**Bacteriophage Therapy: A Shift Towards Sustainability in the Management of Bacterial Diseases in Aquaculture**

**Abstract:**

Aquaculture is a growing industry that contributes to the food supply both locally and regionally. The industry has to contend with serious issues such as antibiotic-resistant bacteria and other infections which pose severe economic threats. In aquaculture, bacteriophage therapy, which uses viruses that infect and kill specific bacteria, is now considered an alternative to antibiotics. This review summarize the current state of research on the use of phage therapy in aquaculture with emphasis on the isolation and characterization of aquaculture specific phages and their actions, and the role of such phages in disease prophylaxis and therapy. Additionally, this review discusses the issues and prospects of using phages therapy for the sustainable development of aquaculture.

**Keywords:**Bacteriophage therapy, aquaculture, antibiotic resistance, infectious diseases, host specific

**Introduction**

Aquaculture is the farming of aquatic animals such as fish, shellfish, aquatic plants etc and, has been a rapidly rising industry in recent decades. It is one of the major source of food for human consumption and is a valuable contributor to the global economy. It plays a vital role in global food production with an important source of protein for human use (Boyd et al., 2022). Nevertheless, the increase in aquaculture practices has also seen an upsurge in the occurrence of bacterial infections, which present great challenges to the productivity and sustainability of the aquaculture industry. Antibiotics have been the traditional means of managing bacterial disease in aquaculture; however, the development of antibiotic-resistant bacteria has raised issues regarding the long-term effectiveness and environmental effects of antibiotic use in aquaculture.

Bacteriophage or phage therapy is an encouraging alternative to antibiotics, which targets the specific bacteria selectively and has minimal chances of resistance development. Phages presents a specific targeted and environment friendly option, which infect and kill only the targeted bacterial species (Viertel et al., 2014). Bacteriophages are viruses that only infect and kill specific bacteria. Phages are considered to be the the most ubiquitous micro-organisms and known to inhabit all environments, including aquatic ecosystems. Bacteriophages are highly specific, in that they infect particular bacterial species or strains, with no harm to other beneficial bacteria or non-target bacteria. This makes them an appealing choice for application in aquaculture since they can specifically target and destroy pathogenic bacteria without harming beneficial bacteria or the environment. Phage therapy has been used in the treatment of bacterial infections in animals for many years. However, the use of phage therapy in aquaculture has only been studied in the past two decades. The first documented application of bacteriophages in aquaculture was in 1999, in Japan, when phages were applied to treat *Lactococcus garviae* infection (Nakai et al., 1999). Ever since, several research studies have been performed in order to assess the effectiveness of phage therapy in various aquaculture species as well as against several bacterial diseases.

Bacteriophages provides a possible substitute for antibiotics in the fight against bacterial infections in fish. Considerable interest has arisen for the use of bacteriophages in treatment following the emergence of antibiotic-resistant bacteria that require new management approaches (Patey et al. 2018). Despite the fact that some regions of the world have historically employed bacteriophage therapy, it is still largely unrecognized in the Western world (Verbeken et al. 2014). Nonetheless, there is an increasing need to include bacteriophages in the therapeutic armamentarium, either as alternatives or complements to antibiotics (Patey et al., 2018). The importance of bacteriophages is that they are specific to target bacterial pathogens, which can assist in addressing the problem of broad-spectrum antibiotic resistance (Wittebole et al., 2013). The extensive genomic variability of bacteriophages, as revealed by high-throughput sequencing, emphasizes their potential to serve as multifaceted therapeutic agents (Putzeys, 2024). In addition, the creation of bacteriophage-derived delivery platforms further expands their utility in many disciplines, such as medicine (Fu & Li, 2016). The essential step towards the use of bacteriophages in medicine is implementing a regulatory framework that oversees their production and application as highlighted by Dublanchet et al. in 2018. Phage therapy is associated with some risk without proper regulation, so it must be monitored to ensure its safety and effectiveness. In addition, advancement in genetic engineering techniques, such as those involving bacteriophage recombinases, have enabled targeted manipulation for research and therapy purposes (Husseiny & Hensel, 2005).

**Bacteriophage Isolation and Characterization**

The isolation and characterization of a bacteriophage is very important towards understanding their diversity, specificity, and possible applications. The different studies emphasize the advances in the phages isolation technique, genomic analysis, and therapeutic evaluation as the major contributors to the integration in the field of medicine, agriculture and biology health with bacteriophage use. Diverse and specific aspects of bacteriophage isolation and characterization has been the subject of study by various researchers. The isolation processes of phages is done using several techniques such as membrane filtration, precipitation, and enrichment (Ghugare et al., 2018; Khan & Joshi, 2022). These methods are mainly employed to enrich and purify bacteriophages from effluent samples such as sewage, soil, fish or clinical isolates. After the bacteriophages are isolated, their lytic activity, host range, morphology, and genomic features are determined (Santos et al., 2010). For example, Santos et al. (2010) reported the isolation of genetically distinct bacteriophages from strains of *Escherichia coli* in postpartum dairy cows suggesting the need to understand the diversity of bacteriophages within a bacterial species.

Studies has also highlighted the need on the specificity and efficacy of the action of bacteriophages. For example, Tan et al. (2021) demonstrated the ability to isolate lytic bacteriophages from seafood sample specific to *Vibrio parahaemolyticus* proving the need for isolation of targeted bacteriophages for particular bacterial pathogens. The advances in genomic sequencing and bioinformatics have also improved the phage discovery and characterization, enabling their targeted use in aquaculture to a greater extent.

**Mechanisms of Action**

Bacteriophages employ a number of strategies to infect and lyse bacterial cells, including lysis in the form of enzyme release and disorganization of the bacterial cell membrane. Phages are used in aquaculture and can be administered via feed or bath, wherein they seek out and infect the pathogenic bacteria in the water or in the host organism (Ramos-Vivas et al., 2021). Upon entering the bacterial cell, phages multiply and discharge progeny virions, which further infect and lyse adjacent bacterial cells. The host specificity of phages reduces the effect on beneficial bacteria and minimizes the risk of upsetting the ecological balance of the aquaculture system.

In order to harness their full therapeutic potential, it is crucial to comprehend how bacteriophages associate with their bacterial hosts. The intricacies of bacteriophage therapeutic utilization have been studied such as how bacteriophages invade and engage cells of the innate immune system. Carroll-Portillo & Lin (2019) revealed the importance of such interactions, gaining insight into the possible importance of bacteriophage-immune system interactions. Talapko & Skrlec (2020) highlighted the role of antimicrobial peptides in enabling the action of bacteriophages as part of more complex mechanisms of phage therapy.

The debate on the use of bacteriophages for treatment of infections caused by bacteria, including multi-drug resistant bacteria, has been very active. Palaniappan & Dayanithi (2021) provided a detailed review of biology of bacteriophages, their infectivity, and possible use of their therapeutic aspects. Dkhili et al. (2021) highlighted the importance of understanding the relationships between phages and bacteria as a crucial step before employing phages in phage therapy. Analyses have also been conducted into the molecular mechanisms of interactions between bacteriophages and bacteria. Debarbieux (2014) examined the molecular interaction that exists between bacteriophages and their host, explaining how the bacteria defend against phage infections and how phages defend against bacterial defences. Ye et al. (2020) uncovered the structural and biochemical processes of a certain bacteriophage immunity mechanism observed in different bacteria and described the spectacle of interplay between phages and their bacterial hosts. Herrlich et al. (1974) examined the bacteriophage T7-induced translational control, revealing its specificity and mechanism. Furi et al. (2019) also examined the complex relationship between bacteriophages and the host defences mechanisms in *Streptococcus pneumoniae*, revealing the molecular characterization of phage infections.

**Bacteriophages Applications in Disease Prevention and Treatment in Aquaculture**

Bacteriophages are emerging as potential agents for disease prevention and treatment in aquaculture. Various researchers have investigated the possible uses of bacteriophages to control bacterial diseases in aquaculture. The application of bacteriophages as a therapeutic agent in aquaculture has been found to be effective in controlling bacterial pathogens and minimizing the use of antibiotics, which is very important in the case of growing antibiotic resistance (Kowalska et al., 2020). Studies have proved the efficacy of bacteriophages to manage a range of bacterial pathogens in aquaculture conditions. Investigations have pointed to the effective use of bacteriophages in the treatment of disease caused by pathogens such as *Vibrio harveyi, V. parahaemolyticus*, and *Aeromonas hydrophila* among fish and other aquatic animals (Lal et al., 2016; Silva et al., 2014; Wang et al., 2017). Bacteriophages are also capable of regulating immunological parameters and increasing survival rates following challenge in rainbow trout, thereby signifying the prospect of utilizing them as a prophylactic treatment against bacterial infection (Schulz et al., 2019).

The evolution of bacteriophage therapy has recently been an area of interest in which its implications in eliminating bacterial infection in the food and aquaculture sectors are considered (Raza et al., 2021). The application of lytic phages to prevent and treat vibriosis in aquaculture has been identified as a promising technique (Kalatzis et al., 2018). Phage therapy has been suggested as an alternative or complement to antibiotic therapy in aquaculture and was shown to be effective in controlling bacterial infections and lowering bacterial contamination in aquaculture systems (Xu et al., 2022). The use of bacteriophages in aquaculture has been linked to lower antibiotic residues and the possibility of treating bacterial diseases effectively (Soliman et al., 2019). Additionally, phage therapy was used for inhibiting *V. anguillarum* infection in fish larvae culture, highlighting the need to choose effective phages and administration routes for effective disease management across various aquaculture environments (Silva et al., 2014). Kowalska et al. (2020) also highlighted the increasing trend of bacteriophage use in aquaculture, emphasizing the prospects and challenges of phage therapy in the fight against bacterial diseases. The use of bacteriophages in aquaculture is applied to different fish species and pathogens. In addition, Tan et al. (2015) examined the effect of vibriophages on biofilm formation by *V. anguillarum* strains, highlighting the potency of phages in interfering with bacterial biofilms under aquaculture conditions.

The phages applications in bacterial disease control and treatment in aquaculture highlights the potential of phage therapy as a valuable resource in the fight against bacterial pathogens and ensuring sustainable aquaculture. The evidence indicates that bacteriophages hold great promise as an alternative to antibiotics, and have the potential to control bacterial infections and improve the overall health and productivity in aquaculture.

**Challenges and Future Directions**

The application of phages in aquaculture has not been adopted in large scale due to various challenges such as proper identification of phages with desirable properties for use in aquaculture, standardization of phage production and administration methods, and regulatory approval of phage products (Droubogiannis & Katharios, 2022). Yet, the promise of bacteriophage therapy as a substitute or adjunct to antibiotic use in aquaculture is clear, and further investigation and development are warranted here. More research must be conducted on the effects of phage therapy on the ecological dynamics of aquaculture systems and on the development of phage resistance in bacterial communities. Future research directions in bacteriophage therapy involve the development of phage-derived enzymes for use in biocontrol and phage-based biofilms for long-term antibacterial action in aquaculture.

**Conclusion**

Bacteriophage therapy has immense potential for controlling bacterial disease in aquaculture. Phages provide a targeted and non-chemical alternative to antibiotics, the ability to decrease chemical intervention dependency and the potential to slow down the development of antibiotic resistance. With continued scientific progress and collaboration, phage therapy has the potential to alter disease management approaches and secure the future of the aquaculture industry. In conclusion, phage therapy offers a promising solution in treating bacterial infections in aquaculture. Its application is still limited and requires extensive research and development, however, the prevailing directions indicate a growing tendency for employing the use of bacteriophages as a viable means to control bacterial diseases in aquaculture.

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