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Targeting surface protein antigen I/II of *Streptococcus mutans* using novel WL10 antimicrobial peptide

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Abstract

Background: *Streptococcus mutans* (*S. mutans*) is a leading cause of tooth decay because it sticks tightly to teeth and builds protective biofilms. With rising antibiotic resistance making traditional treatments less effective, we urgently need new options. Antimicrobial peptides (AMPs) stand out as promising solutions-they're targeted, low-risk, and highly effective against microbes. This study designed a new antimicrobial peptide called WL10 and assessed its safety, bioavailability, and how it binds to *S. mutans* surface protein antigen I/II using computer-based methods.

Methods: WL10 was designed using specialized peptide design tools and visualized with the PepDraw server. Its toxicity was predicted using ToxinPred, and bioavailability was assessed using Peptide Ranker. Physicochemical properties were analyzed using peptide property calculators. Molecular docking simulations were performed using the HPEPDOCK server to evaluate the interaction between WL10 and the antigen I/II protein, with binding affinity and stability assessed based on docking scores.

Results: ToxinPred confirmed WL10 is non-toxic. Peptide Ranker gave it a strong bioavailability score of 0.87, pointing to good biological potential. Docking showed robust binding to the antigen I/II protein, with an affinity of −179 kcal/mol-evidence of a stable interaction that could block the protein's function and disrupt bacterial adhesion.

Conclusion: Computational analyses indicate that the antimicrobial peptide WL10 is non-toxic, biologically active, and exhibits strong binding affinity toward the key surface protein antigen I/II of *S. mutans*. These findings highlight its potential as a targeted anti-adhesive agent capable of inhibiting bacterial colonization and biofilm formation. Further experimental validation, including *in vitro* and *in vivo* studies, is warranted to confirm its therapeutic efficacy and clinical applicability.

Keywords: Antimicrobial peptide, WL10, *S. mutans*, Antigen I/II, Molecular docking

1. Introduction

Dental caries remains one of the most prevalent chronic oral diseases globally and is strongly associated with the cariogenic bacterium *Streptococcus mutans* (*S. mutans*) [1]. *S. mutans* is a key driver of dental plaque and biofilm formation on tooth surfaces, primarily because of its ability to adhere, produce extracellular polysaccharides via glucosyltransferases, and build robust biofilms that shield it from host defences and antimicrobial agents. Among its major virulence determinants, the surface protein antigen I/II plays a central role by mediating bacterial attachment to salivary agglutinin glycoproteins and tooth enamel, thereby facilitating colonization and biofilm maturation [2]. Recent work has further emphasized that antigen I/II not only supports adhesion but also contributes to interspecies interactions in polymicrobial biofilms, highlighting its importance as a therapeutic target [3–5]

In parallel, the escalating problem of antibiotic resistance in oral and systemic pathogens has reinforced the urgent need for alternative antimicrobial strategies that are less prone to resistance development [6]. Antimicrobial peptides (AMPs) have emerged as promising candidates because of their broadspectrum activity, relatively low cytotoxicity toward mammalian cells, high target specificity, and multimodal mechanisms of action, including disruption of bacterial membranes, inhibition of protein-protein interactions, and interference with essential metabolic or celldivision processes [7]. Recent reviews and designfocused studies have demonstrated that rationally engineered AMPs can selectively target cariogenic species such as *S. mutans* while minimizing collateral damage to commensal oral flora, underscoring their potential in precision oral therapeutics [8]. Advances in computational biology and bioinformatics since 2020 have substantially accelerated the discovery and optimization of AMPs, allowing for insilico design that reduces both experimental cost and time. Tools such as ToxinPred and Peptide Ranker enable rapid prediction of peptide toxicity and bioavailability, respectively, while molecular docking platforms facilitate structurebased assessment of peptide-target interactions at atomic resolution [9]. For example, recent studies have employed dockingbased workflows to screen and prioritize AMPs against key virulence factors, including those involved in biofilm formation and adhesion, demonstrating that strong docking score and favourable interaction profiles often correlate with improved antimicrobial efficacy [10]. In the context of *S. mutans*, computational targeting of antigen I/II has been explored as a strategy to block adhesion and biofilm initiation, including with novel AMPs designed to interfere with receptor-ligand recognition.In the present study, a novel antimicrobial peptide designated WL10 was designed using peptidedesign and bioinformatics tools and evaluated computationally for its potential as a therapeutic agent against *S. mutans*. The peptide was analyzed for toxicity using ToxinPred and for bioavailability using Peptide Ranker, while its physicochemical properties were characterized using standard peptideproperty calculators. Subsequently, molecular docking analysis with HPEPDOCK was carried out to investigate the binding interaction between WL10 and the antigen I/II protein of *S. mutans*, with binding energy score or docking score and interaction stability assessed via docking scores. The overall aim of this work was to computationally evaluate whether WL10 can effectively target antigen I/II and thereby interfere with *S. mutans* adhesion and biofilm formation, building on recent trends in AMPbased anticariogenic strategies that increasingly rely on integrated bioinformatics and structureguided design.

2. Materials and Methods

2.1 Design and Evaluation of Antimicrobial Peptide : The antimicrobial peptide was evaluated using a previously established methodology [11]. A novel peptide was rationally designed to target the surface protein antigen I/II (AgI/II) of *Streptococcus mutans* (*S. mutans*), a critical virulence factor involved in bacterial adhesion and biofilm formation. The peptide sequence was generated using computational peptide design tools and subsequently visualized using the PepDraw server, which enables graphical representation and structural analysis based on amino acid composition and predicted physicochemical properties.

2.2 Prediction of Peptide Toxicity : Peptide toxicity was predicted using a previously described methodology [12]. The toxicity profile of the designed peptide was evaluated using the ToxinPred server, an in silico computational platform that assesses peptide toxicity based on amino acid composition, physicochemical properties, and machine learning–based classification. The tool categorizes input sequences as toxic or non-toxic, providing a preliminary evaluation of the peptide's safety for potential therapeutic applications.

2.3 Prediction of Peptide Bioavailability : The biological activity and bioavailability of the designed peptide were predicted using the Peptide Ranker tool. This server estimates the probability that a given peptide sequence will be biologically active, based on sequencederived features and empirical data from known active peptides. Higher scores indicate greater likelihood of functional activity in biological systems [13].

2.4 Physicochemical Property Analysis : The physicochemical properties of the peptide, including molecular weight, net charge, hydrophobicity, and isoelectric point (pI), were analyzed using peptide property calculation tools. These parameters are important for predicting peptide stability, solubility, and potential for interaction with microbial membranes and proteins, and are commonly used to screen candidates during AMP development.

2.5 Helical Wheel Plot Analysis : The amphipathic nature and secondary structural orientation of the peptide were analyzed using a helical wheel plot tool [14]. This visualization helps assess the spatial distribution of hydrophobic and hydrophilic residues along the theoretical αhelix, which is a key feature of many antimicrobial peptides that interact with bacterial membranes and surface proteins.

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2.6 Molecular Docking Analysis: Molecular docking was performed to analyze the interaction between the designed peptide and the antigen I/II protein of *S. mutans* [15]. The threedimensional structure of antigen I/II was retrieved from the Protein Data Bank (PDB) and prepared for docking. Protein–peptide docking was carried out using the HPEPDOCK server, which predicts binding modes and interaction energies between the peptide and the target protein. The results were evaluated based on binding energy scores and residuelevel interaction patterns, including hydrogen bonds, hydrophobic contacts, and electrostatic interactions.

2.7 Protein–Protein Interaction Network Analysis: Protein-protein interaction (PPI) network analysis of antigen I/II was performed using the STRING database to explore its functional relationships with other proteins [16]. The antigen I/II sequence (spaA) was used as the query, and the interaction network was constructed by integrating experimentally validated interactions, coexpression data, and computationally predicted associations. This approach helps to visualize the protein's biological context and identify interaction partners involved in adhesion, biofilm formation, and related virulence pathways.

3. Results

3.1 Peptide Toxicity: Prediction Toxicity prediction using the ToxinPred server indicated that the WL10 peptide was nontoxic, suggesting that it may be safe for biological applications and potential therapeutic use (**Figure 1**).

3.2 Peptide Bioavailability : Prediction Bioavailability prediction using the Peptide Ranker tool showed that the WL10 peptide had a score of 0.87, indicating a high probability of biological activity and suggesting that the molecule possesses strong antimicrobial potential (**Figure 1**).

3.3 Physicochemical Properties of WL10: Peptide Physicochemical property analysis (**Figure 2**) revealed that the WL10 peptide has a molecular weight, net charge, hydrophobicity, and isoelectric point within ranges typical of antimicrobial peptides. The peptide exhibits an amphipathic profile and a charge suitable for interaction with bacterial membranes and surface proteins, supporting its potential as an active AMP. The WL10 peptide consisted of 10 amino acid residues with a molecular weight of 1124.3 g/mol, isoelectric point (pH) of 8.93, extinction coefficient of 5690 $M^{-1}cm^{-1}$, and net charge of +1.9 at pH 7. The peptide showed good water solubility and amphipathic properties.

3.4 Helical Wheel Plot Analysis : Helical wheel plot analysis (**Figure 3**) showed that the WL10 suggested an amphipathic α-helical arrangement of residues. This structural arrangement is characteristic of many membraneactive antimicrobial peptides and is likely to facilitate interaction with *S. mutans* membranes and antigen I/II.

3.5 Molecular Docking Analysis: The docking score obtained from HPEPDOCK was −179 kcal/mol, indicating strong predicted binding interaction. The highly negative binding score indicates a stable peptide-protein complex, and the interaction profile suggests that WL10 may occupy or interfere with functional regions of antigen I/II involved in adhesion, thereby potentially inhibiting bacterial attachment and biofilm formation (**Figure 4**).

3.6 Protein-Protein Interaction Network Analysis : Interaction analysis of the antigen I/II protein using the STRING database (**Figure 5**) showed that it interacts with several key partners, including sspB, scpA, rheb, polA, and topA, along with other associated proteins. These interactors are involved in bacterial adhesion, virulence, DNA replication, and general cellular processes, underscoring the central role of antigen I/II in coordinating *S. mutans* pathogenicity and biofilmrelated activities.

4. Discussion

Streptococcus mutans (*S. mutans*) is a primary etiological agent of dental caries due to its strong adherence to tooth surfaces and its ability to form protective biofilms [17,18]. The present study focused on the design and evaluation of a novel antimicrobial peptide, WL10, targeting the surface protein antigen I/II (AgI/II) of *S. mutans*, a key adhesin involved in bacterial attachment and biofilm formation. Preventing adhesion through surfaceproteintargeted agents is increasingly recognized as a selective anticariogenic strategy, as it aims to block colonization without broadly disrupting the entire oral microbiome. Computational toxicity prediction indicated that WL10 is non-toxic, aligning with the growing emphasis on AMPs that combine potent antimicrobial efficacy with minimal host cytotoxicity. Similar observations have been reported in recent studies [19,20], where rationally designed AMPs demonstrated low toxicity profiles while effectively inhibiting *S. mutans* growth and biofilm formation. The Peptide Ranker score of 0.87 further supports its potential biological activity, which is comparable to previously reported high-ranking AMPs exhibiting significant anti-biofilm activity [21].Helical wheel analysis confirmed the amphipathic nature of WL10, a structural hallmark of many effective AMPs. This feature facilitates selective interaction with bacterial membranes and surface-associated virulence factors. Consistent with earlier reports, including recent findings published in the European Journal of Medicinal Chemistry 2026 WL10-related AMP study [22], amphipathic peptides with balanced hydrophobicity and charge exhibit enhanced binding to adhesion-related proteins and improved disruption of biofilm architecture. Compared to these studies, WL10 demonstrates comparable structural and functional attributes, suggesting its potential as a promising anti-*S. mutans* therapeutic candidate. Furthermore, molecular docking analysis demonstrated strong docking score between WL10 and antigen I/II, suggesting that WL10 may interfere with AgI/IImediated attachment to salivary receptors and tooth surfaces. This is consistent with other recent studies showing that AMPs and peptidebased agents targeting AgI/II or related adhesins can reduce *S. mutans* adhesion, biofilm accumulation, and associated virulence factors such as EPS production and acidogenicity. In particular, analyses of temporinderived peptides and other short AMPs have shown that downregulation of adhesion and biofilmrelated genes can suppress rapid biofilm formation and *invivo* caries development, reinforcing the therapeutic value of targeting adhesionassociated proteins [23,24]. Collectively, the computational findings suggest that WL10 possesses key attributes of promising anti-*S. mutans* peptides, including target selectivity, minimal toxicity, and the ability to interfere with bacterial adhesion and biofilm formation.

5. Conclusion

In conclusion, WL10 demonstrates key attributes of an effective antimicrobial peptide, including low toxicity, favourable bioactivity, and strong binding affinity toward a critical adhesion protein of *S. mutans*. Its potential to interfere with early colonization and biofilm formation highlights its promise as a next-generation therapeutic agent. However, further validation through *in-vitro* and *in-vivo* studies is required to confirm its efficacy and clinical applicability.

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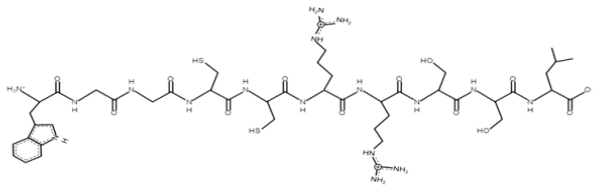
Figures



Peptide Toxicity (ToxinPred)	Non-toxic
Peptide Bioavailability (Peptide ranker)	0.87

Figure 1. Chemical structure of the designed WL10 antimicrobial peptide generated using PepDraw. The peptide was evaluated for toxicity and bioavailability using computational prediction tools. ToxinPred analysis predicted the peptide as non-toxic, and Peptide Ranker showed a bioavailability score of 0.87, indicating high biological activity and potential antimicrobial function.

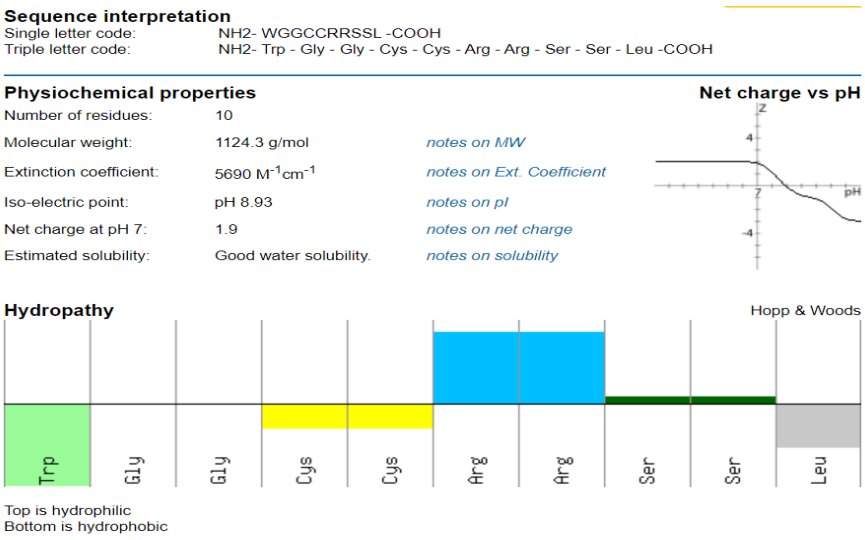


Figure 2. Sequence interpretation, physicochemical properties, net charge vs pH profile, and hydropathy plot of the WL10 antimicrobial peptide. The peptide shows a positive net charge, good water solubility, and amphipathic nature, which are characteristic features of antimicrobial peptides.

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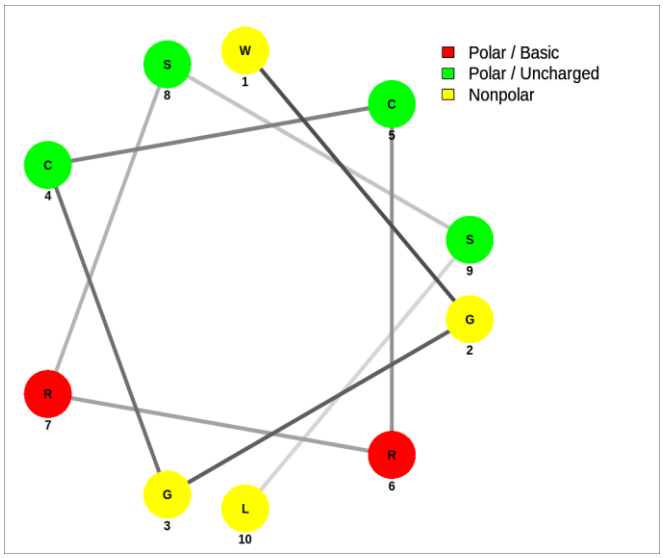

Figure 3. Helical wheel projection representing the secondary structure orientation of the WL10 antimicrobial peptide. The distribution of polar/basic, polar uncharged, and nonpolar residues indicates amphipathic characteristics, which are important for antimicrobial activity and protein interaction.

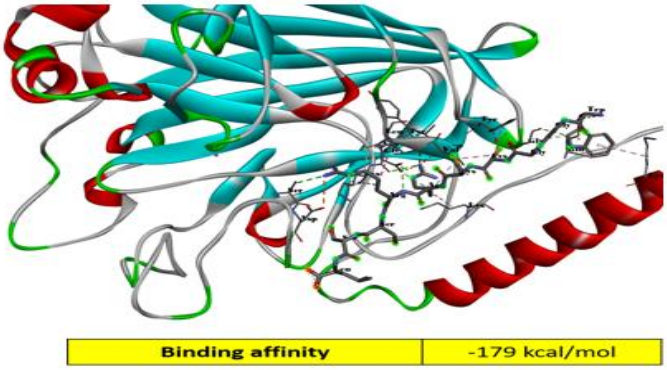

Figure 4. Three-dimensional molecular docking interaction of the WL10 antimicrobial peptide with the surface protein antigen I/II of *S. mutans*. The peptide interacts with active site residues through hydrogen bonding and hydrophobic interactions. The binding affinity of −179 kcal/mol indicates strong and stable interaction between the peptide and the target protein.

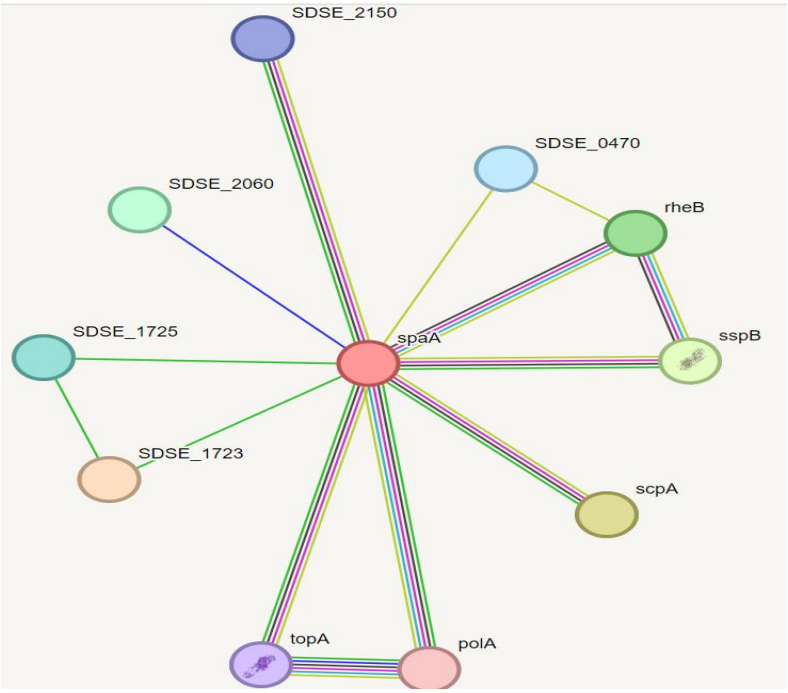

Figure 5. Protein–protein interaction (PPI) network of the surface protein antigen I/II (spaA) of *Streptococcus mutans* constructed using the STRING database. The network illustrates functional associations between spaA and interacting proteins such as sspB, scpA, polA, topA, and other proteins involved in adhesion, virulence, and cellular processes.