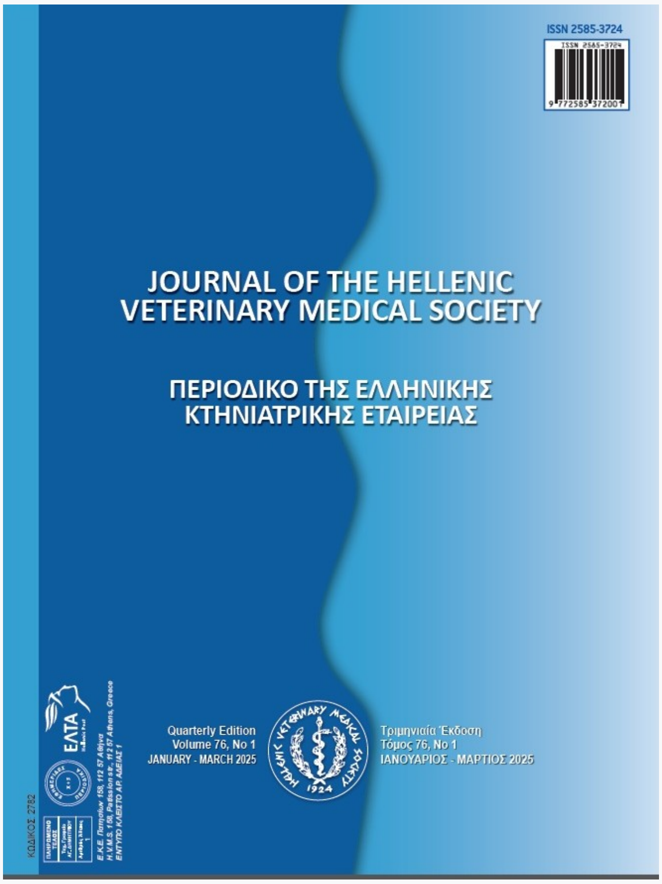
Journal of the Hellenic Veterinary Medical Society

Vol 76, No 1 (2025)



A Comprehensive Review of Herbal and Synthetic Therapeutics in Managing Viral Diseases in Fish Health

SJ Hasani, K Nofouzi, S Meshkiniy, A Enferadi, N Jalilzadeh, A Ravvaz

doi: 10.12681/jhvms.37804

J HELLENIC VET MED SOC 2025, 76 (1): 8805-8818
ΠΕΚΕ 2025, 76 (1): 8805-8818

Research article
Ερευνητικό άρθρο

A Comprehensive Review of Herbal and Synthetic Therapeutics in Managing Viral Diseases in Fish Health

S. J. Hasani[1], K. Nofouzi[2*], S. Meshkini[3], A. Enferadi[4], N. Jalilzadeh[5], A. Ravvaz[6]

[1]*Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.*

[2]*Department of Pathobiology, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran*

[3]*Associate Professor of Fish Hygiene, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran*

[4]*Department of Microbiology, Faculty of Veterinary Medicine, Urmia University, Urmia, West Azerbaijan, Iran*

[5]*Faculty of Veterinary Medicine, Urmia University, Urmia, Iran*

[6]*Faculty of Veterinary Medicine, Urmia University, Urmia, Iran*

ABSTRACT: Disease outbreaks are the main cause of financial loss in aquaculture, resulting in an estimated annual loss of over $10 billion. Viral diseases in fish continue to present a persistent threat to aquaculture production. Despite ongoing advancements within the industry, an estimated 10% of farmed aquatic animals still fall victim to infectious diseases, leading to substantial economic losses. Preventing and treating viral diseases in fish is one of the most difficult tasks due to the varying effectiveness of vaccines, interferons, and other medications. While fish species have been successful in controlling significant bacterial diseases through the use of antibiotics and vaccines, vaccines for viral diseases often prove to be ineffective. Standard antibiotics are not effective in preventing or treating viral diseases in fish. The risk of infectious disease outbreaks, including viral infections, increases with monoculture. Unfortunately, the treatment of viral diseases often fails, highlighting the need for more research to find effective drugs and vaccines to manage viral diseases. This article explores the potential of using herbal and synthetic drugs to combat viral diseases that impact fish populations.

***Key words*:** Aquaculture; Fish viral diseases; Synthetic drugs; Herbal drugs; Vaccine.

Corresponding Author:
Katayoon Nofouzi, Department of Pathobiology, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran
E-mail address: nofouzi@tabrizu.ac.ir

Date of initial submission: 20-05-2024
Date of acceptance: 26-12-2024

INTRODUCTION

In comparison, it can be argued that controlling infectious diseases in aquaculture is more challenging than managing diseases in terrestrial animals. This is primarily due to the aquatic environment in which fish reside and the inherent characteristics of fish themselves. Unlike terrestrial animals, fish cannot be closely observed, making it harder to detect early signs of illness. Furthermore, the aquatic environment facilitates rapid disease transmission, fish are not easily captured without causing stress, they tend to gather in groups, and identifying and characterizing diseases in fish is often a complex task (Cain, 2022; Mishra et al., 2023). Diagnosing fish diseases presents a significant challenge in aquaculture, as the aquatic environment introduces additional complexities. In this scenario, the focus of attention shifts from individual fish to the entire tank/cage which requires thorough examination and diagnosis. To effectively diagnose aquatic animal diseases, it becomes necessary to gather samples not only from the fish but also from the surrounding water. These samples help assess fundamental factors like pH levels, substrate conditions, temperature, and turbidity (Ninawe, Hameed, & Selvin, 2017). Infectious diseases pose a significant global threat to aquaculture. This is primarily due to the growing trade and movement of aquatic animals and their products across international borders. Among the various causes of these diseases in aquaculture, bacteria (54.9%), viruses (22.6%), parasites (19.4%), and fungi (3.1%) are the predominant culprits. Among them, viruses present the greatest challenge in terms of control. This is primarily because young aquatic animals are highly susceptible to viral infections, and our understanding of their natural defense mechanisms against viruses is limited (Manchanayake, Salleh, Amal, Yasin, & Zamri-Saad, 2023; Ouyang et al., 2023). Among the major aquacultured salmon species, namely rainbow trout (*Oncorhynchus mykiss*) and Atlantic salmon (*Salmo salar*), viruses present the most significant threat to their production. Viral diseases such as Infectious Pancreatic Necrosis (IPN), Pancreatic Disease (PD), Infectious Haemorrhagic Necrosis (IHN), Viral Haemorrhagic Septicaemia (VHS), and Infectious Salmon Anaemia (ISA) have the potential to cause substantial economic losses to the global salmonid aquaculture industry annually (Collet, 2014). Atlantic salmon (*Salmo salar*) is a highly valued fish species, with carp species leading in terms of volume. Aquaculture is an important occupation and has a significant impact on food security and social development in many countries (Adams, 2019). The knowledge about fish immunity to viral infections heavily relies on studies conducted on carp and salmon species. This is not surprising, considering that carp and salmon are extensively farmed fish species worldwide (Lulijwa, Alfaro, Merien, Meyer, & Young, 2019; Ortega-Villaizan, Chico, & Perez, 2022). It is widely recognized that diseases in Freshwater farmed fish are predominantly caused by viruses with single-stranded RNA (ssRNA) genomes. Well-established examples of such pathogens include the spring viremia of carp virus (SVCV) affecting carp and pathogens like salmon infectious hematopoietic necrosis virus (IHNV), infectious salmon anemia virus (ISAV), salmonid alphavirus (SAV), and viral hemorrhagic septicemia virus (VHSV) that impact salmon species (Ortega-Villaizan, Chico, & Perez, 2022). The primary challenge in effectively treating viral diseases with antiviral drugs stems from the intimate association between the virus and its host. This close relationship often leads to the toxicity of most antiviral agents. Hence, the most effective strategy in developing antiviral drugs is to focus on targeting specific processes that are exclusive to virus replication. These processes should be distinct from the essential metabolic functions of the host cell (Kibenge, Godoy, Fast, Workenhe, & Kibenge, 2012). Vaccines, interferons and various drugs are used to prevent and manage viral illnesses, though their effectiveness varies depending on the virus. In this article, we have provided a comprehensive and updated review of various methods for preventing and dealing with viral diseases in fish, especially rainbow trout and carp.

ANTIVIRAL IMMUNE STIMULANTS IN FISH SUCH AS VITAMINS, HERBAL SUBSTANCES AND VACCINES

To enhance the innate defense mechanisms of animals and boost their resistance to pathogens during periods of heightened stress (e.g., grading, reproduction, sea transfer, and vaccination), immune stimulants can be utilized. These immune stimulants include dietary supplements that contain vitamin C, beta-glucans, garlic (allicin), and propolis. Vitamins are widely known to increase growth and survival and provoke the immune response. Research has indicated that incorporating vitamins C and E into the diet of Nile *tilapia* can enhance their ability to withstand osmotic stress (Elnagar, Khalil, Talaat, & Sherif, 2024). Studies have demonstrated that vitamin C can enhance the immune response and boost resistance to infections in different species of fish (Ibrahim et al., 2021; Perveen et al., 2022; Zhu et al., 2022). It is important to note that overdosing on vitamins, especially vitamin A, can be dangerous (Lieke, Meinelt, Hoseinifar, Pan, Straus, & Steinberg, 2020). Beta-glucans are non-digestible polysaccharides composed of glucose molecules that are present in the cell walls of bacteria, plants, and fungi, such as brewer's yeast (*Saccharomyces spp.*). These immune-stimulating beta-glucans, particularly ß-1, 3 and ß-1,6 glucans, are commonly utilized in aquaculture (Meena et al., 2013). For optimal administration, it is advisable to administer them orally or through intramuscular injection. It is recommended to use them for a short duration and at appropriate dosages before a stressful event, such as transportation, or during an unavoidable stressor (Barros et al., 2014). Crushed garlic (*Allium sativum*) contains allicin (diallyl thiosulfinate) and various sulfur-allyl compounds. These components possess immune-stimulating, antioxidant, hypolipidemic, antimicrobial, and antihypertensive properties (J. Y. Lee & Gao, 2012). Whole garlic is not effective; only crushed garlic yields satisfactory results. The recommended dosage typically ranges from 5 to 10 grams per kilogram of feed, to be administered for a duration of two to four weeks (Shahsavani, Baghshani, & Alishahi, 2011). It is advisable to avoid higher doses and longer treatment periods, as there have been reports of oxidative tissue damage and instances of acute deaths (Breyer, Getchell, Cornwell, Wooster, Ketola, & Bowser, 2015). Double stranded RNA, such as Poly I: C, can trigger anti-viral defenses in fish by binding to the TLR-3 analog (Bricknell & Dalmo, 2005; Das, Ellis, & Collet, 2009; Fernandez-Trujillo et al., 2008; Jensen, Albuquerque, Sommer, & Robertsen, 2002; Lockhart, Bowden, & Ellis, 2004). There are concerns regarding the potential side effects of immunostimulants on the immune system of fish, especially on the developing immune system of fish larvae (Bricknell & Dalmo, 2005). Although research and experimental trials have shown promising results and some fish vaccines demonstrate moderate to high market potential, only a limited number of approved vaccines are currently available to protect economically important fish species from diseases. While progress in aquaculture has led to more fish vaccines being developed commercially, their range remains relatively narrow. Many fish illnesses still have no standard vaccine options. In these instances, farmers may resort to custom-made vaccines like Autogenous (auto) vaccines designed for specific disease outbreaks on their premises. The number of commercial vaccines available for fish to protect against major bacterial and viral infections has grown from just 2 in the 1980s to more than 50 today (Du, Hu, Miao, & Chen, 2022; Irshath, Rajan, Vimal, Prabhakaran, & Ganesan, 2023). The most efficient way to administer these vaccines is through injection. However, this method is labor-intensive, costly, and impractical for large quantities of fish weighing less than 20 grams. Efforts to create innovative ways of delivering substances orally or through immersion have achieved different degrees of success, but they hold significant promise for the future (Assefa & Abunna, 2018). Vaccines are widely acknowledged as the main method for preventing and managing fish diseases. They are regularly employed in aquaculture, especially for Atlantic salmon (*Salmo salar*). However, in other fish species, their usage is restricted or non-existent due to factors such as the absence of vaccines, subpar effectiveness, or high costs. Vaccination has the potential to decrease the reliance on antibiotics in the aquaculture sector. In different parts of the globe, there have been instances of excessive or improper use of different fish species (Adams, 2019). Excessive use of antibiotics is a major concern as it can lead to antibiotic resistance. Furthermore, the absence of available vaccines for numerous viral diseases that impact valuable fish species in the aquaculture industry, along with the lack of effective treatments to combat these diseases once they have emerged in fish farms, is a significant obstacle to increasing fish production (Pereiro, Figueras, & Novoa, 2021). Excessive use of antibiotics can cause antibiotic resistance, which is a major concern. Additionally, viral diseases affecting valuable fish species in the aquaculture industry lack available vaccines, and effective treatments for these diseases are limited once they appear in fish farms, hindering fish production. To address this issue, fish vaccines that are administered through injection, immersion, or feed using polyvalent vaccines are now commonly used in various farmed species (Bøgwald & Dalmo, 2019; Ma, Bruce, Jones, & Cain, 2019). There are various types of modern vaccines available, such as killed, weakened, DNA, synthetic peptide, recombinant vector, genetically modified, and subunit vaccines. Whole- organism vaccines are generally more effective than other types. While there are many types of modern vaccines available, most do not offer full protection against diseases. Synthetic peptide vaccines, on the other hand, have been effective in preventing certain viral infections, including nodavirus, viral hemorrhagic septicemia, rhabdovirus, and *birnavirus* (Dadar et al., 2017). In the United States, vaccine production must adhere to strict guidelines and regulations. A veterinarian or a qualified fish health specialist must oversee the process, and the vaccines must be produced in a facility that is licensed by the USDA (Covarrubias, Rivera, Soto, Deeks, & Kalergis, 2022). To ensure that the vaccine is effective, it must be kept refrigerated and used within a short time frame, and immune stimulants may be given to enhance the success rate. Vaccination is most effective when administered before exposure or clinical symptoms appear. To reduce the risk of viral infections, it is important to minimize stressors, practice biosecurity, and vaccinate (Assefa & Abunna, 2018; Mugimba, Byarugaba, Mutoloki, Evensen, & Munang'andu, 2021). In the following sections of this article, we will provide further explanations regarding vaccines and their ability to prevent various viral diseases in fish (Table 1).

RHABDOVIRAL INFECTIONS OF FISH

INFECTIOUS HEMATOPOIETIC NECROSIS (IHN)

Infectious hematopoietic necrosis virus is a rhabdovirus of particular concern to the salmon aquaculture industry in British Columbia (Romero et al., 2022). To prevent IHN, disinfecting eggs using iodophors (PVP-I) with a 100 ppm dilution for 10 minutes at a pH of 6 is essential. Increase the water temperature in the breeding environment to above 15 degrees Celsius. Addition of 0.5 grams of PVP-I to the diet of the fish. Ensure that fingerlings are raised in water temperatures exceeding 15 degrees Celsius. Using killed vaccines can help prevent the Infectious Hematopoietic Necrosis virus, *A. salmonicida*, and *V. salmonicida* (Assefa & Abunna, 2018). DNA vaccines are composed of genes from a pathogen and when injected intramuscularly, they offer both immediate and long-lasting protection against economically significant diseases such as infectious hematopoietic necrosis virus and viral hemorrhagic septicemia virus (Ballesteros, Alonso, Saint-Jean, & Perez-Prieto, 2015; Cho et al., 2017). The use of interferon is effective in combating Infectious hematopoietic necrosis virus (IHNV), but it does not have any impact on Infectious pancreatic necrosis virus (IPNV). This finding is consistent with observations made during dual infections involving both viruses, where the presence of IPNV prevents the spread of IHNV (Kim, Oseko, Nishizawa, & Yoshimizu, 2009; Kotob, Menanteau-Ledouble, Kumar, Abdelzaher, & El-Matbouli, 2017). Aquaculture has utilized DNA vaccines to effectively safeguard fish against rhabdovirus infections, including IHNV and viral hemorrhagic septicemia virus (VHSV). The use of DNA vaccines in aquaculture has been successful in protecting fish from rhabdovirus infections, such as IHNV and VHSV. This has resulted in a significant decrease in the negative effects of these viruses on the salmon aquaculture industry (Assefa & Abunna, 2018).

VIRAL HEMORRHAGIC SEPTICAEMIA (VHS)

The origin of VHS can be traced back to a virus with single-stranded negative-sense RNA from the Rhabdoviridae family (Jung, Jung, & Kim, 2022). To tackle VHS effectively, it's crucial to issue health

Table 1. Antiviral vaccines are used against aquatic viral diseases.

	Disease	Vaccines
1	Infectious Hematopoietic Necrosis (IHN)	Using killed vaccines and DNA vaccines.
2	Spring Viraemia of Cyprinids (SVC)	A vaccine called Spring Viremia of Carp Virus
3	Marine birnavirus (MABV)	Using a peptide vaccine.
4	Herpesvirus Salmonis Disease	Using a modified live vaccine
5	Koi herpes virus (KHV)	Using oral DNA vaccines in farms, Gene gun or intramuscular injection vaccinating for few sufferers, Using oral probiotic vaccine (Lactobacillus rhamnosus), Using a vaccine called Koi herpes virus.
6	Viral Nervous Necrosis (VNN)	Using a vaccine called Betanodavirus and a vaccine called Nodavirus vaccine.
7	Infectious Salmon Anemia (ISA)	Administrating the Infectious Salmon Anemia Vaccine.
8	Tilapia lake virus (TiLV)	Using a live attenuated vaccine, Utilizing a β-propiolactone-inactivated TiLV vaccine in combination with the adjuvant Montanide IMS 1312 VG and administering booster immunizations.

certificates, implement health controls during fish transportation, and impose quarantines on imported fish. Be aware that cold-blooded animals native to Europe can carry the virus, so special attention is needed, particularly when transferring *Astachus astachus*. Strengthening fish health can be achieved by incorporating essential vitamins (A, B, E) into their diet. An innovative approach involves administering intramuscular injections of a plasmid that encodes interferon in turbot. This approach has yielded impressive outcomes, lowering VHSV-induced mortality from 100% to 47% and increasing mx gene expression in muscle tissue by 200-fold (Pereiro, Costa, Díaz-Rosales, Dios, Figueras, & Novoa, 2014). The β-defensin (BD)-1 peptide has also been shown to have antiviral activity against VHSV in rainbow trout (Rajanbabu & Chen, 2011). Research has shown that synthetic OF-hepcidin-1 can effectively combat different fish pathogens, including VHSV, with a minimum dose of 50 µM. This indicates its potential as an antimicrobial agent for the aquaculture industry (Y. Lee et al., 2022).

PIKE FRY RHABDOVIRUS DISEASE (PFRD - PFVD)

Pike Fry Rhabdovirus Disease (PFRD or PFVD) results from the presence of rhabdoviruses. To effectively control PFRD, it's advisable to perform ELISA or VI screenings on female broodstock's ovaries and employ iodophors for egg disinfection. Additionally, it's crucial to prevent the transfer of eggs or larvae that are suspected of carrying the virus and implement strict quarantine measures (Hadfield, 2021).

SPRING VIRAEMIA OF CYPRINIDS (SVC)

SVCV is the virus responsible for causing SVC and belongs to the rhabdovirus family (Ahne, Bjorklund, Essbauer, Fijan, Kurath, & Winton, 2002). A viral DNA vaccine has been tested for carp virus spring viremia (Assefa & Abunna, 2018). A vaccine called Spring Viremia of Carp Virus has been developed for common carp to combat Spring Viremia of Cyprinids (Emmenegger & Kurath, 2008). Research has indicated that having a robust interferon response does not necessarily equate to being resistant to virus infection. A case in point is the Spring Viremia of Carp virus (SVCV), which effectively triggers interferon and Mx in carp cells. However, despite this immune response, the infected cells ultimately perish. This phenomenon has also been observed in live organisms, such as zebrafish infected with SVCV, where high levels of ifn and mx are induced, yet mortality rates remain elevated (Mikołaj Adamek et al., 2012; Liu et al., 2020; X.-y. Zhou, Lu, Li, Zhang, Chen, & Li, 2021). Research conducted in live organisms has shown that administering artemisinin after incubation substantially improved the survival rate of common carp by 33.3% and effectively reduced viral loads. Additionally, artemisinin was found to enhance the expression of genes associated with antiviral activity, including type I Interferon (IFN1), Interferon-stimulated gene product 15 (ISG15), Mx1, and viperine (Y. Zhou, Qiu, Hu, Ji, Liu, & Chen, 2022). Hydrogen has been recognized for its potential as an anti-inflammatory agent. It was previously believed that it could prevent virus-related inflammatory responses and mitigate tissue damage. Nevertheless, hydrogen's limited solubility in water markedly restricts its effectiveness when ingested orally. According to Li et al., administering nano-bubble hydrogen water was found to lower the cumulative mortality rate of SVCV-infected zebrafish by 40%. The qRT-PCR findings indicated significant inhibition of SVCV replication after treatment. Nano-bubble hydrogen water (nano-HW) prevented inflammation caused by viral infection in zebrafish, suggesting its potential use in antiviral research and providing a new therapeutic strategy for virus-induced inflammation. Additionally, nano-HW reduced intestinal and brain damage in SVCV-infected zebrafish (C. Li et al., 2022).

REOVIRUS INFECTIONS OF FISH

GRASS CARP REOVIRUS DISEASE OR HAEMORRHAGIC DISEASE OF GRASS CARP

Grass Carp Hemorrhagic Disease is caused by a virus called grass carp reovirus (Rao & Su, 2015). According to certain Chinese researchers, the utilization of rhubarb has been studied. Yu et al. discovered that Moroxydine hydrochloride (Mor) has the potential to inhibit the replication of grass carp reovirus (GCRV) and prevent apoptosis in Ctenopharyngodon idella kidney cells (Yu, Hao, Ling, Zhu, & Wang, 2020).

BIRNAVIRUS INFECTIONS

INFECTIOUS PANCREATIC NECROSIS (IPN)

Aqua-birnaviruses are responsible for triggering Infectious Pancreatic Necrosis (IPN)(Dopazo, 2020). IPN is a highly infectious disease that can be found all over the world. It is caused by a virus called infectious pancreatic necrosis virus (IPNV) (Magnadottir, 2010). To effectively control IPN, follow these measures: Ensure the issuance of health certificates when transferring eggs and larvae, Employ egg sterilization techniques, reduce the breeding water temperature (cold water conditions), Utilize disease-resistant fish breeds, and Implement vaccination protocols. In the event of an outbreak: Promptly report the disease to the relevant authorities, Perform the extermination of all affected fish, Thoroughly disinfect pools and equipment using 200 ppm chlorine or iodophors, Allow pools to dry out, Avoid fish breeding in ponds for a minimum of 6 months. It is worth noting that there is a clear connection between increased production of interferon and improved resistance to IPNV in Atlantic salmon (Reyes-López et al., 2015).

MARINE BIRNAVIRUS (MABV)

Marine birnavirus (MABV) belongs to the Aquabirnavirus genus within the Birnaviridae family (Isshiki, Nagano, Kanehira, & Suzuki, 2004). Marine birnavirus (MABV) is a highly pathogenic virus that affects marine and shellfish species. It has been observed that an outbreak of this virus can result in complete mortality within a short timeframe. To prevent this, some analysts have developed a peptide vaccine (Islam, Mou, & Sanjida, 2022).

IRIDOVIRAL INFECTIONS

VIRAL ERYTHROCYTIC NECROSIS (VEN)

VEN is attributed to the presence of Iridovirus (Pagowski et al., 2019). Regarding prevention and control, research has revealed that the VEN virus utilizes the major capsid protein (MCP) to invade the host cell. By targeting this protein and impeding virus entry, economic losses caused by the pathogen can be reduced. Furthermore, phytochemicals found in *Allium sativum* have shown potential as significant inhibitors of the MCP (Sanjida, Mou, Islam, & SAROWER-E-MAHFUJ, 2022).

LYMPHOCYSTIS

Iridoviruses are responsible for the development of lymphocytosis (Labella, Leiva-Rebollo, Alejo, Castro, & Borrego, 2019). Lymphocystis disease virus (LCDV) is an extremely contagious virus that can infect 125 different species of fish in both freshwater and marine environments. It is known to cause a disease in fish called lymphocystis, which is characterized by an abnormal growth of cells in the connective tissue. This virus is very common in aquaculture, with infection rates as high as 70%, which can lead to significant economic losses for the industry (Borrego, Valverde, Labella, & Castro, 2017). To prevent and manage Lymphocystis: Refrain from transferring fish that are infected or raise suspicions, Implement quarantines for imported fish, Detect and eliminate infected fish, and Isolate aquarium fish that are infected until they recover.

SINGAPORE GROUPER IRIDOVIRUS (SGIV)

Singapore grouper iridovirus (SGIV) can cause significant fish mortality, making it crucial to develop treatments to combat this virus. Green tea, a valuable medicinal and edible plant, has been suggested as a potential treatment for SGIV. According to Li et al., various components of green tea have demonstrated potent antiviral properties against SGIV. These components could potentially be utilized as effective agents for the treatment and control of SGIV infections in grouper aquaculture (P. Li et al., 2022).

HERPES VIRUS INFECTIONS

HERPESVIRUS SALMONIDS DISEASE

Herpesvirus Salmonis Disease, as the name implies, is a condition caused by the herpes virus (Hanson, Dishon, & Kotler, 2011). It has been found that the interferon reaction presents a good correlation with viral loads in herpesvirus-infected carp (Mikolaj Adamek et al., 2019; Xia et al., 2018). Acyclovir (9-(2-hydroxyethoxymethyl) guanine) has been shown to have in vitro effects against channel catfish virus and salmon herpesvirus (Buck & Loh, 1985; Kimura, Suzuki, & Yoshimizu, 1983). A dose of 25 mg per liter of Acyclovir, administered daily for up to 15 days, has been found to possess anti-herpesvirus properties. Both ACV and ACV-MP can inhibit CyHV-3 replication in vitro. Several antiviral medications, including adenine-β-d-arabinofuranoside, phosphonoacetic acid, phosphonoformic acid, and 5-iodo-2′-deoxyuridine, have been discovered to be less efficient in laboratory testing (Buck & Loh, 1985). Yildirim et al. conducted a study that demonstrated significant antiviral effects of propolis against the replication of both *Herpes Simplex Virus Type 1* and *Type 2*. The combination of propolis and acyclovir exhibited a synergistic effect, proving to be more potent against *HSV-1* and *HSV-2* compared to acyclovir alone (Yildirim et al., 2016). A modified live vaccine designed to combat *cyprinid herpesvirus 3* (Cavoy, Novartis Animal Health, Charlottetown, Canada) was authorized for use in koi fish in the United States. However, some facilities observed negative side effects from the vaccine, and as a result, the product was withdrawn from the US market (O'Connor et al., 2014; Weber et al., 2014).

KOI HERPES VIRUS (KHV)

Koi herpes virus (KHV) is a highly lethal and contagious virus that affects cyprinid fish, leading to significant economic losses and challenges for the carp aquaculture industry. Various chemical and herbal remedies can be employed to combat *Koi Herpesvirus (KHV)*. These options include DNA vaccines, exopolysaccharides derived from Arthrospira platensis, and a monoclonal antibody. Exopolysaccharides sourced from *Arthrospira platensis* have emerged as an alternative treatment for *KHV* and have exhibited promising potential in the fight against Koi Herpesvirus Disease (KHVD) (Reichert, Bergmann, Hwang, Buchholz, & Lindenberger, 2017). *Rheum palmatum*, *Chrysanthemum indicum*, and *Sanguisorba officinalis* extracts offer potential solutions for combating the *Koi herpes virus (KHV)*. These extracts can be combined with acyclovir, an antiviral agent, to effectively address herpes virus infections (Bomstein, Marder, & JOWERS, 2020). A monoclonal antibody designed to target *KHV* has been developed and can be utilized for large-scale *KHV* detection (Li et al., 2017). DNA vaccines have proven their capability to induce targeted immune responses and provide immunity against *KHV*. In terms of prevention and control, traditional vaccination methods such as gene gun or intramuscular injection are not suitable for large-scale vaccination of carp. Therefore, the development of oral vaccines that can be easily administered in the field is highly desirable. For instance, researchers have explored the use of chitosan-alginate capsules as a delivery system for an oral probiotic vaccine (*Lactobacillus rhamnosus*) (Huang et al., 2021). This approach shows promise for effectively protecting fish against *KHV* (Huang et al., 2021). A vaccine called *Koi herpes virus (KHV)* has been created in Koi carp against *Koi herpes virus* infection (Dishon, Ashoulin, Scott Weber III, & Kotler, 2014). The most efficient method of preventing *KHV* is by adhering to robust biosecurity practices. This includes isolating newly acquired fish, thoroughly disinfecting equipment, and refraining from introducing fish from unfamiliar sources. Furthermore, ensuring optimal water quality and providing appropriate nutrition can greatly reduce the likelihood of disease outbreaks. In the event of an outbreak, it is imperative to isolate infected fish and employ suitable management techniques, such as reducing stocking density and enhancing aeration to improve water quality. Raising the salinity level to 5 g/L can considerably decrease the incidence of illness and death, and treatment should continue for a minimum of four weeks. It is advisable to conduct PCR testing for *CEV* before removing carp or koi from quarantine. Carp pox, which is marked by epidermal papillomas in common carp and other cyprinids, is caused by *Cyprinid herpesvirus 1 (CyHV-1)* (Rahmati-Holasoo, Ahmadivand, Shokrpoor, & El-Matbouli, 2020).

BETANODA VIRAL INFECTIONS

VIRAL NERVOUS NECROSIS (VNN)

Viral Nervous Necrosis (VNN) is caused by viruses belonging to the Betanodavirus genus, making it one of the most severe diseases in aquaculture (Gye, Oh, & Nishizawa, 2018). Nodaviruses present a significant threat to cultured marine fish globally, particularly perciform species (Ortega-Villaizan, Chico, & Perez, 2022). A vaccine called Betanodavirus has been produced against VNN (Patel & Nerland, 2014). A vaccine called Nodavirus vaccine has been produced in Seabass against Viral Nervous Necrosis (Vimal et al., 2016). Ribavirin at a dose of 20 mg per liter has an anti-nerve necrosis virus effect .Treatment of zebrafish larvae with ribavirin before infection with *NNV* has been found to reduce mortality from the virus up to 10 days after infection. Nanoplastics (NPs) can have a range of adverse effects on aquatic organisms, from single cells to entire organisms, such as cytotoxicity, reproductive issues, behavior changes and oxidative stress. The existence of NPs could impact the infection mechanism of *NNV*, diminishing the fish's capacity to combat the disease, thereby posing an extra threat to marine life (González-Fernández & Cuesta, 2022). Qing Wang and their team created an artificial form of genetic material called synthetic mRNA that contains instructions for making CasRx. They then used CRISPR RNAs to direct CasRx to target the *nervous necrosis virus (NNV)* (Bandín & Souto, 2020; Nishizawa, Furuhashi, Nagai, Nakai, & Muroga, 1997).

ORTHOMYXOVIRUS INFECTION

INFECTIOUS SALMON ANEMIA(ISA)

Infectious Salmon Anemia (ISA) is a viral disease caused by an RNA virus that shares similarities with the Orthomyxoviridae family (Falk, Namork, Rimstad, Mjaaland, & Dannevig, 1997). To prevent and control Infectious Salmon Anemia (ISA), it is crucial to implement certain measures. These include maintaining a safe distance between sea pens containing farmed *Atlantic salmon* and wild stocks, as well as other farmed *Atlantic salmon* and salmon processing plants. Additionally, the administration of the Infectious Salmon Anemia Vaccine can help in mitigating the spread of the disease (Caruffo, Maturana, Kambalapally, Larenas, & Tobar, 2016). Antiviral immune stimulants to deal with viral diseases such as infectious salmon anemia (ISA) are used (Jensen et al., 2002). Furthermore, it has been discovered that administering nucleotide analog ribavirin orally at 6.5 μmol/kg body weight once a day for ten days can decrease the mortality rate of salmon that are potentially infected.

TILAPIA LAKE VIRUS (TILV)

Tilapia tilapinevirus, commonly referred to as *Tilapia lake virus (*TiLV*)*, is an RNA virus that infects both wild and farmed tilapia populations. It belongs to the *Tilapinevirus* genus, which is the only genus in the *Amnoonviridae* family (Jansen, Dong, & Mohan, 2019).Up to this point, there have been few effective therapeutic methods found to control TiLV. As a result, the primary approach remaining is to implement sound management practices, prioritize bio-security, and enforce rigorous quarantine protocols. It is important to adhere to affordable measures for disease prevention and control, such as practicing good farming techniques, maintaining proper water quality, ensuring adequate nutrition and sanitation. Organizations like FAO and OIE offer guidelines and procedures for managing TiLV disease through control measures and bio-security protocols. Farmers are advised to either use tilapia seeds (larvae and fingerlings) from their own farms or procure them from local, regional farmers, or hatcheries with a clean track record that is free from any abnormalities, mass mortality, or reported diseases. It is crucial to avoid obtaining tilapia from areas or countries that are vulnerable to TiLV to prevent the virus from spreading to unaffected regions. In unavoidable circumstances, strict screening and quarantine procedures must be followed meticulously (Aich, Paul, Choudhury, & Saha, 2022). According to a study by Thammatorn, Rawiwan, and Surachetpong (2019), it was discovered that Tilapia fillets that were frozen for 14 days after being subclinically infected with TiLV did not contain any active viral particles (Thammatorn, Rawiwan, & Surachetpong, 2019). This finding suggests that commercial exporters from various countries could adopt this freezing technique to help prevent the virus from spreading further. Recent findings indicate that in a laboratory environment, the use of commonly employed disinfectants may offer a preventive measure against viral infections, as proposed by certain researchers (Jaemwimol, Sirikanchana, Tattiyapong, Mongkolsuk, & Surachetpong, 2019; Soto, Yun, & Surachetpong, 2019). Researchers in Israel have successfully created a live attenuated vaccine for TiLV through experimental methods. When this vaccine was administered to Tilapia that was exposed to TiLV either through bathing or intraperitoneal injection, there was a notable 56%-58% increase in survival rates within 21 days after vaccination. The author of this vaccine has obtained a patent for it (US20160354458A1), although it has not yet been made available for commercial purposes (Kembou-Ringert, Steinhagen, Readman, Daly, & Adamek, 2023). Researchers have found that utilizing β-propiolactone to inactivate viral particles results in a vaccine that provides greater efficacy in protecting against virus challenges, surpassing the effectiveness of formaldehyde. After administering the vaccine, fish were subjected to varying doses of 50% tissue culture infectious dose (TCID50)/mL, specifically 108, 107, and 106. The results showed that without adjuvant, the relative percent survivals were 42.9%, 28.5%, and 14.3%, respectively. However, when administered with the adjuvant, the relative percent survivals increased significantly to 85.7%, 64.3%, and 32.1%, respectively. In addition, the vaccine triggered the production of specific IgM and neutralizing antibodies against TiLV within three weeks of immunization. Furthermore, after a second booster immunization, these antibody levels increased significantly. The levels of various immune response-related genes, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interferon γ (IFN-γ), cluster of differentiation 4 (CD4), major histocompatibility complex (MHC)-Ia, and MHC-II, were observed to be increased, demonstrating successful immune activation against TiLV. Additionally, the vaccine demonstrated the ability to reduce viral loads and significantly improve survival rates. This suggests that the vaccine not only inhibits viral replication but also triggers a protective antibody response. By utilizing a β-propiolactone-inactivated TiLV vaccine in combination with the adjuvant Montanide IMS 1312 VG and administering booster immunizations, tilapia can attain a significant level of protection against virus challenges (Zeng et al., 2021). A review of the literature has shown that fish that survived a TiLV outbreak displayed a certain level of resistance to the virus during subsequent culture phases. This discovery has instilled hope in researchers that effective management of this disease can be accomplished in the near future (Eyngor et al., 2014). Moreover, research has revealed that different strains of Tilapia demonstrate varying levels of vulnerability to this virus (Ferguson, Kabuusu, Beltran, Reyes, Lince, & del Pozo, 2014), which implies the potential for identifying TiLV-resistant strains. The evidence suggests that gene profiling can be used to create Tilapia strains that are genetically enhanced to resist TiLV. The current methods for controlling TiLV disease are difficult to implement due to challenges such as enforcing bio-security and quarantine procedures. The guidelines from FAO and OIE mainly focus on larger commercial farms and are not commonly used for small-scale farms (Aich et al., 2022). The creation of vaccines for TiLV is still ongoing and requires technological advancements, infrastructure, and financial support. Furthermore, there are concerns about the vaccine's effectiveness as a preventative measure, as it can cause illness in young fish with underdeveloped immune systems. Although there are still unresolved inquiries about the classification and spread of the virus, the findings of its ability to resist recurring infections offer prospects for creating vaccines and strains of Tilapia that are resistant to TiLV. The importance of vaccines in preventing and controlling viral and other diseases is widely acknowledged. Conducting thorough scientific research is essential for the development of a potent vaccine against this deadly virus. The creation of SPF (Specific Pathogen-Free) tilapia or selectively bred resistant tilapia could be the key to fighting this lethal disease, and significant efforts should be directed towards this goal (Aich et al., 2022). In a study by Wayamitra et al. (2020), fish were divided into three groups and given different diets: a control diet, a diet with 0.5% probiotic supplementation, and a diet with 1% probiotic supplementation. Following 21 days of experimental feeding, the three groups were infected with TiLV, and their mortality rates and growth performances were observed. Organ samples were collected at different time intervals to assess viral load and the transcriptional changes of immune response markers. The study revealed that there were no notable variances among the groups in terms of weight gain (WG), average daily gain (ADG), feed efficiency (FE), or feed conversion ratio (FCR). However, the groups of fish that were given diets with 0.5% and 1% probiotic supplementation demonstrated a lower cumulative mortality rate (25% and 24% respectively) compared to the control group (32%). Moreover, fish that received a diet enriched with 1% probiotics showed significantly lower levels of the virus compared to those fed with 0.5% probiotics and the control diet at 5, 6, 9, and 12 days after the infection-challenge (dpc). The expression patterns of immune-related genes, such as il-8 (also known as CXCL8), ifn-γ, irf-3, mx, and rsad-2 (also known as VIPERIN), exhibited significant upregulation following probiotic treatment during the peak of TiLV pathogenesis (between 9 and 12 dpc) and throughout most of the study period in fish that received a diet supplemented with 1% probiotics. Collectively, these findings suggest that incorporating *Bacillus spp.* Probiotics in the diet can potentially enhance the immune system of tilapia and improve their ability to resist TiLV infections. Consequently, administering probiotic treatments preventively may help minimize losses resulting from this emerging viral infection in tilapia aquaculture (Table 2) (Waiyamitra et al., 2020).

SIMULTANEOUS AND SECONDARY BACTERIAL AND PARASITIC DISEASES

Simultaneous and secondary bacterial and parasitic infections are very common in nature. When a host is infected with two or more different pathogens at the same time or in succession, co-infections occur and can affect the course and severity of a variety of fish diseases. For instance, the combination of viral hemorrhagic septicemia virus (VHSV) and the ectoparasite Trichodina was detected in whiting (*Merlangius merlangus euxinus*) found in the Black Sea region (Kotob et al., 2017). It is common to see viral fish diseases accompanied by bacterial and parasitic infections. Therefore, in addition to measures to combat viral diseases, measures to address bacterial and parasitic infections should also be taken.

CONCLUSION AND FUTURE PERSPECTIVE

Aquaculture, which is an age-old practice, is still widely prevalent across the globe today. It encompasses various forms, ranging from sustainable aquaculture to large-scale salmon farming. However, the expansion of this industry is significantly hampered by the prevalence of viral diseases. Although certain methods employed to manage viral diseases in land-based livestock have been adapted for use in aquaculture, the aquatic environment poses distinct obstacles. For instance, there are no physical barriers to

Table 2. Antiviral compounds used against aquatic viral diseases.

	Disease	Preventive or therapeutic compounds
1	Infectious Hematopoietic Necrosis (IHN)	Disinfecting eggs using iodophors, Using interferon
2	Viral Hemorrhagic Septicaemia (VHS)	implementing health controls during fish transportation, imposing quarantines on imported fish, Strengthening fish health by essential vitamins (A, B, E), intramuscular injections of a plasmid that encodes interferon, prescription β-defensin (BD)-1 and OF-hepcidin-1.
3	Pike Fry Rhabdovirus Disease (PFRD - PFVD)	performing ELISA or VI screenings on female broodstock's ovaries, Disinfecting eggs using iodophors, Avoiding the transfer of eggs or larvae that are suspected of carrying the virus, implementing strict quarantine measures.
4	Spring Viraemia of Cyprinids (SVC)	Administering artemisinin after incubation, Administering nano-bubble hydrogen water.
5	Grass Carp Reovirus Disease or Haemorrhagic Disease of Grass Carp	Using Moroxydine hydrochloride and Rhubarb.
6	Infectious Pancreatic Necrosis (IPN)	Issuance of health certificates when transferring eggs and larvae, Employing egg sterilization techniques, Reducing the breeding water temperature, and Utilizing disease-resistant fish breeds. In the event of an outbreak perform the extermination of all affected fish, disinfect pools and equipment using chlorine or iodophors, Dry out the pools, and Avoid fish breeding in ponds for a minimum of 6 months.
7	Viral Erythrocytic Necrosis (VEN)	Using phytochemicals found in Allium sativum.
8	Lymphocystis	Refraining from transferring fish that are infected or raise suspicions, Implementing quarantines for imported fish, Detecting and eliminating infected fish, Isolating aquarium fish that are infected until they recover.
9	Singapore grouper Iridovirus (SGIV)	Using Green tea
10	Herpesvirus Salmonis Disease	Prescribing adenine-β-d-arabinofuranoside, phosphonoacetic acid, phosphonoformic acid and 5-iodo-2′-deoxyuridine, Prescribing the combination of propolis and acyclovir.
11	Koi herpes virus (KHV)	Using exopolysaccharides derived from Arthrospira platensis, and a monoclonal antibody, Prescribing the combination of Acyclovir with Rheum palmatum, Chrysanthemum indicum, and Sanguisorba officinalis extracts. Adhering to robust biosecurity practices. In the event of an outbreak, isolating infected fish reduces stocking density and enhances aeration to improve water quality, Raising the salinity level to 5 g/L.
12	Viral Nervous Necrosis (VNN)	Prescribing Ribavirin, Not using nano plastics in aquaculture, Using a synthetic mRNA that contains instructions for making CasRx and targeting the nervous necrosis virus with it.
13	Infectious Salmon Anemia (ISA)	Maintaining a safe distance between sea pens containing farmed Atlantic salmon and wild stocks, as well as other farmed Atlantic salmon and salmon processing plants, Using antiviral immune stimulants, Administering nucleotide analog ribavirin orally.
14	Tilapia lake virus (TiLV)	Implementing sound management practices, Prioritizing bio-security, Enforcing rigorous quarantine protocols, Using commonly employed disinfectants, The creation of SPF (Specific Pathogen-Free) tilapia or selectively bred resistant tilapia, Administering probiotic treatments (incorporating Bacillus spp. probiotics into the diet).

prevent pathogens from being transmitted to wild fish populations, which can serve as reservoirs for these diseases. With many of the traditional treatments used to manage viral diseases in aquaculture slated to be prohibited in Europe, there is a pressing need for alternative solutions. Many synthetic drugs have more or less side effects, some of which are chronic and occur in the long term. If severe side effects are proven after taking a certain drug, its use should be prohibited. Despite the effort to accurately express the dosage of drugs, there are individual possibilities or the occurrence of mistakes. In general, it is recommended that the lowest possible dose be used in unusual species, as well as in sick, old and juvenile fish. The article stresses the need for more research to assess the effectiveness, safety, and impacts of herbal and synthetic drugs in fighting viral diseases in fish. It proposes that a combination of these methods could provide a more complete solution, leveraging the benefits of both natural and synthetic compounds. In general, the investigation of herbal and synthetic drugs as potential treatments for viral diseases in fish is a major advancement in improving disease management strategies in aquaculture. Ongoing research and cooperation between scientists, industry stakeholders, and regulatory bodies are crucial for creating successful and sustainable solutions to combat these difficult diseases.

CONFLICT OF INTEREST

None declared.

REFERENCES

Adamek, M., Matras, M., Dawson, A., Piackova, V., Gela, D., Kocour, M., et al. (2019). Type I interferon responses of common carp strains with different levels of resistance to koi herpesvirus disease during infection with CyHV-3 or SVCV. Fish Shellfish Immunol. 87: 809-819.

Adamek, M., Rakus, K., Chyb, J., Brogden, G., Huebner, A., Irnazarow, I., & Steinhagen, D. (2012). Interferon type I responses to virus infections in carp cells: In vitro studies on Cyprinid herpesvirus 3 and Rhabdovirus carpio infections. Fish Shellfish Immunol. 33(3): 482-493.

Adams, A. (2019). Progress, challenges and opportunities in fish vaccine development. Fish Shellfish Immunol. 90: 210-214.

Ahne, W., Bjorklund, H., Essbauer, S., Fijan, N., Kurath, G., & Winton, J. (2002). Spring viremia of carp (SVC). Dis. Aquat. Organ. 52(3): 261-272.

Aich, N., Paul, A., Choudhury, T. G., & Saha, H. (2022). Tilapia lake virus (TiLV) disease: Current status of understanding. Aquac. Fish. 7(1): 7-17.

Assefa, A., & Abunna, F. (2018). Maintenance of fish health in aquaculture: review of epidemiological approaches for prevention and control of infectious disease of fish. Vet. Med. Int. 2018.

Ballesteros, N. A., Alonso, M., Saint-Jean, S. R., & Perez-Prieto, S. I. (2015). An oral DNA vaccine against infectious haematopoietic necrosis virus (IHNV) encapsulated in alginate microspheres induces dose-dependent immune responses and significant protection in rainbow trout (Oncorrhynchus mykiss). Fish Shellfish Immunol. 45(2): 877-888.

Bandín, I., & Souto, S. (2020). Betanodavirus and VER disease: a 30-year research review. J. Pathog. 9(2): 106.

Barros, M. M., Falcon, D. R., de Oliveira Orsi, R., Pezzato, L. E., Fernandes Jr, A. C., Guimarães, I. G., et al. (2014). Non-specific immune parameters and physiological response of Nile tilapia fed β-glucan and vitamin C for different periods and submitted to stress and bacterial challenge. Fish shellfish immunol. 39(2): 188-195.

Bøgwald, J., & Dalmo, R. A. (2019). Review on Immersion Vaccines for Fish: An Update 2019. Microorganisms. 7(12).

Bomstein, Y., Marder, J., & JOWERS, T. P. (2020). Herbal extracts for treatment of herpesvirus infections: Google Patents.

Borrego, J. J., Valverde, E. J., Labella, A. M., & Castro, D. (2017). Lymphocystis disease virus: its importance in aquaculture. Rev. Aquac. 9(2): 179-193.

Breyer, K. E., Getchell, R. G., Cornwell, E. R., Wooster, G. A., Ketola, H. G., & Bowser, P. R. (2015). Efficacy of an extract from garlic, Allium sativum, against infection with the furunculosis bacterium, Aeromonas salmonicida, in rainbow trout, Oncorhynchus mykiss. JWAS. 46(3): 273-282.

Bricknell, I., & Dalmo, R. A. (2005). The use of immunostimulants in fish larval aquaculture. Fish Shellfish Immunol. 19(5): 457-472.

Buck, C. C., & Loh, P. C. (1985). *In vitro* effect of acyclovir and other antiherpetic compounds on the replication of channel catfish virus. Antiviral res. 5(5): 269-280.

Cain, K. (2022). The many challenges of disease management in aquaculture. JWAS. 53(6).

Caruffo, M., Maturana, C., Kambalapally, S., Larenas, J., & Tobar, J. A. (2016). Protective oral vaccination against infectious salmon anaemia virus in Salmo salar. Fish shellfish immunol. 54: 54-59.

Cho, S. Y., Kim, H. J., Lan, N. T., Han, H.-J., Lee, D.-C., Hwang, J. Y., et al. (2017). Oral vaccination through voluntary consumption of the convict grouper Epinephelus septemfasciatus with yeast producing the capsid protein of red-spotted grouper nervous necrosis virus. Vet. Microbiol. 204: 159-164.

Collet, B. (2014). Innate immune responses of salmonid fish to viral infections. DCI. 43(2): 160-173.

Covarrubias, C. E., Rivera, T. A., Soto, C. A., Deeks, T., & Kalergis, A. M. (2022). Current GMP standards for the production of vaccines and antibodies: An overview. *FPUBH.* 10: 1021905.

Dadar, M., Dhama, K., Vakharia, V. N., Hoseinifar, S. H., Karthik, K., Tiwari, R., et al. (2017). Advances in aquaculture vaccines against fish pathogens: global status and current trends. Rev. Fish. Sci. Aquac. 25(3): 184-217.

Das, B. K., Ellis, A. E., & Collet, B. (2009). Induction and persistence of Mx protein in tissues, blood and plasma of Atlantic salmon parr, Salmo salar, injected with poly I: C. Fish Shellfish Immunol. 26(1): 40-48.

Dishon, A., Ashoulin, O., Scott Weber III, E., & Kotler, M. (2014). Vaccination against koi herpesvirus disease. Fish vac. 321-333.

Dopazo, C. P. (2020). The infectious pancreatic necrosis virus (IPNV) and its virulence determinants: What is known and what should be known. J. Pathog. 9(2): 94.

Du, Y., Hu, X., Miao, L., & Chen, J. (2022). Current status and development prospects of aquatic vaccines. *FPUBH.* 13: 1040336.

Elnagar, M. A., Khalil, R. H., Talaat, T. S., & Sherif, A. H. (2024). A blend of chitosan-vitamin C and vitamin E nanoparticles robust the immunosuppressed- status in Nile tilapia treated with salt. BMC Vet. Res. 20(1): 331.

Emmenegger, E., & Kurath, G. (2008). DNA vaccine protects ornamental koi (Cyprinus carpio koi) against North American spring viremia of carp virus. Vaccine. 26(50): 6415-6421.

Eyngor, M., Zamostiano, R., Kembou Tsofack, J. E., Berkowitz, A., Bercovier, H., Tinman, S., et al. (2014). Identification of a novel RNA virus lethal to tilapia. J. Clin. Microbiol. 52(12): 4137-4146.

Falk, K., Namork, E., Rimstad, E., Mjaaland, S., & Dannevig, B. H. (1997). Characterization of infectious salmon anemia virus, an orthomyxo-like virus isolated from Atlantic salmon (Salmo salar L.).Virol. J. 71(12): 9016-9023.

Ferguson, H. W., Kabuusu, R., Beltran, S., Reyes, E., Lince, J., & del Pozo, J. (2014). Syncytial hepatitis of farmed tilapia, Oreochromis niloticus (L.): a case report. J. Fish. Dis. 37(6): 583-589.

Fernandez-Trujillo, A., Ferro, P., Garcia-Rosado, E., Infante, C., Alonso, M., Bejar, J., et al. (2008). Poly I: C induces Mx transcription and promotes an antiviral state against sole aquabirnavirus in the flatfish Senegalese sole (Solea senegalensis Kaup). Fish Shellfish immunol. 24(3): 279-285.

González-Fernández, C., & Cuesta, A. (2022). Nanoplastics increase fish susceptibility to nodavirus infection and reduce antiviral immune responses. Int. J. Mol. Sci. 23(3): 1483.

Gye, H. J., Oh, M.-J., & Nishizawa, T. (2018). Lack of nervous necrosis virus (NNV) neutralizing antibodies in convalescent sevenband grouper Hyporthodus septemfasciatus after NNV infection. Vaccine. 36(14): 1863-1870.

Hadfield, C. A. (2021). Viral diseases. Clinical Guide to Fish Medicine, 407-430.

Hanson, L., Dishon, A., & Kotler, M. (2011). Herpesviruses that infect fish. Viruses. 3(11): 2160-2191.

Huang, X., Ma, Y., Wang, Y., Niu, C., Liu, Z., Yao, X., et al. (2021). Oral probiotic vaccine expressing koi herpesvirus (KHV) ORF81 protein delivered by chitosan-alginate capsules is a promising strategy for mass oral vaccination of carps against KHV infection. Virol. J. 95(12): 10.1128/jvi. 00415-00421.

Ibrahim, R. E., Amer, S. A., Farroh, K. Y., Al-Gabri, N. A., Ahmed, A. I., El-Araby, D. A., & Ahmed, S. A. A. (2021). The effects of chitosan-vitamin C nanocomposite supplementation on the growth performance, antioxidant status, immune response, and disease resistance of Nile tilapia (Oreochromis niloticus) fingerlings. Aquac. 534: 736269.

Irshath, A. A., Rajan, A. P., Vimal, S., Prabhakaran, V. S., & Ganesan, R. (2023). Bacterial Pathogenesis in Various Fish Diseases: Recent Advances and Specific Challenges in Vaccine Development. Vaccines (Basel). 11(2).

Islam, S. I., Mou, M. J., & Sanjida, S. (2022). Application of reverse vaccinology for designing of an mRNA vaccine against re-emerging marine birnavirus affecting fish species. IMU. 30: 100948.

Isshiki, T., Nagano, T., Kanehira, K., & Suzuki, S. (2004). Distribution of marine birnavirus in cultured marine fish species from Kagawa

Prefecture, Japan. J. Fish Dis. 27(2): 89-98.
Jaemwimol, P., Sirikanchana, K., Tattiyapong, P., Mongkolsuk, S., & Surachetpong, W. (2019). Virucidal effects of common disinfectants against tilapia lake virus. J. Fish Dis. 42(10): 1383-1389.
Jansen, M. D., Dong, H. T., & Mohan, C. V. (2019). Tilapia lake virus: a threat to the global tilapia industry? Rev. Aquac. 11(3): 725-739.
Jensen, I., Albuquerque, A., Sommer, A.-I., & Robertsen, B. (2002). Effect of poly I: C on the expression of Mx proteins and resistance against infection by infectious salmon anaemia virus in Atlantic salmon. Fish shellfish immunol. 13(4): 311-326.
Jung, M.-H., Jung, S.-J., & Kim, T. (2022). Saponin and chitosan-based oral vaccine against viral haemorrhagic septicaemia virus (VHSV) provides protective immunity in olive flounder (Paralichthys olivaceus). Fish shellfish immunol. 126: 336-346.
Kembou-Ringert, J. E., Steinhagen, D., Readman, J., Daly, J. M., & Adamek, M. (2023). Tilapia Lake Virus Vaccine Development: A Review on the Recent Advances. Vaccines (Basel). 11(2).
Kibenge, F. S., Godoy, M. G., Fast, M., Workenhe, S., & Kibenge, M. J. (2012). Countermeasures against viral diseases of farmed fish. Antiviral res. 95(3): 257-281.
Kim, H. J., Oseko, N., Nishizawa, T., & Yoshimizu, M. (2009). Protection of rainbow trout from infectious hematopoietic necrosis (IHN) by injection of infectious pancreatic necrosis virus (IPNV) or Poly (I: C). Dis. Aquat. Organ. 83(2): 105-113.
Kimura, T., Suzuki, S., & Yoshimizu, M. (1983). In vitro antiviral effect of 9-(2-hydroxyethoxymethyl) guanine on the fish herpesvirus, Oncorhynchus masou virus (OMV). Antiviral Res. 3(2): 93-101.
Kotob, M. H., Menanteau-Ledouble, S., Kumar, G., Abdelzaher, M., & El-Matbouli, M. (2017). The impact of co-infections on fish: a review. Vet. Res. 47(1): 1-12.
Labella, A. M., Leiva-Rebollo, R., Alejo, A., Castro, D., & Borrego, J. J. (2019). Lymphocystis disease virus (LCDV-Sa), polyomavirus 1 (SaPyV1) and papillomavirus 1 (SaPV1) in samples of Mediterranean gilthead seabream. Dis. Aquat. Organ. 132(2): 151-156.
Lee, J. Y., & Gao, Y. (2012). Review of the application of garlic, Allium sativum, in aquaculture. JWAS. 43(4): 447-458.
Lee, Y., Kim, N., Roh, H., Park, J., Kim, M., Lee, J., & Kim, D.-H. (2022). Hepcidin-1 in olive flounder (Paralichthys olivaceus): Gene expression, antimicrobial and therapeutic effects of synthetic peptides against bacterial and viral infections. Aquac. 560: 738480.
Li, C., Cao, Y., Kohei, F., Hao, H., Peng, G., Cheng, C., & Ye, J. (2022). Nano-bubble hydrogen water: An effective therapeutic agent against inflammation related disease caused by viral infection in zebrafish model. Virol. Sin. 37(2): 277-283.
Li, P., Huang, S., Xiao, S., Xu, Y., Wei, X., Xiao, J., et al. (2022). Antiviral Activities of Green Tea Components against Grouper Iridovirus Infection In Vitro and In Vivo. Viruses. 14(6).
Li, Y., Zheng, S., Wang, Q., Bergmann, S. M., Zeng, W., Wang, Y., et al. (2017). Detection of koi herpesvirus (KHV) using a monoclonal antibody against Cyprinus carpio IgM. Arch. Virol. 162(8): 2381-2385.
Lieke, T., Meinelt, T., Hoseinifar, S. H., Pan, B., Straus, D. L., & Steinberg, C. E. (2020). Sustainable aquaculture requires environmental-friendly treatment strategies for fish diseases. Rev. Aquac. 12(2): 943-965.
Liu, R., Hu, X., Lü, A., Song, Y., Lian, Z., Sun, J., & Sung, Y. Y. (2020). Proteomic profiling of zebrafish challenged by spring viremia of carp virus provides insight into skin antiviral response. Zebrafish. 17(2): 91-103.
Lockhart, K., Bowden, T., & Ellis, a., AE. (2004). Poly I: C-induced Mx responses in Atlantic salmon parr, post-smolts and growers. Fish shellfish immunol. 17(3): 245-254.
Lulijwa, R., Alfaro, A. C., Merien, F., Meyer, J., & Young, T. (2019). Advances in salmonid fish immunology: A review of methods and techniques for lymphoid tissue and peripheral blood leucocyte isolation and application. Fish shellfish immunol. 95: 44-80.
Ma, J., Bruce, T. J., Jones, E. M., & Cain, K. D. (2019). A Review of Fish Vaccine Development Strategies: Conventional Methods and Modern Biotechnological Approaches. Microorganisms. 7(11).
Magnadottir, B. (2010). Immunological control of fish diseases. Mar. biotechnol. 12: 361-379.
Manchanayake, T., Salleh, A., Amal, M. N. A., Yasin, I. S. M., & Zamri-Saad, M. (2023). Pathology and pathogenesis of Vibrio infection in fish: A review. Aquac. Rep. 28: 101459.
Meena, D., Das, P., Kumar, S., Mandal, S., Prusty, A., Singh, S., et al. (2013). Beta-glucan: an ideal immunostimulant in aquaculture (a review). Fish Physiol. Biochem. 39: 431-457.
Mishra, S., Seshagiri, B., Rathod, R., Sahoo, S. N., Choudhary, P., Patel, S., et al. (2023). Recent advances in fish disease diagnosis, therapeutics, and vaccine development. Frontiers in Aquaculture Biotechnology. 115-145.
Mugimba, K. K., Byarugaba, D. K., Mutoloki, S., Evensen, Ø., & Munang'andu, H. M. (2021). Challenges and Solutions to Viral Diseases of Finfish in Marine Aquaculture. J. Pathog. 10(6).
Ninawe, A., Hameed, A. S., & Selvin, J. (2017). Advancements in diagnosis and control measures of viral pathogens in aquaculture: an Indian perspective. Aquac. Int. 25: 251-264.
Nishizawa, T., Furuhashi, M., Nagai, T., Nakai, T., & Muroga, K. (1997). Genomic classification of fish nodaviruses by molecular phylogenetic analysis of the coat protein gene. Appl. Environ. Microbiol. 63(4): 1633-1636.
O'Connor, M. R., Farver, T. B., Malm, K. V., Yun, S. C., Marty, G. D., Salonius, K., et al. (2014). Protective immunity of a modified-live cyprinid herpesvirus 3 vaccine in koi (Cyprinus carpio koi) 13 months after vaccination. Am. J. Vet. Res. 75(10): 905-911.
Ortega-Villaizan, M. d. M., Chico, V., & Perez, L. (2022). Fish innate immune response to viral infection—An overview of five major antiviral genes. Viruses. 14(7): 1546.
Ouyang, G., Liao, Q., Fan, S., Cai, X., Wang, J., Liu, X., & Xiao, W. (2023). Zebrafish Mavs is essential for antiviral innate immunity. J. Immunol. 210(9): 1314-1323.
Pagowski, V. A., Mordecai, G. J., Miller, K. M., Schulze, A. D., Kaukinen, K. H., Ming, T. J., et al. (2019). Distribution and phylogeny of erythrocytic necrosis virus (ENV) in salmon suggests marine origin. Viruses. 11(4): 358.
Patel, S., & Nerland, A. H. (2014). Vaccination against diseases caused by Betanodavirus. Fish Vac. 341-351.
Pereiro, P., Costa, M., Díaz-Rosales, P., Dios, S., Figueras, A., & Novoa, B. (2014). The first characterization of two type I interferons in turbot (Scophthalmus maximus) reveals their differential role, expression pattern and gene induction. Dev. Comp. Immunol. 45(2): 233-244.
Pereiro, P., Figueras, A., & Novoa, B. (2021). Compilation of antiviral treatments and strategies to fight fish viruses. Rev. Aquac. 13(3): 1223-1254.
Perveen, S., Yang, L., Xie, X., Han, X., Gao, Q., Wang, J., et al. (2022). Vitamin C elicits the activation of immunological responses in swimming crab (Portunus trituberculatus) hemocytes against Mesanophrys sp. Aquaculture. 547: 737447.
Rahmati-Holasoo, H., Ahmadivand, S., Shokrpoor, S., & El-Matbouli, M. (2020). Detection of Carp pox virus (CyHV-1) from koi (Cyprinus carpio L.) in Iran; clinico-pathological and molecular characterization. Mol. Cell. Probes. 54: 101668.
Rajanbabu, V., & Chen, J.-Y. (2011). Applications of antimicrobial peptides from fish and perspectives for the future. Peptides. 32(2): 415-420.
Rao, Y., & Su, J. (2015). Insights into the antiviral immunity against grass carp (Ctenopharyngodon idella) reovirus (GCRV) in grass carp. J. Immunol. Res. 2015.
Reichert, M., Bergmann, S. M., Hwang, J., Buchholz, R., & Lindenberger, C. (2017). Antiviral activity of exopolysaccharides from Arthrospira platensis against koi herpesvirus. J Fish Dis. 40(10): 1441-1450.
Reyes-López, F. E., Romeo, J. S., Vallejos-Vidal, E., Reyes-Cerpa, S., Sandino, A. M., Tort, L., et al. (2015). Differential immune gene expression profiles in susceptible and resistant full-sibling families of Atlantic salmon (Salmo salar) challenged with infectious pancreatic necrosis virus (IPNV). Dev. Comp. Immunol. 53(1): 210-221.
Romero, J. F., Gardner, I. A., Saksida, S., McKenzie, P., Garver, K., Price, D., & Thakur, K. (2022). Simulated waterborne transmission of infectious hematopoietic necrosis virus among farmed salmon populations in British Columbia, Canada following a hypothetical virus incursion. Aquac. 548: 737658.
Sanjida, S., Mou, M. J., Islam, S. I., & SAROWER-E-MAHFUJ, M. (2022). An In-silico approaches for identification of potential natural

antiviral drug candidates against Erythrocytic necrosis virus (Iridovirus) by targeting Major capsid protein: a Quantum mechanics calculations approach. Int. J. Life Sci. Biotechnol. 5(3): 294-315.

Shahsavani, D., Baghshani, H., & Alishahi, E. (2011). Efficacy of allicin in decreasing lead (Pb) accumulation in selected tissues of lead-exposed common carp (Cyprinus carpio). Biol. Trace. Elem. Res. 142: 572-580.

Soto, E., Yun, S., & Surachetpong, W. (2019). Susceptibility of Tilapia Lake Virus to buffered Povidone-iodine complex and chlorine. Aquac. 512: 734342.

Thammatorn, W., Rawiwan, P., & Surachetpong, W. (2019). Minimal risk of tilapia lake virus transmission via frozen tilapia fillets. J. Fish Dis. 42(1): 3-9.

Vimal, S., Farook, M., Madan, N., Abdul Majeed, S., Nambi, K., Taju, G., et al. (2016). Development, distribution and expression of a DNA vaccine against nodavirus in Asian Seabass, Lates calcarifier (Bloch, 1790). Aquac. Res. 47(4): 1209-1220.

Waiyamitra, P., Zoral, M. A., Saengtienchai, A., Luengnaruemitchai, A., Decamp, O., Gorgoglione, B., & Surachetpong, W. (2020). Probiotics modulate tilapia resistance and immune response against tilapia lake virus infection. J. Pathog. 9(11): 919.

Weber, E. S., Malm, K. V., Yun, S. C., Campbell, L. A., Kass, P. H., Marty, G. D., et al. (2014). Efficacy and safety of a modified-live cyprinid herpesvirus 3 vaccine in koi (Cyprinus carpio koi) for prevention of koi herpesvirus disease. Am. J. Vet. Res. 75(10): 899-904.

Xia, S., Wang, H., Hong, X., Lu, J., Xu, D., Jiang, Y., & Lu, L. (2018). Identification and characterization of a type I interferon induced by cyprinid herpesvirus 2 infection in crucian carp Carassius auratus gibelio. Fish Shellfish Immunol. 76: 35-40.

Yildirim, A., Duran, G. G., Duran, N., Jenedi, K., Bolgul, B. S., Miraloglu, M., & Muz, M. (2016). Antiviral activity of hatay propolis against replication of herpes simplex virus type 1 and type 2. Med. Sci. Monit: Med Sci Monit. 22: 422.

Yu, X. B., Hao, K., Ling, F., Zhu, B., & Wang, G. X. (2020). In vivo antiviral efficacy of moroxydine hydrochloride against grass carp reovirus and the drug safety assessment. Aquac. Res. 51(4): 1592-1601.

Zeng, W., Wang, Y., Hu, H., Wang, Q., Bergmann, S. M., Wang, Y., et al. (2021). Cell culture-derived tilapia lake virus-inactivated vaccine containing montanide adjuvant provides high protection against viral challenge for tilapia. Vaccines. 9(2): 86.

Zhou, X.-y., Lu, L.-f., Li, Z.-c., Zhang, C., Chen, D.-d., & Li, S. (2021). Temperature effects on SVCV propagation and the related IFN response in zebrafish. Aquac. 533: 736084.

Zhou, Y., Qiu, T.-X., Hu, Y., Ji, J., Liu, L., & Chen, J. (2022). Evaluation on the antiviral activity of artemisinin against rhabdovirus infection in common carp. Aquac. 559: 738410.

Zhu, X., Hao, R., Zhang, J., Tian, C., Hong, Y., Zhu, C., & Li, G. (2022). Improved growth performance, digestive ability, antioxidant capacity, immunity and Vibrio harveyi resistance in coral trout (Plectropomus leopardus) with dietary vitamin C. Aquac. Rep. 24: 101111.