Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 3600 - 3610

The Clinical Applications of Bacteriophage Therapy in Addressing Antibiotic Resistance and Drug Development: Review

[1]-Abdullah Ali Saad Alghamdi,[2]-Waleed Abdullah Mohammed Hendi,[3]- Abdul Aziz Ali Ahmad Moafa,[4]-Hamza Abdulalh Hussan Alalisi,[5]-Yasser Saleem Alhojily,[6]-Amnha Muharib Alanazi,[7]-Tariq Bunaydir Duhaysan Alharbi,[8]- Norah Hadi Ali Alkhzamin,[9]-Wafa Msdr Almutairi,[10]- Arwa Abdulwahab Naser Amer,[11]- Saud Rabah Taimis Alharbe,[12]-Fawz Nasser Fawaz Alshehri,[13]-Fayez Zeid Zayed Almutairi

1. Ksa, Ministry Of Health, Rumah General Hospital
2. Ksa, Ministry Of Health, Damad General Hospital
3. Ksa, Ministry Of Health, Jazan Health Complex
4. Ksa, Ministry Of Health, Eradah&Mental Health Complex- Eradah Service
5. Ksa, Ministry Of Health, Madinah Health Cluster
6. Ksa, Ministry Of Health, King Fahad Medical City
7. Ksa, Ministry Of Health, Alrass General Hospital
8. Ksa, Ministry Of Health, Aseer Central Hospital
9. Ksa, Ministry Of Health, Erada Hospital And Mental Health
10. Ksa, Ministry Of Health, Aseer Central Hospital
11. Ksa, Ministry Of Health, Madinah Health Cluster
12. Ksa, Ministry Of Health, Eradah Complex Of Mental Health
13. Ksa, Ministry Of Health, Al-Mithneb General Hospital

Abstract

Background: The rise of antibiotic-resistant bacteria poses a significant threat to global health, necessitating innovative therapeutic strategies. Bacteriophages, viruses that specifically target bacteria, have emerged as a promising alternative to conventional antibiotics. This review explores the clinical applications of phage therapy, focusing on their potential in drug development and treatment of resistant infections.

Methods: A comprehensive literature review was conducted, analyzing studies published between 2000 and 2023 that investigated phage therapy's efficacy against multidrug-resistant (MDR) bacteria. Databases such as PubMed, Scopus, and Web of Science were utilized to identify relevant articles, with a focus on clinical trials and case studies demonstrating phage treatment outcomes.

Results: Phage therapy has demonstrated significant effectiveness in treating infections caused by MDR pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE). Clinical studies reported success rates of up to 77% in eradicating targeted bacteria. Additionally, phages have shown promise in biofilm disruption and targeting intracellular infections. The adaptability of phages has also facilitated their use in vaccine development and gene delivery systems, enhancing their therapeutic potential.

Conclusion: Phage therapy represents a revolutionary approach in combating antibiotic-resistant infections, offering specificity and the ability to self-amplify at the infection site. While challenges such as regulatory hurdles and phage stability remain, ongoing research and technological advancements are

paving the way for phage-based therapeutics to become integral in modern medicine. Future studies should focus on optimizing phage engineering and delivery methods to maximize clinical efficacy.

Keywords: Bacteriophages, Antibiotic Resistance, Phage Therapy, Drug Development, Clinical Trials

Received: 07 october 2023 **Revised:** 22 November 2023 **Accepted:** 06 December 2023

1. Introduction

Phage treatment, using bacteriophages to combat bacterial infections, has a historical lineage that traces back to the early 20th century. Bacteriophages, often referred to as phages, are viruses that only target bacteria. Frederick Twort originally identified them in 1915, followed separately by Félix d'Hérelle in 1917, who noted their capacity to eradicate bacterial cultures [1,2]. Notwithstanding their initial potential, the introduction of antibiotics in the 1940s resulted in a reduction in phage research and use in the Western world. The emergence of antibiotic-resistant bacteria has renewed interest in phage treatment as a potential alternative or adjunct to conventional antibiotics [3-5]. The worldwide health emergency caused by antibiotic resistance has necessitated immediate demands for innovative antimicrobial approaches. Multidrug-resistant (MDR) bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and extended-spectrum β-lactamase (ESBL) generating Enterobacteriaceae, pose substantial difficulties to global healthcare systems. Phage treatment provides a precise method to address these microorganisms. In contrast to broad-spectrum antibiotics, phages have a high specificity for their bacterial hosts, hence minimizing effects on beneficial microbiota and reducing the possibility of collateral harm [6].

Phages have shown effectiveness against biofilm-related illnesses, which are notoriously difficult to manage with standard antibiotics. Biofilms, organized bacterial colonies wrapped in a self-generated polymeric matrix, are associated with persistent infections and exhibit resistance to drugs and immunological responses. Phages may infiltrate biofilms, reproduce inside bacterial cells, and dismantle the biofilm matrix, rendering them effective agents against biofilm-related illnesses [7]. Besides addressing external bacteria, phage treatment is being investigated for its capacity to target intracellular infections. Intracellular bacteria, like Mycobacterium TB and Salmonella spp., inhabit host cells, circumventing several medications that fail to penetrate cellular membranes successfully. Progress in phage engineering and delivery systems is creating new opportunities for using phages to address these concealed illnesses [8].

Phage treatment has considerable potential in combating bacterial infections, although it is just one aspect of phage-based pharmaceutical research. Phage-based medication research includes a variety of new uses beyond conventional phage treatment for bacterial diseases [9,10]. In addition to their function in direct bacterial lysis, phages are being used for many new applications, such as vaccine development, cancer treatment, and as vectors for gene delivery systems. Phage display technique, which entails the expression of peptides or proteins on the surface of phage particles, has transformed vaccine development. This approach facilitates the display of antigens inside a highly immunogenic framework, perhaps resulting in more efficacious vaccinations [11,12]. Phages are being explored as anti-cancer drugs in oncology. Researchers are developing phages to target tumor-specific markers in order to specifically deliver therapeutic drugs to cancer cells, thereby reducing harm to healthy organs. Moreover, the immunogenic characteristics of phages may elicit an anti-tumor immune response, providing a dual mode of action against cancer [13,14]. Phages also provide potential as drug-delivery systems (DDS) for gene therapy. Their capacity to encapsulate and transport genetic material to targeted cells renders them ideal vectors for administering therapeutic genes, including those used in CRISPR-Cas systems for gene editing. The precision and efficacy of phage-mediated delivery methods have the potential to transform gene therapy. The extensive range of applications emphasizes the adaptability of phages in tackling diverse medical issues and reinforces the need for a holistic strategy in phage-based medication development.

Notwithstanding these encouraging uses, several technical and regulatory obstacles must be surmounted to fully actualize the promise of phage-based therapeutics. Concerns about phage stability, immunological response, and regulatory licensing need meticulous attention [15,16]. Nonetheless, with continuous study

and technical progress, phage treatment is set to become a crucial element of contemporary medicine, providing optimism in combating antibiotic-resistant illnesses and more. This study seeks to give a thorough examination of the present status of phage-based medication development, including its applications in addressing drug-resistant bacterial infections, biofilm-associated diseases, intracellular pathogens, vaccine formulation, cancer treatment, and gene delivery systems. By thoroughly analyzing and discussing these aspects, we want to highlight the opportunities and obstacles of phage treatment in the current medical environment.

2. Revised Mechanisms of Phage Action

Phages, or bacteriophages, are established viruses that infect bacteria. Their modes of action are varied and sophisticated, including complex interactions with bacterial hosts. Recent breakthroughs in molecular biology and genetics have elucidated these pathways, offering revised views on the impacts of phages.

The first stage of the phage life cycle involves adsorption to the bacterial surface, facilitated by particular interactions between phage proteins and bacterial receptors. Recent investigations have identified novel receptor-binding proteins (RBPs) that enhance phage selectivity and efficacy. Receptor-binding domains of phages exhibit fast evolution, enabling adaptation to changes in bacterial surfaces [17,18]. Labrie et al. elucidate the many defensive mechanisms that bacteria have evolved to counter phage adsorption, highlighting the significance of comprehending these interactions for the advancement of phage treatment [19]. This versatility is essential for creating phages that can target antibiotic-resistant bacteria.

Subsequent to adsorption, phages introduce their genetic material into the bacterial cell. Advancements in cryo-electron microscopy have clarified the intricate architectures of phage tail machinery involved in this process. Hu et al. elucidated the structure of the bacteriophage T7 DNA-injection apparatus, offering insights into the mechanisms by which phages circumvent bacterial defenses during genome injection [20]. Moreover, several phages use advanced techniques to penetrate bacterial cell walls, including the enzymatic breakdown of peptidoglycan layers [86]. These results highlight potential objectives for improving phage-delivery systems in therapeutic applications.

Phages have several replication mechanisms that are closely associated with their categorization in the lytic or lysogenic lifecycle. Salmond and Fineran [21] have extensively examined the development of replication techniques and the regulatory components governing the transition between lytic and lysogenic cycles. Moreover, phage-replication processes exhibit a modular configuration of replication genes within their genomes, enabling a systematic investigation of these techniques across many phages, such as f1/fd, φX174, P2, P4, λ, and T4. These investigations have greatly enhanced our comprehension of DNA replication, especially regarding the interaction between phage-encoded and host-replication components. Weigel et al. emphasize the significance of replication origins and their related proteins, offering a rich resource for further study [22].

Phages often possess genes that encode toxins and enzymes, which promote bacterial cell lysis and exploit host cellular machinery. Penadés and Christie discovered novel categories of phage-encoded proteins that disrupt bacterial metabolism and immunological responses, enhancing comprehension of phage-bacteria interactions [23]. Harper et al. detail phages that generate enzymes proficient in dissolving bacterial biofilms, hence augmenting their therapeutic efficacy against biofilm-related illnesses [24].

Phages are essential in horizontal gene transfer (HGT), facilitating the dissemination of antibiotic resistance genes among bacterial populations. Lerminiaux and Cameron elucidate the methods via which phages facilitate horizontal gene transfer and the consequences for antibiotic resistance [25]. Engineered phages have been created to reduce the possibility of spreading deleterious genes while enhancing therapeutic advantages. Usman et al. emphasize the use of synthetic biology to engineer phages that specifically target and eliminate resistance genes from bacterial genomes [26].

The co-evolution of phages and their bacterial hosts is a dynamic process that affects phage effectiveness. Contemporary high-throughput sequencing methods have elucidated the evolutionary conflict between phages and bacteria. Hampton et al. examine the ongoing development of phages and bacteria, highlighting

its influence on the efficacy of phage treatment and the need of comprehending these dynamics [27]. Wright et al. underscore the need for phage treatments that maintain efficacy over time and do not induce rapid bacterial resistance [28].

The efficacy of phage treatment relies on both the interaction with bacterial cells and the human immune system. Hodyra–Stefaniak et al. shown that phages may influence the immune response, sometimes augmenting it to facilitate bacterial elimination [29]. Sweere et al. found phage proteins that engage with immune cells, paving the way for the development of phage-based immunotherapies [30].

The efficient administration of phages to the infection site is essential for therapeutic efficacy. Durr et al. delineate revised delivery methodologies, including the encapsulation of phages inside biocompatible substances like liposomes and hydrogels to safeguard them from the human immune response and augment their stability [31]. Malik et al. emphasize the progress in delivery methods essential for the development of phage-based therapeutics applicable in various clinical environments [32]. The inhalation of phages as a therapeutic approach for pulmonary infections is a burgeoning field of investigation, presenting a prospective focused therapy modality. Shien et al. shown that direct phage delivery to the lungs by inhalation may more effectively target the illness location, possibly reducing bacterial burden and inflammation while maintaining the normal microbiome. This approach signifies an innovative and focused tactic in combating respiratory infections [33].

The revised comprehension of phage processes introduces regulatory and ethical implications for phage treatment. Abedon et al. emphasize the need of tackling safety, standardization, and public acceptability as phage-based therapies advance towards widespread clinical use [6]. Pirnay et al. [34] underscore the need for continuous investigation into phage mechanisms to guide regulatory frameworks and guarantee the proper advancement of phage-based therapeutics. The methods of phage activity, from adsorption to lysis, underscore the accuracy and efficacy of phages in targeting bacterial illnesses. Comprehending these pathways is essential for enhancing phage treatment and addressing the issues presented by bacterial resistance.

Recent breakthroughs in molecular biology and genetics have enhanced our comprehension of bacteriophages (phages) and their methods of action, which are essential for phage-based medication development. Phages infect bacteria via a number of intricate stages, beginning with adsorption to the bacterial surface, where receptor-binding proteins enhance specificity and effectiveness. Subsequently, phages inject their genetic material into the bacterial cell, a process clarified using cryo-electron microscopy. Their varied replication mechanisms, capable of alternating between lytic and lysogenic cycles, have considerable significance for therapeutic applications. Phages encode toxins and enzymes that promote bacterial cell lysis and destroy biofilms, hence augmenting their therapeutic efficacy. Furthermore, phages are integral to horizontal gene transfer, facilitating the dissemination of antibiotic resistance genes, while modified phages are designed to reduce this danger. Comprehending these complex pathways is essential for enhancing phage treatment and combating bacterial resistance.

3. Phage Therapy for Antibiotic-Resistant Bacterial Infections

The emergence of antibiotic-resistant microorganisms presents a considerable danger to worldwide public health, requiring the formulation of alternative treatment approaches. Phage treatment employs bacteriophages to specifically target and eliminate bacteria, presenting a potential approach to address drug-resistant illnesses.

Antibiotic resistance has emerged as a significant concern in contemporary medicine, resulting in heightened morbidity and death rates. Research by the World Health Organization (WHO) indicates that antibiotic-resistant bacteria account for around 700,000 fatalities per year globally, with forecasts suggesting up to 10 million deaths yearly by 2050 if no effective interventions are implemented [35]. Bacterial evolution and the acquisition of resistance mechanisms have surpassed the advancement of novel antibiotics, underscoring the critical need for alternative therapies.

Phage treatment utilizes bacteriophages to specifically target and destroy harmful bacteria, providing several advantages over conventional antibiotics. In contrast to broad-spectrum antibiotics, phages exhibit excellent specificity, only attacking the bacteria of interest while preserving beneficial microbiota. This selectivity diminishes the likelihood of subsequent infections and alleviates the development of resistance [36]. Moreover, phages possess the ability to self-amplify at the infection site, therefore delivering a prolonged therapeutic impact [37].

Phages have a high specificity for their bacterial hosts, enabling targeted therapy for multidrug-resistant pathogens while preserving beneficial microbiota. This specificity is especially beneficial in addressing infections induced by organisms including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), and carbapenem-resistant Enterobacteriaceae (CRE). Global clinical research are already underway about the use of phages, with a primary emphasis on drug-resistant bacterial diseases. A Belgian collaboration including 35 institutions across 29 cities and 12 countries recently published the findings of a clinical research involving 100 patients of tailored bacteriophage treatment [38]. The research revealed clinical improvement and eradication of the targeted bacteria in 77.2% and 61.3% of illnesses, respectively, indicating the efficacy of phage treatment against drug-resistant bacteria.

4. Vaccines Utilizing Bacteriophages

Phage-based vaccines provide an innovative method for vaccine development, providing specific benefits compared to conventional platforms. This section examines the basics of phage-based vaccine design, including the use of phages as antigen delivery vehicles, the effectiveness of phage display systems, and the advantages of multivalent and adjuvant characteristics. Integrating antigenic peptides into phage architecture enhances immune responses and offers extensive protection against diverse infections. The novel design and adaptable uses of phage-based vaccines highlight its potential to transform vaccine development and tackle many infectious illnesses. Figure 3 depicts the comprehensive pathway of immune response activation by phage-based vaccinations.

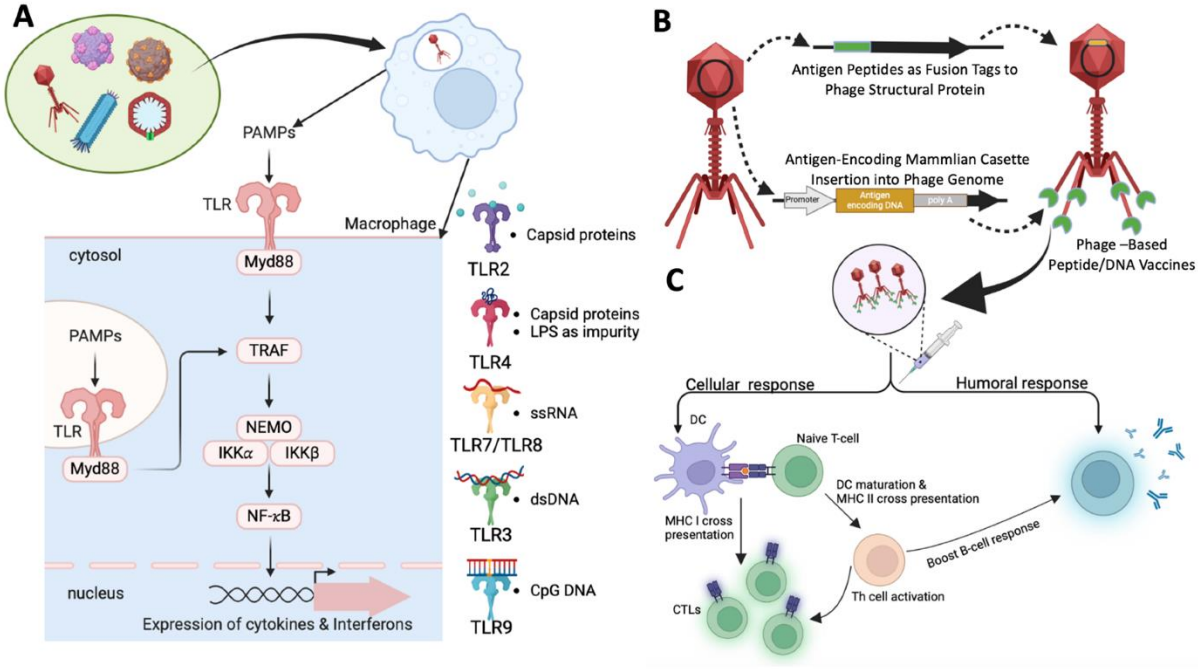

Figure 3. Mechanism of immune response activation by phage-based vaccinations.

Phage-based vaccines use bacteriophages as vectors to convey immunogenic epitopes, leveraging their capacity to efficiently transmit antigenic peptides or proteins to the immune system. This section delineates the fundamental concepts of phage-based vaccine design, including the function of phage-display systems in antigen presentation, the benefits of multivalent vaccines in addressing various infections, and the

inherent adjuvant characteristics of phages that augment immune responses. By incorporating these ideas, phage-based vaccines provide unique and adaptable options for the development of effective vaccinations against many infectious illnesses.

Phage-display systems, particularly filamentous phages like M13 and T7, are essential for displaying foreign antigens on the phage surface. Antigenic peptides or proteins are genetically conjugated to phage coat proteins, which are then produced and shown during phage replication. This approach has been thoroughly examined by González–Mora et al. and Mohammad Hasani et al., emphasizing its effectiveness in antigen delivery [11,39].

Multivalent vaccinations: Phage-based vaccinations may concurrently display numerous antigenic epitopes, therefore augmenting the breadth and specificity of the immune response. Multivalent vaccinations may target many strains or variations of a disease, providing enhanced protection. Bao et al. highlight the adaptability of multivalent phage-based vaccines in offering broad protection against antigenically varied pathogens [40]. The use of this methodology in SARS-CoV-2 vaccines has been investigated by Zhu et al. and Tao et al. [41.42].

Adjuvant characteristics: Phages possess inherent adjuvant characteristics that may activate innate immune responses. They may stimulate Toll-like receptors (TLRs) and other pattern-recognition receptors (PRRs), consequently augmenting antigen presentation and cytokine synthesis. The adjuvant action is essential for the efficacy of phage-based vaccinations. Research conducted by Jepson and March and Górski et al. highlights the capacity of phages to function as adjuvants in vaccine formulations [43,44]. The current study by Krut and Bekeredjian–Ding further investigates the modulation of immune responses by phage treatment [45]. Phage-based vaccinations are both unique in design and diverse in use. Their capacity to present several antigens, together with their adjuvant characteristics, renders them an invaluable asset in the formulation of vaccines for numerous infectious illnesses.

5. Mechanisms of Immune Activation

Phage-based vaccines are emerging as effective instruments in immunotherapy, capable of eliciting both innate and adaptive immune responses via various pathways. This section examines the processes, emphasizing the interactions between phages and the immune system that resulted in successful immunization. It specifically investigates the mechanisms by which phages trigger innate immune responses, enhance antigen presentation, and promote the activation of both T cells and B cells. Key research in the subject highlights the complex mechanisms and promise of phage-based vaccines in enhancing vaccine development.

Phages activate innate immunity by engaging pattern-recognition receptors (PRRs) on antigen-presenting cells (APCs), identifying pathogen-associated molecular patterns (PAMPs). This connection stimulates the synthesis of pro-inflammatory cytokines, chemokines, and Type I interferons, hence augmenting antigen presentation and the recruitment of immune cells. Van Belleghem et al. and Popescu et al. elucidate the complex processes of this activation, emphasizing the importance of phages in regulating the innate immune system [46,47]. Carroll–Portillo and Lin provide significant insights on the impact of bacteriophages on the innate immune-signaling system [48]. Their research demonstrates that phages may engage with immune cells, including macrophages and dendritic cells, and they can influence critical signaling pathways, such as the Toll-like receptor (TLR) pathways. This interaction may result in the activation or inhibition of innate immune responses, contingent upon the circumstances. Phages' capacity to influence these pathways indicates their potential significance in altering the host's immunological milieu, which may have consequences for therapeutic applications and the comprehension of host–pathogen interactions.

Phage-based vaccines proficiently convey antigenic epitopes to antigen-presenting cells, including dendritic cells, macrophages, and B cells. These cells process and communicate antigens to T cells, so starting the adaptive immune response. This process results in the activation and development of antigen-specific T lymphocytes and B cells. The effectiveness of this antigen transport and presentation is shown by

Sartorius et al., who revealed that filamentous bacteriophages may elicit strong immune responses via TLR9-mediated pathways [49]. Xu et al. underscore the efficacy of phage-display technologies in selectively targeting immune cells [50].

Activation of T Cells: Antigens delivered by phages are essential for the activation of antigen-specific T cells. This stimulation leads to the proliferation and differentiation of effector T lymphocytes. CD4+ T cells facilitate B cell antibody generation, but CD8+ T cells play a crucial role in cellular immunity by destroying infected cells. Chatterjee and Duerkop investigate the function of phage-based vaccinations in T cell activation, addressing novel paradigms in phage-eukaryotic host interactions [51].

Phage-based vaccinations induce B cell activation and antibody synthesis targeting the delivered antigens. Activated B cells experience clonal proliferation and develop into plasma cells that generate antigen-specific antibodies. These antibodies neutralize infections and promote their elimination from the body. Eriksson et al. demonstrate that phages may elicit immunological responses resulting in efficient pathogen neutralization [52]. Furthermore, Ragothaman and Yoo examine progress in modified phage-based vaccinations, particularly their influence on B cell activation [53]. The many pathways via which phage-based vaccinations activate both innate and adaptive immune responses highlight their promise as effective instruments in vaccine development and immunotherapy.

Phage-based vaccinations provide a flexible and novel strategy for addressing infectious illnesses and more. This section explores the many uses of these vaccines, emphasizing their effectiveness against bacterial and viral infections, their potential in cancer immunotherapy, and their promise in combating new infectious illnesses. Researchers are using the distinctive characteristics of phages to create advanced vaccines that elicit strong immune responses and provide protection against many health concerns. Significant research illustrates the efficacy and versatility of phage-based vaccines, highlighting their potential to transform vaccine development and public health strategies. Phage-based vaccinations have extensive applications in the prevention of infectious diseases and other areas. Their adaptability makes them indispensable instruments across several domains:

Phage-derived vaccines have been effectively created to address several bacterial infections. Vaccines aimed against *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* use phages to provide bacterial surface antigens, toxins, or virulence factors. This method elicits protective immunological responses that aid in preventing colonization and infection. Yang et al. emphasize the promise of phage-based vaccinations as alternatives to intricate vaccine systems for bacterial diseases [54].

Phage-based vaccines show potential for viral infections, including influenza, HIV, and hepatitis. Engineered phages may display viral antigens to elicit both humoral and cellular immune responses. This technique may improve vaccination effectiveness and provide cross-protection against other virus strains. Gong et al. examine the use of phage-display technology with epitope design to elicit strong antibody responses against emerging diseases such as Tilapia Lake Virus [55].

Phage-based vaccines are emerging as novel instruments in cancer immunotherapy. These vaccines may elicit anti-tumor immune responses by presenting tumor-associated antigens on phage surfaces. The objective is to stimulate cytotoxic T lymphocytes and facilitate tumor shrinkage. Research conducted by Iwagami et al. illustrates the efficacy of lambda phage-based vaccines in eliciting antitumor immunity against hepatocellular cancer [56]. Tao et al. investigate phage T4 nanoparticles for the development of dual vaccines targeting anthrax and plague, demonstrating their adaptability [42].

Phage-based vaccines have considerable potential for rapid responses to emerging infectious illnesses, such as COVID-19. Phages may be modified to present epitopes from emerging infections, facilitating the rapid design and manufacture of vaccines to combat new public health challenges. Staquicini et al. propose targeted phage-based COVID-19 immunization techniques with an efficient cold-free supply chain, illustrating their potential to tackle global health crises [57]. Ul Haq et al. highlight the use of phage-based platforms in the development of multiplex vaccines for COVID-19 [58]. These many uses underscore the

versatility and promise of phage-based vaccines across several domains, including the fight against infectious illnesses, the enhancement of cancer immunotherapy, and the response to future health threats.

6. Conclusions

Phage-based medication development signifies a revolutionary advancement in contemporary medicine, surpassing conventional phage treatment for bacterial illnesses. This method utilizes the adaptability of bacteriophages for many applications, such as cancer therapy, vaccine formulation, and drug-delivery systems (DDS). Researchers are developing engineered phages to target specific disease markers, deliver therapeutic agents, and stimulate immune responses, thereby revealing innovative approaches to tackle intricate medical issues, including improving therapeutic efficacy, combating various pathogens, and surmounting conventional drug-delivery obstacles.

In cancer therapy, phages are being designed to specifically target and eliminate tumor cells or to carry cytotoxic chemicals directly to malignant areas, therefore improving therapeutic effectiveness while reducing harm to healthy cells. This precise targeting is poised to transform oncological care by providing more individualized and effective therapies. Phage-based vaccines are developing as novel vaccination treatments, using phages' capacity to deliver antigens that provoke robust and targeted immune responses. These vaccinations has the capability to battle a diverse range of infections and disorders.

The advancement of phage-based drug-delivery systems (DDS) is a promising direction. Phages may be engineered to provide medications directly to targeted cells or tissues, surmounting conventional delivery obstacles and enhancing therapeutic precision. This feature is especially advantageous in addressing disorders with intricate biological settings or when traditional delivery techniques are inadequate.

Notwithstanding these promising developments, other obstacles need resolution. Guaranteeing the safety and effectiveness of phage-based therapeutics requires thorough assessment of host–phage interactions, possible off-target effects, and genetic stability. Regulatory routes must evolve to accommodate these innovative uses, requiring explicit standards and established methods to enable approval and commercialization. Furthermore, enhancing phage engineering methodologies and delivery methods continues to pose a significant challenge, as does surmounting biological barriers and resistance mechanisms.

Phage-based drug development has significant potential for enhancing treatment approaches in several medical domains. Ongoing study, innovation, and cooperation are crucial to fully harness the promise of phages in combating bacterial infections and other complex illnesses. The evolving sector presents a chance to revolutionize treatment approaches, facilitating the development of more effective, customized, and targeted medical treatments.

References

1. Twort, F.W. An Investigation on the Nature of Ultra-Microscopic Viruses. Lancet 1915, 186, 1241–1243.
2. Corner, E.S. On an invisible microbe antagonistic to dysentery bacilli. Note by M. F. d'Herelle, presented by M. Roux. Comptes Rendus Academie des Sciences 1917; 165:373–5. Bacteriophage 2014, 1, 3–5. [Google Scholar] [CrossRef]
3. Thiel, K. Old dogma, new tricks—21st century phage therapy. Nat. Biotechnol. 2004, 22, 31–36.
4. Frenzel, A.; Schirrmann, T.; Hust, M. Phage display-derived human antibodies in clinical development and therapy. MAbs 2016, 8, 1177–1194.
5. Stevens, R.H.; Zhang, H.; Kajsik, M.; Płoski, R.; Rydzanicz, M.; Sabaka, P.; Šutovský, S. Successful use of a phage endolysin for treatment of chronic pelvic pain syndrome/chronic bacterial prostatitis. Front. Med. 2023, 10, 1238147.
6. Abedon, S.T.; Kuhl, S.J.; Blasdel, B.G.; Kutter, E.M. Phage treatment of human infections. Bacteriophage 2011, 1, 66–85.
7. Donlan, R.M. Preventing biofilms of clinically relevant organisms using bacteriophage. Trends Microbiol. 2009, 17, 66–72.

8. Dedrick, R.M.; Guerrero-Bustamante, C.A.; Garlena, R.A.; Russell, D.A.; Ford, K.; Harris, K.; Gilmour, K.C.; Soothill, J.; Jacobs-Sera, D.; Schooley, R.T.; et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. Nat. Med. 2019, 25, 730–733.
9. Azam, A.H.; Tan, X.E.; Veeranarayanan, S.; Kiga, K.; Cui, L. Bacteriophage Technology and Modern Medicine. Antibiotics 2021, 10, 999.
10. Cui, L.; Veeranarayanan, S.; Thitiananpakorn, K.; Wannigama, D.L. Bacteriophage Bioengineering: A Transformative Approach for Targeted Drug Discovery and Beyond. Pathogens 2023, 12, 1179.
11. González-Mora, A.; Hernández-Pérez, J.; Iqbal, H.M.N.; Rito-Palomares, M.; Benavides, J. Bacteriophage-Based Vaccines: A Potent Approach for Antigen Delivery. Vaccines 2020, 8, 504.
12. Zalewska-Piątek, B.; Piątek, R. Bacteriophages as Potential Tools for Use in Antimicrobial Therapy and Vaccine Development. Pharmaceuticals 2021, 14, 331.
13. Veeranarayanan, S.; Azam, A.H.; Kiga, K.; Watanabe, S.; Cui, L. Bacteriophages as Solid Tumor Theragnostic Agents. Int. J. Mol. Sci. 2021, 23, 402.
14. Shen, Y.; Wang, J.; Li, Y.; Yang, C.-T.; Zhou, X. Modified Bacteriophage for Tumor Detection and Targeted Therapy. Nanomaterials 2023, 13, 665.
15. Nagano, K.; Tsutsumi, Y. Development of novel drug delivery systems using phage display technology for clinical application of protein drugs. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 2016, 92, 156–166.
16. Chen X, Yang R, Shen J, Huang Q, Wu Z. Research Progress of Bioinspired Nanostructured Systems for the Treatment of Ocular Disorders. Pharmaceuticals. 2023 Jan 10;16(1):96.
17. Dowah, A.S.A.; Clokie, M.R.J. Review of the nature, diversity and structure of bacteriophage receptor binding proteins that target Gram-positive bacteria. Biophys. Rev. 2018, 10, 535–542.
18. Labrie, S.J.; Samson, J.E.; Moineau, S. Bacteriophage resistance mechanisms. Nat. Rev. Microbiol. 2010, 8, 317–327.
19. Hu, B.; Margolin, W.; Molineux, I.J.; Liu, J. The bacteriophage t7 virion undergoes extensive structural remodeling during infection. Science 2013, 339, 576–579.
20. Scholl, D.; Adhya, S.; Merril, C. Escherichia coli K1's capsule is a barrier to bacteriophage T7. Appl. Env. Microbiol. 2005, 71, 4872–4874.
21. Salmond, G.P.C.; Fineran, P.C. A century of the phage: Past, present and future. Nat. Rev. Microbiol. 2015, 13, 777–786.
22. Weigel, C.; Seitz, H. Bacteriophage replication modules. FEMS Microbiol. Rev. 2006, 30, 321–381.
23. Penadés, J.R.; Christie, G.E. The Phage-Inducible Chromosomal Islands: A Family of Highly Evolved Molecular Parasites. Annu. Rev. Virol. 2015, 2, 181–201.
24. Harper, D.; Parracho, H.; Walker, J.; Sharp, R.; Hughes, G.; Werthén, M.; Lehman, S.; Morales, S. Bacteriophages and Biofilms. Antibiotics 2014, 3, 270–284.
25. Lerminiaux, N.A.; Cameron, A.D.S. Horizontal transfer of antibiotic resistance genes in clinical environments. Can. J. Microbiol. 2019, 65, 34–44.
26. Usman, S.S.; Uba, A.I.; Christina, E. Bacteriophage genome engineering for phage therapy to combat bacterial antimicrobial resistance as an alternative to antibiotics. Mol. Biol. Rep. 2023, 50, 7055–7067.
27. Hampton, H.G.; Watson, B.N.J.; Fineran, P.C. The arms race between bacteria and their phage foes. Nature 2020, 577, 327–336.
28. Wright, R.C.T.; Friman, V.-P.; Smith, M.C.M.; Brockhurst, M.A. Cross-resistance is modular in bacteria-phage interactions. PLoS Biol. 2018, 16, e2006057.
29. Hodyra-Stefaniak, K.; Miernikiewicz, P.; Drapała, J.; Drab, M.; Jończyk-Matysiak, E.; Lecion, D.; Kaźmierczak, Z.; Beta, W.; Majewska, J.; Harhala, M.; et al. Mammalian Host-Versus-Phage immune response determines phage fate in vivo. Sci. Rep. 2015, 5, 14802.
30. Sweere, J.M.; Van Belleghem, J.D.; Ishak, H.; Bach, M.S.; Popescu, M.; Sunkari, V.; Kaber, G.; Manasherob, R.; Suh, G.A.; Cao, X.; et al. Bacteriophage trigger antiviral immunity and prevent clearance of bacterial infection. Science 2019, 363, eaat9691.
31. Durr, H.A.; Leipzig, N.D. Advancements in bacteriophage therapies and delivery for bacterial infection. Mater. Adv. 2023, 4, 1249–1257.

32. Malik, D.J.; Sokolov, I.J.; Vinner, G.K.; Mancuso, F.; Cinquerrui, S.; Vladisavljevic, G.T.; Clokie, M.R.J.; Garton, N.J.; Stapley, A.G.F.; Kirpichnikova, A. Formulation, stabilisation and encapsulation of bacteriophage for phage therapy. Adv. Colloid Interface Sci. 2017, 249, 100–133.
33. Shein, A.M.S.; Wannigama, D.L.; Hurst, C.; Monk, P.N.; Amarasiri, M.; Badavath, V.N.; Phattharapornjaroen, P.; Ditcham, W.G.F.; Ounjai, P.; Saethang, T.; et al. Novel intranasal phage-CaEDTA-ceftazidime/avibactam triple combination therapy demonstrates remarkable efficacy in treating Pseudomonas aeruginosa lung infection. Biomed. Pharmacother. 2023, 168, 115793.
34. Pirnay, J.-P.; Verbeken, G.; Ceyssens, P.-J.; Huys, I.; De Vos, D.; Ameloot, C.; Fauconnier, A. The Magistral Phage. Viruses 2018, 10, 64.
35. Goel, N.; Hashmi, Z.; Khan, N.; Ahmad, R.; Khan, W.H. Recent Strategies to Combat Multidrug Resistance. In Non-Traditional Approaches to Combat Antimicrobial Drug Resistance; Springer: Singapore, 2023; pp. 1–27.
36. Abedon, S.T. Phage therapy of pulmonary infections. Bacteriophage 2015, 5, e1020260.
37. Sarker, S.A.; Sultana, S.; Reuteler, G.; Moine, D.; Descombes, P.; Charton, F.; Bourdin, G.; McCallin, S.; Ngom-Bru, C.; Neville, T.; et al. Oral Phage Therapy of Acute Bacterial Diarrhea With Two Coliphage Preparations: A Randomized Trial in Children From Bangladesh. EBioMedicine 2016, 4, 124–137.
38. Hitchcock NM, Devequi Gomes Nunes D, Shiach J, Valeria Saraiva Hodel K, Dantas Viana Barbosa J, Alencar Pereira Rodrigues L, Coler BS, Botelho Pereira Soares M, Badaró R. Current clinical landscape and global potential of bacteriophage therapy. Viruses. 2023 Apr 21;15(4):1020.
39. Mohammad Hasani, S.; Ghafouri, E.; Kouhpayeh, S.; Amerizadeh, F.; Rahimmanesh, I.; Amirkhani, Z.; Khanahmad, H. Phage based vaccine: A novel strategy in prevention and treatment. Heliyon 2023, 9, e19925.
40. Bao, Q.; Li, X.; Han, G.; Zhu, Y.; Mao, C.; Yang, M. Phage-based vaccines. Adv. Drug Deliv. Rev. 2019, 145, 40–56.
41. Zhu, J.; Jain, S.; Sha, J.; Batra, H.; Ananthaswamy, N.; Kilgore, P.B.; Hendrix, E.K.; Hosakote, Y.M.; Wu, X.; Olano, J.P.; et al. A Bacteriophage-Based, Highly Efficacious, Needle- and Adjuvant-Free, Mucosal COVID-19 Vaccine. Mbio 2022, 13, e01822-22.
42. Tao, P.; Mahalingam, M.; Zhu, J.; Moayeri, M.; Sha, J.; Lawrence, W.S.; Leppla, S.H.; Chopra, A.K.; Rao, V.B. A Bacteriophage T4 Nanoparticle-Based Dual Vaccine against Anthrax and Plague. Mbio 2018, 9, e01926-18. [Google Scholar] [CrossRef] [PubMed]
43. Jepson, C.D.; March, J.B. Bacteriophage lambda is a highly stable DNA vaccine delivery vehicle. Vaccine 2004, 22, 2413–2419.
44. Górski, A.; Międzybrodzki, R.; Borysowski, J.; Dąbrowska, K.; Wierzbicki, P.; Ohams, M.; Korczak-Kowalska, G.; Olszowska-Zaremba, N.; Łusiak-Szelachowska, M.; Kłak, M.; et al. Phage as a Modulator of Immune Responses: Practical Implications for Phage Therapy. Adv. Virus Res. 2012, 83, 41–71.
45. Krut, O.; Bekeredjian-Ding, I. Contribution of the Immune Response to Phage Therapy. J. Immunol. 2018, 200, 3037–3044.
46. Van Belleghem, J.D.; Dąbrowska, K.; Vaneechoutte, M.; Barr, J.J.; Bollyky, P.L. Interactions between Bacteriophage, Bacteria, and the Mammalian Immune System. Viruses 2018, 11, 10.
47. Popescu, M.; Van Belleghem, J.D.; Khosravi, A.; Bollyky, P.L. Bacteriophages and the Immune System. Annu. Rev. Virol. 2021, 8, 415–435.
48. Carroll-Portillo, A.; Lin, H.C. Bacteriophage and the Innate Immune System: Access and Signaling. Microorganisms 2019, 7, 625.
49. Sartorius, R.; D'Apice, L.; Trovato, M.; Cuccaro, F.; Costa, V.; De Leo, M.G.; Marzullo, V.M.; Biondo, C.; D'Auria, S.; De Matteis, M.A.; et al. Antigen delivery by filamentous bacteriophage fd displaying an anti-DEC-205 single-chain variable fragment confers adjuvanticity by triggering a TLR9-mediated immune response. EMBO Mol. Med. 2015, 7, 973–988.
50. Xu, H.; Li, L.; Li, R.; Guo, Z.; Lin, M.; Lu, Y.; Hou, J.; Govinden, R.; Deng, B.; Chenia, H.Y. Evaluation of dendritic cell-targeting T7 phages as a vehicle to deliver avian influenza virus H5 DNA vaccine in SPF chickens. Front. Immunol. 2022, 13, 1063129.

51. Chatterjee, A.; Duerkop, B.A. Beyond Bacteria: Bacteriophage-Eukaryotic Host Interactions Reveal Emerging Paradigms of Health and Disease. Front. Microbiol. 2018, 9, 1394.
52. Eriksson, F.; Tsagozis, P.; Lundberg, K.; Parsa, R.; Mangsbo, S.M.; Persson, M.A.A.; Harris, R.A.; Pisa, P. Tumor-Specific Bacteriophages Induce Tumor Destruction through Activation of Tumor-Associated Macrophages. J. Immunol. 2009, 182, 3105–3111.
53. Ragothaman, M.; Yoo, S.Y. Engineered Phage-Based Cancer Vaccines: Current Advances and Future Directions. Vaccines 2023, 11, 919.
54. Yang, G.; Gao, Y.; Dong, J.; Xue, Y.; Fan, M.; Shen, B.; Liu, C.; Shao, N. A novel peptide isolated from phage library to substitute a complex system for a vaccine against staphylococci infection. Vaccine 2006, 24, 1117–1123.
55. Gong, Y.-M.; Wei, X.-F.; Zheng, Y.-Y.; Li, Y.; Yu, Q.; Li, P.-F.; Zhu, B. Combining Phage Display Technology with In Silico-Designed Epitope Vaccine to Elicit Robust Antibody Responses against Emerging Pathogen Tilapia Lake Virus. J. Virol. 2023, 97, e00050-23.
56. Iwagami, Y.; Casulli, S.; Nagaoka, K.; Kim, M.; Carlson, R.I.; Ogawa, K.; Lebowitz, M.S.; Fuller, S.; Biswas, B.; Stewart, S.; et al. Lambda phage-based vaccine induces antitumor immunity in hepatocellular carcinoma. Heliyon 2017, 3, e00407.
57. Staquicini, D.I.; Tang, F.H.F.; Markosian, C.; Yao, V.J.; Staquicini, F.I.; Dodero-Rojas, E.; Contessoto, V.G.; Davis, D.; O'Brien, P.; Habib, N.; et al. Design and proof of concept for targeted phage-based COVID-19 vaccination strategies with a streamlined cold-free supply chain. Proc. Natl. Acad. Sci. USA 2021, 118, e2105739118.
58. Ul Haq, I.; Krukiewicz, K.; Yahya, G.; Haq, M.U.; Maryam, S.; Mosbah, R.A.; Saber, S.; Alrouji, M. The Breadth of Bacteriophages Contributing to the Development of the Phage-Based Vaccines for COVID-19: An Ideal Platform to Design the Multiplex Vaccine. Int. J. Mol. Sci. 2023, 24, 1536

التطبيقات السريرية للعلاج بالبكتيريوفاج في مواجهة مقاومة المضادات الحيوية وتطوير الأدوية: مراجعة

الملخص

الخلفية :يشكل انتشار البكتيريا المقاومة للمضادات الحيوية تهديدًا كبيرًا للصحة العالمية، مما يستدعي استراتيجيات علاجية مبتكرة. ظهرت البكتيريوفاج، وهي فيروسات تستهدف البكتيريا بشكل خاص، كبديل واعد للمضادات الحيوية التقليدية. تستكشف هذه المراجعة التطبيقات السريرية للعلاج بالبكتيريوفاج، مع التركيز على إمكانياتها في تطوير الأدوية وعلاج الالتهابات المقاومة.

الطرق :تم إجراء مراجعة شاملة للأدبيات، حيث تم تحليل الدراسات المنشورة بين عامي 2000 و2023 والتي بحثت في فعالية العلاج بالبكتيريوفاج ضد البكتيريا متعددة المقاومة للأدوية .(MDR) تم استخدام قواعد بيانات مثل PubMed و Scopusو Web of Scienceلتحديد المقالات ذات الصلة، مع التركيز على التجارب السريرية ودراسات الحالات التي أظهرت نتائج العلاج بالبكتيريوفاج.

النتائج :أظهر العلاج بالبكتيريوفاج فعالية كبيرة في علاج الالتهابات التي تسببها مسببات الأمراض متعددة المقاومة، بما في ذلك *Staphylococcus aureus*المقاوم للميثيسيلين (MRSA) و *Enterococci*المقاوم للفانكومايسين .(VRE) أفادت الدراسات السريرية بمعدلات نجاح تصل إلى 77% في القضاء على البكتيريا المستهدفة. بالإضافة إلى ذلك، أثبتت البكتيريوفاج فعاليتها في تعطيل الأغشية الحيوية واستهداف الالتهابات داخل الخلايا. كما ساهمت قابليتها للتكيف في استخدامها في تطوير اللقاحات وأنظمة توصيل الجينات، مما يعزز إمكاناتها العلاجية.

الاستنتاج :يمثل العلاج بالبكتيريوفاج نهجًا ثوريًا في مكافحة الالتهابات المقاومة للمضادات الحيوية، حيث يوفر استهدافًا دقيقًا وقدرة على التكاثر الذاتي في موقع العدوى. على الرغم من التحديات مثل العقبات التنظيمية واستقرار البكتيريوفاج، فإن الأبحاث المستمرة والتطورات التكنولوجية تمهد الطريق لاعتماد العلاجات القائمة على البكتيريوفاج كجزء أساسي من الطب الحديث. يجب أن تركز الدراسات المستقبلية على تحسين هندسة البكتيريوفاج وطرق توصيله لتعظيم الفعالية السريرية.

الكلمات المفتاحية: البكتيريوفاج، مقاومة المضادات الحيوية، العلاج بالبكتيريوفاج، تطوير الأدوية، التجارب السريرية.