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ALTERNATIVE THERAPIES TO BACTERIAL INFECTIONS OF THE ORAL CAVITY: A REVIEW

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ABSTRACT

Oral infections are among the most prevalent global health conditions and are driven by dysbiosis of the oral microbiome and biofilm disruption. In health, a balanced microbial community supports mucosal integrity and immune homeostasis. However, shifts driven by dietary sugars, poor oral hygiene, smoking, systemic disease, and antibiotic exposure promote biofilm formation in dental caries, periodontitis, peri-implantitis, and endodontic infections. These biofilm-mediated diseases, commonly involving *Streptococcus mutans, Porphyromonas gingivalis, Fusobacterium nucleatum,* and *Aggregatibacter actinomycetemcomitans,* are not only locally destructive but are increasingly associated with systemic conditions including cardiovascular disease, diabetes, rheumatoid arthritis, Alzheimer's disease, and infective endocarditis. Antimicrobial resistance (AMR) further complicates management, with global mortality exceeding one million deaths annually and a substantial proportion of dental antibiotic prescriptions deemed unnecessary. Conventional therapies, such as mechanical debridement combined with antiseptics and systemic antibiotics, provide short-term microbial reduction but are limited by incomplete biofilm penetration, disruption of commensal microbiota, adverse effects, and accelerated resistance. Emerging therapies such as bacteriophage therapy, nanoparticle-based antimicrobials, photodynamic and photothermal therapies, and antimicrobial peptides offer targeted antimicrobial activity with reduced selection pressure for resistance. These approaches demonstrate promising antimicrobial efficacy while aiming to preserve microbial balance. However, challenges, including toxicity concerns, regulatory barriers, cost, and limited long-term clinical evidence, remain. Therefore, this narrative review advances the precision of antimicrobial interventions and redefines oral infection management by shifting from broad elimination to ecological modulation and targeted biofilm control.

Keywords: Oral microbiome, Antimicrobial resistance, Biofilms, Phage therapy, Nanoparticles

INTRODUCTION

Oral infections are one of the prevalent medical conditions globally, and they are linked tightly to the oral microbiome, ecology of biofilm, and host-microbe interactions (Jao et al., 2023; Li et al., 2022). Increasing antimicrobial resistance has exposed major limitations of conventional antibiotic-based therapy and increased interest in alternative therapies that can bring balance, rather than simply eradicate these oral microbes (Hwang et al., 2025).

The oral cavity comprises hard tissues such as teeth, soft tissues (gingiva, oral mucosa, tongue, palate), saliva, and gingival crevicular fluid, which together provide diverse habitats for microbial colonization (Allaker & Douglas, 2015). Over 700–1,000 microbial taxa (bacteria, fungi, viruses, archaea, and protozoa) have been discovered, organized in structured polymicrobial biofilms on these structures (Radaiac & Kapila, 2021).

In oral health, a eubiotic community maintains barrier integrity and regulates host immunity (Sudhakara et al., 2018). The shift in the function and composition of this healthy community is commonly referred to as 'dysbiosis,' and it is often driven by diet (sugars), poor oral hygiene, smoking, systemic disease, or antibiotics, thereby promoting inflammation and tissue damage (Sedghi et al., 2021). Dysbiotic biofilms underlie dental caries and periodontal diseases, characterized by outgrowth of acidogenic or aciduric streptococci in caries and proteolytic, inflammophilic consortia in periodontitis (Sudhakara et al., 2018; Jao et al., 2023).

Dysbiosis in the oral cavity has been discovered to be tightly linked to systemic conditions, including cardiovascular disease, diabetes, rheumatoid arthritis, Alzheimer's disease, atherosclerosis, and infective endocarditis, via hematogenous spread and chronic low-grade inflammation (Peng et al., 2022). Different routes like oral to gut to liver or oral to gut to brain or even oral to lung explains how oral flora influence distant organs (Hwang et al., 2025).

Common bacterial oral infections include dental caries (dominated by species such as *Streptococcus mutans*), periodontitis and peri-implantitis (complex anaerobic biofilms including *Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum*), endodontic infections, and orthodontic/peri-implant biofilm infections (inflammation around implants and devices, involving composition of periodontopathogens and *Staphylococci* on biomaterials) (Salehi et al., 2020; Gholami et al., 2023; Lasica et al., 2024). These infections are typically polymicrobial and biofilm-based rather than caused by a single species. These infections are typically localized but can lead to bacteremia and systemic infection, particularly in medically compromised patients (Huang et al., 2023).

Antimicrobial Resistance as a Global Burden

Antimicrobial resistance (AMR) has emerged as a defining global health crisis of the 21st century. According to the World Health Organization (WHO), AMR is responsible for approximately 1.27 million deaths annually, with nearly 5 million deaths associated with drug-resistant infections worldwide (WHO, 2025). The economic burden of AMR is equally alarming, with estimates suggesting that by 2050, global GDP losses could reach $100 trillion, pushing millions into poverty (Ahmed et al., 2017). While AMR in systemic infections has been extensively studied, the role of oral pathogens in the AMR crisis remains underappreciated. The oral cavity harbors over 700 bacterial species, many of which exhibit intrinsic or acquired resistance (Milho et al., 2021). Frequent antibiotic prescriptions in dentistry for periodontal infections, tooth extractions, and prophylactic treatments have accelerated resistance among key oral bacteria (Ahmadi et al., 2021). Studies indicate that up to 50% of dental antibiotic prescriptions are unnecessary or inappropriate, contributing to selective pressure for resistant strains (Săndulescu et al., 2024). Conventional antibiotics alone are no longer sufficient to combat drug-resistant oral infections. Alternative therapeutic strategies such as phage therapy, nanoparticle-based antimicrobials, photodynamic therapy, and antimicrobial peptides offer promising solutions.

MATERIALS AND METHODS

Search Strategy

A comprehensive literature search was conducted to identify peer-reviewed articles written in the English language, focusing on alternative antimicrobial therapies for managing oral bacterial infections. The search primarily utilized Google Scholar, supplemented by PubMed, to retrieve relevant studies published between January 2010 and December 2025. The search was executed using a combination of keywords and Boolean operators (AND/OR) to maximize coverage:

i. (“Oral infections” OR “Dental biofilms” OR “Periodontitis” OR “Caries”)
ii. AND (“Antimicrobial resistance” OR “AMR”)
iii. AND (“Bacteriophage therapy” OR “Antimicrobial peptides” OR “Nanoparticles” OR “Photodynamic therapy”).

Inclusion Criteria

Original research and review articles focusing on novel therapies, studies specifically addressing oral bacterial pathogens, and literature discussing the current state of antibiotic use and resistance patterns within clinical dentistry were included in the search.

Exclusion Criteria

Non-peer-reviewed literature, including conference abstracts, editorials, and unpublished theses and studies focused on bacterial infections outside of the oral cavity, was excluded from the search.

Study Selection and Quality Assessment

Following the initial search, duplicate entries were removed. Titles and abstracts were screened for relevance according to the inclusion criteria, followed by a full-text evaluation of the selected articles. Only peer-reviewed articles from reputable journals were utilized in the final manuscript to ensure the reliability of the findings presented.

Conventional Therapies and Their Limitations

Common standard care combines both mechanical and chemical methods, one of which is mechanical debridement. This can be done in different forms, including regular toothbrushing, scaling, and root planning. It helps to disrupt biofilm and reduce bacterial load on the affected organ or tissue. Mechanical debridement has long since been used, it has been discovered that this method does not fully eliminate pathogens in deep pockets or complex root anatomy and is also largely dependent on who is carrying it out (Gholami et al., 2023; Lasica et al., 2024).

Use of topical antiseptics (like chlorhexidine) and systemic antibiotics (such as amoxicillin, metronidazole, tetracyclines, clindamycin, doxycycline/minocycline) is also one of the methods that has been in existence for a long time (Hwang et al., 2025). These are usually used as adjunctive treatment in periodontitis, endodontic infections, and peri-implantitis. They provide a reduction in bacterial counts in the short term and calm inflammations (Jao et al., 2023). These antiseptics and antibiotics, however effective, face several problems such as rapid emergence of antibiotic resistance among causative oral pathogens, especially within biofilms, disruption of microbiota of commensals promoting dysbiosis with repeated broad-spectrum exposure, limited penetration and reduced efficacy against biofilms containing different species and even sometimes, mixed bacterial-fungal communities, adverse effects like staining, taste changes, hypersensitivity, allergic reactions and patient compliance issues (Theuretzbacher & Piddock, 2019; Haque et al., 2022; Mdarhri et al., 2022).

Alternative Therapies

Given the documented limitations of conventional approaches, considerable research interest has shifted toward alternative therapies that can overcome biofilm resistance, preserve commensal microbiota, and reduce dependence on broad-spectrum antibiotics. The following sections examine four of the most actively investigated alternatives: bacteriophage therapy, nanoparticle-based antimicrobials, photodynamic and photothermal therapies, and antimicrobial peptides.

Bacteriophages

Bacteriophages are viruses that specifically infect bacteria, they often exhibit narrow host ranges, allowing targeted elimination of pathogens while preserving commensals (Lasica et al., 2024; Musa et al., 2024). In oral infections (caries, periodontitis, peri-implantitis, endodontic infections), phages act mainly through highly specific killing of pathogenic bacteria and disruption of plaque biofilms. These phages are lytic, meaning they bind specific bacterial receptors such as LPS, teichoic acids, membrane proteins, and capsules, inject their DNA, hijack bacterial replication, and then burst the cell, releasing new phages (Hooshiar et al., 2024). Phages replicate only where target bacteria are present, continuing to propagate until the pathogen population drops (Ramadan et al., 2024). Phyla such as *Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, and Spirochaetes* are predominantly infected by oral phages (Zhu et al., 2025). Lytic phages against *S. mutans* and *F. nucleatum* can reduce cariogenic and periodontal biofilm biomass and significantly decrease viable counts (Li et al., 2022). Phages such as temperate phage φEf11, which targets all genotypes of *E. faecalis,* have been reported to show strong activity against persistent endodontic infections and biofilms (Tinoco et al., 2016). FnpΦ02, a phage isolated from saliva samples, has been reported to be the first phage to infect *F. nucleatum,* a bacterium that contributes to the development of chronic periodontitis (Machuca et al., 2010). Recently, FNU1, a novel lytic bacteriophage, has been discovered to infect *F. nucleatum*, with the ability to intracellularly kill the bacterium, significantly reducing the biofilm mass (Kabwe et al., 2025). Benefits of this therapy include its specificity, as only targeted pathogens will be eliminated, sparing the wider microbiome, some of the phages can penetrate extracellular matrices better than standard antibiotics and disrupt biofilms (Li et al., 2022; Zhu et al., 2025). Bacteriophages have also been reported to exhibit potent activity against bacteria resistant to multiple antibiotics (Yang et al., 2024). Phage therapy comes with its own challenges, there is limited availability of well-characterized oral phages, difficulty in culturing strict anaerobes (like *Porphyromonas, Fusobacterium*), the possibility of oral phages being responsible for the progression of periodontal diseases, and also potential for resistance in phages (Guo et al., 2024; Pospiszyl et al., 2025).

Nanoparticle-based Antimicrobials

Nanoparticles (NPs) are ultrasmall materials usually sized between 1 and 100 nm. Due to their ultrasmall size (1–100 nm) and high surface-area-to-volume ratio, they are able to exhibit superior antimicrobial properties compared to conventional antibiotics (Cheraghiyan, 2025; Agbaje et al., 2023). They are able to exhibit antibacterial activity due to their ability to penetrate bacterial cell walls, leading to structural disintegration and cell lysis (Balhaddad et al., 2019). NPs provide biocidal, anti-adhesive, and drug-delivery functions (Theuretzbacher & Piddock, 2019). Metals such as silver, zinc, and copper, oxides of metals, and polymeric and lipid-based NPs have been reported to exhibit bactericidal effects on oral pathogens like *S. mutans, P. gingivalis,* and many more (Mdarhri et al., 2022). Metal-based nanoparticles (e.g silver, gold, oxides of copper and zinc) produce reactive oxygen species, causing oxidative stress in bacteria, leading to DNA damage and protein oxidation (Yin et al., 2025). They can also interfere with bacterial communication systems, preventing the coordination of virulence and resistance mechanisms. Silver nanoparticles (AgNPs) are widely researched due to their potent antimicrobial activity against oral pathogens, including *S. mutans* and *P. gingivalis* (Balhaddad et al., 2019). AgNP-infused dental adhesives have been tested in clinical trials and demonstrated a 70% reduction in *Streptococcus mutans* biofilm formation after six months (Mallineni et al., 2023). AgNP-coated orthodontic brackets significantly reduced bacterial adhesion, minimizing the risk of plaque accumulation and enamel demineralization (Niu et al., 2025). Polymeric, lipid, carbon dots-based NPs can also act as intrinsic antimicrobials or targeted carriers enhancing local antibiotic or photosensitizer delivery (Yarahmadi et al., 2025; Gajić et al., 2025). In oral infections, nano-systems improve photosensitizer solubility, bioavailability, targeting to biofilms, controlled release, and protection from degradation, while reducing side-effects and resistance development (Silvestre et al., 2020). Carbon dots show potent activity against planktonic, intracellular, and biofilm-embedded oral pathogens and support microbial imaging for early diagnosis (Jiang et al., 2023). Advantages include improved penetration of biofilms and dose sparing, there have been concerns relating to design complexity, toxicity, and cost.

Photodynamic Therapy (PDT) and Photothermal Therapy (PTT)

PDT and PTT have emerged as a potential alternative to conventional antibiotics. PDT generates reactive oxygen species by combining photosensitizer with light of a specific wavelength in the presence of oxygen, eliminating bacteria, fungi and viruses locally while PTT uses photothermal agents to convert light into heat, damaging bacterial cells and biofilms and it is being explored for resistant biofilm infections around teeth and implants (Jiao et al., 2019; Huang et al., 2023). PDT can significantly reduce bacterial pathogen loads in periodontal and peri-implant pockets, persistent endodontic infections, and cariogenic biofilms (Jao et al., 2023). PDT has been shown to have strong efficacy against *Candida* in oral mucosal infections (Gholami et al., 2023). Their major advantages include minimal invasiveness, broad antimicrobial spectrum without known resistance development, and relative selectivity for diseased sites. Despite its many advantages, they come with its own limitations, such as cost, need for specialized equipment, and uncertain long-term superiority over standard care (Jao et al., 2023; Huang et al., 2023).

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are positively charged molecules that demonstrate activity against a wide range of bacterial, fungal, and viral pathogens (Fu et al., 2025). They are an essential component of the human innate immune system and that of many other organisms (Talapko et al., 2022). Unlike conventional antibiotics, which target specific bacterial processes, AMPs disrupt bacterial membranes, leading to rapid cell lysis (Strandberg et al., 2020). This membrane disruption occurs due to the attraction of the AMPs to negatively charged cell membranes of the microorganisms (due to the rich presence of phospholipids, phosphatidylglycerol, and cardiolipin), inhibiting protein synthesis and the synthesis of DNA and RNA (Mahlapuu et al., 2016; Zhang et al., 2021). They can also disrupt lipid packing, form pores, and cause leakage of cytoplasmic contents and cell death (Bechinger et al., 2017). The human oral cavity produces several endogenous AMPs, which contribute to natural defense mechanisms against oral pathogens (Diamond & Ryan, 2011). Among these, defensins, cationic peptides produced by epithelial cells and neutrophils, play a role in oral immune surveillance (Yin et al., 2010). Human β-defensins (hBDs) are peptides secreted by salivary glands and gingival epithelial cells, exerting potent antimicrobial effects against *S. mutans and P. gingivalis* (Ahn et al., 2017). Studies have shown that hBD-3 can inhibit biofilm formation in periodontal pathogens by 60–80%, making it a potential therapeutic agent (Yilmaz et al., 2015). Another AMP, LL-37, part of the cathelicidin family, is found in saliva, gingival crevicular fluid, and epithelial tissues, playing a role in reducing inflammation and promoting wound healing (Bedran et al., 2014). Studies have reported coating of AMPs onto metal (e.g Titanium, Ti), ceramic, and polymer dental implants to fight off oral infections. AMP HBAP1-tet127CaP/HA-coated Ti has been studied and found to be effective against *Streptococcus mutans* (Sun et al., 2023). Some of these natural oral AMPs have been reported to have limited activity due to the action of salivary enzymes and pH. However, synthetic and engineered AMPs have been reportedly designed to improve stability, reduce toxicity, and maintain strong antimicrobial and antibiofilm effects in the challenging oral environment (Talapko et al., 2022). Its major advantage is that it has low resistance potential, making it a safer option (Allaker et al., 2015).

RESULTS AND DISCUSSION

The findings of this review collectively highlight a transition in oral antimicrobial therapy. Conventional therapies, particularly mechanical debridement and antibiotic adjuncts, remain the backbone of clinical practice and have well-documented short-term efficacy. However, their shared inability to fully penetrate mature polymicrobial biofilms, combined with the well-documented disruption of commensal microbiota and accelerating resistance development, underscores an urgent need for complementary or alternative strategies. The four therapies reviewed here, bacteriophage therapy, nanoparticle-based antimicrobials, photodynamic and photothermal therapies, and antimicrobial peptides, each offer distinct advantages over conventional antibiotics, though none is without limitation.

Among the therapies reviewed, PDT stands out as the closest to routine clinical adoption. It has already been incorporated into periodontal and endodontic protocols in several clinical settings, with documented efficacy in reducing bacterial loads in peri-implant pockets and persistent root canal infections (Jao et al., 2023; Gholami et al., 2023). Its non-antibiotic mechanism, the light-activated generation of reactive oxygen species, means that resistance development remains theoretically unlikely, a major advantage over conventional antibiotics, where resistance is both predictable and well-documented. PTT, while mechanistically related, remains largely in the experimental phase for oral applications, with most evidence still derived from *in vitro* studies. Nanoparticle-based antimicrobials, particularly silver nanoparticles, have progressed further along the translational pathway, with clinical trials demonstrating significant reductions in cariogenic biofilm formation *in vivo* (Mallineni et al., 2023). However, concerns about cytotoxicity at bactericidal concentrations, long-term biocompatibility, and the environmental implications of metal nanoparticle use remain unresolved and warrant careful consideration before widespread clinical deployment. Polymeric and lipid-based nanoparticles, while less studied in oral contexts, offer more favourable safety profiles and represent an emerging area of interest for targeted drug delivery in periodontal and endodontic infections.

Bacteriophage therapy and antimicrobial peptides, though scientifically compelling, remain predominantly at the preclinical and early translational stages in the context of oral infections. Phage therapy's main advantage over conventional antibiotics lies in its exquisite host specificity, unlike broad-spectrum agents that disrupt the entire oral microbiome. Phages can be selected or engineered to target individual pathogens, such as *P. gingivalis* or *F. nucleatum,* while leaving beneficial commensals intact (Zhu et al., 2025; Kabwe et al., 2025). This precision is particularly valuable in conditions like periodontitis, where microbiome preservation is now recognized as a therapeutic goal, not merely a side consideration. Nevertheless, the limited availability of well-characterized oral phage libraries, the difficulty of culturing fastidious anaerobic oral pathogens for phage isolation, and the potential for phage-mediated horizontal gene transfer of virulence factors all present real obstacles to clinical translation. AMPs similarly offer a low-resistance-potential alternative with strong *in vitro* evidence, but their oral clinical application is complicated by enzymatic degradation in the saliva, pH sensitivity, and cytotoxicity at higher concentrations. The development of synthetic and engineered AMPs with enhanced stability addresses some of these concerns, though robust clinical data remain sparse (Talapko et al., 2022; Fu et al., 2025).

A common challenge across all four alternative therapies is the scarcity of large-scale, well-designed randomized controlled trials specifically within oral infection contexts. Much of the existing evidence is derived from *in vitro* biofilm models or small pilot studies, which, while valuable for establishing proof of concept, are insufficient to guide clinical practice. Moreover, cost, regulatory complexity, and the need for specialized equipment or expertise create additional barriers to implementation, particularly in low- and middle-income settings where the burden of oral disease is disproportionately high. These realities mean that, for the foreseeable future, alternative therapies are best positioned as adjuncts to, rather than replacements for, conventional treatment. What is particularly encouraging, however, is the growing interest in synergistic approaches such as phage-antibiotic synergy, nanoparticle-mediated photosensitizer delivery, and AMP-coated implant surfaces, all of which represent hybrid strategies that could increase efficacy while reducing the doses and side effects associated with individual therapies.

The oral microbiome is not merely a reservoir of pathogens to be eliminated, it is a dynamic community whose balance is intrinsic to both oral and systemic health. Therapies that restore microbial balance rather than simply reduce bacterial counts align better with this understanding and represent the most promising direction for future research.

CONCLUSION

Oral infections are complex, biofilm-driven diseases rooted in microbial dysbiosis and tightly interconnected with systemic health. The accelerating burden of antimicrobial resistance, compounded by widespread and often inappropriate antibiotic use in dentistry, influences the urgent need to rethink conventional therapeutic strategies. While mechanical debridement and adjunctive antiseptics and local antibiotics remain foundational, their limitations, including incomplete biofilm penetration, microbiome disruption, adverse effects, and resistance development, necessitate more precise and sustainable strategies. Emerging interventions such as bacteriophage therapy, nanoparticle-based antimicrobials, photodynamic and photothermal therapies, and antimicrobial peptides represent promising alternatives. These approaches offer targeted antimicrobial activity, improved biofilm disruption, reduced resistance potential, and in some cases, preservation of commensal microbial communities. Notably, nanoparticle systems and peptide-based coatings also demonstrate translational potential in restorative and implant dentistry. However, despite encouraging *in vitro* and early clinical findings, significant challenges remain, including safety concerns, cost-effectiveness, regulatory barriers, long-term efficacy validation, and large-scale clinical trials. Future research should prioritize clinically validated, microbiome-preserving strategies that move beyond microbial eradication toward ecological modulation.

Authors' Contributions

Ojelabi, A.C., initiated the concept and made a seminar presentation on it. Amodu, S critically reviewed the initial draft of the work and encouraged her to develop the review in a manuscript format. Udochukwu, T.F ensured the accuracy and integrity of the manuscript. All the authors contributed to and read the final manuscript to be published.

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