***Review Article***

**Harnessing Bacteriophages for Sustainable Plant Disease Management: A Review of Their Potential and Market Prospects**

**Abstract**

 Plants play a vital role in human nutrition and food security but are increasingly threatened by bacterial diseases, which significantly impact agricultural productivity. Managing these diseases is particularly challenging due to the limited availability of bactericidal agents, rapid bacterial mutations, and pathogen diversity. Conventional treatments, such as antibiotics and copper-based compounds, have been widely used; however, their long-term application has led to environmental concerns and the emergence of resistant bacterial strains. Phage therapy, which utilizes bacteriophages—viruses that selectively infect and eliminate bacterial pathogens—presents a promising and environmentally friendly alternative. These naturally occurring viruses specifically target harmful bacteria while preserving beneficial microorganisms, making them an ideal tool for sustainable plant disease management. Moreover, bacteriophages pose no risks to eukaryotic cells, further supporting their potential in plant health applications. Although first discovered in the early 20th century, the use of phages declined following the advent of broad-spectrum antibiotics. However, the growing issue of antibiotic resistance has reignited scientific interest in this approach. Recent advancements in phage classification, structural studies, and host-pathogen interactions have paved the way for modern applications. Researchers are exploring naturally occurring bacteriophages, genetically engineered variants, and phage-derived enzymes as effective means to control bacterial crop diseases. This review discusses the historical background, structural characteristics, and potential applications of phage therapy, underscoring its viability as a sustainable alternative to chemical bactericides in modern agriculture.

**Keywords:** Phage therapy, Bacterial diseases, Sustainable agriculture, Bacteriophages, Plant disease management, Antibiotic resistance

**Introduction** Plants are essential for human survival, serving as a primary source of food and ensuring global food security. However, they are constantly threatened by various pests and diseases caused by fungi, viruses, and bacteria, resulting in considerable agricultural losses (Agrios, 2005). Among these, bacterial diseases are particularly difficult to control due to limited treatment options, high mutation rates, and the genetic variability of pathogens (Balogh et al., 2010). Traditionally, antibiotics and copper-based compounds have been widely used to combat bacterial infections in crops. However, prolonged use of these chemical treatments has led to the development of resistant bacterial strains and raised environmental safety concerns (McManus et al., 2002; Svircev et al., 2018). As a result, researchers have turned to eco-friendly alternatives, such as phage therapy, which involves using bacteriophages—viruses that specifically infect and destroy bacteria (Calvo-Garrido et al., 2014; Wiesel et al., 2014). Phage therapy offers two key advantages: it targets specific bacterial pathogens without affecting beneficial microbes, and it poses no known risks to eukaryotic organisms, making it a promising tool for both plant disease management and medical applications (Farooq et al., 2018; Loc-Carrillo & Abedon, 2011). This dual functionality highlights its potential in sustainable agriculture and public health initiatives (Nagai et al., 2017).

 Bacteriophages, commonly referred to as phages, are the most abundant viruses on Earth, infecting bacteria and archaea (Clokie et al., 2011). The term "bacteriophage" originates from the Greek word "phagein," meaning "to devour" or "to consume" (Sakib et al., 2021). Phages are viruses that naturally prey on bacteria, making them a precise and eco-friendly option for biological control. As a sustainable alternative to conventional chemical pesticides, phages support environmentally conscious farming practices (Moye et al. 2018; Holtappels et al. 2021). These microscopic entities act as obligate intracellular parasites, remaining biochemically inactive outside their bacterial hosts but hijacking their biosynthetic machinery once inside to produce viral components. Structurally, phages consist of nucleic acid (DNA or RNA) enclosed within a protein shell, carrying genetic instructions for their replication. They exhibit high specificity in bacterial infections and are widely distributed across diverse ecosystems. Their abundance is directly linked to bacterial populations, with estimates suggesting the presence of over 10³⁰ tailed phages globally (Brüssow & Hendrix, 2002). Phages are commonly found in soil, wastewater, and fecal matter, as well as in aquatic environments such as freshwater and marine ecosystems. In oceanic waters, nearly 10 million virus-like particles can be found per milliliter (Breitbart, 2012; Suttle, 2007). Notably, phages exhibit high specificity, targeting only certain bacterial strains while leaving non-target organisms—including other bacteria, archaea, and all eukaryotes such as plants, animals, and humans—unaffected (Kasman and Porter 2022). This precision has positioned phages at the forefront of sustainable strategies for controlling bacterial crop diseases (Buttimer et al. 2017; Villalpando-Aguilar et al. 2022). Given their ability to selectively eliminate bacterial pathogens, bacteriophages hold immense potential as an alternative to antibiotics. The application of lytic phages or their derivatives to treat bacterial infections is referred to as phage therapy, a strategy that is gaining renewed attention for agricultural and medical use.

**Early History and Research on Bacteriophages**

 In 1896, Hankin identified a substance in the Ganges and Yamuna rivers that was capable of passing through a fine porcelain filter and exhibited antibacterial properties against cholera. The foundation of phage therapy was laid by Frederick Twort (1915) and Félix d'Hérelle (1917), who observed tiny bacterial parasites in cultures and termed them "bacteriophages." These agents were soon recognized for their potential as antimicrobial tools (Hermoso et al., 2007). However, interest in phage therapy declined with the introduction of broad-spectrum antibiotics in the 1940s.

 The association of bacteriophages with plant pathogenic bacteria was first documented by Mallmann and Hemstreet (1924), who demonstrated that filtered decomposed cabbage inhibited the growth of *Xanthomonas campestris* pv. *campestris*. Subsequently, Kotila and Coons (1925) found that bacteriophages could prevent soft rot in potato tuber and carrot slices caused by *Pectobacterium atrosepticum* and *Pectobacterium carotovorum* subsp. *carotovorum*. The first evidence of phage treatment reducing disease incidence in crops was reported by Thomas (1935), who observed a 16.5% reduction in Stewart’s wilt in corn. However, early field trials revealed that phage therapy was less effective compared to newly developed antibiotics (Goto, 2012). This led to a decline in its use, with antibiotics and bactericidal chemicals remaining the primary means of managing bacterial plant diseases for decades (Agrios, 2005). Concerns regarding the environmental and health impacts of these chemicals persisted (Hermoso et al., 2007).

 The emergence of antibiotic, pesticide, and copper-resistant bacterial strains—such as *Erwinia amylovora* (Manulis et al., 2000), *Pseudomonas syringae* (Hwang et al., 2005; Masami et al., 2004), *Xanthomonas campestris* pv. *juglandis* (Lee et al., 1994), *Xanthomonas citri* spp. *citri*, and *Xanthomonas alfalfa* spp. *citrumelonis* (Behlau et al., 2011)—along with the slow progress in developing new antibiotics, redirected scientific interest toward alternative biocontrol strategies for bacterial plant diseases. Stonier et al. (1967) reported that even fewer than ten bacteriophage particles, forming clear plaques during a 21-hour induction period, were sufficient to inhibit tumor formation by the highly virulent *Agrobacterium tumefaciens* corn strain B6.

**Classification of Bacteriophages**

 The introduction of electron microscopy revolutionized phage classification. In 1943, Ernst Ruska categorized phages into three morphological types (Ruska, 1943). A few years later, Holmes (1948) attempted to classify phages under the order *Virales* based on their host range, but this system was not widely accepted. A more comprehensive classification emerged in 1962 when Lwoff, Horne, and Tournier proposed a system based on nucleic acid type (DNA or RNA), capsid structure, presence of an envelope, and the number of capsomers. This led to the assignment of tailed phages to the order *Urovirales* (Lwoff et al., 1962).

 A pivotal moment in virus classification came in 1966 with the establishment of a specialized committee that shifted focus from host specificity to virion morphology and nucleic acid properties (P.C.N.V., 1965). This committee eventually evolved into the International Committee on Taxonomy of Viruses (ICTV), which published its eighth classification report in 2005 (Fauquet et al., 2005).

 Bacteriophage classification can be traced back to Bradley's 1967 system, which described six primary morphological types based on representative phages such as T4, λ, T7, φX174, MS2, and fd (Bradley, 1997). Over time, the classification expanded, leading to the establishment of one order, 14 families, and 37 genera (Fauquet et al., 2005). The ICTV employs the polythetic species concept, defining a species through a combination of distinct characteristics (Van Regenmortel, 1990). However, as new phages continue to be discovered, classification remains dynamic, with ICTV often struggling to keep pace. As of now, over 5,500 phages with identified morphologies have been documented (Ackermann, 2007).

 Currently, ICTV recognizes 19 bacteriophage families, with the most extensively studied being *Myoviridae, Siphoviridae, Podoviridae, Inoviridae,* and *Microviridae*. More recently identified families include *Ackermannviridae* and *Herelleviridae*, all of which are classified under the order *Caudovirales* (Adriaenssens et al., 2018; Walker et al., 2019).

 Phages exhibit diverse nucleic acid compositions, including double-stranded DNA (dsDNA, the most prevalent), single-stranded DNA (ssDNA), single-stranded RNA (ssRNA), and double-stranded RNA (dsRNA, which is relatively rare). Approximately 96% of known phages are tailed, while the remaining 4%—referred to as *CFP phages*—display cubic, filamentous, or pleomorphic forms. The term "cubic" denotes phages with icosahedral symmetry, while filamentous and pleomorphic phages exhibit more flexible structures. Some phages also possess lipid envelopes or internal components, which make them susceptible to solvents like ether and chloroform. Notably, *CFP phages* tend to be small and often have only a single known representative within their group.

**Table 1: Overview of Prokaryote Viruses**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Shape** | **Nucleic acid** | **Family** | **Genera** | **Particulars** | **Example** | **Members** |
| Tailed | dsDNA (L) | Myoviridae | 6 | Tail contractile | T4 | 1320 |
|  |  | Siphoviridae | 7 | Tail long, noncontractile | λ | 3229 |
|  |  | Podoviridae | 4 | Tail short | T7 | 771 |
| Polyhedral | ssDNA (C) | Microviridae | 4 | Conspicuous capsomers | φX174 | 40 |
|  | dsDNA (C,S) | Corticoviridae | 1 | Complex capsid, lipids | PM2 | 3? |
|  | dsDNA (L) | Tectiviridae | 1 | Double capsid, lipids, pseudo-tail | PRD1 | 19 |
|  | dsDNA (L) | SH1∗ |  | Double capsid, lipids | SH1 | 1 |
|  | dsDNA (C) | STIV∗ |  | Turret-shaped protrusions | STIV | 1 |
|  | ssRNA (L) | Leviviridae | 2 | Poliovirus-like | MS2 | 39 |
|  | dsRNA (L, M) | Cystoviridae | 1 | Envelope, lipids | φ6 | 3 |
| Filamentous | ssDNA (C) | Inoviridae | 2 | Long filaments, short rods | M13 | 67 |
|  | dsDNA (L) | Lipothrixviridae | 4 | Envelope, lipids | TTV1 | 7 |
|  | dsDNA (L) | Rudiviridae | 1 | Stiff rods, TMV-like | SIRV-1 | 3 |
| Pleomorphic | dsDNA (C,S) | Plasmaviridae | 1 | Envelope, no capsid, lipids | L2 | 5 |
|  | dsDNA (C,S) | Fuselloviridae | 1 | Lemon-shaped, envelope, lipids? | SSV1 | 11 |
|  | dsDNA (L,S) | - | 1\*\* | Lemon-shaped, envelope | His1 | 1 |
|  | dsDNA (C,S) | Guttaviridae | 1 | Droplet-shaped | SNDV | 1 |
|  | dsDNA (L) | Ampullaviridae∗ |  | Bottle-shaped, helical NC | ABV | 1 |
|  | dsDNA (C) | Bicaudaviridae∗ |  | Two-tailed, development cycle, helical NC | ATV | 1 |
|  | dsDNA (L | Globuloviridae∗ |  | Envelope, spherical, lipids, helical NC | PSV | 1 |

C, circular; L, linear; M, multipartite; NC, nucleocapsid; S, supercoiled; —, no name; ∗, nonclassified; ∗∗, genus Salterprovirus. Members indicate numbers of phages examined by electron microscopy, excluding phage-like bacteriocins and known defective phages (based on computations from January 2006; Ackermann, 2007)

**Structure of Bacteriophages**

 Bacteriophages exhibit a variety of structural forms, but many shares fundamental characteristics. One of the most extensively studied bacteriophages, T4, serves as a model for understanding viral morphology and function. Its structure is composed of two main parts: a head and a tail-like appendage. The head encapsulates the phage’s double-stranded DNA, though the precise mechanism of DNA packaging remains under investigation. Structurally, the head resembles two halves of an icosahedron joined by a short, hexagonal prism, a geometric configuration that facilitates efficient storage of genetic material.

 The tail of bacteriophage T4 has a helical architecture and is notable for its binal symmetry, a characteristic that distinguishes bacteriophages and cyanophages from other viruses. The tail comprises a hollow, cube-shaped tube encased in a contractile sheath. One end is attached to the head via a collar, while the other end features a hexagonal base plate. This base plate is equipped with six small structures known as ‘tail pins’ and six long tail fibers. These fibers play an essential role in the infection process. The long tail fibers are responsible for the initial recognition and attachment to specific receptors on the bacterial cell wall, while the shorter fibers contribute to stabilizing the phage during the infection process. Once attached, the sheath contracts, facilitating the injection of the viral DNA into the host cell.

 During the adsorption process, phage enzymes likely create a small opening in the bacterial cell wall, enabling the injection of genetic material. This marks the onset of the infection process, which can follow one of three distinct pathways: the lytic cycle (as observed in Escherichia coli-infecting T-phages), the lysogenic cycle, or the chronic cycle. Each pathway determines the fate of the bacterial host and the replication strategy of the phage.

**Bacteriophage-Host Interactions**

 Bacteriophages are entirely dependent on their bacterial hosts for reproduction, utilizing host cellular machinery for their replication. They typically follow one of three life cycles: the lytic cycle, the lysogenic cycle, or the chronic cycle (Howard-Varona et al., 2017).

 In the lytic cycle, bacteriophages infect bacterial cells, multiply within them, and ultimately cause cell lysis, releasing numerous new virions. Due to their ability to induce bacterial cell destruction, these are often referred to as virulent phages (Vu and Oh, 2020). The infection process begins with the recognition and attachment of the phage to specific receptors on the bacterial surface, followed by the injection of viral genetic material. Inside the host, the phage genome directs the synthesis of new viral components, culminating in the production of complete phage particles (Stone et al., 2019). To facilitate bacterial cell lysis, phages produce proteins such as holin and enzymes like endolysin (Dy et al., 2018). Effective bacteriophage therapy often requires high concentrations of lytic phages to enhance bacterial elimination while minimizing resistance development.

 The lysogenic cycle differs in that the phage integrates its DNA into the host genome, forming a prophage. The prophage replicates alongside the bacterial chromosome and is passed on to daughter cells. However, under certain environmental stresses, such as antibiotic exposure or metabolic changes, the prophage can transition into the lytic cycle, leading to host cell destruction (Nanda et al., 2015; Davies et al., 2016).

 A third pathway, known as the chronic cycle, has been observed primarily in filamentous phages of the Inoviridae family (Yamada, 2013). Unlike the lytic cycle, this pathway does not result in bacterial lysis. Instead, phages establish a long-term association with the host, continuously producing and releasing new virions without killing the bacterial cell (Howard-Varona et al., 2017; Horiuk et al., 2020). This persistent infection allows phages to propagate while the host continues to grow and divide (Yamada, 2013; Sieiro et al., 2020). Studies on filamentous ϕRSS1 phages infecting Ralstonia solanacearum have shown that infected bacterial cells exhibit unusual behavior, such as increased aggregation and reduced culture turbidity. Moreover, these infections have been linked to changes in bacterial virulence, as seen in tobacco (Yamada et al., 2007) and tomato plants (Addy et al., 2012; Yamada, 2013). Conversely, another filamentous phage, ϕRSS0, has been shown to reduce the virulence of R. solanacearum (Yamada, 2013).

 A variation of the lysogenic cycle, termed pseudolysogeny or the carrier state, occurs when the phage genome remains dormant within the host without immediate replication. This state is often observed under unfavorable conditions, such as nutrient deprivation, where insufficient energy prevents viral gene expression. Once favorable conditions return, the phage either resumes the lytic cycle or establishes stable lysogeny (Cenens et al., 2013).



**Fig. 1: Life cycle of Bacteriphages**

**Receptors Utilized by Phages for Bacterial Detection**

 Various molecular components on bacterial surfaces serve as receptors for bacteriophages, though their composition and location differ depending on specific bacteria-phage interactions. These receptors may be proteins, polysaccharides, lipopolysaccharides (LPS), or carbohydrate moieties (Bertozzi Silva et al., 2016). In Gram-negative bacteria, LPS is commonly used as a receptor. Other key receptors include outer membrane proteins, pili, and flagella (Sorensen et al., 2011).

 The mechanisms of receptor recognition have been extensively studied in the model bacteriophage T4, which infects *E. coli*. This phage initially attaches reversibly to LPS or the outer membrane protein porin OmpC, depending on the strain. Once bound, T4 undergoes irreversible attachment to the outer core of *E. coli* LPS, facilitating infection. Similarly, the T7 phage also relies on LPS as its primary binding site for irreversible attachment (Sorensen et al., 2011).

 For phages targeting Gram-positive bacteria, peptidoglycan serves as a crucial receptor due to its prominence in bacterial cell walls. Additionally, teichoic acids, which are covalently linked to the peptidoglycan layer, function as key recognition sites. Surface-exposed polysaccharides also serve as phage receptors (Bertozzi Silva et al., 2016). Despite the widespread presence of peptidoglycan and teichoic acids, only a limited number of phage receptors have been identified in Gram-positive bacteria. This is partly due to their complex outer structure and the relatively limited research on phages that infect these bacteria. Notable examples include phage 3C, which binds to the *N*-acetylglucosamine component of teichoic acids on the surface of *Staphylococcus aureus*, and phages SP2 and SP10, which recognize the *D*-glucose chains of teichoic acids on *Bacillus subtilis* (Rakhuba et al., 2010).

**Advancements in Phage Therapy**

 Several strategies have been developed to enhance the effectiveness of phage therapy, including the use of natural and engineered phages, phage-derived enzymes, and combinations of phages with antimicrobial agents. These approaches are outlined below:

1. **Traditional Phage Therapy:** This method involves directly administering naturally occurring virulent phages to eliminate bacterial pathogens. In a study by Bruttin and Brussow, 15 adult participants received *E. coli* T4 phage orally. Only a few experienced mild side effects, none of which required medical intervention. This research highlights the safety and therapeutic potential of conventional phage therapy (Bruttin and Brussow, 2002).
2. **Genetically Engineered Phages**: Using genetic modification, phages can be altered to expand their host range while eliminating toxin-producing genes. These engineered phages can be programmed to deliver lethal genes or antimicrobial substances to target bacteria without necessarily causing host cell lysis. For instance, non-lytic filamentous phages have been modified to introduce genes encoding toxic proteins such as restriction endonucleases or addiction toxins, which induce bacterial cell death (Lu & Koeris, 2011).
3. **Phage-Derived Enzymes:** Instead of using entire phages, scientists have explored the use of phage-encoded enzymes to break down bacterial cells. Two key enzyme groups in this category are Virion-Associated Peptidoglycan Hydrolases (VAPGHs) and endolysins. Endolysins, in particular, have demonstrated effectiveness in treating *Staphylococcus* infections, including MRSA, MSSA, VRSA, and VISA, in laboratory settings. These enzymes function as highly selective bacteriolytic agents, even at low concentrations, making them a promising alternative to traditional antibiotics (Fischetti, 2005).
4. **Combination Therapy: Phages and Antibiotics:** The combination of phages with antibiotics has emerged as a powerful strategy to combat antibiotic-resistant bacteria. This dual approach leverages the complementary effects of phages and antibiotics, leading to improved treatment success rates while reducing the risk of resistance development. Research has shown that combining phages with antibiotics like streptomycin effectively inhibits the growth of *Pseudomonas aeruginosa* in laboratory conditions (Torres-Barcelo et al., 2014).

**Recent Applications of Bacteriophages in Plant Disease Management**

1. **Single Bacteriophage Applications:** Much of the research on bacteriophages targeting bacterial pathogens in plants has centered on isolating and characterizing these phages, with some showing therapeutic potential (Rahimi-Midani et al., 2018; Yin et al., 2019). A survey in *Molecular Plant Pathology* highlighted *Pseudomonas syringae* pathovars as major bacterial plant pathogens (Mansfield et al., 2012). In field trials conducted in 2016, a cocktail of six phages was tested against bacterial blight in leeks caused by *P. syringae* pv. porri. The results were mixed but indicated phage therapy’s potential (Rombouts et al., 2016). Other studies have examined different application methods, including soil drenching, foliar spraying, and seed immersion. Soil drenching has been effective in reducing wilting in tomatoes infected with *R. solanacearum* (Elhalag et al., 2018), while foliar spraying has decreased disease incidence from *X. campestris* pv. *campestris*, *Xanthomonas euvesicatoria*, and *P. carotovorum* (Nagai et al., 2017; Gašić et al., 2018). Filamentous phages, like ΦRSM3, have also demonstrated promise by boosting defense-related gene expression in tomatoes and mitigating *R. solanacearum* virulence (Addy et al., 2012). Phage XacF1 significantly reduced various traits of *X. axonopodis* pv. *citri* (Ahmad et al., 2014).
2. **Bacteriophage Mixtures (Cocktails):** While some phages can infect multiple bacterial genera (Ahern et al., 2014), most are specific to strains within a single species, due to the precise interaction between phage attachment structures and bacterial receptors (Sulakvelidze et al., 2001). Bacteria can rapidly evolve resistance to phages through mutation, adsorption-blocking, or CRISPR-Cas systems (Chopin et al., 2005; Ranjani et al., 2018). For example, *R. solanacearum* developed resistance within 30 hours of phage application (Fujiwara et al., 2011), and similar resistance was seen with *Xoo-Sp2* phages after 16 to 17 hours (Dong et al., 2018). To mitigate this, phage cocktails—combinations of different lytic phages—have been used, enhancing host range and reducing the likelihood of resistance (Schmerer et al., 2014; Tewfike and Desoky, 2015). Cocktails have been applied successfully against *R. solanacearum* (Ramírez et al., 2020; Wang et al., 2019), *Xanthomonas* species (Ibrahim et al., 2017; Tewfike and Desoky, 2015), and *P. carotovorum* (Zaczek-Moczydłowska et al., 2020). The development of host-range (h-) mutant phages further expands the range of phage effectiveness, even against strains resistant to original phages, while still targeting the wild-type bacteria. For example, a mixture of five h-mutant phages effectively controlled bacterial blight in geraniums caused by *X. campestris* pv. *pelargonii* (Flaherty et al., 2001), and also reduced bacterial spot severity in tomatoes, improving yields compared to untreated or chemically treated plants (Flaherty et al., 2000).
3. **Combining Phages with Other Antimicrobials:** Combining bacteriophages with other antimicrobial agents, such as plant systemic acquired resistance (SAR) inducers and antibiotics, has shown promise in improving disease control. In 2005, Obradovic et al. (2015) explored the use of SAR inducers with biocontrol agents to combat bacterial spot disease in tomatoes caused by *X. campestris* pv. *vesicatoria*. They found that combining phages with the SAR inducer acibenzolar-S-methyl (ASM) not only alleviated ASM-induced hypersensitive responses but also provided excellent disease control. In field trials targeting bacterial leaf blight of onions caused by *X. axonopodis* pv. *allii*, a mix of phages and ASM reduced disease severity by 50%, outperforming the 31% reduction achieved with copper hydroxide-mancozeb treatment (Lang et al., 2007). In greenhouse trials, integrating phage KΦ1 with copper hydroxide resulted in an 81%-88% reduction in lesion numbers on pepper leaves infected by *X. euvesicatoria*, compared to no significant effect with copper hydroxide alone (Gašić et al., 2018).
4. **Use of Phage-Derived Proteins—Endolysins:** Phage-derived endolysins, enzymes that break down bacterial cell walls during phage replication, offer several advantages over whole phages, such as a broader host range and reduced risk of resistance. Endolysins are classified into five types based on their enzymatic activities, such as N-acetylmuramidases and endo-β-N-acetylglucosaminidases, and can target both Gram-positive and Gram-negative bacteria. For example, endolysins from phages CMP1 and CN77 effectively lysed strains of *Clavibacter michiganensis* (Wittmann et al., 2010), and endolysins from phages Atu\_ph02 and Atu\_ph03 caused rapid lysis in *Agrobacterium tumefaciens* (Attai et al., 2017). Endolysins also showed broad activity against multiple bacterial species and fungi, boosting plant resistance to pathogens like *Rhizoctonia solani* (Dong et al., 2008). However, Gram-negative bacteria present a challenge due to their outer membrane, which protects them from enzymatic action. Strategies such as combining multiple endolysins or using depolymerases to breach bacterial barriers have been developed to improve phage efficacy against these pathogens (Born et al., 2014; Born et al., 2017).

**Phage based products available in market**

 In the United States, the application of phage-based products for agricultural disease management is permitted under the regulatory oversight of the Environmental Protection Agency (EPA). These products offer targeted, eco-friendly alternatives to chemical pesticides, aligning with the growing demand for sustainable agricultural practices. Two notable examples of EPA-registered phage products include XylPhi-PD and AgriPhage™. XylPhi-PD is a phage-based bactericide specifically designed to target *Xylella fastidiosa*, the causal agent of Pierce’s disease in grapevines. This disease significantly impacts grape production, particularly in warmer climates such as California. XylPhi-PD is approved for organic farming and is administered by injecting the phage preparation directly into the xylem of newly growing vines, ensuring localized and effective delivery (Wilbur-Ellis, 2024). The product's targeted action helps manage the pathogen without disturbing beneficial microorganisms or the environment.

 Another prominent product, AgriPhage™, developed by Omnilytics, is an EPA-registered biopesticide used to control bacterial diseases on a variety of fruit and vegetable crops. It is effective against pathogens such as *Erwinia amylovora*, the causative agent of Fire Blight, a serious disease in apple and pear orchards, and *Xanthomonas* spp., which affect tomatoes and peppers. AgriPhage™ is applied through foliar sprays and has been widely adopted due to its specificity, environmental safety, and lack of chemical residues (Omnilytics, 2022). In Europe, products like Erwiphage Plus and BioLyse-PB have shown promising results against Fire Blight and Soft Rot, respectively, highlighting the growing acceptance of phage technology beyond North America. These products exemplify the potential of phage-based solutions in commercial agriculture, offering disease control that is both effective and environmentally sustainable. Their approval and commercial availability in the U.S. mark a significant step toward mainstream adoption of bacteriophage therapy in plant protection.

**TABLE 2. Application of bacteriophages carried out during research**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pathogen** | **Host** | **Disease** | **Information**  | **References** |
| 01 | *Pectobacterium carotovorum* ssp. *carotovorum*, *Pectobacterium wasabiae*, *Dickeya solani* | Potato | Soft Rot | Bioassays with phage 8PD10.3 and 8PD23.1 could reduce severity of soft rot of tubers by 80% on potato slices and 95% with whole tubers from a mixed pathogen infection. | Czajkowski *et al*., 2015 |
| 02 | *Dickeya solani* | Potato | Soft rot/Black leg | Phage vB\_DsoM\_LIMEstone1 and vB\_DsoM\_LIMEstone2 reduced soft rot of inoculated tubers in bioassays and in field trials which produced a potato crop with higher yields. | Adriaenssens *et al*., 2012 |
| Potato | Soft Rot | Bioassays with phage 8D1, 8D2, 8D3, 8D4, 8D5, 8D7, 8D9, 8D10, 8D11 could reduce incidence of soft rot by up to 30–70% on co inoculated potato slices with pathogen and phage. | Czajkowski *et al*., 2014 |
| 03 | *Ralstonia solanacearum* | Tomato | Bacterial spot | Tomato plants treated with phage 8RSL1 showed no symptoms of bacterial wilt during the experimental period; whereas all untreated plants showed wilting 18 days post infection. | Fujiwara *et al*., 2011 |
| Simultaneous treatment of phage PE204 with *R. solanacearum* of the rhizosphere of tomato completely inhibited bacterial wilt. However, pre-treatment with phage before the inoculation of pathogen was not effective with control of bacterial wilt, whereas post treatment of PE204 delayed disease development. | Bae *et al*., 2012 |
| 04 | *Xanthomonas campestris* pv. *vesicatoria* | Tomato | Bacterial spot | Greenhouse experiments with formulated phage cocktails could reduce disease severity with formulated phage cocktails providing better protection in comparison to unformulated. A similar effect was found in three consecutive field trials. | Balogh *et al*., 2003 |
| In field experiments phage treatment was comparable to disease control with copper-mancozeb. Combination of phage and plant activator (ASM) resulted in enhanced control. | Obradovic *et al*., 2004 |
| 05 | *Xylella fastidiosa* | Grapevi ne | Pierce’s Disease | *X. fastidiosa* levels in grapevines were significantly reduced on pre and post inoculation of a four phage (Sano, Salvo, Prado and Paz) cocktail. Pierce disease symptoms could be stopped using phage treatment post infection as well as applying phage prophylactically to grapevines. | Das *et al*., 2015 |
| 06 | *Xanthomonas axonopodis* pv. *allii* | Onion | Xanthom onas leaf blight of onion | Field trial showed that weekly and biweekly applications of phage could reduce disease severity, a result which was comparable to treatments of weekly applications of copper mancozeb. | Lang *et al*., 2007 |
| 07 | *Pectobacterium carotovorum* ssp. *Carotovorum* | Lettuce | Soft Rot | Green house trials showed that phage PP1 could significantly reduce disease development on lettuce plants. | Lim *et al*., 2013 |
| 08 | *Streptomyces scabies* | Radish | Common scab | Phages Stsc1 and Stsc3 could prevent disease development by treating radish seedlings. Non-treated radishes had 30% less weight than negative control, with phage treated radishes having masses similar to negative control. | Goyer, 2005 |
| 09 | *Pseudomonas tolaasi* | Mushro oms | Brown blotch disease | Surface of mushrooms were inoculated with pathogen. The formation of blotches was completely blocked by co-incubation of phages with pathogen. | Kim *et al*., 2011 |
| 10 | *Xanthomonas axonopodis* pv. citri | Grapefr uit | Asiatic citrus canker | Five greenhouse experiments utilizing phage treatment could reduce disease severity by 59%. However, using a skim milk formulation of phage did not have increased disease control. Phage treatment was also capable of reducing disease occurrence in a citrus nursery. Control was less effective than copper-mancozeb. Combination did not give increased disease control. | Balogh *et al*., 2008 |
| 11 | *Xanthomonas axonopodis* pv. *citrumelo* | Orange | Citrus bacterial spot | Phage treatments reduced citrus spot occurrence by 35 and 48% in two trials in commercial citrus nursery. Control was equal or less effective than copper mancozeb. Combination did not give increased disease control. | Balogh *et al*., 2008 |
| 12 | *Pseudomonas* *syringae* pv. *porri* | Leek | Bacterial blight | Specific bio-assays demonstrated the in-planta efficacy of phages vB\_PsyM\_KIL1, vB\_PsyM\_KIL2, vB\_PsyM\_KIL3, and vB\_PsyM\_KIL3b. However, phage cocktail of six phages (vB\_PsyM\_KIL1, vB\_PsyM\_KIL2, vB\_PsyM\_KIL3, vB\_PsyM\_KIL4, and vB\_PsyM\_KIL5 and vB\_PsyM\_KIL3b), were tested with two parallel field trial experiments in three locations which showed variable results. In one trial, symptom development was attenuated. | Rombouts *et al*., 2016 |
| 13 | *Erwinia amylovora* | Pear, Apple | Fire blight | Phages 8Ea1337-26 and 8Ea 2345 reduced infection of detached pear tree blossoms by 84 and 96%, respectively, with *Pantoea agglomerans* as a carrier. Also, infection of potted apple tree blossoms could be reduced by 54% with phage 8Ea1337-26 and P. agglomerans. Control was comparable to streptomycin. | Boulé *et al*., 2011 |
| 14 | *Acidovorax citrulli* | Melon | Bacterial fruit blotch | Phage application after symptom development resulted in 27% disease severity, compared to 80% for the non-treated control. Phage detected in foliar tissue 8 h after addition to soil and leaf tip after 24 h. | Rahimi-Midani and Choi, 2020 |
| 15 | *Pectobacterium atrosepticum* | Potato | Soft rot | Use of the phage cocktail reduced both disease incidence and disease severity by 61% and 64% respectively. | Carstens *et al*., 2019 |
| 16 | *Pectobacterium spp. and Pantoea spp.* | Onion | Soft rot | Over four years, both immersion and spray methods consistently reduced disease severity with uniform results. | Zaczek Moczydłowska *et al*., 2020 |
| 17 | *Pseudomonas syringae pv. actinidiae* | Kiwifruit | Bacterial blight | Within 24 hours post-infection, phages reduced bacterial load on kiwifruit leaves by over 75%. No significant difference was noted between one or two applications, but phages outperformed copper bactericides in disease control. | Flores *et al*., 2020 |
| 18 | *Ralstonia solanacearum* | Tomato | Bacterial wilt  | A phage cocktail killed 98% of live bacteria in sterilized soil one week after spraying. Treatment effectiveness depended on timely application, with early use after initial bacterial wilt signs being crucial. | Wei *et al*., 2017 |
| Phages reduced disease incidence by up to 80% in field experiments. Increasing the number of phages in the cocktail further decreased disease severity. | Wang *et al*., 2019 |
| 19 | *Ralstonia solanacearum* | Banana | Moko wilt | The phage cocktail provided complete (100%) protection against Moko disease, whereas plants treated with single-phage treatments showed disease symptoms. | Ramírez *et al*., 2020 |
| 20 | *Xanthomonas oryzae pv. oryzae* | Rice | Bacterial blight | Spraying rice seedlings with phages 2, 4, 6 days post-inoculation reduced disease severity by 73.9%, 49.6%, and 28.9%, respectively. Pre-inoculation phage spraying reduced severity by 83.1%, while seed treatment achieved a 95.4% reduction. | Ogunyemi *et al*., 2019 |
| The phage formulation with skim milk reduced bacterial leaf blight occurrence to 18.1%, compared to 87% in the untreated control. | Chae *et al*., 2014 |
| 21 | *Xanthomonas euvesicatoria* | Pepper | Bacterial Spot | The most effective disease control was achieved with two phage applications (before and after inoculation). However, the best results came from integrating phage application 2 hours before inoculation with copper hydroxide applied 24 hours prior. | Gašić *et al*., 2018 |
| 22 | *Xanthomonas citri subsp. citri* | Citrus | Canker | Non-formulated phages with ASM reduced disease incidence by 42.4–56.9%, while formulated phages combined with ASM achieved a reduction of 82.1–86.1%. | Ibrahim *et al*., 2018 |
| 23 | *Xanthomonas campestris pv. campestris* | Broccoli | Black rot | Only the nonpathogenic Xanthomonas sp. strain mixed with bacteriophage reduced disease; phage alone had no effect. | Nagai *et al*., 2017 |
| 24 | *Ralstonia. solanacearum* | Tomato | Bacterial wilt | Adding phage suspension one day before bacterial inoculation effectively controlled the disease. | Elhalag *et al*., 2018 |
| 25 | *Pseudomonas savastanoi pv. glycinea* | Soybeans | Bacterial spotting | Phage P421 application reduced disease progression in soybean leaves and lowered infection rates and disease development in pre-treated seeds. | Tarakanov *et al*. 2022 |

TABLE 3.  **List of phage products available for bacterial disease control**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No.** | **Product Name** | **Country** | **Active Ingredient****(Bacteriophage Against Pathogen)** | **PFU/ml** | **Use for Diseases and Crop** | **Company** | **References** |
| 01 | Agriphage | USA | *Xanthomonas campestris* pv. *vesicatoria* and *Pseudomonas syringae* pv. tomato phage | 1.55 × 1013 | Bacterial leaf spot of tomato and pepper | OmniLytics, Inc | OmniLytics, n.d. b |
| 02 | AgriPhage-CMM | USA and Canada | *Clavibacter michiganensis* subsp. *michiganensis* phage | 3.8 × 1012 | Canker of tomato | OmniLytics, Inc | OmniLytics, n.d. a |
| 03 | Agriphage-Fire blight | USA | *Erwinia amylovora* phage | 5 × 1012 | Fire blight of apple and pear | OmniLytics, Inc | OmniLytics, 2018 |
| 04 | Agriphage-Citrus canker | USA | *Xanthomonas citri* subsp. *citri* phage | 5 × 1012 | Canker of citrus | OmniLytics, Inc | OmniLytics, n.d. c |
| 05 | BioLyse-PB | United Kingdom | Soft rot bacteria of potato (*Enterobacteriacea*) phage |  | Soft rot of potato | APS Biocontrol | APS Biocontrol,n.d. |
| 06 | Erwiphage Plus | Hungary | *Erwinia amylovora* phage | 2 × 105 | Fire blight of apple, pear, quinces and loquat | Enviroinvest | Enviroinvest, n.d. |
| 07 | Xylphi-PD | USA | *Xylella fastidiosa* phage | 5 × 109 | Pierce’s disease of grape | A&P Inphatec, n.d | A&P Inphatec, n.d |

**Challenges of Using Bacteriophages for Managing Bacterial Plant Diseases**

Although laboratory studies have shown promising results, applying bacteriophages for plant disease management in the field presents several obstacles. Bacteriophages are commonly applied to the rhizosphere or sprayed on the phyllosphere, but their success depends on various factors:

1. **Challenges in the Rhizosphere:** The availability of water is crucial for the diffusion of bacteriophages in soil. Phages can be trapped in biofilms or adsorbed onto soil particles, limiting their movement. In addition, low soil pH can inactivate phages, preventing them from locating suitable hosts (Gill & Abedon, 2003).
2. **Challenges in the Phyllosphere:** The phyllosphere environment exposes bacteriophages to extreme temperatures, varying pH, and UV radiation, which quickly decreases their population (Galić et al., 2018). Field studies have shown substantial reductions in phage numbers within 36-48 hours of application (Dewlike & Deseky, 2015).
3. **Stability and Formulation:** Techniques like encapsulating bacteriophages in substances such as corn flour, skim milk, or lignin have improved their stability (Arthurs et al., 2006). Additionally, applying treatments during early mornings or evenings has shown promising results (Iriarte et al., 2007).
4. **Inconsistent Field Results:** In vitro traits such as host range and lytic activity do not always predict success in the field (Bar et al., 2012; Bhuta, 2015). Some phages with strong in vitro activity have failed to control diseases effectively in field trials (Maniats et al., 2016).

**Future Prospects for Bacteriophage Use in Plants**

1. **Need for More Field Trials:** While bacteriophage applications have been successful in controlled environments, more field trials are necessary to validate their effectiveness in open fields (Buttimer et al., 2017).
2. **Limited Commercial Products:** Few bacteriophage-based products exist, such as AgriPhages and Erwiphage, despite promising research (Buttimer et al., 2017).
3. **Environmental Impact:** The effectiveness of bacteriophages is often reduced by environmental variability, highlighting the need for improved delivery methods and formulations (Buttimer et al., 2017).
4. **Improvement in Selection Criteria:** Current methods for selecting effective phages are limited, and standardized criteria need to be developed (Ahmad et al., 2014; Rombouts et al., 2016).
5. **Potential of Temperate Phages:** Though less commonly used due to risks of replication, temperate phages could be engineered for beneficial applications, such as reducing virulence (Halugh et al., 2010).
6. **Phage Detection:** Engineered phages may carry marker genes for pathogen detection, which can be useful for both lytic and lysogenic types (Paroon et al., 2018).
7. **Transgenic Plants:** Expression of phage proteins has been shown to enhance plant resistance, though regulatory and consumer concerns need to be addressed (Dong et al., 2008; Wittmann et al., 2016).
8. **Sustainability:** Bacteriophages offer potential for reducing dependence on chemical agrochemicals, supporting more sustainable agricultural practices (Buttimer et al., 2017).

**Conclusion**

 The renewed interest in phage therapy marks a shift toward sustainable and targeted methods for managing bacterial plant diseases. Historical successes, recent developments, and application strategies emphasize the potential of bacteriophages as viable alternatives to traditional treatments. Their environmental compatibility and specificity provide notable benefits, particularly in the face of growing bacterial resistance to antibiotics and chemical methods. While challenges such as bacterial resistance exist, combining phage therapy with antibiotics and genetic engineering shows promising synergy and enhanced effectiveness. Ongoing research, field trials, and regulatory frameworks are crucial for successfully integrating phage therapy into mainstream agricultural practices.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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1.

2.

3.

**REFERENCES**

1. Abedon, S. T., Kuhl, S. J., Blasdel, B. G., & Kutter, E. M. (2011). Phage treatment of human infections. *Bacteriophage, 1*(2), 66–85.
2. Ackermann, H. W. (2005). Bacteriophage classification. In E. Kutter & A. Sulakvelidze (Eds.), *Bacteriophages – Biology and Applications* (pp. 67–89). CRC Press.
3. Ackermann, H. W. (2007). 5500 phages examined in the electron microscope. *Archives of Virology, 152*, 277–243.
4. Ackermann, H. W., & DuBow, M. S. (1987). *Viruses of prokaryotes, Vol. 1: General properties of bacteriophages*. CRC Press.
5. Adriaenssens, E. M., Wittmann, J., Kuhn, J. H., Turner, D., Sullivan, M. B., Dutilh, B.-E., ... & Lobocka, M. (2018). Taxonomy of prokaryotic viruses: 2017 update from the ICTV Bacterial and Archaeal Viruses Subcommittee. *Archives of Virology, 166*, 1125–1129.
6. Agrios, G. (2005). *Plant pathology* (5th ed.). Elsevier Academic Press.
7. Bae, J. Y., Wu, J., Lee, H. J., Jo, E. J., Murugaiyan, S., Chung, E., & Lee, S.-W. (2012). Biocontrol potential of a lytic bacteriophage PE204 against bacterial wilt of tomato. *Journal of Microbiology and Biotechnology, 22*, 1613–1620.
8. Balogh, B., Jones, J. B., Iriarte, F. B., & Momol, M. T. (2010). Phage therapy for plant disease control. *Current Pharmaceutical Biotechnology, 11*, 48–57.
9. Barylski, J., Enault, F., Dutilh, B. E., Schuller, M. B., Edwards, R. A., Gillis, A., ... & Kuhn, J. H. (2018). Taxonomy proposal to create one (1) new family, Herelleviridae, in the order Caudovirales. *ICTV Online*.
10. Behlau, F., Canteros, B. I., Minsavage, G. V., Jones, J. B., & Graham, J. H. (2011). Molecular characterization of copper resistance genes from *Xanthomonas citri* subsp. *citri* and *X. alfalfae* subsp. *citrumelonis*. *Applied and Environmental Microbiology, 77*, 4089–4096.
11. Bertozzi Silva, J., Storms, Z., & Sauvageau, D. (2016). Host receptors for bacteriophage adsorption. *FEMS Microbiology Letters, 363*(4), fnw002.
12. Bradley, D. E. (1997). Ultrastructure of bacteriophages and bacteriocins. *Bacteriological Reviews, 31*, 230–314.
13. Breitbart, M. (2012). Marine viruses: Truth or dare. *Annual Review of Marine Science, 4*, 425–448.
14. Brüssow, H., & Hendrix, R. W. (2002). Phage genomics: Small is beautiful. *Cell, 108*(1), 13–16.
15. Bruttin, A., & Brüssow, H. (2002). Human volunteers receiving *Escherichia coli* phage T4 orally: A safety test of phage therapy. *Antimicrobial Agents and Chemotherapy, 46*(1), 255–263.
16. Buttimer, C., McAuliffe, O., Ross, R. P., et al. (2017). Phages and bacterial plant diseases. *Frontiers in Microbiology, 8*, 34. https://doi.org/10.3389/fmicb.2017.00034
17. Calvo-Garrido, C., Viñas, I., Elmer, P. A., Usall, J., & Teixidó, N. (2014). Suppression of *Botrytis cinerea* on necrotic grapevine tissues by early-season applications of natural products and biological control agents. *Pest Management Science, 70*, 595–602.
18. Cenens, W., Makumi, A., Mebrhatu, M. T., Lavigne, R., & Aertsen, A. (2013). Phage–host interactions during pseudolysogeny: Lessons from the Pid/dgo interaction. *Bacteriophage, 3*, e25029.
19. d’Hérelle, F. (1917). Sur un microbe invisible antagoniste des Bacillies dysentériqué. *Comptes Rendus de l’Académie des Sciences, 165*, 373–375.
20. Farooq, U., Yang, Q., Ullah, M. W., & Wang, S. (2018). Bacterial biosensing: Recent advances in phage-based bioassays and biosensors. *Biosensors and Bioelectronics, 118*, 204–216.
21. Fauquet, C. M., Mayo, M. A., Maniloff, J., Desselberger, U., & Ball, L. A. (Eds.). (2005). *Virus taxonomy: VIIIth report of the International Committee on Taxonomy of Viruses*. Academic Press/Elsevier.
22. Fischetti, V. A. (2005). Bacteriophage lytic enzymes: Novel anti-infectives. *Trends in Microbiology, 13*(10), 491–496.
23. Goto, M. (2012). *Fundamentals of bacterial plant pathology*. Academic Press.
24. ermoso, J. A., García, J. L., & García, P. (2007). Taking aim on bacterial pathogens: From phage therapy to enzybiotics. *Current Opinion in Microbiology, 10*, 461–472.
25. Holmes, F. O. (1948). Order Virales; the filterable viruses. In R. S. Breed, E. G. D. Murray, & A. P. Hitchens (Eds.), *Bergey’s Manual of Determinative Biology* (6th ed., pp. 1126–1144). Williams & Wilkins.
26. Holtappels, D., Fortuna, K., Lavigne, R., et al. (2021). The future of phage biocontrol in integrated plant protection for sustainable crop production. *Current Opinion in Biotechnology, 68*, 60–71. <https://doi.org/10.1016/j.copbio.2020.08.016>
27. Hwang, M. S., Morgan, R. L., Sarkar, S. F., Wang, P. W., & Guttman, D. S. (2005). Phylogenetic characterization of virulence and resistance phenotypes of *Pseudomonas syringae*. *Applied and Environmental Microbiology, 71*, 5182–5191.
28. Kasman, L. M., & Porter, L. D. (2022). Bacteriophages. In *StatPearls*. StatPearls Publishing.
29. Kotila, J. E., & Coons, G. H. (1925). Investigations on the blackleg disease of the potato. *Michigan Agricultural Experiment Station Technical Bulletin, 67*, 3–29.
30. Lee, Y. A., Hendson, M., Panopoulos, N. J., & Schroth, M. N. (1994). Molecular cloning, chromosomal mapping, and sequence analysis of copper resistance genes from *Xanthomonas campestris* pv. *juglandis*. *Journal of Bacteriology, 176*, 173–188.
31. Leverentz, B., Conway, W. S., Camp, M. J., Janisiewicz, W. J., Abuladze, T., Yang, M., & Sulakvelidze, A. (2003). Biocontrol of *Listeria monocytogenes* on fresh-cut produce by treatment with lytic bacteriophages and a bacteriocin. *Applied and Environmental Microbiology, 69*(8), 4519–4526.
32. Lindberg, A. A. (1973). Bacteriophage receptors. *Annual Review of Microbiology, 27*, 205–241.
33. Ling, J. M. L., Waye, M. M. Y., & Ma, Y. Y. (2004). The role of bacteriophages in gene transfer. *Advances in Genetics, 52*, 1–49.
34. Loessner, M. J. (2005). Bacteriophage endolysins—Current state of research and applications. *Current Opinion in Microbiology, 8*(4), 480–487.
35. Molineux, I. J., & Panja, D. (2013). Popping the cork: Mechanisms of phage genome ejection. *Nature Reviews Microbiology, 11*, 194–204.
36. Mosig, G. (1998). Recombination and recombination-dependent DNA replication in bacteriophage T4. *Annual Review of Genetics, 32*, 379–413.
37. Nelson, D., Loomis, L., & Fischetti, V. A. (2001). Prevention and elimination of upper respiratory colonization of mice by group A *Streptococci* by using a bacteriophage lytic enzyme. *Proceedings of the National Academy of Sciences, 98*(7), 4107–4112.
38. Nobrega, F. L., Costa, A. R., Kluskens, L. D., & Azeredo, J. (2015). Revisiting phage therapy: New applications for old resources. *Trends in Microbiology, 23*(4), 185–191.
39. Pires, D. P., Oliveira, H., Melo, L. D. R., Sillankorva, S., & Azeredo, J. (2016). Bacteriophage-encoded depolymerases: Their diversity and biotechnological applications. *Applied Microbiology and Biotechnology, 100*, 2141–2151.
40. Pizarro-Cerdá, J., & Cossart, P. (2006). Bacterial adhesion and entry into host cells. *Cell, 124*(4), 715–727.
41. Rakhuba, D. V., Kolomiets, E. I., Dey, E. S., & Novik, G. I. (2010). Bacteriophage receptors, mechanisms of phage adsorption and penetration into host cell. *Polish Journal of Microbiology, 59*(3), 145–155.
42. Rohde, C., Resch, G., Pirnay, J. P., Blasdel, B., Debarbieux, L., Gelman, D., ... & Paul, T. (2018). Expert opinion on three phage therapy-related topics: Bacterial phage resistance, phage training and Prophages in bacterial production strains. *Viruses, 10*(4), 178.
43. Samson, J. E., Magadán, A. H., Sabri, M., & Moineau, S. (2013). Revenge of the phages: Defeating bacterial defences. *Nature Reviews Microbiology, 11*, 675–687.
44. Sarkar, D. J., Ghosh, M., & Sen, S. K. (2017). Bacteriophage therapy: An alternative to antibiotics in the era of multi-drug resistance. *World Journal of Pharmaceutical Research, 6*(1), 1510–1531.
45. Scholl, D., Adhya, S., & Merril, C. (2005). Escherichia coli K1's capsule is a barrier to bacteriophage T7. *Applied and Environmental Microbiology, 71*(8), 4872–4874.
46. Sillankorva, S., Oliveira, R., & Azeredo, J. (2012). Bacteriophages and their role in food safety. *International Journal of Microbiology, 2012*, Article ID 863945.
47. Svircev, A. M., Roach, D., & Castle, A. J. (2018). Framing the future with bacteriophages in agriculture. *Viruses, 10*(5), 218.
48. Tanji, Y., Shimada, T., Yoichi, M., Miyanaga, K., Hori, K., & Unno, H. (2004). Toward rational control of *Escherichia coli* O157:H7 by a phage cocktail. *Applied Microbiology and Biotechnology, 64*, 270–274.
49. Thiel, K. (2004). Old dogma, new tricks—21st century phage therapy. *Nature Biotechnology, 22*(1), 31–36.
50. Thompson, C. M., Holden, M. T., Wong, M. J., Glover, R. H., & Bentley, S. D. (2007). Bacterial genome sequencing: Challenges, insights, and impact on pathogenesis. *Annual Review of Microbiology, 61*, 359–379.
51. Van Valen, L. (2007). The Red Queen lives. *Nature, 421*, 829.
52. Vinodkumar, C. S., Kalsurmath, S., & Neelagund, Y. F. (2008). Utility of lytic bacteriophage in the treatment of multidrug-resistant *Pseudomonas aeruginosa* septicemia in mice. *Indian Journal of Pathology and Microbiology, 51*(3), 360–366.
53. Wang, I. N., Smith, D. L., & Young, R. (2000). Holins: The protein clocks of bacteriophage infections. *Annual Review of Microbiology, 54*, 799–825.
54. Weitz, J. S., & Dushoff, J. (2008). Alternative stable states in host–phage dynamics. *Theoretical Ecology, 1*, 13–19.
55. Whitman, W. B., Coleman, D. C., & Wiebe, W. J. (1998). Prokaryotes: The unseen majority. *Proceedings of the National Academy of Sciences, 95*(12), 6578–6583.
56. Wommack, K. E., & Colwell, R. R. (2000). Virioplankton: Viruses in aquatic ecosystems. *Microbiology and Molecular Biology Reviews, 64*(1), 69–114.
57. Young, R. (1992). Bacteriophage lysis: Mechanism and regulation. *Microbiological Reviews, 56*(3), 430–481.