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Bacteriophages as sustainable biocontrol agents in agriculture: A review

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Abstract

The increasing concerns over antibiotic resistance, chemical pesticide residues, and environmental degradation have necessitated the exploration of sustainable alternatives for managing bacterial plant diseases. Bacteriophages, viruses that specifically infect and lyse bacteria, have emerged as promising eco-friendly biocontrol agents offering targeted pathogen control without harming beneficial microorganisms or the environment. This review examines the application of bacteriophages in agricultural systems, discussing their mechanisms of action, current applications in crop protection, advantages over conventional methods, implementation challenges, and future prospects. Evidence from field trials demonstrates that phage-based biocontrol can effectively manage bacterial diseases in various crops including tomatoes, peppers, citrus, and pome fruits. However, challenges such as phage resistance development, narrow host ranges, and environmental stability require consideration. The integration of phage therapy with existing agricultural practices presents promising avenues for sustainable disease management aligned with environmental conservation and food safety objectives.

Keywords: Bacteriophages, biocontrol, sustainable agriculture, plant pathogens, integrated pest management, bacterial disease management

1. Introduction

Global agriculture faces mounting pressure to produce sufficient food while minimizing environmental impact. Bacterial plant diseases cause substantial crop losses worldwide, with estimated annual losses exceeding \$200 billion globally. Traditional management strategies relying on chemical bactericides and antibiotics have resulted in significant consequences including antibiotic-resistant bacterial strains, toxic residue accumulation, and disruption of beneficial microbial communities (Sundin & Wang, 2018) ^[14]. The emergence of multidrug-resistant plant pathogens has further complicated disease management, rendering many conventional treatments ineffective (Stockwell & Duffy, 2012) ^[15].

These challenges have reinvigorated interest in biological control methods, particularly bacteriophages as precision antimicrobial agents. Bacteriophages are naturally occurring viruses that exhibit specificity toward bacterial hosts, capable of infecting and lysing target bacteria without affecting eukaryotic cells or beneficial microorganisms (Domingo-Calap & Delgado-Martínez, 2018) ^[12]. With an estimated 10^{31} phages on Earth, they represent the most abundant biological entities and play crucial roles in regulating bacterial populations (Clokier *et al.*, 2011) ^[11].

The application of phages in agriculture offers distinct advantages: high specificity minimizing non-target effects, self-replication at infection sites, environmental safety, and compatibility with organic farming (Jones *et al.*, 2007) ^[16]. This review synthesizes current knowledge on bacteriophages as agricultural biocontrol agents, examining their mechanisms, practical applications, advantages, limitations, and future directions for sustainable integrated pest management.

2. Bacteriophage biology and mechanisms of action

2.1 Phage classification and life cycles

Bacteriophages are classified based on morphology, nucleic acid type, and replication strategy. Most belong to the order *Caudovirales*, characterized by icosahedral heads and tails (Ackermann, 2007) ^[2].

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For biocontrol applications, lytic phages that undergo exclusively virulent replication cycles are preferred over temperate phages capable of lysogenic integration (Gill & Hyman, 2010)^[18].

The lytic cycle comprises adsorption to bacterial surface receptors, injection of genetic material, hijacking of host cellular machinery, assembly of progeny phages, and cell lysis releasing new phage particles. This process typically completes within 30-60 minutes, producing 50-200 progeny phages per infected cell (Calendar & Abedon, 2006)^[8]. The rapid multiplication at infection sites represents a unique advantage, as phage numbers increase with bacterial host density and decline when pathogens are eliminated.

2.2 Host range and specificity

Phage specificity is determined by receptor-binding protein interactions with bacterial surface structures including lipopolysaccharides, outer membrane proteins, pili, and flagella (Rakhuba et al., 2010)^[19]. While ensuring minimal non-target impact, narrow host ranges present challenges as individual phages typically target specific strains within a species. This limitation is addressed through phage cocktails containing multiple phages with complementary host ranges, providing broader spectrum activity (Chan et al., 2013)^[9].

Co-evolutionary dynamics have resulted in sophisticated bacterial resistance mechanisms including receptor modification, restriction-modification systems, and CRISPR-Cas immunity (Labrie). Conversely, phages have developed counter-strategies such as anti-CRISPR proteins (Samson et al., 2013)^[20]. Understanding these evolutionary dynamics is crucial for developing effective biocontrol strategies.

3. Applications of bacteriophages in crop protection

3.1 Control of bacterial spot and speck diseases

Bacterial spot caused by *Xanthomonas* species and bacterial

speck caused by *Pseudomonas syringae* pv. *tomato* represent significant threats to solanaceous crops. The commercial product AgriPhage™ has demonstrated field effectiveness, with trials showing 30-50% disease severity reduction comparable to copper-based bactericides (Balogh et al., 2010; Jones et al., 2012)^[4, 17]. Success depends on application timing, environmental conditions, and phage formulation. Multiple preventive applications throughout the growing season generally provide better control than curative treatments (Obradovic et al., 2003)^[5]. However, phage-resistant bacterial populations have been observed, highlighting the importance of using diverse phage cocktails.

3.2 Management of fire blight

Fire blight, caused by *Erwinia amylovora*, devastates apple and pear production worldwide. Phage applications targeting blossoms during high-risk periods have shown considerable promise, reducing incidence by 60-85% when applied preventively during bloom (Born et al., 2017; Schnabel & Jones, 2001)^[7, 22]. The commercial product Erwiphage™ has been registered for organic production in several countries, representing one of the most successful agricultural phage applications. Effectiveness is enhanced when integrated with cultural practices including infected tissue removal and optimal application timing.

3.3 Other applications

Bacterial canker caused by *Pseudomonas syringae* pv. *syringae* affects stone fruits, and phage applications have shown potential for reducing severity when applied during critical infection periods. Citrus canker management using phage sprays has demonstrated reduced lesion formation, though efficacy under high disease pressure often requires repeated applications (Ibrahim et al., 2017)^[27]. Commercial development has advanced with formulations optimized for tropical and subtropical conditions (Balogh et al., 2008)^[3].

Table 1: Selected bacteriophage applications for controlling plant pathogenic bacteria

Pathogen	Disease	Crop (s)	Efficacy	Reference
<i>Xanthomonas</i> spp.	Bacterial spot	Tomato, Pepper	30-50% reduction	Jones et al., 2012 ^[17]
<i>Erwinia amylovora</i>	Fire blight	Apple, Pear	60-85% reduction	Born et al., 2017 ^[7]
<i>P. syringae</i> pv. <i>tomato</i>	Bacterial speck	Tomato	40-65% reduction	Obradovic et al., 2004 ^[25]
<i>P. syringae</i> pv. <i>syringae</i>	Bacterial canker	Stone fruits	Variable control	Svircev et al., 2011 ^[26]
<i>Xanthomonas citri</i>	Citrus canker	Citrus	Lesion reduction	Ibrahim et al., 2017 ^[27]

4. Advantages of phage-based biocontrol

Bacteriophages offer compelling advantages over conventional chemical pesticides. Their exquisite specificity ensures only target pathogenic bacteria are affected, leaving beneficial microorganisms intact (Gill & Hyman, 2010)^[18]. This preservation of microbial community structure contrasts with broad-spectrum antimicrobials that disrupt entire ecosystems.

The self-replicating nature at infection sites provides sustained antimicrobial activity, potentially reducing application frequency and costs (Abedon, 2009)^[1]. Each infected bacterial cell produces progeny phages that infect additional bacteria, creating amplification effects particularly advantageous when bacterial populations are high. Phages pose no known toxicity to plants, animals, or humans, and leave no harmful residues. This safety profile makes them attractive for organic agriculture and applications on edible plant parts near harvest.

Phages can be rapidly isolated from environmental samples, allowing development of targeted biocontrol agents for emerging pathogen strains (Clokie & Kropinski, 2009)^[10]. This adaptability enables responsive disease management strategies. Finally, phages integrate well with other biocontrol methods, creating synergistic effects that enhance overall disease management (Balogh et al., 2010)^[4].

5. Challenges and limitations

5.1 Development of phage resistance

A primary concern is bacterial resistance development through receptor alteration, extracellular polymer production, or genetic immunity acquisition. Field studies have documented phage-resistant populations following repeated applications, potentially reducing long-term efficacy. However, phage cocktails containing multiple phages with different receptor specificities mitigate this risk, as simultaneous alteration of multiple structures often

carries fitness costs reducing bacterial virulence (Chan *et al.*, 2013) ^[9]. Additionally, phage-resistant mutants frequently exhibit reduced pathogenicity due to evolutionary trade-offs (Mangalea & Duerkop, 2020) ^[23].

5.2 Environmental factors and application technology

Environmental conditions significantly influence phage efficacy. UV radiation can rapidly inactivate phages on exposed surfaces, with 90-99% viability reduction within hours under high UV conditions (Iriarte *et al.*, 2007) ^[24]. Temperature extremes, desiccation, and pH fluctuations also negatively impact phage survival. Protective formulations including UV-blocking compounds, humectants, and microencapsulation technologies can enhance environmental persistence (Balogh *et al.*, 2003) ^[5].

Achieving adequate plant surface coverage represents a practical challenge, particularly for tree crops with large canopies. Standard spray equipment may not deliver sufficient concentrations to all susceptible plant parts.

Optimized spray technologies and adjuvants improve phage delivery and distribution. Preventive applications before pathogen establishment generally provide better control than curative treatments, requiring accurate disease forecasting (Obradovic *et al.*, 2003) ^[15].

5.3 Regulatory and commercial development

Regulatory landscapes vary globally and can present barriers to commercial development. In the United States, phage products are regulated by the EPA under FIFRA, requiring efficacy and safety demonstration (Gill & Hyman, 2010) ^[18]. While generally less stringent than for synthetic pesticides, approval processes still require substantial data generation. Intellectual property protection for naturally occurring phages may be limited, reducing commercial incentives. Additionally, relatively high production and formulation costs compared to conventional pesticides can limit market competitiveness.

Table 2: Advantages and limitations of bacteriophages as agricultural biocontrol agents

Advantages	Limitations
High specificity; minimal non-target effects	Narrow host range requiring cocktails
Self-replication at infection sites	Potential for bacterial resistance
Safe for humans, animals, environment	Environmental instability (UV, temperature)
No harmful residues	Application coverage challenges
Compatible with organic agriculture	Variable efficacy across conditions
Rapid development for emerging strains	Regulatory requirements and costs
Integration with other biocontrol methods	Commercial production costs

6. Future directions and emerging technologies

6.1 Genetic engineering and synthetic biology

Genetic engineering offers opportunities to enhance phage performance. Modifications can broaden host range through engineered receptor-binding proteins, improve environmental stability via capsid modifications, or incorporate monitoring systems (Lu & Collins, 2007) ^[28]. Synthetic biology enables design of novel phages with desired characteristics, though regulatory and public acceptance must be addressed before agricultural implementation.

Phage-derived antimicrobial proteins, particularly endolysins, represent another promising direction. These peptidoglycan-degrading enzymes can rapidly kill bacteria when applied exogenously without requiring phage replication, potentially circumventing resistance and environmental stability issues (Fischetti, 2008) ^[13]. Endolysin-based products have shown efficacy in laboratory studies, with commercial development underway.

6.2 Integration with precision agriculture

Integration with precision agriculture technologies can optimize application strategies. Sensor networks, drones, and satellite imaging provide real-time monitoring of environmental conditions and disease pressure, enabling targeted applications (Bock *et al.*, 2010) ^[6]. Predictive models incorporating weather data, pathogen epidemiology, and phage ecology can guide optimal timing to maximize control while minimizing costs. Decision support systems integrating multiple data streams can help growers make informed decisions about implementing phage biocontrol within comprehensive integrated pest management programs.

6.3 Metagenomics and phage discovery

Metagenomic approaches enable discovery and characterization of novel phages directly from environmental samples without bacterial cultivation. These techniques have revealed vast phage diversity in agricultural soils and plant surfaces, representing untapped biocontrol resources. High-throughput sequencing and bioinformatics can rapidly identify phages with desirable characteristics, accelerating development of improved cocktails for specific pathogens.

7. Conclusion

Bacteriophages represent a promising sustainable approach to managing bacterial diseases in agriculture, offering advantages over conventional chemical pesticides including specificity, environmental safety, and organic production compatibility. Current evidence demonstrates effective disease reduction in various crop systems, with commercial products available for bacterial spot, fire blight, and other diseases. Successful implementation requires addressing challenges including bacterial resistance, environmental stability, application technology, and regulatory frameworks. The future lies in integrating multiple strategies: diverse phage cocktails for broad spectrum activity, protective formulations for environmental persistence, combination with complementary biocontrol methods, genetic engineering to improve performance, and incorporation into precision agriculture platforms. As global agriculture transitions toward sustainability, bacteriophages will increasingly play important roles in integrated pest management strategies balancing productivity, sustainability, and food safety objectives.

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