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A review of functional feeds and the control of *Aeromonas* infections in freshwater fish

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Abstract
To limit the use of antibiotics in farmed fish and their potential negative impacts on public health and the environment, an evaluation of "functional alternatives" is required. The availability of effective treatments to control fish diseases is one of the most significant challenges facing aquacultures and veterinarians to reduce consequences of antimicrobial resistance. This paper includes results from in vivo studies in major freshwater-farmed fish species (salmonids, cyprinids, and cichlids), focusing on the efficacy of functional alternatives against *Aeromonas* spp. infections. It also outlines the recent biocontrol advances and potential alternative treatments in aquaculture. Functional alternative products can increase the resistance against *Aeromonas* spp. particularly by increasing the immunocompetence of fish. Many diverse alternative products such as probiotics, prebiotics, plants, essential oils, algae phages, minerals, and nanoparticles have been tested, but the diversity of the experimental designs makes it difficult to compare the efficacy of the tested products. It suggests the standardization of investigations on functional feed products for each fish species against a specific pathogen. This review also recommends farm research on functional feed alternatives in natural conditions in order to evaluate the decrease of antibiotic consumption in fish farms.

Keywords *Aeromonas* · Infection · Functional feed alternatives · Antibiotic · Freshwater fish

Introduction

Aquaculture has become an economic and safe source of protein for human consumption around the world. Global food fish production has been increasing at an average annual rate of 6.6% since 1995 (FAO 2017) and reached 80 million tons in 2016 (FAO 2018). The production of Nile tilapia, salmon, and other freshwater species has led to a significant growth

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in annual per capita consumption, approximately from 1.5 kg in 1961 to 7.8 kg in 2015 (FAO 2018).

In intensive aquaculture, farmed fish can be affected by various infectious diseases worsened by stress factors which may lead to a decrease of fish resistance. Antibiotic prescriptions may be needed to avoid impaired growth performance and significant economic losses due to bacterial disease (Romero et al. 2012). In aquaculture, antibiotics were mainly added to feed supplement into water, resulting in the discharge of drug and their metabolites into the wastewater (Romero et al. 2012). Even when the antibiotic concentrations are well below the minimum inhibitory concentration, the prolonged presence of antibiotics in water, combined with high numbers of bacteria in the polybacterial matrices as the pond, sediment, or biofilm, may put selective pressure on bacterial populations and allow the exchange of antimicrobial resistance genes between bacteria (Baquero et al. 2008; Muziasari et al. 2016; Watts et al. 2017). The passage of antimicrobial residue, antimicrobial-resistant bacteria, and resistance genes from aquatic animals and their environment to terrestrial livestock and humans presents the increasing risk of a widespread emergence of drug-resistant pathogens (Rasul and Majumdar 2017; Santos and Ramos 2018).

Common infections in freshwater fish are caused by the genus *Aeromonas*. These bacteria are common inhabitants of aquatic animals (fish and shellfish) and aquatic environments such as freshwater, estuarine waters, marine waters, and sediments (Swann and White 1989). In fish farms, the two most frequently encountered species are *Aeromonas hydrophila* and *Aeromonas salmonicida*. *A. salmonicida* subsp. *salmonicida* mainly affects salmonids and is the causative agent of furunculosis. This disease is responsible for severe economic losses by haemorrhagic septicaemia in the acute form and by fish depreciation due to the development of boils in the muscles in the chronic form (Austin and Austin 2012). *A. hydrophila* is a ubiquitous bacterium which is commonly isolated from freshwater ponds and which is a normal inhabitant of the gastrointestinal tract of aquatic animals. It may also cause a disease in fish known as "haemorrhagic septicaemia" (Randy White 1991). *A. hydrophila* is also a zoonotic pathogen that infects humans via foodborne infections or through aquaculture facilities and is a public health hazard (Okocha et al. 2018). *Aeromonas* are opportunistic environmental pathogens of animals and humans. Genotyping analyses and antibiotic resistance profiles of the two main species *A. salmonicida* subsp. *salmonicida* and *A. hydrophila* demonstrated the presence of multidrug resistance plasmids with a high level of interspecies transfer, including human bacteria (Del Castillo et al. 2013; Vincent et al. 2014). *Aeromonas* may persist being attached to biofilms on biotic or abiotic surfaces, and the presence of these bacteria with *E. coli* in polybacterial mixed biofilms promotes the exchange and dissemination of antimicrobial resistance genes (Talagrand-Reboul et al. 2017). Limiting the emergence of antibioresistant *Aeromonas* and the transfer of their resistance genes by decreasing the antibiotic uses in aquaculture is therefore an issue for fish and public health.

To decrease the use of antibiotics, alternative strategies have been developed to improve fish health and aquaculture systems while reducing the potential for the spread of antimicrobial resistance. These include: (i) vaccination, by considering the difficulty of its application and its controversial effectiveness in fish populations (Gudmundsdóttir and Björnsdóttir 2007; Plant and LaPatra 2011), (ii) immune stimulation by using products derived from plants, bacteria or algae with effects on the microbiome and the immunity of the farmed host, (iii) phage therapy, and (iv) biosecurity approaches such as disinfection of water system (Watts et al. 2017).

In this review, we summarize the promising functional feed alternatives, such as probiotics, prebiotics, plants, essential oils, algae, and phages to reduce antibiotics consumption in

aquaculture. The focus of this paper is mainly on their protective efficacies against the most frequent ubiquitous organism (*Aeromonas* spp.) when delivered in vivo in the three major families of freshwater fish, salmonids, cyprinids, and cichlids.

Methodology analysis to evaluate alternative products against *Aeromonas* spp. infection

The survey showed that the majority of studied cases of alternatives were carried on probiotics, plants, and prebiotics, respectively. The other alternatives studied are synbiotic (mixture of prebiotics and probiotics) essential oils, algae, bacteriophage, and other non-classified alternative families, like as mineral and nanoparticles. Alternative products were tested mainly on Nile tilapia (*Oreochromis niloticus*), rainbow trout (*Oncorhynchus mykiss*), rohu (*Labeo rohita*), and common carp (*Cyprinus carpio*).

Mostly, alternative products were tested for their preventive and protective effects. Some studies have also evaluated the curative effect of alternatives like probiotic or triherbal extract-enriched diets (Harikrishnan et al. 2010), aqueous methanolic extracts of tetra (*Cotinus coggygria*) (Bilen and Elbeshti 2019), and therapeutic phages (Imbeault et al. 2006; Kim et al. 2015). All investigations presented a comparative study in the present review which in the test groups, fish were treated with the alternative candidates and in the control/negative group, fish were not treated. Moreover, alternative products efficacies were sometimes compared with antibiotics (oxytetracycline) (Park et al. 2017; Won et al. 2017; Lee et al. 2016b).

To evaluate the preventive efficacy of functional feed alternative against *Aeromonas* spp. infections, pathogen was injected by the intraperitoneal (IP) route but fish were also exposed to *Aeromonas* spp. by immersion (Bandyopadhyay and Das Mohapatra 2009; Liu et al. 2013b), by cohabitation (Irianto and Austin 2003; Hoque et al. 2018; Menanteau-Ledouble et al. 2017), or by oral intubation (Ngamkala et al. 2010; Dong et al. 2018). *A. hydrophila* was mainly used to infect freshwater fish, with the exception of rainbow trout mainly infected with *A. salmonicida*. Various infection doses were investigated in challenge experiments that depended mainly on bacterial strain, fish species, administration routes and the survival rate required by the authors. Indeed, different infectious doses could lead to a same RPS. For example, *A. hydrophila* infection dose at 10^3 and 10^9 CFU ml^{-1} injected by IP route in Mozambique tilapia induced a RPS of 10% (Rajeswari et al. 2016; Suguna et al. 2014). In contrast, a similar infectious dose could lead to very different RPS (*A. salmonicida* doses at 2.4 10^7 and 2.10^7 CFU ml^{-1} induced a RPS of 80 and 12%, respectively, in rainbow trout (Kim and Austin 2006; Park et al. 2017). The post-infection day duration after *Aeromonas* challenge should be also taken to account for the mortality rate records which might vary from hours to weeks, depending on the investigation conditions.

Probiotics

In an expert consensus document, the definition of a probiotic has been recently clarified as: "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al. 2014). In the interest of probiotics use in aquaculture, it was proposed to extend the definition to "living microbial additives that benefit the health of hydrobionts and therefore increase productivity" (Martínez Cruz et al. 2012). In aquatic species, the microbial community in gastrointestinal tract depends on the external environment including water and

feed. Potential probiotic bacteria need to tolerate the temperature of pond water in addition to the bile salts and low pH detected in fish intestines. Potential probiotics must also improve feed utilization and growth by considering their viability under processing conditions when added to fish feed (Irianto and Austin 2002; Lacroix and Yildirim 2007). Moreover, other essential properties are defined relative to safety as a non-pathogenic microorganism and to the absence of plasmid-encoded antibiotic resistance (Martínez Cruz et al. 2012). The mechanistic basis and beneficial activities of probiotics previously were explained as being due to a modification of intestinal microbiota, production of antibacterial or antitoxin substances (bacteriocins and organic acids), modulation of the immune system and competition with pathogens for nutrients, and adhesion to intestines (Myers 2007).

The efficacy of potential probiotic bacteria has been extensively studied in which lactic acid bacteria (*Lactobacillus* spp., *Lactococcus* spp.) and *Bacillus* spp. were the most commonly used probiotic (Table 1). *Saccharomyces cerevisiae* yeasts have also a great promise as a potential probiotic substance (Abdel-Tawwab et al. 2008; Abdel-Tawwab 2012; Ran et al. 2015, 2016; Abass et al. 2018).

Among lactic acid bacteria and *Bacillus* spp., a large diversity of bacterial species and strains were evaluated. For example, for *Bacillus* spp., 11 strains belonging to 7 species have been investigated in this review (Table 1). Potential probiotic bacteria were provided from various sources, either bacteria isolated from fish in a local laboratory, commercial strains that were directly purchased like feed additives as *Lactococcus lactis* (Suprayudi et al. 2017) or even, final commercial product as "Organic green" composed of *Lactobacillus acidophilus*, *Bacillus subtilis*, *Saccharomyces*, and *Aspergillus oryzae* (Aly et al. 2008).

Probiotic products were administered orally as a feed supplement except some cellular components of probiotic bacteria which were injected intraperitoneally (Ramesh et al. 2015; Giri et al. 2015a, b, c; Ramesh and Souissi 2018). They were administered in a very wide range of dosages and durations, from milligrams to grams per kilogramg of feed, and for days to months before the infectious challenge. Generally, for *S. cerevisiae* yeasts, the optimal probiotic dose was proposed to be 1 to 2 g kg^{-1} diet from 56 to 84 days to protect Nile tilapia (*O. niloticus*) against *A. hydrophila* infections (Abdel-Tawwab et al. 2008; Abdel-Tawwab 2012; Ran et al. 2015, 2016) but increased to 70 g kg^{-1} under stress condition (Abass et al. 2018). For potential probiotic bacteria, the optimal dose varied between 10^7 and 10^{10} cfu g^{-1} diet for 2 to 3 months, depending on the species and strain of probiotic and the fish species (Table 1).

The increase of the survival rate and protection effect in the probiotic feeding group compared with the control group was a result of the preventive effect of these probiotics against *Aeromonas* spp. However, the amplitude of the survival rate between the probiotic and control groups varied greatly and depended on the probiotic species, the feeding dosages and durations, and the experimental infection (dose of bacteria, administration route, duration) (Table 1). In *Catla catla*, the effect of *B. circulans* depended on the probiotic dosage: the survival rate was 96.7% with 2×10^5 CFU 100 g^{-1} feed whether 40.0% with 2×10^6 CFU 100 g^{-1} feed and 6.7% in the control group (Bandyopadhyay and Das Mohapatra 2009). Besides dose-dependent effects, the duration of feeding fish with probiotics seemed to be an important matter to achieve a higher protection. For example, the relative level of protection against *A. hydrophila* in Nile tilapia for each probiotic agent *Bacillus pumilus* or mixture of *Lactobacillus acidophilus*, *Bacillus subtilis*, *Saccharomyces*, and *Aspergillus oryzae* showed to be higher at the end of the 2nd month than at the end of the 1st month of the feeding trial (Aly et al. 2008).

Table 1 Summary of *in vivo* studies in three freshwater fish species for probiotics and bacterial secondary metabolites or enzymes

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Saccharomyces cerevisiae yeast	*Aeromonas hydrophila* 2×10^8 cfu ml^{-1}/fish-IP	Nile tilapia *(Oreochromis niloticus)*	30-70 g/kg diet-PO-84d optimal dose: 70g/kg diet under stress condition	D14: 97 % vs 87%	Abass et al. 2018
	Aeromonas hydrophila 5×10^5 cell ml^{-1}/fish-IP		0.50 - 5.0 g/kg diet -PO-84d optimal dose: 2 g/kg diet	D10: 35-55 % vs 20%	Abdel-Tawwab 2012
	Aeromonas hydrophila 5×10^5 cell ml^{-1}/fish-IP		0.25 - 5.0 g/kg diet -PO-84d optimal dose: 1 g/kg diet	D10: 35-55 % vs 25%	Abdel-Tawwab et al. 2008
commercial preparation of live & heat-inactive *Saccharomyces cerevisiae* yeast	*Aeromonas hydrophila* 10^8 cell ml^{-1}/fish-IP		1 g/kg diet (107 cfu/g diet)-PO-56d optimal preparation: live yeast	NS	Ran et al. 2015
commercial preparation of live & heat-inactive *Saccharomyces cerevisiae* yeast	*Aeromonas hydrophila* 10^8 cell ml^{-1}/fish-IP		1 g/kg diet -PO-56d	NS	Ran et al. 2016
commercial preparation of yeast	*Aeromonas sobria* 1.5×10^7 cell ml^{-1}/fish-IP		50 - 250 g/kg diet -PO-30d optimal dose: 250 g/kg diet	D14: 55-70% vs 25%	Reda et al. 2018
Bacillus licheniformis Dahb1 (HM235407.1)	*Aeromonas hydrophila* 10^7 cell ml^{-1}/fish-IP	Mozambique tilapia (*Oreochromis mossambicus*)	10^5,10^7 cfu/g diet-PO-28d optimal dose: 10^7 cfu/g diet	D10: 65-55% vs 14%	Gobi et al. 2018
B. licheniformis KADR5 ; *B. pumilus* KADR6 (separately): live cell (lv) & subcellular components (cp) isolated from rohu gut	*Aeromonas hydrophila* 10^5 cells ml^{-1}/fish-IP	rohu (*Labeo rohita*)	10^8 cfu/g diet -IP(cp)/PO(lv)-14d	D10: 60-80% (cp); 67-77% (lv) vs 20%	Ramesh et al. 2015
B. subtilis KADR1: live cell (lv)& subcellular components (cp) isolated from rohu gut			10^6- 10^{10} cfu/g diet –PO (lv)/IP (cp)-28d optimal dose:10^8 cfu/g diet	D10: 39--80%(lv);77%(cp) vs18%	Ramesh and Souissi 2018
B. aerophilus KADR3 isolated from rohu gut			10^7 - 10^9 cfu/g diet-PO- 42d optimal dose: 10^8 cfu/g diet	D10: 41-72% vs 20%	Ramesh et al. 2017
B. subtilis VSG, Pseudomonas aeruginosa VSG2; *Lactobacillus*	*Aeromonas hydrophila* 10^7 cell ml^{-1}/fish-IP		0.1 mg (cp)/fish-IP (21d) optimal species :Lp & Pa	D21: 50-83 vs 20 %	Giri et al. 2015a

Table 1 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
plantarum VSG3(cp)(separately) from rohu gut					
Bacillus spp. MVF1 (KP256503) isolated from freshwater fish (*Mystus vittatus*) gut			10^5 10^9 cfu/g diet-PO-70d optimal dose: $10^{7\text{-}9}$ cfu/g diet	D10: 30-75%	Nandi et al. 2017
B. amyloliquefaciens CCF7	*Aeromonas hydrophila* 10^7 cell ml^{-1}/fish-IP		10^5 - 10^9 cfu/g diet-PO-70d optimal dose: $10^{7\text{-}9}$ cfu/g diet	NS	Nandi et al. 2018
B. subtilis isolated from *Cirrhinus mrigala* gut	*Aeromonas hydrophila* 10^6 cell ml^{-1}/fish-IP		0.5×10^7- 1.5×10^7 cfu/g diet-PO-15d	D3: not mentioned	Kumar et al. 2008
B. circulans PB7 isolated from the intestine of Catla	*Aeromonas hydrophila* 10^5&10^7cfu/ml-Immersion 1h	Catla (*Catla* catla)	2×10^4 - 2×10^6 cell/100g diet -PO- 60d optimal dose: 2×10^5 cell/100g diet	D10 :40-96% vs 6%	Bandyopadhyay and Das Mohapatra, 2009
B. subtilis	*Aeromonas hydrophila* 8 × 10^9cell ml^{-1}/fish-IP	grass carp (*Ctenopharyngodon idellus*)	2.4×10^7 cfu/g diet-PO-42d	NS	Tang et al. 2018
B. coagulans MTCC9872; *B. licheniformis* MTCC 6824;*Paenibacillus polymyxa* MTCC 122 (separately)	*Aeromonas hydrophila* 10^6 cfu ml^{-1}/fish-IP	common carp *(Cyprinus carpio)*	10^9 cfu/g diet -PO-80 d optimal species: *Paenibacillus polymyxa*	D5 :36-50% vs 20%	Gupta et al. 2014
Bacillus velezensis V4 isolated from marine recirculation aquaculture systems	*Aeromonas salmonicida* 10^4 cfu ml^{-1}-IP	rainbow trout (*Oncorhynchus mykiss*)	10 - 50 g/kg diet -PO-60d	99-93% vs 91%	Gao et al. 2017
B. subtilis (Bs) ; *B. licheniformis* (Bl) & *(Bs + Bl)*	*Aeromonas salmonicida* 2×10^7 cfu ml^{-1}/fish-IP		5 g/kg diet-PO- 56 d	D15: 50% vs 12% oxytetracycline: 55%	Park et al. 2017
B. subtilis AB1 isolated from rainbow gut	*Aeromonas* sp. ABE1 2.3×10^6 cfu ml^{-1}/fish-IP		10^4 - 10^9 cfu/g diet; -PO-14d optimal dose: 10^7 cfu/g diet in all forms	65-100% vs 5-15 %	Newaj-Fyzul et al. 2007
Lactobacillus plantarum isolated from Persian sturgeon gut	*Aeromonas hydrophila* 2.1×10^7 cfu ml^{-1}/fish-IP	common carp *(Cyprinus carpio)*	0.56×10^6 cfu/g diet (0.3g/kg diet) - 1.2×10^6cfu (0.7g)-PO- 80d optimal dose:1.2×10^6 & 0.9×10^6 cfu/g diet	D14: 35-50% vs 25 %	Soltani et al. 2017

Table 1 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Lactobacillus plantarum strains	*Aeromonas hydrophila* 10^8 cfu mL^{-1}/fish-IP		10^8 cfu/g diet -PO-14d	D14: 35% vs 15 %	Kazuń et al. 2018
Lactobacillus rhamnosus or L. sporogenes commercial product	*Aeromonas hydrophila* 1.8 × 10^6cells ml^{-1}/fish-IP		1 g/kg diet	D30: 65-55% vs 15%	Harikrishnan et al. 2010
Lactococcus lactisQ-8, Lactococcus lactisQ-9,and Lactococcus lactisZ-2	*Aeromonas hydrophila* 5 × 10^6cfu ml^{-1}/fish-IP		5 × 10^8 cfu/g diet -PO-56d	48h: 88-90% vs 82%	Feng et al. 2019
Lactobacillus plantarum VSG3 isolated from rohu gut	*Aeromonas hydrophila* 10^7 cfu ml^{-1}/fish-IP	rohu (*Labeo rohita*)	10^6 - 10^{10}cfu/g diet -PO-60d optimal dose:10^8 cfu/g diet	D10: 37-77% vs 14%	Giri et al. 2013
Lactobacillus plantarum SM16 & SM33, *L. fermentum* SM51, *L. brevis* SM56, *Pediococcus pentosaceus* SM64 (together) isolated from rohu gut	*Aeromonas hydrophila* 10^7 cfu ml^{-1}/fish-IP		10^9 cfu/g diet-PO- 30d	D30: 90%,D50:60 %, D70:40% vs 30%	Maji et al. 2017
Lactobacillus plantarum; L. delbrueckii subsp. *bulgaricus* isolated from Shabout *(Barbus grypus)* gut *; L. casei PTCC 1608* as a commercial positive control (separately)	*Aeromonas hydrophila* 3.7 × 10^8cfu mL^{-1}/fish-IP	Shabout (*Barbus grypus*)	5×10^7 cfu/g diet-PO- 60d optimal species: autochthonous probiotics	D15: 63-76% vs 30%	Mohammadian et al. 2016
Lactobacillus casei	*Aeromonas hydrophila*	Shabot (*Tor grypus*)	5×10^6 - 5×10^8 cfu/g diet-PO- 60d optimal dose: $5\times10^{6\text{-}7}$cfu/g diet	NS	Mohammadian et al. 2019
Lactobacillus plantarum; L. delbrueckii subsp. *bulgaricus* isolated from Shabot *(Barbus grypus)* gut *L. casei PTCC 1608* as a commercial positive control (separately)	*Aeromonas hydrophila* 5 × 10^8 cfu mL−1/fish-IP		5×10^7 cfu/g diet-PO- 60d optimal species: autochthonous probiotics	NS	Mohammadian et al. 2018
Lactococcus lactis D1813 (commercial product)	*Aeromonas hydrophila* 10^6 cells ml^{-1}/fish-IP	Nile tilapia *(Oreochromis niloticus)*	0.25 - 1.0 g /kg diet -PO-154d optimal dose: 0.5 g/kg diet	D14: 85-100% vs 55	Suprayudi et al. 2017
Lactobacillus rhamnosus GG	*Aeromonas hydrophila* 0.5 ml bacteria pellets/fish-oral intubation		10^{10} cfu/g diet -PO-14 days	D21: 95% vs 85	Ngamkala et al. 2010

Table 1 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
marine *Lactobacillus plantarum* AH 78	*Aeromonas hydrophila* 5 × 10^7 cells ml^{-1}/fish-IP		5 - 20 g/kg diet (3.4 ×10^8 - 1.3 × 10^9 cfu/g diet)-PO-40d	D14: 66-87% vs 20	Hamdan et al. 2016
Lactobacillus brevis JCM 1170(Lb) ; *L. acidophilus* JCM 1132(La) (separately)	*Aeromonas hydrophila* 10^8 cell/g ; 14-d immersion	hybrid tilapia (*O.niloticus*× *Oreochromis aureus*)	10^5 - 10^9 (La) or (Lb)/g diet -PO- 35d optimal dose and species :10^9 (Lb) cfu/g diet	D14: 15-50% vs 10 %	Liu et al, 2013b
Lactococcus lactis 16-7, isolated from crucian carp gut	*Aeromonas hydrophila* 4 × 10^8 cfu mL^{-1}/fish-*orogastric intubation*	Crucian carp (*Carassius carassius*)	10^9 cfu/g diet-PO- 42d	NS	Dong et al. 2018
Lactococcus lactis CLFP 100 and *Leuconostoc mesenteroides* CLFP 196	*Aeromonas salmonicida*	Brown trout (*Salmo trutta*)	Not available	Significant	Balcázar et al. 2009
Lactobacillus acidophilus (MTCC 10307)	*Aeromonas hydrophila* 4× 10^6cell ml^{-1}-IP	catla (*Catla catla*)	10^7 cfu/fish -IP	NS: induced Catla thymus macrophage cells	Patel et al. 2016
Enterococcus faecalis	*Aeromonas hydrophila* 10^7 cfu ml^{-1}/fish-IP	javanese carp (*Puntius gonionotus*)	10^7cell /g diet-PO-15d	48h: 53% vs 0 %	Allameh et al. 2017
Paenibacillus ehimensis NPUST1 isolated from water samples of tilapia culture pools	*Aeromonas hydrophila* 10^6 cfu ml^{-1}-IP	Nile tilapia *(Oreochromis niloticus)*	10^6,10^7 cfu/g diet-PO-60d optimal dose: 10^7 cfu/g diet	D7: 40-59% vs 20%	Chen et al. 2019
Rummelii bacillus stabekisii	*Aeromonas hydrophila* $10^{5\text{-}6}$ cfu ml^{-1}-IP		10^6,10^7 cfu/g diet-PO-60d optimal dose: 10^7 cfu/g diet	D7: 56-60% vs 33%	Tan et al. 2019
Carnobacterium maltaromaticum B26; C. divergens B33(separately) isolated from Rainbow trout gut	*Aeromonas salmonicida* 2.4 × 10^7 cfu ml^{-1}-IP	rainbow trout (*Oncorhynchus mykiss*)	10^7cfu/g diet-PO-14d	D14: 80% vs 20%	Kim and Austin 2006
Dead cells preparation of unidentified Gram-positive *coccus* A1-6, *V. fluvialis* A3-47S, *Aeromonas hydrophila* A3-51 and *Carnobacterium BA211* separately	*Aeromonas salmonicida* 10^6 cfu ml^{-1}-IP & cohabitation		10^7 cfu/g diet -PO-14d	92-100% vs 40 %	Irianto and Austin 2003

Table 1 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Aeromonas sobria (GC2) and *Brochothrix thermosphacta* (BA211)	*Aeromonas bestiarum* 10^5 cfu ml^{-1}-IP at the base of the dorsal fin		GC2: 10^8; BA211:10 ^{10} cfu/g diet-PO-14d optimal species: *BA211*	D14: 76-88% vs 22%	Pieters et al. 2008
Pseudomonas aeruginosa VSG-2 isolated from rohu gut	*Aeromonas hydrophila* 10^7 cell ml^{-1}/fish-IP	rohu *(Labeo rohita)*	10^5 - 10^9 cfu/g diet -PO-60 days optimal dose:10^7 cfu/g diet	D10: 34-66% vs 11%	Giri et al. 2012
Pseudomonas aeruginosa FARP72 isolated from the skin mucus of freshwater catfish *Clarias batrachus*	*Aeromonas hydrophila* 1.5 × 10^5 cfu ml^{-1}-cohabitation		10^7 cfu ml^{-} with or without *A. hydrophila*-cohabitation-15 min	D10: 64-77% vs 25%	Hoque et al. 2018
mixture of *Saccharomyces cerevisiae*(Sc), *Bacillus subtilis* (Bs) & *Aspergillus oryzae*(Ao)	*Aeromonas hydrophila* 2 ×10^6 cfu ml^{-1}-IP	Nile tilapia *(Oreochromis niloticus)*	5g/kg((Bs):1.5×10^9,(Sc):10^9,(Ao):2×10^9) or 10 g/kg ((Bs):3×10^9,(Sc):2×10^9,(-Ao):4×10^9cfu/g) diet-PO-28d	D21: 22-24 % vs 6 %	Iwashita et al. 2015
Bacillus pumilus (Bp); commercial product (1kg: 10^{11} cells of *Lactobacillus acidophilus, Bacillus subtilis, Saccharomyces* and *Aspergillus oryzae)*	*Aeromonas hydrophila* 10^8 cell ml^{-1}-IP		10^6,10^{12}(Bp)cell/g diet; commercial product at 1&2 g/kg diet- PO- 30& 60d-	D56(after 30&60 feeding days):74-84% vs 68 %	Aly et al. 2008
Saccharomyces cerevisiae(Sc), *Bacillus subtilis* (Bs) and/or *Lactococcus lactis* (Ll)	*Aeromonas hydrophila* 10^6 cfu ml^{-1}-IP	rohu (*Labeo rohita*)	10^8 cfu/g diet -PO- 60d optimal combination: Bs+Ll+Sc	D7:60-85 vs 40 %	Mohapatra et al. 2014
B. subtilisVSG1(Bs), *L.plantarum VSG3*(Lp); *and/or P.aeruginosaVSG2* (Pa*)* isolated from rohu gut	*Aeromonas hydrophila* 10^7 cell ml^{-1}-IP		10^8 cfu/g diet- PO- 60d-optimal combination: Bs+ Lp+ Pa	D15: 46-86% Vs 13	Giri et al. 2014
1-Deoxynojirimycin (DNJ) from *Bacillus subtilis*	*Aeromonas hydrophila* 10^8cfu ml^{-1}-IP	*Yoshitomi tilapia* (*Oreochromis* Spp.*)*	DNJ: -5 mg/L incorporated into the diet – viable cells: 0.2×10^{10} - 4.23×10^{10} cfu/kg diet -PO- 56 d optimal dose: viable cells : 2.5 ×10^{10} cfu/kg diet or more; DNJ:5 mg/L	Viable cells D7: 26-60% vs 24% DNJ D7:14-49 % vs 12%	Tang et al. 2017

Table 1 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Active Cyclo-(Phe–Tyr) or Cyclo-(Phe–Gly) from *Bacillus Licheniformis* XY-52	*Aeromonas hydrophila* 3.5 × 10^7cfu ml^{-1}-IP	common carp *(Cyprinus carpio)*	5 - 20 g/kg diet-PO-21d optimal dose :20g/kg diet	D15: 69% vs 32%	Chen et al. 2015
Phospholipopeptide biosurfactant from *Staphylococcus hominis*	*Aeromonas hydrophila* 10^9 cell ml^{-1}-IP(on day 8)	Mozambique tilapia (*Oreochromis mossambicus*)	2 - 200 mg kg^{-1} body weight-IP optimal dose :200 mg kg^{-1} BW	D7: 40-70% vs 10%	Rajeswari et al. 2016
poly-b hydroxybutyrate ehydroxyvalerate from *Bacillus thuringiensis* B.t.A102	*Aeromonas hydrophila* 10^3 cell ml^{-1}-IP		10-50 g/kg diet-PO-28d optimal dose :50g/kg diet	D14: 25-62% vs 10%	Suguna et al. 2014
Bacillus amyloliquefaciens or xylanase-expressing *B. amyloliquefaciens R8*	*Aeromonas hydrophila* 2 × 10^6 cfu ml^{-1}-IP	Nile tilapia (*Oreochromis niloticus)*	10^6,10^7 cfu/g diet-PO-60d optimal dose: 10^7 cfu/g diet	D7: 40-59% vs 20%	Chen et al. 2019
Lactobacillus plantarum strain JCM1149 and/or AHL lactonase AIO6	*Aeromonas hydrophila* 10^5cfu ml^{-1}-immersion	tilapia (*Oreochromis niloticus*♀ × *O. aureus* ♂)	10^8 cfu/g diet-PO-14d	NS	Liu et al. 2016

Note: *NS*: not studied, *PO*: oral administration; *IP*: intraperitoneal injection; *d*: days of treatment; *SR*: Survival rate; *D*: day post- infection

Due to the influence of many different factors on experimental results, it is difficult to compare the preventive effect of the different probiotics tested against *Aeromonas* spp. infection. However, some publications compared several probiotics under the same experimental conditions. *P. polymyxa MTCC122* seemed to have a better protective effect against *A. hydrophila* than *B. coagulans MTCC9872* or *Bacillus licheniformis MTCC6824* in common carp (Gupta et al. 2014). Similarly, *Lactobacillus brevis JCM1170* had a better efficacy than *L. acidophilus JCM1132* against *A. hydrophila* in tilapia (Liu et al. 2013b). Furthermore, it has been demonstrated that the incorporation of multispecies probiotics of *Saccharomyces cerevisiae*, *B. subtilis*, and *Lactococcus lactis* (Mohapatra et al. 2014) or *B. subtilis*, *L. plantarum*, and *P. aeruginosa* (Giri et al. 2014) improves health status more effectively than the incorporation of a monospecies probiotic in the diet.

The preventive effect of probiotics against *Aeromonas* spp. could be explained in part by their immunostimulant effect. *Paenibacillus polymyxa* had a better immunostimulant effect than *Bacillus coagulans* MTCC9872 or *Bacillus licheniformis* MTCC 6824, which could explain the better protective efficacy of *P. polymyxa* against *A. hydrophila* (Gupta et al. 2014). However, in contrast with the survival rates, a combination of several probiotics did not seem to significantly increase the immunostimulant effect compared with a single probiotic (Park et al. 2017; Aly et al. 2008).

The duration of time that fish are fed probiotics seemed to be also an important factor on influencing the immunological parameters in fish. Several immunological parameters measured in mucus and serum were improved after 28 days but not after 14 days of *B. licheniformis* Dahb1 feeding (Gobi et al. 2018). Similarly, administering *Bacillus aerophilus* KADR3 over a 6-week period resulted in a slightly higher immunostimulant effect than over a three-week period (Ramesh et al. 2017). However, some studies have concluded that immunostimulation can be observed after a 30-day period of probiotic feeding, which is then followed by a declining trend (Giri et al. 2012, 2013, 2014; Mohammadian et al. 2016).

In addition to an immunostimulant effect, the administration of probiotics might protect against tissue lesions induced by *Aeromonas*. Histological analysis demonstrated that the severity of lesions in intestines and gills was less in rohu fish (*L. rohita*) fed with *B. subtilis*, *L. lactis*, and *S. cerevisiae* after the *A. hydrophila* challenge (Mohapatra et al. 2014). In addition, the intestines of Nile tilapia (*O. niloticus*) exposed orally to *L. rhamnosus GG* showed an increased inflammatory cell infiltration and reduced intestinal damages from *A. hydrophila* (Ngamkala et al. 2010). *L. lactis* 16-7 could also reduce intestinal mucosal barrier damage and inflammation induced by *A. hydrophila* by antagonizing the colonization of *A. hydrophila* in crucian carp intestine (Dong et al. 2018). Probiotics could also fortify the intestinal structure. Live baker's *S. cerevisiae* yeast and *Lactobacillus plantarum* AH 78 increased microvilli length of fish intestine (Ran et al. 2015, 2016; Hamdan et al. 2016) and *L. plantarum* JCM1149 and AHL lactonase enzyme had a synergistic effect on the microvilli density (Liu et al. 2016).

Some studies have found that probiotics could also modify freshwater fish microbiota (Carnevali et al. 2017; Akhter et al. 2015; Dimitroglou et al. 2011). Dietary administration of the grass carp (*C. idella*) with *Shewanella xiamenensis* A-1, *Aeromonas veronii* A-7, and *Bacillus subtilis* for 28 days or Nile tilapia with *Rummeliibacillus stabekisii* for 8 weeks, induced benefic alteration of intestinal microbiota by increasing the abundance of *Cetobacterium* genus with potential immunity function, by reducing the abundance of the potential pathogenic bacteria and by promoting the reproduction of potential probiotics (Hao et al. 2017; Tan et al. 2019). In contrast, feed supplementation by either heat-inactivated or live

commercial preparation of the baker's yeast *S. cerevisiae* did not influence Nile tilapia (*O. niloticus*) gut microbiota markedly (Ran et al. 2016).

In addition, probiotics or their secondary metabolites might increase the health status of fish by increasing feed conversion and growth performance (Table 1). Among the different studies analyzed in this review which resulted to higher growth performance after probiotic feeding, there is only one report mentioned that administration of a *S. cerevisiae*, *Bacillus subtilis*, and *Aspergillus oryzae* mixture had no significant effect on growth rates while feed conversion was increased (Iwashita et al. 2015). Probiotic treatments can also have influence on body or organ content. A higher level of proteins and lipids was found in the carcass of fish fed with *Bacillus circulans PB7* (Bandyopadhyay and Das Mohapatra 2009). *Enterococcus faecalis* supplementation also significantly enhanced the production of digestive enzymes in Javanese carp (*Puntius gonionotus*) intestine as well as the level of propionic and butyric acids (short-chain fatty acids) while no significant difference ($P > 0.05$) in acetic acid production was observed (Allameh et al. 2017).

Finally, probiotics could participate to stress control. *S. cerevisiae*-exposed Nile tilapia showed greater tolerance to stress induced by elevated water temperature (40 °C for 48 h) or by a 24-h hypoxia exposure compared with the control group (Abass et al. 2018).

Prebiotics

Prebiotics are non-digestible fibers that are selectively utilized by host microorganisms to confer health benefits and enhance growth performance due to the byproducts generated from their fermentation by gut commensal bacteria, such as changing the composition of the microbiota, inhibiting pathogens, stimulating immune responses and improving stress resistance (Gibson and Roberfroid 1995; Gibson et al. 2017, Ringø et al. 2010, 2014a, b; Patel and Goyal 2012). Prebiotics are defined by three criteria: (a) resistance to gastric acidity, hydrolysis by host enzymes and gastrointestinal absorption; (b) fermentation by intestinal microbiota; and (c) selective stimulation of the growth and/or activity of intestinal bacteria (Gibson et al. 2004). Prebiotics can be classified according to their molecular size or degree of their carbohydrates polymerization into oligosaccharides (inulin, fructooligosaccharides (FOS), mannanoligosaccharides (MOS)) or polysaccharides such as β-glucans (Ringø et al. 2010, 2014a, b; Patel and Goyal 2012).

Among prebiotics investigated to prevent disease in freshwater fish species by *Aeromonas* spp., β-glucan (β-1,3-glucan or β-1,6-glucan) have been paid attention extendingly (Anjugam et al. 2018; Ji et al. 2017; Douxfils et al. 2017; Falco et al. 2012; Barros et al. 2014; Ngamkala et al. 2010; Zheng et al. 2011), which is mostly isolated from the cell wall of the yeast *S. cerevisiae*. Commercial products which consisted of a mixture of β-glucan and MOS were also tested (Gupta et al. 2008; Yarahmadi et al. 2014, 2016; Ebrahimi et al. 2012). MOS (Liu et al. 2013a) and microbial levan as a fructan-polysaccharide (Rairakhwada et al. 2007; Gupta et al. 2008) have also been studied.

Generally, β-glucan products were administered orally and added to the basal diet as a feed supplement and seemed to be efficient in preventing the mortality associated with *Aeromonas* spp. infection, as represented by significant differences ($p \leq 0.05$) in survival rate and protection effect between the prebiotic and control groups (Table 2). However, as seen with probiotics, the level of preventive effects depends on several factors such as dose and duration. However, feeding fish with β glucan at 1 to 2 g kg^{-1} diet for at least 2 weeks seemed to be optimal to high protection and immune response in different *Aeromonas* infected freshwater

Table 2 Summary of *in vivo* studies in three freshwater fish species for prebiotics

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D):SR in test groups vs control	Reference
β-1,3 glucan binding protein based zinc oxide nanoparticles (Ppβ-GBP--ZnO NPs)	*Aeromonas hydrophila* 10^7 cell ml^{-1}-IP	Mozambique Tilapia (*Oreochromis mossambicus*)	0.01- 0.04 g/kg diet-PO-30d optimal dose :0.04g /kg diet	D10: 55-90% vs 15%	Anjugam et al. 2018
β-1, 3-glucan produced by *Saccharomyces cerevisiae*	*Aeromonas salmonicida* 3×10^5 cell ml^{-1}-IP	rainbow trout (*Oncorhynchus mykiss*)	0.5-1-2 g/kg diet-PO-42d optimal dose :2 g/kg diet	D7: 42-68% vs 32%	Ji et al. 2017
commercial product: β-1,3/ 1,6-glucans produced by *Saccharomyces cerevisiae*	non-lethal *Aeromonas hydrophila* 10^8 cfu ml^{-1} -IP		1- 5 g/kg diet-PO-15&30d optimal dose :2 g/kg diet for 15d	NS	Douxfils et al. 2017
	non-lethal *Aeromonas salmonicida* 4×10^8 cell ml^{-1}-IP	common carp *(Cyprinus carpio)*	1g/kg diet-PO-14d	NS	Falco et al. 2012
β-glucan (85% glucan) from *S. cerevisiae* and Vit C	*Aeromonas hydrophila* 10^5 cfu ml^{-1}-IP	Nile tilapia (*Oreochromis niloticus)*	1g β-glucan /kg diet &600 mg Vit C/kg diet -PO-7,15,30,45d; optimal duration : at least 15d	D15: 64-68% (15,30,4-5d) vs 45% (7d)	Barros et al. 2014
Purified glucan powder	*Aeromonas hydrophila* -0.5 ml bacterial pellets/fish-oral endotracheal intubation		10g/kg diet-PO-14d	D21:100% vs 85%	Ngamkala et al. 2010
commercial product, a mixture of partially autolyzed	*Aeromonas hydrophila* 5×10^5 cfu ml^{-1}-IP		4-12 g/kg diet-PO-56d optimal dose:8-12 g/kg diet	D21: 60-73 % vs 53%	Zheng et al. 2011

Table 2 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D):SR in test groups vs control	Reference
brewer's yeast including glucan, dairy ingredient components and dried fermentation products					
mannan oligosaccha-ride (MOS)	*Aeromonas hydrophila* 10^8 cell ml^{-1}-IP	crucian carp (*Carassius auratus gibelio*)	60 - 240, 480mg/kg diet -PO-70d; optimal dose: 240-480 mg/kg	D7:23-60% vs 20%	Liu et al. 2013a
microbial levan	*Aeromonas hydrophila* 1.8× 10^8 cfu ml^{-1}-IP	common carp *(Cyprinus carpio)*	1-10 g/kg diet-PO-75d optimal dose:5 g/kg diet	D10: 66-100% vs 0%	Rairakhwada et al. 2007
		rohu *(Labeo rohita)*	2.5-12.5 g/kg diet-PO-60d optimal dose: 12.5 g/kg diet	D10: 20-60% vs 0%	Gupta et al. 2008
commercial product (mainly includes β-glucan and MOS)	*Aeromonas hydrophila* 1.5× 10^8 cfu ml^{-1}-IP	rainbow trout (*Oncorhyn-chus mykiss*)	2 g/kg diet-PO-42d	D14: 44% vs 7%	Yarahmadi et al. 2016
	Aeromonas hydrophila 4.9× 10^7 cfu ml^{-1}-IP		2 g/kg diet-PO-45d	D10: 64% vs 24%	Yar Ahmadi et al. 2014
	Aeromonas hydrophila 10^8cell ml^{-1}-IP	common carp *(Cyprinus carpio)*	0.5-2.5 g/kg diet-PO-56d optimal dose :1-1.5 g/kg diet	D10: 50-67% vs 44%	Ebrahimi et al. 2012

Note: *PO*: oral administration; *IP*: intraperitoneal injection; *d*: days of treatment; *SR*: Survival rate; *D*: day post- infection; *NS*: not studied

fish species including rainbow trout (*O. mykiss*), common carp (*C. carpio*), and Nile tilapia (*O. niloticus*) (Douxfils et al. 2017; Falco et al. 2012; Barros et al. 2014; Ji et al. 2017). In addition, combination of β-glucan and MOS (commercial product) resulted also in high disease resistance against *A. hydrophila* in rainbow trout (*O. mykiss*) (Yarahmadi et al. 2014, 2016) and common carp (*C. carpio*) (Ebrahimi et al. 2012); however, application of β-glucan and MOS alone has not been demonstrated by the authors.

The immunostimulant effect of prebiotics is well-known and many studies have indicated that immunosaccharides as β-glucan FOS, MOS, or inulin are beneficial to aquatic animals (Das et al. 2017; Ringø et al. 2010, 2014a, b; Merrifield et al. 2010; Song et al. 2014). However, the underlying mechanisms of prebiotics in enhancement of fish immunity need to be further explored. Some studies shown that a diet supplemented with β-glucan could display the gene expression levels of some immune and inflammation-related cytokines in *Aeromonas* spp. infected fish but the response depends on the organ, with an upregulation in the spleen and head kidney but a downregulation in the gut (Ji et al. 2017; Douxfils et al. 2017; Falco et al. 2012; Yarahmadi et al. 2014). Furthermore, in some investigations, no significant effect of dietary β-glucan on immune parameters (leucocyte subpopulations, lysozyme activity, ACH50) assessed in serum of rainbow trout and Nile tilapia has been proved despite a preventive effect against *Aeromonas* infection (Barros et al. 2014; Ji et al. 2017; Douxfils et al. 2017); even more, overdoses and/or prolonged of β-glucan (0.5% for 30 days rather than 2% for 15 days)) led to a poor immune response (Douxfils et al. 2017).

The preventive effect of β-glucan could also be explained by promoting a rapid healing of the intestinal damage and increasing neutrophil infiltration induced by *Aeromonas* spp. (Ngamkala et al. 2010). The improvement of intestinal morphology has been demonstrated with supplementation of β-glucan and MOS by increasing villi height and *tunica muscularis* thickness as well as gut protease and lipase activities resulting to higher trout (*O. mykiss*) growth and feed efficiency (Khodadadi et al. 2018). In addition, higher intestinal villi and improvement of intestinal morphology were observed in MOS-fed (1.5–2 g/kg diet) rainbow trout fish (Yilmaz et al. 2007; Dimitroglou et al. 2009).

Synbiotics

Synbiotics are nutritional supplements, combining a mixture of probiotics and prebiotics in the form of synergism as health-enhancing functional ingredients (Gibson and Roberfroid 1995). In aquaculture, synbiotics can be used in supplementation form or external bath in order to improve growth performance and feed utilization as well as increasing disease resistance, digestibility, and stimulation of the immune system of aquatic organisms (Cerezuela et al. 2011; Ringø and Song 2016; Das et al. 2017). In this paper, synbiotics beneficial effect intended to protect freshwater fish against *Aeromonas* infections have been reviewed like *L. plantarum* JCM1149 and scFOS (Liu et al. 2017), *B. subtilis* and MOS (Kumar et al. 2018), inactivated *E. faecalis* and MOS (Rodriguez-Estrada et al. 2013), *Bacillus* spp. (*B. coagulans* or *B. subtilis*) and Chitooligosaccharide (COS) (Lin et al. 2012; Devi et al. 2019), *L. rhamnosus* GG, and natural source of oligofructose-enrich inulin from Jerusalem artichoke or Kantawan (*Helianthus tuberosus*) (Sewaka et al. 2019) (Table 3). Prior studies revealed that dietary administration of synbiotic induced higher immune modulation (Sewaka et al. 2019; Devi et al. 2019; Kumar et al. 2018; Rodriguez-Estrada et al. 2013; Lin et al. 2012) and disease protection (Sewaka et al. 2019; Devi et al. 2019; Kumar et al. 2018; Rodriguez-Estrada et al. 2013; Liu et al. 2017; Lin et al. 2012), as well as growth rate (Sewaka et al. 2019; Rodriguez-

Table 3 Summary of in vivo studies in three freshwater fish species for synbiotics

Substances	Infectious challenge			Fish species	Substances administration			Day post-infection: SR in test groups vs. control	Reference
	Species	Dose	Route		Dose	Route	Duration (days of treatment)		
Short chain fuctooligosaccharides (scFOS) and *Lactobacillus brevis* JCM1170 and/or *Lactobacillus plantarum* JCM1149	*Aeromonas hydrophila*	10^8 cell g^{-1}	14 days immersion	Hybrid tilapia	1 g scFOS kg^{-1} diet; 10^8 CFU g^{-1} diet; optimal preparation: synbiotics of Lp JCM1149 and scFOS	PO	35 days	Day 28, 30–55 vs. 15%	Liu et al. (2017)
Mannan oligosaccharide (MOS) and *Bacillus subtilis*	*Aeromonas hydrophila*	2×10^7 CFU ml^{-1}	IP	Indian Major Carp (*Cirrhinus mrigala*)	2 levels of probiotic: high (15% × 10^7 CFU ml^{-1}) and low (5.0% × 10^7 CFU ml^{-1}) probiotic and 2 levels of prebiotic: high (0.6%) and low (0.2%) prebiotic; optimal dose: high level of synbiotic	PO	60 days	Day 15, 35–80 vs. 20%	Kumar et al. (2018)
Mannan oligosaccharide (MOS) and/or *Enterococcus faecalis* (Ef)	*Aeromonas salmonicida*	2.4×10^3 CFU ml^{-1}	IP	Rainbow trout (*Oncorhynchus mykiss*)	2.5–5 g kg^{-1} Ef; 2.5–5 g kg^{-1} MOS; optimal dose, 5 g kg^{-1} Ef + 5 g kg^{-1} MOS	PO	84 days	Day 14, 40–75 vs. 15%	Rodriguez-Estrada et al. (2013)
Chitooligosaccharide (COS) and/or *Bacillus coagulans* (Bs)	*Aeromonas veronii*	2.4×10^8 CFU ml^{-1}	IP	Koi (*Cyprinus carpiokoi*))	10^9CFU g^{-1} BS; 2 g kg^{-1} diet COS	PO	56 days	Day 14; 60–64 vs. 33%	Lin et al. (2012)
oligofructose-enrich inulin from Jerusalem artichoke (*Kantawan* (*Helianthus tuberosus*) (JA) and/or *Lactobacillus rhamnosus* GG (LGG))	*Aeromonas veronii*	10^7 CFU ml^{-1}	IP	Juvenile red tilapia (*Oreochromis* spp.)	10^8CFU ml^{-1} LGG and 10 g JA kg^{-1}; optimal preparation: synbiotic	PO	30 days	Day 15, 85–95 vs. 44%	Sewaka et al. (2019)
Chitooligosaccharide (COS) and/or *Bacillus subtilis* (Bs)	*Aeromonas hydrophila*	10^7 CFU ml^{-1}	IP	Rohu (*Labeo rohita*)	1 g kg^{-1} diet of COS or Bs; optimal preparation: synbiotic	PO	30 days	90–95 vs. 20%	Devi et al. (2019)

Note: *PO*, oral administration; *IP*, intraperitoneal injection; *SR*, survival rate

Estrada et al. 2013; Lin et al. 2012) compared with probiotic or prebiotic diets in singular preparations. However, administration of 2 g COS kg^{-1} diet and *B. coagulans* 10^9 CFU g^{-1} separately for 56 days resulted to identical protection in *A. veronii*-infected koi (*C. carpio* koi) in comparison with the combination preparation (survival rate, 60–64% in all treatment groups vs. 33% in control) (Lin et al. 2012).

Synbiotic preparations could have the effects on fish intestinal morphometry. *B. licheniformis* and FOS could improve microvilli length of triangular bream (Zhang et al. 2013) and *L. rhamnosus* GG and oligofructose-enriched inulin increased absorptive area in juvenile red tilapia (*Oreochromis* spp.) intestine fish probably leading to higher absorption of available nutrients and better growth performance (Sewaka et al. 2019).

Plants

Medicinal plants and their secondary metabolites, phytochemical compounds, fractions, and plant extracts have attracted much attention as substitutes for antibiotics in controlling the outbreak of diseases in aquaculture due to their eco-friendly and cost-effectiveness benefits. Plant products have a natural origin and most of these medicinal plants do not represent a hazard for human health, animal health, or the environment (Stratev et al. 2018). Medicinal plants can produce various favorable effects due to their active principles such as alkaloids, terpenoids, tannins, saponins, and flavonoids. They can be used for their anti-stress and antioxidant properties, for their growth performance and appetite stimulation enhancement as well as their immunostimulation effect against fish diseases. They also can have antibacterial, antiviral, antifungal, and antiparasitic activities against fish and shellfish pathogens (Reverter et al. 2017).

In this review, phytochemical compounds included a wide range of medicinal plant families which were purchased or collected locally. Whole plants, parts of plants (leaf, seed, fruit), or secondary metabolites extracted with different solvents (water, methanol, chloroform, ethyl acetate) were tested (Table 4).

Plant products generally were added to feed in a wide range of dosages and durations depending on various phytochemical substances tested in different fish species in previous studies. However, in some studies, plant extracts were injected intraperitoneally (Divyagnaneswari et al. 2007; Alexander et al. 2010; Devasree et al. 2014; Kirubakaran et al. 2016) or fish were immersed in plant extract (Rather et al. 2017). Investigations demonstrated a significant preventive effect of the majority of herbal extracts against *Aeromonas* spp., but the effect depends on the phytochemical products and their administration. For example, the survival rate in Mozambique tilapia (*O. mossambicus*) was higher in fish fed with a chloroform form of *Nyctanthes arbortristis* seed extract at 1 g kg^{-1} diet for 21 days (Kirubakaran et al. 2010) than in fish injected intraperitoneally at 20 mg kg^{-1} with a methanol form of the same seed (Kirubakaran et al. 2016), around 70 and 55%, respectively. However, some plant extracts seem to have no protective effect against *Aeromonas* spp. infection as methanolic extract of black cumin (*Nigella sativa*) (Celik Altunoglu et al. 2017) and oyster mushroom (*Pleurotus ostreatus*) in feeding trials (Bilen et al. 2016a, b) or the mixture of propolis and *Aloe barbadensis* (aloe) (Dotta et al. 2018).

Some combinations of herbal extracts showed a synergistic effect. For example, combination of two Chinese herbs (*Astragalus membranaceus*; *Lonicera japonica*) and boron (Ardó et al. 2008), *Astragalus radix* Chinese herb and *Ganoderma lucidum* fungi (Yin et al. 2009), or *Satureja khuzestanica* Iranian herb mixed with *Oliviera decumbens*

Table 4 Summary of *in vivo* studies in three freshwater fish species for phytochemical compounds

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Guava (*Psidium guava*) & mango *(Mangifera indica*) ethanolic leaf extract alone or together	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP	rohu *(Labeo rohita)*	5, 10 g/kg diet -PO-35d;optimal dose & preparation: 5g/kg diet of each plant	D7: 60-80% vs 35%	Fawole et al. 2016
guava (*Psidium guajava* L.) leaves	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		1,5, 10 , 15, g /kg diet-PO-60 d ;optimal dose:5 g/kg diet	D14: 40- 66% vs 23%	Giri et al. 2015b
Magnifera indica (mango) kernel	*Aeromonas hydrophila* 2× 10^6 cells ml−1/fish-IP		1,5, 10 g /kg diet-PO-60 d ; optimal dose:5 g/kg diet	D10: 74-98% vs 50%	Sahu et al. 2007
ginger *(Zingiber officinale)* extract	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		2, 4, 6, 8, 10 g /kg diet-PO-60d ;optimal dose:8 g/kg diet	D15: 10-65% vs 19%	Sukumaran et al. 2016
Achyranthes aspera seed	*Aeromonas hydrophila* 3× 10^6 cells ml^{-1}/fish-IP		1, 10, 50 g /kg diet-PO-14d ;optimal dose:50 g/kg diet	D9: 30-70% vs 20%	Rao et al. 2006
Ashwagandha *(Withania somnifera) root powder*	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		1, 2, 3 g /kg diet-PO-42d ;optimal dose:2 g/kg diet	D14: 9-42% vs 2%	Sharma et al. 2010
Hybanthus enneaspermus aqueous extract (Violaceae)	*Aeromonas hydrophila* *10^7 cells ml^{-1}/fish-IP*		1, 2, 3, 4 g /kg diet-PO-42 d ;optimal dose:3 g/kg diet	D14: 30-70% vs 10%	Giri et al. 2017
Chlorophytum borivilianum root polysaccharide	*Aeromonas hydrophila*		1, 2, 3,4 g /kg diet-PO-42d ;optimal dose:4 g/kg diet	D30: 36-73% vs 26%	Giri et al. 2015c

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
	10^7 cells ml^{-1}/fish-IP				
banana peels *(Musa acuminate)*	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		10, 30, 50,70 g /kg diet-PO-60d ; optimal dose:50 g/kg diet	D14: 26-70% vs 20%	Giri et al. 2016
grass *Cynodon dactylon* ethanolic extract (Poaceae)	*Aeromonas hydrophila* 10^6 cells ml^{-1}/fish-IP	Catla (*Catla catla*)	0.5,5, 50 g/kg diet-PO-7, 14, 21,28d optimal dose & duration: 50 g/kg for 7d	D28: 21-73% vs10-18%	Kaleeswaran et al. 2011
oyster mushroom (*Pleurotus ostreatus*) or nettle (*Urtica dioica*) methanolic extracts	*Aeromonas hydrophila* 10^8 cells ml^{-1}/fish-IP	rainbow trout (*Oncorhynchus mykiss*)	0.1, 0.5 g/kg diet-PO-30 d optimal extract &doses: 0.1 & 0.5 g nettle /kg diet	D14: 10-60% vs 0%	Bilen et al., 2016a
household garlic (*Allium sativum*) press (Amaryllidaceae)	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		0.5, 1, 5, 10 g/kg diet-PO-14d optimal dose: 0.5,1 g/100g diet	D14: 88-96% vs12%	Nya and Austin 2009a
Oven-dried garlic bulbs	*Aeromonas hydrophila* 10^6 cells ml^{-1}/fish-IP		5, 10 g/kg diet-PO-14d optimal dose: 1 g/100g diet	D14: 54-90% vs 18-20%	Nya and Austin 2011
black cumin (*Nigella sativa*) methanolic extrac(Ranunculaceae)	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		0.1, 0.5 g/kg diet--P30 d	D14: 50% in all treated & control groups	Celik Altunoglu et al. (2017
ginger *(Zingiber officinale)*	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		0.5, 1,5,10 g/kg diet-PO-14 d optimal dose: 0.5 g/100g diet	D14: 84-100% vs 36%	Nya and Austin 2009b

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
aqueous methanolic extracts of tetra (*Cotinus cog-gygria*)	*Aeromonas hydrophila* 10^8 cells ml^{-1}/fish-IP		4, 8, 12 mg/100μl twice a day-PO-10 d optimal dose: 8, 12 mg/100μl	D10: 55-74% vs 53%	Bilen and Elbeshti 2019
Aloe vera powder, (Aloeaceae)	*Aeromonas salmonicida* (Formalin--killed)		5 g/kg diet-PO-42d	NS	Zanuzzo et al. (2015
caper (*Capparis spinosa*) methanolic extract	*Aeromonas hydrophila* 10^8 cells ml^{-1}/fish-IP		0.1, 0.5 g/kg diet-PO-30 d	D14: 70--80% vs 50%	Bilen et al. 2016b
Lupin (*Lupinus perennis)*, mango *(Mangifera indica*) or stinging nettle (*Urtica dioica*)	*Aeromonas hydrophila* 10^7 cells ml^{-1}/fish-IP		10 g/kg diet-PO-14 d	D10: 96--100% vs 32%	Awad and Austin 2010
Polysaccharide of *Ficus carica* (FCPS), *Radix isatidis* (RIPS)& *Schisandra chinensis* (SCPS) alone	*Aeromonas hydrophila* 6× 10^7 cells ml^{-1}-IP	crucian carp (*Carassius carassius*)	500 mg/kg diet-PO-21 d optimal Polysaccharide: FCPS	D14: 42-57% vs 5%	Wang et al. 2016
Leaves from banana (*Musa nana*) or maize (*Zea mays*)	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP	grass carp (*Ctenopharyngodonid-ella*)	Pellets + banana/maize leaves-PO-	D10: 74-90% vs 90%	Mayrhofer et al. 2017
Bioactive Compound from *Dryopteris crassirhizoma*	*Aeromonas hydrophila* 10^7 cells ml^{-1}-IP		Immunised with 1-50 μg/ml per fish -21d	D14: 56-73% vs 23%	Chi et al. 2016
Peperomia pellucida leaf extract ; (Piperaceae)	*Aeromonas hydrophila*	red hybrid Tilapia (*Oreochromis sp.*)	25 – 100 mg/kg diet -PO-7 d	D28: 82-83% vs 17%	Lee et al. 2016a

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
	(10^9 cfu ml^{-1}/fish-IP)				
Miers (*Tinospora cordifolia*) leaf Water soluble fraction (Menispermaceae)	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP on day 7	Mozambique tilapia (*Oreochromis mossambicus*)	6 - 600 mg kg^{-1}BW—IP (Day 1& 4) optimal dose: 6 mg kg^{-1}BW double dose	D15: 50-90 % vs 20 %	Alexander et al. 2010
Solanum trilobatum water (WSF) or hexane soluble (HSF) fractions (Solanaceae)			4 - 400 mg kg^{-1}BW-IP (Day 1& 4); optimal dose:400 mgkg^{-1}BW(WSF) single dose or 4 mg kg-1BW (HSF) double dose	D15: 35-84% vs 20%	Divyagnaneswari et al. 2007
Eclipta alba leaf aqueous extract (Asteraceae)	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP		0.1 - 10 g/kg diet-PO- 7-21d optimal dose & duration: 10g/kg diet for 14 d	D15: 30-80% vs 20%	Christybapita et al. 2007
Guava (*Psidium guava*) aqueous or ethanol leaf extracts (Myrtaceae)	*Aeromonas hydrophila* 10^7 cells ml^{-1}-IP		1 - 10 g/kg diet -PO-30 d optimal dose: 10 g/kg	D10: 35-97% vs 15%	Gobi et al. 2016
Wormwood (*Artemisia afra*) leaf powder (Asteraceae)	*Aeromonas hydrophila* 10^6- 4×10^{6}cfu ml^{-1}-IP		30 - 120 g/kg diet-PO-45 d optimal doses:90 & 120 g/kg diet	D10: 40-90% vs 30-60%	Mbokane et al. 2018a
			30 - 120 g/kg diet-PO-45 d optimal dose: 120 g/kg diet	D10: 30-90% vs 20-50%	Mbokane et al. 2018b
Moringa oleifera powdered leaves	*Aeromonas hydrophila* 10^6- 4×10^{6}cfu ml^{-1}-IP				
Nyctanthes arbortristis leaf water soluble fraction (Oleacea)	*Aeromonas hydrophila* 10^3 cells ml^{-1}-IP on day 7		3.2 - 400 mg kg^{-1}BW-IP(Day 1& 4) optimal dose: 400 mg kg^{-1}BW	96h:30-60% vs 10%	Devasree et al. 2014

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Nyctanthes arbortristis seeds Chloroform extract (Oleacea)	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP		0.1 - 10 g/kg diet-PO-7-21 d optimal dose& duration:1g/kg diet for 21 d	D15: 22-70% vs 15%	Kirubakaran et al. 2010
Nyctanthes arbortristis seeds Methanol extract (Oleacea)			2-200 mg kg^{-1}BW-IP optimal dose: 20 mg kg^{-1}BW	D15: 40-55% vs 25%	Kirubakaran et al. 2016
Toona sinensis Roem.(Meliaceae) hot-Water extract	*Aeromonas hydrophila* 5 $\times10^9$ cells ml^{-1}-IP		4-8 mg/kg diet-PO-45 d optimal dose: 8 mg /kg diet	D7: 63-70% vs 43%	Wu et al. 2010
Cucurbita mixta (L.) seed	*Aeromonas hydrophila* 3.1×10^7 cells ml^{-1}-IP		2-6 g/kg diet-PO-28 d optimal dose: 4&6 g/kg diet	D30: 80-90% vs 10%	Saiyad Musthafa et al. 2017
Mucuna pruriens (L.) seed	*Aeromonas hydrophila* 3.1×10^7 cells ml^{-1}-IP		2-6 g/kg diet-PO-28 d optimal dose: 4&6 g/kg diet	D30: 80-90% vs 10%	Saiyad Musthafa et al., 2018
cinnamon (*C. zeylanicum*) nanoparticles	*Aeromonas hydrophila* 5×10^5 cells ml^{-1}-IP		0.25-10 g /kg diet-PO-56 d optimal dose:3g /kg diet	D7: 80-100% vs 34%	Abdel-Tawwab et al. 2018
crude Propolis or Propolis -ethanolic Extract (PEE)	*Aeromonas hydrophila*	Nile tilapia (*Oreochromis niloticus)*	10 g/kg diet-PO-28 days optimal extract :ethanolic extract	D15: 55-58% vs 15%	Abdel-Tawwab and Ahmad 2009
propolis and aloe (*Aloe barbadensis*) Miller mixture	*Aeromonas hydrophila* 5 $\times10^5$ cells ml^{-1}-IP		10 g/kg diet-PO-15 days	D7: 55% vs 44%	Dotta et al. 2018
Turmeric powder (*Curcuma longa*) (Zingiberaceace)	*Aeromonas hydrophila*		50-200 mg /kg diet-PO-84 d optimal dose:50 mg /kg diet	D15: 80-95% vs 70%	Mahmoud et al. 2017

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
	1.5 $\times 10^8$ cells ml^{-1}-IP				
Chinese herbs (*Astragalus membranaceus*; *Lonicera japonica*) and/or boron (Fabaceae& Caprifoliaceae)	*Aeromonas hydrophila* 5×10^7 cells ml^{-1}-IP		1 g/kg diet for each herb; 0.5 g/kg of boron-PO-28 d;optimal preparation: both herbs with Boron	D10: 25-70% vs 15%	Ardó et al. 2008
Echinacea purpurea or Garlic (*Allium sativum*) (Asteraceae or Amaryllidaceae resp.)	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP		30g/kg(E)diet or 1.0 ppt (G)-P-PO-30,60,90d optimal condition: (E) or (G) for 60 & 90d resp.	D7: 15-50% vs 5-10%	Aly and Mohamed 2010
Withania sominefera root powder	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP		25, 50 g /kg diet-PO-42 d optimal dose:50g /kg diet	D14: 63-80% vs 30%	Zahran et al. 2018
dry leaf powder or dried leaf ethanol extract of guava (*Psidium guajava)*	*Aeromonas hydrophila* 3.44×10^6 cells ml^{-1}-IP		0.1 mg^{-1}ml added to diet-PO-6 d	D14: 90% vs 50%	Pachanawan et al. 2008
Aqueous extract of *Azadirachta indica* (neem) or Green synthesis of silver nanoparticles (G-AgNPs) of neem; (Meliaceae)	*Aeromonas hydrophila*	mrigal carp (*Cirrhinus cirrhosus*)	immersion in 50 μL of treatments daily for 20 d optimal preparation: (G-AgNPs) of neem	D20: 61-74% vs 10%	Rather et al. 2017
stinging nettle *(Urtica dioica*)	*Aeromonas hydrophila* 10^7 cells ml^{-1}-IP	ningu (*Labeo victorianus*)	10 - 50 g/kg -PO-112 d;optimal dose:5% diet	D18: 95% vs 0%	Ngugi et al., 2015
Hairy willow herb *(Epilobium hirsutum)* ethanolic extract (Onagraceae)	*Aeromonas hydrophila* 3×10^8 cells ml^{-1}-IP	common carp *(Cyprinus carpio)*	5,- 30 g/kg diet -PO-56 d;optimal dose:30 g/kg diet	D30: 77-96% vs 75%	Pakravan et al. 2012

Table 4 (continued)

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Mixture of *Ocimum basilicum*, *Cinnamomum zeylanicum*, *Juglans regia* &*Mentha piperita* extracts	*Aeromonas hydrophila* 10^8 cells ml^{-1}-IP	common carp *(Cyprinus carpio)*	0.5 - 1.25 g/kg diet -PO-45d optimal dose:1 g/kg diet	D10: 60-91% vs 48%	Hajibeglou and Sudagar et al. 2010
Basil leaf (*Ocimum basilicum*) ethanolic extract (Lamiaceae)			100 - 1600 mg/ kg diet-PO-60 d optimal dose: 400 mg/kg diet	D10: 49-88% vs 51%	Amirkhani and Firouzbakhsh 2015
Astragalus radix and/ or *Ganoderma lucidum,* Chinese herbs and/or fungi (Faboideae, Ganodermataceae resp.)	*Aeromonas hydrophila* 10^6 cells ml^{-1}-IP		5 g/kg -PO-35d;optimal preparation combination of herbs	D6: vaccinated group: 50-60% vs 40%; non-vaccinated group: 40% vs 10%	Yin et al. 2009
Oliviera decumbens and/or *Satureja khuzestanica* , Iranian herbs (Apiaceae & Lamiaceae)	*Aeromonas hydrophila* 10^6 cells ml^{-1}-IP		5 g/kg -PO-35d;optimal preparation: *S. khuzestanica*	D10: vaccinated group:55-64% vs 50%; non-vaccinated:5-31% vs 0%	Alishahi et al. 2016
fibrous root of *Rhizoma Coptidis* (FRC) and its main alkaloids	*Aeromonas hydrophila* 10^7cells ml^{-1}-IP		12.5-50 g/kg FRC; 0.78 g/kg total alkaloids (TA), 0.78 g/kg berberine (BBR), 0.78 g/kg coptisine (Cop) diet-PO-21 d optimal treatment: FRC-25, FRC-50, TA, BBR and Cop	D10: 55-80% vs 40%	Zhou et al. 2016
Aegle marmelos leaf extract (Rutaceae)	*Aeromonas hydrophila* 1.5×10^4 cells ml^{-1}-IP		5-50 g/kg diet -PO-50 d optimal dose: 5 g/kg	D20: 83-96% vs 60%	Pratheepa et al. 2010
triherbal leaf extract of neem (*Azadirachta indica*), tulsi *(Oscimum sanctum)* & turmeric(*Curcuma longa*)	*Aeromonas hydrophila* 1.8×10^6 cells ml^{-1}-IP		On Day 6 post-infection: 1 g/kg diet-PO-28d	D30: 50% vs 15%	Harikrishnan et al. 2010

Note: *NS*: not studied; *PO*: oral administration; *IP*: intraperitoneal injection; *d*: days of treatment ; *SR*: Survival rate; *D*: day post- infection

(Alishahi et al. 2016) were more efficient in controlling *Aeromonas* infection than applying each plant alone. However, guava or mango ethanolic leaf extract alone resulted in a higher protection of rohu (*L. rohita*) against *A. hydrophila* than feeding them with both at the same level (Fawole et al. 2016).

The protective effect of phytochemical products could be due to their immunostimulant effect. Indeed, in all publications presenting a protective effect of the products, immune responses and oxidative status were enhanced significantly compared with the control groups. In contrast, the lack of protective effect of black cumin (*Nigella sativa*) methanolic extract could be linked to the absence of an immunostimulant effect (Celik Altunoglu et al. 2017). Herbal extracts enhanced fish immunity through different patterns. For example, a higher humoral immune responses of Mozambique tilapia (*O. mossambicus*) was noticed after 3 weeks of *Eclipta alba* leaf aqueous extract feeding in contrast with no significant modulation in the cellular immune responses (Christybapita et al. 2007). Two Chinese herbs (*Astragalus membranaceus*; *Lonicera japonica*) enhanced blood phagocytic cell functions but had a moderate effect on the plasma lysozyme level and no effect on plasma total protein and total immunoglobulin level (Ardó et al. 2008). As result of immunocompetence is increased by plant products, their applications were also studied to enhance the efficacy of some vaccines in farmed fish. *Astragalus radix* Chinese herb could be used in order to obtain higher survival rate in vaccinated common carp (*C. carpio*) after an *A. hydrophila* infection (Yin et al. 2009). However, *Aloe vera* powder did not enhance immune responses against a formalin-killed atypical *A. salmonicida* in rainbow trout (Zanuzzo et al. 2015).

Furthermore, the consumption of a diet containing *Rehmannia glutinosa* RG led to the accumulation of more beneficial microorganisms while inhibiting the growth of potential pathogens as *Aeromonas sp*. in the intestine of common carp (*C. carpio*) and which could have positive effects on the immune response of carp (Chang et al. 2018).

Essentials oils

Essential oils (EOs) are volatile, lipophilic, odoriferous, and liquid substances derived from plants for the food, hygiene, cleaning products, perfumery, and also pharmaceutical industries for their potential therapeutic effects (Edris 2007). Over the past two decades, several studies have evaluated the application EOs as a dietary additive in aquaculture due to their diverse properties (e.g., anesthetic, antioxidant, and antimicrobial) that can improve health, growth, and welfare of fish (Souza et al. 2019). The main biochemical compounds of some EOs may play a major role by acting as an anti-pathogen (Perricone et al. 2015). It has been reported that EOs can protect fish from pathogens by enhancing fish immunity, improving fish growth and feed utilization (Vaseeharan and Thaya 2014), and gut bacterial community modulation (Sutili et al. 2017; Ngugi et al. 2017; Al-Sagheer et al. 2018).

In this paper, the application of EOs to protect freshwater fish from *Aeromonas* infection were analyzed in Table 5 including EOs of lemongrass (*Cymbopogon citratus*) or geranium (*Pelargonium graveolens*) (Al-Sagheer et al. 2018), bitter lemon (*Citrus limon*) (Ngugi et al. 2017), *Litsea cubeba* leaf (Nguyen et al. 2016), and a commercial product (encapsulated oregano, anise, and citrus EOs) (Menanteau-Ledouble et al. 2015) which demonstrated effective protection against *Aeromonas* spp. infection in Nile tilapia (*O. niloticus*), ningu (*L. victorianus*), common carp (*C. carpio*), and rainbow trout

Table 5 Summary of *in vivo* studies in three freshwater fish species for essential oil

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
lemongrass (*Cymbopogon citratus*) or geranium (*Pelargonium graveolens*) alone	*Aeromonas hydrophila* 1.5×10^8 cfu mL^{-1}-IP	Nile tilapia (*Oreochromis niloticus)*	200, 400 mg/kg diet-PO-84 d optimal dose & essential oil: 200mg lemongrass/kg diet & 400mg geranium/kg diet	D14: 85-95 % vs 70 %	Al-Sagheer et al. 2018
bitter lemon (*Citrus limon*) fruit peels (Rutaceae)	*Aeromonas hydrophila* 10^7cell/fish-IP	ningu(*Labeo victorianus*)	10- 80 g/kg diet-PO-28 d optimal dose: 50g/kg diet	D18: 50-80 % vs 0 %	Ngugi et al. 2017
Litsea cubeba leaf (linalool-rich chemotype)	*Aeromonas hydrophila* 10^7 cfu mL^{-1}-IP	common carp (*Cyprinus carpio*)	20 - 80 g/kg diet-PO-21 d optimal dose: 80g/kg diet	D14: 37-63 % vs 27%	Nguyen et al. 2016
Satureja thymbra (Lamiaceae)	*Aeromonas salmonicida* 1.5×10^8 cfu mL^{-1}-IP	rainbow trout (*Oncorhynchus mykiss*)	10 – 800 μg μL^{-1}-IP	0%	Okmen et al. 2012
commercial product (encapsulated Oregano + anise +citrus)	*Aeromonas salmonicida* IP: 7×10^3 cfu mL^{-1}; Immersion: 10^5 CFU ml^{-1} 2h; Cohabitation		0.2g/kg diet-PO-175 d	D35: 82% vs 63%	Menanteau-Ledouble et al. 2015

Note: *PO*: oral administration; *IP*: intraperitoneal injection; *d*: days of treatment ; *SR*: Survival rate; *D*: day post- infection

(*O. mykiss*) respectively by improving immunological response, oxidative status, or growth performance.

Satureja thymbra EO was also tested in rainbow trout (*O. mykiss)* against *A. salmonicida* but effective doses of *S. thymbra* EO determined in vitro caused toxic effects and total mortality shortly after injection and doses with low or no toxic effect did not increase the bactericidal activity of fish blood (Okmen et al. 2012). All of the EOs tested in this paper were administered orally as a feed additive except *Satureja thymbra* EO, which was injected intraperitoneally (Okmen et al. 2012).

Algae

Algae, including both macroalgae (seaweed) and microalgae (unicellular), are fast growing photosynthetic organisms which are potentially good sources of energy because of their high lipid content. They also contain amino acids, minerals, vitamins, chlorophyll, and some substances that have antioxidant effects (Sirakov et al. 2015; Kent et al. 2015). Several advantages of algae as an additive in aquaculture have attracted much attention, such as the positive effect on growth performance, increased triglycerides and protein deposition in muscle, protection of fish from disease, decreased nitrogen output into the environment, increased fish digestibility, physiological activity, starvation tolerance, and carcass quality (Halima 2017; Becker 2004; Mustafa and Nakagawa 1995).

In this review, the efficacy of microalgae as green algae (*Chlorella vulgari*) or blue-green algae (*Spirulina platensis*) were revealed in Nile tilapia (*O. niloticus*) (Abdel-Tawwab and Ahmad 2009; Fadl et al. 2017) (Table 6). The efficacy of polysaccharide fraction of a marine macroalga (*Caulerpa scalpelliformi* or *Padina gymnospora*) was also presented in Nile tilapia (*O. niloticus*) and common carp (*C. carpio*) (Rajendran et al. 2016; Yengkhom et al. 2018). In addition, the favorable protective efficacy of microencapsulated seaweed extracts was revealed against *A. salmonicida* in *O. mossambicus* (Thanigaivel et al. 2019) (Table 6). Algae treatments were administered orally as a feed supplement except the polysaccharide fraction of a marine macroalga (*Caulerpa scalpelliformi*), which was injected intraperitoneally (Yengkhom et al., 2018). All treatments demonstrated significant differences ($p \leq 0.05$) in survival rate and protection effect between algae groups and control groups against *Aeromonas* infection. In addition, a significant increase of non-specific immune responses has been showed in *Aeromonas* challenge due to algal alternatives (Abdel-Tawwab and Ahmad 2009; Rajendran et al. 2016; Fadl et al. 2017; Yengkhom et al. 2018; Thanigaivel et al. 2019). Furthermore, *Chlorella* and *Spirulina* could improve growth performance of fish, and the proteins and lipids contents in Nile tilapia (*O. niloticus*) (Abdel-Tawwab and Ahmad 2009; Fadl et al., 2017).

Bacteriophages

Use of phages, virulent virus which infect and destroy bacteria, would be a highly promising option to control diseases. However, it has not yet been fully investigated in aquaculture (Oliveira et al. 2012). In the present review, few studies evaluated the efficacy of bacteriophage in treating *Aeromonas* infection in farmed freshwater fish. It was seen that bacteriophage HER 110 can protect 90% of brook trout (*S. fontinalis*) in comparison with total mortality in the control group after 4 days of *A. salmonicida* infection (Imbeault et al. 2006). In addition, *Aeromonas* Phage PAS-1 can be

Table 6 Summary of *in vivo* studies in three freshwater fish species for algae

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
microalgae-enriched fodder: green algae (*Chlorella vulgari*) or/and blue-green algae (*cyanobacterium Spirulina platensis*)	*Aeromonas hydrophila* 3 × 10^8 cfu ml^{-1}-IP	Nile tilapia (*Oreochromis niloticus)*	150 g/kg diet-PO-56d	D14:100% vs 61%	Fadl et al. 2017
live Spirulina (*Arthrospira platensis*)	*Aeromonas hydrophila* 5 × 10^5 cfu ml^{-1}-IP		1.25, -10 g/kg diet -PO-84d optimal dose: 5-10 g/kg diet	D10:30-90% vs 20%	Abdel-Tawwab and Ahmad 2009
polysaccharide fraction of a marine macroalga (*Caulerpa scalpelliformi)*	*Aeromonas hydrophila* 5 × 10^5 cfu ml^{-1}-IP		2-200 mg / kg—IP- 7 and 21d	7d post treatment D15: 90-95% vs 55% 21d post treatment D15: 45-65% vs 35%	Yengkhom et al. 2018
methanolic extract of the marine macroalga, *Caulerpa scalpelliformis*			2- 200mg / kg—IP-7d	D15: 36-72% vs 55%	Yengkhom et al. 2019
microencapsulated seaweed (*Gracilaria foliifera or Sargassum longifolium*) extracts	*Aeromonas salmonicida* 10^{3-7} cfu mL^{-1}		10- 50 μl in diet -1d on challenge	D15: 30-85% vs 5-20%	Thanigaivel et al. 2019
polysaccharide fraction of a marine macroalga *(Padina gymnospora)*	*Aeromonas hydrophila* 2.1 × 10^9 cfu ml^{-1}-IP	common carp *(Cyprinus carpio)*	0.1- 10g polysaccharide/kg diet or 10g Macrogard™/kg diet -PO- 7, 14, and 21d optimal dose & duration:10g polysaccharide/kg diet for 14 days	D15: 35-90% vs 25-30%	Rajendran et al. 2016

Note: *PO*: oral administration; *IP*: intraperitoneal injection; *SR*: Survival rate

applied as a biological control of *A. salmonicida* subsp. *salmonicida* infection with increased survival rates and mean times to death in rainbow trout (*O. mykiss*) (Kim et al. 2015).

Others functional products

As mentioned previously, many research studies have focused on the development of functional feed alternatives, examining probiotics, prebiotics and plant-derived compounds or extracts to maintain fish health and performance. There is also a growing interest in nanoparticles due to their antimicrobial effects and as drug delivery systems (Shaalan et al. 2016). For example, 100 μl intraperitoneal injection of fucoidan-coated (marine polysaccharide) gold nanoparticle (Fu-AuNPs) resulted to higher survival rate in treatment group in comparison with control group after 72 h (70 vs. 10%) against *A. hydrophila* in Mozambique tilapia (*O. mossambicus*) (Vijayakumar et al. 2017) (Table 7). However, its mode of action has not been studied in vivo while the synthesized Fu-AuNPs at 100 μg ml^{-1} showed effective inhibition of *A. hydrophila*, which is much higher than that of chloramphenicol in vitro assay (Vijayakumar et al. 2017).

The incorporation of rare earth elements such as azomite, mineral ore (Musthafa et al. 2016) and minerals such as yellow loess (sedimentary deposit of mineral particles) (Lee et al. 2016b; Won et al. 2017) in fish feed has been assessed as a means to control *Aeromonas* infection (Table 7). The efficacy of yellow loess against *A. salmonicida* in rainbow trout represented an improved growth performance, non-specific immune responses, and a furunculosis resistance (Lee et al. 2016b; Won et al. 2017).

Furthermore, the utilization of organic acids has attracted considerable attention recently due to their antimicrobial properties and role in enhancing nutrient availability in aquaculture (Ng and Koh 2017). It has been found that a commercial product which contains formic, propionic, and lactic acids and cinnamaldehyde, may be effective as an alternative method to control the impact of furunculosis in rainbow trout. However, significant difference was not found in the feed conversion ratio with the control group in this assay (Menanteau-Ledouble et al. 2017).

Main perspective

In this review, the efficiency of functional alternative products against *Aeromonas* infection and their potential mechanisms of action in freshwater fish were analyzed and compared. The selected studies tested highly diverse products with wide ranges of doses and durations of administration in different species of freshwater fish which were experimentally infected by *Aeromonas.* Furthermore, the experimental design of *Aeromonas* infection was also varied by the species and the strains of *Aeromonas* bacteria, the infectious doses, and the administration routes. It consequently was almost impossible to compare the studies or to determine whether one product is more effective than another. However, most of these alternatives were added to the basal diet as a feed supplement and were effective in inducing a preventive effect against mortality caused by *Aeromonas* spp. and in increasing growth performance. First, immunostimulation was the main mechanism of action investigated in the studies reviewed; nevertheless, in some studies, the protective effect of the product is clearly linked to the immunostimulant effect, but in other studies, a protective effect was observed without an increase of fish immunocompetence. Second, products feeding could also induce modifications of the gut microbiota (e.g., increase of the beneficial micro-organisms and decrease of the pathogen bacteria) as well as of the intestine morphometry (e.g., beneficial effects on the structure and decrease of tissue lesions induced by bacteria). All these mechanisms of action need to be described and explained in fish because they are clearly gaps that need to be filled in order

Table 7 Summary of *in vivo* studies in three freshwater fish species for non-classified group

Substances	Infectious challenge Species – dose - route	Fish species	Substances administration Dose - Route- Duration	(D): SR in test groups vs control	Reference
Fucoidan (marine polysaccharide) coated gold nanoparticle	*Aeromonas hydrophila* 6×10^8 cfu ml^{-1}-IP	Mozambique Tilapia (*Oreochromis mossambicus*)	100 µl -IP	72h :70% vs 10%	Vijayakumar et al. 2017
Azomite (mineral ore)	*Aeromonas hydrophila*		2- 6 g/kg diet-PO-30d optimal dose: 4 g/kg diet	D30: 80-90% vs 10%	Musthafa et al. 2016
Shilajit, a natural mineral original from India	*Aeromonas hydrophila* 3.1×10^7 cells ml^{-1}-IP		2-6 g/kg diet--PO-28d optimal dose: 4 & 6 g/kg	D14:82-92% vs 10%	Saiyad Musthafa et al. 2018
natural mineral materials: yellow loess, SG (commercial product), Mk (commercial product) or barley stone	*Aeromonas salmonicida* 2×10^7 cfu ml^{-1}-IP	rainbow trout (*Oncorhynchus mykiss*)	4 g/kg diet-PO-56d optimal preparation: yellow loess or SG	D15:30-45% vs 12% oxytetracycline :45%	Won et al. 2017
yellow loess (sedimentary deposit of mineral particles)			5-20 g/ kg diet-PO-84d	D14: 15% vs 0% oxytetracycline :15%	Lee et al. 2016b
commercial product (combination of formic, Propionic, lactic acids and cinnamaldehyde)	*Aeromonas salmonicida* 10^5 cfu ml^{-1} (2h) IP: 2×10^7 cfu ml^{-1} cohabitation		0.8 g/kg diet-PO-175d	D35;IP :70% vs 25% Immersion: all 70% cohabitation: 100% vs 90%	Menanteau-Ledouble et al. 2017

Note: *PO*: oral administration; *IP*: intraperitoneal injection; *d*: days of treatment; *SR*: Survival rate; *D*: day post- infection

to draw conclusions concerning their role in the protective effect of the products. Furthermore, alternative-to-antibiotics researches need to benefit from greater access to expertise in pharmacokinetics and pharmacodynamics, formulation and toxicology, for example, by creation of partnerships with biotechnology companies.

Although there are numerous clinical trials on alternative products in experimental conditions in order to reduce antibiotic use in aquaculture, there is a clear need for careful clinical trial designs in experimental conditions with relevant endpoints: primary endpoints such as reduction of morbidity and mortality but also secondary or surrogate endpoints such as changes in cytokine levels or changes in imaging of infections. Finally, in our knowledge, no evaluation of the functional feed alternative efficiency has been carried out in fish farms, where *Aeromonas* infection could be heterogeneous between fish, in contrast with the experimental conditions and where the environmental bacterial flora and the quality of water could influence the effect of the product. So, there is also a clear need for careful clinical trial designs in fish farm conditions, especially in order to ensure their benefits and their technical feasibility but also to improve the economic models.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors.

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