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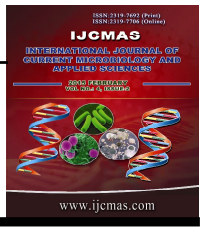

Review Article

Bacteriophages: their use in the treatment of infections in the future

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A B S T R A C T

Although antibiotics have saved millions of lives since their discovery, loss of effectiveness of these miracle drugs is an impending danger in the near future. In the search for alternatives to antibiotics, use of bacteriophages for the treatment of infections could be an effective alternative. The knowledge of phages and their use in the treatment of infections is known since long. these phages being the most abundant forms of nature and with the advantage of no side effects and not affecting the normal flora and being capable of self replication with a single administration ,can be used prophylactically as well as for well established infections. They can be used as a whole phage or any phage product or lysine can be used for treatment. Studies reveal their effective use in a wide variety of infections. Although some problems remain to be solved, phage therapy has potential to find a place in modern medicine in the future.

Introduction

Viruses that infect bacteria are called bacteriophages. As per 2012 statistics ,5360 tailed and 179 cubic, filamentous and pleomorphic bacterial viruses have been examined in the electron microscope . Every year a 100 new bacterial viruses are discovered . Bacteriophages are the largest virus group known.[1] Bacteriophages are one among the most abundant living entities on earth . [2] Since the discovery of antibiotics ,antibiotics have saved millions of lives. Just the world is on the brink of losing these miracle cures or antibiotics and we are heading toward a post-antibiotic era, in which many common infections will no longer have a cure .Thus appropriate action has to be taken to combat the effectiveness of the antibacterial power of phages has been known for nearly 60 years[3]

History of Bacteriophages

Bacteriophages were discovered twice at the beginning of the 20th century. In 1915, the English bacteriologist FW Twort described a transmissible lysis in a “micrococcus” and, in 1917,the Canadian Felix d’Herelle, then at the Pasteur Institute in Paris, described the lysis of Shigella cultures [4] D’Herelle, however, devoted the rest of his scientific life to bacteriophages and the phage therapy

of infectious diseases. He coined the term "bacteriophage" [5]

Classification of bacteriophages

The forerunners of phage classification were the great Australian microbiologist, Sir Macfarlane Burnet, who proved in 1937 that phages differed in size and resistance against physicochemical agents10 and H Ruska, who proved that phages were morphologically diverse.[6]. A Provisional Committee on Nomenclature of Viruses (PCNV) was founded in 1965, later to become the International Committee on Taxonomy of Viruses (ICTV). In 1971, the ICTV issued its first report which included six phage "genera": T-even phages, l, lipid phage PM2, the fX group, "filamentous phage", and the "ribophage group". Groups were listed with type species and properties . This may be considered as the starting point of phage classification.[7] Bradley. H proposed six basic morphological types, corresponding respectively to tailed phages (with contractile tails, long and noncontractile tails, and short tails), small isometric ssDNA viruses, filamentous phages and small ssRNA phages.[8]

Tailed phages constitute the order Caudovirales with three families, characterised by contractile, long and noncontractile, or short tails and named respectively *Myoviridae*, *Siphoviridae*, and *Podoviridae*. They represent over 96% of phages. [9] Classification is necessary for identification of novel and therapeutic phages,and also to know which phages are harmful .[10]

Genetics of bacteriophages

Bacteriophages are viruses which contain either DNA or RNA as the genetic material and both single and double stranded forms of each are known. The structure of these organisms constitutes a polynucleotide chain consisting of a deoxyribose or ribose phosphate backbone to which are attached specific sequences of the four nucleotides - adenine, thymine (or uracil), guanine and cytosine. Two such complementary chain are paired together in the form of a double helix in double stranded bacteriophages. [11].Two phage types can be differentiated according to how they infect host bacteria. Temperate phages undergo a lysogenic cycle during which they integrate their chromosomes into the bacterial genome and stay in a dormant stage as prophage[12]. When the host bacterium encounters circumstances leading to DNA damage,prophages may be activated and turn on the lytic cycle. Temperate phages harbor the risk of altering the phenotype of their target bacteria. They are a key driver in the acquisition of virulence factors in enteric bacteria and of the complex regulating networks that control their expression.[13]

The lytic cycle comprises a series of events that occur between attachment of phage to the production of phage progeny.. The lytic phages are the most suitable candidates for phage therapy, because they quickly reproduce within and lyse the bacteria in their host range, growing exponentially in number in the process. [14].During the final stage of multiplication , most tailed phages produce a lysine peptidoglycan hydrolase to exit the bacterium and disseminate progeny phage after lysing the bacterial cell [9].

History of phage therapy

Phages as therapeutic agents in humans were first used in 1919 just when they were discovered[15] These studies were later abandoned due to the introduction of broad spectrum antibiotics which were cheap and an easy alternative. [16] In 1915, Frederick Twort hypothesized that antibacterial

activity could be due to the virus (phage), but he did not pursue his discovery [17] Intensive studies on the therapeutic use of phages for treating infectious diseases were taken up in 1920. [18] Vibrio cholerae was the first bacteria against which phage therapy was tried but the activity of phage was found to be much higher in vitro than in vivo.. Ernest Hankin first reported the existence of antibacterial activity against *Vibrio cholera* the causative agent of cholera which was considered one of the deadliest peril humans had faced. In 1925 d'He'relle reported treatment of plague (four types) by antiplague phages which drew attention towards phage therapy. Later on he visited India and worked on phage therapy of plague at the Haffkine Institute, Bombay (Mumbai) [19.]

Source & selection of phages

Phage for a given bacterium can be isolated wherever that bacterium grows, such as in faeces, sewage, soil, hot springs oceans. Water from the Ganges in India has been found to be a rich source of vibrio phages. After isolating phage against particular bacteria , selecting the ones most likely to be useful for clinical purposes is very important . This includes lytic phages that have high efficacy and broad spectrum activity on clinically important strains. These should not be temperate phages that carry xigenic genes. Phages should be such that they can be readily produced in large quantity and should be stable during storage. [20]

Commercial production of phages

D'Herelle's commercial laboratory in Paris produced at least five phage preparations against various bacterial infections. The preparations were called Bacté-coli-phage, Bacté-rhino-phage, Bacté-intesti-phage, Bacté-pyo-phage, and Bacté-staphy-phage, and they were marketed by what later became the large French company L'Oréal. Therapeutic phages were also produced in the United States. In the 1940s, the Eli Lilly Company (Indianapolis, Ind.) produced seven phage products for human use, including preparations targeted against staphylococci, streptococci, *Escherichia coli*, and other bacterial pathogens. These preparations consisted of phage-lysed, bacteriologically sterile broth cultures of the targeted bacteria (e.g., Colo-lysate, Ento-lysate, Neiso-lysate, and Staphylo-lysate) or the same preparations in a water-soluble jelly base (e.g., Colo-jel, Ento-jel, and Staphylo-jel). They were used to treat various infections, including abscesses, suppurating wounds, vaginitis, acute and chronic infections of the upper respiratory tract, and mastoid infections. However, the efficacy of phage preparations was controversial, and with the advent of antibiotics, commercial production of therapeutic phages ceased in most of the Western world. Nevertheless, phages continued to be used therapeutically—together with or instead of antibiotics—in Eastern Europe and in the former Soviet Union. Several institutions in these countries were actively involved in therapeutic phage research and production, with activities centered at the Eliava Institute of Bacteriophage, Microbiology, and Virology (EIBMV) of the Georgian Academy of Sciences, Tbilisi, Georgia, and the Hirszfeld Institute of Immunology and Experimental Therapy of the Polish Academy of Sciences, Wroclaw, Poland.The Eliava Institute was founded in 1923 by Giorgi Eliava, a prominent Georgian bacteriologist, together with Felix d'Herelle. The Institute, employed approximately 1,200 researchers and support personnel and produced phage preparations often several tons a day against a dozen

bacterial pathogens, including staphylococci, *Pseudomonas*, *Proteus*, and many enteric pathogens. The Hirszfeld Institute was founded in 1952. The bacteriophage laboratory of the Institute was instrumental in developing and producing phages for the treatment of septicemia, furunculosis, and pulmonary and urinary tract infections and for the prophylaxis or treatment of postoperative and postraumatic infections[21,22,23]

Mode of action

Despite the large number of publications on phage therapy, there are very few reports in which the pharmacokinetics of therapeutic phage preparations is delineated. The few publications available [24] suggest that phages get into the bloodstream of laboratory animals after a single oral dose within 2 to 4 hrs and that they are found in the internal organs (liver, spleen, kidney, etc. in approximately 10 hrs. Phages can remain in the human body for relatively prolonged periods of time upto several days[25]. Therapeutic phages are assumed to kill their target bacteria by replicating inside and lysing the host cell . However, subsequent studies revealed that not all phages replicate similarly and that there are important differences in the replication cycles of lytic and lysogenic phages. Furthermore, the recent delineation of the full sequence of the T4 phage & recent studies on T4 phage replication have shown that lysis of host bacteria by a lytic phage is a complex process consisting of a cascade of events involving several structural and regulatory genes . A group of authors [26] identified and cloned an anti-*Salmonella* phage gene responsible, at least in part, for the phage's potent lethal activity against the *Salmonella enterica* serovar Typhimurium host strains. In another study [27] , a unique mechanism has been described for protecting phage DNA from the restriction-modification defenses of an *S. aureus* host strain.

Advantages of phage therapy

Phages are selfreplicating and self limiting.. One phage particle is sufficient to kill a given bacterium. Phages continue to multiply and penetrate deeper as long as local infection is present. Phages are lytic against specific bacteria sp so they can be targeted more specifically than antibiotics which are active against a group of bacteria. Phages do not harm normal intestinal flora. They have been used in millions of people with no reported side effects. They can be used both prophylactically and also in established infections. Because of their self perpetuating nature in the presence of susceptible bacteria,multiple administrations are not required. [28]

Phages are “living” organisms that undergo mutations, some of which can overcome bacterial mutations. E. g., mutated phage tail fibers can allow binding to a mutant bacterial receptor, or mutated phage DNA can escape cleavage by mutant bacterial endonucleases Although there are some exceptions, phages do not cross species boundaries. Thus even though the targeted bacterial species may become resistant to the phage, it is unlikely that other species will.[29]

Disadvantages of phage therapy

1. Phages tend to have a relatively narrow host range, posing certain disadvantages. A disadvantage is that one should administer only those phage strains shown to be strongly lytic for the bacterial strain infecting the given patient. If the patient’s condition is too critical to take the time required for this matching, then one should use a panel of phages, where each of the

phages therein has a broad-enough host range that most strains of the bacterial target are likely to be targeted. Screen the bacteria infecting a given patient against a panel of phages, to ensure that one of the phage strains will be lytic and develop "multivalent" phages that lyse all or most of the bacterial strains within a given species of pathogen to overcome this.

2. Another disadvantage is the presence of bacterial debris in the phage preparations. Injection of even minute amounts of endotoxin and other bacterial debris can be fatal to patients. Unfortunately, many of the phage preparations used by practitioners in the historical era were crude lysates. When these preparations were injected IV, IP and in some cases even intrathecally, any beneficial effect of the phages would likely have been counteracted by illness and deaths resulting from the endotoxin. But, modern technology allows density centrifugation, banding, and other methods of purification to overcome this.

3. Phage preparations contain live bacteria which is another problem. In order to ensure that phage preparations would not contain live bacteria, some early investigators added mercurials and/or oxidizing agents, while others heated them. It is now known that such agents and procedures will denature or otherwise inactivate the phage coat proteins. The viability of the phages would be lost. To ensure that phage preparations do not contain live bacteria, sterile filtration has to be done. If chemical agents must be used, retitrate the preparation over time to ensure that the phage remains viable.

4. Rapid clearance of phages is another issue. Phages were rapidly cleared by the spleen, liver and other filtering organs of the reticulo-endothelial system. One of the principal reasons phages had failed as a therapeutic was their supposed inactivation by pre-existing antibodies to them. However, any clearance of the phages from the bloodstream of the germ-free animals used by Merril and his group were not be due to antibodies, since those animals had never previously been exposed to bacteria or bacteriophages (and so would not have antibodies). Moreover, the phages in Merril's experiment remained viable in the spleens of these animals over a period of several days, indicating that they were neither neutralized by antibody nor engulfed by macrophages. Rather, they appeared to have been passively entrapped in (these filtering organs. Such trapped phages would be unavailable to reach bacteria.In all species of phage, minor variations in coat proteins might be present that would enable some variants to be less easily recognized by the RES organs and to thereby remain in the circulation for longer periods of time than the "average" wild-type phage. It was elucidated that there is the molecular basis of the mutation in lambda phage that reduced its rate of clearance: a single point mutation, an A to G transition, occurs in the gene encoding the major head protein E. This mutation substitutes a basic amino acid lysine for an acidic one glutamic acid , causing a double charge shift readily seen on 2D gel electrophoresis. A double charge shift in this region of a protein that is highly represented on the surface of the virion would alter the phage's interaction with the microcirculation of the spleen, in such a way that the mutant phage is less easily entrapped than the wild-type.

5. Lysogeny was also a problem . After a period of time days or weeks longer , such prophages can enter the lytic cycle, and will thus appear as plaques on a bacterial lawn. It is likely that some phage therapy trials in the historic era had a negative outcome due to the inadvertent use of phage strains that,

being lysogens, could not provide the rapid lysis and exponential growth in numbers that are needed for full efficacy. Use only phages that are lytic; sequence phages that are strong candidates for clinical trials, looking for among other things, homologies to known genes of lysogeny.

6. Anti-phage antibodies is another issue. There are reports in the literature20 that neutralizing antibodies appear a few weeks after administering phages to humans or animals. Given the time lag, antibodies would not seem likely to interfere with an acute treatment lasting a week or so. However, in chronic treatment, or in treatment of a recurrence of the same bacterial infection, the neutralizing antibodies might prevent some proportion of the administered dose of phages from being able to adhere to the bacterial target. In treating chronic or recurrent infections it may be possible to administer a higher dose of phage, to compensate for those that are rendered non-viable by interaction with neutralizing antibodies.[30,31,32.]

Safety of phage therapy

During the long history of using phages as therapeutic agents through Eastern Europe and the former Soviet Union, there has been no report of serious complications associated with their use [33]. Phages are extremely common in environment and regularly consumed in foods [34.] In fact humans are exposed to phages from birth itself and therefore these constitute the normal microflora of the human body. They have been commonly found in human gastrointestinal tract, skin and mouth, where they are harboured in saliva and dental plaques [35.] Phages are also abundant in environment including saltwater, freshwater, soil, plants and animals and they have been shown to be unintentional contents of some vaccines and sera commercially available . Phages have high specificity for specific bacterial strains, a characteristic which requires careful targeting [36.] Therefore, phage therapy can be used to lyse specific pathogens without disturbing normal bacterial flora and phages pose no risk to anything other than their specific bacterial host [37].From a clinical standpoint, phage therapy appears to be very safe. Efficacy of natural phages against antibiotic-resistant Streptococci, Escherichia, Pseudomonas, Proteus, Salmonella, Shigella, Serratia, Klebsiella, Enterobacter, Campylobacter, Yersinia, Acinetobacter and Brucella are being evaluated by researchers [38]. However, in the last few years, modified phages are being explored increasingly, due to the limitations of phage therapy using lytic phages. Phages can be modified to be an excellent therapeutic agent by directed mutation of the phage genome, recombination of phage 142 Bacteriophages genomes, artificial selection of phages *in vivo*, chimeric phages and other rational designs which confer new properties on the phages. These new modified phages have been shown to successfully overcome challenges to earlier phage therapy [39]. As with antibiotic therapy and other methods of countering bacterial infections, endotoxins are released by the gram negative bacteria as a component of outer membrane. This can cause symptoms of fever, or in extreme cases, toxic shock [40.] To address the endotoxin release issue, recombinant phage derived from *P. aeruginosa* filamentous phage Pf3 was constructed by genetic modifications and the results showed that this filamentous phages could be used as effective anti-infection agent [41]. This phage had the benefit of minimizing the release of membrane associated endotoxins during phage therapy [42]. In order not to compromise on the issue of the safe use of therapeutic phage preparation, rigorous

characterizations of each phage to be used therapeutically should be done, in particular, especially looking for potentially harmful genes in their genome[43].

Clinical application of bacteriophages

Whole Phage therapy in Humans

d'Hérelle carried out the first human therapeutic phage trial.The first article documenting phage therapy was on research conducted in Belgium by Bruynoghe and Maisin in 1921. They reported that phages when injected in six patients targeted staphylococcus near the base of cutaneous boils (furuncles and carbuncles), resulted in improvement within 48 hours and reduction in pain, swelling and fever.

Merabishvili and workers (2009) used phage cocktail, consisting of exclusively lytic bacteriophages for the treatment of Pseudomonas aeruginosa and Staphylococcus aureus infections in burn wound patients in the Burn Centre of the Queen Astrid Military Hospital in Brussels, Belgium. [44]

The first controlled clinical trial of a therapeutic bacteriophage preparation (Biophage-PA) showed efficacy and safety in chronic otitis because of drug resistant P. aeruginosa in UCL Ear Institute and Royal National Throat, Nose and Ear Hospital, London, UK[45]. Weber-Dabrowska et al also report phage therapy success in treated purulent otitis media [46] and Slopek et al report 93.8% positive cases for phage treatment of 16 cases of "Conjunctivitis, blepharoconjunctivitis, otitis media".[47]

One of the most extensive studies evaluating the application of therapeutic phages for prophylaxis of infectious diseases was conducted in Tbilisi, Georgia, during 1963 and 1964 and involved phages against bacterial dysentery [48].

Phages have been reported to be effective in treating various bacterial diseases such as cerebrospinal meningitis in a newborn [49], skin infections caused by pseudomonas, staphylococcus, Klebsiella, Proteus, E. coli , recurrent subphrenic and subhepatic abscesses, Staphylococcal lung infections, *Pseudomonas aeruginosa* infections in cystic fibrosis patients , eye infections , neonatal sepsis , urinary tract infections , and cancer . Abdul-Hassan et al. reported on the treatment of 30 cases of burn-wound associated antibiotic-resistant Pseudomonas aeruginosa sepsis. Bandages soaked with 1010 phages/ml were applied three times daily. Half of the cases were found to be improved.[50]

Markoishvili et al., reported the use of PhagoBioDerm, the phage impregnated polymer, to treat infected venous stasis skin ulcers. To patients that had failed to respond to other treatment approaches, Phago BioDerm was applied to ulcers both alone and, where appropriate, in combination with other treatment strategies. Complete healing of ulcers was observed in 70% of the patients.[51] Mushtaq et al., reported that a bacteriophage encoded enzyme, endosialidase E (endo E) selectively degrades the linear homopolymeric a- 2, 8-linked N acetylneuraminic acid capsule associated with the capacity of E. coli K1 strain to cause severe infection in the newborn infant. In one of the study, PhagoBioDerm which is a wound-healing preparation consisting of a biodegradable polymer impregnated with ciprofloxacin and bacteriophages was used in three Georgian lumberjacks from the village of Lia who were exposed to a strontium-90 source from two Soviet-era radiothermal generators they found near their village. In addition to

systemic effects, two of them developed severe local radiation injuries which subsequently became infected with Staphylococcus aureus. Approximately 1 month after hospitalization, treatment with phage bioderm was initiated. Purulent drainage stopped within 2–7 days. Clinical improvement was associated with rapid (7 days) elimination of the S. aureus resistant to many antibiotics (including ciprofloxacin), but susceptible to the bacteriophages contained in the PhagoBioDerm preparation . [52.]

Bacteriophages have been suggested as effective antibiofilm agents. Curtin and Donlan investigated if hydrogel-coated catheters pretreated with coagulase negative bacteriophage would reduce Staphylococcus epidermidis biofilm formation.[53] Similarly Verma et. al. also evaluated the efficacy of lytic bacteriophage KPO1K2 alone or in combination with another antibiotic,ciprofloxacin for eradicating the biofilm of Klebsiella pneumoniae in vitro [54]. Despite the efficacy of antibiotics as well as bacteriophages in the treatment of bacterial infections, their role in treatment of biofilm associated infections is still under consideration especially in case of older biofilms. The ability of bacteriophage and their associated polysaccharide depolymerases was investigated to control enteric biofilm formation. The action of combined treatments of disinfectant and phage enzyme as a potentially effective biofilm control strategy was evaluated and the results showed that the combination of phage enzyme and disinfectant was found to be more effective than either of these when used alone

"Pio" bacteriophage was used successfully to treat 30 patients with traumatic bacterial keratitis and 16 patients with purulent corneal ulcers. Equal numbers of patients in control groups were treated with gentamicin eye drops. The patients treated with bacteriophage showed a more rapid improvement in inflammation, pain and eye watering, and were discharged on average at 11 days instead of 15. The successful treatment of 32 children with acute bacterial conjunctivitis was also described . The bacteria were antibiotic resistant and the patients were allergic to antibiotics, making antibiotic treatment impossible. All cases improved by the third day and were cured by the seventh day; there were no relapses during the next month of observation.

In Georgia the Intestiphage formulation is routinely employed prophylactically to prevent nosocomial infections, especially in pediatric hospitals, where such gastrointestinal infections are particularly prevalent. Dosing has traditionally been done with phages prepared in tablets,but now the liquid form is used instead .

Phages can be applied to treat various infections of the urogenetical systems either systemically, via direct injection such as into the bladder, or topical application. Eaton and Bayne-Jones in their 1934 report were convinced of the efficacious use of phage therapy against cystitis. Letwiewicz et al describe phage application rectally to target *Enterococcus faecalis* infection of the prostate, with some success. In this case phages are presumed to be taken up through the rectal wall prior to gaining access to the prostate. The result of treatment was elimination of the target bacteria from prostatic fluid.

MRSA is a particular concern due to its inherently reduced susceptibility to antibiotic treatment, wide prevalence in hospital-acquired infections and in the community, and potentially lethal and otherwise serious consequences. These

pathogens are targeted by the anti-*S. aureus* activity of phage preparations such as Pyophage. There was no cross-resistance between phages and antibiotics. Furthermore, very little development of resistance to this family of phages is observed. Thus, so far as phages are concerned, MRSA is simply another strain of Staphylococcus. Treatment of MRSA using phages can be accomplished by local application for local infections or, if necessary, and with substantially more caution, more systemic dosing such as intraperitoneally for systemic infections. The use of phage treatment for local infections, including particularly those due to Staphylococcus, has the distinction of being one of only two phage therapy strategies that were deemed to be convincingly efficacious by the 1934 Eaton and Bayne-Jones report, an otherwise phage-therapy skeptical publication.e. Indeed, the first human phage therapy publication reported on treatment of *S. aureus* skin infections. Phage preparations for systemic application were developed at the Eliava Institute during the 1980s, including safety studies in human volunteers without adverse effect. They were particularly effective in infants, in immune-compromised patients and for infusion into the urethra in cases of pelvic inflammatory disease. The preparation subsequently was used to treat 653 patients. The use of oral phage therapy for targeting MRSA in a nurse who was a carrier. This individual was MRSA colonized in her gastrointestinal tract and also had a urinary tract infection. The result of phage therapy was complete elimination of culturable MRSA. [55]

Phage products or phage lysins

With the increasing worldwide prevalence of antibiotic resistant bacteria, bacteriophage endolysins represent a very promising novel alternative class of antibacterial in the fight against infectious disease.. Vincent Fischetti was the first, however, to focus on the deadlyweapons, the potent and specific enzymes called lysins produced by these viruses. These lysins create lethal holes in bacterial cell walls. Fischetti has identified lysins that can kill a wide range of Gram-positive pathogenic bacteria, and have proven their effectiveness in both preventing and treating infections in mice, an important step towards their potential application in human disease.. As an alternative to "classic" bacteriophage therapy, in which whole viable phage particles are used, one can also apply bacteriophageencoded lysis-inducing proteins, either as recombinant proteins or as lead structures for the development of novel antibiotics. Phage endolysins, or lysins, are enzymes that damage the cell walls' integrity by hydrolyzing the four major bonds in its peptidoglycan component. Phage lytic enzymes have recently been proposed for the reduction of nasopharyngeal carriage of *S. pneumoniae*.

Group B streptococci are the leading cause of neonatal meningitis and sepsis all over the world. A single dose of phaghe lysine, PlyGBS significantly reduces bacterial colonization in both the vagina and oropharynx . These results support the idea that such enzymes may be used in specific high-risk populations to control the reservoir of pathogenic bacteria and therefore control the disease., Schuch and co workers (2002) identified a lytic enzyme PlyG from the gamma phage that is specific for *Bacillus anthracis.*

This approach may be used in post-exposure cases of anthrax, in which individuals can be treated intravenously with PlyG to control the bacilli entering the blood after germination because higher doses of phage lysin or multiple doses will result in nearly 100% protection. [56]

Phage zombies

A conceptually related approach is being pursued by a research team at the Medical University of South Carolina (Charleston, SC, USA). Working with the filamentous coliphage M13, the researchers created a sort of zombie phage—a regular phage body that still seeks out a specific microbial host (in this case, *E. coli*) but that has had its head emptied of the usual DNA necessary for replication. It instead injects only a lethal protein system, killing the host cell but not leading to the lysis of the cell or new phage production. The potential challenge is that filamentous phage are thought to infect only bacteria with a pilus, a spear-like protein tube required for the phage to gain entry. Not all bacterial species, nor all strains within common species, have a pilus.[57]

There is sufficient data and desperate need to find alternative treatment modalities against rapidly emerging, antibiotic-resistant bacteria . Studies so far reveal that phage therapy holds tremendous potential as a powerful way to combat increasingly dangerous bacterial infections. Bacteriophages have several characteristics that make them potentially attractive therapeutic agents. They are highly specific and very effective in lysing targeted pathogenic bacteria, safe and rapidly modifiable to combat the emergence of newly arising bacterial threats.. Furthermore , phages when properly selected, offer the most cost-effective alternative to antibiotics. These have proved to be efficient in bacterial elimination on single application . Phages should be essentially free of contaminating bacterial toxin and also capable of evading the clearance by reticulendothelial system. There are some concerns about the use of phages. It includes the safety and efficacy issues, as well as immune response to the administered phages. Growth optimization and purification strategies of phages are also some issues needed to be addressed. Rapid progress in the fields of biotechnology and molecular biology could answer many questions human beings are having about phage therapy. . Although some problems remain to be solved, phage therapy will find a niche in modern Western medicine in the future.

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