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Bacterial-Chemical Compounds on Fish Microbial Disease Control in Aquaculture: A Systematic Review

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Abstract: Bacterial and viral diseases are the primary limiting factors in aquaculture production. They are associated with severe mortality in both wild and cultured fish. The use of conventional disinfectants, synthetic chemical compounds, and antibiotics to control such infections, and their large-scale misuse, integrates into the fish system, resulting in the emergence and spread of antimicrobial-resistant pathogens and resistance genes. Consuming infected fish and fish products also affects human health and poses a severe health hazard. Currently, aquaculture is one of the world's major food production sectors. Despite encouraging trends, microbial infections remain a major threat and significantly affect the growth of the aquaculture industry. It causes significant economic losses to aquaculture farms in developing countries and also affects the production of fish feed. Drawbacks in the existing control measures include physical and chemical methods, plant extract treatments, antibiotics, vaccines, and bacteriophage therapy, which need to be replaced by newer methods with less or no impact on humans, fish, animals, and the environment. There is a huge scope for the use of Streptomyces and its secondary metabolites as natural antibiotics for the control of fish microbial diseases.

Keywords: aquaculture; fish food; microbial pathogens; probiotics; actinomycetes; *Streptomyces*.

1. Introduction

Aquaculture, an aquatic agricultural food production sector, has grown much faster than other sectors over the past few decades. Production of a variety of aquatic foods, including fish and shellfish, has grown enormously to become an economically important industry [1]. It has greater significance in creating employment opportunities, generating income, and promoting human development. Aquaculture has been developed as an important component of the global food source and food security [2]. Fish is considered an essential commodity due to its potential to improve human health and nutrition. Fish is a major source of protein and provides long-chain omega-3 fatty acids, vitamin A, and several micronutrients that help maintain human health and reduce heart disease. It is easily accessible to the impoverished population, and around 1 billion people worldwide depend on fish as their primary source of animal protein [3]. Fish food supply has increased by 3.2 percent, while world population growth has been 1.6 percent [4]. The total production output from aquaculture was 88 million tons in 2020 [5]. To meet the world’s growing demand for fish feed, aquaculture production must be doubled by 2030. Fish production has a much less environmental impact than other animal source foods.

2. Aquaculture Microbial Diseases

It poses a real threat to aquaculture production worldwide, and intensive aquaculture has increased the risk of disease outbreaks, which affect the economic and socio-economic development of several countries [6]. Effective aquaculture biosecurity, disease surveillance, and control systems need to be established to reduce the negative environmental and social impacts of aquaculture. Increased mortalities of cultured and wild fish are due to poor water quality, inappropriate nutrition, and contamination of the aquatic environment. The OIE International Aquatic Animal Health Code lists several infectious diseases of aquaculture that pose greater challenges to aquaculture development [7]. Disease outbreaks in aquaculture result in loss of several billion US$ per year [8]. Bacterial fish diseases such as hemorrhagic septicemia, edwardsiellosis, pop eye, vibriosis, bacterial gill disease, bacterial kidney disease, dropsy, and fin and tail rot were reported by researchers worldwide [9]. Bacterial diseases cause severe mortality in both cultured and wild fish and shellfish worldwide [10]. Viral diseases are also severely affecting the aquaculture industry; among them, WSSV (White spot syndrome virus) affects shrimp and other crustaceans [11].

Several control measures have been used in the past for disease management in aquatic animals, including hygiene maintenance, the use of synthetic chemicals, chemical-based disinfectants, plant extracts, herbal drugs, and antibiotics. Hygiene maintenance is essential for the prevention of aquaculture diseases [12]. In commercial aquaculture, antibiotics were widely used for disease management, leading to increased pollution and the development of disease-resistant strains. The use of hormones for growth performance is not cost-effective. To replace the use of antibiotics in aquaculture, a search for alternative methods of disease control has been initiated. The excessive use of antimicrobial drugs in the management of aquaculture diseases has increased health risks to humans through the large-scale consumption of fish products. Therefore, to combat diseases and prevent the use of antibiotics, the microbial community has been used as a bioremediation agent, a vaccine, an immunostimulant, for phage therapy, and as a prebiotic and a probiotic [13]. The development of non-antibiotic-based new methods for better health management in aquaculture is associated with the use of probiotics [1].

3. Physical and Chemical Methods in Aquaculture Disease Control

Disinfection in aquaculture is achieved by means of physical methods, including filtration, ozonation, mechanical separation, heat treatment, and ultraviolet (UV) irradiation. Disinfection by UV is the most effective and efficient method. Water treatment with ultraviolet-C (UV-C) is used to prevent bacterial, viral, and fungal diseases [14]. UV-C (254 nm) treatment inactivates the microorganisms by DNA denaturation. The use of low-frequency ultrasound (LFUS) disinfection technique in recirculating aquaculture systems has been reported [15]. A combination of UV-C (to kill viruses and bacteria) and LFUS (to kill eukaryotic parasites) could provide an effective water treatment method in recirculating aquaculture systems [15].

Pesticides, oxidants, disinfectants, algicides, biocides, herbicides, and chemotherapeutic agents are widely used. The nets used are disinfected routinely with benzalkonium chloride solution. An acetic acid (1000 to 2000 ppm) dip for 1 to 10 min is used as a disinfectant for fish. Calcium chloride (150 ppm) is used to increase the hardness of water and maintain osmotic balance during the transportation of fish. Calcium oxide (2000 mg/L) is used for 5 seconds as an external protozoacide for fingerlings to adult fish. Fish are immersed in $MgSO_4$ (30,000 mg/L) and NaCl (7,000 mg/L) solution for 5 to 10 minutes to treat external monogenetic trematode and crustacean infestations [Fish and Fishery products hazards and control guidance, 2011]. Di-n-butyl tin oxide (25g/100 kg fish/ day) for 3 days is effective against most parasites of the gut other than protozoans. Copper sulphate is effective against bacterial infections but is not used due to its toxic effects [16].

4. Plant and Herbal Extracts in Aquaculture Disease Control

Several plant extracts have been used as drugs against aquaculture diseases for centuries. Medicinal herbs serve as a source of herbal drugs [17]. In organic agriculture, bacterial diseases are treated with different herbal extracts. Medicinal plants are rich in phytochemicals, such as tannins, alkaloids, saponins, sterols, and flavonoids, which possess antimicrobial properties. Several medicinal plants, *Aegle marmelos*, Aloe vera, *Allium sativum*, *Aristolochia indica*, *Azadirachta indica*, *Cassia fistula*, *Catharanthus roseus*, *Curcuma longa*, *Cynodon dactylon*, *Lantana camara*, *Melia azedarach*, *Mimosa pudica*, *Momordica charantia*, *Morus alba*, *Ocimum americanum*, *Ocimum sanctum*, *Phyllanthus amarus*, *Phyllanthus emblica*, *Psidium guajava*, *Punica granatum*, *Solanum nigrum*, *Tridax procumban*, *Tylophora indica*, *Zingiber officinale*, etc. have been used in shrimp aquaculture [18]. The medicinal herbs *Curcuma longa*, *Ocimum sanctum*, and *Azadirachta indica* were found effective in goldfish following a disease challenge [19]. In common carp, the application of *Mentha piperita* and *Ocimum bascilicum* against *A. hydrophila* enhanced the immunity [20]. Medicinal plants *Azadirachta indica*, *Cinnamomum verum*, and *Eupatorium odoratum* exhibited excellent antibacterial activity against the bacterial pathogens isolated from diseased ornamental fishes [21]. Methanol extracts of eight species of Lamiaceae and seven species of Apocynaceae showed antimicrobial activity against *Aeromonas hydrophila* [22]. Chinese herbs *Rheum officinale*, *Andrographis paniculata*, *Isatis indigotica*, and *L. japonica* have been reported to enhance the phagocytic activity of white blood cells in Crucian carp [23].

5. Antimicrobial Agents Used in Aquaculture Disease Control

Intensive fish farming has promoted the emergence of several bacterial diseases, thereby increasing the use of antimicrobials [8]. Antibacterial substances are used more widely in aquaculture production to control bacterial diseases. It was estimated that 75% of the antibiotics fed to fish are excreted into the water, posing environmental hazards [24]. The emergence of bacterial drug resistance is driven by the extensive use of antibiotics in aquaculture [3]. The use of antibiotics, which include chloramphenicol, clenbuterol, diethylstilbestrol (DES), dimetridazole, ipronidazole, nitrofurans, fluoroquinolones and quinolones, malachite green, and steroid hormones, was prohibited by the FDA in 2011. Whereas the excessive use of antibiotics in aquaculture has led to the development of antibiotic resistance in aquaculture pathogens, paving the way for the rise of multiple-resistant bacteria. Some drugs that have become resistant to pathogens include streptomycin (resistant to Edwardsiella ictulari), florfenicol (resistant to Enterobacter spp.), and *Pseudomonas* spp. Ampicillin to *Vibrio harveyi*, enrofloxacin to *Tenacibaculum maritimum*, erythromycin to

Salmonella spp, furazolidone to *Vibrio anguillarum*, sulphadiazine to *Aeromonas* spp., tetracycline to *Aeromonas hydrophila,* oxytetracycline to *Aeromonas salmonicida*, etc. [8]. Misuse of antimicrobials not only creates multidrug-resistant strains but may also produce low-quality fish with shorter shelf-life associated with severe health hazards on human consumption [25]. Excessive and unrestricted use of antibiotics in aquaculture is detrimental to fish, terrestrial animals, and human health [26]. Administration of antibiotics not only promotes resistance but also inhibits or kills beneficial microbiota in the gastrointestinal system and leads to the accumulation of antibiotic residues in fish products, making them harmful for human consumption [1].

6. Vaccination in Aquaculture Disease Control

Fish vaccinology has shown an amazing development in recent years. Vaccination is an alternative prophylactic measure to control diseases in aquaculture. It does not provide absolute protection against infection, but it helps fish combat infections [27]. Some vaccines have been proven effective in providing protection against finfish; for shellfish such as shrimp and molluscs, vaccination is not possible. Vaccination is found to be cost-effective and reduces antibiotic use. Vaccines have been commercialized for finfish diseases like furunculosis (*Aeromonas salmonicida),* enteric red mouth (*Yersinia ruckeri),* cold water vibriosis (*Vibrio salmoninarum*, *V. anguillarum* serotypes 01 and 02, and *V. ordalli)*, bacterial gill disease (*Flavobacterium branchiophilum*), enteric septicemia of catfish (*Edwardsiella ictaluri*), and kidney disease caused by bacteria (*Renibacterium salmonarium*)[7]. In aquaculture, commercially available vaccines are either bacterins (formalin-inactivated or live attenuated) or DNA vaccines. Polyvalent vaccines are widely used and have been shown to be more effective than monovalent vaccines, protecting fish species against the majority of diseases [28]. Vaccination was very effective in removing extracellular microorganisms but quite challenging against intracellular microorganisms [29].

7. Phage Therapy in Aquaculture Disease Control

Bacteriophages are used to control bacterial populations in natural systems, including multidrug-resistant pathogens [30]. Phages are used to control fish diseases in aquaculture [31]. Currently, phage therapy is widely used for the treatment of bacterial infections in aquaculture systems [32]. Lytic phages are efficient and can be used against bacterial infections in aquaculture [33]. In shrimp hatcheries, luminous bacterial diseases (*V. harveyi*) are controlled by bacteriophages. It is necessary that phages used as biocontrol agents be able to infect a wide range of strains of the target pathogen. Phages have served as a good source of therapeutics in the biocontrol of bacterial diseases in aquaculture [8]. *V. parahemolyticus* and *A. salmonicida* phages showed desired specificity and improved potential in inactivating a broader range of pathogenic bacteria [34]. Phage therapy is highly effective in treating ulcerative lesions caused by multidrug-resistant Pseudomonas aeruginosa in infected catfish (*Clarias gariepinus*) [35]. The risk of transformation of non-virulent bacterial strains into virulent strains during the use of lysogenic phages likely affects the aquatic food production and food safety [32].

8. Probiotics in Aquaculture Disease Control

The development of non-antibiotic agents, such as probiotics, will help control aquaculture diseases. Probiotics involve multiplying beneficial microbes to compete with the harmful pathogens by inhibiting their growth. Probiotic bacteria produce antagonistic compounds or compete for nutrients or attachment sites, thereby inhibiting pathogens [25,1]. Probiotics are not to be harmful to the host; they must be effective over a wide range of temperatures and salinities, provide benefits to the host, and survive in the body during digestion and remain stable and viable under prolonged storage conditions. Probiotics also inhibit pathogens by producing bacteriocins, exerting immunostimulatory effects, altering enzyme activity, and providing nutritional benefits, such as improved feed digestion and utilization [36]. Various bacteria commercially applied as probiotics in aquaculture include *Lactobacillus acidophilus*, *L. casei*, *L. fermentum*, *L. gasseri*, *L. johnsonii*, *L. lactis*, *L. paracasei*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. salivarius*, *Bifidobacterium bifidum*, *B. breve*, *B. lactis*, *B. longum*, *Streptococcus thermophilus*, and yeast *Saccharomyces cerevisiae* and *Dermocystidium hansenii* [25,16]. The use of different types of probiotics improved growth performance in Nile tilapia, rabbitfish, and European perch. Biogen® is a commercially available probiotic that contains *Bacillus licheniformis* and *Bacillus subtilis* [37]. Biogen administration increases the specific growth rate and feed efficiency ratio of *M. rosenbergii* [38]. *L. rhamnosus* progressively improved villi length in tilapia. Probiotic bacteria such as *B. coagulans*, *B. mesentericus*, and *Bifidobacterium infantis* have been reported to colonize the gut of Puntius conchonius, a freshwater ornamental fish, through competitive inhibition [39]. The probiotic bacterium P. acidilactici has been reported to improve skeletal conformation in rainbow trout and sea bass [40]. Thirty bacterial strains of *V. anguillarum* are found to be effective probiotics against a salmon pathogen, *V. ordalii* [41]. Probiotic bacteria act as growth promoters, immunostimulators, and producers of pathogen inhibitors, thereby improving water quality [42]. Probiotics are reported to be an effective alternative for controlling shrimp aquaculture diseases [42]. Probiotics play many important functions in the host, including reducing disease burden and stress, enhancing immunity, modulating the gut microbiota, supporting nutrition, improving water quality, etc. It has also been reported to increase feed value and animal growth, and to improve spawning and hatching rates in aquaculture animals [43].

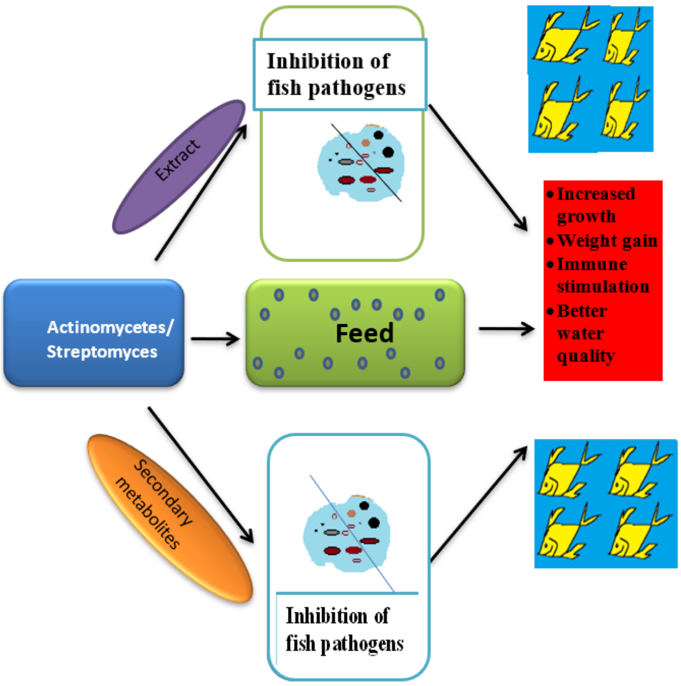

Figure 1. Probiotic activity of actinomycetes and their secondary metabolites: inhibition of fish pathogens.

9. Actinobacteria as Probiotics

Several microorganisms, including members of the genus Actinomycetes, were used as probiotics to control aquaculture diseases. Actinomycetes are known for their incomparable capacity to produce numerous novel secondary metabolites and new chemical compounds with diverse biological activities. Actinobacteria have been used in aquaculture, and colonization of actinomycetes in the host intestine is beneficial, as their exoenzymes aid feed utilization and digestion. Moreover, colonized microflora produces antibacterial substances, thereby conferring resistance to infectious diseases. Probiotic strains adhere to and colonise mucosal surfaces to protect them from pathogens [36]. It was reported that many enzymes produced from marine actinobacteria are used as probiotics, prebiotics, and synbiotics in aquaculture [36]. The probiotic potential of actinomycetes is shown in Figure 1.

10. *Streptomyces* as Probiotics

The genus *Streptomyces* belongs to the actinobacteria, characterized by a branching chain and filamentous morphology. Two-thirds of the antibiotics available in the market are derived from *Streptomyces* sp., which are also known for producing a variety of secondary metabolites and new chemical entities, including antitumor, antiparasitic, immunosuppressive agents, and enzymes [44]. Streptomyces species showing antimicrobial activity against fish pathogens are given in Table 1.

Table 1. Applications of *Streptomyces* species as probiotics inhibiting aquaculture pathogens.

***Streptomyces* species**	**Target pathogen**	**Reference**
Streptomyces sp.	Artemia	[45]
Streptomyces rubrolavendulae M56	*Penaeus monodon*	[46]
Streptomyces M10-77 &	*Vibrio alginolyticus*	[47]
Streptomyces M11-116 (B)	*Vibrio parahaemolyticus*	[47]
	Vibrio harveyi	[47]
Streptomyces sp.	*Penaeus monodon*	[48]
Streptomyces sp.	*Xiphophorus helleri*	[49]
Streptomyces fradiae	*Penaeus monodon*	[50]
Streptomyces sp.	*Vibrio vulnificus*	[51]
Streptomyces sp.	*White spot syndrome virus*	[52]
Streptomyces strain RL8	*Vibrio parahaemolyticus*	[53]
Streptomyces MN2, MN39 & MN40	*Vibrio harveyi, V. parahaemolyticus*	[54]
Streptomyces sp.	Fish bacterial pathogens	[55]
Streptomyces labedae	*Vibrio anguillarum, V.alginolyticus*	[56]
Streptomyces virginiae W18	*Aeromonas veronii*	[57]
Streptomyces termitum N-15	*Aeromonas veronii*	[58]
Streptomyces lateritius (Z1-26)	*Aeromonas hydrophila*	[59]

Among actinomycete genera, Streptomyces has been reported to be a highly effective probiotic [45]. The probiotic *Streptomyces* sp. can compete for nutrients in the host. Colonization of *Streptomyces* sp. in the host intestine may be helpful in facilitating the feed utilization and digestion. *Vibrio* sp., including *V. harveyi*, *V. alginolyticus, V. parahaemolyticus,* and *V. fluvialis* co-cultured with *S. rubrolavendulae* M56 have been proved to be effective in inhibiting the growth of *Vibrio* species [46]. *Streptomyces* M10-77 Pathogens use iron for their growth and biofilm formation. The siderophore produced by *Streptomyces* sp. limits the bioavailability of iron, thereby inhibiting pathogens [47]. Feed supplementation with Streptomyces as a probiotic aids in growth and prevents disease outbreaks in black tiger shrimp, *Penaeus monodon* (Fabricius) [48]. Administration of *Streptomyces* (1%, v/v) treatment to Artemia infected with V. harveyi or V. proteolyticus (106 CFU/mL) resulted in better survival rates than the untreated control group. It was demonstrated that the *Streptomyces* incorporated in the feed increased the weight of *Penaeus monodon* shrimp. It was reported that the amylolytic and proteolytic activity of hydrolytic exoenzymes of *Streptomyces* sp. present in the shrimp digestive tract helped to improve the weight of the shrimp [45]. *Streptomyces* sp. CLS-28, supplemented with feed for 15 days, protected V. harvey i-challenged P. monodon shrimp (LD_{50} at $10^{6.5}$ CFU/mL) [45]. Feeds supplemented with *Streptomyces* improved the growth of shrimp and ornamental fish, *Xiphophorus helleri* (red swordtail fish) [49]. Feed supplementation with Streptomyces is not only cost-effective but also contributes 30–40% of the fish meal, and it is a cheaper alternative protein source in aquaculture feed [49]. Feed supplementation of *Streptomyces fradiae* isolated from mangrove sediment soil increases the growth of the post-larval *P. monodon* [50]. *M. rosenbergii juveniles* infected with *V. vulnificus* showed a high survival rate and no external disease manifestations when treated with as probiotics [51]. The better growth rate of *Xiphophorus helleri* on supplementation of *Streptomyces* with feed is due to the production of the growth-promoting hormone, indoleacetic acid, by the *Streptomyces* sp. In addition to inhibiting bacterial pathogens, *Streptomyces* sp. are also effective against WSSV [52]. Administration of *S. rubrolavendulae* M56 as biogranules in the culture system for 28 days showed decreased mortality of *P. monodon* post-larvae with a significant reduction in *Vibrio* species. Administration of *Streptomyces* strains (RL8) alone or in combination with Bacillus as probiotics showed considerable improvement in growth parameters, regulation of the immune response, modulation of host and water microbiota, and increased resistance to disease [53]. *Streptomyces* MN2, MN39, and MN40, isolated from Caspian Sea sediment (Iran), showed inhibitory activity against Vibrio strains (V. *harveyi*, *V. parahaemolyticus*, and *V. proteolyticus*) [54]. Probiotics not only serve as an effective alternative to antibiotics but also help combat diseases, support growth, and stimulate the host's immune response [55]. *Streptomyces labedae* showed antibacterial activity against *Vibrio anguillarum* and *Vibrio alginolyticus* [56]. It was reported that *Streptomyces virginiae* W18 showed antibacterial activity against *Aeromonas veronii* (57). Similarly, *Streptomyces termitum* N-15 showed antibacterial activity against *Aeromonas veronii* (58), and *Streptomyces lateritius* (Z1-26) showed antibacterial activity against *Aeromonas hydrophila* (59). *Streptomyces* sp., with probiotic activity, was used as a pathogen inhibitor to control aquaculture diseases.

11. *Streptomyces* Derived Secondary Metabolites for Microbial Disease Control

A variety of chemical compounds produced by *Streptomyces* offer several advantages for use as antagonists and antimicrobial agents in aquaculture. *Streptomyces*-derived chemical compounds and their antimicrobial activity against fish pathogens are given in Table 2. *Streptomyces* are also capable of producing anti-quorum-sensing or quorum-quenching compounds responsible for inhibition of biofilm formation [60]. Compounds 2-hydroxy-5-(3-methylbut-2-enyl) benzaldehyde and 2-hepta-1,5-dienyl-3,6-dihydroxy-5-(3-methylbut-2-enyl) benzaldehyde derived from *Streptomyces atrovirens* have been shown to be effective against *Edwardsiella tarda*, *Vibrio anguillarum*, and *Vibrio harveyi* [61]. Anti-virulent activity of phthalic acid extracted from *S. ruber* EKH2 against *A. hydrophila* (2 µg/ml), *E. tarda* (8 µg/ml), and *V. ordalii* (32 µg/ml has been reported by Brakat and Beltagi [62]. A compound N-isopentyltridecanamide extracted from *Streptomyces labedae* ECR77 showed activity against *V. alginolyticus*, followed by *V. cholerae*, *P. fluorescens*, *V. parahaemolyticus*, and *A.* hydrophila [63]. Inhibition of *V. anguillarum* cell growth and *V. anguillarum* peptide deformylase (VaPDF) activity by actinonin extracted from marine *Streptomyces* sp. NHF165 was already reported [64]. A 15 KDa protein extracted from *Streptomyces* has been shown to be effective against fish pathogens, *Aeromonas hydrophila*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Vibrio harveyi*, and *Vibrio* alginaticus [64]. The ethyl acetate extract of *Streptomyces* sp. VITNK9, containing pyrrolo[1,2-A] pyrazine-1,4-dione (56.67%) and hexahydro-3-(2-Methylpropyl) (27.91%), has been shown to be very effective against fish bacterial pathogens, *Aeromonas caviae* (15.33 mm), *Aeromonas hydrophila* (17.66 mm), *Edwarsiella tarda* (18.33 mm), *Vibrio anguillarum* (14.33 mm), and *Vibrio harveyi* (14.33 mm) [65]. A compound 9(10H)-Acridanone extracted from marine *Streptomyces fradiae* sp. VITMK2 has been shown to be effective against WSSV [66]. Recently, the use of *Streptomyces* bacteria as a probiotic agent in aquaculture disease control has been reported [67]. Some of the mechanisms reported for the probiotic *Streptomyces* bacteria for exhibiting the aguaculture disease control are by production of antagonistic/ siderophore compounds, disruption of quorum sensing/antibiofilm, antiviral activity, bioremediation, competitive exclusion of pathogens, enzymatic activities, stimulation in growth and survival, protein source, and modification in gut microbiota [67]. Since many secondary metabolites derived from actinomycetes showed strong antagonistic activity against fish pathogens, these compounds can also be used in the future as probiotic feed supplements to control aquaculture diseases.

Table 2. *Streptomyces* species-derived chemical compounds as inhibitors of aquatic pathogens. (confirmed)

Strptomyces sp.	Pathogen inhibitor metabolite	Target pathogens	Reference
Streptomyces atrovirens	2-hydroxy-5-(3-methylbut-2-enyl)	*E. tarda*	[61]
	Benzaldehyde & 2-hepta-1,5-dienyl-	*V. anguillarum*	[61]
	3,6-dihydroxy -5-(3-methylbut-2-enyl) benzaldehyde	*V. harveyi*	[61]
Streptomyces ruber EKH2	Phthalic acid	*A. hydrophila*	[62]
		E. tarda	[62]
		V. ordalii	[62]
Streptomyces labedae ECR77	N-isopentyltridecanamide	*V. alginolyticus*	[63]
		V. cholera	[63]
		P. fluorescens	[63]
		V. parahaemolyticus	[63]
		A. hydrophila	[63]
Streptomyces sp. NHF165	Actinonin	*V. anguillarum*	[64]
Streptomyces sp. VITNK9	Pyrrolo[1,2-A] pyrazine-1,4-Dione	*A. caviae*	[65]
	Hexahydro-3-(2-Methylpropyl	*A. hydrophila*	[65]
		E. tarda	[65]
		V. anguillarum	[65]
		V. harveyi	[65]
Streptomyces fradiae sp. VITMK1	9(10H)-Acridanone	White spot syndrome virus	[66]

12. Other Agents Used to Control Fish Microbial Diseases

Antibiotics are currently used to prevent and treat microbial infectious diseases and for their growth-promoting effects, resulting in widespread antibiotic-resistant infections in animals and humans [67]. It was reported that *Cymbopogon flexuosus* essential oil was effective against oxytetracycline (OTC)- resistant *Aeromonas hydrophila* [68]. Bovine lactoferrin has been reported to be a highly effective glycoprotein for controlling bacterial and viral diseases in fish [69]. The ubiquitin-like protein interferon (IFN)-stimulated gene product 15 (ISG15) was also used to control fish diseases [70]. Chinese herbal medicine and artemisinin from *Artemisia annua* supplementation have been reported to protect fish from microbial diseases [71]. Bacteriophage (*Myroviridae* family) has been shown to be effective in controlling *A. hydrophila* infection in freshwater- and estuary-living fish [72]. The disease resistance capacity of fish has been reported to be increased by the administration of antimicrobial peptides (C and P) in *Pengze crucian* carp [73]. *Hericium erinaceus* (HE), lion's mane mushroom administration improved microbial disease resistance in Nile tilapia (*Oreochromis niloticus*) [74]. Dietary supplementation of *Bacillus* sp. PM8313 with β-glucan significantly increased pathogen resistance in red sea bream [75]. Replacing rice protein concentrate with 25% of the fish meal protein in the diet of O. niloticus improved microbial disease resistance [76]. Nanoparticles have been extensively used as immunotherapeutic agents in the treatment of aquatic infectious diseases through site-specific, target-oriented drug therapy, gene delivery, vaccination, or as diagnostic tools [77].

11. Conclusions

Disease control methods in aquaculture farms have been used for decades, primarily through conventional methods such as disinfectants and synthetic chemical compounds. Later, antibiotics played a vital role for a few decades, but excessive use has resulted in health hazards to aquatic animals and the human population and has also increased the prevalence of multidrug-resistant pathogens. Even though vaccination and phage therapy appear more promising, they each have drawbacks. Currently, the use of probiotics to control aquaculture infections appears more promising, and, moreover, probiotics have shown a beneficial effect on fish health. Exploring the *Streptomyces* genus as probiotics in controlling aquaculture diseases is more promising. However, more field trials with *Streptomyces* species/ derived secondary metabolites as probiotics/ prebiotics/ synbiotics, postbiotics, and paraprobiotics would help us identify them as better agents for aquaculture disease control and management.

Author Contributions

Conceptualization, K.K.; methodology, K.K.; validation, M.I.N.; formal analysis, M.I.N.; investigation, M.I.N.; resources, K.K.; data curation, M.I.N.; writing—original draft preparation, M.I.N.; writing—review and editing, K.K.; visualization, M.I.N.; supervision, K.K.; project administration, K.K. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

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