

Phage Power: Harnessing Bacteriophages to Control Bacterial Diseases in Aquaculture

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ABSTRACT

Aquaculture is one of the fastest-growing food production systems globally. However, diseases are a key constraint to sustainable aquaculture production systems. Certain bacterial pathogens, e.g., *Aeromonas*, *Vibrio*, *Flavobacterium*, and *Streptococcus*, cause notable economic losses in fish and shellfish farming. Conventional treatments for these diseases include antibiotics. However, their misuse is resulting in antimicrobial resistance, pollution of the environment, and possible hazards to human health. Hence, eco-friendly options for sustainable aquaculture production systems are urgently needed. Bacteriophages are viruses that specifically target and kill bacterial cells. Phage therapy is a method for using bacteriophages for the treatment of bacterial diseases in aquaculture production systems. Phages are viruses that target specific bacterial pathogens while leaving other harmless microbes intact. Several researchers have shown that phage therapy can reduce disease-causing bacteria in aquatic animals and increase their survival rates. Phages are naturally present in aquatic systems and can replicate in infected tissues. Phages are thus an eco-friendly option for sustainable aquaculture production systems. Though bacteriophages have limitations in their use for aquaculture production systems, their use in phage therapy is promising for sustainable aquaculture production system.

INTRODUCTION

Over the years, aquaculture has recorded tremendous growth, making it one of the most significant industries of food production worldwide. This sector is of paramount importance for the production of high-quality protein, nutrients, and employment for millions of people across the globe. As the production of aquaculture is increasing to fulfill the requirements of the increasing demand for seafood, there are various challenges associated with it, among which one of the most significant challenges is the outbreak of diseases. Bacterial diseases cause significant economic losses in aquaculture due to high mortality rates, decreased growth rates, and increased production costs. Pathogenic bacteria such as *Aeromonas* spp., *Vibrio* spp., *Edwardsiella* spp., *Flavobacterium* spp., and *Streptococcus* spp. are some of the most commonly occurring infectious diseases of cultured fish and shellfish. These pathogenic bacteria can cause severe diseases such as hemorrhagic septicemia, ulcer disease, vibriosis, and streptococcosis, which can cause mass deaths of cultured fish and shellfish (Nokhwal *et al.*, 2023). Antibiotics have been the dominant form of controlling and preventing bacterial infections in aquaculture for several decades.

Though antibiotics are known to produce rapid therapeutic results, the improper and uncontrolled use of antibiotics has led to a number of adverse consequences, such as the development of antibiotic-resistant bacteria, antibiotic residues in aquatic ecosystems, and potential health hazards to human beings via the food chain (Oliveira *et al.*, 2012). Antimicrobial resistance has emerged as a worldwide issue, and scientists and aquaculture experts are working towards finding alternative measures for controlling bacterial diseases in aquatic organisms. Bacteriophage therapy has emerged as a

promising alternative, and its potential in controlling bacterial diseases with minimal impact on the aquatic environment has drawn significant attention from scientists and experts in the field. Bacteriophages are a family of viruses that are known to infect and lyse bacterial cells.

Bacteriophages: Natural Predators of Bacteria

Bacteriophages, or phages for short, are viruses that specifically target bacteria. They are believed to be the most abundant form of life on our planet, with a population size estimated to exceed 10^{31} in different ecosystems, including marine and freshwater systems (Liu *et al.*, 2022). Phages occur naturally in aquatic environments, including seawater, sediments, and fish microbiota. Phages are important in microbial communities because of their wide distribution and their ability to regulate bacterial populations. Unlike antibiotics that target both harmful and beneficial microbes in an ecosystem, bacteriophages have a high degree of specificity and target specific bacterial strains.

The bacteriophage virus is composed of a protein coat called a capsid that contains genetic material in the form of DNA or RNA. Most phages have a tail that helps in attaching to and injecting their genetic material into bacterial cells. Once inside their host bacterium, phages use their host's metabolism to replicate and produce new phages.

Because of their ability to target specific bacteria and replicate in their host cells, bacteriophages have been researched for their use as a tool in controlling bacterial diseases in aquaculture systems.

Mechanism of Bacteriophage Infection

The interaction between bacteriophages and bacteria occurs via a particular infection cycle. The two cycles are the lytic cycle and lysogenic cycle.

Lytic Cycle

The lytic cycle is an essential component of the bacteriophage infection mechanism. This cycle is involved in bacteriophage therapy. In this cycle, a bacteriophage binds to a receptor on a bacterial cell surface and injects its DNA into the cell. The bacteriophage utilizes the metabolic machinery of the bacterial cell to synthesize viral components such as DNA and proteins.

These components assemble into a new bacteriophage particle within a bacterial cell. Finally, the bacterial cell membrane ruptures, and a new bacteriophage particle infects other bacterial cells. This cycle results in the elimination of pathogenic bacteria and increases the concentration of bacteriophages at an infection site.

Due to this ability to replicate and lyse pathogenic bacteria, lytic bacteriophages are used in bacteriophage therapy applications.

Lysogenic Cycle

In this cycle, bacteriophage DNA integrates into a bacterial cell and replicates with it. This cycle does not result in cell lysis. However, if certain environmental conditions occur, this cycle proceeds to the lytic cycle. Lytic bacteriophages are used for therapy because they lyse pathogenic bacteria.

Application of Phage Therapy in Aquaculture

Phage therapy is a technique used to treat or control bacterial infections in aquatic animals using bacteriophages. Over the years, numerous studies have demonstrated the

potential of phage therapy as an effective technique for controlling bacterial infections in aquaculture. Phages have been found to effectively target and control certain bacterial infections that affect aquaculture, such as *Aeromonas hydrophila*, *Vibrio harveyi*, *Flavobacterium columnare*, *Edwardsiella tarda*, and *Pseudomonas*, which cause significant diseases in aquaculture.

For example, studies have demonstrated that phage therapy can effectively reduce mortality rates resulting from infections by *Aeromonas hydrophila* in freshwater fish. In a study, it was found that phage therapy administered via immersion and injection effectively protected fish from infection by *Aeromonas hydrophila* if administered shortly after infection. The study showed that mortality rates were reduced by 80% by administering a cocktail of bacteriophages via immersion and injection (Kumari *et al.*, 2023).

Moreover, meta-analysis studies have found that bacteriophages can effectively increase survival rates in aquaculture animals infected with bacterial pathogens. The effectiveness of phage therapy depends on certain factors, such as MOI and duration of treatment, and methods of administration (Yang *et al.*, 2024). Even though numerous studies have been conducted in a controlled environment, the promising results indicate that phage therapy has the potential to be an important aspect of sustainable disease management in aquaculture.

Advantages of Phage Therapy

Bacteriophage therapy has various advantages over traditional antibiotic therapy. The first and foremost advantage of bacteriophages is their high degree of specificity. Bacteriophages have a high degree of specificity for their host cells and do not affect the beneficial microorganisms present in the aquatic environment and fish.

Another important advantage of bacteriophages over traditional antibiotic therapy is their ability to replicate in bacterial cells. Bacteriophages, after infecting the host cells, multiply and propagate to adjacent bacterial cells, thus increasing their efficacy in the infected cells. This reduces the need for repeated dosages of bacteriophages.

Bacteriophages have been found to be effective in treating diseases caused by antibiotic-resistant bacteria. Another important advantage of bacteriophages is their natural presence in the aquatic environment, which makes them environmentally safe. Unlike antibiotic therapy, bacteriophages do not leave behind any chemical residues in the aquatic environment and fish. All these advantages make bacteriophages potential substitutes for antibiotic therapy in aquaculture systems (Nakai and Park, 2002).

Challenges in Phage Therapy

Despite the potential of bacteriophage therapy, there are many challenges that need to be addressed for the successful implementation of bacteriophage therapy in aquaculture practices. One of the challenges is the limited host specificity of bacteriophages, which means that only particular bacteriophages can infect specific bacterial strains. To address this challenge, bacteriophage cocktails can be used, which consist of different bacteriophages that can target different bacterial pathogens. Another challenge associated with bacteriophage therapy is the possibility of phage-resistant bacterial strains emerging. Therefore, there are many challenges associated with bacteriophage therapy, which need to be addressed for the successful implementation of bacteriophage therapy in aquaculture practices (Liu *et al.*, 2022; Yang *et al.*, 2024).

Future Prospects

The prospects for the use of bacteriophage therapy in aquaculture look promising as more scientific studies are carried out on new techniques that can enhance the use of this therapy. Advances in molecular biology have helped in the identification of new bacteriophages with better antibacterial properties. The use of bacteriophage cocktails, genetically engineered bacteriophages, and the use of delivery systems can help in overcoming the limitations of bacteriophage therapy. In addition, the use of this therapy in combination with other techniques such as vaccination, the use of probiotics, and better aquaculture practices can provide an integrated approach for the sustainable management of aquaculture (Nokhwal *et al.*, 2022; Yang *et al.*, 2024).

CONCLUSION

Bacteriophage therapy is an innovative and eco-friendly strategy for the management of bacterial infections in aquaculture systems. As bacterial parasites, bacteriophages can be effectively employed as an alternative to conventional antibiotics to mitigate the risks of antimicrobial resistance.

Despite the challenges that still exist in the large-scale application of bacteriophage therapy, the effectiveness of the therapy in the management of bacterial infections in fish has been proven through scientific studies. With the prospects of scientific breakthroughs in the field, the application of bacteriophage therapy may be integrated into the management of bacterial infections in fish in the future.

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