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In Silico Therapeutic Effects Of Vitis Vinifera Phytochemicals On Periodontitis And Alveolar Periimplantitis Microbiota

[1] lipsa Bhuyan, [2]Abikshyeet Panda, [3]Sangeeta Chhotaray, [4]Kailash Chandra Dash, [5]Pallavi Mishra ,[6]Soumya Jal*

[1] PhD Scholar, Reader, Department of Oral & Maxillofacial Pathology and Oral Microbiology,Kalinga Institute of Dental Sciences, KIIT Deemed To Be University, Campus-5, Patia, Bhubaneswar, 751024. Odisha.ORCID ID: 0000-0002-0811-1974,
Email ID : bhuyanlipsa@gmail.com
[2] Professor, Department of Oral & Maxillofacial Pathology and Oral Microbiology,Kalinga Institute of Dental Sciences,KIIT University, Bhubaneswar, India-751024, ORCHID ID: 0000-0003-4319-8742
[3]PhD Scholar, School Of Paramedics and Allied Health Sciences,Centurion University of Technology and Management,Bhubaneswar-752050; Odisha.ORCID ID- 0009-0008-9778-0723
4 Reader, Department of Oral and Maxillofacial Pathology, Kalinga Institute of Dental Sciences, KIIT Deemed to be University,Patia, Bhubaneswar -751024,
Email ID :kcdash1986@gmail.com,ORCId: 0000-0001-5346-2856
[5]Lecturer, Department of Oral & Maxillofacial Pathology and Oral Microbiology, Kalinga Institute of Dental Sciences,KIIT Deemed to be University, Campus-5, Patia, Bhubaneswar, 751024,ORCID ID: 0000-0001-6987-6009
6 Associate Professor And Dean,School Of Paramedics And Allied Health Sciences,Centurion University Of Technology And Management,Ramachandrapur, Bhubaneswar-752050, Odishaorcid Id: 0000-0001-5509-4874
Corresponding Author:
Dr.Soumya Jal
Associate Professor And Dean,School Of Paramedics And Allied Health Sciences,Centurion University Of Technology And Management,Ramachandrapur, Bhubaneswar-752050, Odisha
Orcid Id: 0000-0001-5509-4874,Email Id- soumya.jal@cutm.ac.in

Abstract *Inflammation of tissues surrounding the teeth and alveolar bone implants placed in the oral cavity is termed as periodontitis and peri-implantitis respectively. Microbial attack has plays a major role for its biological failure. Recently, the efficacies of plant extracts are being widely explored in the treatment of diseases. In this study, an attempt has been made to explore the antimicrobial properties of individual phytochemicals of Vitis vinifera on periodontitis and periimplantis microbiota through in silico analysis.*
Method: The PDB files of phytochemicals of Vitis vinifera were downloaded from PUB CHEM. The molecular interaction procedure between the phytochemicals derived from the grape extracts namely gallic acid, anthocyanin and procyanidin were made to interact with the bacterial proteins with the help of PyMOL and Autodock Vina.
Result: Protein ligand interaction analysis showed that the phytochemical, procyanidin acted as a ligand and tightly bound to the active site of Prevotella intermedia, Compylobacter rectus, Fusobacterium nucleatum, Tannerella forsythia and Porphyromonas gingivalis with highest affinity through a series of favorable covalent interactions. Anthocyanin showed highest affinity for Aggregatibacter actinomycetemcomitans and Candida albicans. Whereas, gallic acid of the grape plant showed least affinity for the active sites of all the microbes..
Keywords: *Phytochemicals, gallic acid, anthocyanin, procyanidin, PyMOL, Autodock Vina, Bioinformatics, in silico Analysis.*

1. INTRODUCTION

There is a serious health issue with periodontitis affecting 13-57% of people worldwide and 65-80% of people in India which when left untreated can lead to a number of systemic diseases.[1] The field of dental implantology has much evolved till date. Although studies have shown a success rate upto 99% over years, there are certain limitations in the techniques. Other than minor prosthetic complications, loosening of implants due to inflammation of its surrounding tissue which is termed as peri-implantitis has posed to be a major concern for its biological failure.[2] Microbial attack plays an important role in the peri-implant health of the tissues. The bacteria associated with the biofilm and plaque accumulation affects the success of dental implants. Various microbial species have been identified as distinct components of the periodontitis and peri implantitis flora.[3] Porphyromonas gingivalis, Prevotella intermedia, Parvimonas micra, Fusobacterium nucleatum, Tannerella forsythia, Campylobacter rectus, Eikenella corrodens and Aggregatibacter actinomycetemcomitans have been widely harvested from the infected tissues around a natural teeth and peri-implant area. 4,5

In ancient times, plant extracts have been widely used in the treatment of diseases. There has been a growing interest in recent times on usage of grapes (Vitis vinifera) as a potential therapeutic agent. The prime phytochemicals found in it are stilbenoid, aromatic acids (hydroxycinnamic and hydroxybenzoic acid), flavonoids, phenolic compounds proanthocyanidin. [6]

In this context, the present study aimed to characterize the less studied phytochemicals from extracts of V. vinifera for the first time, their applicability in the management of peri-implantitis. Furthermore, the antimicrobial activity of these biochemicals was tested on several bacterial strains associated with the host inflammatory processes responsible for peri-implantitis in craniofacial implants.

MATERIALS AND METHODS

Software Used

The PDB files of the target protein of the microbe were retrieved from Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) and the structure data file (SDF) of the phytochemicals of the plant Vitis vinifera were downloaded from PubChem.

In this research, we presented a plugin for PyMOL that allows for molecular docking, virtual screening, and analysis of binding sites to be performed using PyMOL. PyMOL and AutoDock Vina Vina are two popular docking applications. This plugin serves as a bridge between the two programs. With the help of visual support from PyMOL and a graphical user interface, the docking study workflow is executed. This allows to successfully complete the molecular interaction procedure.

List of Phytochemicals and Targeted Microbial Proteins:

Our study involves three primary phytochemicals found in Grapes namely gallic acid, anthocyanin and procyanidin. A detailed and extensive literature search revealed that the most common microorganisms affecting the periodontal health were Prevotella intermedia**,** Campylobacter rectus, Aggregatibacter actinomycetemcomitans**,** Fusobacterium nucleatum, Tannerella forsythia and Porphyromonas gingivalis. Moreover, the pathogens, their pathogenic pathway and the ligand responsible were reviewed and listed as in Table 1. [7-12]

Table 1: List of microbes and the ligand responsible for pathogenesis of the organisms

SI NO	Name of the Organism	PDB No	Name of the Ligand	Function	Reference
1	Prevotella intermedia	3BB7	Prointerpain A fragment 39-359 (mutant C154A)	Gene regulation	Mallorquí-Fernández N et al.
2	Campylobacter rectus	3MD D	Acyl-COA Dehydrogenase	Fatty acid α-oxidation	Kim JJ et al.
3	Aggregatibacter actinomycetemc omitans	4U10	Probing the structure and mechanism of de-N-acetylase from aggregatibacter actinomycetemcomitans	Deacetylation of the PNAG exopolysaccharide	Shanmuga m M et al.

4	Fusobacterium nucleatum	6L1K	NADH-dependent butanol dehydrogenase	Butanol biosynthesis and butyrate metabolism	Bai X et al.
5	Porphyromonas gingivalis	6SLI	Structure of the RagAB peptide transporter	Nutrient uptake	Madej M et al.
6	Tannerella forsythia	6QRO	glutaminyl cyclise	Catalyze the cyclization of N-terminal glutamine/glutamate residues of peptides and proteins with concomitant release of ammonia/water	Taudte N et al.

Exploiting this knowledge of the protein or ligand responsible in the pathogenesis of the microorganisms, the structure data file of phytochemicals from the grape seed extracts namely gallic acid, anthocyanin and procyanidin were made to interact with the bacterial proteins using PyMOL and Autodock Vina molecular docking procedure in nine docking modes. The bonding affinity and root-mean-square deviation (lower bound and upper bound) of distance from the best mode were charted as in Table 2.

RESULTS

Protein ligand interaction analysis showed that the phytochemical, procyanidin acted as a ligand and tightly bound to the active site of Prevotella intermedia, Campylobacter rectus, Fusobacterium nucleatum, Tannerella forsythia and Porphyromonas gingivalis with highest affinity through a series of favorable covalent interactions of −7.5 kcal/mol, −8.8 kcal/mol, −8.1 kcal/mol, −8.4 kcal/mol, −7.2 kcal/mol respectively. Molecular interaction of the bioactive compound, anthocyanin of the plant Vitis vinifera showed maximum affinity of −7.5 kcal/mol for Aggregatibacter actinomycetemcomitans when compared to procyanidin. The biomolecule gallic acid of the grape plant showed least affinity for the active sites of all the microbes. [Table 2]

Table 2: Docking values of Procyanidin, Anthocyanin and Gallic acid against the microorganisms

Organism [PDB]		**Docking Values of Procyanidin**			**Docking Values of Anthocyanin**			**Docking Values of Gallic acid**		
	Docking modes	affinity (kcal/mol)	dist from best mode		affinity (kcal/mol)	dist from best mode		affinity (kcal/mol)	dist from best mode	
			rmsd l.b	rmsd u.b		rmsd l.b	rmsd u.b		rmsd l.b	rmsd u.b

Prevotella intermedia [3BB7]	1	-7.5	0.000	0.000	-6.9	0.000	0.000	-4.0	0.000	0.000
	2	-7.5	2.957	7.618	-6.4	21.428	22.143	-3.7	1.135	5.324
	3	-7.3	1.792	2.357	-6.2	1.673	3.042	-3.7	1.697	4.984
	4	-7.1	2.428	7.934	-6.2	1.589	2.297	-3.6	21.114	21.451
	5	-7.0	2.964	7.840	-6.1	20.409	21.474	-3.6	3.264	4.601
	6	-6.8	2.320	6.914	-6.1	21.474	22.878	-3.6	21.235	21.892
	7	-6.8	29.144	32.512	-6.0	1.080	6.031	-3.5	25.703	26.580
	8	-6.5	2.489	7.371	-6.0	6.353	7.765	-3.4	26.185	26.513
	9	-6.5	2.455	4.002	-6.0	21.387	22.072	-3.4	3.503	4.087
Campylobacter rectus [3MDD]	1	-8.8	0.000	0.000	-6.8	0.000	0.000	-3.9	0.000	0.000
	2	-8.6	3.406	8.167	-6.7	24.196	25.586	-3.7	2.357	4.034
	3	-8.2	3.343	8.219	-6.7	2.779	6.081	-3.5	3.190	3.910
	4	-7.9	3.010	7.440	-6.5	0.953	1.959	-3.5	2.419	3.006
	5	-7.9	2.164	8.149	-6.2	4.575	7.971	-3.4	2.775	3.224
	6	-7.9	2.112	6.137	-6.1	12.574	14.454	-3.4	2.781	3.798
	7	-7.9	2.008	3.552	-6.1	2.203	3.125	-3.3	3.089	4.553
	8	-7.8	7.669	11.444	-6.1	1.053	6.080	8 -3.2 1.830 3.326	8 -3.2 1.830 3.326	8 -3.2 1.830 3.326
	9	-7.7	3.763	8.748	-6.0	4.139	7.704	9 -3.1 19.837 20.720	9 -3.1 19.837 20.720	9 -3.1 19.837 20.720
	1	-7.8	0.000	0.000	-7.9	0.000	0.000	-4.7	0.000	0.000
	2	-7.6	28.353	31.218	-7.4	0.647	5.868	-4.7	34.278	35.372
	3	-7.3	4.488	7.150	-7.1	1.375	6.296	-4.1	25.966	26.274

Aggregatibacter actinomycetemcomitans [4U10]	4	-7.0	6.244	10.066	-7.1	1.273	1.890	-4.1	26.161	26.885
	5	-7.0	4.313	7.080	-6.7	18.169	19.779	-3.7	25.693	26.319
	6	-7.0	11.305	15.758	-6.7	1.507	6.186	-3.5	25.583	26.434
	7	-6.9	33.120	36.077	-6.6	18.304	19.851	7 -3.5 25.175 25.843	7 -3.5 25.175 25.843	25.843
	8	-6.9	4.965	10.788	-6.5	20.376	21.689	-3.5	12.882	14.308
	9	-6.9	8.086	12.071	-6.4	20.537	22.217	-3.4	25.446	26.229
Fusobacterium nucleatum [6L1K]	1	-8.1	0.000	0.000	-7.5	0.000	0.000	-3.1	0.000	0.000
	2	-8.0	3.061	5.840	-7.2	0.847	5.966	-3.1	8.990	10.245
	3	-8.0	2.299	7.409	-6.8	1.001	6.161	-3.1	12.937	14.287
	4	-7.9	1.958	7.071	-6.3	4.436	7.788	-3.1	19.247	19.686
	5	-7.7	8.780	11.355	-6.2	3.775	5.762	-3.1	2.231	4.201
	6	-7.7	14.870	19.283	-6.2	19.264	22.231	-3.1	20.959	22.397
	7	-7.5	5.256	11.593	-6.1	4.205	7.850	-3.1	9.431	10.682
	8	-7.4	2.832	4.392	-5.9	21.155	23.887	-2.9	20.718	21.655
	9	-7.3	2.947	4.029	-5.8	17.427	20.566	-2.9	17.591	18.851
Porphyromonas gingivalis [6SLI]	1	-7.2	0.000	0.000	-6.4	0.000	0.000	-5.0	0.000	0.000
	2	-7.2	16.341	18.725	-6.4	0.650	5.858	-5.0	0.015	2.402
	3	-6.8	16.353	19.088	-6.4	0.926	1.969	-5.0	15.071	16.341
	4	-6.7	2.818	6.813	-6.4	0.903	6.265	-4.9	3.946	4.823
	5	-6.6	11.674	13.769	-6.3	16.216	16.983	-4.9	4.156	6.304
	6	-6.6	15.306	17.282	-6.1	46.687	48.570	-4.9	1.502	2.443
	7	-6.5	2.096	6.583	-6.1	45.694	48.015	-4.9	1.484	2.943

	8	-6.5	2.896	7.481	-6.0	46.098	47.999	-4.9	4.142	6.588
	9	-6.5	13.682	15.581	-5.8	16.375	17.265	-4.8	15.078	16.488
Tannerella forsythia [6QRO]	1	-8.4	0.000	0.000	-7.5	0.000	0.000	-4.0	0.000	0.000
	2	-8.3	1.742	6.607	-7.2	1.477	5.995	-3.8	21.388	22.865
	3	-8.2	4.177	8.908	-7.2	21.925	23.803	-3.8	21.114	22.233
	4	-8.2	12.792	15.974	-7.2	1.822	6.259	-3.8	20.666	22.517
	5	-8.0	2.123	5.854	-7.0	23.029	25.049	-3.7	20.862	22.502
	6	-8.0	1.909	6.250	-7.0	1.040	1.064	-3.6	20.522	22.150
	7	-7.8	2.804	6.995	-6.8	19.673	22.009	-3.6	21.333	22.021
	8	-7.7	9.336	13.346	-6.8	20.542	22.387	-3.6	21.571	22.805
	9	-7.6	2.629	6.164	-6.8	12.657	13.653	-3.6	21.319	22.046

DISCUSSION

Periodontitis and peri-implantitis are inflammation of the soft and hard tissues forming a bacterial biofilm on the teeth and implant surface which destroys the surrounding bone and affects osseointegration associated with marginal tissues. [13] Progressive bone loss of the marginal peri-implant bone is a key symptom of chronic inflammation. Compromised oral hygiene, diabetes mellitus and tobacco smoking among others are the factors responsible for periodontitis and peri-implantitis. [14] The most frequent periodontal pathogens present in a peri-implantitis lesions are Bacteroides, Prevotella and Porphyromonas. Understanding the peri-implant microbiota and management of peri-implantitis is still challenging since the scientific data regarding the microbiota responsible for initiation and progression of peri-implantitis is still inconclusive. [13]

Bioinformatics is a discipline which combines biology and information technology. A considerable amount of scientific information has been stored in databases which can be easily accessed and retrieved. Molecular interaction like protein-protein, protein-nucleic acid, drug-nucleic acid, drug-protein and enzyme-substrate are vital for many essential biological function including transport, cell regulation, signal transduction, gene expression control, antibody-antigen recognition and enzyme inhibition.

Molecular docking is the study of how two or more molecular structures interact with each other. For instance, a drug and an enzyme or a receptor of a protein are examples of molecular structures that are studied. Software for molecular docking is most commonly utilized in the pharmaceutical research sector. Docking software's most significant application is virtual screening (VS). For the purpose of virtual screening, a great number of tools have been developed, including GEMDOCK, DOCK, AutoDock, and GOLD. The VS process is comprised of four primary parts, which include the creation of the compound library and the target protein, docking, and post-screening analysis.

In this study AutoDOCK was used for binding mode and analyzing affinity between interacting molecules necessitates the understanding of the tertiary structure of proteins. So, docking analysis helps in understanding the protein-ligand interaction the protein-ligand interaction or protein-protein without carrying out tedious and expensive experimental procedure. [15]

Though Vitis vinifera commonly known as Grapes are one of the widely consumed fruits, there has been a recent increase in interest due to its pharmacological values. Phytochemicals are the bioactive compounds found in various parts of plants that are non nutritive and have disease preventing effect to humans. [6] Though there are many phytochemicals which can be extracted from grape vine, in the present study we have taken procyanidin, anthocyanin and gallic acid due to limited research in this area. Hydroxybenzoic acid like gallic acid is present in grape leaves, grape seed extracts, stem and grape vine canes. Procyanidin can be extracted from the grape skin, seeds and leaves. Anthocyanin can be harvested from the skin, black grape seeds and leaves. [6] Several studies have been carried out on the antioxidant properties of Vitis vinifera, but fewer studies have been carried out on its antimicrobial properties. A strong covalent bond is formed with the bacterial protein by the phytochemical which acts as a ligand molecule. This mechanism effectively suppresses the microbe. This study, therefore aims to probe the properties of bioactive procyanidin, anthocyanin and gallic acid as an anti-microbial agent on the microbes of peri implantitis of dental implants.

Prevotella intermedia, major periodontopathogen release proteases as virulence factors that cause deterrence of host defenses and tissue destruction. Prointerpain A fragment 39-359 (mutant C154A) in which the active-site Cys^{154} had been mutated to alanine (C154A) and thereafter termed pro-cd-InpA C154A is the ligand responsible for involved in pathogenicity of the bacteria. [7] [Table 1] Procyanidin acted as a ligand and tightly bound to this active site of Prevotella intermedia, with highest affinity of −7.5 kcal/mol. Anthocyanin on the other hand had a lower affinity of -6.9 kcal/mol. Gallic acid displayed minimal affinity of -4.0 kcal/mol. [Figure 1,Table 2]

Campylobacter rectus previously called as Wolinella rectus is abundantly found along the periodontal crevicular space in the oral cavity and couples H2 oxidation with S0 reduction .[h] Procyanidin competes with Acyl-COA Dehydrogenase responsible for fatty acid α-oxidation and bonds with highest affinity of -8.8 kcal/mol. [8] Anthocyanin and Gallic acid displayed minimal affinity of -6.8 kcal/mol and -3.9 kcal/mol respectively. [Figure 1,Table 2]

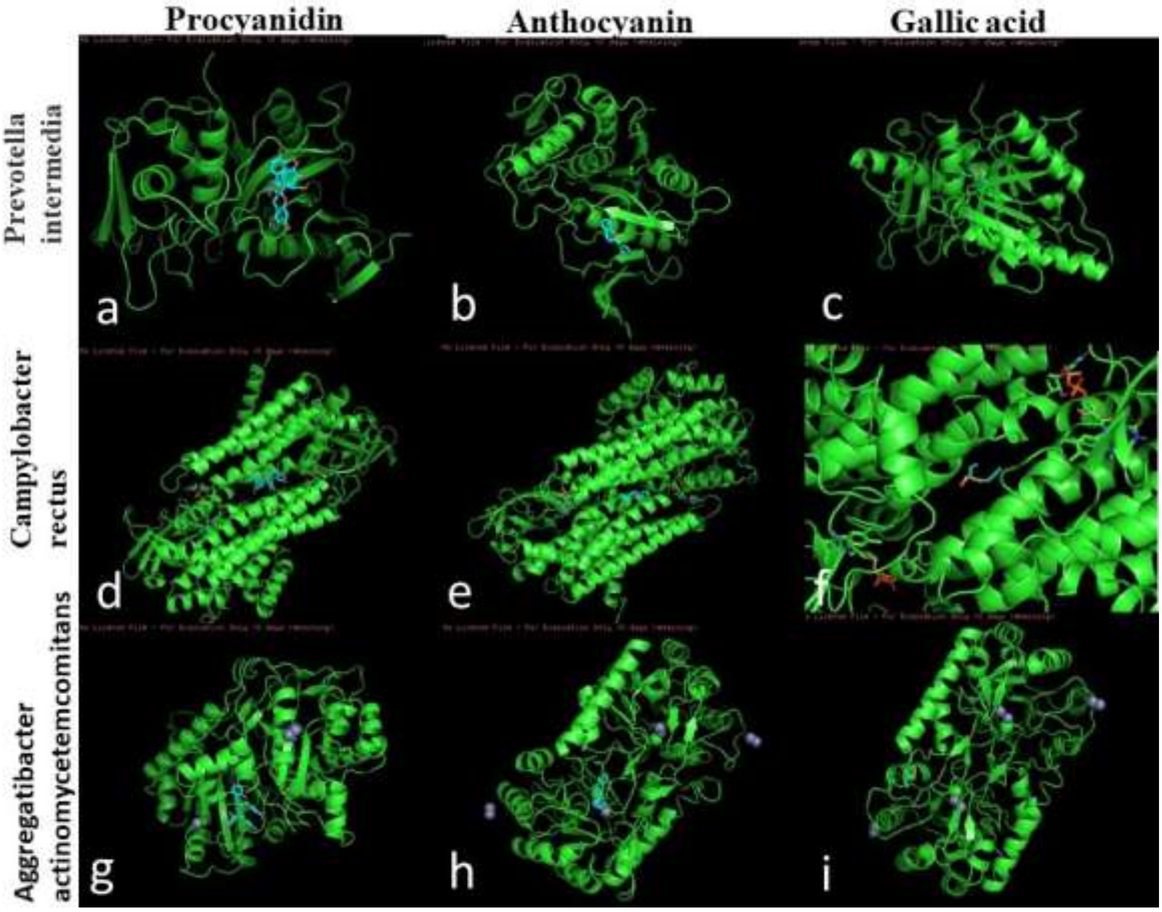

Figure 1: The output file acquired from the docking analysis contains different favourable binding postures, together with their corresponding binding affinities measured in kcal/mol. The ligand-binding conformation

with the highest binding affinity and the lowest root mean square deviation (RMSD) was chosen. The protein-ligand interaction in three-dimensional structures was visualised using PyMOL. 3D visualisation of the interaction between several proteins of microorganisms and specific phytochemicals. a. The binding model of procyanidin with Prointerpain A fragment 39-359 (illustrated in purple) of Prevotella intermedia and acarbose (illustrated in red) with α-amylase protein(illustrated in dark green) leading to Procyanin A - α-glucosidase interaction and acarbose - α-glucosidase interaction. b. Prevotella intermedia with Anthocyanin, c. Prevotella intermedia with Gallic acid , d. Campylobacter rectus with Procyanidin , e. Campylobacter rectus with Anthocyanin , f. Campylobacter rectus with Gallic acid , g. Aggregatibacter actinomycetemcomitans with Procyanidin , h. Aggregatibacter actinomycetemromitans with Anthocyanin , i. Aggregatibacter actinomycetemcomitans with Gallic acid

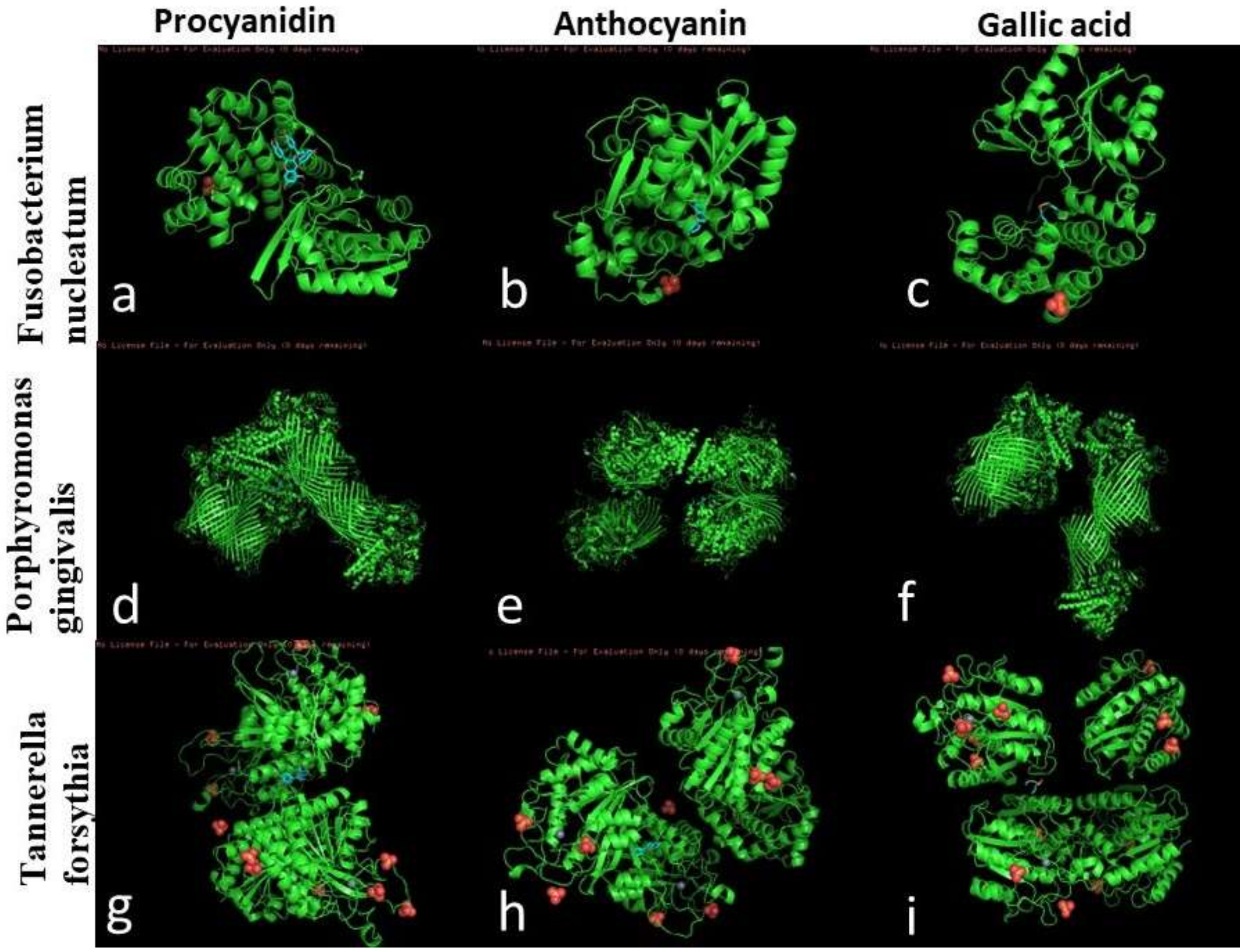

Figure 2 : Interactions between proteins and ligands occur with the active binding site of a target receptor, specifically with certain phytochemicals. 3D visualisation of the interaction between several proteins of microorganisms and specific phytochemicals. a. Fusobacterium nucleatum with Procyanidin b. Fusobacterium nucleatum with Anthocyanin, c. Fusobacterium nucleatum with Gallic acid , d. Porphromonas gingivalis with Procyanidin , e. Porphromonas gingivalis with Anthocyanin , f. Porphromonas gingivalis with Gallic acid , g. Tannerella forsythia with Procyanidin , h. Tannerella forsythia with Anthocyanin , i. Tannerella forsythia with Gallic acid

Aggregatibacter actinomycetemcomitans is a Gram-negative bacterium which is a normal commensals of oral microbiota and also causative agent of aggressive periodontitis and periimplantitis. De-N-acetylase plays a key role in virulence by deacetylation of the PNAG exopolysaccharide.[9] The biomolecule anthocyanin and procyanidin

bonds with highest affinity of -7.8 kcal/mol and -7.9 kcal/mol. [Figure1,Table 2]
F. nucleatum is an obligate anaerobe but can grow in environments containing more than 6% oxygen by volume in the air. A series of dehydrogenase enzymes known as F. nucleatum butanol dehydrogenases (FnYqdH) help butyraldehyde and butanol interconvert at the expense of a cofactor called NAD(P)H. [10] The biomolecule anthocyanin tightly bound to this active site of F. nucleatum, with highest affinity of −7.2 kcal/mol followed by procyanidin with an affinity of -7.5 kcal/mol. Gallic acid displayed minimal affinity of -3.1 kcal/mol.
Dysbiosis caused by the main pathogen Porphyromonas gingivalis and other anaerobic bacteria like Tannerella forsythia, disrupts tissue homeostasis and the immune system as a whole. This insufficient inflammatory host response ultimately causes periodontal tissue to deteriorate. The development of small molecule inhibitors for glutaminyl cyclases (QCs) from the oral pathogens Porphyromonas gingivalis, Tannerella forsythia, and Prevotella intermedia is appealing because these enzymes are likely to stabilise important periplasmic and outer membrane proteins by N-terminal pyroglutamination. [12] For growth, P. gingivalis uses protease-generated peptides obtained from extracellular proteins, and RagAB is a dynamic importer for acquiring oligopeptides from the outer membrane that is crucial for P. gingivalis' effective uptake of proteinaceous nutrients. [11] Anthocyanin is less efficient than procyanidin against Tannerella forsythia and Porphyromonas gingivalis. Gallic acid showed the least efficiency.

CONCLUSION

The establishment of a targeted therapy would greatly enhance the management of periodontitis and related conditions. Natural therapies are believed to be safer, have fewer side effects, and can also be used to prevent disease. From this current research work, it is found that out of the three phytochemicals of Vitis vinifera procyanidin and anthocyanin are the most effective against the common periodontal and periimplantitis pathogens whereas gallic acid has the least efficacy. Thus the outcome of this study will be helpful for development of better and effective alternative medicine for treatment of periodontal and periimplantitis thus promoting good oral health.

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