Received: 22 March 2024 | Revised: 06 May 2024 | Accepted: 02 July 2024
DOI: 10.48309/JMPCR.2025.449462.1149
Journal of Medicinal and Pharmaceutical Chemistry Research
SAMI

FULL PAPER

Bacteriophage therapy: Unleashing the potential of bacteriophages in modern medicine

G.K. Megha |M.N. Sumana* |Ramesh Nachimuthu |Rashmi P. Mahale

Department of Microbiology, JSS Medical College & Hospital, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

Multidrug-resistant bacterial infections are one of the major concerns in the medical field across the globe. The pipeline of the new drug development is almost dried anticipating the urgent need of alternative therapy options to save the lives. Bacteriophages are the viruses that infect bacteria, have emerged out as captivating and versatile in many areas especially in medicine and biotechnology. It can act as best alternative option in the treatment of multidrug resistant bacterial infections. In this comprehensive study, we unleash the potential of bacteriophages and their future prospects in the field of medicine along with its hurdles to adopt it as alternative to antibiotics. In an era of increasing antibiotic resistance, understanding and harnessing the power of bacteriophages may hold the key to addressing and pressing global health challenges.

***Corresponding Author:**
M.N.Sumana
Email: mnsumana@jssuni.edu.in
Tel.: +9845128274

KEYWORDS
Antibiotic resistance; bacteriophage therapy; bacteriophage cocktail; alternative therapy for MDR.

Introduction

Antibiotics are the most successful intervention of mankind. Millions of lives have been saved by antibiotics. These are powerful drugs in the medicine history. Antibiotics are essential for the development of medical advances such as anti-bacterial agents used in the treatment of patients with organ transplantation and cancer chemotherapy and many more. Unfortunately, the misuse and overuse of antibiotics over time have led a concerning rise in multi-drug-resistant organisms' number, placing humanity at the doorstep of the post-antibiotic era [1,2].

Multidrug-resistant organisms are pathogens that are resistant to 3 or more classes of antibiotics resulting in treatment failure.Rapidly evolving antibiotic resistance is a global emergency instigating the need for alternative therapy. According to WHO's (World Health Organization) 2020 reports, an average of 700,000 people die because of antimicrobial resistant organism caused infections and this is anticipated to increase significantly during the upcoming years. These studies highlight the difficulties associated with Antimicrobial resistance (AMR) today and the pressing need to develop novel, efficient anti-AMR treatments. One such alternative is bacteriophage therapy which can function as a better alternative treatment option [1,3].

Bacteriophages are viruses that are capable of infecting and killing bacteria and they are efficient substitutes for antibiotics against bacterial infections. Phages can be used alone or in combination to kill bacteria without affecting the normal flora of the host. After the Second World War, there was an increase in the use of safe and effective drugs available which temporarily overshadowed bacteriophage studies until the 1980s. Bacteriophages are present in the environment naturally where bacteria exist. Phages are used as therapy for infection as an alternative to antibiotics [1,4].

Although it is not a novel treatment approach, bacteriophage therapy is an intriguing alternative for treating organisms that are resistant to many drugs. It appears to offer hope for combating AMR. Recently, research on bacteriophages came out in surplus numbers after the 2000s along with clinical trials and phage banks for personalized phage delivery. Bacteriophage therapy was abundantly used in the Soviet Union in all age groups of patients suffering from a wide range of infections. The treatment outcome was considered very satisfactory and has been published in several reports.Phage therapy was used to treat cholera in the Punjab region of India in 1931. D'Herelle saw a 90 percent decrease in death rates, with 74 fatalities in the control group and only 5 in the experimental group. 73 experimental patients received phage treatment and 118 control volunteers were among the cohort [5,6,70,81-85].

However, these are only a few success stories we have discussed here. More research is required to bring this bacteriophage therapy into clinical practice to tackle multidrug-resistant organisms. The present review of bacteriophage therapy discusses the history of phages, phage biology, and present research on phage therapy practicality and efficacy as an option for treating infections caused by multi-drug resistant organisms and the newer updates in the field of phage therapy like, resistance of bacteria to bacteriophages and synergy effects of bacteriophages with antibiotics [9-13].

History of phage therapy

In 1915, Frederick Twort was the first to define the distinctive area of lysis linked to bacteriophages**.** He observed ultramicroscopic virus particles in the vaccinia virus culture and identified them as lytic phages, which were the contaminants of the viral culture [7].

However, Felix d'Herelle discovered the cause of this phenomenon and concluded that bacterial viruses were responsible for the plaques. He introduced the word "bacteriophage," which refers to "bacteria eater," in 1917 at the Pasteur Institute of Paris, France. Ehrlich clarified that the bacteriophage model was going to be the "magic bullet" that would transform the field of public health. D'Herelle envisioned using phages therapeutically, and he was credited with the first recorded clinical application of phage therapy in 1919 at the Hospital of Infants-Maladies in Paris [1,7-8].

Phage suspensions were given systemically via oral methods and/or by injection[9-13] or topically [14,15].At both the individual and population levels, d'Herelle and his 'disciples' succeeded admirably in treating many infections with bacteriophage therapy like Staphylococcal infections of the skin, bones, eyes, and other body parts [16-18], intestinal diseases including typhoid, dysentery, cholera [1,7-8], and systemic infections like septicemia. Also, he effectively used the phages as a precautionary alternative to bacterial infection of the gastrointestinal tract by introducing them into water supply sources in high epidemic areas [19-21].

D'Herelle's early investigations encountered intense debates and criticism for inadequate bacterial control, despite a few successful trials. Nevertheless, he continued to advance phage therapy in the early 20th century, treating dysentery, cholera, and the

bubonic plague. Soon after numerous phage therapy facilities and industrial phage manufacturing facilities were established in Europe and India [22].

Biology of bacteriophages (BPs)

During the lytic cycle, the phage uses the bacterial molecular machinery to multiply within the cell. The newly formed phage leads the bacteria to lyse after rapid and widespread multiplication within the host cell, facilitating further phage-host interactions. The phages attack the host bacterium in the lysogenic cycle and insert their DNA directly within the genome of the bacteria, passing the genetic information to succeeding generations through replication cycles. These phages wait for the right conditions (such as ultraviolet light, temperature, oxidative stress, etc.) to trigger specific genes to break free from the latent lysogenic cycle and start replicating their genetic material inside the bacterial chromosome [25]. "Prophage" is a viral genome incorporated in host cell nucleic acid and a non-infective form of bacteriophage; this is noticeably different from the term "provirus" for viral DNA that has been incorporated into eukaryote cells, these phages are called temperate phages [1,26,91-92].

The discovery and subsequent characterization of a drug is essential to its successful development. Similarly it's important to know the phages efficacy against specific bacteria along with the thermal stability, genome sequencing of isolated phages to facilitate the development of phage cocktails and to know effectively about phages, which can help scientists to increase the target approach of phages against bacteria and also in many other fields [8,77,79,92].

AMR in present era

MDR (Multi drug resistant) is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR (Extensively drug-resistant) stated as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR (Pan-drug resistant) denotes non-susceptibility to all agents across all antimicrobial categories [3,73,75].

Antimicrobial resistance (AMR) has emerged as one of the most significant risks to public health, notably compromising the ability to prevent and cure chronic diseases and signaling an uncertain future for healthcare. Antimicrobial resistance emerged because of various antibacterial agents being misused and overused in agricultural sectors, veterinary, marine and medical field. Nowadays, doctors are using last-resource drug classes like carbapenems and polymixins, which come with several adverse effects, and are expensive, aren't always easily accessible in developing nations [28]. The phrase "the silent tsunami menacing modern medicine" has been frequently used to describe antibiotic resistance [28]. Bacteria that cause common or serious infections have gradually, and to varying degrees, become resistant to every new antibiotic that enters the market. In this situation, it is critical to take action and prevent a growing global healthcare crisis [29].AMR has gotten to the stage of emergency in a lot of hospitals worldwide. Multidrug-resistant (MDR) Gram-negative organisms and *Methicillin-resistant Staphylococcus aureus* (MRSA) are present in the majority [30,86-90].

According to the analysis, published in the Lancet on January 19 2019, estimates that, 4.95 million people died from illnesses in which bacterial Antibiotic resistant genes (ARG's) played a major part and resulted 1.27 million deaths. More individuals died from drug-resistant illnesses than from malaria (643,000 fatalities) or HIV/AIDS (864,000 deaths) [31]. Infectious diseases continue to be the primary cause of death in developing

nations, where estimates of economic loss are unavailable. These deaths are being made worse by newly emerging and reemerging infectious diseases. Due to the paucity of quick diagnostic techniques to identify ARGs and bacterial infections; Broad-spectrum antibiotics are used frequently and inappropriately in clinical settings [32]. The WHO has established a list of priority pathogens for which new antibiotics are urgently required to concentrate and direct research toward the development of new antibiotics. The microbes recognized as ESKAPE pathogens are as follows: *Klebsiella pneumoniae , Acinetobacter baumannii, Staphylococcus aureus, Enterobacter species, Enterococcus faecium, and Pseudomonas aeruginosa*. In both community and clinical settings, ESKAPE pathogens serve as the paradigm for pathogenesis, resistance, and disease transmission, and this is made worse by the acquisition of ARGs [32,33].

The fundamental processes underlying ESKAPE pathogen development are widely common, despite genetic heterogeneity. Common resistance mechanisms shared by all ESKAPE pathogens include drug deactivation, alteration of the antibiotic binding site, and decreased antibiotic deposition in bacterial cells. Among these, the spike of drug resistance in Gram-negative bacteria (MDR-GNB) like *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species have emerged as significant threats for healthcare practitioners [32,33].

The structure of the cell wall distinguishes gram-negative bacteria from gram-positive bacteria, which affects how antimicrobial agents penetrate and are retained by the former. These bacteria's outer membrane acts as a permeability barrier, preventing the cell from being penetrated by some medications and antibiotics. One of the primary causes of the intrinsic antibiotic resistance seen in Gram-negative bacteria is this characteristic. These bacteria can acquire resistance by gene mutations that cause the development of surplus efflux pumps or antibiotic-inactivating enzymes (Extended spectrum beta-lactamase, Carbapenamase producers) inside the bacteria. The resistance can be also obtained through, plasmids, transposons / integrons, and via horizontal gene transfer from other bacteria. With regard to GNB, research indicates that resistance genes and related insertion elements transferred on plasmids are frequently found concentrated in big multi-resistance regions (MRR), especially in the Enterobacteriaceae family [33]. For example, ESBL and plasmids expressing carbapenemase may harbor resistance genes for other classes of antibiotics, such as fluoroquinolones and aminoglycosides. "The Big Five Carbapenemase producers" are particularly significant among these acquired resistances and include:

- KPC (Klebsiellapneumoniaecarbapenemase),
- IMP (Imipenemasemetallo-beta-lactamase),
- NDM (New Delhi metallo-beta-lactamase),
- VIM (Verona integron-encoded metallo-beta-lactamase), and
- OXA (Oxacillincarbapenemases).

Recently, critically sick patients with infections caused by multidrug-resistant GNB-particularly those resistant to carbapenem were treated with polypeptide colistin, which is a reserve antibiotic. However, reports are already coming out of numerous nations regarding the development of the transferable gene mcr-1, leading to colistin resistance [33]. It is predicted that by 2050, the mortality rate due to AMR, particularly with multi- and pan-drug-resistant bacterial infections, will surpass the annual deaths caused by more prevalent diseases such as cancer and diabetes exceeding 10 million annual deaths. Global public health is seriously threatened by antibiotic-resistant infections, especially those triggered by MDR organisms (MDROs) [1].

Although MDROs are a major concern worldwide, they are particularly dangerous in low- and middle-income countries (LMIC), where a large percentage of healthcare facilities lack adequate and sufficient supply of common infection prevention and control supplies. These countries also lack appropriate and effective antimicrobial stewardship programs. India is one of the largest LMICs and the biggest user of antibiotics. The widespread use of broad-spectrum agents has contributed to the MDROs emergence in both community and hospital settings [34-38].

Data on AMR rates and trends in frequently isolated bacteria from countries, territories, and areas (CTAs) are compiled in the 2020 edition of the GLASS report. Lower AMR rates in lower CTAs are reported in the study, along with generally superior coverage for the majority of pathogen drug-infection site combinations. For instance, after taking into account of all reported CTAs, the median resistance to methicillin resistance in *Staphylococcus aureus* in Bone Cement Implantations (BCIs) and third-generation cephalosporins in *Escherichia coli* was significantly greater than with a superior testing coverage (above the 75th percentile). However, the duration indicates specific AMR types of concern, which is in line with the study of 2020 data, which was based on a larger pool of CTAs and took into account all CTAs with ≥10 BCIs with AST in 2020. For instance, time-series analysis also revealed substantial percentage resistance (>50%) to carbapenems in *Acinetobacter spp*. (median: 73.1% [2017]-72.9% [2020]) and *K. pneumoniae* (median: 61.5% [2017]-63.7% [2020]) in bloodstream BCIs [51-53]. Also emphasized was the need for more study to confirm the actual upward trend in antimicrobial resistance (AMR) rates that occurred for these combinations during the COVID-19 pandemic. The rest of the time series showed changes of less than 15% over the course of the study, such as the methicillin-resistant *S. aureus*, whose median proportion increased from 16.6% in 2017 to 18.3% in 2020, a change of 10.7%.

These global reports showbacteria that cause common or serious infections have gradually, and to varying degrees, gaining resistant to every new antibiotic that enters the market. This critical situation demands action to prevent a growing global health care crisis and also to look for alternative approaches to combat this issue. One of such most promising avenue is bacteriophage therapy.

Phage therapy today

Patients who are aware of phage therapy desire to receive it for emergency health issues. Phage treatment can be used appropriately as an unlicensed medicine because there are no legal restrictions. However, giving phage therapy to individual patients requires a lot of effort right now [39]. To date, just 12 cases of potential clinical side effects from current phage therapy have been reported but none of these were thought to be directly related to phages according to the authors of the report [40-43,98]. A substantial amount of evidence also supports the effectiveness of phage therapy. In accordance with a recent systematic analysis of clinical data, 79% out of the 1904 patients treated with phage showed clinical improvement, and 87% of the 1461 patients had their bacteria eradicated [39,44]. Phage therapy has been administered to 12 patients in the UK over the past two years, and there is growing clinical interest. There are active phage therapy practices in many Eastern European nations, with Georgia and Poland's work being the most well-known. Numerous efforts have been made to examine the documentation of their creation, experimentation, and implementation; nonetheless, because of military concerns, Soviet-era customs, and linguistic limitations, it is uncertain how much of the relevant data is available. The

conversion of phages into medicinal products for human use has been permitted since 2018 in some countries [1,93-96]. Phage usage is not widely accepted and appreciated globally, but a few accepted countries are Georgia, Russia and Poland where phage therapy is practiced by clinical professionals [27]. The main benefit of naturally existing anti-bacterial substances is that they are relatively easy to find, but the main benefit of bacteriophages in particular is that, if properly characterized, they can effectively target specific bacteria. It is necessary to weigh the advantages of phages their abundance and selective toxicity against their frequently constrained host range. Combining different phage lysates into cocktails is one method that has been used to address this problem [24,97,105,110].

One of the most significant and effective ways of using phage is to combine them with clinically used antibiotics. The combination of phage and antibiotics may result in various outcomes. They might act additively together or might act synergistically in which their effect is greater than the individual effect of each of them [25]. Sub lethal concentration of some antibiotics can increase the release of the daughter phages from bacterial cells. Because of the several bactericidal processes involved in antibiotic and phage action on bacteria, the Phage Antibiotic Synergy can lower the amount of antibiotics used in therapy and progressively slow the establishment of antibiotic resistance.Several studies were conducted starting in 1940 to assess various treatment combinations of antibiotics and phages [45-47].

Phage antibiotic synergy

The first documented Phage Antibiotic Synergy (PAS) demonstrated in 1941 when a combination of phages with sulphanilamide and sulphapyridine obstructed the in vivo bacterial growth of Staphylococcus aureus and Escherichia coli [48]. MacNeal *et al.* conducted a study in 1942 in order to compare the efficacy of phage therapy and combination phage-sulphathiazole therapy for 56 rabbits infected with staphylococcal meningitis. One rabbit survived out of the six that received early sulphathiazole treatment, 13 survived out of the 22 that received an early combination of sulphathiazole and phages, and all 23 rabbits that received no treatment died. The five rabbits that received a late combination of sulphathiazole and phages also died [49]. 130 million Staphylococci/mL were broth grown by Himmelweit*et al.* in 1945. They then added (a) penicillin, (b) phages, and (c) a mixture of penicillin &phage both. Completion of lysis was seen in 6 hours and 3 minutes for penicillin alone (a), 1 hour and 55 minutes for phages alone (b), and 1 hour and 25 minutes for the combination of phage and penicillin(c) [47]. According to a study made by Kim *et al.*, the injection of sub lethal levels of antibiotics causes changes in bacterial cell shape, which in turn causes delayed lyses, resulting in increased phage formation [50].

To know the outcomes of PAS, optically based microtiter plate assay method is used in a study where measured bacterial growth is exposed to antibiotic doses that cover the MIC throughout numerous orders of magnitude of phage titer over time. This process of determining phage – antibiotic efficacy across stochiometries in each clinically relevant situation is referred to as synography [46].

Mechanisms expected to be involved in PAS

There are various mechanisms suggested to explain the PAS mechanism, they can be listed as follows:

1. Cell elongation by antibiotics,
2. Increased plaque size by antibiotics,
3. Decrease of and /or antibiotic-resistant mutant appearance,
4. Increased antibiotic susceptibility due to presence of phages,
5. Lowered MIC of antibiotics after adding phages to antibiotics, and

6. Depolymerization of the bacterial polysaccharides by phage enzymes that increase antibiotic diffusion and cell penetration [47].

Along with synergy another interaction present between phage and antibiotic named antagonism. Research has demonstrated that, in addition to PAS, phage-antibiotic antagonism can also be seen in other situations and that, when compared to individual therapies alone, the therapeutic efficacy has been observed to be reduced. According to some research, certain phages combined with low-dose antibiotics may result in antagonistic interactions [46].

Chaudhry *et al.*'s work demonstrated the antagonistic relationship between phages and antibiotics in *Pseudomonas aeruginosa* biofilms when phages and high tobramycin concentrations were used [51]. Possible reason expected for this mechanism might be a high concentration of tobramycin inhibited the replication of phages or it might also be involved in lower bacterial density in the host hindering the replication of phages. Another theory for this phage-antibiotic antagonistic reaction is that antibiotics can prevent phage replication by inhibiting cell components like DNA gyrases or ribosomes that are essential for this process. A different study demonstrated a negative interaction between the polyvalent Myoviridae phage SaP7, which infects strains of *Salmonella and E. coli*, and BETA-lactam drugs, like amoxicillin in mouse models and amoxicillin/potassium clavulanate in piglet models [47,52].

Compassionate therapy

Compassionate Phage Therapy (cPT) involves the use of unapproved medicines outside of clinical trials for patients with no other treatment options. The "World Medical Association Declaration of Helisinki Ethical Principles for medical research involving human subjects" is a global accord that covers various aspects of clinical research. It provides guidelines for the compassionate use of phages in addition to patient consent and placebo control. The doctor, the patient's support team, or the patient themselves typically recommends the use of phages. Although the statement did not specifically support using unproven treatments until it was revised in 2000. Article 37 grants physicians the authority to act in the best interests of their patients by selecting experimental treatments after all other approved treatment failure. The doctor as well as the patient or guardian's permission is necessary. The Food and Drug Administration's (FDA) schemes of emergency investigational new drug (eIND), the French National Agency for Medicines and Health Products Safety's temporary use authorization (ATU), the TGA's special access programs in Australia, and Poland's national regulation have all approved cPT. Several phage products have been covered under expanded/special access programs in the US and Australia, which make it easier for patients to receive medications that are still in the clinical development stage for compassionate therapies. Phages are produced by biotech companies for clinical usage. Other manufacturers like PherecydesPharma (France), Ampliphi Biosciences (US, Australia), and Adaptive Phage Therapeutics (US) have also been among the 'manufacture and supply of phages to cPT receiving patients. Ampliphi Biosciences reported an 84% experimental success rate with their programs performed to treat illnesses brought on by *Pseudomonas aeruginosa* or *Staphylococcus aureus* [53].

Since the 1970s Poland's LudwikHirszfeld Institute of Immunology and Experimental Therapy, use phages to treat patients as experiment with outpatient care. This institute has passed laws allowing phage therapy without receiving commercial permission for phage products. Since its establishment in Poland in 2005, the Phage

Therapy Unit (PTU), which administers phage therapy a national regulatory framework, has released case reports and reviews on around 1,500 infected individuals. In the US, France, or Australia, cPT is now delivered to the patient without charge along with treating institution; this is an approach that is not very financially viable for small biotech or research labs [53,100-102].

The Central Drugs Standard Control Organization (CDSCO), India's medical regulatory body, has established the rules for importing small amounts of drugs that are not regulated in India, solely for personal use, when accompanied with a prescription from a doctor licensed to practice medicine in India. By making this critical step possible, patients wouldn't have to travel across borders to receive phage treatment. The present situation of compassionate bacteriophage therapy in India can be represented in Figure 1.

The Eliava Institute's diagnostic lab was the only place in India where patients could have their samples tested for phage sensitivity in the past, and doing so included higher shipping fees and a longer turnaround time (TAT). Now, patients can have their samples tested for phage sensitivity at an authorized lab in India. Every patient from India who has received phage therapy starting in 2020 has benefited from this action, which has seen the testing of over 400 samples locally over the past three years since phage sensitivity testing started first in India. More than 200 patients with antibiotic resistant organism caused infections have been able to receive phage therapy since Vitalis was founded in early 2018 with a success rate was more than 70% [52,54,103-104].

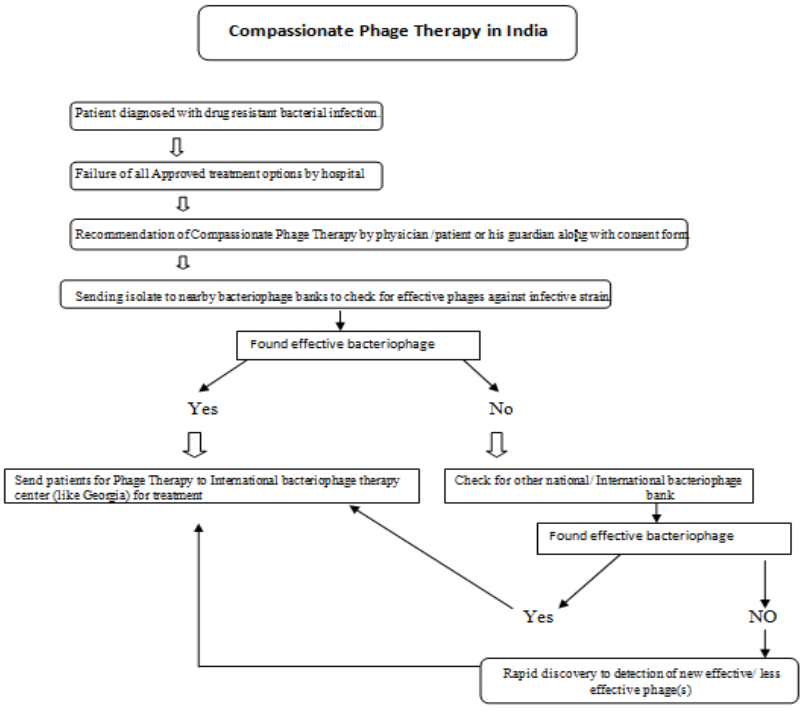

FIGURE 1 Present scenario of compassionate bacteriophage therapy in India

Effectiveness and Safety of Bacteriophage Therapy

Advantages: The benefits of phage therapy compared to prescription antibiotic use are best described as follows.

Targeted approach: Bacteriophage therapyoffers a highly specific and targeted approach treating bacterial infections. Phages can selectively infect and kill specific strains of bacteria, sparing the beneficial bacteria in the body [99].

Have the best killing ability: phages are bactericidal substances that impair the viability of bacteria effectively infected by obligate lytic phages which cannot be recovered. Contrarily, other antibiotics, like tetracycline, are bacteriostatic and may consequently facilitate bacteria to evolve toward resistance [50,55-56].

Less disruption of normal flora: Bacteriophages effectiveness does not harm the normal flora of the host as antibiotic does. Hence, it is safe to use. Whereas, majority antibiotics, which often have larger broad range activity, are more likely to breach the normal flora and cause super infections such as *Candida albicans* yeast infections or antibiotic-associated Clostridium difficile colitis [50,55-56].

Biofilm evacuation: Antibiotic resistance in biofilms is typically much higher than that individual bacterial cells in different layers. The presence of depolymerizers helps in degrading the biofilm of bacteria and expose and sensitize to antibacterial or immune system. Bacteriophages can actively infiltrate biofilms and lyse exopolymers may explain why phages have been shown to remove biofilms [69,119-121].

Automatic Dose adjustment: Even though there are some restrictions, such as a reliance on relatively high bacterial concentrations, phages are still capable of proliferating and increasing their number throughout the bacterial-killing process, particularly where its hosts (bacteria) are present. The reason for auto "dosing" is that the phages themselves help choose the phage dose depending on the bacterial population in the host [63].

Phages are organic substances: The phages are natural components of the environment, and the increased resistance to medications manufactured in laboratories or genetically altered species not applicable to non-engineered phage products [111-113].

Inexpensive: The process of making phages frequently includes both the host's development and eventual purification [32]. The cost of growing the host varies according to the kind of bacterium, but as technology develops, phage purification appears to be becoming less expensive [64,115-118].

Phage synthesis prices are often comparable to pharmaceutical production costs when considering unit costs. However, the costs of identification (isolation) and characterization can be quite low [58].

Lesser possibility to create resistance: The variety of bacterial species with specialized phage-resistance mechanisms can be selected is constrained by the generally limited host range demonstrated by most phages [57]. In contrast, a sizable portion of bacteria can be killed by the majority of chemical antibiotics. In addition, some resistance mutations have a detrimental effect on the fitness or virulence of bacteria because of the lack of pathogenicity-related phage receptors [65-66].

Disadvantages

A narrow range of host:Typically phage host ranges are limited to a few numbers of strains, species or much less frequently, generaof bacteria [50,57]. Before the treatment, pathogen susceptibility to particular phages or other antibacterial was determined [26,50].

Phages are not a special type of medication:Phages are biological agents that are based on proteins and have the ability to interact with the body's immune system. They are also capable of actively proliferating, may even alter while being created or utilized, albeit they are not unique in this sense. As an example, live-attenuated vaccines actively proliferate and evolve, even when they infect human tissues, and a range of protein-based treatments can strengthen the immune system by releasing bacterial toxins in the affected area.

Not every phage is a useful therapeutic: Effective therapeutic phages should be able to eradicate bacteria with a high degree of efficiency while posing little risk of adversely

altering the ecosystems in which they are used. These qualities can be reliably guaranteed as long as phages are obligatory lytic, stable at normal temperatures and storage settings, the subject of suitable efficacy and safety investigations, and ideally fully sequenced to verify the lack of unwanted genes such as toxin coding genes. Temperate phages exhibit super infection immunity, which encodes components of bacterial pathogenicity such as toxins, and turn phage-sensitive bacteria into insensitive ones, making it challenging to use them as pharmaceuticals.

Limited Spectrum: Bacteriophage therapy is highly specific and limited to targeting only certain strains of bacteria. This restricts its broad applicability, as different strains may require different phages, making it challenging to develop a comprehensive phage library.

Lack of clinical data: Although phage therapy has shown promising results in laboratory settings and early clinical trials, the overall clinical evidence is still limited. Large-scale, controlled clinical trials are needed to establish its safety and effectiveness.

Regulatory hurdles: Compared to traditional antibiotics, the regulatory approval process for bacteriophage therapy can be complex and time-consuming. The stringent regulatory requirements pose challenges to widespread adoption and availability of phage-based treatments.

Chances of spreading AMR: Lysogenic phages are more likely to transfer virulent genes from host bacteria that exhibit AMR characteristics to lesser virulent bacteria. This can occur via transduction. It's one of the main routes by which AMR genes are transferred horizontally or through lysogenic conversion, in which non-essential prophage genes, like those that form the toxins (Cholera toxin, Shiga toxin, and Vibrio toxin), are introduced into the bacteria, causing phenotypic changes that promote the emergence of resistance mechanisms in addition to increased virulence.

The main barrier to phage therapy would be Western medical systems' ignorance of phages as antibacterial agents. They are not the only ones, as was already mentioned, to use the numerous phage oddities as medicines. In reality, a few phage products have already complied with legal standards, received the USDA's usage clearance, the FDA's GRAS (Generally Regarded as Safe) designation, and registered with the EPA. However, it is possible for the general population to wrongly think of phages as viruses that resemble viral infections which are harmful to human life. However, public opposition has not yet materialized, thus it may be advantageous that bacterial viruses are classified as phages instead [50,58].

Conclusion

To sum up, phage treatment can be acceptable within India's current regulatory system. Bacteriophage (phage) therapy is quite promising as an antibacterial approach that has capacity to revolutionize the management of MDR bacterial infections along with antibiotics. Though there are no phages currently licensed for use in India, on compassionate grounds unlicensed pharmaceutical phage products may be utilized when licensed alternatives like antibiotics fail to meet patients' needs. With the support of a large number of well-characterized phages through research that is safe for treatment purpose in humans, morbidity and mortality due to MDR infections can be reduced. Health Services can thus be strengthened with phage therapy that is scalable, cost-effective, and sustainable.

Acknowledgments

Words cannot express my gratitude to my guide Dr. M N Sumana who constantly supported me, corrected and encouraged to

finish this paper. I am also thankful for my Co-guide Dr. Rashmi P Mahale and external expert Dr. P N Ramesh for editing help, late-night feedback. I am grateful to my PhD friends for their moral and emotional support.

Funding

Self-funded.

Authors' Contributions

G.K. Megha: Literature search and data collection
M.N. Sumana: Conceptualization and supervision
Ramesh Nachimuthu: Review and editing, guidance
Rashmi P Mahale: Review and editing

Conflict of Interest

The authors have no conflict of intrest to declare.

Orcid:
G.K.Megha:
https://orcid.org/0009-0003-7192-6791
M.N.Sumana:*
https://orcid.org/0000-0002-8877-0602
RameshNachimuthu:
https://orcid.org/0000-0002-8350-1809
Rashmi P. Mahale:
https://orcid.org/0000-0002-3509-3257

References

[1] H. Ling, X. Lou, Q. Luo, Z. He, M. Sun, J. Sun, Recent advances in bacteriophage-based therapeutics: Insight into the post-antibiotic era, *Acta Pharmaceutica Sinica B*, **2022**, *12*, 4348-4364. [Crossref], [Google Scholar], [Publisher]

[2] S.N. Arumugam, P. Manohar, S. Sukumaran, S. Sadagopan, B. Loh, S. Leptihn, R. Nachimuthu, Antibacterial efficacy of lytic phages against multidrug-resistant Pseudomonas aeruginosa infections in bacteraemia mice models, *BMC Microbiology*, **2022**, *22*, 187. [Crossref], [Google Scholar], [Publisher]

[3] A.P. Magiorakos, A. Srinivasan, R.B. Carey, Y. Carmeli, M. Falagas, C. Giske, S. Harbarth, J. Hindler, G. Kahlmeter, B. Olsson-Liljequist, Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, *Clinical Microbiology and Infection*, **2012**, *18*, 268-281. [Crossref], [Google Scholar], [Publisher]

[4] P. Lokesh, S.S. Narayani, Phage as medicine for bacterial diseases, **2022**. [Google Scholar], [Publisher]

[5] N. Chanishvili, Phage therapy—history from Twort and d'Herelle through Soviet experience to current approaches, *Advances in Virus Research*, **2012**, *83*, 3-40. [Crossref], [Google Scholar], [Publisher]

[6] V.H. Aswani, S.K. Shukla, An early history of phage therapy in the United States: Is it time to reconsider?, *Clinical Medicine & Research*, **2021**, *19*, 82-89. [Pdf], [Google Scholar], [Publisher]

[7] D.E. Fruciano, S. Bourne, Phage as an antimicrobial agent: d'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West, *Canadian Journal of Infectious Diseases and Medical Microbiology*, **2007**, *18*, 19-26. [Crossref], [Google Scholar], [Publisher]

[8] A. Compton, antidysenterybacteripphage in the treatment of bacillary dysentery, A record of sixty-six cases treated, with inferences, **1929**. [Google Scholar], [Publisher]

[9] R.J. Dubos, J.H. Straus, C. Pierce, The multiplication of bacteriophage in vivo and its protective effect against an experimental infection with Shigelladysenteriae, *The Journal of Experimental Medicine*, **1943**, *78*, 161. [Crossref], [Google Scholar], [Publisher]

[10] W.E. Ward, Protective action of VI bacteriophage in Eberthellatyphi Infections in mice, *The Journal of Infectious Diseases*, **1943**, 172-176. [Google Scholar], [Publisher]

[11] A. Compton, Phage therapy in diarrhoea and dysentery, **1944**. [Google Scholar], [Publisher]

[12] J.-M. Desranleau, Progress in the treatment of typhoid fever with Vi bacteriophages, *Canadian Journal of Public Health/Revue Canadienne de Sante'ePublique*, **1949**, *40*, 473-478. [Google Scholar], [Publisher]

[13] N. Dagli, M. Haque, S. Kumar, Exploring the bacteriophage frontier: a bibliometric analysis of clinical trials between 1965 and 2024, *Cureus*, **2024**, *16*, e56266. [Google scholar] [Publisher]

[14] S.L. Karn, S.K. Bhartiya, A. Pratap, S.K. Saroj, R. Kumar, M. Sahu, M. Gangwar, G. Nath, A randomized, placebo-controlled, double-blind clinical trial of bacteriophage cocktails in chronic wound infections, *The International Journal of Lower Extremity Wounds*, **2024**, *17*, 15347346231226342. [Google scholar] [Publisher]

[15] A.C. Cipollaro, A.E. Sheplar, Therapeutic uses of bacteriophage in the pyodermias, *Archives of Dermatology and Syphilology*, **1932**, *25*, 280-293. [Crossref], [Google Scholar], [Publisher]

[16] a) A.E. Town, F.C. Frisbee, Bacteriophage in ophthalmology: A preliminary report, *Archives of Ophthalmology*, **1932**, *8*, 683-689. [Crossref], [Google Scholar], [Publisher]; b) M. I.M.I. Humeri, I. Zuhria, R. Loebis, *Journal of Medicinal and Pharmaceutical Chemistry Research*, **2024**, *6*, 1840-1853. [Crossref], [Publisher], [Pdf]

[17] F.H. Albee, The treatment of osteomyelitis by bacteriophage, *JBJS*, **1933**, *15*, 58-66. [Google Scholar], [Publisher]

[18] W.J. MacNeal, F.C. Frisbee One hundred patients with Staphylococcus septicemia receiving bacteriophage service, *The American Journal of the Medical Sciences*, **1936**, *191*, 179-95. [Google Scholar] [Publisher]

[19] D.E. Fruciano, S. Bourne, Phage as an antimicrobial agent: D'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West, *Canadian Journal of Infectious Diseases and Medical Microbiology*, **2007**, *18*, 19-26. [Google Scholar] [Publisher]

[20] A. Górski, E. Jończyk-Matysiak, M. Łusiak-Szelachowska, R. Międzybrodzki, B. Weber-Dąbrowska, J. Borysowski, The potential of phage therapy in sepsis, Frontiers in immunology, **2017**, *11*, 1783. [Google Scholar] [Publisher]

[21] A. Sulakvelidze, Z. Alavidze, J.G. Morris Jr, Bacteriophage therapy, *Antimicrobial Agents and Chemotherapy*, **2001**, *45*, 649-659. [Crossref], [Google Scholar], [Publisher]

[22] S. Matsuzaki, M. Rashel, J. Uchiyama, S. Sakurai, T. Ujihara, M. Kuroda, M. Ikeuchi, T. Tani, M. Fujieda, H. Wakiguchi, Bacteriophage therapy: A revitalized therapy against bacterial infectious diseases, *Journal of Infection and Chemotherapy*, **2005**, *11*, 211-219. [Crossref], [Google Scholar], [Publisher]

[23] B.K. Chan, S.T. Abedon, C. Loc-Carrillo, Phage cocktails and the future of phage therapy, *Future Microbiology*, **2013**, *8*, 769-783. [Crossref], [Google Scholar], [Publisher]

[24] N. Principi, E. Silvestri, S. Esposito, Advantages and limitations of bacteriophages for the treatment of bacterial infections, *Frontiers in Pharmacology*, **2019**, *10*, 457104. [Crossref], [Google Scholar], [Publisher]

[25] S.T. Abedon, P. García, P. Mullany, R. Aminov, Phage therapy: Past, present and future. *Frontiers in Microbiology*, **2017**, *8*, 981. [Crossref], [Google Scholar], [Publisher]

[26] P. Dadgostar, Antimicrobial resistance: Implications and costs, *Infection and Drug Resistance*, **2019**, 3903-3910. [Crossref], [Google Scholar], [Publisher]

[27] F. Prestinaci, P. Pezzotti, A. Pantosti, Antimicrobial resistance: A global multifaceted phenomenon, *Pathogens and*

Global Health, **2015**, *109*, 309-318. [Crossref], [Google Scholar], [Publisher]

[28] I. Gould, The epidemiology of antibiotic resistance, *International Journal of Antimicrobial Agents*, **2008**, *32*, 2-9. [Crossref], [Google Scholar], [Publisher]

[29] T. Thompson, The staggering death toll of drug-resistant bacteria, *Nature*, **2022**. [Google Scholar], [Publisher]

[30] D.M. De Oliveira, B.M. Forde, T.J. Kidd, P.N. Harris, M.A. Schembri, S.A. Beatson, D.L. Paterson, M.J. Walker, Antimicrobial resistance in ESKAPE pathogens, *Clinical Microbiology Reviews*, **2020**, *33*, 10-1128. [Crossref], [Google Scholar], [Publisher]

[31] M. Exner, S. Bhattacharya, B. Christiansen, J. Gebel, P. Goroncy-Bermes, P. Hartemann, P. Heeg, C. Ilschner, A. Kramer, E. Larson, Antibiotic resistance: What is so special about multidrug-resistant Gram-negative bacteria?, *GMS hygiene and Infection Control*, **2017**, *12*. [Crossref], [Google Scholar], [Publisher]

[32] E.Y. Klein, T.P. Van Boeckel, E.M. Martinez, S. Pant, S. Gandra, S.A. Levin, H. Goossens, R. Laxminarayan, Global increase and geographic convergence in antibiotic consumption between 2000 and 2015, *Proceedings of the National Academy of Sciences*, **2018**, *115*, 3463- 3470. [Crossref], [Google Scholar], [Publisher]

[33] V. Mave, A. Chandanwale, A. Kagal, S. Khadse, D. Kadam, R. Bharadwaj, V. Dohe, M.L. Robinson, A. Kinikar, S. Joshi, High burden of antimicrobial resistance and mortality among adults and children with community-onset bacterial infections in India, *The Journal of Infectious Diseases*, **2017**, *215*, 1312-1320. [Crossref], [Google Scholar], [Publisher]

[34] C. Lim, E. Takahashi, M. Hongsuwan, V. Wuthiekanun, V. Thamlikitkul, S. Hinjoy, N.P. Day, S.J. Peacock, D. Limmathurotsakul, Epidemiology and burden of multidrug-resistant bacterial infection in a developing country, *Elife*, **2016**, *5*, e18082. [Crossref], [Google Scholar], [Publisher]

[35] R. Laxminarayan, R.R. Chaudhury, Antibiotic resistance in India: Drivers and opportunities for action, *PLoS Medicine*, **2016**, *13*, e1001974. [Crossref], [Google Scholar], [Publisher]

[36] N. Teerawattanapong, P. Panich, D. Kulpokin, S.N. Ranong, K. Kongpakwattana, A. Saksinanon, B.-H. Goh, L.-H. Lee, A. Apisarnthanarak, N. Chaiyakunapruk, A systematic review of the burden of multidrug-resistant healthcare-associated infections among intensive care unit patients in Southeast Asia: the rise of multidrug-resistant Acinetobacter baumannii, *Infection Control & Hospital Epidemiology*, **2018**, *39*, 525-533. [Crossref], [Google Scholar], [Publisher]

[37] J.D. Jones, C. Trippett, M. Suleman, M.R. Clokie, J.R. Clark, The future of clinical phage therapy in the United Kingdom, *Viruses*, **2023**, *15*, 721. [Crossref], [Google Scholar], [Publisher]

[38] S. LaVergne, T. Hamilton, B. Biswas, M. Kumaraswamy, R.T. Schooley, D. Wooten, Phage therapy for a multidrug-resistant Acinetobacter baumannii craniectomy site infection, *Open forum Infectious Diseases,* **2018**, 5, 64. [Crossref], [Google Scholar], [Publisher]

[39] A. Ujmajuridze, N. Chanishvili, M. Goderdzishvili, L. Leitner, U. Mehnert, A. Chkhotua, T.M. Kessler, W. Sybesma, Adapted bacteriophages for treating urinary tract infections, *Frontiers in Microbiology*, **2018**, *9*, 1832. [Crossref], [Google Scholar], [Publisher]

[40] R.M. Dedrick, C.A. Guerrero-Bustamante, R.A. Garlena, D.A. Russell, K. Ford, K. Harris, K.C. Gilmour, J. Soothill, D. Jacobs-Sera, R.T. Schooley, Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus, *Nature Medicine*, **2019**, *25*, 730-733. [Crossref], [Google Scholar], [Publisher]

[41] A. Sulakvelidze, Z. Alavidze, J.G. Morris Jr, Bacteriophage therapy, *Antimicrobial Agents and Chemotherapy*, **2001**, *45*, 649-659. [Crossref], [Google Scholar], [Publisher]

[42] S. Uyttebroek, B. Chen, J. Onsea, F. Ruythooren, Y. Debaveye, D. Devolder, I. Spriet, M. Depypere, J. Wagemans, R. Lavigne, Safety and efficacy of phage therapy in difficult-to-treat infections: A systematic review, *The Lancet Infectious Diseases*, **2022**, *22*, 208-220. [Crossref], [Google Scholar], [Publisher]

[43] Z. Chegini, A. Khoshbayan, S. Vesal, A. Moradabadi, A. Hashemi, A. Shariati, Bacteriophage therapy for inhibition of multi drug-resistant uropathogenic bacteria: A narrative review, *Annals of Clinical Microbiology and Antimicrobials*, **2021**, *20*, 1-13. [Crossref], [Google Scholar], [Publisher]

[44] C. Gu Liu, S.I. Green, L. Min, J.R. Clark, K.C. Salazar, A.L. Terwilliger, H.B. Kaplan, B.W. Trautner, R.F. Ramig, A.W. Maresso, Phage-antibiotic synergy is driven by a unique combination of antibacterial mechanism of action and stoichiometry, *MBio*, **2020**, *11*, 10-1128. [Crossref], [Google Scholar], [Publisher]

[45] M. Łusiak-Szelachowska, R. Międzybrodzki, Z. Drulis-Kawa, K. Cater, P. Knežević, C. Winogradow, K. Amaro, E. Jończyk-Matysiak, B. Weber-Dąbrowska, J. Rękas, Bacteriophages and antibiotic interactions in clinical practice: what we have learned so far, *Journal of Biomedical Science*, **2022**, *29*, 23. [Crossref], [Google Scholar], [Publisher]

[46] H. Zaytzeff-Jern, F.L. Meleney, Studies in bacteriophage VI: The effect of sulfapyridine and sulfanilamide on staphylococci and B. Coli and their respective bacteriophages, *The Journal of Laboratory and Clinical Medicine*, **1941**, *26*, 1756-1767. [Crossref], [Google Scholar], [Publisher]

[47] W.J. Macneal, M.J. Spence, A. Blevins, Cure of Experimental Staphylococcal Meningitis, *Proceedings of the Society for Experimental Biology and Medicine*, **1942**, *50*, 176-179. [Crossref], [Google Scholar], [Publisher]

[48] C. Loc-Carrillo,S. T. Abedon, Pros and cons of phage therapy, *Bacteriophage*, **2011**, *1*, 111-114. [Crossref], [Google Scholar], [Publisher]

[49] F. Himmelweit, Combined action of penicillin and bacteriophage on staphylococci, **1945**. [Google Scholar], [Publisher]

[50] D. Ma, L. Li, K. Han, L. Wang, Y. Cao, Y. Zhou, H. Chen, X. Wang, The antagonistic interactions between a polyvalent phage SaP7 and β-lactam antibiotics on combined therapies, *Veterinary Microbiology*, **2022**, *266*, 109332. [Crossref], [Google Scholar], [Publisher]

[51] S. McCallin, J.C. Sacher, J. Zheng, B.K. Chan, Current state of compassionate phage therapy, *Viruses*, **2019**, *11*, 343. [Crossref], [Google Scholar], [Publisher]

[52] D.M. Lin, B. Koskella, H.C. Lin, Phage therapy: An alternative to antibiotics in the age of multi-drug resistance, *World journal of gastrointestinal pharmacology and therapeutics*, **2017**, *8*, 162. [Google Scholar] [Publisher]

[53] R.M. Carlton, Phage therapy: Past history and future prospects, *ArchivumImmunologiae Et TherapiaeExperimentalis-English Edition-*, **1999**, *47*, 267-274. [Google Scholar], [Publisher]

[54] C.W. Stratton, Dead bugs don't mutate: Susceptibility issues in the emergence of bacterial resistance, *Emerging Infectious Diseases*, **2003**, *9*, 10. [Crossref], [Google Scholar], [Publisher]

[55] P. Hyman, S.T. Abedon, Bacteriophage host range and bacterial resistance, *Advances in Applied Microbiology*, **2010**, *70*, 217-248. [Crossref], [Google Scholar], [Publisher]

[56] M. Skurnik, M. Pajunen, S. Kiljunen, Biotechnological challenges of phage therapy, *Biotechnology Letters*, **2007**, *29*, 995-1003. [Crossref], [Google Scholar], [Publisher]

[57] J. Alisky, K. Iczkowski, A. Rapoport, N. Troitsky, Bacteriophages show promise as antimicrobial agents, *Journal of Infection*, **1998**, *36*, 5-15. [Crossref], [Google Scholar], [Publisher]

[58] B. Weber-Dąbrowska, E. Jończyk-Matysiak, M. Żaczek, M. Łobocka, M. Łusiak-Szelachowska, A. Górski, Bacteriophage procurement for therapeutic purposes, *Frontiers in Microbiology*, **2016**, *12*, 1177. [Google Scholar] [Publisher]

[59] R. Gupta, Y. Prasad, Efficacy of polyvalent bacteriophage P-27/HP to control multidrug resistant Staphylococcus aureus associated with human infections, *Current Microbiology*, **2011**, *62*, 255-260. [Crossref], [Google Scholar], [Publisher]

[60] M.R. Clokie, A.D. Millard, A.V. Letarov, S. Heaphy, Phages in nature, *Bacteriophage*, **2011**, *1*, 31-45. [Google Scholar] [Publisher]

[61] S.T. Abedon, C. Thomas-Abedon, Phage therapy pharmacology, *Current Pharmaceutical Biotechnology*, **2010**, *11*, 28-47. [Crossref], [Google Scholar], [Publisher]

[62] J.J. Gill, P. Hyman, Phage choice, isolation, and preparation for phage therapy, *Current Pharmaceutical Biotechnology*, **2010**, *11*, 2-14. [Crossref], [Google Scholar], [Publisher]

[63] R. Capparelli, N. Nocerino, M. Iannaccone, D. Ercolini, M. Parlato, M. Chiara, D. Iannelli, Bacteriophage therapy of Salmonella enterica: A fresh appraisal of bacteriophage therapy, *The Journal of Infectious Diseases*, **2010**, *201*, 52-61. [Crossref], [Google Scholar], [Publisher]

[64] M. Skurnik, E. Strauch, Phage therapy: Facts and fiction, *International Journal of Medical Microbiology*, **2006**, *296*, 5-14. [Crossref], [Google Scholar], [Publisher]

[65] J. Onsea, P. Soentjens, S. Djebara, M. Merabishvili, M. Depypere, I. Spriet, P. De Munter, Y. Debaveye, S. Nijs, P. Vanderschot, Bacteriophage application for difficult-to-treat musculoskeletal infections: development of a standardized multidisciplinary treatment protocol, *Viruses*, **2019**, *11*, 891. [Crossref], [Google Scholar], [Publisher]

[66] E. Kutter, D. De Vos, G. Gvasalia, Z. Alavidze, L. Gogokhia, S. Kuhl, S.T. Abedon, Phage therapy in clinical practice: treatment of human infections, *Current Pharmaceutical Biotechnology*, **2010**, *11*, 69-86. [Crossref], [Google Scholar], [Publisher]

[67] D.M. Lin, B. Koskella, H.C. Lin, Phage therapy: An alternative to antibiotics in the age of multi-drug resistance, *World Journal of Gastrointestinal Pharmacology and Therapeutics*, **2017**, *8*, 162. [Crossref], [Google Scholar], [Publisher]

[68] S. Aslam, E. Lampley, D. Wooten, M. Karris, C. Benson, S. Strathdee, R.T. Schooley, Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States, *Open Forum Infectious Diseases*, **2020**, *7*, 9. [Crossref], [Google Scholar], [Publisher]

[69] J.B. Doub, E. Wilson, Observed transaminitis with a unique bacteriophage therapy protocol to treat recalcitrant Staphylococcal biofilm infections, *Infection*, **2022**, *50*, 281-283. [Crossref], [Google Scholar], [Publisher]

[70] D.E. Fruciano, S. Bourne, Phage as an antimicrobial agent: d'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West, *Canadian Journal of Infectious Diseases and Medical Microbiology*, **2007**, *18*, 19-26. [Crossref], [Google Scholar], [Publisher]

[71] N. Wu, J. Dai, M. Guo, J. Li, X. Zhou, F. Li, Y. Gao, H. Qu, H. Lu, J. Jin, Pre-optimized phage therapy on secondary Acinetobacter baumannii infection in four critical COVID-19 patients, *Emerging Microbes & Infections*, **2021**, *10*, 612-618. [Crossref], [Google Scholar], [Publisher]

[72] T. Tkhilaishvili, M. Merabishvili, J.-P. Pirnay, C. Starck, E. Potapov, V. Falk, F. Schoenrath, Successful case of adjunctive

intravenous bacteriophage therapy to treat left ventricular assist device infection, **2021**, [Crossref], [Google Scholar], [Publisher]

[73] M.-C. Chan, S.-K. Chiu, P.-R. Hsueh, N.-C. Wang, C.-C. Wang, C.-T. Fang, Risk factors for healthcare-associated extensively drug-resistant Acinetobacter baumannii infections: A case-control study, *PLoS One*, **2014**, *9*, e85973. [Crossref], [Google Scholar], [Publisher]

[74] D. Ben-David, R. Kordevani, N. Keller, I. Tal, A. Marzel, O. Gal-Mor, Y. Maor, G. Rahav, Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections, *Clinical Microbiology and Infection*, **2012**, *18*, 54-60. [Crossref], [Google Scholar], [Publisher]

[75] S.R. Shrivastava, P.S. Shrivastava, J. Ramasamy, World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics, *Journal of Medical Society*, **2018**, *32*, 76-77. [Crossref], [Google Scholar], [Publisher]

[76] R.C. Founou, L.L. Founou, S.Y. Essack, Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis, *PloS One*, **2017**, *12*, e0189621. [Crossref], [Google Scholar], [Publisher]

[77] M. Kutateladze, R. Adamia, Bacteriophages as potential new therapeutics to replace or supplement antibiotics, *Trends in Biotechnology*, **2010**, *28*, 591-595. [Crossref], [Google Scholar], [Publisher]

[78] N.M. Hitchcock, D. Devequi Gomes Nunes, J. Shiach, K. Valeria Saraiva Hodel, J. Dantas Viana Barbosa, L. Alencar Pereira Rodrigues, B.S. Coler, M. Botelho Pereira Soares, R. Badaró, Current clinical landscape and global potential of bacteriophage therapy, *Viruses*, **2023**, *15*, 1020. [Crossref], [Google Scholar], [Publisher]

[79] D.E. Fruciano, S. Bourne, Phage as an antimicrobial agent: d'Herelle's heretical theories and their role in the decline of phage prophylaxis in the West, *Canadian Journal of Infectious Diseases and Medical Microbiology*, **2007**, *18*, 19-26. [Crossref], [Google Scholar], [Publisher]

[80] K. Rajagopal, S.J. Chandy, J. P. Graham, A one health review of community-acquired antimicrobial-resistant Escherichia coli in India, *International Journal of Environmental Research and Public Health*, **2021**, *18*, 12089. [Crossref], [Google Scholar], [Publisher]

[81] L. Marongiu, M. Burkard, U.M. Lauer, L.E. Hoelzle, S. Venturelli, Reassessment of historical clinical trials supports the effectiveness of phage therapy, *Clinical Microbiology Reviews*, **2022**, *35*, 62-22. [Crossref], [Google Scholar], [Publisher]

[82] O. Adebayo, R. Gabriel-Ajobiewe, M. Taiwo, J. Kayode, Phage therapy: A potential alternative in the treatment of multi-drug resistant bacterial infections, *Journal of Microbiology & Experimentation*, **2017**, *5*, 173. [Crossref], [Google Scholar], [Publisher]

[83] N.M. Hitchcock, D. Devequi Gomes Nunes, J. Shiach, K. Valeria Saraiva Hodel, J. Dantas Viana Barbosa, L. Alencar Pereira Rodrigues, B.S. Coler, M. Botelho Pereira Soares, R. Badaró, Current clinical landscape and global potential of bacteriophage therapy, *Viruses*, **2023**, *15*, 1020. [Crossref], [Google Scholar], [Publisher]

[84] N. Chanishvili, Phage therapy—history from Twort and d'Herelle through Soviet experience to current approaches, *Advances in Virus Research*, **2012**, *83*, 3-40. [Crossref], [Google Scholar], [Publisher]

[85] S. Sagar, S. Kaistha, A.J. Das, R. Kumar, S. Sagar, S. Kaistha, A.J. Das, R. Kumar, Bacteriophage: A new hope for the control of antibiotic-resistant bacteria, *Antibiotic Resistant Bacteria: A Challenge to Modern Medicine*, **2019**, 153-164. [Crossref], [Google Scholar], [Publisher]

[86] H. Jeong, S. Kang, H.-J. Cho, Prevalence of multidrug-resistant organisms and risk factors for carriage among patients

transferred from long-term care facilities, *Infection & Chemotherapy*, **2020**, *52*, 183. [Crossref], [Google Scholar], [Publisher]

[87] T.R. Awasthi, N.D. Pant, P.R. Dahal, Prevalence of multidrug resistant bacteria in causing community acquired urinary tract infection among the patients attending outpatient Department of Seti Zonal Hospital, Dhangadi, Nepal, *Nepal Journal of Biotechnology*, **2015**, *3*, 55-59. [Google Scholar], [Publisher]

[88] A. Pop-Vicas, J. Strom, K. Stanley, E.M. D'Agata, Multidrug-resistant gram-negative bacteria among patients who require chronic hemodialysis, *Clinical Journal of the American Society of Nephrology*, **2008**, *3*, 752-758. [Crossref], [Google Scholar], [Publisher]

[89] A. Älgå, S. Wong, M. Shoaib, K. Lundgren, C.G. Giske, J. von Schreeb, J. Malmstedt, Infection with high proportion of multidrug-resistant bacteria in conflict-related injuries is associated with poor outcomes and excess resource consumption: A cohort study of Syrian patients treated in Jordan, *BMC Infectious Diseases*, **2018**, *18*, 1-6. [Crossref], [Google Scholar], [Publisher]

[90] C. Kothari, R. Gaind, L.C. Singh, A. Sinha, V. Kumari, S. Arya, H. Chellani, S. Saxena, M. Deb, Community acquisition of β-lactamase producing Enterobacteriaceae in neonatal gut, *BMC Microbiology*, **2013**, *13*, 1-6. [Crossref], [Google Scholar], [Publisher]

[91] M.J. Catalao, F. Gil, J. Moniz-Pereira, C. Sao-Jose, M. Pimentel, Diversity in bacterial lysis systems: bacteriophages show the way, *FEMS Microbiology Reviews*, **2013**, *37*, 554-571. [Crossref], [Google Scholar], [Publisher]

[92] G.F. Hatfull, R.W. Hendrix, Bacteriophages and their genomes, *Current Opinion in Virology*, **2011**, *1*, 298-303. [Crossref], [Google Scholar], [Publisher]

[93] L. Valente, J. Prazak, Y.-A. Que, D.R. Cameron, Progress and pitfalls of bacteriophage therapy in critical care: A concise definitive review, *Critical Care Explorations*, **2021**, *3*, e0351. [Crossref], [Google Scholar], [Publisher]

[94] R.N. Ng, A.S. Tai, B.J. Chang, S.M. Stick, A. Kicic, Overcoming challenges to make bacteriophage therapy standard clinical treatment practice for cystic fibrosis, *Frontiers in Microbiology*, **2021**, *11*, 593988. [Crossref], [Google Scholar], [Publisher]

[95] R. Nir-Paz, E.J. Kuijper, Bacteriophage therapy in humans, *Clinical Microbiology and Infection*, **2023**, *29*, 679-681. [Crossref], [Google Scholar], [Publisher]

[96] M. Kwiatek, S. Parasion, A. Nakonieczna, Therapeutic bacteriophages as a rescue treatment for drug-resistant infections–an in vivo studies overview, *Journal of Applied Microbiology*, **2020**, *128*, 985-1002. [Crossref], [Google Scholar], [Publisher]

[97] T. Ha, O. Alvarez, A literature review and survey of bacteriophage therapy against multidrug-resistant organisms and the perceived barriers to clinical research, **2019**. [Google Scholar], [Publisher]

[98] J. Borysowski, A. Górski, Ethics of phage therapy, *Phage Therapy: A Practical Approach*, **2019**, 379-385. [Crossref], [Google Scholar], [Publisher]

[99] L. Fernández, D. Gutiérrez, P. García, A. Rodríguez, The perfect bacteriophage for therapeutic applications—a quick guide, *Antibiotics*, **2019**, *8*, 126. [Crossref], [Google Scholar], [Publisher]

[100] O. Adesanya, T. Oduselu, O. Akin-Ajani, O.M. Adewumi, O.G. Ademowo, An exegesis of bacteriophage therapy: An emerging player in the fight against anti-microbial resistance, *AIMS Microbiology*, **2020**, *6*, 204. [Crossref], [Google Scholar], [Publisher]

[101] A. Alsaadi, B. Beamud, M. Easwaran, F. Abdelrahman, A. El-Shibiny, M. F. Alghoribi, P. Domingo-Calap, Learning from mistakes: The role of phages in pandemics, *Frontiers in Microbiology*, **2021**, *12*, 653107. [Crossref], [Google Scholar], [Publisher]

[102] N.I. Sternberg, Cloning high molecular weight DNA fragments by the bacteriophage P1 system, *Trends in Genetics*, **1992**, *8*, 11-16. [Crossref], [Google Scholar], [Publisher]

[103] S. Uyttebroek, B. Chen, J. Onsea, F. Ruythooren, Y. Debaveye, D. Devolder, I. Spriet, M. Depypere, J. Wagemans, R. Lavigne, Safety and efficacy of phage therapy in difficult-to-treat infections: A systematic review, *The Lancet Infectious Diseases*, **2022**, *22*, e208-e220. [Crossref], [Google Scholar], [Publisher]

[104] Z. Naureen, D. Malacarne, K. Anpilogov, A. Dautaj, G. Camilleri, S. Cecchin, S. Bressan, A. Casadei, E. Albion, E. Sorrentino, Comparison between American and European legislation in the therapeutical and alimentary bacteriophage usage, *Acta Bio Medica: AteneiParmensis*, **2020**, *91*. [Crossref], [Google Scholar], [Publisher]

[105] S.L. Karn, M. Gangwar, R. Kumar, S.K. Bhartiya, G. Nath, Phage therapy: A revolutionary shift in the management of bacterial infections, pioneering new horizons in clinical practice, and reimagining the arsenal against microbial pathogens, *Frontiers in Medicine*, **2023**, *10*, 1209782. [Crossref], [Google Scholar], [Publisher]

[106] A. Monribot, R. Delattre, N. Dufour, C. D'humieres, N. Pons-kerjean, J. Bataille, Bacteriophages in clinical practice: Follow the guide!, **2021**. [Google Scholar], [Publisher]

[107] M. TaatiMoghadam, A. Khoshbayan, Z. Chegini, I. Farahani, A. Shariati, Bacteriophages, a new therapeutic solution for inhibiting multidrug-resistant bacteria causing wound infection: lesson from animal models and clinical trials, *Drug Design, Development and Therapy*, **2020**, 1867-1883. [Google Scholar], [Publisher]

[108] H. Ling, X. Lou, Q. Luo, Z. He, M. Sun, J. Sun, Recent advances in bacteriophage-based therapeutics: Insight into the post-antibiotic era, *Acta Pharmaceutica Sinica B.*, **2022**, *12*, 4348-4364. [Google Scholar] [Publisher]

[109] M. Delbrock, Bacterial viruses or bacteriophages, *Biological Reviews*, **1946**, *21*, 30-40. [Crossref], [Google Scholar], [Publisher]

[110] I.U. Haq, W.N. Chaudhry, M.N. Akhtar, S. Andleeb, I. Qadri, Bacteriophages and their implications on future biotechnology: A review, *Virology Journal*, **2012**, *9*, 1-8. [Crossref], [Google Scholar], [Publisher]

[111] A. Parisien, B. Allain, J. Zhang, R. Mandeville, C. Lan, Novel alternatives to antibiotics: Bacteriophages, bacterial cell wall hydrolases, and antimicrobial peptides, *Journal of Applied Microbiology*, **2008**, *104*, 1-13. [Crossref], [Google Scholar], [Publisher]

[112] C.V. Kumar, H. Makari, H. Srinivasa, K. Basavarajappa, S. Kalsurmath, Bacteriophage therapy: A potential use of phages in medical field, *The Journal of Infection in Developing Countries*, **2014**, *8*, 129-136. [Crossref], [Google Scholar], [Publisher]

[113] H. Raghu, G. Manju, S. Mishra, P. Sawale, Beneficial face of bacteriophages: Applications in food processing, *International Journal for Quality Research*, **2012**, *6*. [Google Scholar], [Publisher]

[114] P. Domingo-Calap, P. Georgel, S. Bahram, Back to the future: Bacteriophages as promising therapeutic tools, *Hla*, **2016**, *87*, 133-140. [Crossref], [Google Scholar], [Publisher]

[115] B. Fathima, A.C. Archer, Bacteriophage therapy: Recent developments and applications of a renaissant weapon, *Research in Microbiology*, **2021**, *172*, 103863. [Crossref], [Google Scholar], [Publisher]

[116] P.W. Taylor, P.D. Stapleton, J.P. Luzio, New ways to treat bacterial infections, *Drug Discovery Today*, **2002**, *7*, 1086-1091. [Crossref], [Google Scholar], [Publisher]

[117] M.K. MeghaKadam, M. Jhala, Bacteriophage therapy-a road not taken, **2002**. [Google Scholar], [Publisher]

[118] P. Connerton, A. Timms, I. Connerton, Campylobacter bacteriophages and

bacteriophage therapy, *Journal of Applied Microbiology*, **2011**, *111*, 255-265. [Crossref], [Google Scholar], [Publisher]

[119] H. Hathaway, S. Milo, J.M. Sutton, T.A. Jenkins, Recent advances in therapeutic delivery systems of bacteriophage and bacteriophage-encoded endolysins, *Therapeutic Delivery*, **2017**, *8*, 543-556. [Crossref], [Google Scholar], [Publisher]

[120] C. Chang, X. Yu, W. Guo, C. Guo, X. Guo, Q. Li, Y. Zhu, Bacteriophage-mediated control of biofilm: a promising new dawn for the future, *Frontiers in Microbiology*, **2022**, *13*, 825828. [Crossref], [Google Scholar], [Publisher]

[121] Z. Guo, M. Liu, D. Zhang, Potential of phage depolymerase for the treatment of bacterial biofilms, *Virulence*, **2023**, *14*, 2273567. [Crossref], [Google Scholar], [Publisher].

How to cite this article: G.K. Megha, M.N. Sumana, P.N. Ramesh, Rashmi P. Mahale, Bacteriophage therapy: Unleashing the potential of bacteriophages in modern medicine. *Journal of Medicinal and Pharmaceutical Chemistry Research*, 2025, 7(2), 282-300. **Link:** https://jmpcr.samipubco.com/article_200390.html