Phage Therapy in Aquaculture Management

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Therapeutic bacteriophages, commonly called as phages, are a promising potential alternative to antibiotics in the management of bacterial infections of a wide range of organisms including cultured fish. Their natural immunogenicity often induces the modulation of a variated collection of immune responses within several types of immunocytes while promoting specific mechanisms of bacterial clearance.

Keywords: aquaculture ; bacteriophages ; disease management ; fish ; immunology ; lytic enzymes ; pathogens

1. Phage Biology and Spatial Distribution

Bacteriophages or phages, in short, are an alternative to antimicrobials to fight against bacteria due to their unique host range that provides them with an excellent specificity. In addition, contrary to the antibiotic's negative physiological effects on the host and the generation of bacterial resistance, the use of phages is eco-friendly and without major drawbacks [1][2]. Besides, phages produce lytic enzymes with the ability to act directly on the bacterial cell wall. An important associated advantage is that phages are ubiquitous to all fresh and saltwater environments representing a virtually unlimited source of virions and lytic enzymes. In seawater, the number and variety of phages have a direct and crucial impact on the variability of microbial communities which directly modulate the global biogeochemical cycles in the oceans [3][4]. Quantitative analyses of marine waters using transmission electron microscopy demonstrated that non-tailed viruses are the most abundant, followed by tailed viruses of the families Myoviridae and Podoviridae [5]. This example represents a huge gene reservoir across Earth's ecosystems. Despite the great awakening interest in phage therapy and the discovery of a vast reservoir of new genes available in the phages of aquatic ecosystems, the composition the phage populations in the different fish species in aquaculture, either from freshwater or saltwater environments are not yet fully understood.

2. Phage's Life Cycle

The phages like any other viruses depend on the metabolism of their bacterial host for reproduction. During the reproductive process, most phage types completely consume the resources of their host and kill them when releasing their progeny [6]. Initially, phages must infect their host bacteria through the binding of specific receptors that selectively sense specific components of the target bacterial cell wall such as the lipopolysaccharide in Gram-negative, or peptidoglycan in Gram-positive, capsular polysaccharides, and superficial appendages such as pili and flagella [7][8][9]. Following the classical viral reproductive strategies, once the phage inserts their nucleic acid into the bacterium's cytoplasm, the host cellular machinery is highjacked to induce extensive replication through the lytic cycle (**Figure 1**). Alternatively, a phage also has the capacity to insert its genetic information into the genome of the host bacterium, thus becoming a prophage. The process of prophage incorporation into the host chromosome is called lysogenization, and the resulting bacterium with the prophage is called a lysogen. Therefore, the genetic material of the prophage is transferred to each daughter cell through cell division following the lysogenic cycle (**Figure 1**). A huge advantage associated with the lysogenic cycle is that daughter cells will not produce new virus particles until conditions are favorable for the virus or some external stimuli stress the cell and activate the highjacked genes. An additional less known phage reproductive cycle is the so-called pseudo-lysogenic. In the pseudo-lysogenic type, the information encoded by the genome of the phage is not translated immediately, perhaps due to the lack of nutrients and energy for the bacterium. However, it remains inactive inside the host, waiting until the optimal conditions recover for the bacterium to restart its metabolic processes. Then, the phage has the capacity to start again performing the lytic or lysogenic life cycles [10].

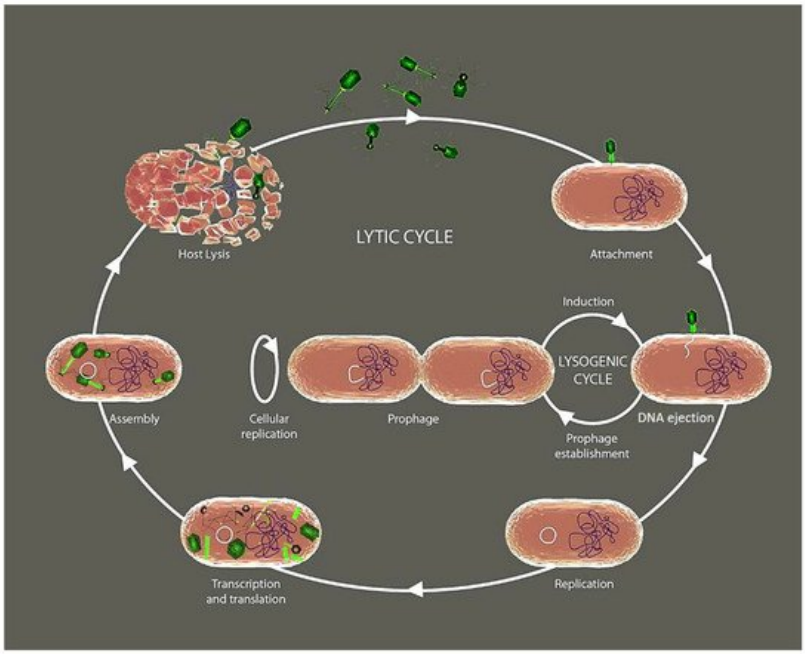

Figure 1. The lytic and lysogenic cycle of bacteriophages. The lytic cycle comprises a series of events from attachment of the bacteriophage to the bacterial cell membrane, to the release of daughter phages by the destruction of its bacterial host. In the lysogenic cycle, phage DNA integrates into the bacterial genome without major consequences for the bacterial cell, and where the nucleic acid of the virus replicates along with that of its host.

3. Phage Lytic Enzymes and Depolymerases

Lysins derived from phages degrade bacterial peptidoglycans and are classified into five groups, depending on the bonds these enzymatic proteins cleave in the bacterial peptidoglycan [11]. Although their function is exclusively to degrade the cell wall of bacteria, the lytic enzymes of phages present a tremendous structural diversity and a significant number of different mechanisms of action [12][13][14][15].

In general, lysins are more likely to lyse Gram-positive bacteria because their cell wall peptidoglycan is directly exposed on the cell surface unlike Gram-negative bacteria. However, the study of phages or their lysins has been limited to a few fish pathogens such as Streptococcus agalactiae, Lactococcus garvieae, Renibacterium salmoninarum, Streptococcus iniae, and S. dysgalactiae, which are highly associated with disease outbreaks in fish farms.

4. Interactions between Phage and the Fish Immune System

4.1. Phage-Mediated Activation of Inflammation

Bacteriophage treatment was associated with opposite shifts in the inflammatory response in several test models, both in vivo and in vitro [16][17][18][19]. However, the results seem to depend not only on the cellular or animal model used but also on the type of phage applied and the panel of cytokines analyzed. Phage therapy in humans can also modify the levels of some cytokines produced by blood cells in treated patients [20]. In fish, some researchers have analyzed the cytokines' response to the presence of bacteriophages alone or the coinfection of phages with their target bacteria. For example, phage therapy reduced the expression of the proinflammatory cytokines tnfa and il1b in the inflammatory response generated by Pseudomonas aeruginosa infection in zebrafish embryos [21][22]. Besides, using the adult zebrafish (Danio rerio) and the E. tarda model of infection, other authors also showed that although a phage treatment induced the expression of cytokine genes at specific time points, a robust proinflammatory response was undetected in the host [23]. Furthermore, a recent study has shown that a phage lysate of A. hydrophila induced a more robust immune response in Cyprinus carpio when compared to a formalin killed vaccine [24]. As a proof-of-concept, a novel commercial preparation containing three bacterial phages (BAFADOR®) applied on European eel (Anguilla anguilla) caused the stimulation of cellular and humoral immune parameters in response to an experimental challenge with A. hydrophila and P. fluorecense [25].

4.2. Phage-Specific Adaptive Responses

Due to the protein structure of the phage envelope, these proteins are the target of the adaptive immune system, which response with the production of neutralizing antibodies against them. Early studies with mice and even amphibians

showed that phage exposure of the animals induced primary and secondary antibody responses [26][27][28]. It is expected that some phage epitopes stimulate an antibody response in experimental models. However, antibody production depends on the route of phage administration, the application schedule and dose, and individual features of a phage. Consequently, the results of studies where an antibody response to phages has been verified are very heterogeneous. Phagocytosis by immune patrolling cells seems to be a significant process of bacteriophage neutralization within animal bodies [29]. Moreover, although blood in humans and animals, including fish, is deemed sterile, genomic analysis has shown a rich phage community, which inevitably comes into continuous contact with immune cells in this rich fluid [30]. Despite these mechanisms of phagocytosis, antigen presentation, and antibody production by the immune cells against phages, the number of antibodies produced does not affect phage therapy outcomes.

On the other hand, due to the numerous and constant presence of large numbers of phages in our microbiota, it is not surprising that a low but stable background of antibodies against them is produced. Therefore, in some human or animal tests, high antibody levels have not been found against the phages used. Phage-derived RNA and ssDNA could directly contribute to B cell activation and the synthesis of anti-bacteriophage antibodies [31][32]. Despite the production of antibodies by animals against phage core or tail proteins, the induction of antibodies seems irrelevant for treating infections because the antibacterial effects of phages are faster than antibody formation in acute infections [33]. Conversely, the production of antibodies against phages could interfere with the outcome of the infection in chronic infections [34]. However, no robust studies have demonstrated an antibody-mediated immune response after inoculation or experimental infection with phages in fish.

5. Potential of Phage Therapy in Aquaculture Settings

During the fish and shellfish production cycle, these animals are already in daily contact with billions of bacteriophages, which assures us that they are safe. However, in their use against bacterial infections where massive phage production is required, we must consider several factors.

As phage treatments constantly require isolating the bacterium causing the disease, once a helpful phage is characterized against this bacterial strain, a stable batch of technically challenging preparations must be produced for field use. Consequently, one of the most critical challenge for microbiologists working directly or indirectly with aquaculture is the standardization of stocks used to treat infections or combat biofilms in aquaculture facilities. These stocks require strict quality control for purity, viability, and stability, implying that the correct conservation of the stocks is necessary for preparations containing single or mixed phages (phage cocktail). Titer, dosage, and quality of phage preparations are crucial parameters in standardizing experiments in the laboratory and experimental infections in field trials. Since we know that while some phages can grow exponentially inside a bacterial population from a low initial concentration, other phages need to maintain a relationship between the number of bacteria and the number of phage particles to achieve an adequate performance. Therefore, we must empirically verify this critical parameter. Very recently, a phage cocktail containing seven bacteriophages (three against A. hydrophila and four against P. fluorescens) has been tested in the European eel (Anguilla anguilla) and rainbow trout (Oncorhynchus mykiss), reducing the mortality of fish challenged with strains of these two species of bacteria [25][35]. Cocktails have also been used successfully in laboratory tests or small field trials in food protection or veterinary and human medicine [36][37][38][39]. In these and other studies, many phages (cocktail) are used to carry out the experiments, but in most cases, only the phage that has presented better results in vitro is subsequently characterized [40][41][42][43]. Second, it would be desirable to know phage genetics with sufficient precision. After all, we must consider that when we intend to use bacteriophages in aquaculture, they may contain genes for resistance to antibiotics or bacterial virulence genes that can produce noticeable side effects because they replicate exponentially in contact with their target bacteria. We must also remember that many antibiotic residues end up in continental or oceanic waters due to anthropogenic activities. Therefore, we must be aware that even phages isolated from aquatic environments can carry antibiotic resistance genes or virulence factors [44][45]. At present, although each time their number increases, not all phages used in in vitro or in vivo assays against fish or shellfish bacterial pathogens have been entirely genetically analyzed or characterized (**Table 1** and **Table 2**).

The list of species of fish bacterial pathogens in which lytic phages have been studied is not complete. It may be essential to conduct these studies in species of greater interest in aquaculture, such as Photobacterium damselae subsp. piscicida, bacterial anaerobes, mycobacteria, Nocardia, several Aeromonas species, Enterobacterales, pseudomonads, vibrios, and the Gram-positive bacteria mentioned above. Few studies with fish bacterial pathogens have characterized or evaluated the presence or evolution of phage-resistant strains. Some works have investigated this phenomenon in various fish pathogens such as Flavobacterium [46][47][48], Yersinia ruckeri [49], Aeromonas salmonicida [40][50], and Vibrio anguillarum [51]. The mechanisms by which bacteria become resistant to phages is also an area of intensive research, especially since the discovery and application of the clustered regularly interspaced short palindromic repeats (CRISPR) system.

Most of the studies with fish pathogens have used controlled laboratory conditions to verify the control exerted by these lytic phages to their pathogenic bacterial host. However, more studies on these interactions under natural conditions would be desirable. One of the critical parameters is the multiplicity of infection (MOI). The use of high or low multiplicities of infection seems to be a key parameter for achieving effective lysis of the bacterial population and the appearance of resistance to the phages used. Therefore, comparative studies are needed to relate MOIs used in vitro and in aquatic environments, where phages are exposed to environmental conditions and factors such as dilution or variability of the target bacteria in their natural environment. A better understanding of the biology of viruses and a greater capacity to standardize the settings related to preclinical or laboratory research can also help in the advancement of regulatory affairs. As bacteriophage research continues to grow, we believe that microbiologists and immunologists working in areas related to aquaculture can use phages or their lytic enzymes to offer many promising advances in the fight against pathogenic bacterial species affecting cultured fish and shellfish.

Table 1. Phages used against Gram-negative bacterial fish and shellfish pathogens.

Gram-Negative Targets	Source	Enrichment ϕ	Characterization Method	Phage Strains Name	Family *	Genome Length	References
Aeromonas hydrophila	River water	No	TEM	ϕ2 and ϕ5	Myoviridae	~20 kb	[52]
	Fishponds; Polluted rivers	Single	TEM	N21, W3, G65, Y71 and Y81	Myoviridae; Podoviridae	n.d.	[53]
	Stream water	Single	TEM, dsDNA	pAh-1	Myoviridae	~64 kb	[54]
	Sea water	Single	TEM, DNA sequencing	Akh-2	Siphoviridae	114,901 bp	[55]
	Carp tissues	Single	TEM	AHP-1	Myoviridae	n.d.	[56]
	Lake water	Single	TEM, dsDNA, DNA sequencing	AhyVDH1	Myxoviridae	39,175 bp	[57]
	River water	No	TEM, dsDNA, DNA sequencing	MJG	Podoviridae	45,057 bp	[58]
	Sewage water	Single	TEM	AH1	n.d.	n.d.	[59]
	Striped catfish pond water	Single	TEM, dsDNA, DNA sequencing	PVN02	Myoviridae	51,668 bp	[60][61]
	River water		TEM, dsDNA	pAh1-C pAh6-C	Myoviridae	55 kb 58 kb	[62]
	Wastewater	No	TEM, dsDNA, DNA sequencing	Ahp1	Podoviridae	~42 kb	[63]
Aeromonas punctata	Stream water	Single	TEM, dsDNA	IHQ1	Myoviridae	25–28 kb	[64]
	River waters, two passing through fish farms	Single	TEM, DNA sequencing	SW69-9 L9-6 Riv-10	Myoviridae	173,097 bp, 173,578 bp and 174,311 bp	[65]
	River water	Single	TEM, DNA sequencing	phiAS5	Myoviridae	225,268 bp	[66]
Aeromonas salmonicida	Sediment of a Rainbow trout culture farm	Single	TEM, dsDNA, DNA sequencing	PAS-1	Myoviridae	~48 kb	[67]
	Wastewater from a seafood market	No	TEM, DNA sequencing	AsXd-1	Siphoviridae	39,014 bp	[68]
	Sewage network water from a lift station	Single	TEM	AS-A AS-D AS-E	Myoviridae	n.d.	[40][41]
	River water	No	TEM	HER 110	Myoviridae	n.d.	[69][70]

Gram-Negative Targets	Source	Enrichment ϕ	Characterization Method	Phage Strains Name	Family *	Genome Length	References
Aeromonas spp.	Gastrointestinal content of variated fish species	No	TEM, DNA sequencing	phiA8-29	Myoviridae	144,974 bp	[71][72]
Citrobacter freundii	Sewage water	No	TEM, DNA sequencing	IME-JL8	Siphoviridae	49,838 bp	[73]
Edwardsiella ictaluri	Water from catfish ponds	Single	TEM, dsDNA, DNA sequencing	eiAU eiDWF eiMSLS	Siphoviridae	42.80 kbp 42.12 kbp 42.69 kbp	[74][75]
	River water	Multiple	DNA Sequencing	PEi21	Myoviridae	43,378 bp	[76][77]
	Striped catfish kidney and liver	Single	TEM, dsDNA	MK7	Myoviridae	~34 kb	[78]
	Seawater	Single	TEM, dsDNA	ETP-1	Podoviridae	~40 kb	[23]
Edwardsiella tarda	River water	No	TEM, DNA sequencing	pEt-SU	Myoviridae	276,734 bp	[79]
	Wastewater	Single	DNA sequencing	PETp9	Myoviridae	89,762 bp	[80]
	Fish tissues and rearing seawater	No	TEM, DNA sequencing	GF-2	Myoviridae	43,129 bp	[81]
Flavobacterium columnare	River water	Single	TEM, DNA sequencing	FCL-2	Myoviridae	47,142 bp	[82][83][84]
	Fishpond's water and bottom sediments	No	TEM, dsDNA	FCP1-FCP9	Podoviridae	n.d.	[42]
Flavobacterium psychrophilum	Rainbow trout farm water	Single/double	TEM, dsDNA	ø (FpV-1 to FpV-22)	Podoviridae Siphoviridae Myoviridae	(~8 to ~90 kb)	[85][86]
	Ayu kidneys and pondwater collected from ayu farms	Multiple	TEM, dsDNA	PFpW-3, PFpC-Y PFpW-6, PFpW-7 PFpW-8	Myoviridae; Podoviridae; Siphoviridae	n.d.	[87]
Photobacterium damselae subsp. damselae	Raw oysters	Single	TEM, dsDNA	Phda1	Myoviridae	35.2–39.5 kb	[88]
	Gastrointestinal tract of lollipop catshark	Single	TEM, DNA sequencing	vB_Pd_PDCC-1	Myoviridae	237,509 bp	[89]
Pseudomonas plecoglossicida	Ayu pond water and diseased fish	No	TEM, DNA sequencing	PPpW-3 PPpW-4	Myoviridae Podoviridae	43,564 bp 41,386 bp	[90][91]
Pseudomonas aeruginosa	Wastewater	No	TEM, DNA sequencing	MBL	n.d.	42,519 bp	[92]
Shewanella spp.	Wastewater from a marketplace	Single	TEM, DNA sequencing	SppYZU01 to SppYZU10	Myoviridae; Siphoviridae.	SppYZU01 (43.567 bp) SppYZU5 (54.319 bp)	[93]
Tenacibaculum maritimum	Seawater	Multiple	TEM, DNA sequencing	PTm1 PTm5	Myoviridae	224,680 bp 226,876 bp	[94]

Gram-Negative Targets	Source	Enrichment ϕ	Characterization Method	Phage Strains Name	Family *	Genome Length	References
Vibrio alginolyticus	Aquaculture tank water	Single	TEM, DNA sequencing	VEN	Podoviridae	44,603 bp	[95]
	Marine sediment	No	TEM, DNA sequencing	ValKK3	Myoviridae	248,088 bp	[96]
	Marine water	Single	TEM, dsDNA	St2 Grn1	Myoviridae	250,485 bp 248,605 bp	[97]
Vibrio anguillarum	Soft tissues from clams and mussels	No	TEM, dsDNA	309 ALMED CHOED ALME CHOD CHOB	Several shapes	~47–48 kb	[98]
	Sewage water	Double	dsDNA	VP-2 VA-1	n.d.	n.d.	[51]
	Water samples from fish farms	Multiple	TEM, DNA sequencing	ø H1, H7, S4-7, H4, H5 H8, H20 S4-18, 2E-1, H2	Myoviridae Siphoviridae Podoviridae	~194–195 kb ~50 kb ~45–51 kb	[99]
Vibrio campbellii	Host strain (V. campbellii) isolated form a dead shrimp	No	TEM, DNA sequencing	HY01	Siphoviridae	41.772 bp	[100]
	Hepatopancreas of Pacific white shrimp	Single	dsDNA, DNA sequencing	vB_Vc_SrVc9	Autographiviridae	~43.15 kb	[101]
	Shrimp farm, hatcheries and marine water	Multiple	TEM, dsDNA	A	Siphoviridae	n.d.	[102]
	Vibrio harveyi	No	TEM, dsDNA	VHML	Myovirus-like	n.d.	[103]
	Shrimp pond water	Single	TEM, dsDNA	PW2	Siphoviridae	~46 kb	[104]
	Water and sediment samples	Single	TEM, dsDNA	VHM1, VHM2 VHS1	Myoviridae, Siphoviridae	~55 kb, ~66 kb ~69 kb	[105]
	Hatchery water and oyster tissues	Single	TEM, dsDNA	vB_VhaS-a vB_VhaS-tm	Siphoviridae	~82 kb ~59 kb	[106]
Vibrio harveyi	Commercial clam samples	Multiple	Genomic analysis, dsDNA	ø VhCCS-01 VhCCS-02 VhCCS-04 VhCCS-06 VhCCS-17 VhCCS-20 VhCCS-19 VhCCS-21	Siphoviridae, Myoviridae	n.d.	[107]
	Oyster, clam, shrimp, and seawater samples	No	TEM, DNA sequencing	VHP6b	Siphoviridae	78,081 bp	[108]
	shrimp hatchery and farm water, oysters from estuaries, coastal sea water	Multiple	TEM, dsDNA	Viha10 Viha8 Viha9 Viha11 Viha1 to Viha7	Siphoviridae - Siphoviridae Myoviridae (Viha4)	n.d. ~44–94 kb ~85 kb (Viha4)	[109][110]
	Seawater sample	Single	TEM	VhKM4	Myoviridae	n.d.	[111]
Vibrio ordalii	Macerated specimens of mussels	No	TEM, DNA sequencing	B_VorS-PVo5	Siphoviridae	80,578 bp	[112]

Gram-Negative Targets	Source	Enrichment ϕ	Characterization Method	Phage Strains Name	Family *	Genome Length	References
Vibrio parahaemolyticus	Sewage sample	No	TEM, dsDNA	VPp1	Tectiviridae	~15 kb	[113]
	Polluted seawater	No	TEM, dsDNA	KVP40 KVP41	Myoviridae	n.d.	[114][115]
	Seawater or mussels	Single	dsDNA	SPA2 SPA3	n.d.	~21 kb	[116]
	Coastal water	Single	TEM, DNA sequencing	pVP-1	Siphoviridae	111,506 bp	[117][118]
	V. parahaemolyticus isolated from sewage samples collected from an aquatic product market	No	TEM, DNA sequencing	vB_VpS_BA3 vB_VpS_CA8	Siphoviridae	58,648 bp 58,480 bp	[119]
	Shrimp pond water	Single	TEM, DNA sequencing	VP-1	Myoviridae	150,764 bp	[120]
	Coastal sand sediment	double	TEM, DNA sequencing	VpKK5	Siphoviridae	56,637 bp	[121][122]
Vibrio splendidus	Raw sewage obtained from local hatcheries	Single	TEM	PVS-1, PVS-2 PVS-3	Myoviridae; Siphoviridae	n.d.	[123]
	Seawater near a fish farm cage	Single	TEM, DNA sequencing	vB_VspP_pVa5	Podoviridae	78,145 bp	[124]
Vibrio coralliilyticus	sewage in oyster hatchery	Single	TEM	pVco-14	Siphoviridae	n.d.	[125]
Vibrio vulnificus	Seawater sample	Single	TEM, DNA sequencing	SSP002	Siphoviridae	76,350 bp	[126][127]
	Abalone samples	No	TEM, sequencing	VVPoo1	Siphoviridae	76,423 bp	[128]
	Initial host strain (V. vulnificus)	No	TEM	VV1 VV2 VV3 VV4	Tectiviridae	n.d.	[129]
Vibrio sp.	Sewage draining exits	Single	TEM, DNA sequencing	VspDsh-1 VpaJT-1 ValLY-3 ValSw4-1 VspSw-1	Siphoviridae	46,692 bp 60,177 bp 76,310 bp 79,545 bp 113,778 bp	[130]
Yersinia ruckeri	Wastewater containing suspended trout feces from a settling pond at a trout farm	Single	TEM	NC10	Podoviridae	n.d.	[49]
	Sewage	No	TEM	YerA41 (several phages)	icosahedral head, contractile tail	n.d.	[131]
	Sewage	No	TEM, DNA sequencing, dsDNA	R1-37	Myoviridae	~270 kb	[132][133]

ϕ Phage enrichment with "single" or "multiple" bacterial hosts; * Classification determined by the authors; TEM (Transmission Electron Microscopy); dsDNA (Double stranded DNA); n.d. (Not determined); ø Several phage strains were isolated but only selected strains were fully characterized.

Table 2. Phages used against Gram-positive bacterial fish and shellfish pathogens.

Gram-Positive Targets	Source	Enrichment ϕ	Characterization Method	Phage Strains Name	Family *	Genome Length	References
Lactococcus garvieae	L. garvieae isolated from diseased yellowtail	No	TEM, dsDNA	PLgY(16)	Siphoviridae	n.d.	[134]
	Yellowtail (Y) Water (W) Sediments (S)	Single	TEM, dsDNA	PLgW1-6 PLgY16 PLgY30 PLgY886 PLgS1	Siphoviridae	>20 kbp	[135][136][137]
	Domestic compost	Single	TEM, DNA sequencing	GE1	Siphoviridae	24,847 bp	[138]
	L. garvieae host	No	TEM, DNA sequencing	PLgT-1	Siphoviridae	29,284 bp	[139][140][141]
	Rainbow trout farm water	Single	TEM, DNA sequencing	WP-2	Picovirinae	18,899 bp	[142]
Streptococcus agalactiae	Tilapia pond	No	TEM	HN48	Caudoviridae	n.d.	[143]
S. iniae	S. iniae host	No	TEM, dsDNA	vB_SinS-44 vB_SinS-45 vB_SinS-46 vB_SinS-48	Siphoviridae	~51.7 kb ~28.4 kb ~66.3 kb ~27.5 kb	[144]
Weissella ceti	W. ceti host strain	No	TEM	PWc	Siphoviridae	38,783 bp	[145]

ϕ Phage enrichment with "single" or "multiple" bacterial hosts; * Classification determined by the authors; TEM (Transmission Electron Microscopy); dsDNA (Double stranded DNA); n.d. (Not determined).

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