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Potential of nutraceutical fucoidan against periodontal pathogens: a novel molecular docking study

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Abstract

Introduction: Fucoidan from seaweed has gained significant attention due to its diverse therapeutic properties. Its antibacterial potential in periodontitis needs exploration. **Objective:** This paper aims to explore the suitability of fucoidan to treat periodontitis by molecular docking methods. **Methods:** Molecular docking of fucoidan was done with targets from *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*. Binding energy, inhibition constant, number of hydrogen bonds, aminoacid residues involved in H-Bond were identified. Control docking was done with chlorhexidine and compared. **Results:** Docking of *Porphyromonas gingivalis* enzyme, gingipain K (Kgp) with fucoidan had an inhibition constant of -6.83, ODP from *T. denticola* with fucoidan had binding energy of -4.52, anti-CRISPR protein AcrIF9 with fucoidan had a binding energy of 4.81 and *Tannerella forsythia* potempin E with Fucoidan had a binding energy of -3.09 all expresssed as kcal/mol. Respective inhibition constants were 67.3 µM, 485.11µM, 295.72 µM and 5.47 mM. All binding energies ranged from -3 to -6 range suitable for inhibition of their targets. **Conclusion:** Inhibition constant for targets from *T. denticola* and *A. actinomycetemcomitans* had highest values indicating that fucoidan inhibits *T. denticola* and *A. actinomycetemcomitans* more significantly than *P. gingivalis* and *T. forsythia*.

Keywords: Binding energy. Drug discovery. Fucoidan. Inhibition constants. Molecular docking simulation. Periodontal dysbiosis.

Introduction

Periodontitis is a chronic inflammatory condition caused by microbial dysbiosis in the oral cavity. The balance is shifted from healthy flora to pathogenic flora. As a result, diseases ranging from gingivitis to periodontitis occur, leading to the progressive destruction of the periodontium **[1,2]**. It is currently the leading cause of tooth loss globally, alongside dental caries **[3]**. The periodontal inflammation has systemic implications and can precipitate emergencies in a lot of systemic medical conditions, such as endocarditis, diabetes, atherosclerosis, etc. Therefore, treating periodontitis has become a global interest and needs effective measures to control the pathogenic flora **[4,5]**.

In the past, individual pathogens were thought

to cause periodontitis; however, the advancing research in the past decade has shown that pathogenicity may not be from a single species of organism but due to complex and well-orchestrated interactions between several species of organisms **[6,7]**. Therefore, the entire microbiome contributes to the disease, showing that any single group of antibiotics may not effectively eliminate the dysbiosis. Of the pathogenic dysbiome, well-known pathogens, *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, and *Fusobacterium nucleatum* play central roles in disrupting the immune responses of the host **[8]**. They form biofilms that are highly resistant to conventional antimicrobial therapies. Therefore, newer therapies should focus on agents that can disrupt biofilm and inactivate this microbiota without forming resistance in bacteria **[9]**.

Fucoidan is a sulfated polysaccharide that is derived from brown algae and some marine invertebrates. It has gained significant attention in contemporary biomedical research due to its diverse therapeutic properties **[10]**. These claimed therapeutic effects are reported in various researches. Its anti-inflammatory activity is known to be mediated by selectin inhibition in addition to reduced pro-inflammatory cytokines. Other known therapeutic properties include anticancer effects by apoptosis induction, cell cycle arrest, and immunomodulation, antioxidant properties, neuroprotective potential, anticoagulant, antiviral, and angiogenic modulation effects **[11-19]**.

Fucoidan ($(C_6H_8\text{-}10O_7\text{-}10S_{1\text{-}2})n$) is made from fucose-rich chains with sulfate groups, bestowing its unique biological activities **[20]**. Some properties relevant to periodontal therapy are antimicrobial, anti-inflammatory, and biofilm-inhibitory effects. Its potent ability to inhibit microbial adhesion and biofilm formation makes it a putative candidate for effectively managing the microbial communities associated with periodontal diseases. Prior to its use in a clinical setup, it is necessary to evaluate its properties systematically. Since fucoidan is an abundantly and naturally available biomaterial, it can be used for periodontal therapy and regeneration. Hence, the relationship between periodontal pathogens and fucoidan needs to be tested by molecular docking studies.

Molecular docking studies are powerful tools to calculate the interaction mechanisms between bioactive compounds and microbial proteins. These computational approaches, at economical cost, help identify binding affinities, inhibition constants, and critical molecular interactions, enabling us to predict the therapeutic efficacy of the drug. This study focuses on finding the potential of fucoidan as an antimicrobial agent against key periodontal pathogens. In summary, this research aims to explore the suitability of fucoidan in treating periodontitis.

Materials and Methods

The following dry lab procedures were conducted with standard procedures: ADMET Analysis, Bioactivity & target Prediction, PPI Interaction & Network Pharmacology, Protein Homology Modelling and Evaluation, and Small Molecule Modelling.

Preparation of ligand and target protein

Generated protein models were utilized for the process of molecular docking. The three-dimensional structure of fucoidan ($(C_6H_8\text{-}10O_7\text{-}10S_{1\text{-}2})n$) was analyzed for error using PyMOL software. Similarly, the ion molecules and standard inhibitors, if present, were also removed using the PyMOL visualization tool. The Chem3D Ultra 11.0 software was used to construct the three-dimensional structures of the ligands (Figure 1) to be studied. Polar hydrogen bonds were added to the protein while simultaneously all bound water ligands were removed.

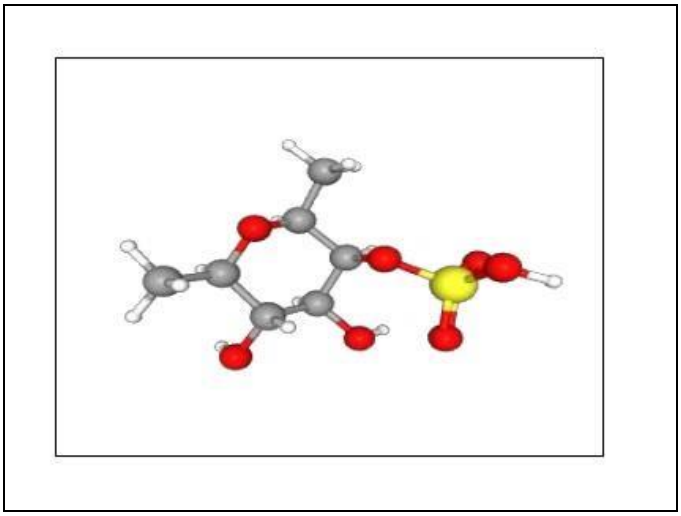

Figure 1. Three-Dimensional structure of Fucoidan. Source: Own authorship.

Protocol of Docking Studies

The latest version of Auto Dock software was used for the automated docking study. The procedure was based on previously reported procedures **[21]**. The auto grid, a component of auto dock, was used to compute the grid maps with the interaction energies depending upon the macromolecule target of the docking study. The grid center was placed on the active target site region of the enzyme. The binding

free energy of the inhibitors was evaluated using automated docking studies. Precisely, Grid boxes were centered on the protein centroid with dimensions ranging from 45–70 Å to allow blind docking of fucoidan. Exhaustiveness was set to 20. The best docking pose was selected based on the lowest binding energy and RMSD of 0.0 Å. Inhibition constants were automatically calculated by the software (Autodock 4.2) used for docking. The best conformation search was done by adopting the genetic algorithm with local search (GA-LS) method. The docking parameters were set to default values with 100 independent docking runs using the software ADT (Auto-Dock Tool Kit). Root mean square deviation (RMSD) of 2.0 Å was performed using structures generated after completion of docking via cluster analysis. Molecular graphics and visualization were performed with the UCSF Chimera visualization tool. 100 evaluations were carried out for each ligand with all protein targets and the posed. The binding energy and bond length of each interaction are mentioned in Table 1.

Table 1. Binding energy of Fucoidan (1-4) and chlorhexidine (5-8) with target proteins.

S.No	Targets (Figures 2-5)	Binding energy	Inhibition Constant kI	No of Hydrogen bonds	Aminoacid residues involved in H-Bond with bond length
1	6I9A	-6.93	67.3 µM	2	Gln677 B (3.798), Gln 679 B (2.727)
2	6QNM	-4.52	485.11µM	2	Phe 173 A (3.387), Arg 108 B (2.990)
3	7BB5	-4.81	295.72 µM	4	Val 5 A(2.049), Val 4 A(2.957), Val 4 A (2.637), Val 4 A (3.116)
4	8EHD	-3.09	5.47 mM	2	Pro 53 A (1.788), Pro 53 A (2.973)
5	6I9A	-8.18	1 .0 µM	2	Pro258B (2.174) Glu254B (1.964)
6	6QNM	-5.71	65.3 µM	2	Ser104B (3.307, 3.478)
7	7BB5	-3.24	4.23mM	1	Gln26A(2.134)
8	8EHD	-7.56	2.89 µM	3	Tyr56A (2.372) Tyr68A (2.096) Ile52A (2.035)

Source: Own authorship.

Results

With regard to ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile, fucoidan is moderately absorbed orally and is shown to permeate cell membranes well, but is poorly absorbed through skin. It has moderate distribution potential and does not cross the blood -brain barrier. It may persist free in plasma owing to its low protein binding, which might increase its availability to peripheral tissues. It also has the potential for various drug interactions, mainly with inhibitors of CYP2C19 and CYP2C9. Therefore, it affects the metabolism of other drugs. It has a lower clearance rate, suggesting some retention. With regard to toxicity, it is non-carcinogenic and has proved to be anti-carcinogenic in liver cancer.

With regard to acute toxicity in an animal model (LD50), all the values were much above the typical toxicity threshold, making it practically non-toxic in mammals. With regard to the half-life, fucoidan disintegrates quickly in the air and does not bioaccumulate. However, in soil and sediment, it has moderate to high persistence, posing a risk for terrestrial and aquatic systems. In water, theoretical half-lives are too long and show extreme chemical stability in aqueous environments.

Fucoidan is environmentally safe at the intended concentrations. These findings therefore suggest favourable pharmacokinetics and ecological compatibility, favouring its biomedical or nutraceutical use. Its promising pharmacological activities that have high predicted activity probabilities (Pa ≥ 0.90) were Benzoate-CoA ligase inhibition (Pa = 0.983), Sugar-phosphatase inhibition, G-protein-coupled receptor kinase inhibition, beta-adrenergic receptor kinase inhibition, and various glucosidase/hydrolases inhibitions. This may indicate that fucoidan may have both strong enzyme-inhibiting and metabolic-modulating effects, leading to its anti-inflammatory, antiviral, and anticancer activities.

Fucoidan exhibited some selective cytotoxicity toward normal lung and skin fibroblast cells. However, it is not highly potent (Pa < 0.5). Safety profile apparently is acceptable for most normal cells, including immune or endothelial cells (WIL2-NS, HMEC). The Gene Ontology analysis shows that fucoidan potentially impacts enzyme regulation (especially hydrolases and oxidoreductases), metal-dependent pathways, cell signalling via receptors, gene expression via transcription factor interaction, protein–protein or protein–peptide interactions, and neuroprotective mechanisms (e.g., amyloid-beta binding). These corroborate with known pharmacological effects of fucoidan, such as anti-inflammatory, anticancer, immunomodulatory, antiviral, and neuroprotective effects.

The grid box was centered at the geometric centroid of the respective proteins. For

Porphyromonas gingivalis gingipain K (Kgp), a grid box was 70 × 70 × 70 Å, for oxidoreductase protein (ODP) from *Treponema denticola*, it was 60 × 60 × 60 Å, for anti-CRISPR protein AcrIF9, it was 50 × 50 × 50 Å; and for *Tannerella forsythia* potempin E, the grid box of 45 × 45 × 45 Å was used.

The results and their interpretation were derived from the binding energy, inhibition constants, and hydrogen bonding. The target 6I9A had the strongest binding affinity (-6.93 kcal/mol) and the least inhibition constant (67.3 μM). This means that it forms a highly stable ligand-target complex. However, with 8EHD, fucoidan demonstrated the weakest binding energy (-3.09 kcal/mol) and the greatest inhibition constant (5.47 mM). This shows relatively weak interactions. Intermediate affinities were observed with 6QNM (-4.52 kcal/mol, 485.11 μM) and 7BB5 (-4.81 kcal/mol, 295.72 μM) (Figures 2 to 5).

The number of hydrogen bonds showed variation between two and four, contributing significantly to the ligand's stability. Target 7BB5 formed the maximum number of hydrogen bonds (four), predominantly involving Val 4 A, suggesting a significant interaction network. In contrast, targets 6I9A, 6QNM, and 8EHD each formed only two hydrogen bonds, though the involved residues differed. 6I9A interacted with Gln677 B and Gln679 B, whereas 6QNM formed bonds with Phe173 A and Arg108 B. Target 7BB5 showed strong hydrogen bonding with multiple Val residues, enhancing its interaction stability. Finally, 8EHD demonstrated less complex bonding, relying solely on Pro53 A.

A comparative docking analysis of fucoidan and chlorhexidine across targets 6I9A, 6QNM, 7BB5, and 8EHD demonstrated that fucoidan exhibits interaction patterns that are, in certain cases, comparable to the reference compound. For 6I9A, fucoidan showed a binding energy of −6.93 kcal/mol with a Ki of 67.32 μM, forming two hydrogen bonds, which is within a reasonable micromolar range relative to chlorhexidine (−8.18 kcal/mol; 1.0 μM). In 6QNM, fucoidan (−4.52 kcal/mol; 485.11 μM) displayed moderate binding with two hydrogen bonds, approaching the interaction profile of chlorhexidine (−5.71 kcal/mol). Notably, in 7BB5, fucoidan (−4.81 kcal/mol) demonstrated better binding energy than chlorhexidine (−3.24 kcal/mol) and formed four hydrogen bonds, indicating enhanced interaction stability. Although fucoidan showed weaker binding toward 8EHD, its overall interaction profile, particularly against 6I9A and 7BB5, suggests binding behavior that is partially comparable to the standard compound.

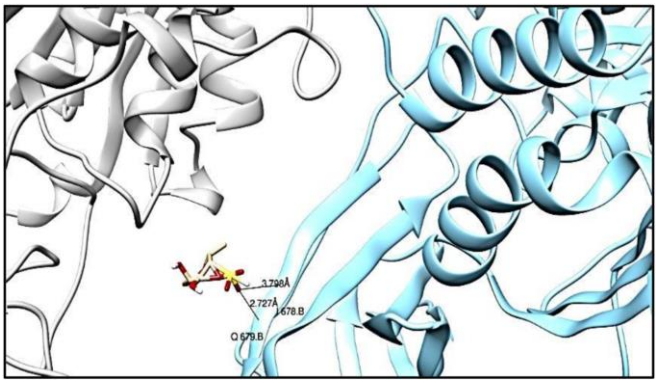

Figure 2. Molecular Docking of *Porphyromonas gingivalis* enzyme, gingipain K (Kgp) with Fucoidan. Source: Own authorship.

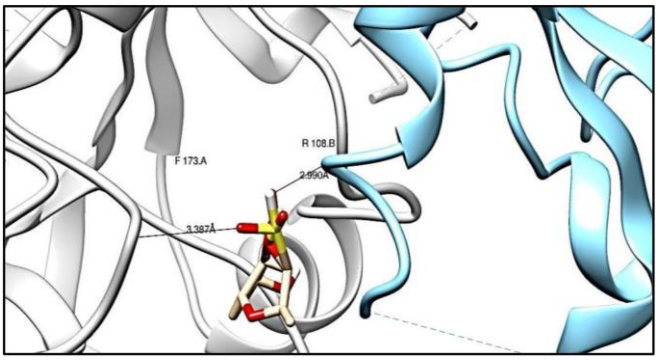

Figure 3. Molecular Docking of ODP from T. *denticola* with Fucoidan. Source: Own authorship.

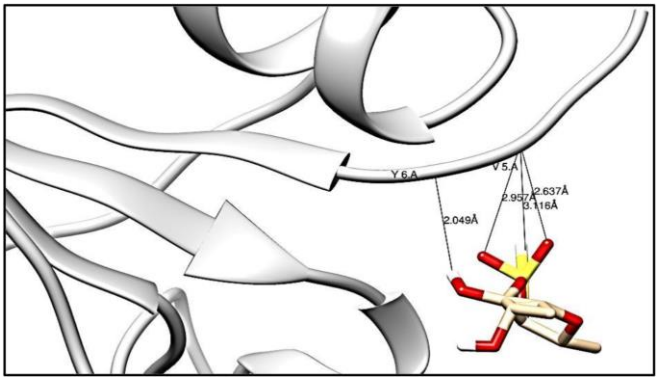

Figure 4. Molecular Docking of anti-CRISPR protein AcrIF9 with Fucoidan. Source: Own authorship.

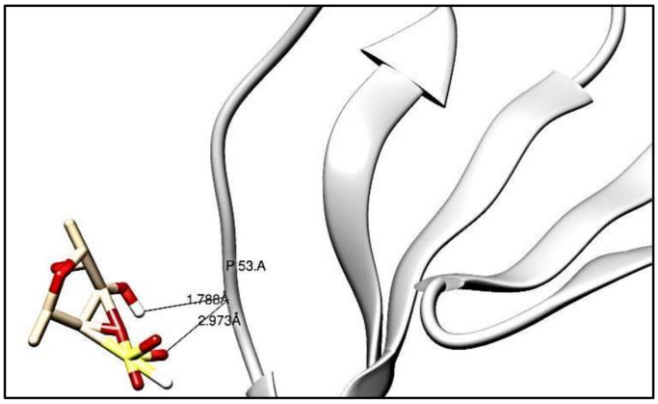

Figure 5. Molecular Docking of *Tannerella forsythia* potempin E with Fucoidan. Source: Own authorship.

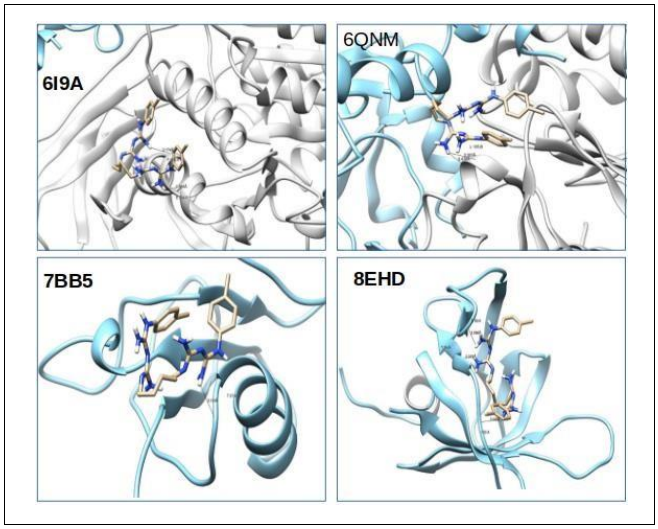

Figure 6. Molecular Docking of Chlorhexidine with respective targets. Source: Own authorship.

Discussion

With regard to periodontal therapy, the action of fucoidan is basically by inhibition of inflammatory pathways and their constituent minor pathways. Specifically, fucoidan is reported to suppress the production of nitric oxide and prostaglandin E2. It also suppresses the expression of various pro-inflammatory enzymes such as inducible nitric oxide synthase and cyclooxygenase-2 **[22]**. Further, it also downregulates the level of nuclear factor kappa B and mitogen-activated protein kinases. It can be observed that the major and pivotal inflammatory pathways are influenced by fucoidan. Its sulfate groups are shown to be instrumental in these molecular interactions, thereby reducing inflammation and potentially preventing periodontal disease progression **[23]**.

In addition, fucoidan's binding affinity against target periodontal pathogen proteins proves that fucoidan can be used as an effective therapeutic drug against periodontitis **[24]**. Previous insilico studies have supported these findings, thus providing a basis for its use in developing novel therapeutic agents for periodontal disease prevention and treatment **[25]**.

The ADMET profile of fucoidan has shown its promising pharmacokinetic and safety characteristics, therefore supporting its biomedical use. Environmentally, it has extreme chemical stability in water. From the pharmacological standpoint, fucoidan has inhibitory activities against various enzymes and kinases, including Benzoate-CoA ligase, sugar-phosphatase, and G-proteincoupled receptor kinases. The gene ontology analysis shows a link of fucoidan to the regulation of key enzymes, receptor-mediated signaling, and neuroprotective pathways. Fucoidan showed mild cytotoxicity in normal fibroblast cells but not in other cell types. Therefore, a balanced profile of fucoidan warrants further evaluation in docking and wet lab studies.

While the current focus is on the use of fucoidan to manage periodontitis, this study has shed light on its molecular interactions with major pathogens causing periodontitis. The result of the current docking study shows effective interactions between ligands and targets used in the study. This study underscores 6I9A as the most promising target due to its superior binding energy and inhibition constant. The robust hydrogen bonding of 7BB5 also warrants further exploration. Conversely, the weak interactions with 8EHD suggest limited therapeutic or functional potential. These findings provide a foundation for further biochemical and pharmacological investigations.

6I9A, 6QNM, 7BB5, 8EHD are important targets from *Porphyromonas gingivalis,* gingipain K (Kgp) in complex with inhibitor KYT-36, Apo state of chemotaxis sensor ODP from *T. denticola*, anti-CRISPR protein AcrIF9 from *Aggregatibacter actinomycetemcomitans,* and *Tannerella forsythia* potempin E, respectively. All binding energies in the -3 to -6 range are suitable for inhibition of these targets. Inhibition constant for 6QNM and 7BB5, i.e, *T. denticola* and *A.actinomycetemcomitans* based targets, had the best inhibition constants. Though fucoidan inhibits all four targets significantly, it inhibits *T. denticola* and *A.actinomycetemcomitans* better than *P. gingivalis* and *T. forsythia.*

Previous works have highlighted the role of Fucoidan on bone cells in the anabolic aspect. Fucoidan has stimulated bone formation and can be of great benefit in periodontal defects. Fucoidan can inhibit bacterial invasion in periodontitis along with its anabolic effect on bone **[26-28]**. Previous studies have also shown good antimicrobial properties of fucoidan on various human pathogens, such as gut and oral flora in general **[29-33]**. However, this study has highlighted the specific inhibitory mechanisms related to periodontal pathogens. Lakshmanan et al. (2022), Hudiyati et al. (2024), and Sanghvi et al. (2026) have shown various promising therapeutic aspects of fucoidan, like antioxidant properties, and Kim et al. (2023) have indicated its potential against periodontal inflammation **[34-37]**. Another report by Ma et al (2025) **[38]** has followed a similar methodology for the effects of certain phytochemicals against periodontitis, while current research has focused on fucoidan alone. However, this study is one of the pioneering studies to report the interaction of fucoidan with pathogenic proteins of periodontal pathogens. Findings of the current study clearly show that fucoidan shows promising therapeutic potential in periodontitis, involving both host-modulatory and

antimicrobial pathways.

Docking results in this study have reported moderate binding affinities due to fucoidan's high molecular weight. It may also be due to multivalent electrostatic and hydrogen-bond interactions, characteristic of large molecules. The stronger interactions with *T. denticola* and *A. actinomycetemcomitans* may suggest their preferential inhibition of the bacteria. Considering the limitations of the rigid receptor models and structural heterogeneity of fucoidan, the results must be applied with caution. More in vitro tests to be done with fucoidan to analyse the physical properties so that it can be used as a potential drug against periodontal pathogens.

Conclusion

The current in silico study has demonstrated that fucoidan exhibits favourable properties as an adjunctive therapeutic agent for treating periodontitis. The ADMET predictions have shown moderate oral absorption, limited skin permeability, clear absence of blood–brain barrier penetration, in addition to low protein binding, suggesting peripheral bioavailability. While interactions with CYP2C9 and CYP2C19 inhibitors do suggest caution, the overall clearance rate, along with high LD50, shows low systemic toxicity. Environmental modelling has suggested minimal ecological risk at therapeutic concentrations, in spite of its persistence in aqueous systems. Docking analysis shows meaningful ligand–target interactions across proteins of major periodontal pathogens. Among the evaluated proteins, gingipain K from *Porphyromonas gingivalis* had the strongest binding affinity, clearly predicting stable complex formation. With regard to other targets, 7BB5 had enhanced interaction stability, 6QNM had moderate inhibitory potential, while 8EHD bound in comparatively weak interaction. Fucoidan's overall interaction profile was partially comparable to that of chlorhexidine, with superior hydrogen bonding stability in some cases. Therefore, fucoidan is predicted to exert multi-target inhibitory effects with safety, thereby supporting further experimental validation for periodontal therapy.

CrediT

Author contributions: **Conceptualization-** All authors; **Data curation-** B Bhuvaneswari, S Gopalakrishnan, U Arunmozhi; **Formal Analysis-** All authors; **Investigation-** All authors; **Methodology-** B Bhuvaneswari; **Supervision-** Thodur Madapusi Balaji; **Writing - original draft-** All authors; **Writing-review & editing-** All authors.

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Ethical Approval

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Informed Consent

Not applicable.

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Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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