glide XP docking for top lead hits

Virtual screening was performed against beta amyloid target protein and find the top hits of

KDM library data base of ChemDiv. The glide energy obtained was respectively, from top hits lead compound 612, glide energy -37.6 with a Glide score (K Cal mol-1 was -3.81 (Fig. 1). There were three hydrogen bond interactions with Asn27, Val40, and Ala42. Second lead compound 3201, have glide score -3.47 and glide energy -39.4, and two hydrogen bond interaction observed Gln15, Asp23. Next, third lead have glide score value -3.40 and glide energy -34.7 with two hydrogen bond Gln15 and Asp23. Fourth, leads have glide energy -29.4, & glide score -3.38 bounded with three hydrogen bonds respectively, Asn27, Val40, and Ala42. Fifth, leads have glide score value -3.34 and glide energy -38.6 with two hydrogen bonds as Val40, & Ala42.

3.2 Glide XP Docking Analysis

HTVS does the primary screening, then the secondary is docking of the SP. Survivors of those preliminary screenings would move on to docking Glide XP. The results of the ligands virtually screened above with the known ligand (curcumin) were further given for Glide XP docking to find hydrogen bond interactions, electrostatic interaction, hydrophobic enclosure. The top five ligands and their hydrogen bonding interactions are shown in Figs. 1 and 2.
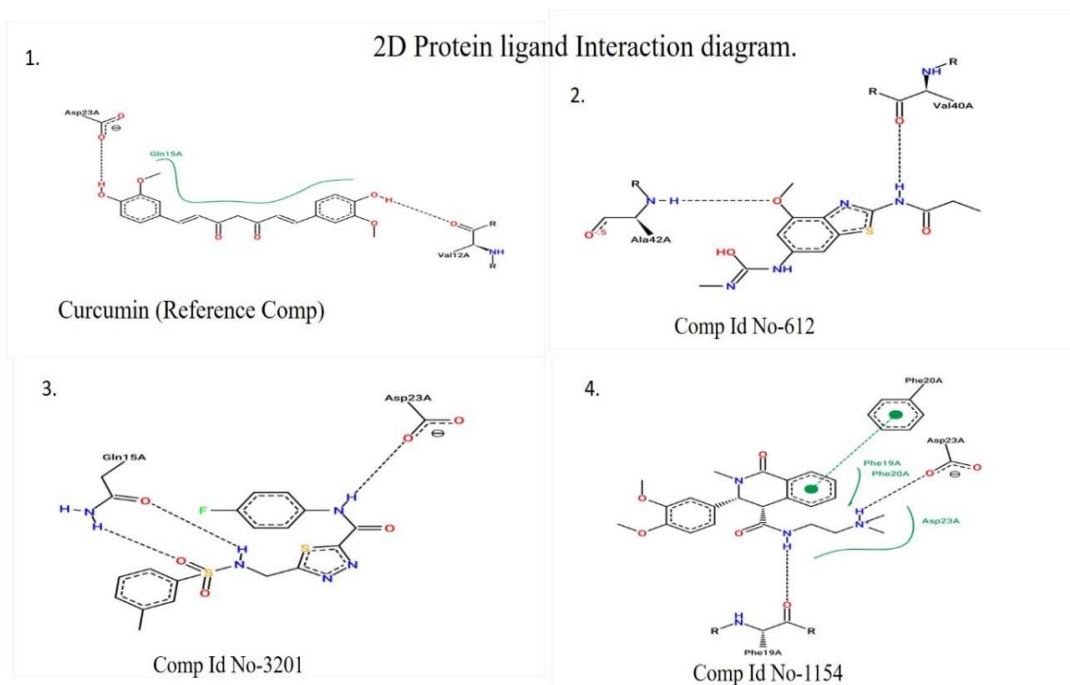

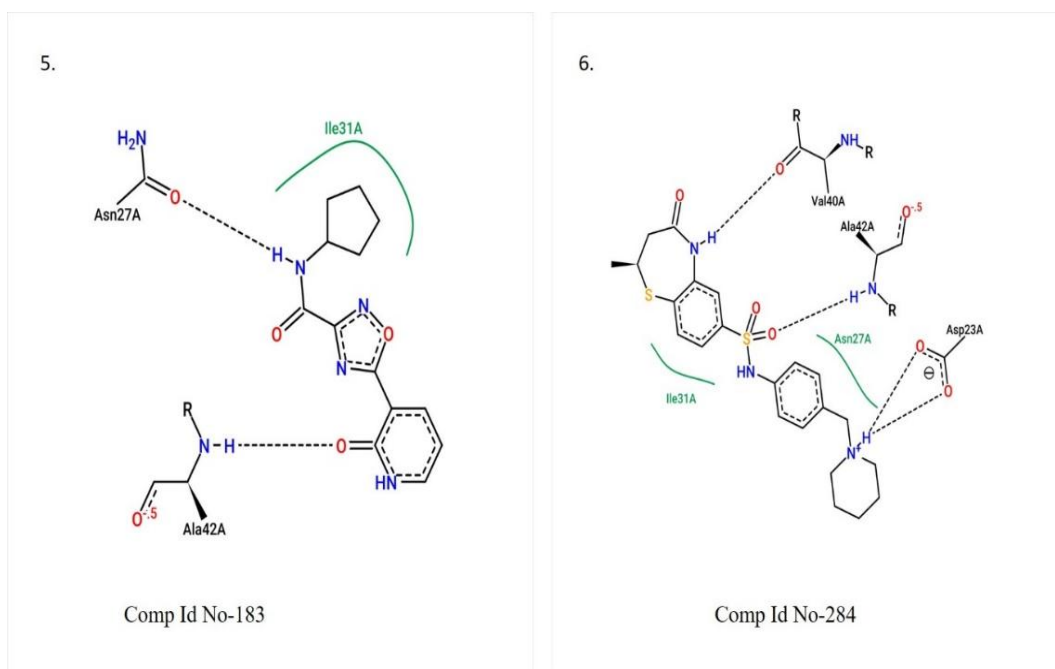**Fig. 1. Hydrogen bonding interactions of the top three ligands (2-4)**

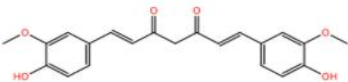**Fig. 2. Hydrogen bonding Interactions of the top Ligand (5-6)**

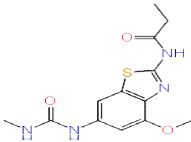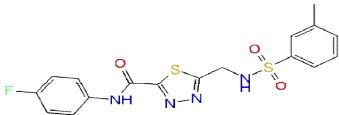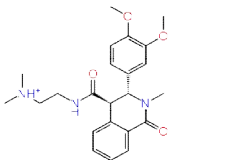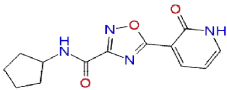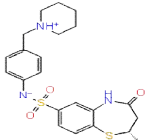## 4. DISCUSSION

In recent years, de novo drug discovery has faced serious problems due to its cost and time consuming.Several studies have proven a significant link between amyloid load and periodontal diseases [4]. Plasma $A\beta_{1-42}$ levels were observed to be higher in patients who have severe periodontal disease. The presence of periodontitis may be responsible for the association between $A\beta$ and cognitive impairment [5].

Here, in this study, we have focus on screened potential leads molecule for Chronic Periodontitis and AD, and targeted the beta amyloid for searched potential leads molecule against screening KDM library data from ChemDiv database. The beta-amyloid protein has a typical orientation inside the membrane and it has a pocket that projects inward from the surface of the enzyme membrane. Hydrogen bond interactions have been found between the precise hydrophobic pocket residues of beta-amyloid. The best results were then checked for their orientation with the known ligand. Therefore, compared to the known ligand, the ligands we report accept Lipinski's rule of five.Based on this virtual screening of the KDM library, Standard Data Format (SDF)data, provided by the ChemDiv database server, the search for the top five ligand inhibitors shows good G-Score, H-Bonds, we conclude that the top five ligands are a potential inhibitor of chronic periodontitis and AD. While investment in pharmaceutical companies has increased, the number of new drugs approved has stagnated; therefore, the in-silico reuse of drugs is an effective and encouraging tool to discover new uses from already existing drugs.drugs with polypharmacological interactions. In the present study, we focus on the conventional targets of AD. For the receiver, approximately three to five drug poses were analysed to identify the pose with the lowest docking score and minimum sliding energy. The docking score of the five main lead molecules interacting with the target protein was studied and their pharmacological activity of the target protein. The docked orientation is represented in Fig. 3. Consistent with this approach, molecules from the KDM library were found to be the best leads in the context of curcumin (referenced) on the basis of its dock score (Table 1), slip energy, and molecular interactions. with the target protein (Table 1 and Figs. 1 and 2). The best results showed a lower docking score than curcumin. This observation suggests that potent anti-Alzheimer's activity has been observed. A lead molecule is considered to be an effective oral drug when it is rapidly and completely absorbed from the gastrointestinal tract, delivered to the specific site in the body where it is to act.

Table 1. Protein-ligand interactions for top hit compounds and referenced approved (Curcumin)

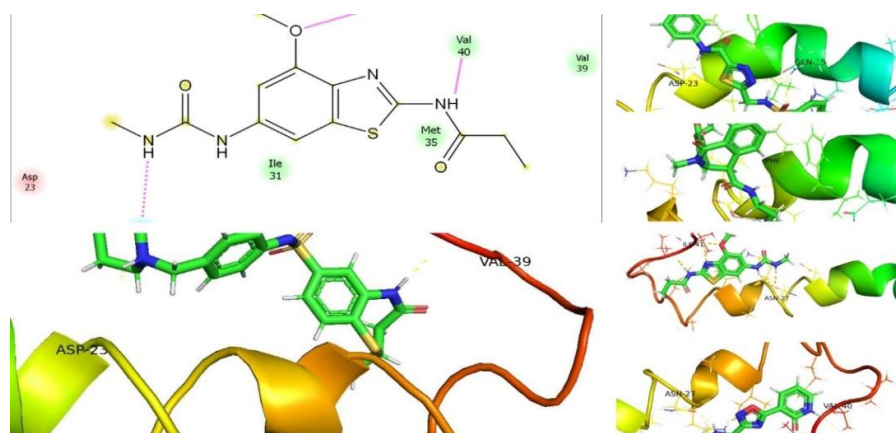| SR No	2D structure of the small molecule	Compound Id Number of KDM Library	Docking Score	Glide Energy	Glide Emodel	Residues interaction
R1.		Curcumin- 969516 (Reference)	-3.3	-30.6	-34	Val12, Phe19, Phe20, Asp23
1.		KDM-612	-3.8	-32.0	-40	Asn27, Val40, Ala42
2.		KDM-3201	-3.4	-39	-50	Gln15, Asp23
3.		KDM-1154	-3.4	-34	37	Gln15, Asp23
4.		KDM-183	-3.3	-29	-37	Asn27, Val40, Ala42
5.		KDM-184	-3.3	-38	-45	Val40, Ala42

Fig. 3. View of docked ligand (Serial No.1 to 5) in the binding site of protein of PyMol

Virtual screening proceeds against beta amyloid, five highest scoring compounds were selected from ChemDiv data from the KDM library with the highest XP glide score against the well-known FDA approved curcumin inhibitor and selected for this study presented in Table 1.

5. CONCLUSION

We used virtual screening, molecular docking, and analysis to identify inhibitors against beta amyloid. The compounds were classified according to the glide score and their mode of binding. We document the five major ligand molecules as potential inhibitors of Chronic Periodontitis and Alzheimer's disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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