

Bacteriophage Therapy as a Promising Adjunct in Dental Infections: A Review

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Abstract The article examines the potential applications of bacteriophages in dental practice. It describes the main biological features of bacteriophages and the mechanisms of their interaction with bacterial cells, along with findings from microbiological research and clinical trials involving phage therapy in periodontal diseases. Studies demonstrate that bacteriophages are effective against periodontopathogenic microorganisms, including antibiotic-resistant strains, both in vitro and in vivo. The review also outlines the key benefits and current limitations of phage therapy, emphasizing the limited clinical experience accumulated so far. *Objective:* To review and analyze different literature regarding the efficacy of phage therapy in dentistry.

Keywords Bacteriophage, Phage therapy, Oral biofilm, Antibiotic resistance, Periodontal disease, Endodontics

1. Introduction

Periodontitis continues to be among the most widespread oral diseases worldwide, affecting nearly half of the adult population. Endodontic infections likewise represent a major cause of tooth loss and persistent inflammation. In recent years, the increasing prevalence of antibiotic-resistant microorganisms, particularly *Enterococcus faecalis* and *Staphylococcus aureus*, has limited the effectiveness of conventional antimicrobial therapy.

Because traditional antibiotics often fail to control resistant biofilms, attention has shifted toward alternative biological strategies. One of the most promising among them is phage therapy, which employs bacteriophages – viruses that specifically infect and destroy bacteria – to restore microbial balance and combat infection. Within the dental field, this approach is gaining recognition for its ability to target pathogens associated with periodontitis, peri-implantitis, and apical lesions.

The purpose of this review is to summarize the available experimental and clinical data on bacteriophages and their enzymes in dental medicine. Particular focus is placed on their antibacterial mechanisms, preclinical and clinical applications, and the challenges that still prevent widespread clinical adoption.

Given the limited efficacy of antibiotics, phage therapy

has emerged as a promising strategy. This review aims to evaluate the current evidence on the use of bacteriophages and their enzymes in dentistry, highlighting experimental, preclinical, and clinical findings [1].

2. Characteristics of Bacteriophages

Bacteriophages are viruses capable of selectively destroying bacteria. Currently, more than 6,000 species of bacteriophages have been described [2]. The main role of these organisms on Earth is to significantly accelerate the decomposition of organic matter. Thus, phages, influencing global geochemical processes, sustain the circulation of matter and energy in the Earth's biosphere [3].

Typical bacteriophages are characterized by a protein capsid of variable geometry (often 45–140 nm in diameter) and, in many cases, a tail structure that can extend up to 200 nm. Other bacteriophages have no tail, some are round, others filamentous, sized 8 × 800 nm. The capsid usually contains the phage genome (DNA or RNA) tightly packed together with a minimal proportion of structural proteins [4]. Besides nucleic acids and protein, phages contain up to mainly nucleic acids and proteins, with rare cases of lipids or carbohydrates in certain phages, as well as enzymes [5]. Outside host cells, most phages exist as virions. They reproduce only inside bacterial cells since their genome is insufficient for autonomous existence [6].

By type of antibacterial activity, bacteriophages are divided into two groups [7]:

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Received: Oct. 3, 2025; Accepted: Oct. 21, 2025; Published: Oct. 31, 2025

Published online at <http://journal.sapub.org/ajmms>

- Temperate phages integrate their genome into the genome of bacteria, multiply together with them and only after some time lyse the bacterial cell (lysogenic cycle).
- Lytic (virulent) phages infect the bacterial cell and immediately lyse it (lytic cycle).

While this classification is well established, its practical implications for dental infections remain underexplored. Overall, these biological properties explain both the therapeutic promise and the inherent challenges of phage application in oral healthcare.

3. Specificity of Action

Each bacteriophage causes lysis of a specific bacterial species, and some of certain types and even strains. By the degree of specificity, phages are divided into three groups [5]:

- Broad host range phages – active against several related species of bacteria;
- Narrow host range phages – lysing microbes of one species;
- Strain-specific phages – lysing only certain types of a given bacterial species.

For phage therapy at present, only virulent lytic phages are used, mainly phages of the order Caudovirales, as well as filamentous phages of the families Leviviridae (single-stranded RNA genome) and Inoviridae (single-stranded circular DNA genome) [6]. Preparations for phage therapy are produced in the form of solutions and gels for local and external use, as well as for oral administration.

4. Application in Dentistry (Focused on Oral Infections)

The activity spectrum of phages is usually quite narrow. This allows elimination of a specific microorganism without disturbing the integrity of the entire bacterial community of the human body. Corresponding bacteriophages are applied to specific bacterial species. Thus, for suppurative-inflammatory infections of the skin and mucous membranes caused by staphylococci, a staphylococcal phage is used. For treatment and prevention of suppurative-complicated wounds, abscesses, as well as other coli-infections – a coli phage. For treatment of purulent skin infections, abscesses, other surgical infections, suppurative wounds, the *Pseudomonas aeruginosa* phage is expedient. In furuncles, carbuncles, suppurative-complicated wounds infected with staphylococci, purulent tonsillitis, phlegmons, the polyvalent pyobacteriophage (sexaphage) is effective [8].

On the other hand, in urgent therapy situations, it is necessary to lyse several bacterial species simultaneously. Such problems are solved with phage cocktails – mixtures of various bacteriophages acting against different pathogens [6].

In dentistry, bacteriophages may be used in complex treatment of infectious-inflammatory diseases, including inflammatory periodontal diseases.

5. Experimental and Clinical Evidence

A number of studies are devoted to evaluating the effectiveness of bacteriophages against periodontopathogenic flora.

The group of researchers led by M. Fenton studied recombinant lysins of *S. pyogenes* and established their 100% effectiveness after intranasal and oral administration in mice together with *S. pyogenes* bacteria. The lysin MV-L obtained from phage MR11 against methicillin-resistant *S. aureus* proved effective against these bacteria after intranasal administration in mice. Six hours after treatment, in 1 of 9 mice bacteria completely disappeared, while in the others a significant decrease in bacterial titer was noted. The lysin PlyV12 obtained from a bacteriophage to *E. faecalis* showed high cross-infection activity against vancomycin-resistant enterococci, staphylococci, and streptococci [11].

S.P. Szafranski, A. Winkel and M. Stiesch studied the effectiveness of recombinant lytic enzymes of bacteriophages against *Actinomyces naeslundii*, *Aggregatibacter actinomycetemcomitans*, *Enterococcus faecalis*, *Fusobacterium nucleatum*, *Lactobacillus* spp., *Neisseria* spp., *Streptococcus* spp., and *Veillonella* spp. It was established that recombinant lytic enzymes are active against *A. naeslundii* and *Streptococcus* spp., which form oral biofilms contributing to the development of dental diseases [12]. Under the action of these enzymes, biofilms are destroyed. P. Machuca et al. confirmed the effectiveness of the DNA-containing bacteriophage FnpΦ02 targeting *Fusobacterium nucleatum* [13].

J. Fujiki et al. studied the activity of the endolysin Lys-phiSA012 against *S. aureus*. The endolysin showed high lytic activity against staphylococcal strains, including MRSA [14]. Laboratory research also confirmed the effectiveness of murein peptidase derived from bacteriophages of *S. aureus* against methicillin-resistant strains [15].

R.M. Donlan, studying bacteriophages T4 and F116 against biofilms of *E. coli* strains 3000XIII and K12 respectively, concluded that phages reduce the viability of *E. coli* biofilms. A staphylococcal phage against biofilms of *Staphylococcus epidermidis* strains showed its effectiveness: a significant decrease in the optical density of biofilms in several strains was observed [10].

D.M. Lin et al. confirmed the effectiveness of a bacteriophage against *Pseudomonas aeruginosa* after oral administration in mice. In the test group, mortality decreased by 66.7%. After intraperitoneal administration of an imipenem-resistant phage to the same bacterium, mortality decreased by 100% [16].

S. Latz et al. revealed activity of phages SL1, SL2, and SL4 against multidrug-resistant *P. aeruginosa*. Planktonic cells of 4 out of 5 tested bacteria were suppressed within 16

hours without regrowth. Phage SL2 proved the strongest in suppressing planktonic cultures, while SL4 showed enhanced antibacterial activity. In vitro experiments on wax moth larvae infected with *P. aeruginosa* confirmed the effectiveness: larvae survived, with the highest survival rate when SL1 phage was used [17].

T.M. Santiago-Rodriguez *et al.* studied the bacterial community of 16 saliva samples: 9 from periodontally healthy individuals and 7 from patients with periodontal disease. They concluded that oral RNA-containing phages regulate their gene expression. Studies showed that in periodontal disease some lytic activity genes are more strongly expressed, indicating the ability of phages to enhance lytic gene expression in periodontal disease [18].

Clinical studies also confirm the effectiveness of bacteriophages in treating inflammatory periodontal diseases. K.E. Isadzhanyan successfully applied the dental gel 'Phagodent', including 56 phages against 18 pathogenic microorganisms, in patients with periodontitis and gingivitis [19]. E.G. Mikhaylova, in complex therapy of chronic generalized periodontitis, used dental gels containing a mixture of staphylococcal, streptococcal, *Wolinella*, and actinobacillary phages. Patients in the study group showed improved local status: reduced pain, decreased hyperemia, bleeding, swelling of the gums and interdental papillae.

Phages may also be used in endodontics, especially in treating chronic apical periodontitis. G. Pinto *et al.* conducted *ex vivo* studies on extracted teeth with infected root canals. Bacteriophage EFDG1 showed effectiveness against *E. faecalis* ATCC 29212 in the treated canals. A phage to *Aggregatibacter actinomycetemcomitans* (PAA005) also demonstrated high efficacy. Phages JBD4 and JBD44, active against *Pseudomonas aeruginosa* PA14, reduced bacterial biomass in 24-h and 96-h biofilms. However, phages to *S. sanguis*, *Actinobacillus*, *Actinomyces*, *Bacteroides*, *Capnocytophaga*, *Eikenella*, *Eubacterium*, *Fusobacterium*, *Haemophilus*, *Lactobacillus*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella*, *Rothia*, *Selenomonas*, *Streptococcus*, *Treponema*, and *Wolinella* in root canals did not show effectiveness [20].

6. Advantages of Phage Therapy

Based on the accumulated data, several factors make phages attractive for dental use [21]. They can eliminate pathogens resistant to standard antibiotics, are generally well-tolerated even in sensitive groups such as children and pregnant women, and spare the beneficial microbiota due to their high specificity. Their ability to act within biofilms and their adaptability for topical or systemic administration further expand their potential.

7. Limitations and Challenges

Although the accumulated evidence supports the therapeutic potential of bacteriophages in dentistry, several obstacles

still impede their translation into routine practice.

- First, the requirement for precise identification of the causative pathogen before treatment is both a strength and a limitation. The narrow host range of phages ensures selective targeting but complicates their use in polymicrobial infections typical of the oral cavity. While phage cocktails provide partial solutions, the effectiveness of these mixtures is often unpredictable without individual microbial testing [22].
- Second, current therapeutic approaches rely almost exclusively on strictly lytic phages [23]. Temperate phages, due to their ability to integrate into bacterial genomes, carry theoretical risks such as enhanced virulence or persistence of the host microbe, making them unsuitable for acute dental infections [24–26].
- Another concern involves the lack of standardized production protocols. Different laboratories prepare phages under non-uniform conditions, and information about the interactions between various phages within a single formulation remains scarce. Without harmonized guidelines, reproducibility between studies and clinical trials remains limited [27,28].
- Concerns have also been raised regarding the potential transfer of genetic material by phages. While horizontal gene transfer is a rare event, its possibility cannot be ignored, as it could inadvertently spread antibiotic resistance or virulence factors [29,30].
- The genome of phages has not been completely decoded; the function of many genes and their role in possible side effects remain unstudied [31,32].
- Lytic phages, destroying bacterial cells, contribute to the release of endotoxins from Gram-negative bacteria, which can lead to temporary intensification of inflammation. However, this potential problem also applies to existing antibacterial drugs [33].
- Since bacteriophages are viruses, they may be recognized by the patient's immune system as antigens and may be quickly eliminated from the bloodstream or inactivated by adaptive immunity. This may reduce their effectiveness with prolonged or repeated use and also lead to allergic reactions [34].
- Development of resistance mechanisms by host bacterial cells due to mutation, selection or temperate phage uptake can reduce effectiveness. At least four mechanisms may increase bacterial resistance to a phage, including receptor loss, structural change, or masking [35,36]. Nevertheless, the overall risk of resistance development is considered low [22,37].

8. Conclusions

Bacteriophage therapy represents a promising addition to modern dental infection control. Despite the current challenges, evidence from laboratory and clinical research suggests that phages can effectively combat pathogens resistant to antibiotics and act selectively within biofilms.

Their high specificity, minimal effect on the normal microbiota, and potential compatibility with topical or systemic delivery forms make them a valuable tool for future dental therapeutics.

Nevertheless, the clinical application of phages in dentistry is still at an early stage. Further work should focus on developing standardized phage cocktails, studying their pharmacokinetics in the oral cavity, and conducting multicenter randomized clinical trials to validate their safety and efficacy. In our view, the earliest practical implementation may occur in the treatment of periodontitis, endodontic infections, and peri-implantitis, where conventional antimicrobial methods remain insufficient.

Funding. The study had no sponsorship.

Conflict of interest. The authors declare no conflict of interest.

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