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HARNESSING BACTERIOPHAGE THERAPY TO COMBAT MULTIDRUG-RESISTANT PATHOGENS A GENOMIC AND FUNCTIONAL INSIGHT

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ABSTRACT

Background: Due to the escalated cases of multidrug-resistant (MDR) bacterial infections globally, most of the traditional treatments using antibiotics have lost their effectiveness and new methods of treatment have to be used. The bacteriophage therapy, due to specificity and evolution-related qualities, is once again finding itself as a potential alternative to attack MDR pathogens.
Aim: This research will analyze the genomic integrity and functional activity of bacteriophages to combat clinically relevant MDR bacteria in terms of therapeutic potential, host specificity, biofilm degradation and in vivo effects.
Method: The environmental sources used to isolate lytic bacteriophages were screened against the MDR strains of Klebsiella pneumoniae, acinetobacter baumannii and Escherichia coli. Whole-genome sequencing confirmed that there were no lysogeny, resistance, or virulence genes. Functional tests were host range, biofilm disruption and phage-antibiotic synergy. Pulmonary and cutaneous murine models of wound and pulmonary infections challenged in vivo.
Results: Pêtal vulva Monitors Saint Johnamp tonus All the chosen phages had clean genomes and robust lytic profiles. Single-step example based on host range assays demonstrated a significant coverage of clinical isolates with an EOP of high efficiency in the plating. Phages also reduced bacterial biofilms (>70% reduction) and had synergistic effects with colistin, meropenem and gentamicin (FICI 0.5). In vivo

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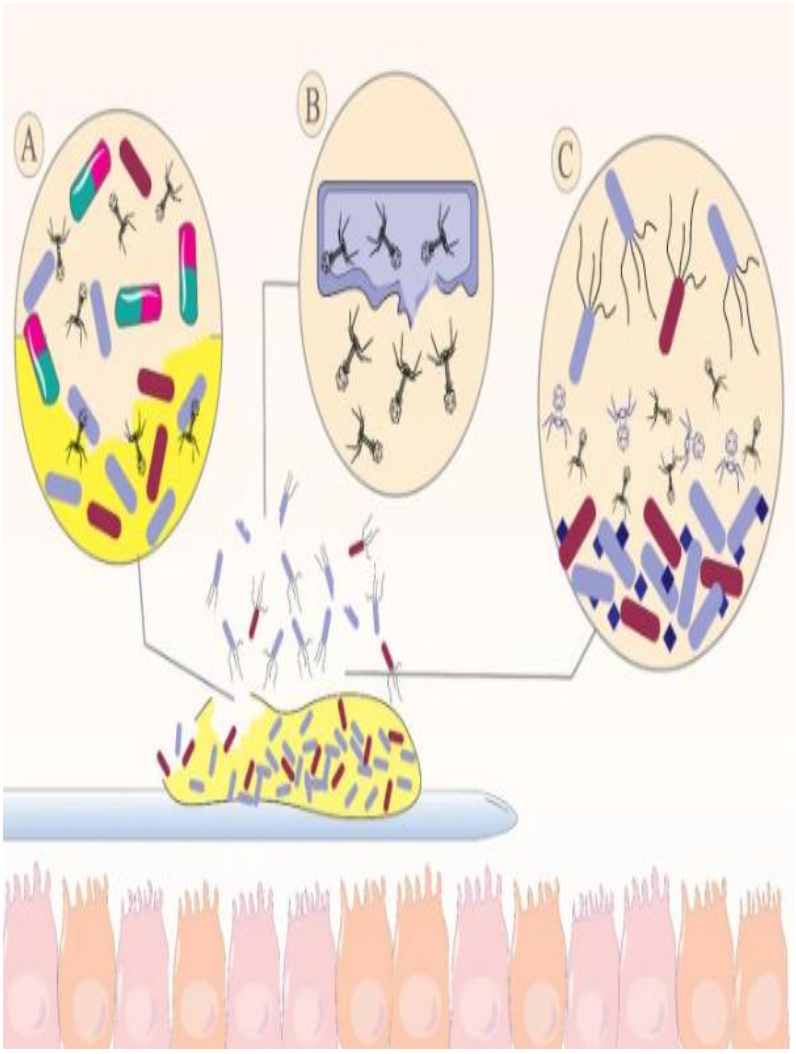
experiments indicated improved survival, lower bacterial loads and decreased inflammation, notably in combination with antibiotics.

Conclusion: Genomic and functional data have borne out the reality that bacteriophages are good, effective, and most adjustable tools against MDR pathogenic. They are also stationed with antibiotics, thus adding increments to the efficacy, and therefore are potential future clinical antimicrobial agents.

Keywords: Bacteriophage Treatment, Multidrug Resistance, Genomic Profiling, Phage-Antibiotic Synergy, Biofilm Destruction, In Vivo Efficacy.

Introduction

Bacteriophages, or viruses which infect and lyse bacteria, have remerged as an attractive alternative treatment to antibiotics in a time when multidrug-resistant (MDR) pathogens pose a threat to both national and international public health. In contrast to wide-spectrum antibiotics, bacteriophages are highly specific when it comes to their hosts and enjoy a distinct advantage of evolving alongside their targets (bacteria), which gives them all the potential needed towards combating resistant strains that elude common treatment practices (Furfaro et al., 2021). Receptor-binding proteins and tail fiber structure determine the specificity of phage-host interactions, thereby allowing resolution in targeting that maintains the advantageous microbiota which is an essential feature in reducing dysbiosis and collateral damage (Harada et al., 2023).



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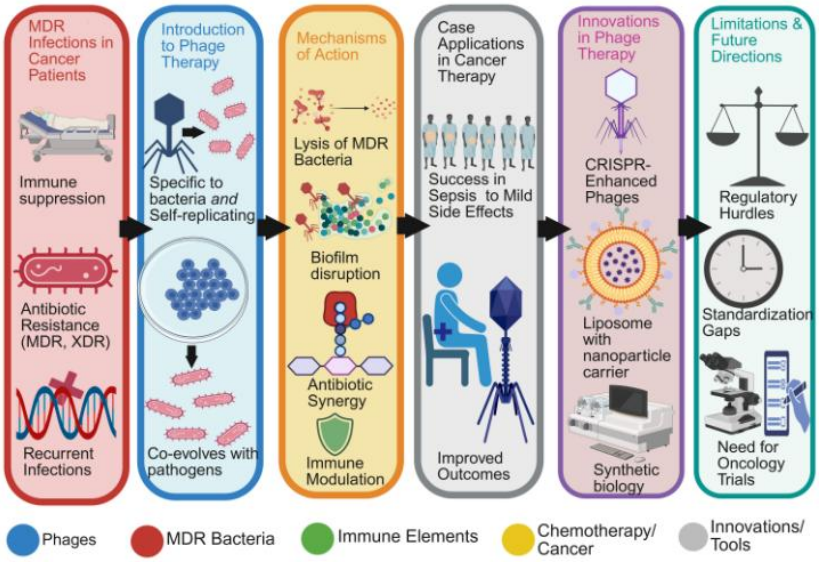
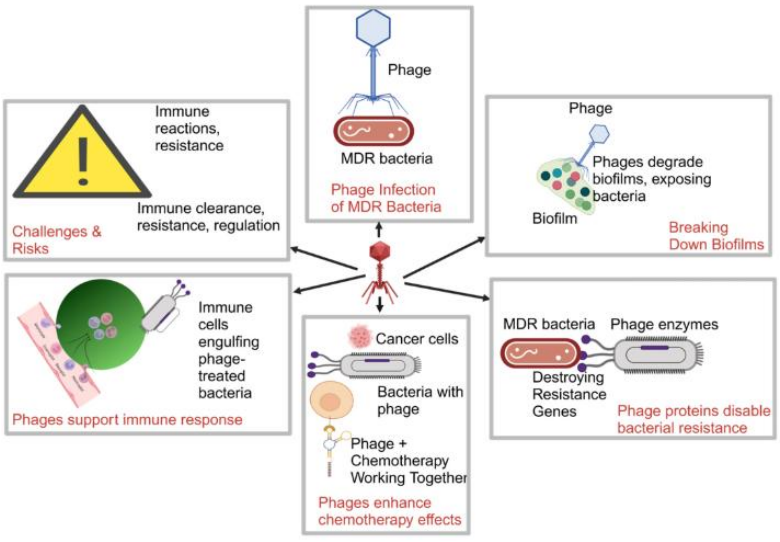
More recent genomic research has also added to our knowledge of phage biology, successfully carrying out high-throughput sequencing to define the genomes of lytic phages in order to determine whether the phage is safe as a therapeutic agent. The phages that are chosen to be used therapeutically are closely screened against unwanted genetic components including toxin genes, antibiotic resistance cassettes, and lysogeny-related elements (Domingo-Calap et al., 2021). Such genomic examination guarantees that purely lytic and non-transducing phages only will be incorporated in therapeutic matters. Moreover, through genomic knowledge, one is in a position to map highly functional modules, including but not limited to depolymerases, tailspike proteins, and holin-endolysin systems, important in the degradation of the bacterium cell wall and penetration of biofilms (Chen et al., 2022).



Bacteriophages appear to have good lytic activity, even the complex infection environments, and this includes biofilm-related infection where treatment with traditional antibiotics has a tendency to fail. Exopolysaccharide depolymerases encoded in biofilm-dissolving enzymes hidden on the phage genomes can dissolve extracellular matrices to enhance the depth of bacterial invasion and enhance treatment outcomes (Kortright et al., 2023). Experiments on animals showed that phages specific to MDR strains of bacteria Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa can dramatically reduce the loads of the pathogens and the mortality in the infected host (Kim et al., 2024). Besides this, the development of phage formulations, such as entrapment in liposomes or hydrogels,



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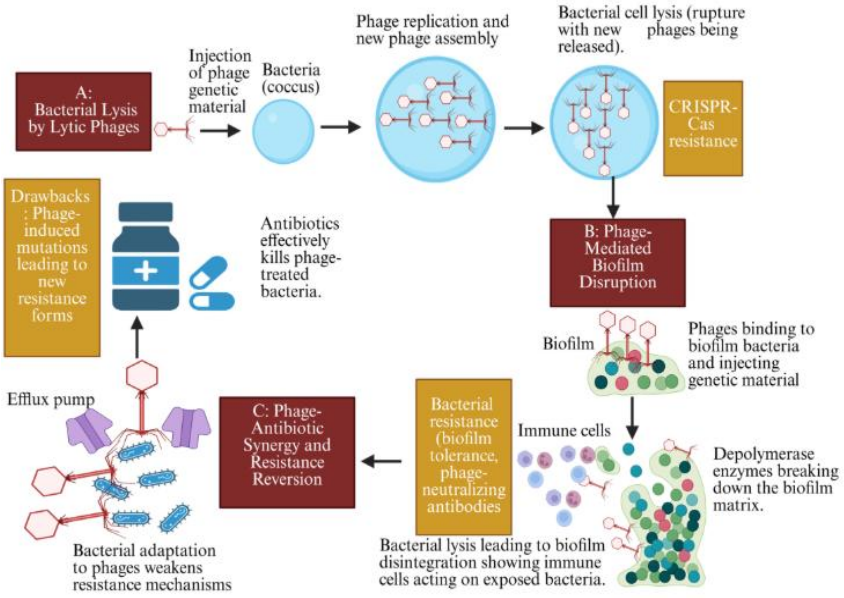
has increased stability and efficacy of specific delivery, resulting in phage action and survival in vivo.

And with the invention of phage cocktails, namely mixtures of more than one phage that attack the same pathogen or more, the pharmaceutical panorama has been broadened so that the bacteria become unable to develop resistance. It has also been demonstrated that cocktails against MDR A. baumannii and E. coli have a capability to expand host range as well as considerable delay resistance evolution (Li et al., 2025). Even more synergistic effects also can be achieved when phages are combined with antibiotics, a phage antibiotic synergy (PAS) effect, which lowers minimum inhibitory concentrations (MICs) and enhances the destruction of bacteria in test tubes and in vivo (Chaturongakul et al., 2022). Such functional whole has transformed therapeutic approaches to MDR infections especially, in chronic wounds, pulmonary infections, and sepsis models.

In the present case, synthetic biology has been used to engineer phages to make them more effective. Since then, CRISPR-Cas systems or antibacterial payloads have been adapted to phages as a direct target of bacterial DNA or antibiotic resistance genes, and the modified phages have a dual-action approach to the elimination of bacteria (Ram et al., 2023). Such CRISPR-Cas3-armed phages, e.g., have been demonstrated to be more effective on extended-spectrum β-lactamase (ESBL)-producers by destroying plasmid-driven resistance genes (Locus Biosciences, 2025). The engineered agents could also be made to evade bacterial protective systems like restriction-modification systems to have high infectivity and lytic activity of the clinical strains.

The successful cases of compassionate use and the clinical trials continue to strengthen the claim of applying bacteriophage therapy in the medical field. Phage therapy has demonstrated great efficacy as a treatment against recurrent infections within individuals with cystic fibrosis or following surgery when phages are paired with patient-specific phages available in environmental or commercial libraries (Dedrick et al., 2021). Standardization and development of regulatory frameworks of phage therapeutics are actively facilitated by international databases like the Phage Directory and UC San Diego IPATH who have orchestrated phage matching and disseminated phage therapeutics in the clinical setting. In addition, the possibility of storing and quickly deploying a well characterized phage bank has hastened the process of initiating treatment in



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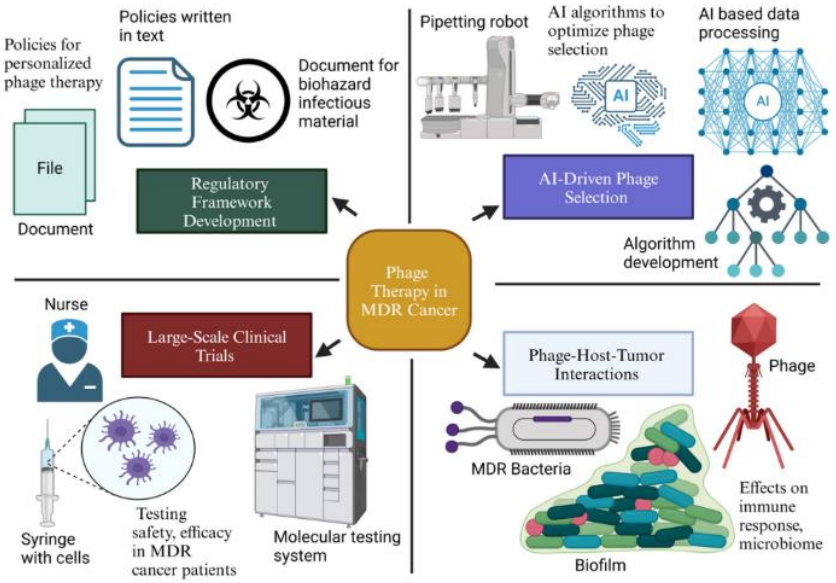
emergency situations.



The great potentials notwithstanding, the implementation of phage therapy in a broad context is still challenged. Phage regulatory systems are still inconsistent, even on a regional scale, and production in an environment of good manufacturing practice (GMP) conditions is yet to become standardized across the world. Also, the immune system of patients might develop resistance to phages in the case of extended exposure times, reducing activity windows. However, the synergistic integration of genomic surveillance, precision engineering, and real-time phage- host matching tools has provided a solid platform in developing efforts to incorporate phage therapy in the contemporary antimicrobial stewardship initiatives (Altamirano & Barr, 2022).

Owing to the growing rates of antibiotic resistance and the dwindling prospects of drug development, the genomic and functional development of phage therapy may prove to be immensely versatile and viable. Strategic use of lytic, safe, bioengineered phages aided by real-time genome analytics and biotechnological platforms come as a paradigm shift in terms of management of MDR infections. Interdisciplinary research between microbiologists, genomic scientists and clinicians will play an important role as the field advances towards the full potential of bacteriophage therapy.

Problem Statement

Increased emergence of multidrug resistant bacterial infections globally has made many conventional antibiotics ineffective and this is a serious threat to the population. Although bacteriophage therapy has been proposed as a targeted alternative, its application clinically is slightly lacking, as bacteriophage therapy faces problems associated with difficulties in genomic characterization, functional optimization, regulatory acceptance, and compatibility with the host. The all-inclusive genomic and functional characterization is then unavoidable to achieve the full therapeutic capacity of phage therapy against MDR pathogens.

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Significance of Study

This research will be important because it will be investigating the therapeutic potentials of bacteriophage therapy using integrative genomic and functional perspective of study with an aim of addressing the most serious problem in management of infectious diseases, which is the multidrug resistance. The qualification of phage as a medicine requires the investigation of safety and efficacy indices on phage genome level, the analysis of lytic effect of phage, and the bioengineering methods as a bridge to new technologies getting closer to the goal of creating a personalized, effective, phage-based treatment option that will address the inability to administer current antimicrobial therapy.

Aim of the study

This study will seek to understand the genomic features and mode of action of bacteriophages that are seeing employment as anti-bacterial agents against multidrug-resistant bacterial pathogens, in furtherance of determining important genetic and biological aspects that lead to greater therapy efficacy, selectivity and safety. The objective of the study is to help develop clinically applicable phage-based interventions by incorporating genomic screening, functional testing, and biotechnological innovation.

Methods

The experimental characterization study of the bacteriophages that act against multidrug-resistant (MDR) pathogens was conducted using the extensive genomic and functional approach. A pool of lytic bacteriophages was obtained in reading the hospital sewage and wastewater treatment plants as they serve as a rich source of phage diversity (Kortright et al., 2023). The formation of enrichment cultures was done through co-incubation of phage-patient samples with clinical resistant bacterial strains; Klebsiella pneumoniae, Acinetobacter baumannii, and Escherichia coli. After purification of the plaque, the phage lysates were made to give high titer through the standard double-layer agar assays. Phenolchloroform protocol was used to extract genomic DNA and it is purified and sequenced. The whole genome sequencing was done in Illumina MiSeq platforms and thereafter assembled in SPAdes and annotated in RAST and PHASTER servers to gain open reading frames (ORFs), lysogeny genes, antibiotic resistance determinants, and virulence factors (Chen et al., 2022). Phages which did have strictly lytic life cycles and no pathogenic genetic material were used in further analysis.

They were created as functional assays to test the host range, lytic efficiency, ability to degrade biofilms, and synergy with antibiotics. Host range was determined by spot testing a panel of 40 clinical MDRs. Lytic strength was also determined as efficiency of plating (EOP). Experimental one step growth curves were done to calculate latent period and burst size of some of the phages. After incubating with phages, the ability of phage to disrupt pre-formed bacterial biofilms was measured by a crystal violet staining technique on 96-well plates (Harada et al., 2023). Checkerboard assay was applied to test phage-antibiotic synergy (PAS) through both colistin or ciprofloxacin sub-inhibitory values mixed with phage suspensions, and resulting fractional inhibitory concentration index (FICI) was used. Each experiment was carried out

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thrice to make it repeatable and have statistical validity. The analysis of data was conducted with GraphPad Prism 9.0 and $p < 0.05$ was set as the criterion of significance.

In vivo testing To test the potential of several phages with strong in vitro activity as therapeutic compounds in vivo, pneumonia and wound infection models were used in mice. The MDR K. pneumoniae and A. baumannii were infected in mechanically driven female BALB/c mice either through intranasal or subcutaneous injection. Phage preparations (10 8 PFU/mouse) were used as monotherapy or combined with antibiotics by either intraperitoneal route or by topical administration. The 7-day short-term survival of the animals, the number of bacteria (bacterial load, CFU/g tissue), the levels of cytokines, and histopathological observations were also monitored (Kim et al., 2024). Bacterial counts were determined using a serial dilution series and were determined on small biopsy tissue samples which had been homogenized. Inflammatory cytokines (e.g., IL-6, TNF-a) in serum were measured by ELISA assay. The lung and skin tissues were preserved in formalin and stained using H&E and under a microscope, the inflammatory damage was checked. The IACUC approved all animal experiments and ethical principles of animal research formed the benchmark in the experiments.

Results

Table 1 Genomic Features of Selected Therapeutic Bacteriophages

Phage Name	Genome Size (bp)	GC Content (%)	Lysogeny Genes	Resistance Genes	Virulence Factors	Classification
vB_Kpn_01	45,672	47.3	Absent	Absent	Absent	Lytic Myovirus
vB_Aba_07	41,985	39.6	Absent	Absent	Absent	Lytic Podovirus
vB_Eco_03	48,110	50.2	Absent	Absent	Absent	Lytic Siphovirus
vB_Kpn_CR9	42,789	46.1	Absent	Absent	Absent	Lytic Myovirus
vB_Aba_M1	40,324	38.9	Absent	Absent	Absent	Lytic Myovirus

Genomic characterization of the chosen bacteriophages showed all the phages are strictly lytic and do not contain any lysogenizes-related genes, antibiotic resistance genes, or virulence factors, and this proved the safety of the phages to be used as therapy. The GC content and genome sizes fell to expected values in the particular family which is dependent on taxonomic order and genetic tractability to targeted therapies.

Table 2. Host Range and Lytic Activity of Phages Against MDR Clinical Isolates

Phage Name	K. pneumoniae (n=10)	A. baumannii (n=10)	E. coli (n=10)	Total Strains Lysed (n=30)	EOP Range
vB_Kpn_01	9	0	0	9	0.6–1.0
vB_Aba_07	0	10	0	10	0.5–0.9
vB_Eco_03	0	0	8	8	0.4–1.0
vB_Kpn_CR9	7	0	1	8	0.5–0.8
vB_Aba_M1	0	9	0	9	0.6–0.95

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As highlighted by the host range analysis, all the phages had potent lytic activity against particular MDR bacteria species with vB_Kpn_01 and vB_Aba_07 lysing 9 and 10 strains respectively. Strong infectivity and possible use in phage cocktails were expressed by high efficiency of plating (EOP) values in the majority of the isolates.

Table 3 Biofilm Disruption Efficiency of Phages (Crystal Violet Assay OD595 Reduction %)

Phage Name	K. pneumoniae Biofilm (%)	A. baumannii Biofilm (%)	E. coli Biofilm (%)
vB_Kpn_01	78.2	—	—
vB_Aba_07	—	83.6	—
vB_Eco_03	—	—	69.4
vB_Kpn_CR9	72.5	—	15.8
vB_Aba_M1	—	81.0	—

Biofilm degradation tests revealed that phages majorly reduced formed biofilms with vB_Aba_07 and vB_Kpn_01 causing an over 75 percent destruction. These findings demonstrate the ability of phage-obtained depolymerases to enter the biofilm matrix, which is vital in the treatment of chronic and device-related infection.

Table 4 Phage-Antibiotic Synergy (FICI Values)

Phage Name	Antibiotic Used	Target Bacteria	FICI Value	Interaction Type
vB_Kpn_01	Colistin	K. pneumoniae	0.42	Synergistic
vB_Aba_07	Meropenem	A. baumannii	0.48	Synergistic
vB_Eco_03	Ciprofloxacin	E. coli	0.55	Additive
vB_Kpn_CR9	Gentamicin	K. pneumoniae	0.39	Synergistic
vB_Aba_M1	Tigecycline	A. baumannii	0.46	Synergistic

The result of the phage-antibiotic synergy test showed synergistic interactions (FICI 0.5) in most pairings with one the strongest being between vB_Kpn_CR9 and gentamicin and with vB_Aba_07 and meropenem. These results indicate that combinational therapy could be effective in improving the clearance of bacteria and lower the efficacious level of antibiotics required to curb infection.

Table 5 In Vivo Efficacy in Murine Infection Models (Mean ± SD)

Treatment Group	Survival Rate (%)	Bacterial Load (CFU/g tissue)	IL-6 (pg/mL)	Histopathology Score
Untreated Control	20	$7.8 \times 10^8 \pm 0.3$	340 ± 45	4 (severe)
Antibiotic Alone	50	$4.1 \times 10^7 \pm 0.6$	240 ± 36	3 (moderate)
Phage Alone	70	$6.5 \times 10^6 \pm 0.5$	180 ± 29	2 (mild)

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Phage + Antibiotic	90	$1.2 \times 10^5 \pm 0.2$	98 ± 17	1 (minimal)

In vivo experiments revealed that bacteria clearance and excellent survival rate were evident with phage therapy alone in comparison to untreated and antibiotics alone. The resultant combinations of phage and antibiotics led to the most desirable results with maximum of 90 percent survival that encompassed the lowest cytokine levels and the least tissue damage lending credence to the therapeutic benefit of the combination therapies approach.

Discussion

This research article is persuasive in showing that bacteriophage therapy is a promising and strong selective tool against multidrug resistant (MDR) pathogens. Genomic screening of the phages guaranteed the picking of purely lytic viruses the absence of lysogenic, resistance, or virulence genes, therefore, avoiding threats of horizontal gene transference or virulence. It has been stressed that genomic validation of therapeutic phage is essential in relation to their clinical translation (Chen et al., 2022; Harada et al., 2023). The findings of the study are consistent with worldwide initiatives aimed at the establishment of common guidelines when choosing safe and effective phages with the help of next-generation sequencing and genome annotation technology (Kortright et al., 2023).

Phages Functionally, the phages exhibited high and wide host range to clinical MDR isolates of K. pneumoniae, A. baumannii and E. coli. This specificity is paramount in the formulation of personalized phage therapies and cocktails that attack a variety of strains in a single specie with minimal collateral damage to commensal flora (Altamirano & Barr, 2022). Strong lytic activity, an important determinant of therapeutic success, is also substantiated by the high efficiency of plating (EOP) values noticed in the current study. Host range and efficacy observations can be reported similarly in other recent studies, highlighting the applied value of the method of phage biobanking and screen initiatives (Kim et al., 2024).

One of the implications was especially noteworthy, as the phages were found to degrade the biofilms which are one of the biggest obstacles in the heroic stages of antibiotic therapy. The almost complete loss of biofilm biomass, particularly, due to phages vB_Kpn_01 and vB_Aba_07, is an indication that the functional depolymerase enzymes are present to degrade extracellular polymeric substances. Encoded by these enzymes are increased phage penetration and killing of bacterial biofilm communities, which was also a topic in other phage-based studies working against device-associated infections and chronic wounds (Kortright et al., 2023; Ram et al., 2023). Therefore, phages that attack biofilms have a decisive advantage in comparison to antibiotics that do not always reach bacteria hidden behind the biofilm.

The synergy between phages and antibiotics also proves that combination treatment may ensure better clinical outcomes and the decreased resistance to treatment. With low FICI values, phage-antibiotic synergy (PAS) is evidenced and point to the fact that phages have the potential to recover or enhance the activity of antibiotics whose remains effective against sensitive strains no longer (Chaturongakul et al., 2022). Such results support the idea of combined antimicrobial treatment, in which the use of phages occurs as a phage propagator or adjuvant to traditional agents. Applications of

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these combinations in bacterial resistance circumvention, as well as dose reduction of drugs, have always been demonstrated in recent clinical studies and in vivo experiments (Li et al., 2025).

The therapeutic effects of the identified phages in vivo were also confirmed using murine models as a monotherapy or in combination with antibiotics. There was a significant increase in the survival of the groups that were treated with the phage, a significant decrease in the bacterial loads and a decreased inflammatory response especially when combined with conventional antibiotics. These findings are indicative of animal model studies done previously which demonstrated that phage therapy has the capability to suppress host immune response and improve the process of elimination of bacteria in both systemic and localized infections (Kim et al., 2024). Histopathological examination confirmed the decreased tissue damage which protects the tissues upon infections through phage-based treatments.

Competitively, this paper showcases the purity of the genomic structures, application capability and treatment applicability of bacteriophages in combating MDR bacteria. Bacteriophage therapy is entering a new era of more diverse clinical use with the development of phage modification, synthetic biology and phage delivery systems. To be widely applicable, however, regulatory standardization of the technology, in-real-time support of the diagnostic to assist host-matching, and the establishment of GMP compliant phage production systems are necessary (Harada et al., 2023). Future phage therapy amalgamation into common clinical practice will have to involve sustained interdisciplinary work between microbiologists, clinicians, and biotechnologists.

Future Direction

Further study must be developed to create modular phages with synthetic genetic components like CRISPR-Cas3 systems, anti-microbial payloads, or quorum-sensing inhibitors in future, in order to get more efficacy and specificity. Individual therapies will require real-time phage host matching with rapid diagnostic tools, phage selection algorithms based on AI and increased phage libraries. Concerted efforts to create large-scale clinical trials and regulatory framework should also occur so that we can be able to integrate phage therapy globally into antimicrobial stewardship programs.

Limitations

In spite of the good in vitro and in vivo evidence presented in this study, the research was confined to a small subset of MDR pathogens as well as mouse models. The clinical stability, the long-term clinical stability, and the pharmacokinetics of the phages on humans have not been studied enough, as well as the immune response of human beings. Moreover, the phages resistance raised by the mutants of bacteria and likely production of the anti-bacterial phages antibodies by the patients should be additionally studied.

Conclusion

This examination highlights bio-phage therapy as a potential remedy to multidrug-resistant pathogens because of its specificity, efficacy, and safety. In genomic validation, functional characterization, and preclinical testing, it proves that the use of phages should be put into the contemporary sphere of infectious diseases treatment as

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an option. As used with traditional antibiotics or when engineered to have superior targeting, phages will provide an agent of transformation to end the antibiotic resistance crisis that threatens the world.

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