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BACTERIOPHAGES AS ANTIBIOTICS ALTERNATIVES TO COMBAT MULTIDRUG RESISTANT PATHOGENS: A REVIEW ARTICLE

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Abstract

Antibodies, probiotics, and antimicrobial peptides are currently undergoing clinical studies as potential options to treat infections as bacteria become more resistant to traditional antibiotics and as more medications lose their efficacy against drug-resistant bacteria. In various regions of the world, bacteriophages have also been employed as a form of therapy. The advantage of these approaches is that the disease-causing bacteria are the only ones that are treated, leaving the beneficial commensal microbial communities of the host intact. This antimicrobial does not typically have an impact on commensal bacteria in addition to its pathogenic targets, as do the majority of antibiotics. The phage exhibits a great bactericidal effect while altering the normal flora very little. The medical benefits of phages for antibiotic-resistant and sensitive robotic microorganisms are comparable These unique disease-treating techniques must be further developed in order to improve their availability, effectiveness, and dependability as antibiotic substitutes**.**

Keywords: *Bacteriophage, Antibiotics, Alternatives, Resistant, Pathogens*.

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Bacteriophage

To cure bacterial diseases, bacteriophages have been used in both people and animals since their discovery in 1915 because of their extraordinary capacity to infect only one kind of bacterial host without having an impact on other bacterial populations. (1).

Small viruses called bacteriophages have the capacity to infect bacteria.They are essential to maintaining the microbial balance in our environment, which has a big effect on it. Phages may be found in all natural environment, including aquatic and terrestrial systems, as a result of their bacterial hosts. It has been possible to identify and describe morphologically more than 6000 distinct phages. (2). in terms of phenotype, genotype, and host range, bacteriophages are a diverse group of viruses. Just strong phages are considered harmless for use as bio-control agents because they do not spread antibiotic- and genes responsible of toxin-resistant from one bacterial host to another. As a result, they are regarded as harmless, and the regulatory bodies have previously given their goods approval as food additives and antimicrobials. (3).

They have a wide variety of morphologies, including spherical, icosahedral, filamentous, and tailed forms. (4), have a substantial genetic resource , frequent gene transfer, intricate host-phage interactions, and profound ecological effects. (5).

Life cycles of phages

With a variety of life cycles, phages are obligatory hosts' internal parasites. Lytic, lysogenic, and pseudolysogenic cycles are among the life cycles. In the lytic cycle, the phage initiates viral progeny generation as soon as it becomes infected and releases them by lysing the host. Prophages, which are phage genomes that replicate in tandem with host DNA during the lysogenic cycle and either integrate into the host's chromosome or live in a free, plasmid-like state, create a long-lasting stable cohabitation with the host (6). Prophages begin the lytic cycle after leaving the lysogenic stage, and under stressful circumstances, they explode into virion. (7) Temperate phages are those that can develop both lytically and lysogenically. (8).

A non-classical phage life cycle known as pseudolysogeny occurs when phages do not lyse the host or integrate into the genome to create a long-lasting stable association (9). When the status of the host cell improves, pseudolysogeny often results, but then transforms into the lysogenic or lytic cycles. (10).

Immune Response's Role in Phage Therapy

Phages may possibly activate innate and adaptive immune cells, which might affect how well phage treatment works. It is possible to identify three main areas of phage-immune interaction. First, using the pattern recognition receptor (PRR) for immune recognition (11). Second, phage-neutralizing antibodies that have been promoted can impair the effectiveness of therapy, and this impact can get worse with repeated treatment. (12). Third, it is well known that humoral (adaptive) immunity and the production of anti-phage antibodies has a suppressive effect on phages. In the system of mammalian.

Effects appear to be dose-dependent, with only very large dosages administered repeatedly producing a given response. (13).

Phages against multi-drug resistsnt bacteria

Antibiotic resistance is currently developing at a far faster rate than new antibiotics are being discovered and developed, which is dangerous for global public health. Antimicrobial resistance is predicted to result in up to 10 million deaths yearly by the year 2050. (14).

The World Health Organization (WHO) highlighted the special risk by Gram negative organisms that are resistant to several medicines in 2017. The development of novel and alternative antimicrobial medicines must be prioritized. With almost 700,000 fatalities each year, infections brought on by h multidrug resistant microorganisms have emerged as one of the major causes of illness and death globally (15 , 16).

For patients whose standard antibiotic medication is unsuccessful, there is a need to explore for alternatives. As a result, PT has replaced antibiotics as an option due to its unique mode of action. (16). Choosing the right phages, participants (people), and target microorganisms, as well as ensuring that they are properly characterized, are vital pieces of information for clinical trials. Formulations, dose, and effectiveness are additional data that are needed, but they are useless without the basis of described and well-planned objectives. Replication and expansion of earlier studies would be made possible by detailed reporting, which would enhance the caliber of future research. How to sellect suitable targets for treating diseases using phage is another factor. (17).

Kutter *et al.* have provided a detailed account of recent clinical investigations on phage therapy, including those conducted in Poland and Georgia. (18).

Two clinical studies using phage therapy to treat venous leg ulcers are being conducted are referenced as examples across the field. (19) also safety with efficacy in chronic otitis (20). Rhoads and colleagues examined the safety of phage administration in a small phase I research including individuals with venous leg ulcers and found no negative effects. (19). Anti-Pseudomonal phages were shown to be effective and safe against late-stage recurrent otitis that is mostly caused by MDR *P. aeruginosa* by Wright *et al.* These are some of the first controlled studies on humans carried out in the west. Several clinical studies have been recorded more recently, as shown in Figure 1. (21).

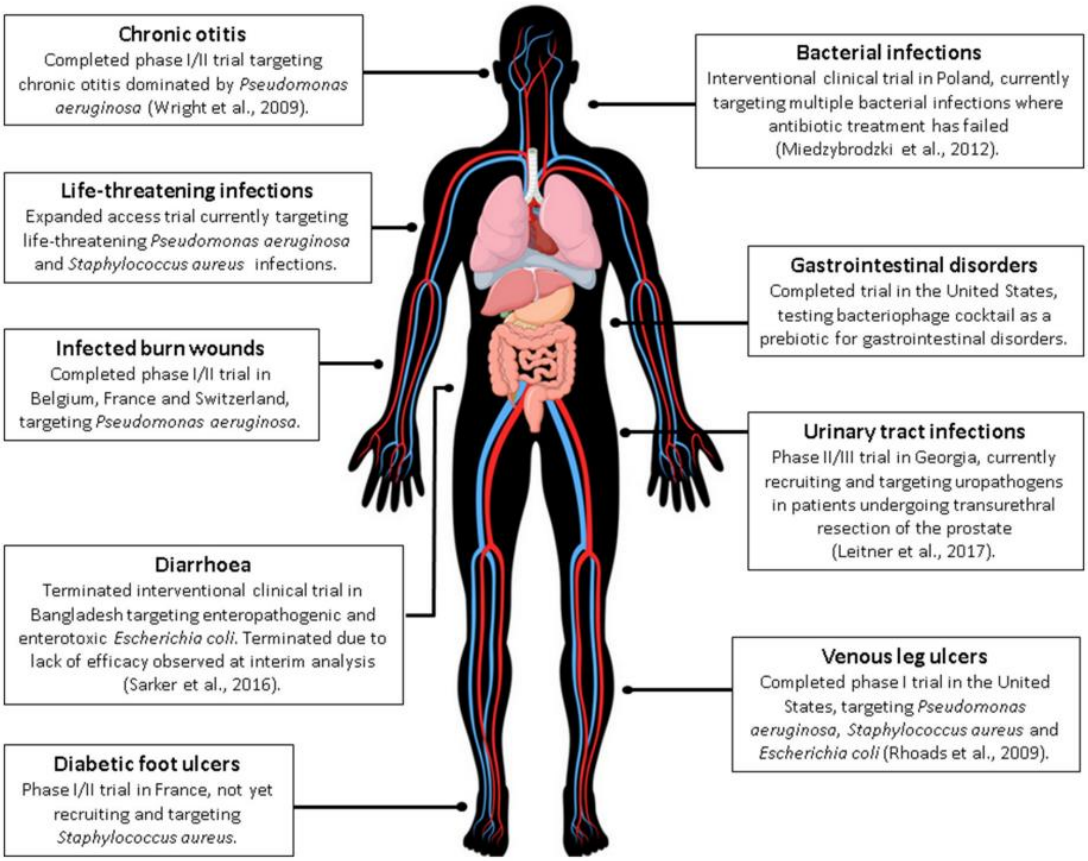

Figure 1. Latest information on human phage treatment trials and the variety of infections/target areas. This figure contains a legally obtained picture that the authors have got.

Phages' Control over the Intestinal Microbiota's Diversity

Predation

By locating particular membrane receptors on the bacterial surface, phages can choose out target bacteria for "predation". In general, for lytic phages to infect bacteria, they must first be specifically recognized by the structural proteins on their surface and then adsorb to the host bacteria's surface receptors. This mostly reliants on compatibility between the protein of phage tail and the bacterial surface binding site's molecular structure (21). To produce offspring phages, tail phages primarily use lytic enzymes to hydrolyze the peptidoglycan of cell walls. By suppressing synthesis of peptidoglycan with a single protein or by enzymatically lysing peptidoglycan with lysin and perforation-lysozyme systems, lytic enzymes able to lyse bacterial peptidoglycan (22). The two primary classes of enzymes that dissolve biofilms of bacteria are exolytic enzymes, which stimulate genome entrance inside bacteria in the early stages, and endolytic enzymes, which breakdown the host bacterium to release offspring phages in the late stages. Additionally, after eliminating intestinal bacteria by this particular "predation" behavior, the bacterial genomes are modified by intestinal phages using particular CRISPR spacer sequences. (23). The discovery of these sequences revealed that bacterial

mortality caused by ordinary phages commonly happens in both humans in addition to animals and significantly contributes to the stability of gut microbiota. (24).

Lysogenic Transformation

By enhancing the condition of the host bacteria, temperate phages make up for their own negative effects on the host bacteria and give a new phenotype to the host. This occurrence is referred to as "lysogenic conversion." Gene integration is carried out by the temperate phage once it has entered the host bacteria, preventing macrophage identification and clearance and enabling long-term coexistence. The host bacteria's capacity for adhesion also colonization, environmental tolerance, and antibiotic resistance can all be increased by lysogenic conversion. (25).

Seesaw Effect

Under the influence of genetic selection, strains of bacteria become resistant to drugs as a result of contact to the antibacterial drug environment. The traits of phage resistance are lost in the developed strains. Similar to this, the exposure of bacteria to phage circumstances eventually miss their ability to fight antibiotics (26). For example, Ho et al. (27) discovered that alterations in the bacterial gene EPAR result in an increase in the sensitivity of bacteria to the antibiotic daptomycin while decreasing the *Enterococcus faecalis* adsorption by phages. The capacity of homologous phages to feast on bacteria rises when antibacterial medications cause phenotypic changes in bacteria. The "seesaw effect" is another name for this ebb-and-flow phenomena (28).

Epithelial Protection

In addition to phagocytosing and lysing pathogenic bacteria, phages can decrease the number of pathogenic bacteria that colonize the intestinal mucus layer surface (29,30) According to Barr et al.'s research, some phages in the intestine of human attach to the mucosa and restrict their own diffusional mobility, producing what appears to be a protective barrier with the epithelial tissue (31).

Phage-Mediated Immune Response

In order to facilitate their entry into the immune system, phages able to induce macrophages, through opsonization, to phagocytize bacteria. The way phages interact with their hosts is determined by the intestinal mucosa. To produce phage-mediated immune responses, phage communities make contact with mucosal barriers. Virus-Mediated Immune Control Additionally to reducing immunological and inflammatory responses and maintaining immune homeostasis, intestinal phages can actively scavenge invading microorganisms (23). Pathogen-associated molecular patterns (PAMPs), which are produced by phage-mediated lysis, might transfer and trigger an immune reaction when permeability of intestine increases (24).

Some phages can also amplify the immunological response in the stomach. Gogokhia *et al.* claim that. (28), Phages able to induce intestinal immunity through the signaling route for interferon that is reliant on toll-like receptor 9 and promote the expansion of CD4+ and CD8+ T cells in Peyer's patch. Studies (30) also demonstrated that phages of *Escherichia coli* can suppress the immune system, limit the growth of intestinal immune cells, and bind to lipopolysaccharide to produce adhesion proteins that regulate the inflammatory response brought on by lipopolysaccharide. Phages can alter the structure of the intestinal microbiota and decrease the invasion of foreign pathogens through the aforementioned key modes of action, as well as the ability of probiotics to colonize the intestines and maintain their balance figure 2.

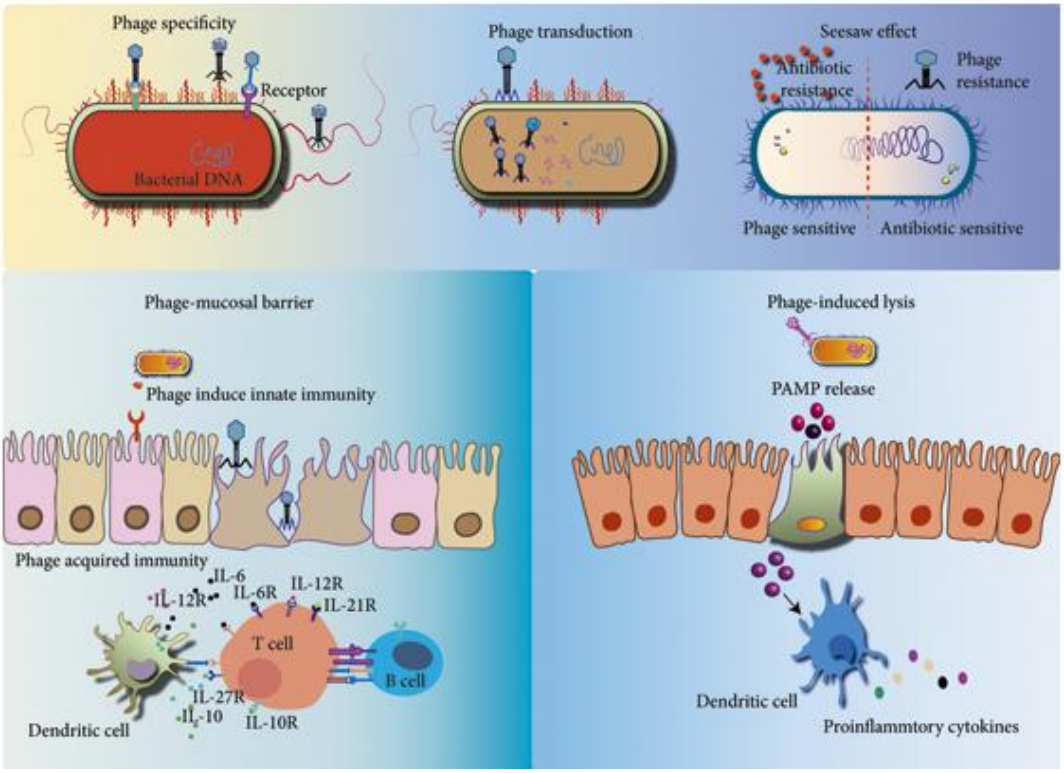

Figure 2. The way that phage treatment works**.**

Phage-encoded binding proteins, during the infection of phage lytic cycle, locate and bind to the receptors present on the surface of bacteria, like fimbriae, flagella, porins, or efflux pumps receptor proteins. When the bacteria lyse to escape and then infect other susceptible bacteria, the phage reattaches and transfers the genomic material to the bacteria. Viral reproduction then takes place inside the cytoplasm. When bacteria change to resist a phage attack, phage treatment can kill the target bacteria while substantially favoring bacterial virulence or antibiotic resistance. Phage treatment can also control immunological reactions in the stomach. The way that phages and their hosts interact is determined by the intestinal mucosa. To generate phage-mediated innate immune responses, phage communities make contact with mucosal barriers. Pathogen-associated molecular patterns (PAMPs), which are

produced by phage-mediated lysis, could move and cause an immunological reaction if intestinal permeability increases.

Clinical Applications of Phages and the Relationship between Phages and Disease

Phages and contagious diseases

Phage formulations were subsequently used successfully to treat bacillary dysentery, cholera, and other diseases at the turn of the 20th century (31). Phage treatment has since been used to treat a variety of infectious disorders that are recalcitrant. Phage treatment was utilized to treat 1307 patients with infected with multidrug-resistant bacteria in a Polish research facility, and 85.9% of them saw clinical improvement or were cured (32, 33). Refractory Clostridium difficile infection can be successfully treated using fecal filtrate, which is made by extracting phages from healthy human feces. Additionally, the majority of phage preparations that are now undergoing clinical trials aim to infect bacteria that are multidrug resistant. Fecal Clostridium difficile infection can be successfully treated using fecal filtrate, which is made by extracting phages from healthy human feces (34). Additionally, the majority of phage preparations that are now undergoing clinical trials aim to infect bacteria that are multidrug resistant. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* are the principal targets of the current phage formulations (35).

A cystic fibrosis patient brought on by *Pseudomonas aeruginosa* and *Mycobacterium* abscessus was described by Dedrick *et al.* (36) as having symptoms that dramatically improved following six months of therapy with "cocktails of three-phage." *Acinetobacter baumannii* (pancreatic pseudocyst) infection in old patient (68 years) had diabetes mellitus was described by Schooley et al. (37) as worsening after numerous antibiotic treatments. After the concentrated solution was analyzed, nine particular phages were chosen, and they were administered together with antibiotic therapy into the abscess cavity. After receiving mixture therapy, the infection was successfully under control. According to Bao et al. (38), phage "cocktail" therapy helped a 63-year-old patient with repeated infections of urinary tract brought on by *Klebsiella pneumoniae* that was sulfamethoxazole-resistant recover. 13 patients with severe Staphylococcus aureus infections were treated by Petrovic Fabijan et al. (39) phage preparation AB-SA01, which demonstrated no unfavorable effects in addition to successfully reducing the infection.

Infections of the Skin and Soft Tissue

The primary complication of severe burns is infection, which can cause sepsis, develop numerous organ failure, and even postpone wound healing. It is a significant contributor to burn-related fatalities. Common bacteria with medication resistance include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. Phage therapy is frequently used in the treatment of burns, and there are numerous instances when it has demonstrable therapeutic results. The pathogenic bacteria responsible for skin

infections mainly include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Proteus*. 90% (39, 40, 41) of these individuals had a full recovery, a persistent dystrophic sore is vulnerable to coinfections, which are frequent in conditions like diabetes and atherosclerosis. Ulcer healing is significantly influenced by infection, and prompt infection clearance can accelerate wound healing. Staphylococcus aureus and Pseudomonas aeruginosa dominate its pathogenic bacteria, and they frequently develop antibiotic resistance due to the poor effects of prolonged antibiotic use. Patients with chronic ulcers were treated using a wound dressing infused with different phages, and the results demonstrated that this dressing is not only efficient but also secure. Rhoads et al. used the "cocktail" phage WPP-201 topically during a clinical experiment on persistent venous leg ulcers caused by bacterial infection. On top of leg ulcers, the "cocktail" phage WPP-201 was applied. Even though the phage-treated group's rate of wound healing was the similar to that of the control antibiotic therapy group, the former's side effects were markedly less severe than those of the latter (42).

Bacterial Resistance to bacteriophage

Although bacteria have evolved a wide range of complex defensive mechanisms to combat phage infections, phages are usually successful against germs that are resistant to antibiotics. Therefore, phage resistance is distinct from resistance to antibiotics in terms of how it works, but multiple studies have established that microorganisms that are MDR, XDR, and PDR are also bacteriophage resistant (43).

Endonucleases, which are frequently depended as a component of systems called restriction-modification (R-M) and may break phage DNA, are among these methods. The injected phage DNA has degraded as a result of the CRISPR sequences' interference with the development of adaptive immunity (44), There's little doubt that mutations in gene reduce the virulence of bacteria and contaminate or change the molecules that the phage exploits as receptors since the majority of bacterial receptors for phage adsorption are virulent components or essential chemicals for the bacterial cell. Phage receptors can occasionally change their phase or hide behind an extracellular polymer like a capsule or another extracellular polymer. Proteins called super infection exclusion (Sie) systems stop phage DNA from entering the cytoplasm of bacteria. These proteins are linked to the membrane's components or connected to the membrane itself. Numerous bacteria have prophages attached to them, and those that do can fend off subsequent phage infections thanks to the lysogenic phage they contain. Just an insufficient number of these organizations, which are categorized in both Gram-positive and Gram-negative bacteria, have been documented (45). Another innovative method of bacterial defense is called bacteriophage exclusion (BREX), that DNA methylation process in the host cell prevents the DNA replication of phage. *Bacillus cereus* has six-gene cassettes called BREX defensive systems that are subject to substantial horizontal transfer of gene and offer total phage resistance to a wide range of phages, including lytic and temperate ones (46).

Regulation of quorum-sensing is a defensive tactic used by pathogens to switch between several phage defense systems according to population cell mass. Quorum sensing controls the reducing adsorbtion of phage receptor at high cell densities, making bacteria less susceptible to phage infection. However, quorum sensing has no impact on the expression of the phage receptor when there is a low cell density, leaving the cells extremely vulnerable to phage.Citation. A new sort of anti-phage mechanism called DISARM (defense island system associated with restriction-modification), which is extensively distributed in bacteria and archaea, limits incoming phage DNA and consequently fights viruses from different families of tailed phages. A DNA methylation gene plus four other genes with annotations for helicase domains, phospholipase D domains, and DUF1998 make up the five-gene DISARM system (47).

The advantages and disadvantages of bacteriophage therapy

By increasing the amount of self-reproductions, bacteriophages show a large bactericidal influence while little changing the normal flora. The advantages of bacteriophages in medicine for bot microorganisms that are susceptible to and resistant to antibiotics are comparable, yet their inherent toxicity in vivo is minimal. Conclusion : in a number of ways, bacteriophage therapy is preferable than conventional antibiotics. Such as, Bactericidal agents, Formulation and global applicability, reproductive ability, differentiated toxicity, lack of antibiotic cross-resistance, and speedy discovery. While drawbacks include issues with safety, low stability, and the potential for unique diversity introduced by self-renewing phages, mutants with bacteriophage resistance (48).

Resistance to Phages

The potential for bacterial resistance is a crucial factor in phage therapy. More than 80% of research focusing on the intestines and 50% of studies employing sepsis models have shown phage-resistant bacteria, and phage resistant variations have also been found in human trials (49). Similar to antibiotic resistance, phage resistance can develop spontaneously through a variety of methods. A total loss of adsorption or a reduction in adsorption, for instance, could result from the cell surface target receptor(s) not being expressed or developing a mutation. Both phage therapy and traditional antibiotic therapy have this drawback. The reduction of resistance for both methods will be aided by knowledge of the receptor site(s), their stability, and their conservation across strains. Another topic that needs research for both therapy modalities is acquired resistance. Genes encoding antibiotic resistance can be found in accessory genetic elements like as plasmids, temperate phages, and mobile genetic islands. Acquired resistance for phages can include CRISPR-Cas systems (24).

The uncommon but significant ability of temperate phages to produce immunity proteins and the advancement of DNA restriction-modification methods. Phage therapy has a key advantage over other kinds of treatment in that it uses phage mixtures to stop the

formation of resistance. Using a large number of phages, each of which has a specific receptor and comes from a different genetic lineage, will increase the capacity to compensate for the loss of host genetic defenses or adsorption processes. Genetic engineering could possibly offer a ways of enhancing the variety and directing efficiency of phages in order to prevent resistance. Another consideration is the fact that bacterial fitness costs typically occur from mutations that provide phage resistance. Consequently, it may be beneficial to be aware of and take advantage of the fitness costs to resistant bacteria during treatment. (50).

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