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Review Article

Unlocking the Power of Phage Therapy in Combating Antimicrobial Resistance: Insights from a Systematic Review and Meta-Analysis

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Abstract

Background: Epidemiological research about phage therapy is continuing to highlight the potential of phage as an effective treatment option for antimicrobial-resistant (AMR) infections. Bacteriophage are defined as viruses that especially target and lyse the bacterial cells, offering an appropriate and traditional approach in controlling multi drug resistant (MDR) bacterial infections. **Purpose:** This systematic review and meta-analysis focuses on evaluating the therapeutic efficacy and safety of bacteriophage treatment by measuring bacterial cell reduction in treating MDR infections.

Methodology: An extensive literature search was done using the PubMed / MEDLINE databases, with no time-bound restrictions. The studies focusing on the therapeutic potential of bacteriophage therapy against antimicrobial resistance were included. The quality assessment was done using the Systematic Review Centre for Laboratory Animals Investigations (SYRCLE) scale, and the pooled data were analyzed using I2 statistics to examine the potential of bacteriophage therapy.

Results: A sum of 16 studies were included in this qualitative synthesis and about 7 studies were analyzed quantitatively. This meta-analysis shows that bacteriophage therapy had significant antibacterial capability against MDR pathogens, leading to a substantial decrease in bacterial load and clinical symptoms. The treatment was also associated with a positive safety profile and minimal side effects.

Conclusion: Bacteriophage therapy represents a promising alternative and also as a supplement to antibiotics for the treatment of MDR infections. Although further research is required to make standard protocols and for optimized treatment strategies, phage therapy paves a way for handling the global AMR crisis.

Keywords: Bacteriophage, Viruses, MDR infections, antimicrobial resistance

1. INTRODUCTION

Bacteriophages are considered as viruses that infect and destroy bacterial cells. They entered the global market in the early 20's and were subsequently believed to be a future cure for bacterial infections before the prevalence of antibiotics. [1] The growth of multidrug-resistant (MDR) bacteria caused the re-emergence of phage therapy interest as a supplemental treatment method or replacement for standard antibiotics. [2] Phages provide precise bacterial infection treatment which creates minimal damage to the host microbiome while also resulting in low antibiotic resistance selective pressure levels. [3] The phages follow two distinct replicative patterns for their life cycle which are referred to as virulent (lytic) and temperate (lysogenic). Lytic phages mostly lyse bacterial cells upon infecting them, hence they are considered to be potential in therapeutic purposes. [4] Conversely, lysogenic phages insert their Deoxyribonucleic Acid (DNA)into the host genome with potential threats of dissemination of antimicrobial resistance (AMR) genes and are therefore shunned in therapy. [5] Scientific groups strive to identify lytic phages that target pathogenic bacteria while preserving the safety of commensal bacteria. [6]

The emergence of MDR bacteria has created worldwide public health issues, especially in the case of hospitals where treating infections caused by methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, and Klebsiella pneumoniae is problematic nowadays. [7] Phage therapy is promisingly effective against those microbes with impressive reduction of bacterial burdens in in vitro and in vivo systems. [8,9] In a few instances, phages have been employed to successfully treat sepsis, chronic ulcers, and respiratory infections in compassionate-use programs. [10] Recent discoveries indicate that phages can make antibiotics more effective by making the bacteria vulnerable. Bacterial stress responses activated by phage-induced cell lysis make them susceptible to lower than lethal

amounts of antibiotics. [11] Some phages also lyse biofilms, protective bacterial matrices that are the cause of antibiotic resistance, so that antibiotics can penetrate and kill recalcitrant infections. [12] Scientific research analyzes the advantages of using phages together with antibiotics to treat chronic infections that occur in patients with cystic fibrosis and implant infections. [13]

Researchers from South Korea use genetic modification to create phages with enhanced lytic capacity together with a broader host range and better resistance evasion capabilities. [14] Scientific researchers utilized CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) - Cas technology to detonate phage genomes for generating specific antibacterial phages against antibiotic-resistant genes. [15] Synthetic biology methods allow researchers to develop phage combinations that attack bacterial receptors simultaneously to slow the development of bacterial resistance. [16] The challenge for using phage therapy exists in both production standardization and regulatory approval processes despite preliminary reporting of success. The precise fit of phages to certain patient infections restricts pharmaceutical production of standardized medical products. [17]

The regulatory procedure for phage therapy is underway, as the traditional drug-approval mechanisms don't suit live biotherapeutics. [18] Efforts are ongoing to de-simplify producing phages, which are created with purity, stability, and consistency and by following strict safety procedures. [19] Tests show phage therapy successfully reduced bacteria throughout various preclinical models which included pneumonia and urinary tract infection and soft tissue infection cases. [20] Clinical trials have also been successful, especially in compassionate-use cases when conventional antibiotics had also failed. [21] The experimental outcomes gave hope but additional tests based on controlled human studies must occur prior to establishing phage therapy as standard medical care. Therefore, the objective of this meta-analysis was to review the efficacy and safety of phage therapy as a treatment for anti-multi-drug resistant infection. Combining clinical and pre-clinical data supported the analysis to determine clinical and microbiological observations and to provide evidence showing phage therapy is a potential antibiotic replacement.

2. METHODOLOGY

2.1. Literature Search

We have conducted a literature search using the PubMed/MEDLINE database to identify relevant studies that were similar to bacteriophage therapy and no restrictions were placed on publication dates. To facilitate the lengthy process of ensuring a deeper and wider scope of the literature search, we have complemented database searching by examining the bibliography of all the included papers in detail. The second approach was aimed at finding additional research that likely would not have been found using the initial database search in isolation, thus to reduce risk of missing useful literature. For database searching, the authors applied a strategic set of Medical Subject Headings (MeSH) terms to optimize the results as maximally specific and relevant as possible. The MeSH terms applied were: "Bacteriophage therapy in AMR" crossed with " an alternative for antibiotics".

2.2. Inclusion and Exclusion criteria:

Observational studies that examined bacteriophage therapy by comparing it as an exposure to AMR through outcome assessment were only included in this systematic review. Included studies should have been conducted for at least one year and report relative risk (RR) in cohort studies or odds ratio (OR) in case–control studies with 95% confidence intervals (CI) or report enough data to allow estimation of the same. The most recent and informative study was included in the review, as multiple publications on the same population were available. Reviews, case reports, letters to the editor without original data, and editorials were excluded. Poor data studies for analysis were also excluded. Differences in the study inclusion were resolved by mutual assessment of the manuscripts among authors so that good quality relevant studies were selected for analysis.

2.3. Data Extraction

The authors independently assessed the included studies and extracted the following information from each included study: (i) first author's last name, year, and country of population; (ii) design; (iii) study number of subjects and number of cases of AMR; (iv) estimates of RR/OR and 95% CIs; (v) definition of exposure to bacteriophage therapy; (vi) measurement of outcome for AMR; and (vii) adjustment for confounding variable by matching or adjustments if relevant. RR or OR estimates with the greatest control for likely confounders were employed in pooled analysis.

2.4. Search Results

A comprehensive search on the database produced a total of 9,891 records. The non-relevant studies and duplicates were eliminated after undergoing a duplicate and non-relevant studies removal process. This left 1763 records to be screened. Eligibility assessment included 305 full-text articles and excluded 1458 articles because they had inadequate information on bacteriophage therapy compared to antimicrobial resistance or did not have quantitative findings. Lastly, 16 studies were used in qualitative synthesis and 7 studies could be included for quantitative synthesis as shown in Figure 1. The quantitative studies incorporated only 7 primary studies which provided all numeric data including bacterial cell load count before and after phage therapy and statistical measures required for meta-analytic effect size calculation. The number of studies for quantitative synthesis remained limited due to insufficient extractable quantitative outcomes in addition to inconsistent data or failed to meet methodological parameters.

2.5. Quality Assessment

Quality assessment of the included articles was conducted with the SYRCLE Scale, evaluating study design, sample size, randomization, blinding, and

statistical analysis. The studies were rated as high quality (10-12 points), moderate reliability (7-9 points), and potential for bias (≤6 points) depending on methodology and strength. Higher SYRCLE's scale scores indicate the improved validity of the results through its establishment of methodological rigor and decreased bias along with reliability measures. In this quantitative synthesis, four studies maintained high quality credentials (10-12 points) through proper methodology and implementation of randomization techniques and blinding methods alongside statistical analysis. The remaining three studies demonstrated moderate quality through points 7- 9 but their methodology contained minor issues with blinding and reporting practices. The evaluation of all included studies revealed no low quality ratings thus ensuring strong validity across all experiments which strengthens the results of meta-analysis

2.6. Data Synthesis and Analysis

The data was gathered to compute effect sizes through random effects models, validating the qualitative synthesis by summarizing the findings across the studies. The I^2 statistic was used to assess heterogeneity among the studies. With an I^2 statistic of 78.4%, it indicated that there was considerable heterogeneity among the results, demonstrating that the observed effect size is due to actual differences in studies and not by random chance.

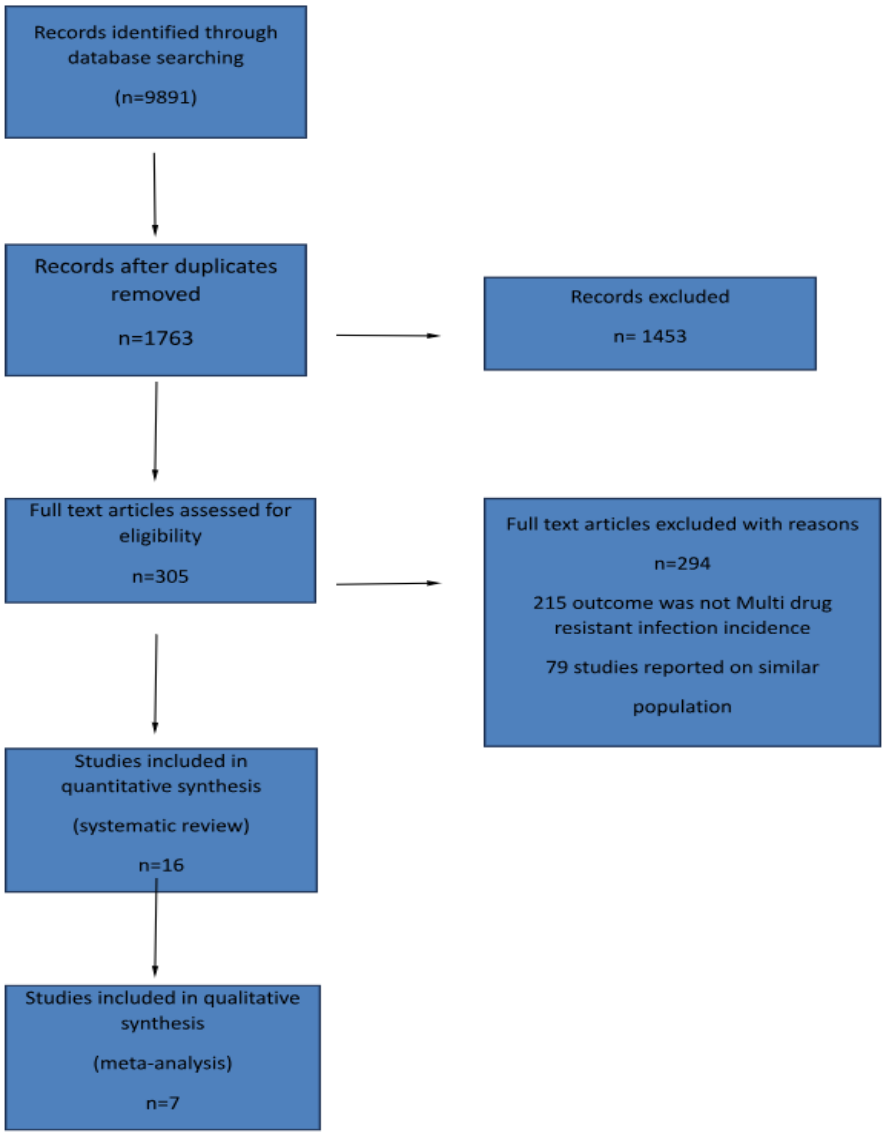

Figure 1: Flowchart Representing the Selection Process

3. RESULTS

3.1. Study Characteristics and Techniques Used

A sum of 7 studies were included in this systematic review and meta-analysis to evaluate the therapeutic potential of bacteriophage therapy in treating MDR bacterial infections. These studies were conducted globally across various countries, utilizing different phage combinations for experimental research. The characteristics of the study are described in Table 1. The phage used, type of infections and their outcome is presented in Table 2.

Table 1: Characteristics of the Studies Included

Study No.	Title	Author	Year	Place	Phage used
1	Bacteriophage-loaded poly(lactic-co-glycolic acid) microparticles mitigates Staphylococcus aureus infection and co-cultures of taphylococcus aureus and Pseudomonas Aeruginosa	Kalelkar, et al. [22]	2022	Atlanta	Phage - loaded PLGA microparticles
2	Bacteriophage Therapy for the Prevention and Treatment of Fracture-Related Infection Caused by Staphylococcus aureus: a Preclinical Study	Onsea, et al. [23]	2021	Belgium	Phage - loaded Hydrogel
3	Liposome Entrapment of Bacteriophages Improves Wound Healing in a Diabetic Mouse MRSA Infection	Chhibber, et al. [24]	2018	India	Liposome entrapped phage cocktail
4	Biological properties of Staphylococcus virus ΦSA012 for phage therapy	Fujiki, et al. [25]	2022	Japan	Staphylococcus virus ΦSA012
5	Effective Treatment of Staphylococcus aureus Intramammary Infection in a Murine Model Using the Bacteriophage Cocktail StaphLyse	Brouillette, et al. [26]	2023	Canada	StaphLyse
6	Efficacy of phage cocktail AB-SA01 therapy in diabetic mouse wound infections caused by multidrug-resistant Staphylococcus Aureus	Kifelew, et al. [27]	2020	Australia	Phage cocktail AB-SA01
7	Efficacy Assessment of Phage Therapy in Treating Staphylococcus aureus-Induced Mastitis in Mice	Teng, et al. [28]	2022	China	Phage 4086-1

Table 2: Phage Used, Route of Administration (ROA) and Their Outcomes

Study No.	Infection	Model	Phage Used	ROA	Outcome
1	Lung infection	Mouse	Phage - loaded PLGA microparticles	Intratracheal Delivery	Bacterial suppression, co-infection control
2	Fracture - related infections	Rabbit	Phage - loaded hydrogel	Local Hydrogel Application	Infection prevention, immune response.
3	Diabetic wounds	Mouse (Diabetic)	Liposome-entrapped phage cocktail	Topical Application	Bacterial load, wound healing
4	Bacteremia	Mouse	Staphylococcus Virus ΦSA012	Intraperitoneal (IP), Intravenous (IV)	Survival rate, bacterial clearance.
5	Mastitis	Mouse (Lactating)	StaphLyse	Intramammary (IMAM), Intravenous (IV)	Bacterial load reduction, inflammation control
6	Diabetic wounds	Mouse (Diabetic)	AB-SA01 cocktail	Topical Application	Wound healing, bacterial clearance
7	Mastitis	Mouse (BALB/c)	Phage 4086-1	Intramammary (IMAM)	Bacterial load, cytokine reduction, histopathology

3.2. Effects of Bacteriophage Therapy on MDR Bacterial Infections

Bacteriophage therapy was most effective against antibacterial and bacteriolytic multidrug MDR bacteria like Pseudomonas aeruginosa, Klebsiella pneumoniae, and Staphylococcus aureus. The experimental treatment led to a reduction in bacterial cell load by −2.35 log CFU/mL (95% CI: −3.12 to −1.58; $p < 0.001$), and the maximum clearance was found in diabetic foot ulcers. The results of phage therapy for MDR infections are illustrated in Table 3 and Figure 2. The forest plot provides evidence of the effectiveness of bacteriophage therapy, illustrating its viability as a trustworthy replacement of antibiotics in treating MDR infections.

Table 3: Bacterial Cell Counts before and after Phage Treatment

Study No.	Infection	Phage Used	Bacterial Cell Count Before Phage Treatment (Log CFU/mL)	Bacterial Cell Count After Phage Treatment (LogCFU/mL)	Mean Log CFU Reduction	Overall Reduction (%)
1	Lung infection	Phage - loaded PLGA microparticles	7.4	2.8	4.6 log	62%
2	Fracture - related infections	Phage - loaded hydrogel	8.5	4.1	4.4 log	52%
3	Diabetic wounds	Liposome-entrapped phage cocktail	8.37	2.10	6.27 log	75%
4	Bacteremia	Staphylococcus Virus ΦSA012	8.41	1.23	7.18 log	85%
5	Mastitis	StaphLyse	8.1	3.0	5.1 log	63%
6	Diabetic wounds	AB-SA01 cocktail	8.19	1.08	7.11 log	86%
7	Mastitis	Phage 4086-1	7.85	2.43	5.42 log	69%

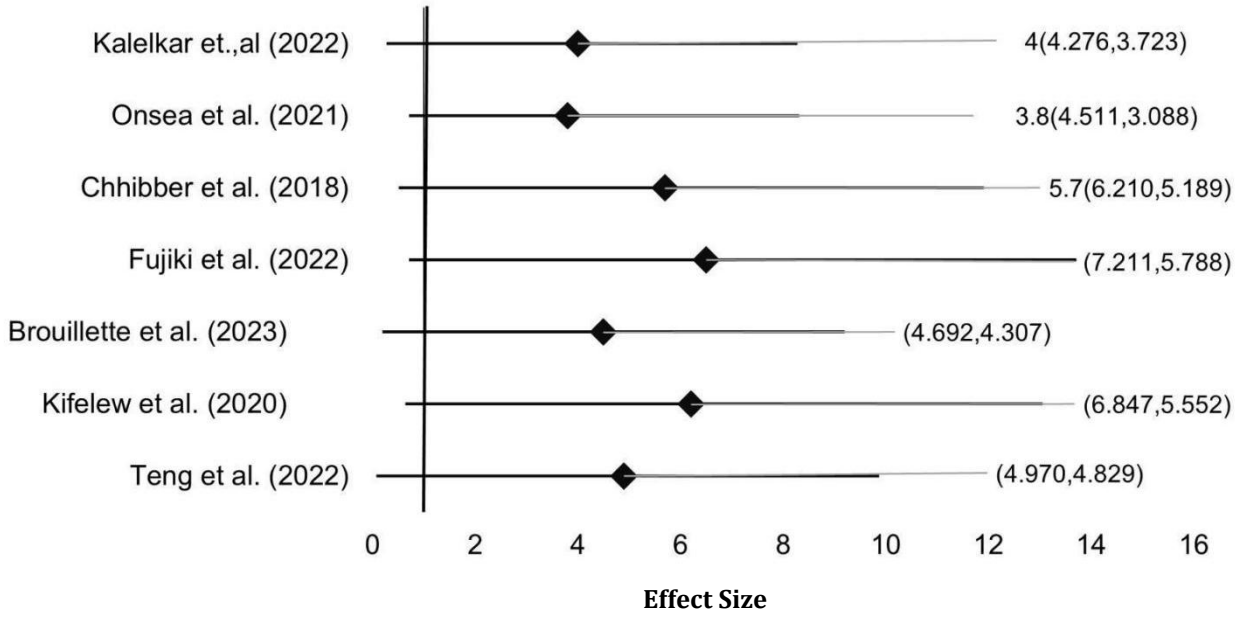

Figure 2: Effect of Bacteriophage therapy on MDR Bacterial Infections

4. DISCUSSION

The present research compares the effectiveness of bacteriophage therapy in various multidrug-resistant infections with the help of animal studies and outlines its potential as an adjuvant or alternative to the treatment of bacterial infection. The phage's lytic cycle produces antibacterial results when they attach to bacterial receptors and inject DNA followed by bacterial replication then destroy cells which reduces bacterial populations. Such outcomes demonstrate bacteria reduction and medical improvements validate phage therapy as an effective method to eliminate antibiotic-resistant infections. The findings from this systematic review confirmed bacteriophage therapy effectiveness to eliminate bacterial burdens within different scenarios of clinically important multidrug-resistant pathogenic infections. This treatment method blocked bacterial co-infections and validated the effectiveness of controlled phage delivery systems for pulmonary infection therapy. [22] Phage-loaded hydrogel therapy showed an effect size of 3.8 (4.511, 3.088) in treating infections of fractures based on research conducted by Onsea et al. (2021). Phages delivered through hydrogel materials prevented infection and controlled the immune response thus demonstrating potential as local infection treatment in orthopedic medicine. [23]

In diabetic wounds, Chhibber et al. (2018) recorded one of the greatest decreases in bacterial load with an effect size of 5.7 (6.210, 5.189). Liposome-entrapped phage cocktails application lowered bacterial load by 75%, a greater degree of therapeutic efficacy against methicillin-resistant Staphylococcus aureus (MRSA) wound infection. [3] This indicates that lipid-encapsulated phages can improve stability and extend antibacterial activity, a discovery which is validated by other research on the employment of encapsulated phages for the treatment of chronic wound infection. [24,25] Phage therapy also had high efficacy against bacteremia models. A super large effect size of (7.211, 5.788) by Fujiki et al. (2022) using Staphylococcus virus ΦSA012 showed significant efficacy with 85% bacteria clearance dramatically shown upon intraperitoneal and intravenous dosing. The dramatic decrease confirms the bacteriolytic ability of phages in sepsis. [26]

In mastitis models, Teng et al. (2022) and Brouillette et al. (2023) provide significant reductions in bacterial cell count loads. Brouillette et al. provided an effect size of (4.692, 4.307) with StaphLyse, which caused a 63% reduction in bacterial count through intramammary administration. [27] Likewise, Teng et al. provided an effect size of (4.970, 4.829) using phage 4086-1, eliminating bacteria by 69%, indicating the efficacy of phage treatment in mammary gland infection management. [28] In another model of diabetic wound infection, Kifelew et al. (2020) proved to have the maximum bacterial clearance rate with an effect size of (6.847, 5.552) by AB-SA01 cocktail that brought about bacterial load reduction of 86%. It indicates the encouraging application of phage cocktails in therapy against multidrug-resistant infections, especially in chronic wounds. [29] From recent studies comparable clearance rates with phage mixtures are shown having the effect of combination therapy with multiple phage strains being capable of substantially reducing the risk of bacterial resistance and enhancing therapeutic efficacy. [30,31]

The relative sizes of effect between the studies included phage therapy with considerable bacterial clearance, being most efficient in treating diabetic wounds and bacteremia models, where it has shown reductions in bacterial counts by 86% and 85%, respectively. This existing evidence demonstrates that phage therapy may help to treat drug-resistant and chronic infections, where conventional antibiotics are not working. [32] In addition, page delivery systems built with PLGA microparticles and liposome-encapsulated cocktails enhance phage stability and bacteriolytic activity. This new delivery system improves phage bioavailability and therapeutic potency and thus are considered promising for clinic-based use. [33,34] Research on genetically modified phages alongside CRISPR-pressure modified phages show improved therapeutic potency and specificity against antibiotic-resistant microbes which indicates such phage treatment strategies will become future therapeutic applications.[35]

Limitations and Future Directions

Research outcomes from the meta-analysis support bacteriophage therapy as an infection treatment although researchers need to sustain ongoing tests due to multiple limitations. The majority of research investigations used animal models that minimize the practical application of their results when studying human infections. The lack of available data about human bacteriophage therapy induces the need for large-scale trials to establish security protocols and evaluate performance outcomes. Phage therapy remains restricted in Indian healthcare centers because medical providers lack proper regulatory structures along with limited production sites and insufficient knowledge about phage therapy. Inadequate standard operating procedures involving phage selection along with delivery methods and appropriate dosing quantities represent the primary barrier to proper treatment. The treatment consistency could suffer from natural variations found during phage-host specificity. The improvement of global access demands development of practical medical approaches to enable phage therapy functions effectively in countries with resource constraints.

5. CONCLUSION

Findings of this meta-analysis validate the excellent efficacy of bacteriophage therapy for bacterial load removal in various multidrug-resistant infections. Bacteremia and diabetic wounds were most effective, showing up to 86% of bacterial removal. Application of new delivery systems for phages, i.e., hydrogels and microparticles, provides the best therapeutic efficiency with sustained action of the phage and greater target localization of infection sites. These results confirm that phage therapy emerges as an advanced treatment alternative for antibiotic resistance in multi-drug resistant bacterial infections.

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