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Review Article

Novel Uses of Bacteriophages in the Treatment of Human Infections and Antibiotic Resistance

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Abstract: As the world is facing a great challenge as a result of antibiotic resistance genes among microbial pathogens to conventional antibiotics, the exploration of the alternatives are highly essential. Scientist now struggle to eliminate the otherwise easy to treat bacterial infection as well as hospital associated infections "nosocomial infections" like methicillin resistance *Staphylococcus aureus* (MRSA) and vancomycin resistance enterococcus etc. Theoretically, the use of bacteriophages for treatment is simple, though, with the scope of this straightforwardness, a complex pharmacokinetics concerns exist. The basics of drug actions involve two fundamental components: pharmacodynamics and pharmacokinetics. Pharmacodynamics entails the study of the interaction of drugs with their receptors, the transduction systems to which these are linked and the changes they bring about in cells, organs, and the whole organism. While phages distribution from compartment a - b is termed phage pharmacokinetics. To achieve immediate distribution of therapeutic phages into the systemic circulation parenteral route was preferred, and oral delivery was mainly used to treat gastrointestinal infections. Human infections successfully treated using phages include, skin ulcers, wound prophylaxis, burns, gastrointestinal tract infections, respiratory tract infections and otitis etc. PhagoBioderm® was used in the treatment of skin ulcers, and contains a cocktail of bacteriophages as antibacterial agents in patients resistant to other treatment. In conclusion, phage therapy has a greater diversity of mechanisms of action in comparison with antibiotics; it is very clear that phage therapy has many advantages, to harness this, is a challenge particularly in the face of existing rigorous regulatory practices as well as the reluctance of pharmaceuticals to invest in the field as a result of poor intellectual property and many aspects are not patentable because they are natural entities.

Keywords: Phage Therapy, Antibiotic Resistance, Pharmacodynamics, Pharmacokinetics

1. Introduction

Upon the great achievements and advancements in the field of antibiotic therapy, a threat to the long-term viability and effectiveness of antimicrobial therapy shown by antibiotic resistant genes among microbial pathogens, has challenged the treatment bacterial infections, elimination of nosocomial infection is becoming harder to treat [1]. Described as "ubiquitous in the world" – in the oceans, soil, deep sea vents, the water we drink and food we eat; Bacteriophages are the most abundant living entities on earth. It plays an important regulatory scenario in maintaining microbial balance in every ecosystem where this has been explored as it ranges from 10^{30} to 10^{32} in total [2].

The therapeutic uses of Bacteriophage in the treatment of bacterial infection were highly controversial in the West at the start, probably as a result of the discovery of antibiotics in 1928 by Alexander Flaming and the advancement in the area decades after. This was evident especially with the

introduction of Sulfa drugs and penicillin in the 30s and 40s respectively. Early studies were widely criticized as it lacks appropriate controls and consistent results, the Council on Pharmacy and Chemistry of the American Medical Association concluded that "the evidence for the therapeutic value of lytic filtrates was, for the most part, contradictory, unconvincing, and recommended additional research to confirm its purported benefits" [1].

This review will look at the History and Origins of Phage therapy, Biology and as well as uses in the treatment of human bacterial infections and therapy, citing experiment and clinical research conclusions.

2. Historical Overview of Phage Research

In the late 19th Century, working to Government of the United Provinces and the Central Provinces of India, the Naturalist and British bacteriologist, Ernest Hanbury Hankin, observed unknown substances infiltrate Millipore filters, demonstrated to retain larger microorganism like bacteria; possess antimicrobial activity were responsible for halting the spread of cholera in the waters of rivers Ganga and Yamuna (Ganges and Jumna) [3]. Bacteriophages were discovered by Frederick W. Twort in 1915 and Felix D'Herelle in 1917 respectively. Twort described it as "dissolving material" obtained from a bacterial culture which exhibits transparent patches in bacterial colonies. Two years later D'Herelle published a similar findings termed "invisible microbes", and persisted in claiming priority for his discovery [4]. However, D'herelle pioneered the application of the term "bacteriophage"; a microbe that has the potential to attack bacteria and kill them, and that the agent responsible for the bacterial cleansing was a virus [5].

In 1917, under the clinical supervision of Professor Victor-Henri Hutinel at the Hospital des Enfants-Malades in Paris, D'Herelle began testing his phage in human patients; he demonstrated the safety of his phage by ingesting them. The next day, he established their efficacy by administering them to a 12-year-old boy with severe dysentery. The patient showed a tremendous improvement with a single treatment and made a complete recovery [6]. Sabouri and Mohammadi reported that "the exact nature of phage had yet to be determined, and it remained a matter of active and lively debate. The lack of knowledge of the essential nature of DNA and RNA as the genetic essence of life hampered a fuller understanding about phage biology in the early 20th Century [5]".

3. The Phage Biology

Viruses that infect bacteria are called bacteriophages or shortened as phages. Like all viruses, Phages are absolute parasites, although carry all the information to direct their reproduction in an appropriate host, they have no machinery for generating energy and no ribosomes for making proteins. They are defined as an obligate intracellular bacterial parasite that lacks an independent metabolism. A century of phage research has revealed that, these viruses are extremely different and ubiquitously present in the biosphere, preying on Eubacteria and Archaea in a broad range of biological niches. Accordingly, the genome sizes of phages vary enormously, from a few thousand base pairs up to 498 kilobase in phage G, the largest phage sequenced to date. Although the size of this genome resembles that of an average bacterium, even phage G lacks genes for essential bacterial machinery like ribosomes, emphasizing the purely parasitic nature of these organisms [7]. The High level of specificity, durability, long-term tolerance and the inherent potentials to reproduce rapidly in an appropriate host contribute to their maintenance of dynamic balance among the great diversity of bacterial species in any natural ecosystem [8].

Based on their size and shapes, bacteriophages can be categorized into three. Icosahedron Bacteriophages, Filamentous Bacteriophages, and Complex Bacteriophages.

- Icosahedron bacteriophages: an almost spherical shape, with twenty triangular facets, the smallest is icosahedron phages are about 25nm in diameter.
- Filamentous bacteriophages: long tubes formed by capsid protein assembled into the helical structure; they can be up to about 900nm in diameter.
- Complex bacteriophages: icosahedral heads attached to helical tails; may also poses base plates and tail fibers.

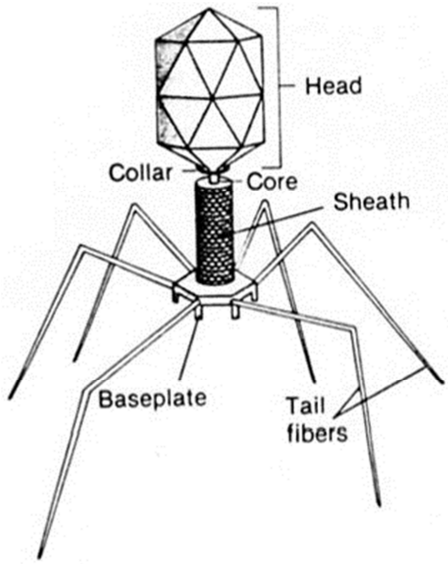

Figure 1. *Lytic bacteriophage [9].*

In addition to shape, bacteriophages can be categorized by the types of nucleic acid they contain. They can be Single-Stranded DNA Phages (ssDNA), Double-Stranded DNA phages (dsDNA), Single-Stranded RNA phages (ssRNA) and Double-Stranded RNA phages (dsRNA). Bacteriophages can be categorized by the actions that follow after the invasion of the bacterial cell; some are virulent phages, whereas others are temperate phages [10].

As virus infecting bacteria, phages exhibit different life cycles within the bacterial cell: lytic, lysogenic pseudo-lysogenic, and chronic infection. However, the primary focus in phage therapeutic application is on lytic phages of the three families of Caudavirales order: the

Myoviridae with the biggest capsid head and contractile tail, the Siphoviridae with a relatively small capsid head and a long flexible non-contractile tail, and the Podoviridae with a small capsid head and a short tail [11]. Wittebole *et al.*, summarized the general description of those phages as follows:

- The genetic materials are contained in a protein shell or capsid which has a form an icosahedron;
- The head is connected to a color to the tail which may be contractile or otherwise and whose distal extremity is in connection with tail fibers with tips that identify attachment sites on receptors of the bacterial cell surface.

The virulence bacteriophages always cause what is called lytic cycle, which results in the killing of the bacterial cell. The actions of lytic phages as bacterial predators achieves several steps to attain host destruction [10, 11]. Viz:

- Attachment to binding molecules- this process is specific involving complementary receptors on both of the surface of the host cell and infecting agent.
- Penetration or DNA Injection- phage injects its DNA into the bacterial cell after peptidoglycan degradation and pore formation in the host cell.
- Synthesis, redirection of host metabolism to phage DNA replication and phage protein biosynthesis- Here the phage genes are expressed, which redirects the host synthetic machinery to the reproduction of viral nucleic acid and proteins.
- Assembly- complete viral particles are produced.
- Lysis- the host cell burst open, and all the new virions are released. Phage late proteins including lysin, holins, or murein synthesis inhibitors cause the bacterial cell lysis.

4. Phage Pharmacology

Pharmacology, the study of drug-body interaction in the context of phage therapy, can be used interchangeably with ecology because it represents a phage environmental interactions. The interactions between phages and bacteria as well as between phages and body tissues. When health declines, external control on the body's ability to maintain a clear-cut general state of health become essential; hence the use of drugs. For therapeutics to be successful and safe, the control of phages on the host and the influence of the bacteria on the phages most be considered [12].

Theoretically, using phages for therapy is simple, though, with the extent of this straightforwardness, a complex pharmacokinetics concerns exist [13]. The basics of drug actions involve two fundamental components: pharmacodynamics and pharmacokinetics. Pharmacodynamics entails the study of the interaction of drugs with their receptors, the transduction systems to which these are linked and the changes they bring about in cells, organs, and the whole organism. The drugs impact on the body can either be positive (i.e., maintaining or restoring health) or negative (i.e., effecting toxic side effects). Pharmacokinetics deals with the absorption, distribution, metabolism and excretion of the drug; otherwise body's impact on the drug. Both drug absorption and drug distribution require drug movement throughout the body, at first to the blood and then (or instead) beyond the blood. Absorption and distribution also can be viewed regarding drug density within the body, such as specific tissues or compartment. Drug metabolism and drug excretion are often mentioned in contrast, to declines in drug density, though with two prominent exceptions. These are when drugs are converted to their active form through metabolism or when drugs are delivered to their site of activity via excretion [12].

4.1. Pharmacodynamics of Phage Therapy

Phage is in the class of drug that advances itself for a form of active treatment- with features of automated dosing [14] mimicking homeostatic mechanism better than standard pharmaceuticals. This type of active treatment could be distinguished with the more traditional passive treatment. As a result of their low toxicity and self-amplification, phages are considered active antibacterials against pathogenic and nuisance bacteria. For self-amplifying drug, appropriate dosing by clinicians may be less important since the drug otherwise is held responsible for attaining therapeutic levels. Abedon and Thomas-Abedon extensively reported that "an ignorance of phage pharmacodynamics could result in compromises to phage therapy efficacy [12]".

Phage safety, a topic almost covered in every review of phage therapy, the uniqueness of phages other than their ability to kill bacteria (antibacterials), is their relative low inherent toxicity and rapid recovery as well as biofilm clearance to a certain extent [15]. This low toxicity is a consequence of phage composition, which for tailed phages is entirely protein and DNA. Disruption of normal body flora is minimal, phage interaction with the body's metabolism and various aspect of the immune system can result in the degradation of phage virions. This ability is in contrast to the metabolic decay of certain antibiotics; its degradations does not lead to production and accumulation toxic byproducts. Intact phages are less efficient at interacting with other features of the body's metabolism such as specifically binding to or otherwise manipulating body tissues. Phage therapy, in principle, can be very safe [12]. This safety is however not unconnected with the body's routine exposure to a large number of endogenous phages, after all, is not qualitatively outside of the normal body experience [16].

The potentials of phage in eliminating bacteria, as expressed in pharmacodynamics are to kill or, at least, prevent the replication of one or more bacteria while not excessively harming the treated patient. Unlike synthetic antibiotics, only a single phage is enough to kill a single bacterium. Therefore, fewer units of phages are required per treatment. In short, phages can be said to show a unique pharmacodynamics because of a combination of their single-hit killing kinetics, their lack of dissociation from bacterial targets once adsorbed, and they are potential to multiply adsorb individual bacteria. To achieve bacterial killing only one of those attachment properties is necessary, that is the Phage's killing titer [12, 15, 17]. A killing titer is a measure of phage density in a solution which determines the ability of phages to kill bacteria and not the phage's ability to replicate [18].

Mixtures of phages with bacteria and subsequently plating for plaque-forming units (PFUs) is carried to determine killing titers. The fewer PFUs viable, the higher the killing titer. By assuming a poison distribution of phages adsorbing to bacteria, the bacterial killing can be converted into an absolute killing titer. The number of surviving bacteria is to be a function of initial bacterial density with the phage multiplicity of infection [18].

4.2. Pharmacokinetics of Phage Therapy

Phages control bacterial infection in a couple of ways, through active treatment, as mentioned earlier, where most of the bacteria are killed by secondary infection after the large reproduction and transmission of the phage. Secondly, where phages do not increase in number, but the initial dose is large sufficient to engulf the bacteria by primary infection, termed passive treatment [19]. Pharmacokinetics (body's impact on drugs) as hinted above may be differentiated into consideration of drug absorption, distribution, metabolism, and excretion. Weber-Dabrowska *et al*., (1987) demonstrated the presence of circulating phages (against *Staphylococcus, Escherichia, Pseudomonas,* and *Proteus*) in the majority of blood samples taken on day 10th of oral treatment of patients with various bacterial infections resistant antibiotics and hence phage translocation. Absorptions start with the drug application, which could be systematic (intended for systemic delivery, and internalization into body tissues (via injection, application to the skin, mucus membrane application, and the nasal cavity) and non-systemic (topical, enteric, via inhalation, or enteral); phages are readily absorbed [20].

In general, movement of drugs within the body, except either to or within blood in pharmacokinetics is described as distribution. Such phage change as it occurs between body compartments a and b can be conceptualized using the standard first-order reaction kinetics where movement from compartment a (e.g. the small intestine) into compartment b (e.g. the blood) occurs as the rate which is phage-density depended as well as depended on both forward and reversed translocation rate constants. Thus; if K1=rate of forward movement (e.g. form intestine to blood, x and y respectively) Then, K1Px = forward rate constant times the density of phages in compartment x). This defines the rate of movement from compartment x to y. whereas; K2Py (= reverse rate constant times the density of phages in compartment y describes the kinetics of the reverse reaction. If Py or K2 are small, in relation to Px or K1, then, the reverse reaction can be disregarded (from compartment y back into compartment x). The result is that movement of phages from compartment x to y will, at least, vary as a function of the Px, (phage density in x). Thus, the more phages provided, the greater the predicted movement, maybe with limitations imposed by saturation of essential translocation machinery. It is always possible to consider calculations which take the volumes of the compartment into accounts. However, this could be avoided by the standard enzyme-kinetic assumption that densities remain effectively constant despite movement/reaction, which is near zero within the recipient compartment. Qualitatively, excretion is an important phenomenon in phage delivery to the urinary tract. Excretion is the main channel through which drug density is reduced within the body, perhaps not so significant quantitatively. Phage decay – inactivation or excretion both associated with metabolism, influences the potential for phage populations to proliferate and persist; this contributes to the success of the phage therapy [12, 17 and 21].

5. Phage: Delivery Mechanisms

Several delivery routes has been proven to be effective by phage researches in this field; many reviews are indicating the preferred delivery routes to achieve a successful phage treatment. Ryan et al., highlighted the most active and successful route of administration for the treatment of systemic infection was via the parenteral route; this is as a result of the immediate distribution of the phages into the systemic circulation. Oral delivery is primarily used to treat gastrointestinal infections. The study also argues that no formulation details were seen in many of the reviews [19].

However, significant success of phage therapy was recorded through specific sites of administration – intramuscular (IM), subcutaneous (SC) or intraperitoneal (IP) and formulation. Barrow *et al.*, Biswal *et al*. and Cerveny *et al*, all in Ryan *et al*., demonstrated the efficacy of sites of administration as IM, IP, and IV for septicemia, bacteremia and systemic infection respectively, all the study was conducted using model mice. Mc Vay *et al*. proved beyond reasonable doubt that IP administration is the most useful for phage therapy in a case of mice compromised by a burn injury and subject to a fatal injection with a strain of *P. aeruginosa* (PAO1) were administered a single dose of *P. aeruginosa* cocktail. The phages administer intramuscularly or subcutaneously reduced the rates of mortality to 72% and 78% respectively. While the rate of mortality was reduced by 12% when phages are delivered by IP injection [19]. All the successes depend on the phage concentration used.

Oral and local phage delivery have also proven successful. The earlier was very successful in the treatment of gastrointestinal infection and some cases systemic infection. The challenge is the phage stability in the highly acidic and proteolytic active environment of the stomach. Protection from gastric acidity by methods such as polymer microencapsulation may add value to the orally administered phages. The advance of hydrogel and impregnated would-healing formulations has increased the success rates of treatment via topical application. Local phage therapy for areas other than the skin has also received attention [19 and 20].

6. Phage Treatment of Some Human Infections

i. Skin Ulcers:

Abedon *et al.,* described the success of phage in the treatment of skin ulceration. "Overall, the employment of phages to treat infected skin ulcerations within the context of western medical practice would appear to be quite promising.

Infected skin ulcerations can be chronic and resistant to antibiotic treatment. Phages can be topically applied with impressive success though rarely if ever within the context of rigorous, double-blinded and peer-reviewed studies [22]". PhagoBioderm® A microbial wound dressing/healing biodegradable polymeric film, containing bacteriophages "cocktail" as antibacterial agents were used for patients resistant to other treatment. PhageBioDerm® was applied to ulcers both alone and, where appropriate in combination. The result showed 70% of almost 100 patients were completely healed from the Ulcers as reported by Markoishvili *et al.,* [22]. In a study conducted by Abedon *et al.,* a 95.0% successful positive cases for phage treatment of 162 "Disease of the skin and subcutaneous tissue" which includes furunculosis and decubitus ulcer. Also stated in the review was a study involving 6000 patients in which recovery were recorded in 4-8 days, and 70-100% of patients were healed in 1957 [22].

ii. Wound Prophylaxis:

The term wound doesn't necessarily imply infection, wounds can result from surgery, accident or burns. Of concern in wound care is "avoid infection", wounds can become infected with a variety of pathogens. Phages play an important role in the major tertiary care centers as well as wound and burn facilities in Georgia. Thus, phages are used for prophylaxis to prevent infection and prophylaxis for surgical site infection too. Phage therapy is indicated in Georgia under circumstances where antibody penetration difficulties in the site of infection caused by poor circulation, chronic osteomyelitis wounds covering a large area. Phages are one component of successful wound care and treatment of surgical infections and treatment of multi-resistant infections in Georgia [22 and 23].

Phage preparations usually polyclonal introduced into the wound can be applied in a number of ways; by irrigation of wounds with a phage preparation after surgical debridement, ultrasonic debridement of the wound with the phage preparations, soaking of wound bandages in the liquid preparations, the periodic introduction of phages through drainage tubes. PhageBioderm ® commercially released in 2000 is a phage containing anti-microbial polymeric bio-composite materials developed by Georgian chemists and microbiologists since 1995. For deeper wounds, PhageBioderm is mostly used in addition pyophage wound irrigation. The first peer-reviewed report of the therapeutic efficacy of PhageBioDerm published by Markoishvili *et al.,* [22]. In summary, 107 patients with ulcers resistant to conventional treatment (antibiotics) were treated with PhageBioderm as reported: "alone or in combination". 70% of the wound healed completely, Microbiological data available correlates the healing with the concomitant elimination of or a marked reduction in a number of specific pathogenic bacteria in the ulcers. Slopek *et al.,* reported 90.8% positive cases for phage treatment of 305 injuries [2 and 22]

iii. Burns:

Burns are highly susceptible to microbial infections (bacteria, viruses, and fungi). The most important threat comes from bacteria and usually from opportunistic once. Within a day, burn patients experience attacks from opportunistic bacteria, this can vary from simple infection treatable by antibiotics and to a more complicated types which acquired resistance to drugs. Results have shown that phage therapy has a 90% success against *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumonia* [24]. In burn patients, *P. aeruginosa* is the most common cause of lethal infection and one of the most thoroughly studied and demonstrably effective targets in Georgia. Pirnay *et al.,* conducted a one-year study of *P. aeruginosa* to elucidate the scale of the burn wound infection problem in the Queen Astrid Military Hospital, Brussels's Burn Wound Centre (BWC). 441 patients were treated at the 32 bed BWC, 70 were colonized with *P. aeruginosa*, 57 (13%) of whom acquired the bacteria nasocomically [23]. Eight patients infected with *P. aeruginosa* died, 3 of them no bacteria were detected, and death was attributed to the *P. aeruginosa* infection. Kutter *et al.,* also reported the Soothil findings in the UK of a case of a 27-year-old male with 50% total body surface area burned and excised burn wounds covered with skin grafts and became infected with *P. aeruginosa*, despite appropriate antibiotic treatment grafted areas broke down. Hence, treatment with 'purified' phages was started, 43 to 1200 fold increase of phages was observed in the wound, after 72 hours, *P. aeruginosa* could no longer be isolated, and later, extensive grafting was successful [23].

iv. Gastrointestinal infection:

The advantages of phages treatment of gastrointestinal infections over antibiotics is the reduced disruption of gut microbial flora. Eastern Europe and Georgia conducted experimental anti-dysentery trials though with insufficient documentation. Abedon *et al.,* (2011) argued that much of the knowledge relies on abstracts presented at meetings held at Eliava Institute as well as dissertations. There is several reports phage therapy success in the treatment of gastrointestinal tract infection [22]. Slopek *et al.,* reported the trials between 1981 and 1986 shows 91-100% positive cases for phage treatment of 42 diseases of the digestive system and six infection diseases of the alimentary tract. In events of gastrointestinal infections, the intestiphage formulations are routinely employed prophylactically to prevent nosocomial infection in Georgia especially in wards (hospital) where this is particularly prevalent [22].

Clinical trials of phage therapy which hopes to demonstrate the potentials of a new form of therapy for childhood diarrhea in Bangladesh and other developing countries carried out under the leadership of Harad Brussow of the Nestle Corporation, Lausanne, Switzerland in 2009. The therapy is being applied to the standard oral rehydration solution, and a novel cocktail of T4 like phages to treat ETEC and EPEC induced diarrhea in children and to determine its safety and efficacy. Abedon *et al.,* maintained that, the work in particular demonstrates all of the phages being used has been studies in several mouse experiments and the phages being used for the key experimental arm of the trial were isolated from the stools of pediatric diarrhea patients in Bangladesh and probably useful broad-spectrum ones turning out to be the members of the highly studies T4 family pf phages. Also reported the

details of their very extensive genomic and gut related infection studies of their several groups of T4 like phages in their set [22].

Unfortunately, this trial was terminated in 2013 as indicated in clinicaltrials. gov (NCT00937274) [25].

v. Respiratory Tract Infection:

Phage therapy for respiratory tract infection is limited to those who have a bacterial origin or etiology. Weber-Dabrowska et al., and Slopek et al., both reported success in treating pneumonia in six cancer patients and 87% positive cases for phage treatment of 180 diseases of the respiratory system respectively [22]. In cystic fibrosis, a successful treatment of *P. aeruginosa* infection of the lung of the seven-year-old patient along with *S. aureus* co-infection using pyophage was also reported [22]. Saussereau *et al.,* assessed the effectiveness of phages in the sputum of cystic fibrosis patients in which a cocktail of ten bacteriophages infecting *P. aeruginosa,* 58 samples in total from CF patients and 10 samples which did not contain *P. aeruginosa* were not further analyzed. In the 48 samples, observation shows bacterial counts ranging 33%, 60%, 90% increase in the absence and from 18% to 98% reduction in the presence of bacteriophages. The microenvironment in the lung of CF patients does not inhibit bacteriophage activity as the number of bacteriophages increased over the threshold value in 86.4% (41 out of 48 samples containing *P. aeruginosa* strains). The study argues that the independent patient efficacy supports the further development of phage treatments [26].

vi. Chronic Otitis:

The bacteria in chronic otitis are largely organized into biofilms and are relatively protected from both antibiotics and immune cells. Indeed, a common difficult to treat the condition as *P. aeruginosa* is particularly hard to eradicate due its antibiotic resistant attributes while the aminoglycoside use has been curtailed due to its ototoxic effects if the tympanic membrane is perforated. This, in particular, has been the initial target of the British Phage therapy firm, Biocontrol Limited. Phase I/II human trial approval was obtained by the company as it scientist carried out a successful trial of phage against Pseudomonas dog ear infections earlier [27]. Soothil *et al.,* reported "the ears of dogs in which *P. aeruginosa* was the predominant pathogen were treated with topical Biovet-PA, a combination preparation of six bacteriophages. Biovet-PA infects 90% of dog (and 86% of human) clinical isolates of *P. aeruginosa*. 11 ears were treated; bacteriophages multiplied in all and the condition of all the ears improved. In three ears the *P. aeruginosa* infection resolved. Counts of *P. aeruginosa* fell in all but one ear. No adverse effects were noted despite clinical monitoring of relevant indicators. Only one dose of bacteriophage was needed, an advantage of using competent replication bacteriophages. After 2 days, reduced numbers of *P. aeruginosa* were counted, and clinical improvement was seen in all dogs treated [27]".

7. Conclusion

Bacteriophage (s) or phage cocktails are a possible alternative for the treatment of bacterial infections, especially the multi-drug resistant pathogens (e.g. P. aeruginosa, S. aureus, etc). Phages exhibit several features that make them attractive therapeutic agents, they are very specific (host specificity) and can effectively lyse target bacteria (pathogen). The safety of phages cannot be overestimated, its safety, however, is not unconnected with the body's exposure to a large number of endogenous phages which is part of the normal body experience and disruption of normal body flora is minimal. The relative abundance of phages in the environment makes it simple to identify them against any given bacterial pathogen. Phage clearly shows a greater diversity of mechanisms of action in comparison with antibiotics; it is very clear that phage therapy has many advantages, to harness this, is a challenge particularly in the face of existing rigorous regulatory practices as well as the reluctant of pharmaceutical interest to invest in the field. This investment is believed to be a fraction of what is required in conventional pharmaceutical products and probably due to the lack of strong intellectual property and many aspects are not patentable because they are natural entities.

Several hundreds of review papers are available, but there is the unmet desire to fight drug-resistant strains of bacterial infectious agents. To achieve this, there is the need to deploy and conduct rigorously open clinical trials in the field of human phage therapy.

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