Aquaculture International (2022) 30:227–262
https://doi.org/10.1007/s10499-021-00795-2

Viral infections in cultured fish and shrimps: current status and treatment methods

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Received: 26 May 2021 / Accepted: 15 October 2021 / Published online: 4 November 2021

Abstract
Aquaculture is growing post-haste in recent years particularly in the fish and shrimp production. The rapid growth of aquaculture and increasing demand for fish have led to a rapid development of the fish and shrimp industry, resulting in increased production of both fish and shrimps. As a result, there is a greater risk of disease outbreaks. Mass mortalities in aquaculture are primarily due to infectious diseases caused by bacteria, viruses, and fungi. Among them, viral diseases are the most devastating, causing huge loss in the production of both cultured fish and shellfishes. There are several effective methods of treatment for these disease outbreaks. This review focuses on various methods of controlling the viral pathogens using various treatment methods like use of medicinal plants and seaweed extracts, bioactive compounds from actinomycetes, vaccines, probiotic microbes, chemicals, nanoparticles, and green synthesis of nanoparticles.

Keywords Aquaculture · Disease outbreak · Infectious · Efficacious · Treatments

Introduction

Aquaculture is considered as the major source for enhancing the fish supply (Reverter et al. 2014). It is considered as a major food-producing sector for a rapidly increasing population as it constitutes up to 45% of the total production of fish around the globe (Aseefa and Abunna 2018; Chauhan and Singh 2019). India ranks second in aquaculture and third in fishery production. Fisheries contribute to 1.07% of the total GDP of India. According to the National Fisheries Development Board, the fishery industry generates an export earnings of Rs 334.41 billion (Kushankar Dey 2020). Since it is now a global industry, the total production has exceeded 50 million tonnes annually with an estimated value of around 80 billion US$ (FAO 2009; Walker and Winton 2010). The rapid growth of aquaculture and increasing demand for fish has led to rapid

Handling Editor: Gavin Burnell

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growth of the fish industry, increasing exacerbation for fish and hence intensifying the risk of disease outbreaks (Reverter et al. 2014). At present, infectious disease outbreak in aquaculture is the major reason for the increasing economic loss to the fish industries. Carp, shrimps, and oysters are the major species produced in Asia accounting for 98%, 88%, and 95% respectively of the production. Countries like Norway, the US, Canada, and Chile account for 94% by value and 88% by volume of Atlantic Salmon produced (FAO 2008; Walker and Winton 2010). From the year 1970 to 2007, with an average growth of 6.9% annually, aquaculture has proved to be a rapidly growing food-producing sector, since it can soon overtake the capture fisheries as the main source of seafood (FAO 2008; Walker and Winton 2010). Excluding China, the share of Asian fish production in aquaculture has risen from 19.3% in the year 2000 to 42% in 2018 (FAO 2020).

Fish and shrimps are exposed to various viral pathogens in the environment and also within aquaculture sites (Scott et al. 2011). Viral diseases are reported to be the one of the main causes of mass mortalities in aquaculture (Muroga 2001).

As far as viral diseases in fish are concerned, a review by (Crane and Hyatt 2011) reported that viral pathogens which include aquabirnaviruses and infectious hematopoietic necrosis virus reported in fin fish are known since the first half of the twentieth century. In addition, betanodaviruses which have also emerged as pathogens in aquaculture have undergone dramatic expansion in the past few decades.

In 2001, a review paper regarding various viral infections in fish and shellfish in Japanese hatcheries was published. This paper gave a brief information of herpesvirus infections like viral epidermal hyperplasia occurring in Japanese flounder, nodavirus infections such as viral nervous necrosis in the Japanese parrotfish as well as in striped jack, birnavirus infections like viral ascites in yellowtail, baculoviral infections like baculoviral mid-gut gland necrosis, and unclassified virus infections like panaeid acute viremia in kuruma prawn (Muroga 2001).

In 2007, another review article which gave an insight into the viral pathogens was published. The authors covered several topical viruses causing problems in aquaculture as well as methods for their control and prevention (Austin and Austin 2007). Also, another review study done by (Munang'andu et al. 2016) reported the control and preventive measures for curing viral pathogens in aquaculture by reducing their prevalence.

Viral diseases in shrimp were reviewed in a paper on viral infections and their diagnosis as well as control measures in aquaculture was published in the year 2017. Some of the major viral pathogens like white spot syndrome virus (WSSV), hepatopancreatic parvovirus (HPV), white tail disease (WTD), monodon baculovirus (MBV), viral nervous necrosis (VNN), and infectious hypodermal and hematopoietic necrosis baculovirus (IHHNV) that predominately affected shrimp and fish aquaculture were reported (Ninawe et al. 2017). To deal with these pathogens which have been emerging, expanding, and responsible for disease outbreaks and threats of outbreaks, several efficacious treatments have been developed and reported.

The aim of the present review is to highlight the methods of controlling several viral pathogens in aquaculture using various treatment methods. In this study, the control of these pathogens using treatments like medicinal plants, seaweeds, actinomycetes, vaccines, probiotic microbes, chemicals, nanoparticles, and green synthesis of nanoparticles against viral pathogens of fish and shrimps is reviewed.

Prophylactic and treatment methods for viral diseases of fish and shellfish

Among the pathogenic diseases observed in the aquatic organisms, viral pathogens are mostly responsible and associated with half of them after bacterial pathogens followed by others (McLoughlin 2006). The treatment methods that can be used to cure infectious viral pathogens are mentioned below:

Prophylactic approach by administration of vaccines

Vaccination is one of the traditional methods of effectively preventing several infectious diseases. The different kinds of vaccines available for use in fishes includes attenuated vaccines, recombinant technology vaccines, killed vaccines, DNA vaccines, and synthetic peptide vaccines. The techniques and modes of administration of these vaccines in fish involves oral, immersion, and injection methods (Aseefa and Abunna 2018).

In the aquaculture industry, vaccines create a huge impact by reducing the use of certain antibiotics, thereby avoiding the possibility of drug resistance and protecting the fishes from these infectious diseases. Novel vaccine registration and its need for licensing is considered much simpler than antibiotics (Plant and LaPatra 2011).

Currently, killed vaccines are the most commonly used commercial vaccines in the aquaculture industry, since they can be designed effortlessly, are cheap, remain stable in storage, and have no problem of being virulent (Pridgeon and Klesius 2012). Several infectious diseases such as those caused by pathogens like infectious hematopoietic virus can be prevented using killed vaccines (Aseefa and Abunna 2018). On the contrary, few studies have also reported that inactivated/killed vaccines generate insufficient immunity as in the case of red sea bream iridovirus (RSIV) disease or salmon pancreas disease virus (SPDV) (Evensen and Leong 2013).

From laboratory studies, the efficacy of the live vaccines in fishes was observed, since it stimulated humoral, mucosal, and also cellular immunity (Shoemaker et al. 2009). The attenuated organisms were reported to replicate inside the targeted host without showing clinical signs (Lillehaug 2014).

DNA vaccines when injected intramuscularly give durable protection immediately from infections occurring in the farmed salmonids against certain infectious diseases like hematopoietic necrosis virus which have an economic impact (Ballesteros et al. 2015). It also acts against viral hemorrhagic septicemia virus (Cho et al. 2017). These vaccines have also been studied in infections involving viral hemorrhagic septicemia virus (VHSV), infectious hematopoietic necrosis virus (IHNV), and salmonid rhabdoviruses and were found to be very beneficial and effective against them for reducing the effect of these viruses. Moreover, these two DNA virus vaccines have been experimented on more viral diseases of fishes such as hirame rhabdovirus and spring viremia carp virus (Aseefa and Abunna 2018). It has been reported that nearly all DNA vaccines were developed for treatment of viral infections of fish (Dhar et al. 2014). For the protection of salmon from infectious diseases like salmon anemia and hematopoietic necrosis recombinant vector vaccines were developed in which viruses were used to express in the vectors (Dadar et al. 2016). Subunit vaccines are safer but since their immunogenicity is poor compared to whole organism, inactivated vaccine adjuvants are needed to improve their immunogenicity (Dadar et al 2016). Vaccines developed now use modern vaccine technology that targets particular

pathogen components. Recombinant DNA or subunit vaccines that contain novel antigens produced with the aid of several expression systems are examples of this (Kelly and Rappuoli 2005; Cimica and Galarza 2017; Ma et al. 2019). Other expression systems that have been reported in the production of fish subunit vaccine experimentally include baculovirus for VHSV or IHNV proteins (Estepa et al. 1994; Lecocq-Xhonneux et al. 1994; Lorenzen and Olesen 1995; Cain et al. 1999; Biering et al. 2005; Crane and Hyatt 2011). Live attenuated vaccines can replicate to a lower titer value and can therefore stimulate both cellular and humoral immunity (Dadar et al. 2016).

Since there existed a lack of knowledge and understanding of the immune responses of fishes against various antigens which were also considered less potent, a carrier molecule was required. This is why many studies reported that vaccination of fish with the peptides is almost impracticable (Mweemba et al. 2014). Emmenegger et al. (1995) developed synthetic vaccines earlier in aquaculture in which the synthetic peptide antigen for IHNV was produced by coupling the antigens to bovine serum albumin (BSA). Later, Lin et al. (2002) made synthetic peptides to protect the freshwater shrimps against white spot disease by expressing the glycosylated phosphatidylinositol (GPI) anchoring membrane protein and immobilization antigen (I-antigen) using an assembly PCR technique to manufacture these peptides. Joshi et al. (2021) reported an in silico design of an epitope-based vaccine against seven banded grouper nervous necrosis virus affecting fish species. Recently, a study was reported by Kulkarni et al. (2021) on the immunoprotection trials and immune responses in the crustaceans focusing mainly on shrimps which highlighted potential development of effective immunoprophylactic strategies in shrimp. These vaccines have been used for a long time in the prevention of many infectious diseases including birnavirus, nodavirus, viral hemorrhagic septicemia, and rhabdovirus (Dadar et al. 2016).

Most of the viral vaccines for aquaculture available at present are mainly based on recombinant subunit proteins or inactivated/killed virus (Sommerset et al. 2005). Live viral vaccines have been found to show good results when tested in fishes (Benmansour and de Kinkelin 1997; Lopez-Doriga et al. 2001; Ronen et al. 2003). Kim et al. (2000) reported that DNA vaccines in fish induce an early, non-specific antiviral protection mediated by an alpha/beta interferon and, later, a specific immune response. Sommerset et al. (2005) reported that recombinant VP35 protein can induce immunity and protect grass carp against grass carp reovirus infection and that it could be used as a subunit vaccine.

Some diseases caused by pathogens like infectious pancreatic necrosis virus (IPNV), birnavirus, are reported to cause major problems in salmonids (Biering et al. 2005). Marine IPNV strains commonly known as aquatic birnaviruses are also reported to be pathogenic in a wide range of marine fish species that includes European sea bass, Japanese eel, halibut, yellowtail, and turbot, for which vaccines are unavailable (Sommerset et al. 2005). In addition, infectious hematopoietic necrosis virus (IHNV) (in North America and France), the rhabdoviruses, and viral hemorrhagic septicemia virus (VHSV) (in France and Denmark) were found to be predominantly affecting the salmonids and causing highly infectious diseases (Sommerset et al. 2005). Betanodaviruses causing viral nervous necrosis (VNN) have been affecting various farmed marine fish species such as Atlantic halibut, European sea bass, barramundi, and groupers (Munday et al. 2002) for which commercial vaccines are now available. Two formalin-inactivated commercial vaccines ICTHIOVAC® VNN (Hipra) and ALPHA JECT micro® 1Noda (Pharmaq) have been made available for vaccination in sea bass against red grouper nervous necrosis virus (RGNNV) genotype in the Mediterranean region (Valero et al. 2021).

Water temperature may be an important factor in deciding the time of vaccination. In addition, the size of fish is also responsible for the regulation of immune competence

development (Vallejos-Vidal et al. 2014). Since oral feeding prevents stress in fish, oral vaccination can be easily administered by either incorporating it into the feed during its production or by encapsulating or coating with the pellets (Lillehaug 2014). Immersion method of vaccination is especially convenient in the case of smaller fishes and fingerlings in which other methods of vaccination are impractical. During immersion, vaccines are applied on the surface of the fish. The uptake of the antigen takes place through gills, skin, and also via the lateral line. Besides, this method causes minimal level of stress in fishes. Moreover, the vaccine solution can also be reused. Vaccination by injection gives the best protection in the case of adjuvant vaccines (Harikrishnan et al. 2011). This method of vaccination requires a relatively minimal amount of dose, since calculating the accurate dosage is simple as well as economical in the case of larger fishes. This method of injecting a vaccine is however not suitable for smaller fishes because of stress, adhesion formation, reduction in intake of feed, and damage occurring at the time of injection that may lead to massive deaths in fishes (Lillehaug 2014).

Recently, Zeng et al. (2021) reported a newly emerging pathogenic virus, tilapia lake virus (TiLV), that has created a huge impact on the tilapia industry globally for which currently no vaccines or antiviral drugs are available for its prevention and control. They developed a β-propiolactone inactivated TiLV vaccine that exhibited a higher protection efficacy against this virus compared to formaldehyde. β-Propiolactone inactivated vaccine combined with Montanide IMS 1312 VG adjuvant can result in higher level of protection from TiLV infection in tilapia fish (Zeng et al. 2021). In the year 2019, a study regarding fish immunization as an effective treatment method for the prevention of a wide range of viral and other pathogenic diseases was reported (Ma et al. 2019). Currently, there are many vaccines which have been approved for use in aquaculture in salmonids, catfish, rainbow trout, common carp (*Cyprinus carpio*), koi carp (*Cyprinus rubrofuscus)*, Indian major carps, tilapia, grouper, lobster, and sea bass (Aseefa and Abunna 2018).

Treatment using chemicals

Therapeutic substances are often added into the water for controlling several infectious diseases affecting gills and body surface. In a few cases, therapeutic baths have also been used, since the active substances are absorbed via skin and thereby control these causative agents. Based on their exposure period, the therapeutic baths have been categorized as immersion baths (up to 5 min), short-term baths (from 5 min to 2 h and long-term baths (2 h to a few days). The chemical substances used in immersion bath of fishes include Lysol, $KMnO_4$, lime milk, ammonia and trypaflavine, $CuSO_4 \cdot H_2O$. In the case of short-term baths, NaCl, formaldehyde, and $KMnO_4$ are added. For long-term baths carried out in ponds as well as fish culture reservoirs, acriflavine, metronidazol, antibiotics, trichlorphon, formaldehyde $KMnO_4$, and NaCl have been used (Tesarčík and Svobodová 1991). Shamsuzzaman and Biswas (2012) reported that chemicals like timsin and emsin are effective in destroying viruses by preventing viral infections. Rao (2020) reported that this is an eco-friendly solution for the treatment of viral diseases (currently, traditional preparations such as Wescodyne or Incodyne have been used on an increasingly large scale, since it helps in controlling viral diseases of the fish eggs (Tesarčík and Svobodová 1991)). Amend and Pietsch (1972) reported that two iodophors, Wescodyne® and Betadine® showed virucidal activity against salmonid viruses like IHNV, IPNV, and VHSV.

The therapeutic substances have been administered either in the form of granulated medicated feeds where the pellets have been incorporated with the drug or are amalgamated

with the feeds. Poly(vinylpyrrolidone)–iodine (PVP-I), a broad-spectrum antiseptic was reported as one of the first antiviral compounds used in aquaculture that helps in inhibition of viral release as well as spread from the infected cells by blocking viral attachment to the cellular receptors (Sriwilaijaroen et al. 2009; Pereiro et al. 2020). There was a reduction observed in both morbidity and mortality in brook trout *Salvelinus fontinalis* caused by IPNV when fed with PVP-I (Pereiro et al. 2020; Economon 1963, 1973). Batts et al. (1991) reported that iodine was found to be effective in treating the IHNV infection in rainbow trout when added to water at lower concentrations. Moreover, several studies reported the ability of iodine complexes to destroy fish pathogenic viruses like IHNV, VHSV, and IPNV (Pereiro et al. 2020; Amend and Pietsch 1972; Elliott and Amend 1978). PVP-I is currently used to disinfect the surfaces of eggs in aquaculture (Cipriano et al. 2001). Boriskin et al. (2008) reported that arbidol hydrochloride is a fusion step of another compound that can block viral attachment to the target membranes. However, it was found to be ineffective against the iridovirus SGIV-infected grouper spleen (GS) cells at the particularly tested concentration (Jia et al. 2018; Pereiro et al. 2020).

Sushila et al. (2018) reported that lysosomotropic agent NH_4Cl and clathrin-mediated endocytosis inhibitor chlorpromazine (CPZ) exhibited antiviral activities against nervous necrosis virus (NNV) infection in the Sahul Indian sea bass kidney cell line (SISK). Adachi et al. (2007) also demonstrated the efficacy of various lysosomotropic agents such as NH_4Cl, monensin, bafilomycin A1, and chloroquine (CQ) against betanodavirus NNV infection in snakehead fish cell line E11. Huang et al. (2017) reported similar results in Asian sea bass cells against NNV virus-like particles (VLPs). In addition, both CQ and NH_4Cl, chemical inhibitors of endosomal acidification, inhibited the entry of VLP (Huang et al. 2017; Pereiro et al. 2020). Guo et al. (2012) observed that NH_4Cl, sucrose, CQ, and CPZ were inefficient in reducing the infection of fish iridovirus (ISKNV) in cell line of Mandarin fish fry (MFF-1), while phorbol 12-myristate 13-acetate (PMA) significantly reduced the virus entry. Vigant et al. (2013) reported that LJ001, a derivative of lipophilic thiazolidine, displayed its broad-spectrum antiviral activity against 3 different kinds of fish rhabdoviruses IHNV, SVCV, and VHSV infections (Balmer et al. 2017, 2018; Pereiro et al. 2020).

The efficacy of CQ against IHNV infection has been demonstrated in chinook salmon embryo (CHSE-214) cells by Hasobe and Saneyoshi (1985a, 1985b) but only an insignificant level of protection was observed when IHNV-infected rainbow trout fry was treated with CQ dissolved in water (Hasobe and Saneyoshi 1985b). De Las Heras et al. (2008) reported that CQ was efficient in reducing IHNV binding to bluegrill fry (BF-2) cell line but was found to be ineffective against VHSV and IPNV. Moreover, De Las Heras et al. (2008) observed the efficacy of tributylamine, another lysosomotropic compound against these three pathogenic fish viruses. Recently, Jaemwimol et al. (2019) reported that a buffered acid peroxygen solution called Virkon®, a multipurpose disinfectant, was effective against TiLV infection with greater than 5 $\log_{10}$ reduction condition.

Treatment using bioactive compounds from actinomycetes

Actinomycetes are the gram-positive bacteria which inhabit both terrestrial and marine environments. These species are known to be fastidious and hence are difficult to culture as well as isolate.

Marine actinomycetes are regarded as a beneficial source of several antimicrobial agents. In addition, it can also produce various antiviral drugs against DNA as well as RNA

viruses. Since usage of these antiviral drugs in large amounts for treating viral diseases can stimulate mutagenicity as well as cross-resistance, marine actinomycetes are considered as a novel source that can be used as an antiviral drug (Moussa et al. 2015). Since they are important producers of mainly antibiotic compounds and vitamins, antitumor agents, enzymes, immunomodifying agents and are widespread, they have a major role in the production of pharmaceuticals (Lam 2006).

Sree Kumar et al. (2006) reported the antiviral property and effectiveness of marine actinomycetes in penaeid shrimps against WSSV. The isolated actinomycetes were used as feed additives to the WSSV-infected post-larvae of black tiger shrimp, *Penaeus monodon*, which displayed post-challenge survival ranging from 11 to 83%. A review paper by Jakubiec-Krzesniak et al. (2018) presented secondary metabolites of Actinobacteria, which possess antibacterial, antifungal, and antiviral activities.

Diseases transmitted by all kinds of microorganisms especially viruses are increasingly becoming a threat to society. Hence, to control the spread of these pathogens and also due to the increasing resistance to chemical drugs, there is an urgent need to develop novel antimicrobial agents extracted from these actinomycetes (Ganesan et al. 2017).

Use of probiotics

Probiotics usually consist of bacteria but can also include other microorganisms like microalgae, yeast, or fungi (Cordero et al. 2014). Use of probiotics is a positive alternative approach to prevent, control, and treat infectious diseases. Its effects include growth stimulation, improvement of digestion, immune response enhancement, and also recuperation of water quality. Generally, probiotics exhibit various antiviral properties which are beneficial to fishes, since they fight against these pathogens and thus improve their overall health. Currently, use of probiotics in aquaculture and its efficacy in aquatic environments needs to be explored (Chauhan and Singh 2019).

Probiotics that are used in the aquaculture are available in dry and liquid form. The former has a higher shelf life and is either mixed with the water or feed while the latter form of the probiotic is blended with the feed or is added into the tanks directly (Decamp and Moriarty 2007). Studies reported that due to lower density, the liquid form gives a much better and positive results compared to the dry form of probiotics (Nageswara and Babu 2006). Several aquatic probiotics have been reported to show activity against viral pathogens for the improvement of growth and even immunity of host (Chauhan and Singh 2019). The main search has always been for compounds that can be incorporated into the feed and hence orally delivered to the fish while others may be injected along with the vaccines (Chauhan and Singh 2019).

Based on their mode of administration, probiotics in liquid form are further classified into two categories which are used in shrimp and finfish aquaculture. The first class involves the probiotic bacteria being mixed with the feed supplement for enhancing the beneficial bacteria inside gut region. The second class deals with the probiotics added to the water directly so that available nutrients in the water can be consumed and pathogen proliferation can also be inhibited (Nageswara and Babu 2006; Sahu et al. 2008).

Methods of enhancing the natural defense mechanism of a fish have always been the main focus of research in aquaculture, since it has a lot of useful advantages (Defoirdt et al. 2011). Biological control of diseases in aquaculture has become the best approach for controlling the infectious diseases (Maqsood et al. 2011). Probiotics are considered non-pathogenic to fishes and other aquatic animals, since they are the bacterial cultures

isolated from bacterial strains (Sharifuzzaman and Austin 2017). In other words, they can be described as a live organism that is administered to the hosts for developing a defensive immune system which after administration to the fishes later multiplies to inhabit the fish gut. Thus, they are useful in maintaining the normal microflora and also the microbial balance in hosts (Mastan 2015).

In aquaculture, among the many microorganisms, there are a few which have been reported as aquatic probiotics and are used in fishes and even in various cultured animals for disease prevention as well as weight gain promotion. They can either be incorporated to the feed or added directly to the water. The other method of administration is encapsulation which is useful for improving the nutritional value as well as delivering the microbe properly to the host (De et al. 2014). The microbes at high density are encapsulated in colloidal matrices by using alginate, pectin, carboxymethylcellulose, or chitosan for physical as well as chemical protection of the microorganisms (Hermosillo et al. 2012).

Currently, the most widely applied method of their administration is incorporation of the probiotics directly in to the feed pellets. In order to maintain the viability of the probiotics after their addition, they must be monitored continuously for confirming protective escalated immunity in fish. In addition, they can even be added as freeze-dried cultures which are later mixed with the lipids as dressings at the top of the feed (De et al. 2014).

Aquatic probiotics are popular because of their antiviral properties against various known pathogens. Although, some reports indicate that in aquaculture, virus inactivation can also take place by using different bacterial probiotic strain extracts, the mechanism by which probiotic bacteria show antiviral activity is unknown (Hasan and Banerjee 2020). However, in vitro analysis has revealed that viruses can be inhibited when bacteria such as *Aeromonas*, *Pseudomonas*, *Corynebacterium*, and *Vibrio* species secrete extracellular enzymes which are effective against infectious hematopoietic necrosis virus (IHNV) (Kamei et al. 1988; Zorriehzahra et al. 2016). It has been reported that probiotic strains like *Bacillus megaterium* increased the resistance against white spot syndrome virus (WSSV) in *Litopenaeus vannamei.* Vibrio species are also effective in protecting *Litopenaeus vannamei* against WSSV (Li et al. 2009; Balcazar 2003). Liu et al. (2012) reported that 50% higher survival rate and enhanced resistance was observed in some grouper fish infected by iridoviruses when the probiotic *Bacillus subtilis* E20 strain was used in comparison to the non-probiotic group. Another study by Son et al. (2009) reported higher rate of survival in grouper *Epinephelus coioides* against iridovirus by dietary administration of probiotic *Lactobacillus plantarum.* Moreover, *Lactobacillus* when used as a probiotic either as single strain or in combination with Sporolac gave better resistance against lymphocystivirus found in a marine fish, olive flounder *Paraliichthys olivaceus* (Harikrishnan et al. 2010a, b, c). Similarly, when yellow jack fish *Carangoides bartholomaei* was experimentally infected with Sima-aji neuro necrosis virus (SJNNV), the bacterial strain *Pseudoalteromonas undina* VKM-124 showed an inhibitory activity towards SJNNV (Maeda et al. 1997). Likewise, a review paper by Chiu et al. (2010) revealed the probiotic efficacy of dietary *Saccharomyces cerevisiae* which gave protection against iridoviruses (GIV) to grouper fishes at 5.3×10^7 CFU/kg.

Due to the occurrence as well as spread of various viral diseases such as white spot syndrome virus (WSSV), infectious hypodermal and hematopoietic necrosis virus (IHHNV), and lymphocystis disease virus (LCDV, shrimp aquaculture has faced huge economic loses compared to fish (Hoseinifar et al. 2018). Treatment of shellfishes like shrimp with probiotics has been reported by Lakshmi et al. (2013) as an efficient way for both control and prevention of these viral diseases. Most of studies conducted on the dietary administration

Table 1 Probiotic bacteria showing antiviral activities against viruses in aquaculture

Probiotic bacteria	Target viral pathogens	Major antiviral substance(s) produced	Mode of action	Highlights of the results of the experiment/bioassay conducted	Reference(s)
Bacillus megaterium	WSSV	*Bacillus* OJ with isomalto-oligosaccharides (IMO)	Not reported	Feeding trial	Li et al. 2009
Lactobacillus with Sporolac	Lymphocystis disease virus (LCDV)	Not reported	Not reported	Phagocytosis activity, plasma lysozyme activity, complement activity, superoxide anion production of blood leukocytes	Harikrishnan et al. 2010a, b, c
Saccharomyces cerevisiae P13	Grouper iridovirus (GIV)	Not reported	Colonized the fish intestine and improve feed deficiency and growth rate	Feeding trial Assays: phagocytic activity (PA), serum lysozyme activity, serum alternative complement activity (ACH_{50}), superoxide dismutase activity (SOD), respiratory bursts, hemagglutination (HA)	Chiu et al. 2010
Lactobacillus plantarum	Iridovirus	Not reported	Colonized the fish intestine and improve feed deficiency and growth rate	Feeding trial Assays: ACH_{50}, lysozyme activity, PA, glutathione peroxidase activity (GPx), respiratory bursts, SOD	Son et al. 2009
Pedicoccus pentosaceus and *Staphylococcus hemolyticus*	WSSV and IHHNV	Not reported	Not reported	Feeding trial	Levya-Madrigal et al. 2011
Bacillus subtilis E20	Iridovirus	Not reported	Colonized the fish intestine and improve feed deficiency and growth rate	Feeding trial Assays: PA, ACH_{50}, serum lysozyme activity, respiratory bursts, SOD	Liu et al. 2012

Table 1 (continued)

Probiotic bacteria	Target viral pathogens	Major antiviral substance(s) produced	Mode of action	Highlights of the results of the experiment/bioassay conducted	Reference(s)
Lessonia nigrescens	Grouper iridovirus (GIV)	Not reported	Not reported	Feeding trial Assays: lysozyme activity, PA, ACH_{50}, SOD, respiratory bursts, HA	Yeh et al. 2008

of these probiotics revealed antiviral effect depending on the shrimp species (Hoseinifar et al. 2018). The antiviral activities of probiotics against the viruses are listed in Table 1.

A study conducted by Direkbusarakom et al. (1998a, b) on tiger shrimp infected with *Vibrio* spp. reported stronger antagonistic activity against both *Oncorhynchus masou* virus (OMV) and IHNV. Likewise, treatment of the whiteleg shrimp *Litopenaeus vannamei* by administration of 10^5 CFU/mL probiotic *Vibrio alginolyticus* showed enhanced resistance against WSSV in comparison to the shrimps that were not treated (Rodríguez et al. 2007). In another similar study, 10^{10} CFU/mL of probiotic *Bacillus megaterium* when administered against shrimp WSSV gave improved protection and higher survival rate (Li et al. 2009). A study by Leyva-Madrigal et al. (2011) reported a decrease in WSSV infection after treatment of the white shrimp with either *Staphylococcus hemolyticus* or *Pediococcus pentosaceus*. Dietary administration of 10^5 CFU/g multiple strains of lactic acid bacteria like BC1, BAL3, BAL7, and CIB1 were ineffective against WSSV infection in whiteleg shrimp *Litopenaeus vannamei* (Partida-Arangure et al. 2013).

Bacillus sp. LMG20363 administered as a feed in the diet of shrimp *Litopenaeus vannamei* has shown decrease in the viral infection against WSSV (Balcázar et al. 2006). Chai et al. (2016), isolated *Bacillus* PC465 from the gut of the Chinese white shrimp *Fenneropenaeus chinesis* to evaluate its antiviral effects against WSSV infections. An enhancement of the gut microbial structures by promoting the immune system of the shrimp against WSSV was reported by them. Although the mechanisms by which the probiotics protect against WSSV infection remains unclear, some researchers have reported that the immunomodulatory nature of probiotics plays a key role in protection against WSSV infections (Merrifield et al. 2010).

Treatment using nanoparticles

Nanotechnology with the aid of its novel nanotools has a lot of potential in the aquaculture industry. However, very little data is available regarding the role of several nanoparticles in the prevention of fish diseases (Shah and Mraz 2019).

The use of antibiotics as well as chemical disinfectants against viral pathogens has created problems in the aquaculture industry (Huang et al. 2015). The use of nanoparticle-based vaccines against many viral pathogens is a developing field in fish medicine research (Shaalan et al. 2016). The efficacy of a construct DNA containing nodavirus's extra small virus antisense gene encapsulated with the chitosan nanoparticles in giant freshwater prawn *Macrobrachium rosenbergii* has been reported to increase its survival rate (Ramya et al. 2014).

The production of the feed is one of the major applications of nanotechnology in aquaculture. An important application of nanotechnology in aquaculture is feed production. In this, the use of NPs has proven to be effective in many ways like (i) micronutrient delivery, (ii) amount of produced feed per unit time, and (iii) growth promotion (Khosravi-Katuli et al. 2017). The application of chitosan nanoparticles has been reported to increase the shelf life of vitamin C and its delivery significantly in the rainbow trout after feeding for 20 days (Alishahi et al. 2014). Similarly, chitosan nanoparticles were reported to have been applied in liver cell lines of zebra fish for delivering ascorbic acid and even for in vivo treatment in the case of the rotifer *Brachionus plicatilis*, since nanoparticles can easily penetrate the epithelium of fish intestine exhibiting a significant rise up to twofold in the level of ascorbic acid (Jiménez-Fernández et al. 2014).

Chitosan nanoparticles have been used in the encapsulation of nutrients which can be degraded easily while in contact with the water (Chatterjee and Judeh 2016; Ji et al. 2015). In addition, when coated chitosan nanoparticles were encapsulated with the calcium alginate, it was found to prevent the leakage of shark liver oil (Peniche et al. 2004). Another in vitro study reported that when these chitosan nanoparticles were encapsulated with oil droplets of tuna fish, their physical stability was enhanced and fatty acids liberated from emulsions were subsequently reduced (Klinkesorn and McClements 2009). Moreover, when SWCNTs (Fraser et al. 2011; Bisesi et al. 2015), C60 (Fraser et al. 2011), and nTiO2 (Ramsden et al. 2009) were added to rainbow trout, fathead minnows, and rainbow trout food, the physical properties of fish pellet were changed making them more compact than usual, thereby reducing the leaching of nutrients' and their resultant waste in fishpond.

A study reported that polyamine carbon quantum dots (CQDs), carbonaceous nanoparticles in *Litopenaeus vannamei*, act against WSSV virus by attachment to the virus envelope which later resulted in inhibition of the viral infection. They described some antiviral strategies and therapeutic treatment methods using polyamine CQDs in aquaculture (Huang et al. 2020). The antiviral activities of NPs against the respective viruses are listed in Table 2.

Supplemental selenium nanoparticles due to its defensive antioxidant and bioavailability properties (Sonkusre et al. 2014) were reported to enhance the end weight and activity of glutathione peroxidase (GSH-Px) level in the blood plasma and liver and protein content in the muscle as well as reduced FCR activity in the crucian carp fish *Carassius auratus gibelio* (Zhou et al. 2009). In addition, selenium nanoparticles were shown to cause LDH enhancement and also increase in SOD, protein cellular contents, GSH-Px, and K^+/Na^+-ATPase in the crucian carp; the effect of this being both dose dependent and also dependent on the size of the nanoparticles (Wang et al. 2013). Moreover, Se nanoparticles at both moderate and high doses were reported to have a significant effect on Nile tilapia fish *Oreochromis niloticus* growth due to the spiked feed resulting in weight gain (Deng and Cheng 2003).

Zinc oxide nanoparticles was reported as a dietary zinc source that was found to show immune response as well as growth improvement in the grass carp fish *Ctenopharyngodon idella* (Faiz et al. 2015). Additionally, after feeding with zinc oxide nanoparticles feed for 90 days, there was also a significant rise in the protein content level, activity of the antioxidant enzymes, and increase in the weight of the freshwater prawn *Macrobrachium rosenbergii* (Muralisankar et al. 2014). Titanium oxide nanoparticles were used for improving the growth performance in *Oncorhynchus mykiss* rainbow trout fish (Ramsden et al. 2009).

In vivo studies using silver nanoparticles (AgNPs) highlighted their diverse characteristics, along with their antimicrobial effects in controlling shrimp diseases like white spot disease (WSD) caused by WSSV (Camacho-Jiménez et al. 2020) that can result in complete devastation of the shrimp culture (Sánchez-Martínez et al. 2007). The patented formulations of both Agrovit-4® (Romo-Quiñonez et al. 2020) and Agrovit® (Juarez-Moreno et al. 2017; Ochoa-Meza et al. 2019) have confirmed the antiviral effects of AgNPs against WSSV infections. Moreover, WSSV-infected shrimp *Litopenaeus vannamei* when treated with Agrovit® showed no signs or symptoms of white spot disease. Enhanced survival rate ranging from 70 to 80% was reported (Juarez-Moreno et al. 2017). Likewise, shrimp fed Argovit-4-supplemented feed did not show signs of toxicity for the assayed doses over the 192-h experiment period. The third and fourth bioassays showed that shrimp challenged with WSSV at 1000 µg/g feed exhibited reduced mortality (Romo-Quiñonez et al. 2020).

Nano-encapsulated vaccines have been developed against WSSV, i.e., white spot syndrome virus, IMNV, i.e., infectious myoncronis virus in shrimp farming (Rajeshkumar

Table 2 Nanoparticles showing antiviral activities against viruses in aquaculture

Nanoparticles (NPs)	Target viral pathogens	Major antiviral substance(s) produced	Mode of action	Highlights of the results of the experiment/bioassay conducted	Reference(s)
Carbonaceous NPs	WSSV	Carbon quantum dots (CQDs)	Inhibition of the infection by attachment to the virus envelope	In vitro inhibition of WSSV infection, antioxidant defense mechanism, in vivo antiviral activity	Huang et al. 2020
Silver NPs (AgNPs)	WSSV	Agrovit-4	Not reported	Bioassay 1: determination of minimum WSSV infectious dose by intramuscular route Bioassay 2: inhibition of pathogenicity by application of WSSV–Agrovit-4 mixture Bioassay 3: toxic effect of Agrovit-4 supplemented in feed against WSSV Bioassay 4: immunostimulatory activity of Agrovit-4 towards immune-related genes by performing RT-qPCR in hematocytes	Romo-Quiñonez et al. 2020
Extra small virus antisense (XSVAS) gene encapsulated with chitosan NPs	Nodavirus	Not reported	Not reported	Plasmid concentration of 100 ng μL^{-1} when conjugated with chitosan NPs was found to be more effective in increasing the survivability of the infected prawn *Macrobrachium rosenbregii*	Ramya et al. 2014

et al. 2009; Chalamcheria 2015), and *Listonella anguillarum* in the Asian carp fish (Rajeshkumar et al. 2009). Polyanhydride nanoparticles were used for encapsulation as well as liberation of the vaccine antigens for determining the immunization route, i.e., via feed or immersion (Ross et al. 2014). Nanoparticle-based carriers such as PLGA, i.e., polylactic-co-glycolide acid, alginates, and chitosan used for the vaccine antigens along with mild inflammatory inducers orally showed a higher level of protection to fishes and shellfishes with a relative survival rate up to 85% in the cultured shrimps (Rajeshkumar et al. 2009). Additionally, silica-based NPs can be used for drug (i.e., pharmaceuticals or other therapeutics) administration due to its porous structure and ability to incorporate high dose of administration (Strømme et al. 2009).

Treatment using medicinal plant extracts

Medicinal plants, herbal medicines, and plant extracts are being widely used in the aquaculture industry as a sustainable and effective alternative treatment to vaccines or chemicals. Since they consist of multiple bioactive compounds, there has been an enormous increase in the use of these natural plant products to control disease outbreaks in aquaculture (Reverter et al. 2014).

Due to the presence of bioactive molecules like alkaloids, flavonoids, terpenoids, phenolics, tannins, glycoside, steroids, saponins, and essential oils, these plant products are reported to enhance appetite and weight gain, toxicity enhancement, and culture species maturation. They also act as immunostimulant, growth promoters, and aphrodisiac and also have antipathogenic properties in shellfish and other fish in aquaculture (Citarasu 2010; Chakraborty and Hancz 2011). However, to convince the aquaculturists about their efficacy in aquaculture, there is a huge need to publicize the advantages of using these natural products.

In a review paper, it was reported that leaves of *Azadirachta indica* (neem) contain azadirachtin, nimbin, and meliantroil that possess several antiviral properties (Pandey and Sharma 2012). Similarly, a paper published by Balasubramanian et al. (2008a, b) reported that *Panaeus monodon* (black tiger shrimps) infected with white spot syndrome virus (WSSV), when treated with the extract of Bermuda grass *Cynodon dactylon* showed no symptoms of disease and zero mortality in comparison to the controls. Additionally, various plant extracts have exhibited strong antiviral property against shrimp and fish pathogenic viruses. Aqueous and ethanolic extract of guava (*Psidium guajava*) were found to show antiviral activity against infectious hematopoietic necrosis virus (IHNV) and Oncorhynchus masou virus (OMV) by reducing 65–100% and 21–100% plaques respectively in CHSE214 cell lines (Direkbusarakom et al. 1996). Moreover, extracts of *Phyllanthus acidus*, *Psidium guajava*, *Phyllanthus amarus*, and *Cassia alata* exhibited reduction in plaques on virus adsorption by 100% for IHNV, while *P. acidus* and *C. alata* showed 92–100% for infectious pancreatic necrosis virus (IPNV). On the other hand, effects of *Ostreopsis siamensis* and *P. acidus* extracts on viral replication displayed plaque reduction by 100% for IPNV and OMV (Direkbusarakom et al. 1996). *P. amarus* has been reported to show high antiviral efficacy against IHNV and OMV like fish viruses and the shrimp virus yellowhead virus (YHV) (Direkbusarakom 2004). Several antiviral tests were also carried out against the yellowhead virus (YHV) of shrimp via injection route by Direkbusarakom et al. (1997). Moreover, the extract of the herb, *Clinacanthus nutans*, showed efficacy against YHV of shrimp and also controlled the YHV infection effectively in shrimp (Direkbusarakom et al. 1998a, b).

A major compound, oleuropein (Ole), derived from the leaves of olive tree *Olea europaea* showed potent antiviral activity against RNA and DNA viruses (Fredrickson 2000) and controlled several fish viruses like viral hemorrhagic septicaemia virus (VHSV) and salmonid rhabdovirus (Micol et al. 2005). Another compound gymnemagenol ($C_{30}H_{50}O_4$) extracted from leaves of miracle fruit plant, *Gymnema sylvestre*, when tested against grouper nervous necrosis virus (GNNV) and fish nodavirus under in vitro conditions using Sahul Indian Grouper Eye (SIGE) cell lines inhibited the GNNV proliferation up to 53% (Khanna et al. 2011). Under similar in vitro conditions, dasyscyphin C ($C_{28}H_{40}O_8$) derived from the extract of false daisy plant *Eclipta prostrata* exhibited antiviral property against GNNV and fish nodavirus when tested in SIGE cell lines (Harikrishnan et al. 2010a, b, c). A recent study by Sun et al. (2021) reported inhibitory activity of almost 13 medicinal herbs in *Procambarus clarkii* crayfish against WSSV. Naringenin (NAR), an active compound from the extract of the plant *Typha angustifolia*, displayed high potency to inhibit the WSSV infection by 92.85%. The antiviral activities of medicinal plants against the respective viruses are listed in Table 3.

In the year 2015, Sivasankar et al. reported the significance of plant herbal extracts as a treatment method against viral diseases in fish and shrimp aquaculture. Several herbal extracts that showed antiviral activity in fish include *Calophyllum inophyllum* (tamanu), *Clinacanthus nutans* (snake grass), *Cassia alata* (candle bush), *Glinus oppositifolius*, *Momordica charantia* (bitter gourd), *Ochrocarpus siamensis*, *Hura crepitans* (sandbox tree), *Ocimum sanctum* (white) (basil/tulsi), *Ocimun sanctum* (red) (tulsi), *Phyllanthus acidus* (gooseberry), *Phyllanthus debilis*, *Phyllanthus urinaria* (chamber bitter), *Phyllanthus amarus* (gale of the wind), *Phyllanthus reticulatus*, *Tinaspora cordifolia* (heart-leaved moonseed), *Tinaspora crispa*, and *Psidium guajava* (guava) (Direkbusarakom 2004). Likewise, in shrimp aquaculture, various medicinal plants such as *Allium sativum* (garlic), *Azadirachta indica* (neem), *Aegle marmelos* (Indian bael), *Aristolochia indica*, *Solanum nigrum* (black nightshade), *Curcuma longa* (turmeric), *Cassia fistula* (golden shower), *Lantana camara* (West Indian lantana), *Catharanthus roseus* (Madagascar periwinkle), *Cynodon dactylon* (Scutch grass), *Morus alba* (mulberry), *Psidium guajava* (guava), *Tylophora indica*, *Phyllanthus emblica* (Indian gooseberry), *Phyllanthus amarus* (gale of the wind), *Mimosa pudica*, *Ocimun Americanum* (American basil), *Melia azedarach* (chinaberry), *Momordica charantia* (bitter melon), and *Tridax procumban* were used (Balasubramanian et al. 2007). Among these plants, the aqueous extract of *C. dactylon* showed strong antiviral activity at the concentration of 100 mg/kg of animal body weight. The methanol extract of *M. charantia* showed significant antiviral activity at the concentration of 150 mg/kg of animal body weight. The aqueous extract of *L. camara* and *P. amarus* and the methanol extract of *A. marmelos* showed partial antiviral activity at the concentration of 150 mg/kg of animal body weight.

There is a huge advantage of the use of extracts of medicinal plants in aquaculture, since they cannot only cause reduction in the treatment costs but are also more eco-friendly. This is because they are biodegradable more easily when compared to the synthetic molecules and also due to the increasing diversity of the plant extract-based molecules, they are less likely to develop drug resistance in parasites (Logambal et al. 2000; Blumenthal et al. 2000; Olusola et al. 2013). However, there is still very little information regarding the long-term efficacy of these plant extracts on fish physiology. There is also a lack of sufficient information on the standardization of herbal extract administration. To try and homogenize the main aspects such as method of extraction, dose and method of administration of extract, and effect of herbal extracts in different fish species in aquaculture, more studies are needed.

Table 3 Medicinal plants and herbs showing antiviral activities against viruses in aquaculture

Botanical name of medicinal plants	Target viral pathogens	Major antiviral substance(s) present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Dipteryx odorata	Spring viremia of carp virus (SVCV)	Coumarin derivatives: D5, BBC, B4 and C2, C3007	D5 had impact on SVCV glycoprotein structure to disrupt viral binding to cell surface or translocation to cytosol and suppresses SVCV-activated autophagy to restrict viral replication; BBC results in a higher phosphorylation of PKCα/β that activates erythroid 2-related factor 2 (Nrf2) phosphorylation to favor Nrf2 translocation to nucleus; B4 and C2 enhanced antioxidative enzyme gene expression and trigger Nrf-2 pathway to balance intracellular redox state	In vivo and in vitro anti-SVCV activity	Chen et al. 2018a; Shen et al. 2018a, b; Liu et al. 2017; 2018, 2019, 2020; Qiu et al. 2020
Curcuma longa	VHSV	Curcumin or diferuloylmethane	Suppression of viral entry by rearranging F-actin/G-actin ratio via downregulation of heat-shock cognate 71 (HSC71) protein	Inhibitory activity against Inosine monophosphate dehydrogenase (IMPDH) enzyme, CELL counting assay	Moghadamtousi et al. 2014; Jeong et al. 2015

Table 3 (continued)

Botanical name of medicinal plants	Target viral pathogens	Major antiviral substance(s) present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Arctium lappa	SVCV, IHNV	Arctigenin	**SVCV**: inhibit inducible nitric oxide synthase (iNOS) via modulation of cytokines, inhibit SVCV-induced autophagy needed for virus replication **IHNV**: affect early replication of IHNV	**SVCV**: anti-inflammatory activity, cytopathic effect (CPE) reduction assays, caspase activity assays, cell nuclear damage assay, fluorescence assay **IHNV**: time-of-addition and viral binding assays, anti-IHNV activity	Gao et al. 2018; Shen et al. 2018a, b; Chen et al. 2018b; Hu et al. 2019a, b
Heliotropium filifolium	IPNV	Ester filifolinyl senecionate	Inhibit viral genomic RNA synthesis, ester interacts with viral RNA during viral cycle	In vitro antiviral activity via virus plaque inhibition assay	Modak et al. 2010
Viola philippica	Singapore grouper iridovirus (SGIV)	Not mentioned	Does not induce damage to viral particles but could disturb viral binding, entry, and replication in host cells	Cytotoxic activity, in vitro and in vivo inhibitory activity	Yu et al. 2019
Litchi chinensis	Viral nervous necrosis (VNN) virus	Oligonol	Inhibition of virion attachment to host cells at an early stage	Time-of-addition assay, attachment inhibition assay	Ichinose et al. 2013
Magnolia officinalis	Grass carp reovirus (GCRV)	Magnolol and honokiol	Inhibited replication of virus in cells	Cytotoxicity assays, cell viability assays and antiviral activity assays	Chen et al. 2017
Polygala tenuifolia	Grass carp reovirus (GCRV)	1,5-Anhydro-D-glucitol and 3,4,5-trimethoxy cinnamic acid	Not reported	WST-8 Kit assay, in vitro antiviral activity	Yu et al. 2014

Table 3 (continued)

Botanical name of medicinal plants	Target viral pathogens	Major antiviral substance(s) present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Celosia cristata and *Raphanus sativus*	VHSV	Not mentioned	Inhibits viral replication	Antiviral activity assay	Park et al. 2017
Rhus verniciflua	IHNV, VHSV	Fisetin	Induces apotosis of cells, thus exerting antiviral activity	Cell-based assay, antiviral activity via plaque reduction assay	Kang et al. 2012
Heliotropium huascoense	Infectious salmon anemia virus (ISAV)	Alpinone	Not mentioned	In vitro antiviral activity	Valenzuela et al. 2018
Boerhaavia diffusa	WSSV	glycoprotein	Reaction between bioactive compound in the extract and virus envelope proteins prevents entry of virus in host cell	Growth-promoting potential activity, feed utilization activity	Chithambaran and David 2011
Punica granatum	Lymphocystis disease virus (LDV)	Not mentioned	Enhances innate immune responses and disease resistance	Phagocytic activity, alternative complement activity, respiratory burst activity and lysozyme activity	Harikrishnan et al. 2010a, b, c
Pongamia pinnata	WSSV	Bis(2-methylheptyl) phthalate	Not mentioned	Antiviral activity against WSSV	Rameshthangam and Ramasamy 2007
Olea europaea	Viral hemorrhagic septicaemia rhabdovirus (VHSV)	LExt and oleuropin (Ole)	Inhibits cell-to-cell membrane fusion by VHSV and their in vitro infectivity in uninfected cells resulting in interactions with virus envelope	Cytotoxicity assays, viral infectivity assays, VHSV assay by methylcellulose plaque formation	Micol et al. 2005

Table 3 (continued)

Botanical name of medicinal plants	Target viral pathogens	Major antiviral substance(s) present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Cassia alata	IHNV, IPNV, OMV, YHV, WWSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 99%, IPNV: < 0%, OMV: 100%, YHV: 100%, WWSV: 53.3%	Direkbusarakom 2004; Direkbusarakom et al. 1998a, b
Psidium guajava	IHNV, IPNV, OMV, YHV, WSSV	Not mentioned	Viral inactivation due to reaction with viral envelope	Plaque reduction assay IHNV: 100%, IPNV: < 0%, OMV: 100%, YHV: 100%, WWSV: 85% Cytotoxicity assay	Velmurugan et al. 2012; Direkbusarakom 2004; Direkbusarakom et al. 1998a, b; Direkbusarakom et al. 1997; Balasubramanian et al. 2007
Cyanodon dactylon	WSSV	NA	Viral inactivation occurs by the reaction between extract and virus envelope resulting in inhibition of transcriptional and translational processes of VP28 gene	In vitro antiviral activity, in vivo antiviral activity, immunological assays	Balasubramanian et al. 2008a, b
Ocimum sanctum	IHNV, IPNV, OMV, YHV, WWSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 100%, IPNV: < 0%, OMV: 100%, YHV: 100%, WWSV: 0%	Direkbusarakom 2004; Citarasu et al. 2001
Calophyllum inophyllum	IHNV, IPNV, OMV, YHV, WWSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 97%, IPNV: < 0%, OMV: 92%, YHV: 100%, WWSV: 100%	Direkbusarakom 2004; Direkbusarakom et al. 1998a, b
Momordica charantina	IHNV, IPNV, OMV, YHV, WWSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 68%, IPNV: < 0%, OMV: 47%, YHV: 0%, WWSV: 45%	Direkbusarakom 2004

Table 3 (continued)

Botanical name of medicinal plants	Target viral pathogens	Major antiviral substance(s) present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Tinaspora crispa	IHNV, IPNV, OMV, YHV, WWSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 97%, IPNV: < 0%, OMV: 91%, YHV: 80%, WWSV: 68%	Direkbusarakom 2004
Phyllanthus amarus	IHNV, IPNV, OMV, YHV, WSSV	Not mentioned	Not mentioned	Plaque reduction assay IHNV: 100%, IPNV: < 0%, OMV: 100%, YHV: 100%, WWSV: 58%	Balasubramanian et al. 2007; Direkbusarakom et al. 1995; Direkbusarakom and Herunsalee 1993
Clinacanthus nutans	Yellow-head rhabdovirus (YRV)	Not mentioned	Inhibits both DNA and RNA viruses, mechanism yet to be elucidated	Toxicity test Feeding trial	Chavalittumrong et al. 1995; Direkbusarakom et al. 1996; Direkbusarakom et al. 1998a, b

Kolkovski and Kolkovski 2011; Sivasankar et al. 2015; Pereiro et al. 2020

Treatment using seaweed extracts

Seaweeds are aquatic plants which are considered to be a major part of the marine food web which plays a significant role in the human diet. They have high nutritional value and also exhibit antioxidant, antimicrobial, and immunostimulatory activities. In the last two decades, there has been a vast increase in work on several seaweed extracts to study their antimicrobial or therapeutic application in the aquaculture industry. Among all the genera of seaweeds that manifest a broad and remarkable range of antimicrobial activities against various infectious diseases of marine fishes and shrimps are the brown seaweed *Sargassum* spp. and red seaweed *Asparagopsis* spp. that are outstanding (Vatsos and Rebours 2014).

Seaweeds in general contain highly bioactive components such as fatty acids, phenolics, polysaccharides, proteins, and terpenes that display significant antiviral, antitumor, and also antioxidative activities (Balboa et al. 2013). Moreover, polysaccharides that are isolated from seaweeds help in the inhibition of viral replication by preventing viral attachment to the target cells, its antiviral activity being totally dependent on the degree of polysaccharide's sulfation (Ghosh et al. 2009; Plouguerné et al. 2013; Shi et al. 2017).

Similarly, there are several extracts which are water-soluble and are derived from the three red, green, and brown genera of seaweeds and contain sulfated polysaccharides that display various antiviral factors against most pathogenic viruses, like the Japanese encephalitis virus (flavivirus) (Chiu et al. 2012), the herpes simplex virus (Saha et al. 2012; Son et al. 2013), and the influenza virus (Jiao et al. 2012). Studies also disclose how the seaweed extracts regulate the virus replication as well as delay the exhibition of symptoms of these diseases by enhancing the rate of survival of the infected organisms. Beside these bioactive compounds, carrageenans, sulfoglycolipids, and fucoidans are the other substances reported in the seaweed extracts (Mohamed et al. 2012). Most of the sulfated polysaccharide's function is by binding either to the surface of particularly enveloped viruses or to their receptors on the surface of host cells, thus disrupting their attachment as well as adsorption to host cells (Wang et al. 2012). A few carrageenans also display post-binding impeding effects that affect the stages of cellular activity within the cell of the infective agents (Buck et al. 2006), specifically replication and transcription of the virus (Wang et al. 2012). Apart from polysaccharides, antiviral fatty acids, terpenes, and alkaloids have also been isolated from algae (Soares et al. 2012; Pinto et al. 2012).

In the year 1992, the WSSV virus that was first isolated in Taiwan had been reported to cause deaths extensively in crustaceans like crabs and shrimps and also other aquatic animal species (Lo et al. 1996; Hossain et al. 2001). Recently, several studies have reported the activity of various seaweed species against WSSV virus (Lin et al. 2011; Sirirustananun et al. 2011). The extracts of red seaweed *Gracilaria tenuistipitata* have been found to increase significantly the immunological activities of the whiteleg shrimp *Litopenaeus vannamei* against WSSV, and hence, the shrimp mortality was reduced (Sirirustananun et al. 2011). Similarly, significant antiviral activity has also been reported in freshwater crab *Paratelphusa hydrodomous* against WSSV infection when treated with the methanolic extract of red macroalga *Hypnea spinella* (Dinesh et al. 2014).

In a review study by Mori et al. (2005), a protein named griffithsin was reported to be isolated from the aqueous extract of red alga *Griffithsia* sp. for the first time. It is the

only compound so far isolated from microalgae that has reached the stage of clinical trials (Riccio et al. 2020) revealing both its in vivo as well as in vitro antiviral activities against different varieties of clinically enveloped viruses like HIV with minimum level of host toxicity (Lee 2019). In the year 2016, another study was published on the red algae *Graciliaria chilensis* that showed a clear antiviral activity against infectious salmon anemia (ISA) virus when added to the fish diet at a minimum concentration of 10% (Lozano et al. 2016).

Recently, a study conducted by Klongklaew et al. (2020) for determining the antiviral efficacy of hot water crude extracts (HWCEs) of 3 species of local Thai green macroalgae, namely, *Ulva rigida* (Ur), *Ulva intestinalis* (Ui), and *Caulopa lentillifera* (Cl) and even a commercial ulvan, *Ulva armoricana* (Ua), in Pacific white shrimp *Litopenaeus vannamei* against WSSV and YHV infections reported stronger antiviral efficacy of HWCEs from the alga *U. intestinalis* to inhibit both WSSV and YHV infections. Studies need to be carried out on several other emerging virulent viruses like Taura syndrome virus (TSV) and shrimp hemocyte iridescent virus (SHIV) that lead to mass mortalities in marine shrimp (Klongklaew et al. 2021). The antiviral activities of seaweeds against the viruses are listed in Table 4.

Administration of active seaweed compounds can be done either through seaweed water released from the sea weed directly or by adding the compounds in to it after their extraction from the water and also through medicated feed after extraction of sea weed compounds. (Vatsos and Rebours 2014). Another method, namely, incorporation of these extracts into feeds is reported to be the safest method of delivery, since the extract dose per organism is known to be more accurately calculated which is applicable to most farms and hence can reduce the bacterial load in the cells or tissues (Immanuel et al. 2004). These extracts when incorporated into the dry or live feeds function either by stimulating the immune system or by acting against the pathogens directly. Hence, this can be the most effective and easily applicable method for treatment and also containment of several infectious pathogens (Vatsos and Rebours 2014).

Treatment using green synthesis of nanoparticles

The synthesis of nanoparticles and its formation by using the plant extracts had a head start in terms of its association with the surroundings, since it is considered completely eco-friendly and hence even its waste is not harmful. Extracts of several plants like aloe vera, tea leaves, coriander, lemongrass, neem, ginger, cinnamon, eucalyptus, gooseberry, seaweeds, hibiscus, mint, extracts of mangrove plants, tulsi, lotus, latex, and banana have been used for the synthesis of green nanoparticles (Kurcheti et al. 2020). Sources of green syntheses of nanoparticles are mainly bacteria, plants, and fungi. In the aquaculture industry, nanoparticles have many uses like drug delivery, improvement of the water quality, and diagnosis and management of diseases. However, there are very few studies regarding the green synthesis of nanoparticles, since it is a relatively new field of aquaculture (Kurcheti et al. 2020).

Conclusion

Aquaculture is a rapidly growing industry worldwide. Since it is a rapidly growing industry, there are many major challenges and limitations which the industry is currently facing. One of the major challenges the industry is facing is the outbreak of infectious diseases, since it causes massive loss in the aquaculture output. Hence, based on principles that have been globally accepted as well as the strategies that are applicable locally, various

Table 4 Seaweed extracts/products showing antiviral activities against viruses in aquaculture

Seaweeds used	Target viral pathogens	Major antiviral compounds present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Ulva intestinalis (green)	WSSV, YHV	Not mentioned	Not reported	In vitro antiviral activity, median lethal dose assay (96-h LD_{50})	Klongklaew et al. 2020
Sargassum fusiforme (brown)	WSSV	Not mentioned	Not reported	Total hemocyte count (THC) assay, prophenoloxidase (proPO) assay, SOD assay	Li et al. 2018; Pereiro et al. 2020
Ecklonia cava (brown)	VHSV	Eckol and phlorofucofuroeckol A	Not reported	Inhibitory activity, plaque reduction assay, antiviral activity	Yang et al. 2018; Pereiro et al. 2020
Arthrospira platensis (blue green)	Fish herpesvirus (CyHV-3)	Not reported	EPS prevents attachment of the virus and penetration, inhibits replication	Cytotoxicity and growth inhibition, antiviral activity	Reichert et al. 2017; Pereiro et al. 2020
Gracilara chilensis (red) and *Pyropia columbina*	Infectious salmon anemia (ISA) virus	Not reported	Inhibition of viral replication	Ex vivo assay: plaque reduction neutralization assay	Lozano et al. 2016
Polysiphonia morrowii (red)	IHNV, IPNV	3-Bromo-4,5-dihydroxybenzyl methyl ether and 3-bromo-4,5-dihydroxybenzaldehyde	Not specified	In vitro assays: cytotoxicity assay, cytopathic effect reduction assay, plaque reduction assay	Kim et al. 2011
Sargassum wightii (brown)	WSSV	Fucoidan	Not reported	In vivo assays: enrichment of *Artemia nauplii* with fucoidan, enrichment of *Artemia franciscana* nauplii, immersion challenge, viral load using nested PCR	Sivagnanavelmurugan et al. 2012; Immanuel et al. 2012

Table 4 (continued)

Seaweeds used	Target viral pathogens	Major antiviral compounds present in the extract	Mode of action	Highlights of the results of experiment/bioassay conducted	Reference(s)
Sargassum wightii (brown), *Sargassum duplicatum* (brown)	WSSV	Not reported	Not reported	In vivo assays: enrichment of *Artemia salina*, immersion challenge of shrimp post-larvae	Immanuel et al. 2010
Eisenia bicyclis (brown)	IHNV, hirame rhabdovirus (HRV), OMV	Cholorophyll c2 derivative	Inactivation of viral particles	Antiviral activity assay, in vitro cytotoxicity assay	Kamei and Aoki 2007
Monostroma nitidum (green)	IHNV	Not reported	Not reported	Cytotoxicity assay, antiviral activity	Kang et al. 2008
Sargassum polycystum (brown)	WSSV	Fucoidan	Mechanism not reported	In vivo assays: immersion challenge and feeding trial	Chotigeat et al. 2004
Acrosiphonia orientalis (green)	WSSV	Not reported	Not reported	In vivo assays: immersion challenge and feeding trial, phenoloxidase activity	Manilal et al. 2009
Cladosiphon okamuranus (brown)	WSSV	Not reported	Not reported	In vivo assays: immersion challenge and feeding trial	Takahashi et al. 1998
Sargassum wightii (brown)	WSSV	Not reported	Inactivation of WSSV by chemical disinfectant, UV irradiation, heat and extreme pH conditions	In vivo assays: inactivation of virus by injecting extract into shrimp	Balasubramanian et al. 2006
Gracilaria tenuistipitata (red)	WSSV	Not reported	Not reported	In vivo assays: injection challenge and feeding trial	Sirirustananun et al. 2011

approaches regarding controlling and preventing these problems are recommended. These approaches must first focus on preventing and curtailing the growth and development of these infections. Although combinational use of biological methods, legally approved drugs like antibiotics, and even immunoprophylaxis may result in a huge improvement in fish health, treatment methods like the use of extracts of medicinal plants, seaweeds, probiotics, actinomycetes, and green synthesis of nanoparticles have proved to be a great alternative treatment to vaccines or chemicals in aquaculture.

Among the pathogenic diseases observed in the aquatic organisms, about 50% of them are mostly associated with bacterial pathogens followed by viral, parasitic, and fungal diseases. Viral pathogens have either been around for decades or have emerged as new diseases and are also the indicators of some major serious disease outbreak problems which pose a threat to the aquaculture industry.

Actinomycetes, particularly *Streptomyces* species can be considered as the most significant group that is responsible for the production of antimicrobial agents, antibiotics, and several other antiviral drugs for treating viral diseases in fishes. Nanoparticles are currently of specific interest as a sensitive tool for diagnosing the viral diseases in aquaculture and hence have enormous potential for improving aquaculture with several novel nanotools.

The use of green synthesis of nanoparticles in aquaculture has become a simple, eco-friendly, and efficient way of using the antimicrobial activities of nanoparticles against various marine fish pathogens. Use of synthetic antibiotics often results in the development of antibiotic resistance in bacteria. Thus, biogenic nanoparticles can be used as an effective alternative for controlling several aquatic pathogens. Similarly, use of probiotics as a biological control agent has greatly improved the performance of fishes, disease prevention, immune response enhancement, and quality of the water in recent years. A few probiotics that have been tested in vitro may become effective probiotics which can be produced commercially. However, their use in controlling viral diseases needs to be explored thoroughly.

There are number of emerging viral diseases that affect both fishes and shrimps. Vaccination is one of the methods for treating these viral infections. However, vaccinating each and every fish and shrimp is not a feasible method. Nowadays, natural methods of treatments such as use of extracts of medicinal plants and seaweeds are being used for treating the infections, in addition to the use of probiotics and nanoparticles. For controlling fish diseases, adjuvants and immunostimulants that are being used in the case of fish vaccines may be capable of acting as a substitute to antimicrobial agents. Extracts of medicinal plants can be used as an immunostimulant not only against several infectious diseases but also as infection preventers, growth promoters, and stress-resistant boosters. Plants being rich in a wide variety of phytochemical constituents and secondary metabolites like alkaloids, flavonoids, terpenoids, phenolics, tannins, glycoside, steroids, saponins, polysaccharides, volatile oils, proteoglycans, and essential oils act against various types of diseases. Similarly, some seaweeds have high nutritional value and also exhibit antioxidant, antimicrobial, and immunostimulatory activities in fishes. Antibiotics are being used for treatment but they cause resistance. In order to prevent this, natural methods of prevention and treatment can be adopted.

Our take on this review by anchoring on currently available data is that the key challenge which exists is the significant increase in the number of emerging fish and shellfish viral diseases and the limited options available for preventing these infections. The solution to this specific problem includes the use of antiviral drugs, actinomycetes, nanoparticles, probiotics, and medicinal plants to combat the emerging viral infections. Therefore, the use of a multifaceted approach that involves several preventive as well as control strategies may provide much more effective and long-lasting solutions to reduce these viral diseases in

marine aquaculture as compared to using certain single disease-controlling approaches like antibiotics and vaccination. Further studies however are necessary to gain more information regarding the treatment methods used for different types of infectious diseases as it has become a key issue for the rapidly growing aquaculture industry.

Treatment using plant extracts with their intriguing applications in aquaculture have been very useful. Very little information is available on the mode of action of most medicinal plants as well the safest and suitable form for effective administration which remains a grey area. Moreover, in order to develop a proper treatment strategy, it is necessary to obtain traditional knowledge from the fish farmers who handle plants regularly. Similarly, use of algae and seaweeds, and their bioactive compounds can also be considered as an alternative to improve fitness of fish and shellfish. For the development of novel therapeutics or enhancement of the mode of action of therapeutics currently available, incorporation of nanoparticles can be highly effective. In addition, evolution in technology specifically exploiting the diverse and dynamic nature of nanomedicine is necessary for combating the infectious pathogens effectively. Bioactive compounds extracted from actinomycetes function as potential antiviral antibiotics and hence when incorporated in feed can lower viral infections in fish and shrimps. We can now foresee a future where various non-synthetic antiviral agents effective against viral infections in aquaculture will be developed.

Acknowledgements The authors are thankful to VIT, Vellore, for providing the required facilities to carry out this work.

Author contribution Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Conflict of interest The authors declare no competing interests.

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