Bacteriophage therapy an alternative to antibiotic for oral infections- A review

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***Abstract*—**Bacteriophages are dynamic against planktonic microorganisms and, of more noteworthy interest for oral and dental medicines, against microbes coordinated in biofilms. Phage therapy, like many other medical professions, opens up new avenues for dentistry, both therapeutically and scientifically. Oral phage must reflect the ecology of their bacterial hosts to some extent, although the occurrence of mutualistic and antagonistic connections between phage and hosts is not fully understood. Phage therapy could be beneficial in oral and dental therapies. Bacteriophages attack planktonic bacteria and cells encased in biofilms. Because phage treatment has long been utilised to treat infections, phage therapy for the dentistry sector might advance quickly. Following the resuscitation of phage therapy, numerous researchers have been able to dig further into this therapeutic option and develop more conservative procedures as complements to conventional treatments.

Keywords: Bacteriophage therapy; bacteriophages;Antibiotics;Viral treatment; Oral Phages

I. INTRODUCTION

Viruses that can infect and multiply inside bacteria are bacteriophages .They are biological systems that can be found all over the world and are quite diverse genetically[1] Depending on the biological cycle they execute, lytic or lysogenic, phage are classed as virulent or temperate.[2]Lysins are phage-encoded enzymes that cause bacterial cell wall lysis at the end of the lytic cycle, and they're interesting because they can break up biofilms.[3] The most ideal phage's for therapeutic treatment against bacterial illnesses are those that are very virulent.[4] Phage treatment began back in 1896 when Ernest Hankins initially detailed the presence of antibacterial action against *Vibrio cholera*e the causative specialist of cholera which was viewed as one of the deadliest hazard people had confronted. [5]Even though the thought of phage treatment has been around for almost a century, it is as yet viewed as a trial treatment in Western nations and has not been endorsed for human use yet, to some degree because of non-existing phage treatment guidelines and the absence of protected and very much portrayed phage arrangements. Moreover, the way that phage treatment is imagined as customised medication presents additional difficulties in the administrative pipeline. [6]The quick ascent of multi-drug safe microscopic organisms worldwide has prompted an interest in phage treatment as a potential option in contrast to anti-infection agents or, in any event, a strengthening approach for the treatment of a few bacterial contaminations. As of late, the consequences of bacteriophage and phage mixed drink application for the treatment of different diseases have been accounted for in various clinical cases, case series and clinical preliminaries.[7]From the start, the clinical utilization of bacteriophages was centered around the therapy of extreme gastrointestinal sicknesses, and skin infections. Thereafter, bacteriophages were applied in cautious practice for the therapy of purulent wounds and postoperative powerful ensnarement's, and this approach was used in the USSR in the thirties and forties of the twentieth century. [8]Bacteriophages are presently being investigated as possible remedial devices for the end of oral bacterial microbes.[9]More than 700 types of microbes have been recognised in human oral depression, with unmistakable microorganisms assuming a part in oral well-being and illness. Phages that are dynamic against *Aggregatibacter actinomycetemcomitan* and *Fusobacterium nucleatum* causing periodontal diseases such as localized aggressive periodontitis (LAP) and various Streptococcus species have been identified. Preferably, phages that are dynamic against *Streptococcus mutans* could be utilised to diminish dental caries. [10]Anti-infection treatment isn't species-explicit and can influence pathogenic, as well as commensal species. Hence, phages, which are species-explicit, might be a promising elective methodology for caries treatment and avoidance. [11]Bacteriophages are dynamic against planktonic microorganisms and, of more noteworthy interest for oral and dental medicines, against microbes coordinated in biofilms. In any case, microorganisms in biofilms may shape hostile to bacteriophage shelters, with the goal that bacteriophages and microscopic organisms may coexist. [11]Although the quantity of papers in the phage treatment field has expanded significantly as of late, there has been a particular absence of a spotlight on the impact of bacteriophage treatment for oral infection. This review will endeavor to address these lacunae in our present information by examining bacteriophage therapy for oral bacterial infection.[12]

II. COLLECTION AND PRELIMINARY PROCESSING OF DATA

The article reviews on the recent trends on antimicrobial efficacy of bacteriophages on bacteria causing oral infections in India as well as globally. The data is derived from various peer reviewed research articles published in Scopus and PubMed.

III. EPIDEMIOLOGY

DISCOVERY OF BACTERIOPHAGES AND PRELIMINARY FINDINGS OF PHAGE THERAPY

Early studies corroborated the presence of a microorganism that could cross the Millipore filters without any barrier from the water sample of Indian rivers (Ganga and Yamuna) by Ernest Hanbury Hankin in 1896 and Nikolay Gamaleya in 1898, however, the clarity of these early observations is still questionable. [13]Frederick Twort was the first to speculate that the observed antibacterial activity was driven by a virus through his studies on the growth of the vaccinia virus on cell-free agar media.[14] However, he was unable to substantiate his hypothesis, owing in part to a lack of finance, and it was not until later that bacteria viruses were definitively found and termed bacteriophages by Felix d'Herelle. [15] He introduced the utilization of bacteriophages in clinical medicine and published many non-randomised trials, he also proposed treatment with an intravenous phage for invasive infections, and he summarised all of his findings and observations in 1931.[16] Bruynoghe and Maisin published the first clinical trial in France, in 1921, in which phages were injected into and surrounding skin lesions caused by staphylococcal infections, to treat cutaneous furuncles and carbuncles, the infection disappeared within 48 hours.[17] Furthermore, thousands of people were treated with bacteriophage preparations for a variety of infections in the 1920s, as this therapy grew in popularity.[18]By the 1930s and early 1940s, phage therapeutics was being commercialized. With the invention of the electron microscope, Helmut Ruska described phage particles. [19]More than 350 conference attendees attended the first major international gathering devoted to phage biology in August 2004 in Florida. [20]In recent years, certain Western European countries (Belgium, and France) have permitted the therapeutic use of phages, while phage therapies are being developed for clinical application by a number of companies in the United States.[21] Bacteriophages are gaining a lot of attention these days because of their potential to be employed as antibacterial and phage display systems [20], However, despite all the traits of lytic phages that would seem to support their therapeutic application, their efficacy is still increasing in popularity and they are not frequently used globally for prophylaxis or therapy.This condition is the result of numerous factors, some of which are outlined in Table 1.[22-27]

Table 1- Bacteriophage as therapeutic agents- Pros and Cons [22-27]

PROBLEMS	COMMENTS
Narrow host range of phages	Due to the high specificity of phages, many negative results may have been obtained because of the failure to select phages lytic [22]
Lack of understanding of the heterogeneity and mode of action of phages (i.e., lytic vs lysogenic phages)	Failure to differentiate between lytic and lysogenic phages resulted in using lysogenic phages, which are much less effective.[23]
Failure to establish scientific proof of the efficacy of phage treatment	clinical studies using therapeutic phages were conducted without placebo controls [24,25]

Poor stability and/or viability of phage preparations	Some commercial phage preparations were supplemented with mercurial or oxidizing agents or were heat treated to ensure bacterial sterility.[26]
Exaggerated claims of effectiveness of commercial phage preparations	*Enterophagos*, which was marketed as being effective against herpes infections, urticaria, and eczema-Conditions against which phages could not possibly be effective.[27]

Bacteriophages as therapeutic agents

Mode of action

Virus therapy, the use of phages as antibacterial agents, is based on the notion that phages detect and bind to certain proteins and quickly grow within bacterial host cells resulting in cell lysis. [28]

Only a few studies have examined the pharmacokinetics of therapeutic phage preparations, despite the fact that there have been many investigations into phage therapy. Within 2 to 4 hours, phages enter the bloodstream of laboratory animals, and after 10 hours, they are discovered in the internal organs.

Therapeutic phages were once thought to kill their target bacteria by replicating inside and lysing the host c ell (i.e., via a lytic cycle). However, later research showed that not all phages replicate in the same way and that lytic and lysogenic phages have significant differences in their replication cycles. [29]

Comparison of bacteriophages and antibiotics

Antibiotics cause selective toxicity by interacting with specific bacterial cellular targets, mutation and gene transfer can produce genes for various targets, and natural selection can amplify these mutations in a population. Antibiotics are still effective in treating most bacterial infections, but there are a few instances where frontline medicines are no longer effective. (Table 2) [29]

Table 2- Antibiotics versus Bacteriophage Therapy [29-35]

Antibiotic therapy		**Bacteriophage therapy**	
		Pros	**Cons**
Number of agents	Less than 30 antibiotics are available	Expansible	High screening cost, long time between diagnosis and treatment
Antimicrobial spectrum	Broad spectrum	High species/strain specificity	Pathogenic bacterial strains are required to allow a customizable

			phage screening
Anti biofilms activity	Less effective	Some phages can penetrate and destroy biofilms	Phages Anti-biofilm activity is very specific, pre-testing needed
Safety	Safe under rational use	Generally considered safe	Phage neutralizing antibody induced
Regulatory pathway	Slow	Rapid discovery process	Require innovative regulations for approving and manufacturing
Clinical acceptance	Widely accepted for infections prophylaxis and treatment	Phage lysis capacity Uncorrelated with bacterial low-resistance level	Used as a last resort treatment

Note: Table 2 compares antibiotic therapy to the more current bacteriophage therapy, as well as its benefits and drawbacks. Antibiotics have more side effects than phage therapy. Most antibiotics, on the other hand, have a significantly broader host range. [29-35]

Carbapenemase-producing strains of *Pseudomonas aeruginosa*, MRSA, VRE, and *Acinetobacter* spp. are some of the bacterial treatments that demanded an alternative to the regular antibiotic treatment, which further led to the development of phage therapy. [30]
Therapeutic phages are more effective than antibiotics in treating certain infections in humans and experimentally infected animals [31, 32, and 33]. In one study, *S. aureus* phages were used to treat patients having a purulent disease of the lungs and pleura. [34]

Application of phage therapy
Temperate phages lysogenize their bacterial hosts, and exist as prophages following chromosome integration, or as plasmid-like extra-chromosomal components.[34] Phage treatment is being promoted as a "new" potential technique for combating antibiotic-resistant illnesses.[35,36] (Table3).

Table 3- Application of Phage Therapy against Various Pathogens [36-50]

Causative agent	**Sample**	**Disease**	**Findings**
Clostridium difficile	Hamster	Ileocecitis	Co-administration with *C. difficile* prevented infection [37]
Escherichia coli	Murine	Meningitis and Sepsis	100% and 50% reduced mortality for meningitis and sepsis, respectively [49]
MDR *S. aureus*	Human	Diabetic foot ulcer	All 6 treated patients recovered [44]
S. aureus	Rabbit	Wound infection	Co-administration with *S. aureus* prevented infection [40,44]
Salmonella Typhi	Human	Typhoid	In a cohort of 18577 children, phage treatment was associated with a 5-fold decrease in typhoid incidence compared to placebo [45]
Acinetobacter baumannii, *P. aeruginosa* and	Murine	Sepsis	Animals protected against a fatal dose of *A. baumannii* and *P. aeruginosa* but not *S. aureus* [36,48,50]

Staphylococcus aureus			
MDR Vibrio parahaemolyticus	Murine	Sepsis	92% and 84% reduced mortality for intraperitoneal and oral routes, respectively [46]
Unclassified bacterial dysentery	Human	Dysentery	Phage cocktail improved the symptoms of 74% of 219 patients [38]
Vancomycin-resistant Enterococcus faecium	Murine	Bacteraemia	100% reduced mortality [38,39]
Antibiotic-resistant *P. aeruginosa*	Human	Chronic Otitis	Phage treatment safe and symptoms improved in double-blind, placebo-controlled Phase I/II trial [50]
β-*lactamase producing Escherichia coli*	Murine	Bacteremia	100% reduced mortality [50]
Imipenem- resistant P. aeruginosa	Murine	Bacteraemia	100% reduced mortality [50]
Shigella dysenteriae	Human	Dysentery	All four treated individuals recovered after 24 h [36]

Pseudomonas aeruginosa	Murine	Sepsis	66.7% reduced mortality [48]
Vibrio cholerae	Human	Cholera	68 of 73 survived in the treatment group and only 44 of 118 in control group [46]

Usage of phage for a variety of applications

1. Phage treatment against pathogens-

Phage treatment against *P. Aeruginosa*-When challenged with gut-derived sepsis due to *P. aeruginosa*, oral administration of phage saved 66.7% of mice from mortality compared to 0% in the control group. Phage cocktails have also been used to treat antibiotic-resistant *P. aeruginosa* infections of the skin, lungs, and gastrointestinal tract in animal models (Table 3). [36]

Phage treatment against *Clostridium difficle*-Phage combinations also significantly reduced *C. difficile* growth in vitro and limited proliferation in vivo using a hamster model. In a hamster model of *Clostridium difficile* (*C. difficile*)-induced ileocecitis, a single dose of phage concurrent with C. difficile administration was sufficient prophylaxis against infection; phage treatments post-infection saved 11 of 12 mice whereas control animals receiving *C. difficile*, and clindamycin died within 96 hours (Table 3). [37]

Phage treatment against *E.faceium*- Intraperitoneal administration of a single phage strain was sufficient to rescue 100% of mice in bacteraemia models. Additional animal studies show similarly promising results for multidrug-resistant *E. faecium*, *Vibrio parahaemolyticus*, *S. aureus*, and *A. baumanii* (Table 3).[39]

Phage has been widely used by The Eliava Institute in the preclinical and clinical treatment of common bac terial pathogens like *S. aureus*, *E. coli*, *Streptococcus* spp.,
P. aeruginosa, and *Proteus* spp., with successful applications ranging from surgical to gastroenterological, both therapeutic and prophylactic. [40]

In a clinical trial performed in 1938, 219 patients with bacterial dysentery (138 children and 81 adults) received the sole treatment of a cocktail of phages that targeted *Shigella flexneri*, *Shigella Shiga*, *E. coli*, *Proteus species, P. aeruginosa, Salmonella Typhi, Salmonella Paratyphi A* and *B, Staphylococcus* species, *Streptococcus* species, and Enterococcus spp.; cocktails were administered both orally and rectally (Table 3).[41,42,43]

Phage treatment of oral sores-Chronic tropic ulcers are a complication of some illnesses, such as chronic blood circulation deficiency.[34] Only one infectious agent was discovered in 7% of infected ulcers, according to 16S rDNA pyrosequencing analysis of 3,000 lesions.[51]. Phage therapy could be an alternative to antibiotics for the treatment of infected ulcers. Biodegradable polymers contain different antimicrobial substances and are of particular interest because of their ability to degrade slowly and release active antimicrobials, including phage particles, for a long time.[52] Phage therapy without antibiotics resulted in subsequent wound healing in all treated patients. Phage treatment was most effective in ulcers with one bacterial agent (100%) but a personalized approach led to the elimination of pathogens.[53]

Phage treatment of infected burns-Burns is rapidly colonized by bacteria, which can produce biofilms. Phage therapy could potentially be used to treat burns and prevent sepsis. Topical application of phages led to the elimination of *P. aeruginosa* or successful skin graft in 18 of 30 patients with burns.[[54]

Phage display approach for mAbs (monoclonal antibodies)-This process entails creating a library of peptides or antibody variants, which were then chosen based on their affinity for the target of interest. All surface proteins of bacteriophages can be engineered for display, but the most used are pVIII and pIII from M13 filamentous phages. [55]

Bacteriophages and oral health

Phage populations inhabiting the oral cavity-Early studies of phage in the human oral cavity relied on particle-like particles (VLPs) using electron microscopy to speculate that there may be many phages present in dental plaque.[56] Because these types of studies could not also taxonomically characterize the phage present, it was unclear whether the presence of VLPs represented a few relatively abundant phages or many different differently distributed phages.[57,58,59]Metagenomics techniques based on shotgun sequencing approaches have proven effective in uncovering the membership and diversity of oral phage communities.[60 ,61]

The oral cavity is home to a diverse variety of viruses, many of which are bacteriophages.[62] Phage appears to be more prevalent, which may represent the high bacterial cell-to-human cell ratio in the oral cavity. To eliminate viruses from the oral virome,[63] biomicroscopic methods such as caesium chloride (CsCl) could be used. Several eukaryotic viruses have been identified in these studies, including torque teno viruses, circoviruses, herpesviruses (HSV), and Epstein-Barr virus (EBV), among others, but phage appears to be more abundant, which may reflect the high ratio of bacterial cells to our own cells in the oral cavity. [63, 64] Smaller viruses such as human papillomaviruses may be readily detected after CsCl gradient enrichment. Most studies of human viromes have focused on DNA viruses, so the constituents and potential roles of RNA phage communities' lag. [65]

Principally among these factors include under-sampling of the phage community [66] and an inability to properly assemble phage genomes from complex communities. [61]

A rank-abundance model based on the complete spectra of assembled and size-sorted phage contigs is used to assess phage divergence in human saliva. Contig Spectrum (PHACCS) phage communities [67] could give light on the diversity of viral communities in oral phages.[68]

In the human mouth cavity, phages are less equally dispersed than had been anticipated. [69] It also demonstrates that the diversity of phages in the oral cavity is generally homogeneous between various human individuals and is far bigger than is calculated in the colon.

Dental Health using phage therapy-Dental issues are arguably the most prevalent infection-related disorders in adults. Almost all infectious diseases that threaten oral health involve biofilm. Sensitivity is lacking in current treatments for oral infections caused by biofilm.

Phage treatment, a viable alternative strategy, uses bacteria. Phages are strain-specific, extremely effective against biofilm, and simple to extract and manipulate. [70]

Phage therapy may be useful for oral and dental treatments. Bacteriophages are active against planktonic bacteria and biofilm-embedded cells. [71] Virions may access dense biofilm and spread through neighbouring cells, weakening the whole structure. Some phage therapies use various types of depolymerases to penetrate a bacterial capsule or biofilm matrix.[72]

Some bacteriophages can be found in human saliva, and the most common hosts are Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria and Proteobacteria [73] Biofilms begin with bacteria *attaching* to surfaces and to each other. This is followed by a bacterial transition from planktonic to sessile lifestyles (*colonization*) and then to increases in biofilm bulk, i.e., as a consequence of a combination of biofilm-bacteria replication and extracellular matrix production (*growth*). Net growth ceases in association with biofilm *maturation*. Biofilms also can display various forms of cell *dispersion*, allowing for the colonization of new surfaces Figure 1. [74]

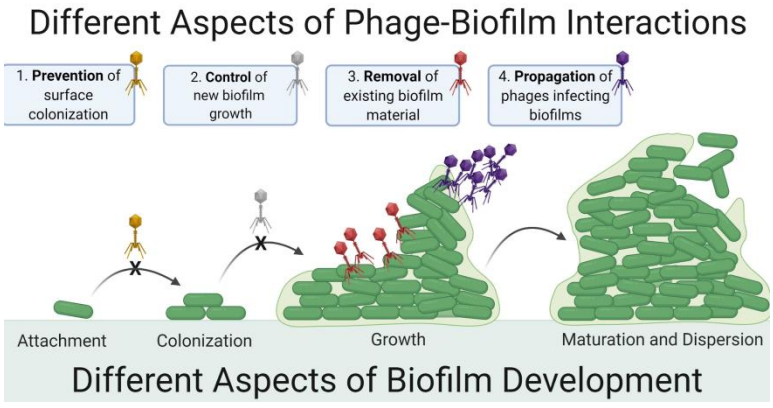

Figure 1- Different aspects of phage-biofilm interactions [74]
Note: (1) Phage *prevention* of bacterial surface colonization (mustard-coloured virions), (2) phage-associated *control* of growth in biofilm bulk (gray-coloured virions), and (3) phage-mediated *removal* of existing biofilm material (red-coloured virions).(4) phages can produce new virions (*propagation*, purple-coloured virions)

A recent study [75] reviewed the main findings
about bacteriophages and oral bacteria, summarized as-Bacteriophage interaction with streptococci contributes to biofilm development. Blocking co-aggregation with bacteriophages may reduce biofilm formation without eliminating health associated *Actinomyces*. [76]
Lysogeny has been observed in *E. faecalis* strains of oral origin. [56] *Enterococci*, occasionally involved in oral infections, may be controlled with a wide range of available bacteriophages. This may be especially helpful in cases of persistent endodontic lesions.[77]
Fusobacterium nucleatum bacteriophages have been isolated from saliva samples.[78] *Porphyromonas*, *Prevotella* and *Tannerella* spp have not been detected in vitro.[79] More studies about these important anaerobic periodontopathogens should be conducted.
Phage enzymes digest bacterial cell walls to liberate assembled phage particles. Lipopolysaccharides (LPS) protect gram-negative bacteria from lysins. Lysins have been successfully tested against *Actinomyces. naeslundii* and a range of *Streptococcus* species. [80, 81,82]
In vitro, some bacteriophages genetically modified against *E. faecalis* biofilm reduced the number of viable cells, which adds to our understanding of phage therapy's dental implications.[83]

Bacteriophages and their potential application in dentistry
Veillonella phages: *Veillonella*, non-motile gram-negative diplococcus, is part of the normal flora of the mouth and is associated with oral infections. Around 25 Veillonellae phages have been isolated from mouthwash specimens. Virion morphology was studied only for functional phages N2, N11, and N20.[84]
Lactobacillus: Bacteriophages for caries associated with 12 strains of Lactobacillus including *Lactobacillus casei* have been isolated. PL-1 is a lytic phage and temperate phage *phi FSW* of *L. casie.*[85]
Periodontal diseases: Bacteriophage communities are regarded to be vital for periodontal health, and it has been suggested that medicines based on them could be developed. Periodontal illnesses, such as dry, irritable, swollen teeth, and gum disease, are linked to a variety of aerobic and anaerobic bacteria.[86]
Endodontic lesions: The effect of bacteriophages on endodontic lesions has only been studied in *Enterococcus faecalis* [87,88]. Endodontic biofilms have a diverse microbial community, suggesting that more research is needed in this area.
Periimplantitis: Phage may interfere with the biofilms that cause periimplantitis (clinical trials are still in the early stages). The discovery of a bacteriophage that adheres to the surface of zirconia well indicates

that phages exist.[89]

Oral mucosal infections: Because phage therapy for skin wounds has been utilized for a long time, phage therapy in this field may advance quickly. Bacteriophage peptides have been shown to stimulate epithelial cell proliferation in the human oral mucosa without causing tumorigenesis. [90]

Clinical use of phage therapy in oral environment

Human phage therapy has been practiced in France since 1919 when it was first successfully used to treat children with dysentery.[91] Phage therapy continued on a small scale until the advent and diffusion of antibiotics in Europe and the U.S. in the 1950s and 1960s. [92]

Until 1974, the Pasteur Institute in France manufactured phage preparations against a variety of infections (Pseudomonas, Staphylococcus, Escherichia coli, and Serratia).[92] Antibiotics were supposed to "cure" infection without the need to detect the true causative agents, making them a convenient option to treat patients. We suspect that phage therapy was discontinued because antibiotics were supposed to "cure" infection without ever having to screen for the true causative agents, making it a simple approach to treat patients. Skin infections, septicaemia, osteomyelitis, wound infections, urinary tract infections, and middle ear and sinus infections were all treated with these phages.[93] In the United States, phages have been used mainly for the preparation of human and animal vaccines. With safety trials completed in 1959, SPL was licensed for human therapeutic usage [94] and was administrated by several different routes: intranasal application by aerosol, topically, orally, subcutaneously, and even intravenously.

During the 1920s and 1930s,[95] phage therapy and interest in phages moved to the United States. Furthermore, multiple studies [96] described the treatment of MRSA using phages, which can be performed by local application for local infections or, if necessary and with great caution, more systemic doses, including intraperitoneally for systemic infections.[97] Larkum reported treatment of 208 patients with chronic tuberculosis at the Michigan Department of Health; 78 percent of the patients had no reoccurring infections for at least six months after therapy, and only 3 percent exhibited no recovery.[103]

Phage therapy is limited in efficacy in those that have a bacterial infection. About 80% of infections caused by *Klebsiella pneumoniae* are due to multidrug-resistant strains.[98] Phage SS specific for *K. pneumoniae* is well characterized,[99] and its potential as a therapeutic agent is evaluated in an experimental model of lobar pneumonia.[100] Overall phage therapy efficacy was demonstrated in a clinical trial (the late 1950s to early 1960s) in which 607 patients, all of whom had failed to respond to conventional treatment by antibiotics, were treated by phage therapy. Production of SPL for human use was suspended in the 1990s, and the preparation is currently approved only for veterinary applications. The results were reportedly good: 80% of the patients recovered, 18% improved, and only 2% exhibited no changes.[93] In 2012, a phage research team in Los Angles discovered phage 11P, which is effective on
P. acnes.[101]

Host-phage relationship in oral cavity

Oral phage must reflect the ecology of their bacterial hosts to some extent, although the occurrence of both mutualistic and antagonistic connections between phage and hosts. It is difficult to forecast the dynamics of any host/phage association. Another variable that influences mouth microbial ecology is the exchange of our oral microbiota with those of our close acquaintances. In terms of oral communication, many phages are transferred among intimate contacts via intimate touch or shared environmental reservoirs.[102]

Numerous oral infections have been implicated in the development of periodontal disease [103, 104] but no single pathogen has been identified as being present in every instance.

A recent study observed identical oral phage amongst unrelated household members, even in the absence of such personal activities as kissing, implying that intimate contact is not essential for the transfer of oral microbiota. However, another study recently showed that oral microbiota is considerably transferred during intimate kissing [105] implying that the more intimate the contact, the greater the possibility for

microbiota sharing.
The sharing of viromes among intimate contacts has enormous implications. Many phages carry antibiotic-resistance genes, such as beta-lactamases (associated with antibiotic resistance such as Penicillin), which could affect the local microbiota's tolerance to antibiotic perturbations. This implies that antibiotic resistance may not necessarily result from selective antibiotic pressure. The survival of oral phages affords significant potential for sharing among close contacts.[106]

IV. RESULTS AND DISCUSSION OF THE EXPERIMENTS

In this review, we provide a summary of the state-of-the-art in bacteriophage therapy in the oral cavity in this review.[107] Phage treatment in the oral cavity is currently receiving considerable attention as more and more bacteria develop resistance to the available antibiotics. [108] The modern approach to phage therapy has discussed a variety of strategies, including natural and manufactured phage, phage-derived enzymes, and the use of phages in combination with antimicrobial agents. [108] Reports suggest that in a clinical trial conducted in 1938, 219 patients with bacterial dysentery [86] (138 children and 81 adults) received the sole treatment of a cocktail of phages. When challenged with gut-derived sepsis due to P. aeruginosa, oral administration of phage saved [61] 66.7% of mice from mortality compared to 0% in the control group.

Due to difficulties with regulation, host range restrictions, bacterial resistance to phages, production, bacterial lysis side effects, and administration, bacteriophage therapy is still a relatively underutilised treatment option. [107]
These technical challenges might be overcome by recent developments in: -
(A) Biotechnology such as the determination of the genome's structure and sequence, bioinformatics analyses that take into account all pertinent databases, and, of course, evidence that the phage(s) can be used for a certain purpose [109]
(B) Phage diagnostics are used to detect and control bacterial pathogens in agriculture. Phage detection takes advantage of the specificity of interaction between phage and their hosts and is cost-effective. The full potential of phage detection and diagnosis has not yet been wholly realised or commercialized.[110]
(C) Synthetic biology. [111] Several clinical trials are currently being conducted that will show that bacteriophages are both safe and effective antimicrobials for the oral cavity. [28]

V.CONCLUSION

Therapeutic intent

Several Western European nations have recently approved the use of phages for therapeutic purposes, and phage treatments are being developed for clinical use. Bacteriophages are gaining popularity these days due to their potential as antibacterial and phage display systems. Virus therapy is based on the idea that phages identify and bind to specific proteins in bacterial host cells, causing cell lysis. Some bacteriophages genetically modified against E. faecalis biofilm reduced the number of viable cells in vitro, adding to our knowledge of the dental implications of phage therapy. Because phage therapy has been used for a long time to treat many infections, phage therapy for the dental field could move swiftly. Further studies are needed in order to evaluate whether the combination of phages with antibiotics might be a successful choice for oral bacteria.

Conservative care

Following the resuscitation of phage therapy, numerous researchers have been able to dig further into this therapeutic option and develop more conservative procedures as complements to conventional treatments. In this field, there should be a call to action. As a result, dental surgeons should get familiar with bacteriophages.

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