International journal Orofacial Sciences
(IJOS)
E-ISSN: 0000-0000

Original Article,

Identification of Interaction of Potent Inhibitors Against Dental Infections and Bio-Ceramics with IL1R1 Through Molecular Docking of Drug Designing

Najatallah Taha Jazzaa[1], Maha Mishaal Turki[2], Wafaa Tali Radef[3], Ahmed AbdulJabbar Suleiman[4]

1,2 College of Dentistry, University of Anbar, Anbar, Iraq

3 Head quarter, University of Anbar, Anbar, Iraq

4 Department of Biotechnology, College of Science, University of Anbar, Anbar, Iraq

https://orcid.org/0000-0001-8440-0105

Corresponding author:- Ahmed AbdulJabbar Suleiman ahmed.suleiman@uoanbar.edu.iq

Received: 02/11/2025
Revised: 09/12/2025
Accepted: 12/01/2026
Published: 01/03/2026

DOI:

10.32649/ijos.2026.0000

How to Cite:

Jazzaa, N. (2026). Identification of Interaction of Potent Inhibitors Against Dental Infections and Bio-Ceramics with IL1R1 Through Molecular Docking of Drug Designing. International Journal of Orofacial Sciences, 1(1),.

Abstract: Dental infection is a major issue of current time. It affects most people especially those without sufficient dental care. Bacterial and pathogenic organisms are the main cause of dental and mucosal infections in humans. Dental infections arise in the tooth structure and surrounding tissues. This type of infection commonly occurs when bacteria occupy the pulp area and surrounding tissues due to major factors such as trauma and dental procedures. In most cases, oral and dental infection leads to carcinogenesis. Dental infections may activate malignant transformation in most of the tissues related to the mouth and other organs. Dental caries and periodontal diseases are considered as top oral health diseases in the world. Around 20–50% of the population are affected by dental infections worldwide. Early diagnosis and suitable therapy may help to overcome this major issue. Methodology: This study focuses on the molecular docking of target protein with FDA approved drugs for the identification of potent inhibitor. Therefore, in this study, we have used different computational approaches to target protein structures of Interleukin-1 Receptor, type1 (IL1R1). Results and discussion: The ligands and bio-ceramic chemical compounds are docked against the IL1R1 protein and the results indicate a better affinity for specific compounds. Moreover, the interaction analysis is also carried out on the best-docked compounds with target protein which can be helpful for the identification of a lead compound that can treat dental infections effectively.

Keywords: IL1R1; Bio-Ceramic; Teeth Infections; CADD; Tetracycline.

1. Introduction

In the early 20th century, the cause of dental infection was not identified. The Mortality rate increased day by day and tooth infections were listed among the pandemic diseases. Due to an increase in mortality rate, people started to consider dental infection into two terms such as mortality and morbidity . Around 20–50% of the population are affected by dental infections worldwide. Early diagnosis and suitable therapy may help to overcome this major issue. The bacterial pathogen can spread into the oral cavity through various ways such as the tongue, pharynx, and mucous membrane . Multiple oral bacteria colonizing into the tooth surfaces and forming oral biofilms (dental plaque). A dental infection or abscess commonly develops by the invasion of bacteria to the pulp through the dentinal tubules (Shown in Figure 1). The pulp induced acute inflammation in the teeth area, which later on caused chronic dental abscess. Dental infections are associated with periodontitis, aggressive caries, poor dental hygiene, and bruxism. Other factors are also involved to cause cancer in patients who are mostly drug addicts .Previous studies have shown that dental infections may lead to cause cancer in some patients such as oral cancer and gastrointestinal malignancies. Studies show that cytokines influence carcinogenesis and cause inflammation in the body, which in turn mediates the actions of various growth factors (immune and non-immune cells) . Carcinogenesis is a multi-step process in which cells accumulate and cause changes in genetic material . Several Studies have shown that dental plaque is directly associated with cancer and increases the mortality rate. Dental plaque is a composite biofilm that accumulates on the surface of the teeth in the oral cavity . Dental caries is also a source of cancer. Cariogenic bacteria have been shown to induce polarization of the Th1 cytokine response and cell-mediated immune response .

Dental practitioners are accustomed to the plain-film radiographic technique to evaluate malignancy in patients . In recent years, the use of bioceramics has become essential for dentists in treating various forms of dental caries. Bioceramics are considered an important part of biomaterials that serve as efficient bone substitutes . Bioceramics are primarily used in dental medicine. Bioceramics have attracted increasing interest among dental professionals and researchers over the past decades . Previous studies indicate that the Interleukin-1 Receptor, type1 (IL1R1) receptor is involved in certain dental infections, which further leads to cancer in patients .Interleukin-1 Receptor, type1 (IL1R1) is also called CD121a. IL1R1 is an important mediator involved in various cytokine signaling pathways that induce inflammatory and immune responses. Dental practice shows that certain therapies are used to treat dental infections. Antibiotics play an important role in the treatment of dental infections. But these antibiotics are not safe to use on all patients, such as Nifedipine and Cyclosporine. The use of Nifedipine and Cyclosporine A causes the gingival enlargement in adults . The use of antibiotics in dental practice is based on etiological factors. However, the witness reports that dentists improperly use antibiotics to treat dental or oral infections in daily practice . Several NSAIDs (Non-steroidal anti-inflammatory drugs) are used for the treatment of dental or oral infections, but these drugs seem to cause teeth discoloration in adults.

2. Methodology

The key mechanism is to identify a potent drug or lead compound that can treat dental infections effectively through an in silico approach. We have used computational drug designing techniques, such as molecular docking, to achieve this mission. The target protein Interleukin-1 Receptor, type 1 (IL1R1) is found to be involved in the causation of various diseases, including dental infections that lead to cancer. The 3D crystal structure of Interleukin-1 Receptor, type1is retrieved from RCSB PDB (http://www.rcsb.org/pdb) with PDB Id 1ILR (shown in Figure 1). Furthermore, we have performed the energy minimization (steepest descent and conjugate gradient) of the target protein (1ILR) through UCSF Chimera. The most commonly used 4 (Gallic acid, Acrylic, Alumina, Hydroxyapatite, and Zirconium oxide) bioceramics are selected based on the literature. Moreover, we selected FDA-approved ligands. Total 10 ligands (Tetracycline hydrochloride, Doxycycline, Chlorhexidine, Amoxicillin, Meloxicam, propolis_benofuran, oracillin, Trimellitic anhydride, Chloramphenicol, and Acyclovir) are selected according to Lipinski's rule of five. Chemical structures of ligands are retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Afterward, perform the protein-ligand docking through Autodock Vina. Docking results depict the lead compound or potent inhibitor based on binding affinity. The protein-ligand interactions are also analyzed using an online tool, i.e., PLIP (protein-ligand interaction profiler), because protein-ligand interactions are a fundamental process in the pharmacological intervention of various diseases. PLIP is publicly available at (https://projects.biotec.tu-dresden.de/plip-web/plip/). Furthermore, Mcule is used to analyze the toxicity of lead compounds and a bioceramic, as some chemical compounds exhibit some toxicity. Mcule is publicly available at (https://mcule.com/). The complete methodology is shown in Figure 2.

Figure 1. Crystal structure of the interleukin-1 receptor antagonist

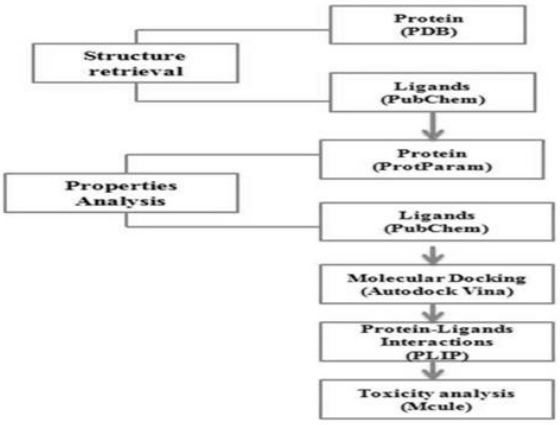

Figure 2. The complete methodology of CADD

3. Results

The Physicochemical properties of proteins and ligands are analyzed to better understand their binding. The energy minimization process is performed to add H- atoms to proteins using the steepest descent and conjugate gradient algorithms. Furthermore, all excess water molecules are removed to purify the protein for docking. Autodock Vina is used to dock proteins with ligands by using maximum coordinates (x, y, and z).

The docking results of protein-bio-ceramic indicate the standard binding affinity of Hydroxyapatite compound among other compounds (shown in Figure 3). Interaction analysis shows the linkage between the amino acids of the compound at a specific position within the protein's pocket (shown in Figure 4). The protein-ligand docking indicates the binding of the protein with the ligand at a specific position. According to molecular docking results, Tetracycline hydrochloride shows a standard binding affinity (-9.5) and is comparable to doxycycline (-9.4) among other chemical compounds (shown in Figure 5). Moreover, doxycycline is a tetracycline derivative. Based on its binding affinity, Tetracycline hydrochloride is selected as a lead compound and a potent inhibitor for the effective treatment of dental infections. Protein-ligand interactions are also used to analyze conformational changes or linkages. Interaction results indicate the formation of chemical bonds within the protein's binding site. Interaction results depict the linkage of amino acids at a specific position with the protein (shown in Figure 6).

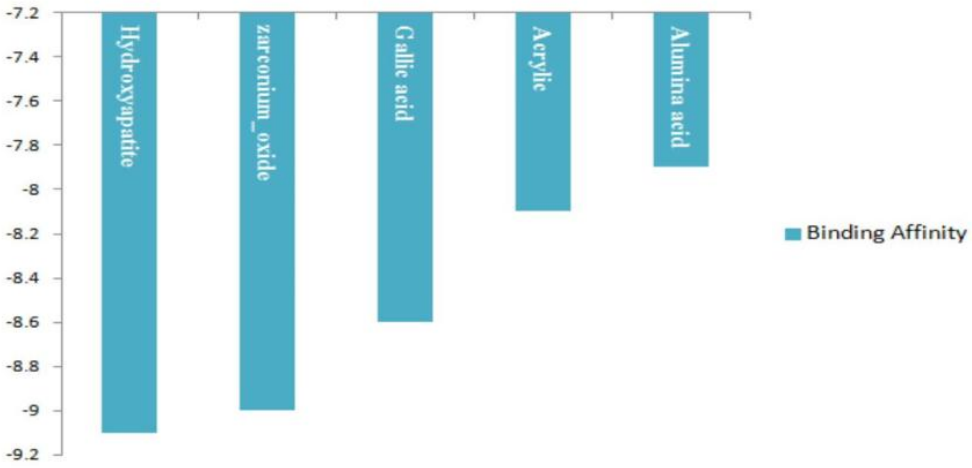

Figure 3: Binding affinity of Bio-ceramic

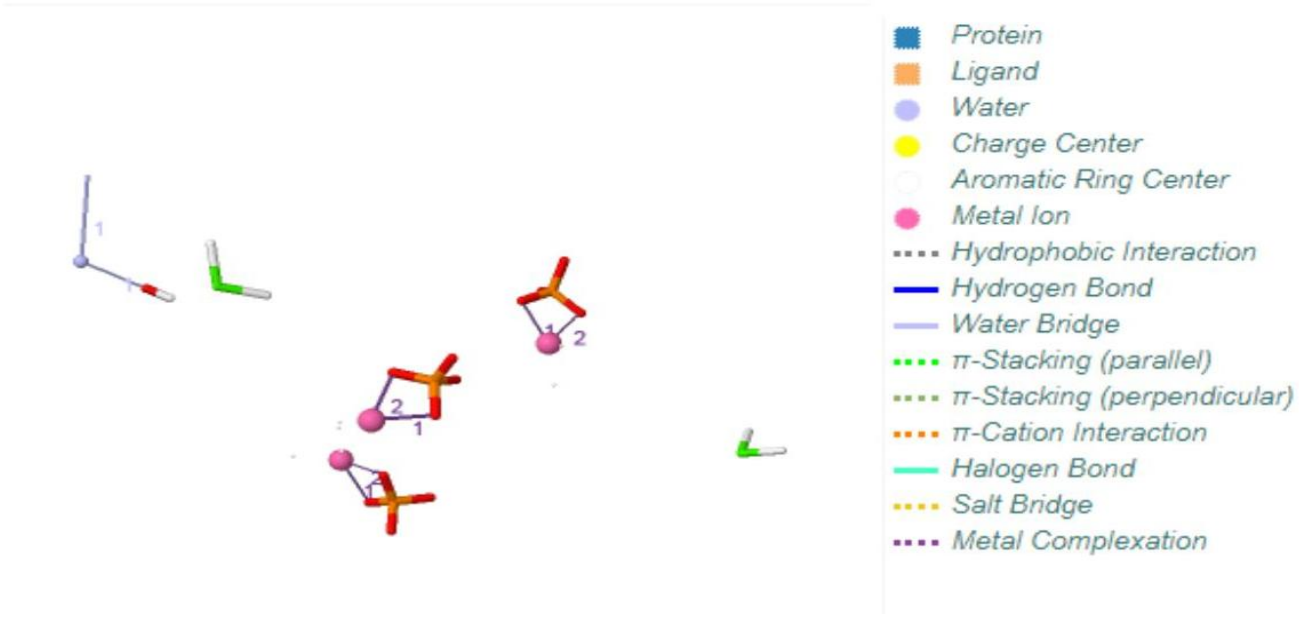

Figure 4: Interaction of protein with bio-ceramic (Hydroxyapatite)

Figure5: Binding affinity of ligands

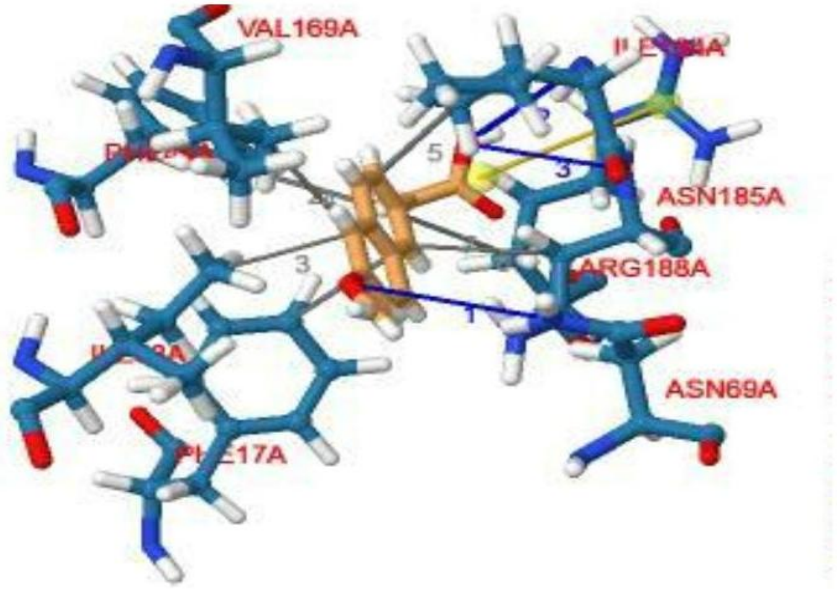

Figure 6: Interaction of protein with ligand (Tetracycline hydrochloride)

4. Discussion

This study investigates the bio-ceramics and potent inhibitors against dental infections. Dental infections are caused by the colonization of multiple bacteria on the tooth surfaces and the formation of oral biofilms [14]. Studies indicate that Interleukin-1 Receptor, type1 (IL1R1) is a causative agent of various types of dental infections that lead to cancer, including oral and gastrointestinal cancer. In this study, we used molecular docking to identify a standard chemical compound that binds to the protein's specific binding site. According to the docking results, Hydroxyapatite is a standard bio-ceramic that can be used in teeth manufacturing. Previous studies also investigated the Hydroxyapatite bio-ceramic as an effective material for tooth manufacturing due to its anticarcinogenic properties [15]. We have also performed docking of protein and FDA-approved ligands to identify Tetracycline hydrochloride as a potent inhibitor that can treat different types of dental infections. Tetracycline hydrochloride has various applications in dental infections, including tooth surgery. Tetracycline hydrochloride has anti-collagenase and anti-inflammatory properties [16]. This study compared the binding affinities of bio-ceramics and FDA-approved ligands, as conventional studies have not focused on comparative analysis. Comparative analysis indicates the standard binding affinity of Hydroxyapatite and Tetracycline hydrochloride among other biochemical compounds. Protein-bio-ceramic and protein-ligand interactions are also performed to analyze the linkage of amino acids within the pocket of the protein at a specific distance. Interaction is an important step in Computer-Aided Drug Designing (CADD).

5. Conclusions

This study is designed to analyze a potent inhibitor for the treatment of dental infections. Previous studies showed that the target protein (Interleukin-1 Receptor, type1) was involved in causing dental infections that can further lead to cancer. IL1R1 is an important mediator of cytokine signaling pathways that induce inflammatory and immune responses. For this purpose, Computer-Aided Drug Designing (CADD) is used to perform protein-ligand docking. Bio-ceramic docking results indicate that Hydroxyapatite is a standard. compound that can be used to manufacture teeth materials. Molecular docking results for the protein and ligands indicate that Tetracycline hydrochloride is a potent inhibitor with high binding affinity and can effectively treat dental infections. Interactions between proteins and chemical compounds also reveal the standard amino acid linkage within the binding pocket of the Interleukin-1 Receptor, type 1 (IL1R1).

Supplementary Materials:
No Supplementary Materials.
Author Contributions:
All authors have equal contributions. All authors have read and agreed to the published version of the manuscript.
Funding:
Self-funded.

Institutional Review Board Statement:
Not applicable.
Informed Consent Statement:
Not applicable.
Data Availability Statement:
Data available upon request.
Conflicts of Interest:
The authors declare no conflict of interest.
Acknowledgments:
Not applicable.
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