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Computational Discovery of Drug Targets and Potential Phytochemical Inhibitors for *Porphyromonas gingivalis*

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Abstract

The current work attempts to discover some new drug targets in the case of *Porphyromonas gingivalis* ATCC 33277 using computational methods. The 245 numbers of selected essential genes in the case of bacteria *P. gingivalis* ATCC 33277 were obtained by searching the total no. of 463 genes available in the Database of Essential Genes (DEG) database by using Basic Local Alignment Search Tool (BLAST) tool against the Human (*Homo sapiens)* genome. Screening of the target molecule was performed based on (expectation) E-value, similarity score, and query coverage. Further, the gene interaction network was constructed by the STRING database, and potential hub genes were identified by the Cytohubba module of the Cytoscape tool. rplR gene encoding large ribosomal subunit protein was chosen as the target. Further receptor-based screening of traditional Chinese medicinal compounds using docking, toxicity, and molecular dynamics simulations identified Mulberroside C as a potential inhibitor. Since it is a computational work further experiment is necessary to validate the prediction.

Keywords: *Porphyromonas gingivalis*, essential genes, BLAST score, drug target, compound screening, docking, Molecular dynamics simulation

Introduction

Porphyromonas gingivalis is a Gram-negative, obligate anaerobic bacterium that resides in the oral cavity and is the primary causative agent of chronic inflammatory periodontitis. This infection affects 10–15% of adults throughout the world and can lead to significant health complications and mortality in severe cases. The existence of drug-resistant forms of *Porphyromonas* is currently a major challenge for the discovery of novel effective drugs. Periodontal disease refers to a group of inflammatory conditions in the oral cavity, triggered by pathogenic microorganisms that create a complex biofilm on tooth surfaces, leading to the destruction of the supporting structures of the teeth. The severity of this illness varies from moderate gingival inflammation (gingivitis) to chronic breakdown of connective tissues, the creation of a periodontal pocket, and loss of teeth (1-2). Periodontal diseases are commonly found in most of the human populations across the world and they result in a significant and a major, gradual health concern. According to a report from the World Health Organization (WHO), 10-15% of the adult populations worldwide (~538 million) are affected by periodontal disease (3-4-5). According to recent epidemiological data periodontal disease is most prevalent in the adult population specifically over 30 years of age and causes tooth loss among adults (6). Many recent clinical, experimental,

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and epidemiological studies and evidence in the literature suggest the significant impact of the pathogen *Porphyromona*s either directly or indirectly on overall human health. For example, establishing the relationship between periodontal diseases and inflammation and the progression of other systemic diseases is an interesting aspect for researchers to conduct multidisciplinary research. Several studies have shown that the disease periodontitis is associated with various non-oral and potentially deadly systemic diseases, including cardiovascular diseases, cancer, diabetes type II, respiratory tract infection, AIDS, Down's syndrome, musculoskeletal, neurodegenerative diseases e.g., Alzheimer disease (AD) and so on (7-8-9-10-11). Also, a gene expression study explored the molecular link between periodontitis and rheumatoid arthritis (RA) to identify shared therapeutic targets. Differentially expressed genes (DEGs) from both conditions were analyzed, and the key interconnecting gene involved periodontitis and RA (12).

Antibiotic treatments somehow show a few side effects and some adverse conditions. So, with the identification of potential targets and a target-based approach in the drug design, we can target the particular metabolic pathway or some of the specific target proteins that is critical to the growth, metabolism, survival, and pathogenesis of the bacteria. In this review, some of the actions of drugs and antibiotics along with different methods used to identify potential drug targets with therapeutic effects were discussed in brief (13-14). So as an alternative therapeutic molecule, several phytochemicals are currently being studied to explore their potential inhibitor nature against *P. gingivalis*. Schmuch et al. investigated the anti-adhesive effects of a proanthocyanidin-enriched extract from *Rumex acetosa* on *Porphyromonas gingivalis* that contains compounds such as flavan-3-ols, oligomeric proanthocyanidins, and flavonoids (15). A study by Bezerra, J. J. L., & da Silva suggested the non-toxic natural products obtained from *Punica granatum* can be considered as an alternative to the recommended commercial products used for the treatment of gingivitis (16). Peeran et al. investigated the antibacterial and anti-inflammatory potential of *Momordica charantia* extracts. Phytochemical analysis revealed significant levels of alkaloids, flavonoids, phenols, and tannins exhibited inhibitory nature against *Porphyromonas gingivalis* (17).

The objective of the work is to use computational methods to predict a suitable drug target for *Porphyromonas gingivalis* and screen suitable phytochemical inhibitors against the predicted target.

Materials and Methods

Retrieval of essential genes of Porphyromonas gingivalis ATCC 33277

The essential genes of the pathogen *Porphyromonas gingivalis* ATCC 33277 were searched and retrieved from the Database of Essential Genes (DEG) (http://tubic.tju.edu.cn/deg/) (accessed on 24.10.2023) (18). DEG is user friendly freely accessible database, contains the record for all the available essential genes. Along with nucleotide and protein sequence information each entry also contains a unique DEG identification number with function details.

Searching of human non-homologous retrieved essential genes

To study and investigate the non-homologous essential genes of the bacteria *P. gingivalis* ATCC 33277, the Basic Local Alignment Search Tool (BLAST) program was used. Among these Position Specific Iterated BLAST (PSI-BLAST) was chosen to accurately investigate the essential genes of *P. gingivalis* ATCC 33277, which are non-homologous to the human.

Protein-protein interaction study and prediction of hub genes

The functional protein association networks of the non -homologous genes were obtained using the STRING (Search Tool for the

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Retrieval of Interacting Genes) database available at https://string-db.org/. Subsequently, the hub genes were identified by using the plug-in CytoHubba (https://apps.cytoscape.org/apps/cytohubba) in the Cytoscape version 3.10.3 tool. From the Cytohubba application, identification of the best 6 hub genes occurs by using the maximal clique centrality (MCC) method.

Selection of the receptor proteins and screening of phytochemicals from the traditional Chinese medicine library database

The interacting proteins were analyzed and the best one was selected as the receptor molecule from the hub-gene network. Since the experimental 3D structures were not available, hence the Alpha fold predicted structure was considered for further study (https://alphafold.ebi.ac.uk/search/text/AF-B2RLX6-F1). The structure was validated by plotting the Ramachandran plot with the PROCHECK program and computing quality by ERRAT by using the SAVES server (https://saves.mbi.ucla.edu/). Further, the receptor molecule was used in the DrugReP server for screening of potential phytochemicals from the traditional Chinese medicine library (http://cao.labshare.cn/drugrep/). Drug rep is a server that facilitates both receptor-based or ligand-based screening over drug libraries for a given molecule. The screening results were obtained in the ranked form according to the docking scores (19).

Selection of potential phytochemicals and MD simulation

Screening of the resulting molecules from the DrugReP was performed by using Lipinski's rule of five (20), ligand interaction analysis by the Biovia discovery studio visualization program (https://www.3ds.com/products/biovia/discovery-studio) and subsequent analysis of the toxicity of compounds by Protox III server (https://tox.charite.de/protox3/). Further, the stability of the complex was studied by using MD simulation in water using the YASARA software tool (https://www.yasara.org/). In the preparatory phase of MD simulation, the simulation cell was set to periodic boundary conditions. The simulation was carried out in a water environment (using the TIP3 water model), at constant pressure, with 298 K (25ºC) by using an AMBER14 force field. The MD simulation was carried out for 12 nanoseconds (ns) with 121 snapshots generated every 100 pico seconds by using YASARA version 21.12.19. L.64. The parameters such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg) and free energy of binding by using MM-PBSA (Molecular mechanics-Poisson– Boltzmann Surface Area) methods were analyzed after the simulation (21-22).

Results and Discussion

Retrieval of essential genes and BLAST analysis against human

463 numbers of essential genes of *Porphyromonas gingivalis* ATCC 33277 were identified from the DEG database and the protein sequences were retrieved. PSI-BLAST tool against the non-redundant protein sequence (nr) database of *Homo sapiens* (taxid:9606), resulted in 245 essential genes showed no significant similarity (non-homologous) to humans, among them genes 108 genes are likely to be encoding hypothetical proteins where obtained.

Protein-protein interaction and analysis of hub genes

All 246 sequences were used in the STRING server to analyze the network and subsequently interacting genes resulted in 6 selected hub genes (Figure 1) and the corresponding protein sequence and structural information are shown in Table 1.

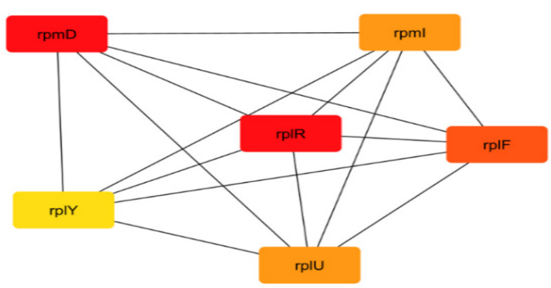

Figure 1: Showing the hub genes obtained by using Cystoscope tool

Table 1: Structural features and functional domain details of the selected hub gene product

S. N	Name of the gene	Function	Length of the protein	Domain*-details	Domain Position	% of residues in the most favoured regions in Ramachandran plot	ERRAT quality factor
1	rPl R	Attachment of the 5S RNA into the large ribosomal subunit	114	Ribosomal_L18p	2-114	94.1%	99.0291
2	rpl Y	Binds to the 5S RNA in the ribosome	192	Ribosomal_L25p Ribosomal_TL5_C	6-92 100-182	97.6%	93.4211
3	rplU	Binds to 23S rRNA in the presence of protein L20	105	Ribosomal_L21p	1-103	94.6%	95.3846
4	Rpl F	Binds to the 23S rRNA, and is important in its secondary structure.	183	Ribosomal_L6 Ribosomal_L6	11-82 90 to 169	92.2%	97.2973
5	rpml	Belongs to the bacterial ribosomal protein bL35 family	65	Ribosomal_L35p	2-62	96.6%	100
6	rpmD	Annotation is not available	58	Ribosomal_L30	4 to 54	92.3%	100

**Domains were predicted by SMART server (http://smart.embl-heidelberg.de/)by using the protein sequences*

Screening, selection, and binding study of potential phytochemicals

DrugRep server resulted in 100 phytochemicals from TCMPD and this was analyzed by Lipinski's rule resulted in 33 phytochemicals. Further, the top 10 compounds based on the docking score were selected. Prediction of toxicity classes showed three compounds were predicted as non-toxic (Table 2) and hence considered for further analysis. The interaction analysis of the complex showed, the molecule Mulberroside C was able to form 2 hydrogen bonds with RpLR protein receptor Gly-93 and Arg-32 as shown in Figure 2., hence considered as the potential one. Subsequently, MD simulation was performed with this complex to validate the result.

Table 2: Drug-like and toxic properties of the selected phytochemicals

ID	Name	Docking Score	MW	HBD	HBA	RB	NOA	LogP	Toxicity class	Plant sources
T5S1959	Asarinin	-7.6	354.35	0	0	2	6	2.6	Class: 3	Sichuan pepper; Dodder seed
T5691	paulownin	-7.2	370.4	1	1	3	7	1.6	Class: 3	Paulownia; Cattail pollen; Agastache
T5S1598	Mulberroside C	-7	458.46	5	5	8	9	1.5	Class:5	Hydnocarpus

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TQ0214	Dimethylcur-cumin	-6.9	396.43	1	2	10	6	4.6	Class: 5	Turmeric; Galangal
T2781	Sangui-narine	-6.9	332.33	0	0	0	5	4.4	Class: 4	Macleaya; Greater cel-andine; Sichuan pepper
T4518	Licochalcone D	-6.8	354.4	3	4	9	5	4.5	Class: 4	Sargentodoxa; Licorice
TN1969	N-(p-Cou-maroyl) serotonin	-6.8	322.4	3	3	8	5	3	Class: 4	Safflower
T5687	Withaferin A	-6.7	470.6	2	4	5	6	3.8	Class: 3	Sophora root
T6S0139	Neobavaiso-flavone	-6.7	322.36	2	3	5	4	3.6	Class: 5	Psoralea
T2787	Picroside I	-6.6	492.47	5	6	13	11	-1.1	class 4	Picrorhiza

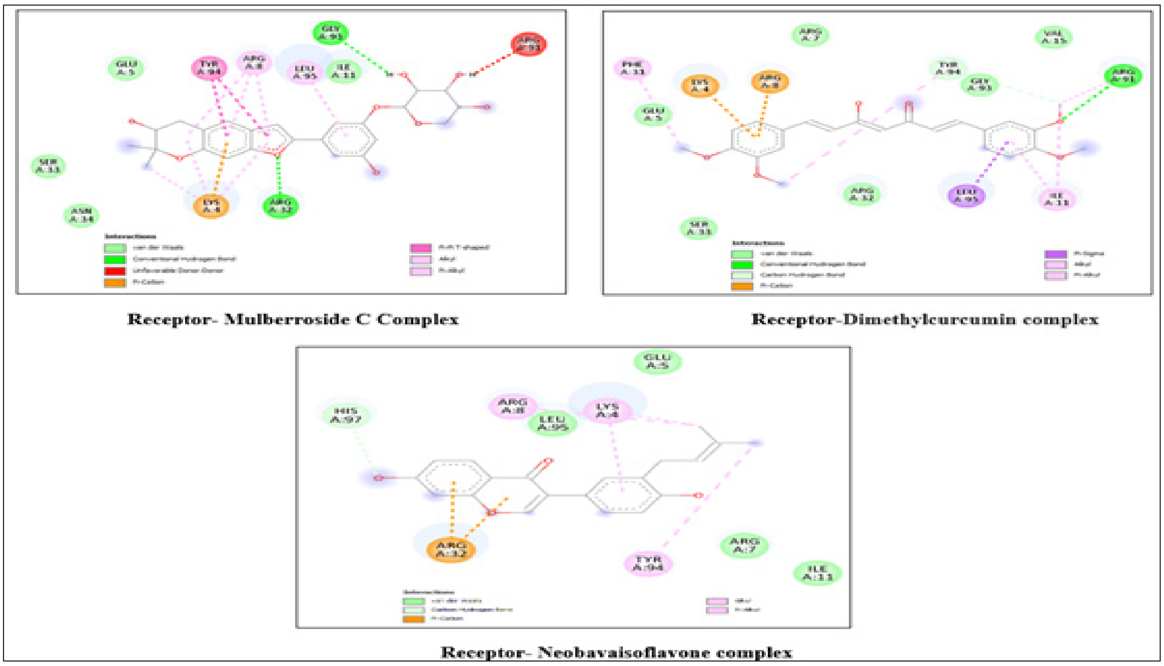

Figure 2: Ligand Interaction analysis of the selected ligands (highlighted in Table 2)

Results of Molecular dynamics simulation

The stabilities and binding affinities of the mulberroside C-rpl R protein were accessed by using the MD simulation. The significant stabilization of the complex was observed after the first 2-3 ns (Figure 3 (A). The structure of the mulberroside C-rpl R protein complex was considered stable as the RMSD values were observed to be less than or equal to 2.5 Å throughout the simulation (23-24). During these MD simulations, the RMSF value was also monitored for the complex. The regions where mulberroside C has a large impact on rpl R residue sequences were also evaluated by RMSF analysis and the region was identified as residues number 15-25, due to greater RMSF and more flexible (25-26) (Figure 3 (B). Similarly, the compactness of the receptor-ligand complex was analyzed by Rg plot and consistent values were obtained (Figure 3 (C) (27).

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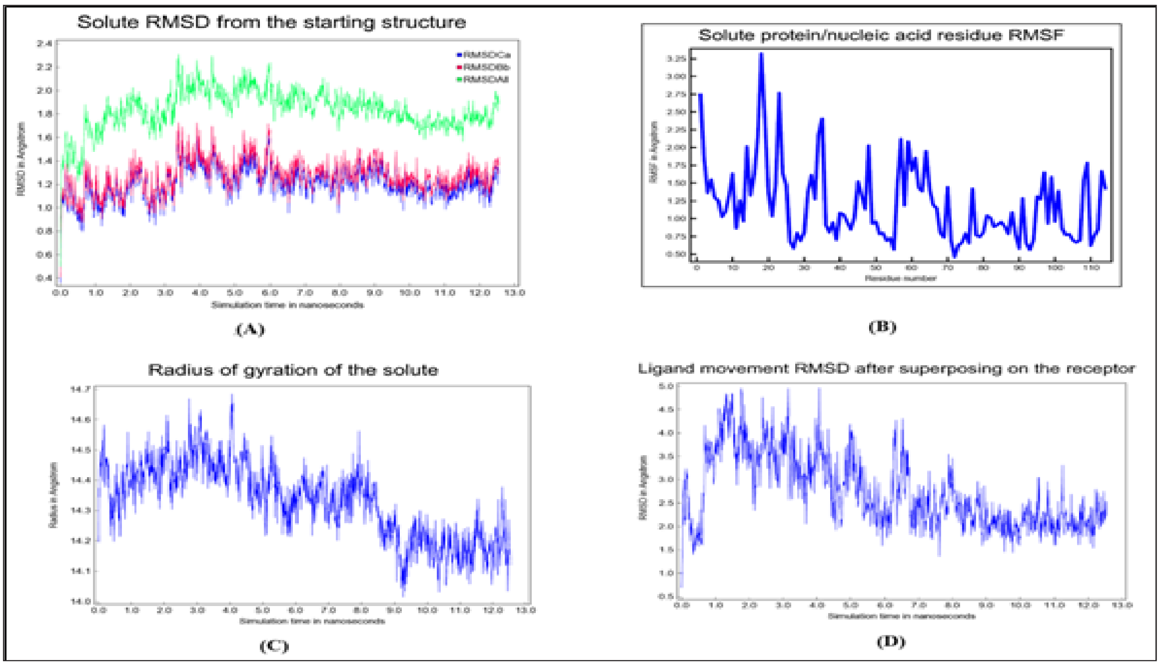

Figure 3: Parameters computed from MD simulation of rplR-Mulberroside C complex

The movement profile of the ligand within the target's active site was analyzed by calculating the Root Mean Square Deviation (RMSD) of ligand displacement during the simulation. The calculated RMSD revealed a displacement exceeding 5 Å within the initial 1–5 nanoseconds. However, this displacement showed a decreasing trend over time, with the RMSD dropping to less than 2 Å between 5 and 12 nanoseconds. This indicates that the compound mulberroside C was able to maintain proximity to the binding site of the rplR-receptor protein (28, 36). Further, the binding free energy of the complex was analyzed by the MM-PBSA method, which evaluates the binding energy by computing the differences in free energy between bound and unbound state structures in the receptor-ligand complex (37).

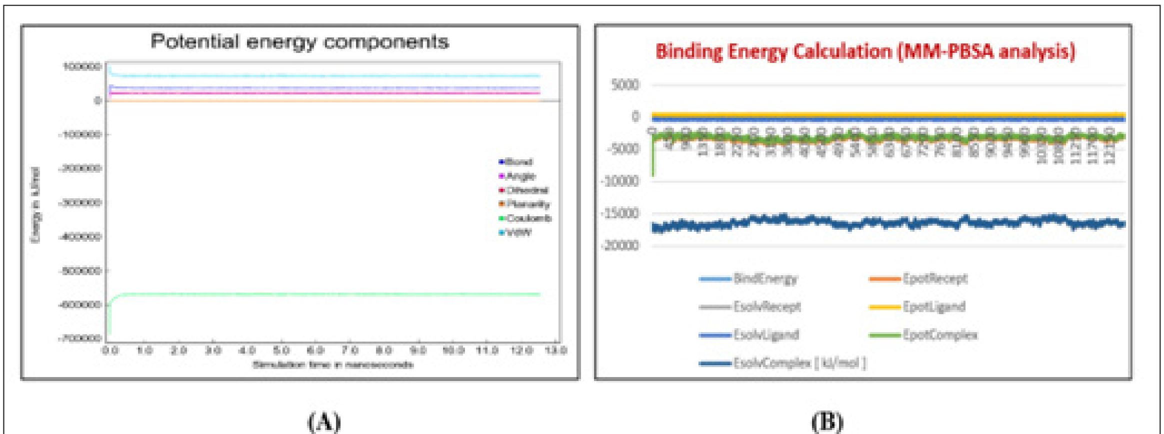

Figure 4: Potential energy components (A) binding energy calculations (B) for rpl R-Mulberroside C complex

The mean binding free energy in the MM/PBSA solvation model was calculated for the mulberroside C -rpl R protein complex as -107.336 KJ/mol (Figure 4 B). Further, the binding energy of Mulberroside C was observed to be supported by only Coulomb energy; which might be responsible for producing significant binding to the receptor (Figure 4 A). The ligand movement observed during the simulation aligns with the calculated average MM-PBSA binding energy. (29-30).

Discussion

The target *rplR gene* products function in the ribosome assembly process thus essential for maintaining the life cycle of the bacteria for the for-cell growth, viability, and translation in the bacteria. Hence this can be used as a suitable drug target for *P.gingivalis* (31-32-33). Several computational pipelines have been used to identify targets in *P. gingivalis* and identify suitable inhibitors against it. Molecular docking and MD simulations are currently treated as one of the important screening tools to identify therapeutic compounds against specific receptors (34-35). Drug target identification is integrated into these methods to expedite the compound selection process. Comparing the whole metabolic pathway of *Porphyromonas gingivalis* and *Homo sapiens* followed by non-homologous human protein identification has identified several targets of the pathogen (36). A high-throughput virtual screening of the ZINC chemical library identified potential small-molecule inhibitors targeting meso-diaminopimelate dehydrogenase (*P. gingivalis*), establishing a framework for developing new antimicrobials targeting this enzyme (37). The phytochemical Mulberroside C predicted in this work is from the mulberry plant belonging to the Moraceae family. In traditional Chinese medicine, the plant parts of the Mulberry have been used to treat fevers, liver infections, eyesight loss, obesity, diabetes, and bacterial infections (38-39-40-41-42). Cao et al. identified the potential inhibitory action of the Mulberroside C on Enterovirus A71 the infection causes cause of hand, foot, and mouth disease in children (43). Vora et al., (2019 and 2020) implemented computational methods (docking, QSAR, and ADMET) as well as experimental methods to identify plant-derived molecules, including Mulberroside C, as promising candidates targeting multiple HIV metabolism (44-45). Similarly, in another work by Vora et al., in 2020 performed in silico methods such as pharmacophore mapping, molecular docking, molecular dynamics simulations, and ADME prediction, the study identified mulberry side C as an inhibitor for potential targets of dengue virus (46). Looking at the results of the computational study and the therapeutical importance of mulberry side C, it can be predicted that, the molecule can act as a suitable inhibitor against the rpl R protein of *P*. *gingivalis*.

Conclusion

In this study, the essential genes of the pathogenic bacteria *Porphyromonas gingivalis* ATCC 33277 were retrieved from the DEG database. The essential genes are aligned against the human using the PSI-BLAST algorithm. Out of 463 essential genes, 245 genes are found to be non-homologous to humans i.e., with no significant similarity, and 108 genes found to be encoding hypothetical proteins. The human non-homologous genes were subjected to protein-protein interaction analysis followed by hub genes prediction resulting in the rplR as the drug target. Further, receptor-based screening of phytochemicals from a traditional Chinese medicine library database identified 100 promising phytochemicals as inhibitors. As a subsequent study, further screening by drug-like properties, docking score with rplR protein, ADMET, and Molecular dynamics simulation analysis identified Mulberroside C from the plant Mulberry as the potential one that maintains stability during simulation. Since *Porphyromonas gingivalis*, a major pathogen in oral biofilms, is strongly associated with chronic inflammatory periodontitis and often resists conventional antibiotics, the proposed molecule can be tested experimentally to study its effectiveness in eradicating infections. Further studies, both *in vitro* and *in vivo*, are required to better understand the efficacy of mulberroside C against *Porphyromonas gingivalis* infection.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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