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Effect of the Antimicrobial Peptide GL13K on Dental Implant Surfaces: A Review

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Abstract

The GL13K peptide is beneficial for dental implants, improving biocompatibility and modulating osteoclast activity. This article focuses on GL13K-peptide-modified titanium surfaces, analyzing their influence on dental implants. The success of a dental implant is dependent on osseointegration, which is a combined function of osteoblasts and osteoclasts. While most studies focus on osteogenic differentiation, the activity of osteoclasts is rarely studied. The GL13K peptide, which is antimicrobial, can be covalently grafted onto titanium surfaces by a silanization method, which is advantageous because it forms biocompatible surfaces that also partially suppress osteoclastogenesis. Research has shown that titanium surfaces modified with GL13K peptides (GL13K-Ti) exhibit reduced expression of osteoclastogenic genes and proteins and inhibited actin ring formation. Further studies have demonstrated that GL13K-Ti alters osteoclast secretion of pro-inflammatory cytokines, causing osteoclasts to be less active by an epigenetic mechanism, namely, changing the methylation of histone H3K27 on the NFATc1 promoter region during RANKL-driven osteoclast formation. These results imply that the modification of dental implant surfaces with the GL13K peptide may have two applications, namely, improving biocompatibility and regulating osteoclast activity through epigenetic mechanisms. This method offers a novel way to enhance dental implant outcomes, especially in difficult clinical situations. The coating process should be optimized, long-term stability and efficacy should be examined, and possible synergistic effects with other surface modifications or bioactive molecules should be investigated in future studies.

Categories: Advanced Materials, Biotechnology and Engineering, Materials Engineering
Keywords: antimicrobial peptide, gl13k, dental implant surfaces, osseointegration, biofilm, peri-implantitis

Introduction And Background

Dental implants have become a cornerstone of restorative dentistry, offering patients a functional and reliable tooth replacement for missing teeth. With high success rates, however, the lifespan of implants is greatly jeopardized by peri-implant diseases, especially peri-implantitis. Peri-implantitis, caused by microbial biofilms and host-mediated inflammatory processes, leads to progressive peri-implant bone loss and ultimately results in implant failure [1]. Traditional management approaches, such as systemic or local antibiotics, mechanical debridement, and surface decontamination, tend to incompletely eliminate biofilms and fail to prevent disease relapse [2,3].

Among new trends, antimicrobial coatings for titanium implants have drawn significant attention. Conventional solutions, involving coatings with metallic ions such as silver or copper, exhibited antibacterial activity but also introduced cytotoxicity, unintended release, and long-term biocompatibility issues [4]. Concurrently, nanostructured bioinspired bactericidal surfaces have been explored, with encouraging results but restricted scalability to clinical translation [5,6]. Against this context, antimicrobial peptides (AMPs) have been highlighted as potential candidates for implant surface modification, with GL13K being highlighted for its human origin, stability, and selective antibacterial efficacy [7,8].

Although GL13K exhibits a substantial antimicrobial effect against peri-implant model microorganisms in monoculture and early biofilm models, its effectiveness may be reduced against mature, multispecies biofilms commonly found in oral infections. The complex interaction within biofilms and their protective polymeric matrices can indeed hamper peptide penetration and interaction. In fact, proteinaceous coatings could be vulnerable to degradation by cellular enzymes and protein adsorption in a biological setting. On the other hand, bioinspired nano-textured surfaces on titanium are known for their mechano-bactericidal properties, independent of bacterial species and their viability [5,6]. Current literature indicates that although AMPs like GL13K can provide cytocompatible and biologically inspired remedies, their long-term efficacy can be improved by cooperating nano-engineered surfaces and multifunctional coatings [9,10].

Among the multifunctional approaches, AMPs have gained significant attention. AMPs are short, positively charged bioactive molecules that bind to negatively charged bacterial membranes, leading to rapid disruption and cell death. Unlike traditional antibiotics, AMPs are less prone to resistance

development, making them particularly valuable in the era of rising antimicrobial resistance [11,12]. Apart from their antimicrobial activity, numerous AMPs have immunomodulatory and wound-healing activities, thus presenting highly diverse biomolecules for dental use [13,14]. Their use in the prevention of caries, the treatment of periodontal disease, and enhanced outcomes from implantology, where infection control and biocompatibility are equally vital, has been addressed in reviews [15,16].

GL13K, an AMP from the human parotid secretory protein, is a very promising candidate. Through substitution of certain amino acids with lysine, GL13K becomes more cationic, showing increased affinity toward bacterial membranes but sparsity for mammalian cells. Biophysical studies validate its selective capacity to rupture microbial membranes without damaging host tissues [8]. In vitro tests indicate that GL13K drastically inhibits biofilms of resistant microorganisms, such as *Pseudomonas aeruginosa*, and also exhibits activity against major oral pathogens such as *Streptococcus gordonii*, *Porphyromonas gingivalis*, and methicillin-resistant *Staphylococcus aureus* (MRSA) [17,18].

GL13K, as an implant coating, was immobilized onto titanium surfaces through silanization chemistry [7]. This modification resulted in stable antimicrobial activity with retained biocompatibility with host cells. Subsequently, glutaryl-urea-polymyxin-based peptide GL13K immobilized onto SLA-treated titanium showed great efficacy against MRSA, again confirming its clinical application [18]. These results validate that GL13K coatings can be strongly bonded to implant surfaces without sacrificing osteoblast compatibility, an essential condition for successful osseointegration. Further, GL13K coatings have been demonstrated to support immunomodulatory responses, such as macrophage polarization to a pro-healing phenotype, thus establishing an environment conducive to implant integration [4,19].

Recently, GL13K has been paired with nanostructured titanium surfaces for enhanced immobilization and sustained antimicrobial activity [5,6]. Novel self-assembly techniques have also been exploited to facilitate stimuli-responsive release of the peptide [20]. In addition, hybrid coatings combining GL13K with growth factors or other biomolecules are being developed as multifunctional solutions that not only inhibit infection but also support tissue regeneration and osseointegration [15,19].

This article aims to synthesize the clinical implications of GL13K for implant dentistry by analyzing its physicochemical properties, mechanisms of antibacterial action, ways of immobilization, and the resulting in vitro and in vivo studies. This review consolidates findings from in vitro antibacterial studies, surface characterization, and preclinical studies to articulate the effectiveness, longevity, and translational potential of GL13K-modified implants. In addition, other bio-inspired antimicrobial and GL13K modification strategies, such as nanotopographical modifications and polymeric coatings, were included to provide context regarding GL13K's position in the overarching framework of antibacterial implant innovations [5,6,9].

Problem statement of this review

Dental implants are widely used for functional and esthetic rehabilitation, but peri-implantitis caused by bacterial colonization and biofilm formation continues to threaten their long-term success. Current antimicrobial strategies, such as antibiotic or metallic coatings, offer only transient protection and are associated with limitations including cytotoxicity, resistance development, and insufficient durability. AMPs, particularly GL13K, have gained attention as a promising alternative due to their broad-spectrum activity, favorable biocompatibility, and potential for stable integration into implant surfaces. Experimental studies indicate that GL13K coatings can inhibit bacterial adhesion, reduce biofilm formation, and support osseointegration, suggesting clinical utility in preventing implant-related infections.

Despite these advantages, several challenges hinder translation into routine practice. These include peptide instability in the oral environment, optimization of release kinetics, manufacturing costs, and regulatory complexity associated with drug-device combination products. Furthermore, the lack of large-scale clinical trials limits knowledge of long-term performance. Addressing these gaps requires a critical evaluation of existing research to determine the true potential of GL13K in enhancing implant longevity and reducing peri-implant complications.

Review

Materials and methods

This narrative review evaluated the effect of the AMP GL13K on dental implant surfaces through a structured but non-systematic literature search of PubMed, Scopus, Google scholar, and Web of Science (2013-2025) using the keywords "antimicrobial peptide", AND "GL13k", AND "dental implant surfaces", AND "osseointegration", AND "biofilm", AND "peri-implantitis". The inclusion criteria comprised peer-reviewed studies assessing GL13K coatings or modifications on titanium or implant surfaces with antibacterial, osseointegration, osteoimmunomodulatory, or cytocompatibility outcomes in vitro, in vivo, or in translational models. In contrast, non-English papers, conference abstracts, and unrelated studies

were excluded. Data extraction and thematic synthesis were performed to assess the translational potential of GL13K in implantology, and a total of 54 studies met the inclusion criteria (Figure *1*).

FIGURE 1: Study selection process for narrative review effect of the antimicrobial peptide GL13K on dental implant surfaces

Applications of GL13K in dental implant surfaces

The utilization of the AMP GL13K in dental implantology has been explored through various strategies, including chemical immobilization, nanostructured coatings, hydrogel-mediated release, nanoparticle incorporation, immunomodulatory modulation, and hybrid systems (Figure *2*).

FIGURE 2: Applications of GL13K on dental implant surfaces

Holmberg et al. initially demonstrated the covalent immobilization of GL13K on titanium using silanization chemistry [7]. This strategy yielded steady attachment under physiological states and maintained antimicrobial efficacy as well as osteoblast compatibility, suggesting its dual use in the prevention of infection and osseointegration. Based on this, Chen et al. established that GL13K-modified titanium exhibited high bactericidal effectiveness against *Streptococcus gordonii*, destroying cell walls and preventing biofilm formation, thereby treating peri-implantitis-related biofilms [4].

Expansion beyond titanium has also been successful. Hu et al. functionalized polyetheretherketone (PEEK) with GL13K through carbodiimide chemistry, which improved hydrophilicity and peptide binding [21]. Such modified surfaces exhibited long-term antibacterial functionality with good cytocompatibility, making them promising for dental and orthopedic implants. Likewise, Mutreja et al. demonstrated chemoselective modification of GL13K onto titanium, which avoided loss of the peptide and improved stability, bolstering the dependability of site-specific conjugation methods [22].

Nanostructuring has also offered extra advantages by allowing controlled release. Li et al. used titanium dioxide nanotubes (TiO_2-NTs) as high-surface-area substrates for the deposition of GL13K [23]. The nanotubes allowed the long-term release of the peptide and promoted osteoblast growth. Zhou et al. built on this by developing a thermosensitive hydrogel coating that promoted sustained release of the peptide for 2 weeks, with maximum antimicrobial efficacy in the first week against *Porphyromonas gingivalis*, while concurrently minimizing inflammatory reactions [24]. Similarly, Kazemzadeh-Narbat et al. used polyelectrolyte multilayers for controlled kinetics release of GL13K, without causing burst release and maintaining antimicrobial effects, thus improving the usability of GL13K coatings [25].

Hybrid and multifunctional nanoplatforms incorporate anti-infection properties along with other biological functions, such as immunomodulation and bone regeneration, aiming at improving implant performance. In that context, Zhang et al. prepared GL13K-grafted zinc oxide nanoparticles for developing hybrid coatings with the capacity to combine membrane-disruptive peptide activity together with reactive oxygen species (ROS)-mediated oxidative stress, thus exerting broad-spectrum antimicrobial efficiency in high-risk implant environments [26]. Functionalization of the titanium surface with GL13K was also shown by Gao et al. to epigenetically modulate the differentiation of osteoclasts through changes in the expression of H3K27me3, thus testifying that the role of GL13K does not only encompass antibacterial protection but extends toward osteoimmune modulation and bone-healing processes [27]. These indications confirm that GL13K-based coatings could be considered multifunctional nanoplatforms capable of tackling infection control and stability of the peri-implant bone.

Immunomodulatory activities have been investigated directly in macrophage models. Chen et al. indicated that GL13K-modified titanium surfaces biased macrophages toward an M2 phenotype, correlated with tissue repair and decreased secretion of pro-inflammatory cytokines [28]. Such dual functionality - antibacterial activity in conjunction with immune-regulation - makes GL13K a multifunctional biomolecule that can facilitate peri-implant tissue healing.

Mechanistic understanding from computational and structural studies has supplemented experimental data. Hamidabad et al. demonstrated in molecular dynamics simulations that GL13K has a propensity to form β-sheet structures, which accounts for its stability upon immobilization [29]. Also, Youssef and DeWolf have demonstrated interfacial self-assembly of GL13K into crystalline β-sheets responsible for surface stability and extended antimicrobial activity [30]. Such mechanistic insight gives rational design

guidelines for maximizing peptide coatings.

Hybrid biomaterials combining GL13K illustrate their agility as well. Qi et al. combined GL13K with tetrahedral framework nucleic acid-hyaluronic acid hydrogels to create antimicrobial and anti-inflammatory materials, effective in wound healing and perhaps transferable to implantology [31]. Eberliköse et al. created nanofiber coatings on xenografts containing GL13K, exhibiting concurrent antimicrobial protection and bone regeneration, illustrating the trend toward multimodal biomaterials that combine antibacterial, regenerative, and immunomodulatory activities [32].

Although these encouraging developments are ongoing, translational barriers still exist. Extensive exposure to peptides has the potential to select against *Staphylococcus aureus* small-colony variants, which highlights potential resistance development risks [33]. Bechinger and Gorr also documented bacterial adaptation processes to AMPs, emphasizing careful clinical validation [34]. More comprehensive reviews on AMP use highlight other challenges, like the high cost of synthesis, enzymatic degradation in oral environments, and regulatory complexities. These complications require deeper refinement of delivery systems, peptide stabilization methodologies, and extensive preclinical and clinical studies on a large scale [35-37].

In the 21st century, dental implants are not only made of pure titanium but also from titanium alloys like Ti6Al4V, ceramics, polymers, aluminum, and titanium and zirconium oxides. Zirconia and titanium-zirconium alloys have come into prominence in recent times as novel substitutes. Though the effect of GL13K has been studied on titanium, its alloys, and on polymeric materials like PEEK, more research is required to assess its possible effects on other implant surface materials [21,28].

Collectively, GL13K displays robust antibacterial activity, superior cytocompatibility, and new emerging immunomodulatory functions vital for implant survival. Computational and structural insight further corroborates experimental data and offers design templates for future use. Although obstacles in terms of resistance, cost, and approval for regulatory use still exist, the multifaceted strategies made for GL13K application create a firm groundwork for furthering its clinical value in dental implantation (Table *1*).

Application	Substrate/Material	Key Findings	Significance	Refs.
Covalent immobilization via silanization	Titanium	Stable GL13K attachment (no detachment after 7 days), retained antibacterial and osteoblast-compatible properties	Dual action - prevention of infection and enhancement of osseointegration	[7]
GL13K-modified titanium surface	Titanium	High bactericidal efficiency against *S. gordonii*, disrupting biofilm formation	Effective for peri-implantitis prevention	[4]
Carbodiimide-mediated grafting	PEEK (polyetheretherketone)	Improved surface hydrophilicity, strong peptide adhesion, and long-term antibacterial activity	Extends GL13K use to non-metallic implant materials	[21]
Chemoselective maleimide-thiol conjugation	Titanium	>90% peptide retention, improved coating stability and durability	Reliable site-specific conjugation for dental implants	[22]
GL13K loading in TiO_2 nanotubes	Nanostructured titanium	Controlled release up to 5 days, enhanced osteoblast proliferation, and ALP activity	Nanostructuring enhances loading and osteogenesis	[23]
Thermosensitive PLGA/PEG hydrogel coating	Titanium	Sustained release for 14 days, >90% bacterial inhibition in the first week, reduced inflammation	Dual antibacterial and anti-inflammatory function	[24]
Polyelectrolyte multilayer (PEM) system	Titanium	Controlled release without burst, antibacterial protection for 7 days	Enables precise peptide delivery kinetics	[25]
ZnO nanoparticle–GL13K conjugation	Titanium	Combined oxidative and peptide antibacterial mechanisms	Broad-spectrum efficacy and improved surface stability	[26]
Epigenetic modulation by GL13K	Titanium	Controlled osteoclast differentiation via H3K27me3 modification	Demonstrated osteoimmunomodulatory potential	[27]
Silanization with the macrophage model	Titanium	Induced M2 macrophage polarization, reduced IL-6 and TNF-α	Anti-inflammatory and immunoregulatory effects	[28]
Molecular dynamics simulation	Computational model	GL13K forms β-sheet aggregates conferring surface stability	Structural insight into peptide conformation	[29]
Self-assembly studies	GL13K β-sheet model	Peptide forms crystalline β-sheets, enhancing long-term activity	Provides a mechanistic understanding of coating stability	[30]
TFNA–HA hybrid hydrogel	Hydrogel scaffold	Antibacterial, anti-inflammatory, and wound-healing properties	Translational potential for peri-implant soft tissue repair	[31]
GL13K nanofiber xenograft coatings	Xenograft bone scaffold	Enhanced bone regeneration with concurrent antimicrobial activity	Multifunctional biomaterial for regenerative applications	[32]

TABLE 1: Applications of GL13K on dental implant surfaces

Streptococcus gordonii (*S. gordonii*). Titanium dioxide (TiO_2). Alkaline Phosphatase (ALP). Polylactic acid-co-glycolic acid (PLGA). Polyethylene glycol (PEG). Zinc oxide (ZnO). Histone H3 Lysine 27 Trimethylation (H3K27me3). Activated macrophage (M2). Interleukin-6 (IL-6). Tumor Necrosis Factor-alpha (TNF-α). Tetrahedral Framework Nucleic Acids (TFNA). Hyaluronic Acid (HA).

Challenges and solutions in the application of GL13K on dental implant surface

While GL13K has great potential as a multifunctional AMP for dental implant modification, there are a number of obstacles preventing its clinical translation. A major challenge lies in peptide stability, as GL13K is inherently vulnerable to proteolytic degradation by salivary and bacterial enzymes, which can shorten its antimicrobial lifespan in the peri-implant environment. To overcome this, Mahlapuu et al. proposed strategies such as amino acid substitutions, cyclization, and PEGylation to enhance protease resistance [38]. Similarly, Mutreja et al. showed that encapsulation in biocompatible nanocarriers such as chitosan or polylactic acid-co-glycolic acid (PLGA) nanoparticles can shield GL13K until delivery, while covalent immobilization on titanium surfaces via chemoselective linkages improves durability [22]. Another limitation is the amount of peptide released, as excessive peptide release risks cytotoxicity,

whereas insufficient release fails to prevent biofilm formation. Zhou et al. demonstrated that thermosensitive hydrogels could sustain GL13K release for 2 weeks, with peak activity during the first week, while Kazemzadeh-Narbat et al. showed that layer-by-layer assemblies enable pH-responsive controlled delivery [24,25].

Even with good cytocompatibility, GL13K may exert toxic effects on gingival fibroblasts and osteoblasts at high concentrations [39]. Zhou et al. proposed several methods to mitigate issues, including refining dosage levels, utilizing nanoscale surface patterns, and integrating GL13K with bone-growth stimulating agents like bone morphogenetic protein-2 (BMP-2) [40]. From a manufacturing standpoint, large-scale synthesis remains expensive due to the need for sequence modifications. Mahlapuu et al. suggested recombinant production and improved solid-phase synthesis methods as emerging solutions [38]. Finally, concerns remain about bacterial resistance and economic feasibility. Souza et al. suggested combining therapies with metallic ions or photodynamic agents and tiered patient applications may mitigate resistance and improve cost-effectiveness [41]. Ultimately, integrating stability enhancements, controlled release systems, scalable synthesis, and regulatory alignment will be crucial for the clinical adoption of GL13K-modified implants.

Advantages and disadvantages of GL13K-coated dental implants

The incorporation of the AMP GL13K onto dental implant surfaces has emerged as a promising strategy to combat peri-implantitis and promote long-term implant success. One of the most notable strengths of GL13K is its broad-spectrum antimicrobial activity, which targets both Gram-positive and Gram-negative bacteria that are typically found in oral infections [39,42]. Chen et al. reported that, unlike traditional antibiotics, whose mechanism of action usually targets specific metabolic pathways, GL13K acts by interfering with bacterial membranes, thus avoiding mechanisms that predispose bacteria to resistance [43]. This novel mechanism of membrane disruption is especially beneficial in today's clinical environment, in which antibiotic resistance is an alarming worldwide health risk [44,45]. The lower chance of resistance occurrence makes GL13K a sustainable, dependable antimicrobial for application to implants. In addition, GL13K is highly stable, maintaining its activity in the oral environment despite enzymatic degradation and pH fluctuations [7,8]. This stability is necessary to guarantee the long-term performance of the coating because the oral environment presents many biochemical challenges that often undermine the function of other antimicrobial agents.

Besides its capacity to combat microbes, GL13K is also highly biocompatible, a factor required for the long-term viability of dental implants. Experiments affirm that GL13K facilitates osseointegration and fails to compromise the viability or activity of osteoblasts, the bone cells responsible for bone growth and the integration of the implant into the host tissue [21,23,27]. Due to its good biological profile, GL13K is both an infection-preventing coating and a bone-healing-compatible coating. Notably, GL13K is covalently immobilized onto titanium surfaces, providing stability and protection from environmental wear, including mechanical loading and standard cleaning [22,46]. Such immobilization, in turn, prevents premature bacterial adhesion and subsequent biofilm development, greatly reducing the risk of peri-implantitis, which continues to be one of the major causes of implant failure globally [47-49].

In addition, GL13K is compatible with diverse surface modification methods, including silanization, maleimide-thiol conjugation, and hydrogel-based systems, thereby providing flexibility in design while enhancing antibacterial and immunomodulatory properties [28,50]. Collectively, these properties promote an optimal environment for bone integration while preventing microbial colonization, a dual benefit that has been highlighted across different implant surface studies [50-53].

Despite these clear advantages, several challenges remain before GL13K-coated implants can achieve routine clinical adoption. The foremost limitation is the high production cost of peptide synthesis, which restricts large-scale application, though future advances in recombinant peptide expression may help lower costs [28]. Another limitation is the lack of long-term in vivo evidence from large-scale clinical trials; most findings to date stem from in vitro studies or animal models, creating uncertainty regarding the peptide’s long-term efficacy and systemic safety [25,42]. While GL13K is generally biocompatible, the risk of immunogenicity from repeated or chronic exposure cannot be entirely excluded, emphasizing the need for extended longitudinal studies [3,54]. Concerns also remain about durability over decades of use, as the oral cavity’s proteases and acidic conditions may partially deactivate the peptide and reduce its antimicrobial efficacy in high-risk cases [24,40]. Moreover, while resistance is less likely than with conventional antibiotics, the theoretical risk of bacterial adaptation to sub-lethal doses of GL13K remains a concern requiring ongoing surveillance [41]. In addition to these scientific challenges, regulatory and commercial barriers must also be overcome; as a drug-device hybrid, GL13K-coated implants face complex approval processes and a lack of standardized evaluation protocols, which may delay clinical translation [9,21].

In summary, GL13K-coated dental implants hold significant potential due to their unique antimicrobial mechanism, biocompatibility, durability, and compatibility with surface engineering techniques. Nevertheless, challenges such as production costs, missing clinical data, immunogenicity disadvantages,

and regulatory hurdles need to be addressed to maximize their clinical potential (Table 2).

Advantages	Disadvantages
1. Broad-spectrum antimicrobial activity	1. High cost of production
2. Mechanism of action - interfering with bacterial membranes to avoid resistance	2. Lack of long-term in vivo evidence from large-scale clinical trials
3. Stable in the oral environment	3. Risk of immunogenicity from repeated exposure
4. Biocompatible	4. Durability over decades of use
5. Facilitates osseointegration	5. Risk of bacterial adaptation to sub-lethal doses
6. Bone-healing-compatible coating	6. Regulatory and commercial barriers yet to overcome
7. Compatible with diverse surface modification methods	7. Complex approval processes and a lack of standardized evaluation protocols

TABLE 2: Advantages and disadvantages of GL13K on dental implant surfaces

Quantifiable analysis of GL13K

Antibacterial and Antibiofilm Efficacy of GL13K Against Oral Pathogens

GL13K showed robust and stable antibacterial and antibiofilm activity in various studies. On titanium, it caused a >90% reduction of biofilm biomass from *Streptococcus gordonii* and inhibited 75-80% of persistent *Pseudomonas aeruginosa* biofilms [17,39]. Against drug-resistant strains like MRSA, immobilized GL13K on SLA titanium had an Minimum Inhibitory Concentration (MIC) of 32 µg/mL, 85% reduction of Colony-Forming Unit (CFU) after 48 h, and a 70% biofilm inhibition [18]. Sustained-release systems were further improved, with hydrogels retaining >90% inhibition for 7 days and lasting for 14 days, while also inhibiting inflammatory cytokines [24]. Likewise, TiO_2 nanotube-GL13K composites prevented >80% biofilm formation with >2-log CFU reduction [23], and multilayered coatings released peptides for more than 5 days, decreasing *S. aureus* biofilms by ~2-3 log units [25]. Further, GL13K-silanized titanium decreased CFUs by ~80% and inhibited pro-inflammatory markers in macrophage models [28]. Overall, MIC values are generally 16-32 µg/mL, corresponding to 2-3 log reductions in CFU (~99.9% kill) and biofilm inhibition between 70% and 90%, demonstrating its strong activity against sensitive and resistant oral pathogens with extended protection during the critical healing period (Table 3).

Pathogens	Model	Key Quantitative Findings	Interpretation	Refs.
Streptococcus gordonii	GL13K-coated titanium in vitro	• >90% reduction in biofilm biomass after 24h • CFU reduction of ~3-log compared to uncoated titanium	GL13K coatings are highly bactericidal and prevent early biofilm establishment	[39]
Pseudomonas aeruginosa	Biofilm assay	• 75–80% reduction in established biofilm mass • Significant CFU decline vs. control ($p < 0.01$)	Demonstrates efficacy against resilient biofilms	[17]
MRSA (Methicillin-resistant *Staphylococcus aureus*)	GL13K immobilized on SLA titanium	• MIC against MRSA ~32 µg/mL • ~85% CFU reduction after 48 h on coated implants • 70% inhibition of biofilm formation	Effective against multidrug-resistant bacteria	[18]
Mixed oral pathogens (*S. aureus, E. coli*)	GL13K-loaded hydrogel on titanium	• Sustained antibacterial effect over 14 days • >90% bacterial inhibition in first week • Reduced inflammatory cytokines	Long-term release and dual antibacterial with anti-inflammatory effects	[24]
Escherichia coli, S. aureus	TiO_2 nanotube + GL13K	• >80% biofilm inhibition • Significant CFU reduction (>2-log) compared with bare titanium	Synergistic effect of nanotopography and peptide	[23]
Staphylococcus aureus	GL13K multilayered release coating	• Peptide release maintained >5 days • ~2–3 log CFU reduction in early biofilms	Sustained-release prevents peri-implant colonization	[25]
Staphylococcus aureus	GL13K-silanized titanium with macrophage model	• Significant CFU reduction (~80%) on peptide-coated surfaces • Also reduced pro-inflammatory markers	Dual antibacterial and immunomodulatory effect	[28]

TABLE 3: Antibacterial and antibiofilm efficacy of GL13K against oral pathogens

Escherichia coli (E. coli). *Staphylococcus aureus (S. aureus)*. Sandblasted, Large-grit, Acid-etched (SLA). Colony-Forming Unit (CFU). Minimum Inhibitory Concentration (MIC). Titanium dioxide (TiO_2).

Aspects of GL13K immobilization techniques on dental implant surfaces

GL13K has been immobilized on implant surfaces by various methods, each with varying quantitative results. Silanization methods produced stable surface loads of 1-2 µg/cm², which expressed a durable antibacterial effect within 3-7 days [7,28,39]. Nanostructured carriers promoted loading, with TiO_2 nanotubes loading 10-15 µg/cm² and releasing peptides steadily for 5 days, and ZnO-GL13K nanoparticle conjugates loading 15 wt% peptide and releasing completely within 5 days [23,26]. Polyelectrolyte multilayers enabled controlled kinetics, sustaining release for up to 7 days without burst effects [25]. More advanced conjugation methods improved stability even further, with maleimide-thiol chemoselective coupling providing 2.5-3.0 µg/cm² and >90% retention resistant to degradation for 14 days [22]. Hydrogel carriers were found to carry the highest payloads, with PLGA/PEG hydrogels delivering 20 µg/cm² and maintaining release for 14 days, and hybrid Tetrahedral Framework Nucleic Acid-Hyaluronic Acid (TFNA-HA) systems exhibiting 80% encapsulation efficiency with biphasic release over 10 days [24,31]. GL13K immobilization on PEEK reached 2.1 µg/cm² with 75% loading efficiency and 5-day stability [21]. Together, silanization and conjugation approaches provide stable but lower densities, whereas nanostructures and hydrogels improve peptide loading and sustained release throughout the crucial peri-implant healing period (Table *4*).

Immobilization Method	Surface/Carrier	Reported Quantitative Findings	Outcomes	Refs.
Silanization + covalent immobilization	Titanium	• Stable immobilization with ~1.2–1.8 μg/cm² peptide density • No detectable detachment after 7 days under physiological conditions	First demonstration of durable immobilization	[7]
Silanization	Titanium discs	• Effective antibacterial action with peptide loading of ~1.5 μg/cm² • Retained activity against *S. gordonii* biofilms for >72h	Showed both bactericidal and anti-biofilm efficacy	[39]
TiO_2 nanotube adsorption	Nanostructured titanium	• Loading: ~10–15 μg/cm² GL13K within nanotubes • Controlled release profile up to 120 h (5 days) with gradual decline	Nanotubes enhanced the loading capacity	[23]
Polyelectrolyte multilayer (PEM)	Titanium	• Peptide incorporated in layer-by-layer films (up to 12 bilayers) • Release sustained for 5–7 days without burst release	Controlled multilayer kinetics	[25]
Silanization	Titanium	• Immobilized surface density ~1–2 μg/cm² • No significant peptide loss after repeated washing cycles	Dual antibacterial and immunomodulatory effect	[28]
Carbodiimide coupling	PEEK	• Loading efficiency ~75% of applied peptide • Surface density ~2.1 μg/cm² • Stable antibacterial activity for 5 days	Extended GL13K beyond titanium	[21]
Chemoselective conjugation (maleimide-thiol)	Titanium	• High-efficiency coupling with >90% peptide retention • Surface density ~2.5–3.0 μg/cm² • Resistant to hydrolytic degradation up to 14 days	Strongest stability among tested methods	[22]
Thermosensitive hydrogel (PLGA/PEG-based)	Titanium	• Peptide loading capacity: ~20 μg/cm² • Release: ~60% in first 7 days, sustained up to 14 days	Dual antibacterial and anti-inflammatory	[24]
Hybrid hydrogel (TFNA + HA)	Hydrogel scaffold	• Encapsulation efficiency: ~80% • Release profile: biphasic (burst in 24h, sustained up to 10 days)	Also promoted wound healing and regeneration	[31]
Nanoparticle conjugation (ZnO–GL13K)	ZnO NPs on titanium	• Loading: ~15 wt% GL13K per nanoparticle system • Release: 50% in 24 h, complete within 5 days	Dual oxidative and peptide antibacterial effects	[26]

TABLE 4: GL13K immobilization techniques on dental implant surfaces

Titanium dioxide (TiO_2). *Streptococcus gordonii (S. gordonii)*. Poly D, L-lactic-co-glycolic acid (PLGA). Polyglycolic acid (PGA). Tetrahedral Framework Nucleic Acids (TFNA). Hyaluronic Acid (HA). Zinc Oxide (ZnO). Zinc Oxide Nanoparticles (ZnO NPs).

Cytocompatibility of GL13K-modified implant surfaces

GL13K-modified implant surfaces consistently showed excellent cytocompatibility with numerous cell types. Silanization of titanium sustained >95% fibroblast viability without cytotoxicity and 90% keratinocyte viability equivalent to controls [7,39]. Nanostructured TiO_2 nanotubes stimulated osteogenic responses, with pre-osteoblast proliferation 120% greater and Alkaline Phosphatase (ALP) activity 1.4-fold higher than controls [23]. Covalent immobilization elicited dual effects: >90% viability of osteoblasts, lowered pro-inflammatory cytokines (Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) reduced by 30-40%), and macrophage polarization to M2 [28]. On PEEK surfaces, GL13K enhanced osteoblast proliferation (115% of control) and cell adhesion [21]. Chemoselective conjugation preserved >95% viability of fibroblasts for 14 days with no cytotoxicity [22]. Hydrogel systems also enhanced bioactivity, with osteoblast growth increased 130% and Interleukin-1 beta (IL-1β), TNF-α decreased by 40-45%; fibroblast/endothelial growth increased 120%, Vascular Endothelial Growth Factor (VEGF) secretion increased 50%, and ROS decreased 35%, advancing angiogenesis [24,31]. ZnO-GL13K nanoparticles exhibited >90% osteoblast viability, ALP activity increased 1.5-fold, and collagen secretion increased 40% [26]. Together, GL13K coatings are non-cytotoxic, promote osteogenic differentiation, inhibit inflammation, and expand compatibility between fibroblasts, keratinocytes, osteoblasts, macrophages, and endothelial cells (Table *5*).

Surface/Immobilization	Cell Type	Quantitative Findings	Outcomes	Refs.
Silanization on titanium	Human gingival fibroblasts	• >95% viability after 7 days; no cytotoxicity detected	Demonstrated safety of GL13K coating	[7]
Silanized titanium discs	Human oral keratinocytes	• ~90% cell viability, similar to unmodified controls	Retained fibroblast adhesion and morphology	[39]
TiO_2 nanotube loading	MC3T3-E1 pre-osteoblasts	• 120% proliferation rate at day 5 vs. control • Alkaline phosphatase (ALP) activity increases ~1.4-fold	Indicated osteogenic enhancement	[23]
Covalent immobilization on titanium	Macrophages and Osteoblasts	• Cell viability >90% (osteoblasts) • Polarization: M1 decreases ~35%, M2 increases ~40% • IL-6, TNF-α reduced by ~30–40%	Dual cytocompatibility with immunomodulation	[28]
Carbodiimide coupling on PEEK	Osteoblasts	• Proliferation ~115% of control at 72 h • Cell adhesion improved (spreading area increases ~25%)	Expanded GL13K to polymer substrates	[21]
Chemoselective conjugation (maleimide-thiol)	Human fibroblasts	• >95% viability after 14 days • No cytotoxic effect under ISO 10993	Long-term cytocompatibility stability	[22]
Hydrogel-based GL13K release	Pre-osteoblasts and macrophages	• Osteoblast proliferation increases ~130% at day 7 • Inflammatory cytokines reduced: IL-1β decreases ~45%, TNF-α decreases ~40%	Synergistic antibacterial with osteogenic	[24]
Hybrid GL13K hydrogel (TFNA + HA)	Fibroblasts and endothelial cells	• Fibroblast proliferation increases ~120% vs. control • VEGF secretion increases ~50% • Reduced ROS production by ~35%	Promoted angiogenesis and wound healing	[31]
ZnO–GL13K nanoparticles on titanium	Osteoblasts	• Viability >90% after 5 days • ALP activity increases 1.5-fold • Collagen secretion increases ~40%	Enhanced osteogenic differentiation	[26]

TABLE 5: Cytocompatibility of GL13K-modified implant surfaces.

Titanium dioxide (TiO_2). Embryonic mouse calvarial pre-osteoblast cell line (MC3T3-E1 pre-osteoblasts). Activated macrophages (M1, M2). Interleukin-6 (IL-6). Tumor Necrosis Factor-alpha (TNF-α). Polyetheretherketone (PEEK). Biological evaluation of medical devices series of standards (ISO 10993). Interleukin-1 beta (IL-1β). Tetrahedral Framework Nucleic Acid (TFNA). Hyaluronic Acid (HA). Vascular Endothelial Growth Factor (VEGF). Reactive Oxygen Species (ROS). Zinc Oxide (ZnO).

Critical analysis of this review

Evidence on GL13K-coated dental implants shows strong potential but remains mostly limited to in vitro and short-term animal studies. While these models establish proof of concept, they cannot fully replicate the complex, multifactorial oral environment, leaving uncertainty about long-term human outcomes. Variability in experimental approaches such as immobilization methods, peptide concentrations, and bacterial models-further restricts comparability and standardization.

A major strength of GL13K is its multifunctionality. Beyond antibacterial action, it demonstrates immunomodulatory, osteogenic, and angiogenic properties, suggesting utility in both infection prevention and tissue integration. However, most studies emphasize antimicrobial effects, with limited investigation into host immune modulation and long-term osseointegration under real-world clinical risk factors such as diabetes or smoking.

Key translational challenges include peptide instability in protease-rich oral environments, high production costs, and complex regulatory pathways for drug-device hybrids. While strategies like nanocarriers, hydrogels, and covalent immobilization improve stability and release control, they add manufacturing complexity. Large-scale, cost-effective production without compromising purity remains unresolved.

Safety concerns also persist. Although GL13K appears biocompatible at therapeutic doses, long-term effects on host tissues and immune sensitization require further study. Moreover, while AMPs are less prone to resistance than antibiotics, the possibility of bacterial adaptation under sub-therapeutic exposure cannot be dismissed.

GL13K offers an innovative, multifunctional solution for enhancing implant surfaces, supported by compelling preclinical evidence. Yet, critical barriers in stability, scalability, safety, and regulatory

approval must be addressed. Long-term clinical validation is essential to determine whether GL13K can transition from laboratory innovation to a viable strategy for reducing peri-implant infections and improving implant survival.

Future perspectives on GL13K in dental implantology

The destiny of GL13K-coated dental implants relies on an interdisciplinary approach that transitions the technology from experimental phases toward clinical use. A possible path is the creation of hybrid coatings, where GL13K is mixed with bioactive compounds like calcium phosphates or titanium nanotubes to offer both antimicrobial activity and improved osseointegration [50]. Another major innovation is in the form of stimulus-responsive release systems, whereby GL13K can be delivered selectively in response to infection, thus prolonging its functional lifetime and minimizing potential cytotoxic effects [24].

Synergistic methodologies are also being investigated, for example, combining GL13K with metallic nanoparticles, whereby the peptide concentration can be reduced while increasing antibacterial efficacy [25]. Likewise, the use of regenerative factors, such as BMPs, provides multifaceted benefits of infection control and rapid bone healing. Improved digital dentistry and 3D printing also facilitate patient-specific designs and optimized GL13K distribution [7]. Large-scale clinical trials and regulatory streamlining will ultimately become essential to make GL13K coatings a standard treatment for high-risk dental implant patients. The future of GL13K-coated dental implants depends on a multidisciplinary strategy that moves the technology from experimental stages to clinical application.

One promising direction is the development of hybrid coatings, where GL13K is combined with bioactive materials such as calcium phosphates or titanium nanotubes to provide both antimicrobial defense and improved osseointegration [50]. Another key innovation lies in stimuli-responsive release systems, which can deliver GL13K selectively in response to infection, thereby extending its functional lifespan and reducing potential cytotoxic effects [24]. Synergistic approaches are also under exploration, such as integrating GL13K with metallic nanoparticles, which can lower the required peptide concentration while enhancing antibacterial efficacy [25]. Similarly, the incorporation of regenerative factors, including BMPs, offers the dual advantage of infection control and accelerated bone healing. Advances in digital dentistry and 3D printing further enable patient-specific implant designs with optimized GL13K distribution [7]. Ultimately, large-scale clinical trials and regulatory streamlining will be critical for establishing GL13K coatings as a routine solution for high-risk dental implant patients.

Limitations

The major drawbacks of existing research on GL13K-coated dental implants are the limited number of studies and the heavy overrepresentation of in vitro data. Although these studies present promising antibacterial and biocompatibility outcomes, they are too often based on simplified models, including single-species bacterial cultures, that do not mimic the complex, multispecies oral environment and host immune responses of actual patients.

Conclusions

Based on the evidence reviewed, the AMP GL13K presents a promising, biomimetic solution for addressing peri-implant infections. Its broad-spectrum antibacterial activity and antibiofilm effects, coupled with its proven compatibility with osteoblast attachment, make it a strong candidate for the next generation of implant coatings. However, its widespread clinical adoption depends on overcoming significant challenges, including a limited number of long-term human clinical studies, variability in current research methodologies, high production costs, and regulatory hurdles. Future research must prioritize standardized testing, large-scale clinical trials, cost-reduction strategies, and integration into patient-specific treatment plans. By addressing these scientific and translational gaps, GL13K has the potential to become a new benchmark in dental implantology, ensuring enhanced infection resistance and long-term implant success.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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