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Bacteriophages in green agriculture

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80%

The share of fund-raisings targeted at animal feeds, with the balance for biological pesticides

46

The number of investors in agri-food companies developing phages solutions

The Technology

Bacteriophages ("phages") have growing applications in agriculture, including as biological pesticides and natural feed additives. Phages are viruses that infect and replicate within bacteria specifically. They can bind to specific lipopolysaccharides and proteins that are expressed on the surface of bacterial cells, which then allows them to infect and destroy these. Animal cells do not express Lipopolysaccharide capsules, so phages are not able to adhere to and infect animal or plant cells, making them a highly selective, and safer pesticide.

As with some other agtech life science innovations, phages have an original history in medicine, now being turned to use in agriculture. Phages were used in 1920 before antibiotics to treat infections, but antibiotics became more popular, in part due to a lower cost of manufacture and storage. As antibiotic resistance rises, phage therapy is once again becoming more popular in medicine, to treat antibiotic resistant bacteria. Following are some examples of products and applications in the agriculture space:

1. **Biological pesticides -** Phages can be used to control bacterial plant pathogens that cause diseases. Each phage type targets specific bacteria, leaving non-target organisms unharmed. Phages can be applied directly to crops, for example, sprayed onto plants or used in irrigation systems to control bacterial diseases like bacterial spot, soft rot, or canker. Examples:
   - OmniLytics manufactures a phage that targets bacterial diseases in crops, particularly targeting pathogens like Xanthomonas and Pseudomonas, which affect tomatoes, peppers, and other vegetables. Phages can be applied to crops, infecting and destroying harmful bacterial pathogens without affecting the plants or beneficial bacteria in the soil.
   - EcoPhage has developed phage-based crop protection solutions to manage bacterial plant diseases. The company's platform comprises screening and characterization of phage collections, resulting in the selection of most promising candidates, which form the basis for phage cocktails for antimicrobial crop protection.
2. **Natural Feed Additives** - Phages are also being explored as natural additives in animal feed, particularly in livestock farming, to promote gut health by targeting harmful bacteria. Phages targeting Salmonella or E. coli in poultry or cattle help reduce bacterial infections without the use of antibiotics, lowering the risk of antibiotic resistance transfer to humans through the food chain. Examples:
   - Proteon Pharmaceuticals focuses on phage-based solutions to improve livestock health, primarily in poultry, aquaculture, and cattle. Their flagship products, like BAFASAL® and BAFADOR®, are bacteriophage feed additives designed to combat specific pathogens such as Salmonella and Aeromonas.
   - Cytophage Technologies Inc develops customized phage therapies to address bacterial pathogens in poultry, specifically targeting antibiotic-resistant bacteria.
   - PhageLab says it develops phage-based treatments that control and eradicate bacteria in the poultry, livestock and aquaculture industries, reducing the need for antibiotics.

Efficacy

Bacteriophages are a promising area of research, but they do have some limitations when compared to chemical interventions. Since they are not as widely available, they tend to cost more and are more specific to a given pest, and so may have to be applied in conjunction with wide-spectrum chemical or antibiotic products. Another hinderance is the shelf life of live microbes, which may need to be stored at low temperatures, and in highly controlled environments. In addition, bacteriophages can suffer from resistance within the target bacterial population. Xanthomonas campestris, a bacteria linked with the bacterial spot disease of pepper and tomato, now has several strains, each requiring application of different phages.

Regarding specific efficacy data, one of the first phages used to treat bacterial infections in plants was OmniLytics Inc's Agriphage, used to treat bacterial spot in tomatoes and peppers. The company observed 58% infected leaves in a phage-untreated group, compared with 22% infected leaves in a phage-treated group, in trials where the plants were inoculated with the pest bacteria.

A particular feature of phages is their ability to penetrate bacterial biofilms, and thereby destroy these. A 2011 study of bacteriophages used against C. jejuni, a common poultry-based bacteria, showed after phage application there was a 1- 2.5 log10 CFU/cm2 decrease in viable bacteria. However, of the remaining bacteria, some 85-90% was resistant to the phage.

Environmental Benefits

Using bacteriophages in agriculture as biological pesticides, natural feed additives, and antibiotic-free interventions offers environmental and social benefits. These technologies reduce the need for chemical pesticides and antibiotics, minimizing soil and water pollution while lowering the risk of developing antibiotic-resistant bacteria. Phages target harmful pathogens without disrupting beneficial organisms, preserving biodiversity, enhancing soil health, and supporting regenerative farming practices. While there are some harmful bacteria in the soil, most are essential for soil health, such as Pseudomonas and Rhizobium bacteria, which produce vitamin B12, in turn absorbed by plants and consumed by animals.

Regulation

The main driver for the adoption of bacteriophages is growing regulation on antibiotic use. Following is a brief review of applicable regulation:

- The European Union's Ban on Routine Antibiotics in Farming has enacted strict regulations (e.g., Regulation (EU) 2019/6) that prohibit the use of antibiotics for routine disease prevention in healthy animals. As of 2022, the law also restricts the import of animal products from countries that use antibiotics as growth promoters.
- In the United States, the Veterinary Feed Directive (VFD), implemented by the FDA (Food and Drug Administration), restricts the use of medically important antibiotics in animal feed and water, except where deemed necessary by a licensed veterinarian, and aims to curb routine antibiotic use and bring this under veterinary supervision.
- In Britain, under Targeted Reduction Goals, the Veterinary Medicines Directorate (VMD) has established reduction targets for antibiotics in livestock, aiming for further reductions by promoting disease prevention measures (like vaccination) and the development of alternatives.
- In China, a Ban on Antibiotic Growth Promoters in 2020 applies to domestic livestock production.
- Meanwhile, the the World Health Organization's Global Action Plan on Antimicrobial Resistance encourages countries to implement policies that reduce the misuse of antibiotics in humans and animals, promoting research into alternatives. And the World Organisation for Animal Health provides guidelines that encourage judicious use of antimicrobials, and the development of alternatives to support global food security and public health.

Figure 1. The technology of Bacteriophages in agriculture

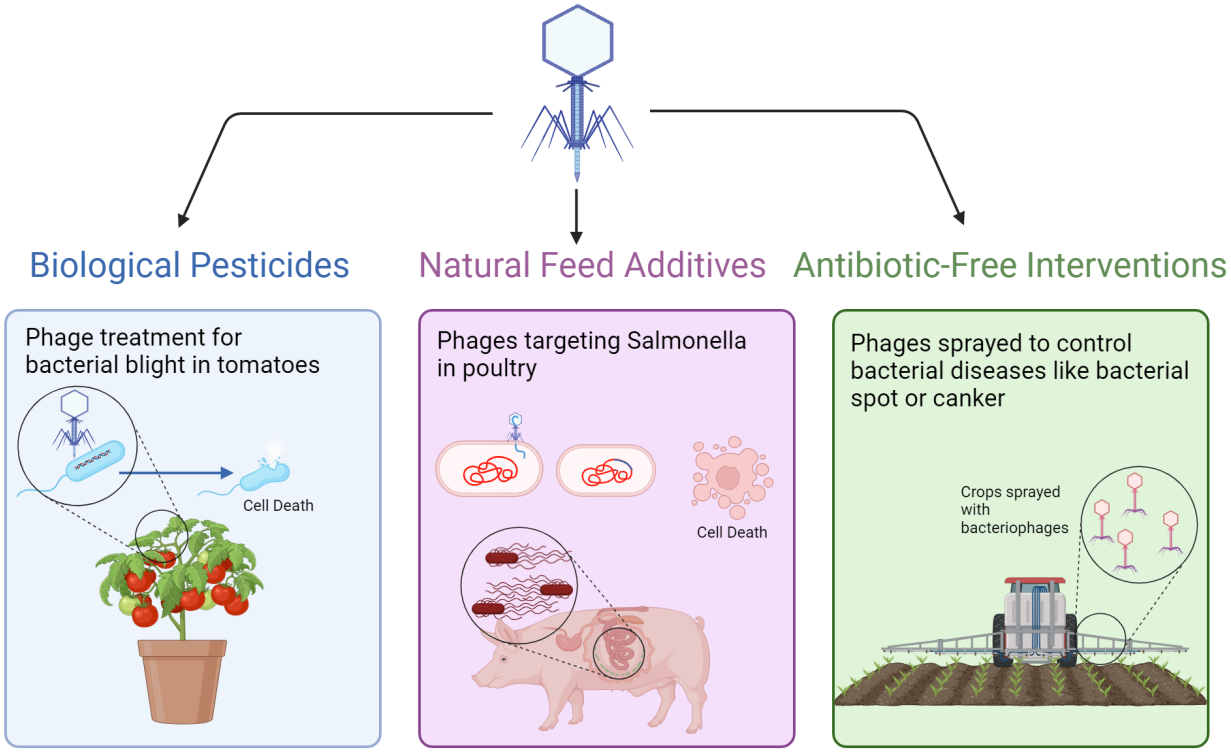

Figure 2. Phage life cycle