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Bacteriophage Therapy Against Antibiotic-Resistant Bacteria: A Critical Appraisal

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Abstract Bacteriophages are bacteria-specific viruses that reduce or eliminate pathogenic or nuisance bacteria. It helps treat bacterial infections in animals, humans, birds, fish, plants, and food materials. All phages have a head structure that can vary in size and shape. When a virulent phage infects a host bacterium, it replicates much faster than the host cell does, causes lysis and death, simultaneously liberating many progeny phages for another cycle by infecting new neighboring bacterial cells. Phages can be administered orally, topically, in drops, intravenously, or via inhalation. After a single dose, phages are resorbed and reach the bloodstream within 2–4 h and the internal organs within a duration of 10 h, eventually being eliminated from the body within three days. Phage therapy can be used in many animals, including poultry, swine, cattle, and sheep, to treat various bacterial diseases caused by *Salmonella*, *Escherichia coli*, and *Campylobacter*. In modern technology, bacteriophages are genetically modified and engineered in such a way as to capacitate the expression of proteins and target the gene networks of bacteria on which antibiotics fail to act directly. The potential *in vivo* elimination of phages, phage-neutralizing antibodies, reticuloendothelial system clearance of phages from the patients, and phage-resistant mutants are the major limitations of phages. However, bacteriophages offer several advantages over antibiotics, including high host specificity. Therefore, phage therapy is a promising alternative for mitigating the burden of antibiotic-resistant bacteria.

Keywords: *Antibiotics, Bacteria, Bacteriophages, Phage Therapy*

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1. Introduction

Bacteriophages, commonly referred to as phages, are viruses that infect bacteria. Phages are ubiquitous. They are the most abundant organisms in the biosphere. Bacteriophage-bacterial host interactions have been exploited by scientists as tools to understand basic molecular biology, genetic recombination events, horizontal gene transfer, and how bacterial evolution has been driven by phages [1]. Recently, interest in phage therapy, in which phages are used as novel therapeutic agents to treat pathogenic bacteria, has increased [2]. Bacterial infections are known to cause high mortality worldwide; however, there has been little success in the development of new drugs against multidrug-resistant pathogens. Antibiotic-resistant opportunistic pathogens in hospital environments are a growing concern, particularly because of their heightened risk to immunocompromised patients. Since the discovery of antibiotics, bacterial viruses called bacteriophages (phages) have been used to treat and prevent infectious diseases in humans and animals [3,4].

In the past three decades, no novel classes of antibiotics have been identified despite advancements in modern biotechnology, including genetic engineering [5]. Thus, exploring alternative approaches to develop antibacterial products is a worthwhile task, and re-examining the potential of promising older methods might be valuable. Bacteriophage therapy has been proposed as a potential alternative to antibiotics for antimicrobial treatment [6,7]. This approach demonstrates the importance of phage therapy as a promising strategy for combating drug-resistant bacterial infections. However, its effectiveness as a therapeutic agent is contingent on addressing these limitations [8,9]. Almost a decade before the discovery of penicillin, the controversial practice of phage therapy was developed as a treatment for bacterial infections. Phage therapy, a method that uses phages for the

treatment of bacterial infectious diseases, was introduced by Félix d'Herelle, who discovered phages in approximately 1920. At the time of its discovery, phage therapy was regarded as a possible treatment for bacterial infectious diseases [10,11].

Phage therapy offers several advantages over conventional chemotherapy. It is effective against multidrug-resistant pathogenic bacteria because its bacteriolytic mechanisms differ entirely from those of antibiotics. Additionally, it has a high specificity for target bacteria, preventing the emergence of substituted microbes. Phages can also rapidly adapt to phage-resistant bacterial mutants through mutations. Furthermore, developing a phage-based treatment is more cost-effective than developing a new drug [12]. Therefore, this paper aims to review bacteriophage therapy against antibiotic-resistant bacteria and highlight its applications and major importance.

2. Literature Review

2.1. Phage Biology

2.1.1. Morphology of Phages

Most phages ranged from 24–200 nm in length. T4 is one of the largest phages; it is approximately 200 nm long and 80–100 nm wide (Figure 1). All phages contain a head structure that can vary in size and shape. Some are icosahedral (20 sides), whereas others are filamentous. The head encloses the nucleic acid and acts as a protective covering. Some phages have tails attached to their heads. The tail is a hollow tube through which nucleic acids pass during infection. The T4 tail is surrounded by a contractile sheath that contracts during bacterial infection. At the end of the tail, phages such as T4 have a base plate and one or more tail fibers attached to it. The base plate and tail fibers are involved in the binding of the phage to bacterial cells. However, not all phages have base plates and tail fibers [13].

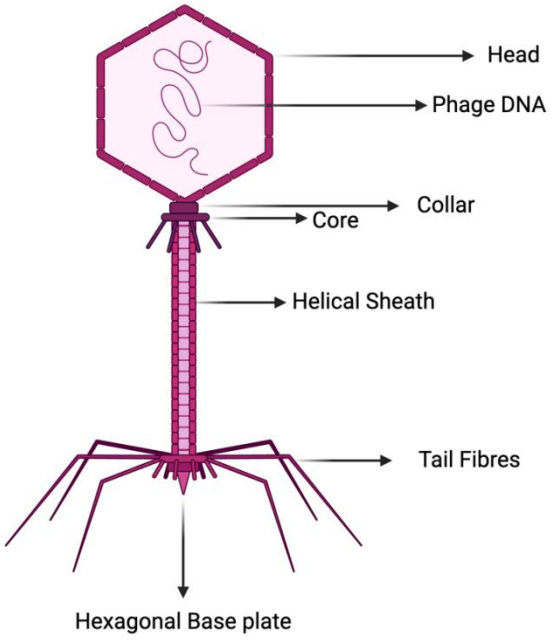

Figure 1. Morphology of phage T4 Source: [14]

2.1.2. Types of Phages

At least 12 distinct groups of bacteriophages, which are highly diverse in structure and genetics, infect bacteria and Archaea (Figure 2) [15]. Phages have played an essential role in laboratory research since the 20th century. The first phages studied were those designated type 1 (T1) to type 7 (T7). The T-even phages, T2, T4, and T6, were used as model systems for studying virus multiplication. In 1952, Alfred Day Hershey and Martha Chase used the T2 bacteriophage in a famous experiment in 1952 which supported the theory that DNA is the genetic material. Certain phages, such as lambda, Mu, and M13, are used in recombinant DNA studies. The entire nucleotide sequence of the phage was first, a feat accomplished by Frederick Sanger and colleagues in 1977 [16].

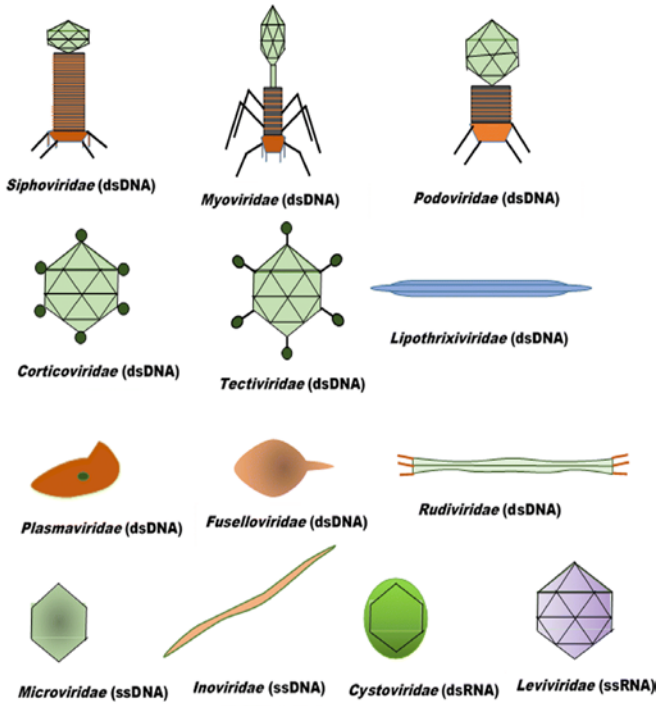

Figure 2. Types of phages Source: [15].

2.2. Life Cycle of Bacteriophages

2.2.1. Lytic Phages

Phages are parasites that depend on their host for propagation, which is influenced by various factors, such as temperature, nutrients, light, and other environmental forces. Virulent phages subvert the host's biological processes and exploit the host's cellular machinery for replication. Upon infecting a host bacterium, the phage replicates at a rate that outpaces the host cell's normal processes, completing the entire cycle within 30–40 min. This leads to lysis and death of the host cell, releasing a significant number of progeny phages, each of which is then primed to initiate another cycle by infecting adjacent bacterial cells. This cycle is known as the lytic 'virulent' cycle [17]. The lytic cycle or 'virulent phages' fit into the class of 'natural antimicrobial controlling agents' and are arguably the most abundant biological entities on Earth. These methods are being exploited in various areas of biotechnology, including rapid bacterial detection, food bioprocessing, and removal of bacterial biofilms [18].

2.2.2. Lysogenic Phages

Other particles, called lysogenic phages, are 'temperate' or dormant phages that may take the form of a 'prophage' by integrating with the viral DNA in the host chromosome (Figure 3). They become a part of the host cell and replicate along with the host chromosome for many generations, coexisting as opposed to lysing the host cell [17]. This phenomenon is called 'lysogeny', which also provides immunity against infection by further phage particles of the same type, ensuring that there is only one copy of the phage per bacterial cell. The unique characteristics of lysogenic or 'temperate' phages and their potential for exploitation have been demonstrated in a system that restores antibiotic efficiency by reversing pathogen resistance to antibiotics [19].

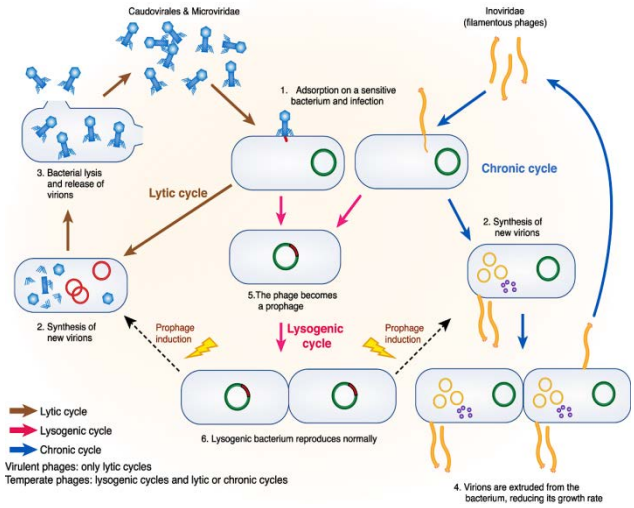

Figure 3. Temperate phage replication (life cycle) [20]

2.3. Bacteriophage Therapy and Its Application

2.3.1. Route of Administration Oral Administration

Gastrointestinal and systemic infections have been successfully treated with oral phage delivery [21]. The main difficulty with phage delivery through this route is that phages can be inactivated under the highly acidic conditions of the stomach. To mitigate this issue, polymer microencapsulated phages are employed, offering protection against inactivation by stomach acid while simultaneously enhancing phage efficacy. Alternatively, neutralization of stomach acidity before phage administration can be achieved via the use of sodium bicarbonate or sodium bicarbonate-enriched mineral water [22]. Phages administered via the oral route may be taken three times daily before meals. To increase their efficacy, gastric acid neutralization is performed a few minutes before phage administration, typically through the oral intake of a "stomach acid neutralizing agent," such as sodium bicarbonate or bicarbonated mineral water.

Local Route Administration

The *in vivo* pharmacokinetics of bacteriophages differ considerably from those of antibiotics in terms of tissue uptake and diffusion, largely because antibiotics are small molecules, whereas phages are complex protein assemblies. Compared with antibiotics, this reduced mobility of phages, can be advantageous for local delivery as it ensures that phages are concentrated and released at the site of infection [23]. This is the most successful route of phage administration, where phage suspensions are directly applied to the infected area [24]. Local route phages can also be applied locally by applying moist and phage-containing dressings to infected areas. (1) In the form of suspensions (drops), phages are applied to the nasal mucosa, eye, and middle ear. (2) IV route: Phages are administered intravenously to the animals. Phages are also available in the form of creams, tampons, aerosols, and rinses. (3) Inhalational: The application of inhalation technologies to phage therapy is a recent advance in the field. Considering the previous successes of bacteriophage therapy in local and systemic applications, bacteriophages could also be used to combat bacterial lung infections [22].

An experiment was conducted on mice with burn wound injury and infection with *Pseudomonas aeruginosa*. The mice were administered a dose of *P. aeruginosa* phage (containing three different *Pseudomonas aeruginosa* phages) via three different routes: intraperitoneal (IP), intramuscular (IM), and subcutaneous (SC). The results indicated that the route of administration is highly important and imparts efficacy to the treatment. The intraperitoneal route provided 87% protection. The pharmacokinetics of bacteriophages suggest that the dose delivered to the blood, spleen, and liver via the intraperitoneal route is delivered earlier and for a more sustained period than doses delivered via the intramuscular or subcutaneous route [25]. In addition to the above routes, phages can also be administered to humans intravenously (IV), intraperitoneally (IP), intramuscularly (IM), or subcutaneously (SC) [22].

2.4. Phage Pharmacokinetics

Many experiments have been performed to evaluate the therapeutic efficacy of bacteriophages; however, the kinetics of blood clearance have not been well described [26]. Therefore, understanding the blood kinetics of bacteriophages is crucial for enhancing their therapeutic efficacy. This information is essential for determining the optimal therapeutic approach, as it helps guide the proper administration and dosage of phages for maximum effectiveness [27,28].

After a single oral dose, phages are resorbed and enter the bloodstream within 2 to 4 h and internal organs within 10 h [11]. Data on bacteriophages indicate that they can persist in the body's circulation for extended periods, even for several days [29]. Following administration, the phage levels rapidly decreased within the first 8–12 h, followed by a gradual decline, ultimately disappearing within three days, exhibiting a pattern consistent with a two-compartment model. The initial rapid decline (alpha phase) is attributed to the distribution of phages to various organs, whereas the subsequent phase (beta phase) reflects the elimination of phages from the body [26]. Pharmacokinetics refers to the study of a drug's ability to reach specific target cells or tissues at concentrations sufficient to produce the primary pharmacodynamic effect [30]. It encompasses the processes of drug distribution, absorption, metabolism and elimination. In the case of bacteriophages, metabolism represents the "inactivation"

of phages because the host immune system interacts with and inactivates the phage or "activates" due to phage replication inside the host body [31].

For the success of phage therapy, the generation of an adequate number of phages is necessary near specific target bacteria that cause pathogen eradication from the body at an adequate rate. The number of bacteriophages increases through in situ replication in the host body, which is called active treatment. Thus, the main pharmacological goal is to achieve sufficient phage densities in the vicinity of target bacteria, leading to bacterial eradication [32].

2.5. Phage Preparation and Storage

There are five phage preparations with medical importance, each targeting different bacterial infections: Baste-coli-phage, Baste-rhino-phage, Baste-intestine-phage, Baste-pyro-phage, and Baste-staph-phage [33]. Because phages are bacterium specific, it is often necessary to obtain a swab from a patient and culture it before treatment. Although isolating therapeutic phages can take several months, phage cocktails for the most common bacterial strains in a given geographical area are typically available [34]. Phages can be freeze-dried and converted into pills without materially impacting their efficiency. A recent study suggested that encapsulating phages, particularly with stabilizing agents such as trehalose or skim milk, could provide an effective method for shipping and storing phages, ensuring their viability over extended periods [35]. Some types of phages in pill form have shown temperature stability up to 55°C and a shelf life of 14 months. The application of these materials in liquid form is possible and they are preferably stored in refrigerated vials [15].

2.6. Phage Applications in Different Animal Species

2.6.1. Phage Applications in Poultry

Poultry is a major reservoir for two of the world's most prominent food pathogens, *Salmonella* and *Campylobacter*, which are responsible for salmonellosis and campylobacteriosis in humans. Several studies on the application of phages to control foodborne pathogens in poultry [36,37,38] have demonstrated the efficacy of phages in reducing the levels of both *Campylobacter jejuni* and *C. coli* in the ceca of *Campylobacter*-colonized chickens. The biocontrol ability of bacteriophages against *Salmonella typhimurium* in chickens has been demonstrated [39]. A recent study demonstrated that bacteriophage treatment, particularly with both B1 and B2 phages, improved growth, reduced mortality, and increased carcass weight in *Salmonella*-infected native Vietnamese Noi chickens, although further genetic characterization is needed for broader application [40]. The use of a mixture of three phages administered 24 h after infection with *Salmonella* enteritis via aerosol spray or in drinking water effectively reduced the incidence of *S. enteritis* in chickens over 20 days. Single-phase administration over seven days did not decrease *Salmonella* shedding. However, a significant reduction in *Salmonella* shedding was observed when a mixture of two phages was used for 21 days [41].

2.6.2. Phage Applications in Swine

Relatively few studies have reported the use of phages to control foodborne pathogens in swine [42]. Preliminary studies demonstrated that administering an anti-Salmonella phage mixture via oral lavage significantly reduced Salmonella titers in the ilea, ceca, and tonsils of three- to four-week-old pigs during transport and holding before slaughter. Similarly, in market-ready pigs, phages achieved up to a 95% reduction in cecal contamination and a 90% reduction in ileal contamination [43].

2.6.3. Phage Applications in Cattle

Several *in vivo* studies have been conducted to control the colonization of *Escherichia coli* O157:H7 in cattle, focusing on the efficacy of bacteriophages in reducing fecal shedding of the pathogen. The main route of *E. coli* O157:H7 transmission in humans is through the consumption of food of bovine origin. Many *in vivo* studies have been conducted to control the colonization of *E. coli* O157:H7 in cattle. The efficacy of both oral and rectal administration of *E. coli* O157-specific bacteriophages in reducing fecal shedding of *E. coli* O157:H7 in experimentally inoculated cattle was evaluated. Shedding was monitored for 3 months for oral, rectal, and oral-plus-rectal administration and control experiments following multiple treatments with an O157-specific bacteriophage mixture. A trend toward reduced shedding was observed in orally treated cattle, whereas the rectal and oral plus rectal administration groups did not show a significant reduction in shedding compared with the control group. The authors concluded that continuous administration of phages is required to effectively control *E. coli* O157:H7 shedding in feedlot cattle [42].

2.6.4. Phage Applications in Sheep

Ovine ruminants are also considered significant reservoirs of *E. coli* O157:H7 [42,44]. The potential use of bacteriophages to reduce the levels of *E. coli* O157:H7 in experimentally inoculated sheep was investigated. On day 0 of challenge, the sheep were inoculated with a mixture of four nalidixic acid-resistant strains of *E. coli* O157:H7, each at a concentration of 10^9 colony-forming units (CFUs). A cocktail of three bacteriophages, administered at a concentration of 10^{11} plaque-forming units (PFUs), was administered on different days throughout the trial. Fecal samples were collected on 14 occasions over the 21-day challenge period, and the results showed that oral administration of bacteriophages reduced the shedding of *E. coli* O157:H7 [42,44].

2.6.5. Genetically Altered Phages

Modern Phage Technology: Obstacles and Indications.

It involves the use of genetically modified and nonreplicating phages to treat *Helicobacter pylori* and *Pseudomonas aeruginosa* infections. When phages or antibiotics target bacterial cells, a side effect often occurs in addition to their therapeutic effect: the release of endotoxins from the cell wall of gram-negative bacteria. These endotoxins can induce general pathological

conditions, such as septicemia. To address this issue, a novel approach involving genetically engineered, nonlytic, and nonreplicating phages has been explored. These phages are encoded by specific proteins that are harmful to bacteria, helping to combat bacterial infections while minimizing the release of endotoxins [45]. Genetic engineering can improve phage therapy to overcome many obstacles involved in the use of wild-type phages. *Helicobacter pylori* and *Pseudomonas aeruginosa* infections have been successfully treated with these genetically engineered and non-replicating bacteriophages [24,45]. Engineered bacteriophages can increase the killing of antibiotic-resistant bacteria, persister cells, and biofilm cells, reduce the number of antibiotic-resistant bacteria that arise from an antibiotic-treated population, and act as strong adjuvants for other bactericidal antibiotics [46].

2.6.6. Engineered Bacteriophages as Adjuvants

To increase the effectiveness of phage therapy, engineered bacteriophages have been designed to promote the expression of specific proteins and target bacterial gene networks that antibiotics cannot directly affect. Thus, phages also function as adjuvants, amplifying their therapeutic action. In addition to quinolones, these genetically altered bacteriophages act as strong adjuvants for many other antibiotics e.g., β-lactams and aminoglycosides.) Therefore. Genetically engineered bacteriophages that can overexpress proteins to target bacterial gene networks on which antibiotics cannot work and increase the destruction of bacteria by antibiotics have been developed. With recent advances in DNA synthesis, synthetic phages have been developed and are well-suited for incorporating targets identified via systems biology in a modular fashion to create effective antibiotic adjuvants. These ever-improving technologies will enable large-scale modifications of phage libraries to produce antibiotic–adjuvant phages that target different gene networks and can be applied with different antibiotic drugs against a wide range of bacteria. Combination therapy, which couples antibiotics with engineered antibiotic adjuvant phages, is a promising antimicrobial strategy for the future [46].

2.7. Obstacles and Future Use

Although phage therapy has been practiced for several decades in some former Soviet Union countries and Poland, there are still many doubts regarding its ability to replace antibiotics [19]. They are not yet ‘‘magic bullets’’ and may not work in certain settings [47]. The development of obligate lytic phages may provide a modality to kill specific pathogens without harming beneficial flora. Other issues need to be addressed, including the potential in vivo elimination of phages, phage-neutralizing antibodies, and phage-resistant mutants [47].

Dual phage-antibiotic therapy could reduce the emergence of antibiotic-resistant strains. For phage therapy to become widely accepted as an effective antibacterial strategy, it is essential to recognize its potential shortcomings and address them. Like to antibiotics, bacteria have been reported to develop resistance to phage infections. However, this can be addressed in several ways. Because phages are ubiquitous, alternative phages that adsorb different receptor molecules on bacteria can be readily isolated from the environment via simple, low-cost techniques [48].

Notably, phage resistance is associated with reduced bacterial virulence [48]. This is often because the phage receptor also acts as a virulence factor. The fact that phages are so specific in their choice of host can also be disadvantageous because an individual phage strain cannot be used as a generic treatment against various infections. Therefore, it is necessary to isolate and characterize the infectious bacterium and match it with an effective lytic phage before proceeding with treatment. To circumvent the limitations of phage specificity, mixtures of phages targeting various host strains have been successfully employed [49]. To date, phages have been used in cases where antibiotics have failed. Therefore, antibiotic-resistant bacteria have a low level of genetic variability, thus reducing the problem of phage specificity [50].

2.8. Advantages and Disadvantages of Bacteriophages

2.8.1. Advantages of Bacteriophages

Compared with classical antibiotics, bacteriophages are potential unique therapeutic agents with many advantages [51,52]. In addition to their general advantages, phage therapy offers several specific benefits, such as "auto-dosing." During the bacterial-targeting process, the number of phages can increase precisely at the site of infection, ensuring that the phages deliver the optimal dose required to target the host bacteria; this process is referred to as auto-dosing. Furthermore, phages have low inherent toxicity because they are primarily composed of nucleic acids and proteins, making them inherently nontoxic to the host organism. The relatively narrow host range exhibited by most phages limits the number of bacterial types for which selection for specific phage resistance mechanisms can occur. Thus, there is a low pressure of resistance associated with phage therapy. Because phages infect and kill via mechanisms that differ from those of antibiotics, specific antibiotic resistance mechanisms do not translate into phage resistance mechanisms [52].

2.8.2. Disadvantages of Bacteriophages

The therapeutic use of lytic phages is that the development of phage resistance may hamper their effectiveness in treating bacterial infections. Bacterial resistance to phages undoubtedly develops; however, according to some authors, the rate of resistance development to phages is approximately 10-fold lower than that to antibiotics. Furthermore, the development of phage resistance can be forestalled together if phages are used in cocktails (preparations containing multiple types of phages) and/or in conjunction with antibiotics. Phage and antibiotic therapies are synergistic when they are coapplied [53]. Unlike antibiotics, phages mutate and can evolve to counter phage-resistant bacteria [53]. As phages attack bacteria by attaching to receptors on the bacterial cell surface, phage-resistant mutants (which lack these receptors) are often less pathogenic than phage-susceptible bacteria [54,48].

The development of phage-neutralizing antibodies is another possible problem that may hamper phage effectiveness in lysing targeted bacteria in vivo. The development of neutralizing antibodies after parenteral administration of phages has been well documented [55]. The effectiveness of phages in treating diseases caused by intracellular pathogens remains unclear because these bacteria primarily multiply inside host cells, making them inaccessible to phages. Consequently, phages may have limited utility in treating infections caused by intracellular pathogens [56]. In addition to these problems, various hypotheses have been proposed to explain the ineffectiveness of phage therapy. That is, the reticular endothelial system clearance of phages from patients may be a potential problem because it might reduce the number of phages to a level that is insufficient to combat the infecting bacteria [57].

3. Conclusion and Recommendations

In veterinary and clinical applications, bacteriophages have been used primarily in aquaculture and various food products to prevent food-borne and zoonotic bacterial pathogens. Although phage therapy has been practiced for several decades in certain countries, doubts remain regarding its ability to replace antibiotics. Phages are not yet "magic bullets" and may not be effective in all settings. Potential issues that could limit the effectiveness of phage therapy include in vivo elimination of phages, development of phage-neutralizing antibodies, clearance of phages by the reticuloendothelial system, and emergence of phage-resistant mutants. Despite these limitations, bacteriophages, alone or in combination with antibiotics, can serve as a promising first-line treatment options for bacterial infections in both animals and humans.

In light of the aforementioned conclusions, the following recommendations are proposed: further research is necessary to enhance the understanding of the efficacy of phage therapy and its effects on the host immune response in animal models. The significant rise in antibiotic-resistant bacteria underscores the need for phage therapy as a viable alternative to address this burning issue. Short-term training programs should be implemented for veterinarians to increase their awareness and understanding of phage therapy. Researchers should prioritize comprehensive studies on clearance mechanisms and estimation of probable clearance periods for various types of bacteriophages.

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Contribution of Authors

All the authors made significant contributions to the study.

Conflict of Interest

The authors declare no conflicts of interest.

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