Present status, limitations, and prospects of using *Streptomyces* bacteria as a potential probiotic agent in aquaculture

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Abstract

Streptomyces is a Gram-positive bacterium, belonging to the family Streptomycetaceae and order Streptomycetales. Several strains from different species of *Streptomyces* can be used to promote the health and growth of artificially cultured fish and shellfish by producing secondary metabolites including antibiotics, anticancer agents, antiparasitic agents, antifungal agents, and enzymes (protease and amylase). Some *Streptomyces* strains also exhibit antagonistic and antimicrobial activity against aquaculture-based pathogens by producing inhibitory compounds such as bacteriocins, siderophores, hydrogen peroxide, and organic acids to compete for nutrients and attachment sites in the host. The administration of *Streptomyces* in aquaculture could also induce an immune response, disease resistance, quorum sensing/antibiofilm activity, antiviral activity, competitive exclusion, modification in gastrointestinal microflora, growth enhancement, and water quality amelioration via nitrogen fixation and degradation of organic residues from the culture system. This review provides the current status and prospects of *Streptomyces* as potential probiotics in aquaculture, their selection criteria, administrative methods, and mechanisms of action. The limitations of *Streptomyces* as probiotics in aquaculture are highlighted and the solutions to these limitations are also discussed.

Keywords: Aquaculture, Probiotics, Pathogens, *Streptomyces*, Toxicity, Microflora.

Authors' Contributions

Usman Dawood Butt and Bin Wu conceived and designed the sketch of the study. Usman Dawood Butt, Sumaikah Khan, Liu Xiaowan, and Xiaoqin Zhang wrote the main manuscript text. Usman Dawood Butt, Sumaikah Khan, and Bin Wu checked the logicality and language of this manuscript. Usman Dawood Butt and Bin Wu were responsible for the overall study coordination of this manuscript. Usman Dawood Butt prepared figures and tables 1-2. Awkash Sharma revised the whole manuscript and tables. All authors reviewed and approved the final manuscript.

Declaration

Competing Interest

The authors declare that they have no competing financial interests or personal relationships that seem to affect the work done in this paper.

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1. Introduction

Sustainable aquaculture has recently emerged as a profitable alternative to provide proteinaceous diets to human consumers. This artificial way of rearing fish and shellfish not only helps to satisfy global demand but also contributes to the recovery of depleting natural resources. The global aquaculture production (aquatic animals only) reached a record 87.5 mt in 2020 [1] which as per the recent report of the Organization for Economic Co-operation and Development (OECD) and the Food and Agriculture Organization (FAO) of the United Nations (UN) is projected to reach 103 mt by 2030, rising by 17.7% as compared to 2020 [2]. However, the first, second, and third waves of COVID-19 and later the arrival of Omicron and Delta variants and their sublineages (by far the most mutated and transmissible of all the variants of concern identified in the history of the COVID-19 pandemic) may affect the projected values. As far as the current situation is concerned, the world economy is on the verge of recovery from the post-pandemic crisis as it bounced back in 2021 with 5.6% growth defying the previous trends [3]. The development of COVID-19 vaccines and medications greatly reduced its impact on global production and trade [4].

The escalation of aquaculture practices has caused major disease outbreaks in the aquaculture sector due to high fish stocking densities in the ponds and a lack of hygiene, making the cultured stocks vulnerable to mortalities. The estimated annual global loss due to various epizootics is a quarter billion US dollars [5]. Especially, the outbreak of several pathogens during aquaculture resulted in fatal diseases which caused large-scale mortalities of fish and shellfish [6–9]. Recently, experiments have been conducted on the use of bacterial species as potential probiotics to treat diseases in aquaculture [10–13]. There are several non-profit and commercial probiotic products prepared from different bacterial species, for instance, *Arthrobacter* spp., *Acinetobacter* spp., *Bacillus* spp., *Clostridium* spp., *Enterococcus* spp., *Janthinobacterium* spp., *Lactobacillus* spp., *Lactococcus* spp., *Pediococcus* spp., *Pseudomonas* spp., *Rhodococcus* spp., *Rhodopseudomonas* spp., *Synechocystis* spp., *Streptococcus* spp., *Streptomyces* spp., and the yeast *Saccharomyces cerevisiae* among others [14–17]. *Streptomyces,* in particular, have emerged among those that demonstrated numerous beneficial effects in aquaculture i.e., the production of industrially important enzymes and a broad range of biologically active secondary metabolites [18] such as antibiotics [19, 20], antioxidants [21], antifungal agents [22], and anticancer agents [23, 24]. In addition to producing secondary metabolites and exhibiting antimicrobial activity in aquaculture, *Streptomyces* strains also produce antagonistic and siderophore compounds to prevent bacterial infections and demonstrate antiviral and antibiofilm activity [25–27]. Other benefits of *Streptomyces* as potential probiotics include enhancement in the growth and survival of cultured species, disease resistance, competitive exclusion of pathogens, alteration in gastrointestinal microflora, and amelioration of water quality [28–31].

This review aims to provide detailed insight into the use of *Streptomyces* as a potential probiotic agent for sustainable aquaculture, including current evidence on the prospects of their use. Despite demonstrating promising results in aquaculture, *Streptomyces* also have a few limitations which we have discussed along with their possible solutions.

2. Probiotics

2.1 Background on probiotics

The word probiotic is a combination of the Latin preposition "pro," which means "for" and the Greek terminology "biotic" meaning "life" [32]. This term was first coined by German scientist Werner Georg Kollath in 1953 where he proposed probiotics as "active substances essential for a healthy development of life". Later, several definitions of probiotics were proposed by researchers and research organizations. Fuller [33] defined them as "a live feed supplement that enhances the intestinal microbial balance of the host". According to World Health Organization (WHO), probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [34]. This definition is adopted as a consensus statement by the International Scientific Association for Probiotics and Prebiotics (ISAPP) [35]. Although the majority of proposed definitions of probiotics describe them as beneficial, their effect varies from species to species and host to host. As a result, it is critical to ensure that the probiotic being employed is not harmful to the host [36].

Before being considered for aquaculture practices, probiotics have shown remarkable beneficial effects on humans and terrestrial-based animal cultures. They were first tested in aquaculture in 1986 to determine their ability to escalate the growth of aquatic organisms [37]. The exact pathways of probiotic action in aquaculture are not well known, however, several possible modes of action have been proposed in recent experiments. The theoretical mechanisms of action of probiotics in aquaculture (except *Streptomyces*) mentioned in the literature are presented in **Table 1**.

Table 1. Mechanisms of action demonstrated by probiotics (except *Streptomyces*) in aquaculture.

Mechanism of Action	Probiotic Strain	Host	Results	References
Stimulation in immune responses/parameters	*Lactobacillus acidophilus*	Koi carp *(Cyprinus carpio)* fingerlings	Improved IR and development.	[38]
	Bacillus subtilis and *trans*-cinnamic acid	Rainbow trout *(Oncorynchus mykiss)*	Improved IR and DR against *Yersinia ruckeri*.	[39]
	Bacillus velezensis V4	Atlantic salmon *(Salmo salar L.)* juvenile	Modulated IP.	[40]
Disease resistance	*Bacillus licheniformis*	Common carp *(Cyprinus carpio)*	Increased resistance against artificially induced pathogenic fish infection.	[41]
	Bacillus subtilis HAINUP40	Nile tilapia *(Oreochromis niloticus)*	Enhanced GP, IR and DR.	[42]
	Enterococcus casseliflavus	Rainbow trout (*Oncorynchus mykiss*)	Enhanced DR against *Streptococcus iniae* pathogen.	[43]
Competitive prohibition of pathogens	*Aeromonas sobria* GC2 *Bacillus sp.* JB-1	Rainbow trout (*Oncorhynchus mykiss, Walbaum)*	Proved inhibitory against *Aeromonas salmonicida, Lactococcus garvieae, S. iniae, Vibrio anguillarum, V. ordalii* and *Y. ruckeri.*	[27]
	Bacillus subtilis AB1	Rainbow trout (*Oncorhynchus mykiss, Walbaum)*	Prohibited the virulent *Aeromonas* sp.	[44]
Modification in gut microbiota	*Bacillus* OJ + IMO	White shrimp *(Litopenaeus vannamei)*	Addition in feed altered IM.	[45]
	Arthrobacter XE-7	Pacific white shrimp *(L. vannamei)*	Addition in feed modulated IM and increased resistance against *V. parahaemolyticus.*	[46]
	Leucosnostoc mensenteroides	Penaeus monodon	Reduced the growth of pathogenic *V. angillarum* from hepatopancreas, gut and intestine.	[47]
Competition for space/blocking of adhesion sites	*Bacillus subtilis* *Lactococcus lactis* *Saccharomyces cerevisiae*	Indian major carp *(Labeo rohita)*	Efficiently converted OM into nutrients and adhered to the intestine.	[48]
	Lactococcus lactis CLFP 101 *Lactobacillus plantarum* CLFP 238 *Lactobacillus fermentum* CLFP 242	Rainbow trout (*Oncorynchus mykiss*)	Reduced the adhesion of *A. salmonicida, A. hydrophila, Y. ruckeri* and *V. anguillarum* to intestinal mucus.	[49]
Stimulation in growth and survival	*Pseudomonas sp.* RGM2144	Rainbow trout (*Oncorynchus mykiss*)	Increased survival to 92.7 ± 1.2% against *Flavobacterium psychrophilum* challenge.	[43]
	Enterococcus faecium	Big-belly seahorse (*Hippocampus abdominalis*)	Enhanced GP and SR against *pathogenic Edwardsiella tarda.*	[42]
Enzymatic activities	*Bacillus subtilis* and *trans*-cinnamic acid	Rainbow trout (*Oncorynchus mykiss*)	Produced intestinal amylase enzyme and reduced coliform and *Enterobacteriaceae* count.	[50]
	Kocuria sp. *Rhodococcus* sp.	Rainbow trout (*Oncorynchus mykiss*)	Produced EEs to inhibit the growth of *V. anguillarum, V. ordalii, E. coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*.	[51]
Bioremediation	Commercial *Bacillus megaterium*	Major carps *(Cirrihinus nrigala, Labeo rohita* and *Catla catla)*	Showed significant effect on BOD, DO, COD, TDS, ammonia, alkalinity and pH.	[52]
	Limosilactobacillus fermentum	*In vitro* experiment	Elevated Arsenic, Cadmium and Lead resistant patterns and exhibited excellent Arsenic removal efficiencies.	[53]
	B. velezensis AP193	Channel catfish (*Ictalurus punctatus*)	Significantly improved WQ by reducing TP (19%), TN (43%) and nitrate (75%).	[54]
Disruption of quorum sensing/ antibiofilm activity	*Bacillus* sp. QSI-1	Zebrafish (*Danio rerio*)	Efficiently disrupted QS-mediated virulence factors and attenuated biofilm formation of the fish pathogen *A. hydrophila.*	[55]
	Pheaobacter inhibens S4Sm	*In vitro* experiment	Produced N-AHL against oyster pathogen *V. coralliilyticus* and disrupted QS pathway that activates protease transcription of *V. coralliilyticus.*	[56]
	Bacillus sp. YB1701	Gibel carp (*Carassius auratus gibelio*)	Significant QQ of the fish pathogen *A. hydrophila*.	[57]
Antiviral/antifungal activity	*Bacillus* OJ + IMO	White shrimp *(Litopenaeus vannamei)*	Reduced mortalities of shrimp challenged with WSSV.	[45]
	Pseudomonas species M162 *Pseudomonas* species M174 *Janthinobacterium* species M169	Rainbow trout *(Oncorynchus mykiss)*	Improved IR against saprolegniasis.	[58]

Abbreviations: IR: immune response, IP: immune parameters, GP: growth performance, DR: disease resistance, IMO: isomaltooligosaccharide, IM: intestinal microbiota, OM: organic matter, SR: survival rate, EEs: extracellular enzymes, BOD: biological oxygen demand, DO: dissolved oxygen, COD: chemical oxygen

demand, TDS: total dissolved solids, WQ: water quality, TP: total phosphorus, TN: total nitrogen, QS: quorum sensing, QQ: quorum quenching, WSSV: white spot syndrome virus, N-AHL: N- Acyl Homoserine Lactone

3. *Streptomyces*

3.1 Taxonomic and morphologic background of Streptomyces

Streptomyces is a genus of kingdom Bacteria, phylum Actinomycetota, class Actinomycetes, order Streptomycetales, and family Streptomycetaceae [59]. It was first proposed in 1943 [60] and initially classified based on its morphology, chemotype, whole-cell sugar patterns, phospholipid and fatty acid profiles, and composition of the cell wall and later based on its phenotypic and genotypic constitutional traits. To date, 1147 species and 73 subspecies of *Streptomyces* have been validly described (www.bacterio.net).

Genus *Streptomyces* is a Gram-positive, multicellular, mycelial, and filiform aerophilous bacteria that mainly live as saprophytes in soil [61]. Interestingly, some exist as marine or rhizosphere symbionts, growing on thermal springs or gamma-irradiated surfaces [62]. Some *Streptomyces* strains are pathogens associated with humans, animals, or plants such as *Streptomyces scabies* that cause potato scab disease [63]. The cell wall of *Streptomyces* contains a simple peptidoglycan mesh surrounding the cytoplasmic membrane [64]. Morphogenesis in *Streptomyces* is determined by the establishment of aerial hyphae (that can differentiate into spores or arthrospores) that emerge from the substrate mycelium containing LL-diaminopimelic acid as the predominant diamino acid [65, 66]. The spores help to enhance the survival of *Streptomyces* in the soil during the dormant phase as *Streptomyces* are resistant to water and nutrient deficiencies as well as extreme temperatures [61].

The increasing interest of researchers in the use of *Streptomyces* as a probiotic is due to its antagonistic behavior against pathogens, effect on the host metabolism, diversity in morphology, genomic size, genetic content such as Guanine + Cytosine (G + C), and the size of the coding sequences. *Streptomyces* are also distinguished by their large linear chromosomes with 8.5–12 Mb of DNA length and high G + C content averaging between 67–78 mol % [66–68]. The large size of the *Streptomyces* genome can explain its ability to produce distinctive secondary metabolites at a large scale [69]. Specialized metabolite production on this scale is unique to *Streptomyces*, and it has been proposed that these bacteria require a diverse metabolic repertoire to support their unusual life cycle [70].

3.2 The biological rhythm of Streptomyces

Streptomyces are abundant in nature and remain quiescent as spores before they obtain favorable conditions for growth. *Streptomyces* undergo the following development cycle: (1) the initial mitotic phase (dispersal of spores during the sporulation process), (2) germination (the dispersed spores settle and germinate), (3) primary mycelium formation (development of the vegetative hyphae), (4) secondary mycelium formation (development of the aerial hyphae) and, (5) sporulation (the formation of spores). The complete life cycle of *Streptomyces* is illustrated in **Figure 1**.

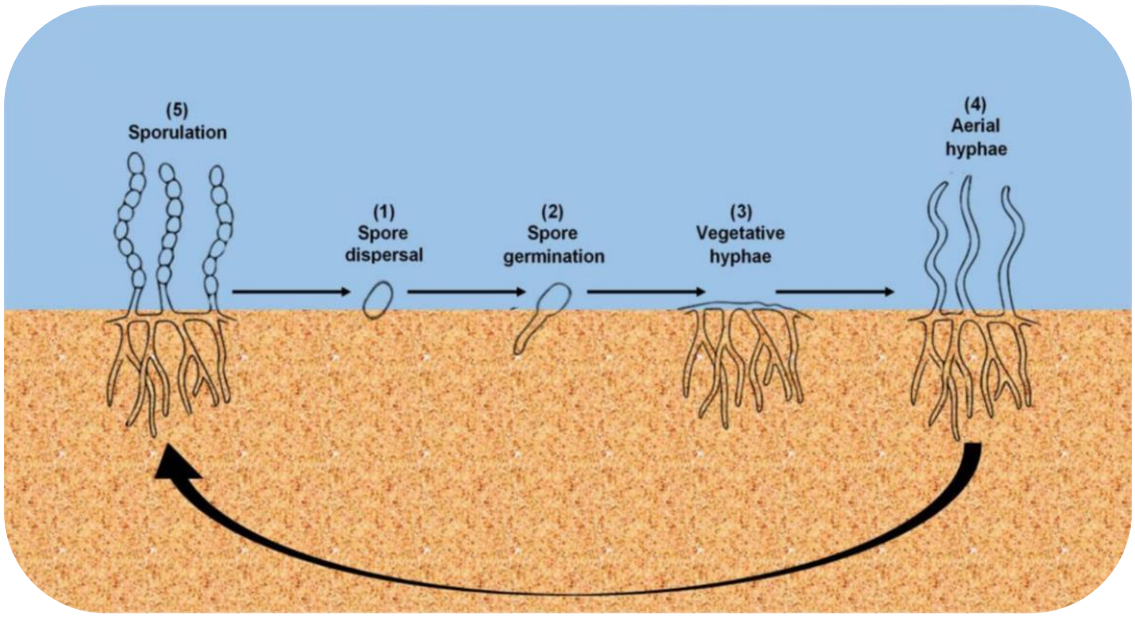

Figure 1. The life cycle of *Streptomyces*.

Once the dispersed spore settles in a nutrient-rich environment, it exits its dormant stage and starts germinating. Germination results in sprouting spores into germ tubes, which further develop into branching filaments during vegetative growth and form a mesh of hyphae called the vegetative mycelium. The vegetative mycelium stimulates the formation of an aerial mycelium on the colony surface possibly due to limited nutrient and cell density signals [65, 71, 72]. The aerial mycelium is a reproductive structure that transforms into spore chains that mature and ultimately liberate the spores.

Understanding the mechanisms underpinning the different developmental transitions during the *Streptomyces* life cycle has been easier because of advancements in both genomics techniques and cell biology. Till now, the investigations have focused on the study of single-species cultures. However, it was recently unearthed that the co-culture of several *Streptomyces* species with yeasts leads to a novel mode of its growth and development that had not been seen previously for *Streptomyces* cultured alone. This novel way of *Streptomyces* growth is described as 'exploration', named for the ability of explorer cells to rapidly lie across solid surfaces. This process is stimulated by fungal interactions and is associated with the production of an alkaline Volatile Organic Compound (VOC) which is capable of inducing exploration by other Streptomycetes. For detailed information regarding this novel phenomenon, please read Jones and Elliot [70].

3.3 Selection criteria of Streptomyces strains as probiotics

All strains of *Streptomyces* should first be analyzed through a laboratory-based screening process consisting of the following steps: (1) preliminary screening, (2) experimental screening, and (3) post-experimental screening. Considering the above methods, Hariharan and Dharmaraj [28] listed the following steps that should be followed to select *Streptomyces* strains as probiotics: (a) gathering preliminary details

about sampling areas, (b) isolation and identification of strains, (c) conducting strain survivability tests against low pH, pepsin, bile, and pancreatin, (d) testing colonization potential (co-cultivation with pathogens to test strain dominance, hydrophobicity, hydrophilicity, and auto-aggregation), (e) conducting safety assessment of strains through antibiotic sensitivity test and nonhemolytic activity, (f) assessment of the antagonistic capacity of strains against pathogens existing in a particular environment and, (g) evaluation of the effects of probiotic strains on the host. Cost-effectiveness analysis of the probiotic strains may also be considered for their selection [73].

According to Verschuere et al. [74], selected strains should also possess the following properties: (1) nonpathogenic to the host; (2) can be administered through feed; (3) can exert targeted effect where needed; (4) effective *In vivo* as per *In vitro* findings; and (5) must not be virulent or possess antibiotic resistance genes.

3.4 Methods of Streptomyces administration in aquaculture

Methods for *Streptomyces* administration in aquaculture and their associated benefits are listed below.

a) When used via intramuscular injection technique, reduces the occurrence of White Spot Syndrome Virus (WSSV) [75].

b) When administered/supplemented via feed, provides numerous beneficial effects [30, 76–79].

c) When added directly in the ponds as a water additive, reduces *Vibrio* count [80].

d) When added to inoculate or vaccinate ponds, increases the decomposition of organic matter [78].

e) When administered as bio-encapsulated *Streptomyces* cells, increases survival against *Vibrio* [77].

f) When sprayed on feed pallets as bacterial suspension, increases survival during the challenge experiment [81].

g) When administered in form of crude extract, shows average activity against fish-associated pathogens [82].

h) When Added as Single-Cell Proteins (SCPs), enhances growth [83].

Evidence shows that all species of *Streptomyces* can be administered as probiotics in one way or another, and there is no specificity regarding administration techniques. However, some species may not be able to withstand some administrative methods, compromising their viability. Also, the frequency of administration is vital for the proper functioning of probiotics [84].

Several *In vitro* experiments were also conducted to further test the capabilities of *Streptomyces* strains. *Streptomyces* when cultured *In vitro* on Chrome Azurol S (CAS) agar medium, produced siderophore compounds and demonstrated antibacterial activity [85]. *In vitro* bioassays of *Streptomyces* strains demonstrated antibiofilm activity [86]. Similarly, seaweed-associated *Streptomyces* strains when co-cultured with pathogens under lab conditions, competitively suppressed pathogenic strains [87]. A few of the administrative methods of *Streptomyces* are graphically represented in **Figure 2.**

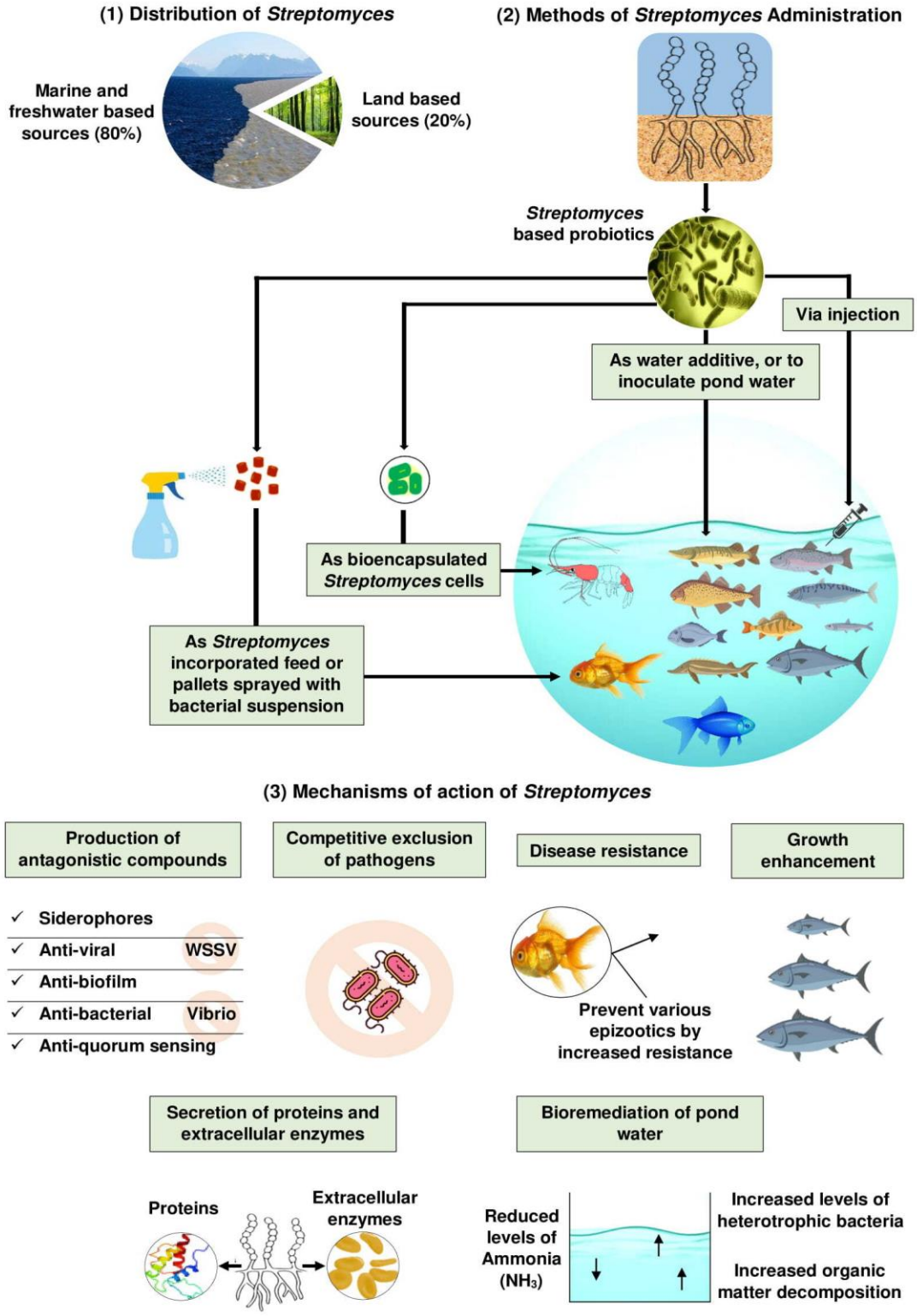

Figure 2. Distribution, methods of administration and mechanisms of action of *Streptomyces* in aquaculture.

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3.5 Mechanisms of action of Streptomyces in aquaculture

Streptomyces strains demonstrate similar mechanisms as other probiotics; however, some mechanisms are unique and only associated with *Streptomyces*. Listed are the detailed mechanisms exhibited by *Streptomyces* during different experiments and research-based studies.

3.5.1 Production of bioactive, inhibitory and siderophore compounds

Streptomyces are widely recognized as important microorganisms due to their ability to produce a variety of chemical compounds [88] such as streptomycin, polyoxins, oxytetracycline, blasticidin-S, validamycin, natamycin, kusagamycin, actinovate, milbemycin, abamectin/avermectins, polynactins, emamectin benzoate, and mycostop [89]. *Streptomyces* can also produce antimicrobial compounds such as chalcomycin A, which was extracted from *Streptomyces termitum* N-15, demonstrated significant antibacterial activities when used as an antimicrobial agent against 5 different bacterial fish pathogens including *Aeromonas hydrophila*, *Aeromonas veronii*, *Aeromonas sobria*, *Aeromonas salmonida*, and *Plesiomonas shigelloides* [90]. Actinomycin D and Mycinamicin III glycoside isomer derived from *Streptomyces* strain showed antimicrobial activities against *Bacillus cereus* and *Fusarium oxysporum* [91]. Actrinomycin D, a chromophoric phenoxazine, inhibits microbial growth by being incorporated into the base pair of a double helical DNA molecule and interfering with RNA polymerase [92, 93] while Mycinamicin III, an aglycone, confers antibacterial activity against pathogens [94]. Phenazinolin D, izumiphenazine A, B, and E are bioactive compounds produced by the termite-associated strain *Streptomyces showdoensis* BYF17. Izumiphenazine B has strong antagonistic activity against *Pseudomonas syringae* pv. *Actinidiae*, *Escherichia coli*, *Staphylococcus aureus*, and *Micrococcus tetragenus* with zones of inhibition 20.6, 12.9, 12.6, and 13.3 mm, respectively. Phenazinolin D, izumiphenazine A, and E showed antagonistic activity against *Staphylococcus aureus* and *Micrococcus tetragenus* with the zone of inhibition values of 10.3, 10.6, 11.7 mm and 15.9, 11.2 mm, respectively [95]. *Streptomyces* strains in aquaculture may benefit from the ability to produce antagonistic compounds to compete for nutrients, space, and binding sites in the host (see **Figure 2**). You et al. [85] found that seven *Streptomyces* isolates from shrimp farm sediments (*Streptomyces cinerogriseus* A03, A05; *Streptomyces griseorubroviolaceus* A26, A42; *Streptomyces lavendulae* A41; *Streptomyces roseosporus* A45; *Streptomyces griseofuscus* B15) can compete for iron and produce siderophore compounds to prevent pathogen*ic Vibrio* species during *In vitro* challenge experiment.

3.5.2 Disruption of quorum sensing and antibiofilm activity

Pathogenic bacteria associated with aquaculture frequently produce many virulence factors and cause widespread mortality in fish and shellfish. Such virulence factors are induced by high cell density and abundant quorum-sensing signals. In aquaculture, some *Streptomyces* species have shown antiquorum sensing and anti-biofilm activities. The *Streptomyces* strain IM20 obtained from the gut of Indian mackerel *(Rastrelliger kanagurta)* isolated from Kovalam coastal area of Tamil Nadu tested for antiquorum sensing violacein production against pathogenic strain *Chromobacterium violaceum* MTCC 2656 and *Serratia*

marcescens. For 6 days, strain IM20 was grown on ISP2 plates at 30°C. After 6 days, overnight cultures of *Chromobacterium violaceum* MTCC 2656 and *Serratia marcescens* were spread on the bioassay plates and incubated for 24 hours at 30°C. As strain IM20 suppressed violet pigment production in the subjected strains without affecting bacterial growth, the antiquorum sensing screening activity resulted in the formation of turbid halo pigment-less areas [96, 97].

Streptomyces albus A66 isolated from near-shore marine sediments of the South China Sea was examined as per the screening system used by You et al. [85], disrupted the biofilm formation of *Vibrio harveyi* (isolated from infected white shrimp *Litopenaeus vannamei*) by 99.3% and scattered the mature biofilm of *Vibrio harveyi* by 75.6% when used at a concentration of 2.5% (v/v). This antibiofilm activity was seen since *Streptomyces* metabolites reduced the number of *Vibrio harveyi* microcolonies by nearly tenfold and degraded the quorum sensing factor *N*-AHLs (*N*-acylated homoserine lactone) [86].

3.5.3 Antiviral activity

In addition to suppressing the pathogenic bacterial growth in aquaculture, the secondary metabolites extracted from the *Streptomyces* have the ability to induce an antiviral effect against different aquaculture-associated viruses. Marine *Streptomyces* sp. VITSDK1 produced the secondary metabolite furan-2-yl acetate ($C_6H_6O_3$), which demonstrated an inhibitory effect against the replication of fish nodavirus in the cell lines of Sahul Indian Grouper Eye (SIGE) with 90% cell survival when used at a minimum concentration of 20 $\mu g\ mL^{-1}$ [98]. Ethyl acetate secondary metabolites extracts (unspecified) of haloalkaliphilic *Streptomyces* sp. AJ8 isolated from the solar salt works of Kovalam, Kanyakumari, Tamilnadu, India. This strain was incubated with White Spot Syndrome Virus (WSSV) suspensions and injected intramuscularly into the Indian white shrimp, *Fenneropenaeus indicus*, according to Balasubramanian et al. [99], resulting in significant antiviral activity by reducing the occurrence of WSSV by 85% ($P < 0.001$) [75] (see **Figure 2**).

3.5.4 Amelioration of water quality

The physicochemical status of pond water plays a crucial role in the well-being and growth of organisms in aquaculture as they are heavily dependent on their environment [52]. Deterioration of culture water mainly occurs when the metabolic waste from living organisms accumulates in the system or by the decay and decomposition of biotic material and unutilized feed. This affects the survival of the fish and shellfish against infections and diseases [100]. However, the addition of probiotic strains either in water or diet enhances water quality and improves the growth and survival of the host [52, 101]. The outcome of the bioremediation or bioaugmentation process depends greatly on the nature of the probiotics being used. Thus, probiotics should be added as per their specificity to perform bioremediation under the right environmental conditions at the correct population density to achieve the desired results.

According to Wang et al. [102], the probiotics tested on the ponds containing *Penaeus vannamei* during intensive farming, resulted in the following beneficial effects:

- Improved water quality.

- Improved microbial interactions and diversity.
- Increased beneficial microbial count, ammonifying, and protein mineralizing bacteria.
- Increased organic matter decomposition and reduced nitrogen (N) and phosphorus (P) concentrations.
- Higher Dissolved Oxygen (DO) concentration and better algal growth.

Some species of *Streptomyces* also increase the count of heterotrophic bacteria in the culture system (see **Figure 2**) when used at a proper concentration at regular intervals, which plays a significant role in accelerating the decomposition of organic waste and reduction in the level of ammonia [76, 78]. *Streptomyces coelicoflavus* (A6), *Streptomyces diastaticus* (A44), *Streptomyces parvus* (A56) and *Streptomyces champavatii* (R32) in form of biogranules effectively decompose organic matter and ameliorate shrimp culture systems [103]. *In vitro*, soil-isolated *Streptomyces* sp. MOE6 was evaluated against complex pollutants such as heavy metals and oil spills. MOE6 strain's siderophore compound "hydroxamate" and secondary metabolites "extracellular polysaccharides" reduced hazardous pollutants in metal removal assays and emulsification activity tests [104].

3.5.5 Protection against pathogens during challenge experiments

Before the introduction of probiotic strains into the actual aquaculture environment, laboratory-based challenge experiments are necessary to determine the viability of probiotic strains to compete against pathogens. Multiple *In vivo* challenge experiments demonstrate the importance of *Streptomyces* as a protective agent when employed as probiotics in aquaculture. Marine sediment-derived *Streptomyces* sp. SH5 strain was isolated from Xinghai Bay, Dalian, China, and used for the challenge experiment in zebrafish larvae. *Aeromonas hydrophila* pathogenic strain was isolated from silver carp (*Hypophthalmichthys molitrix*) infected with *Aeromonas*. Prior to the challenge, zebrafish larvae were pretreated with SH5 dilutions of 1:100 or 1:1000. After 24 hours of challenge, there was no mortality in the pretreated group, with 80% and 50% survival after 36 hours and 72 hours of challenge, respectively. There was no noticeable difference in survival rate between larvae treated with different dilution rations. Pretreatment of zebrafish larvae with SH5 effectively inhibited *Aeromonas hydrophila* colonies by 67.53%. Multiple factors contributed to the SH5 strain's potential, including an improvement in zebrafish metabolism due to a reduced inflammatory response, repression of virulence factors, a reduction in pathogen colony potential, and improved immune parameters [105]. Juvenile and adult *Artemia* treated with *Streptomyces* cells at 1% concentration (v/v) through bioencapsulation ensued a higher survival rate as compared to the control group after being challenged with *Vibrio* pathogens at 10^6 CFU/mL [77]. *Streptomyces* CLS-28 supplemented with feed for 15 days at the same concentration, increased protection of shrimp *Penaeus monodon* against 12 hours *Vibrio* challenge as median lethal dose (LD_{50}) at $10^{6.5}$ CFU/mL. *Streptomyces* sp. N7 and *Streptomyces* sp. RL8 sprayed on pelleted feed as a bacterial suspension at 1×10^8 CFU g^{-1} weekly increased the survival of *Litopenaeus vannamei* during the *Vibrio* challenge [81]. Ethyl acetate crude extract of *Streptomyces* VITNK9 evaluated for its efficacy as a protective agent against different fish-associated pathogens showed a moderate response against *Aeromonas hydrophila*, *Edwardsiella tarda*, *Vibrio anguillarum*, *Vibrio harveyi* and *Aeromonas caviae* [82].

3.5.6 Competitive exclusion of pathogens from the system

In addition to the *In vivo* challenge *Streptomyces* also competitively excluded pathogens from the culture system (see **Figure 2**). The isolation of compound 1-(2-hydroperoxycyclopentyl)-4-hydroxytridecan-7-one (HCHD) with the chemical formula $C_{18}H_{34}O_4$ and the molecular weight 314.46 g/mol was achieved through bioactivity-guided extraction of ethyl acetate crude extract from *Streptomyces* sp. VITNK9. When used at a concentration of 100 g/ml against *Edwardsiellatarda* and *Aeromonas hydrophila*, the isolated compound demonstrated significant antipathogenic activity with an inhibition zone of 19.33 ± 0.47 mm and minimal inhibitory concentration of 3.125 µg/ml and 16.66 ± 0.47 mm and 12.5 µg/ml respectively. HCHD treatment inhibited the bacterial acetate kinase to disrupt bacterial metabolism [106]. According to these findings, bioactive extracts of *Streptomyces* sp. VITNK9 could competitively exclude pathogens from the system. Biogranules of *Streptomyces rubrolavendulae* M56 reduced the mortality rate of *P. monodon* (Post Larvae) and the viable *Vibrio* count in the rearing system after 28 days of treatment. *Streptomyces rubrolavendulae* M56 also antagonized *V. harveyi, V. alginolyticus, V. parahaemolyticus*, and *V. fluvialis* growth during *In vitro* co-culture experiment [29]. *Streptomyces* sp. RL8 isolated from marine sediments excluded *V. parahaemolyticus* from the culture system when used as a water additive [80].

3.5.7 Modulation of enzymatic activities

Feed utilization and digestion in cultured fish and shellfish depend on the ability of the host to produce enzymes. Probiotics can potentially produce digestive, extracellular, and antioxidant enzymes and/or modulate enzymatic activity [107–109]. Antioxidant enzymes protect the host against oxidative stress [110]. Soil-derived *Streptomyces chartreusis* KU324443 was used to prepare a basal-based diet for common carp (*Cyprinus carpio*) for three different experimental groups (S1, S2, and S3) at a concentration of 10^5, 10^6, and 10^7 CFU/g, properly blended and pelletized using a meat grinder. The prepared diets were fed to all three experimental groups for two months, and antioxidant enzyme activity (both in serum and skin mucus) was measured using a commercially available kit Zellbio®, Berlin, Germany. Serum antioxidant enzyme activity treatment groups showed higher superoxide dismutase (SOD) levels ($P > 0.05$) and moderate changes in catalase (CAT) and glutathione peroxidase (GPx). In terms of skin mucus antioxidant enzyme activity, no significant differences were observed between the treated and control groups [111]. *Streptomyces*' ability to stimulate oxidative protection enzymes in the host that are hostile to oxidative stress could be attributed to the production of Exopolysaccharide (EPS). To prevent the harmful consequences of free radicals in various tissues, EPS production induces robust DPPH radical scavenging activity [112, 113]. *Streptomyces* also produces several hydrolytic enzymes that decompose organic matter to provide nutrients for mycelium formation. These nutrients can then be reutilized to produce spores by activating the reproduction process of aerial development [114]. *Streptomyces* can further secrete exoenzymes that colonize the host's intestine to facilitate the digestion of food. For example, *Streptomyces* strains supplemented with feed secreted hydrolytic

exoenzymes which improved the amylolytic and proteolytic activity in the digestive tract of *Penaeus monodon* to enhance feed utilization [77].

3.5.8 Stimulation in growth and survival

The proper utilization of feed is also essential for the development and survival of cultured fish and shellfish. *Streptomyces virginiae* W18 cultures were grown in AM6 medium for 6 days before being mixed with *Carassius auratus* feed in two different concentrations: 1:1 (Group II) and 1:2 (Group III). *Carassius auratus* was fed the prepared concentration for each group for 30 days, and the fish (n = 10/group) were randomly selected from both groups to observe their growth. In addition, fish (n = 10/group) from each group were selected for the challenge experiment and administered with 100 µL of *Aeromonas veronii* (1.0×10^8 CFU/mL) injection. Both groups fed W18-associated feed grew at a rate of 27.10% and 24.87%, respectively. In comparison to the control group's 10% survival, groups challenged with *Aeromonas veronii* demonstrated 70% and 50% survival, respectively [115]. *Streptomyces* sp. supplemented with feed at a concentration of 5% fish body mass fed to *Xiphophorus helleri* once a day for 50 days. Absolute growth rate (AGR), specific growth rate (SGR), and relative growth rate (RGR) were all increased with overall 140.54% growth, 45% feed conversion efficiency, and 54.72% protein content [79]. *Streptomyces* sp. N7 supplemented feed increased the survival rate of *Litopenaeus vannamei* (Post Larvae) compared to the control group, whereas *Streptomyces* sp. RL8 increased the survival rate and stimulated weight gain in *Vibrio*-challenged shrimp. Both strains made the host more resistant to disease when given as a feed supplement at a concentration of 10^8 CFU g^{-1} for 30 days [31].

3.5.9 Source of protein to aquaculture species

Conventionally, animal-based proteins are used to fulfill the protein requirement of fish and shellfish in aquaculture due to a good amino acid balance and digestibility. However, probiotics based on *Streptomyces* are being considered an inexpensive and accessible alternative to animal-based proteins [79]. Single-Cell Protein (SCP) based on *Streptomyces* has been used as an alternative to animal-based proteins during *Xiphophorus helleri* culture, as it increases feed conversion and growth rate [83]. Another study demonstrated that using *Streptomyces* strains as SCP for 30 days of SCP-based feeding trials on *Xiphophorus helleri* resulted in significantly higher Absolute Growth Rate (AGR), Specific Growth Rate (SGR) and Feed Conversion Ratio (FCR) than the control group [116]. SCPs based on *Streptomyces* could thus play an important role in aquaculture nutrition and should be studied further.

3.5.10 Alteration in gut microflora

The intestinal ecology in aquaculture is important as the fish gut microbiome regulates health and determines the onset of disease [14]. A healthy gut microbiome aids in the digestion and absorption of feed, maintenance of an osmotic balance, and enhances immunity. Whereas an unhealthy gut can induce various diseases and cause mortalities. Artificially altering the fish gut microflora using probiotics is the focus of

researchers recently. When a dietary intervention trial of *Streptomyces* sp. RL8 was undertaken on white shrimp *Litopenaeus vannamei* modulation in the gut microbiota and an increased *Bacteriovorax* population was observed, which protected shrimp against *Vibrio* infection [30].

A tabular representation of the specie/strain-wise mechanism of action of *Streptomyces* can be seen in **Table 2**.

Table 2. Mechanisms of action demonstrated by potential probiotic *Streptomyces* in aquaculture.

Mechanism of Action	*Streptomyces* Strains	Host	References
Production of antagonistic/ siderophore compounds	*Streptomyces cinerogriseus* A03, A05 *Streptomyces griseorubroviolaceus* A26, A42 *Streptomyces lavendulae* A41 *Streptomyces roseosporus* A45 *Streptomyces griseofuscus* B15	*In vitro* experiment	[85]
	Streptomyces termitum N-15		[90]
	Streptomyces showdoensis BYF17		[95]
	Streptomyces IM20	*In vitro* experiment	[96]
Disruption of quorum sensing/ antibiofilm	*Streptomyces albus* A66	*In vitro* experiment	[86]
Antiviral activity	*Streptomyces* sp. AJ8	Indian white shrimp *(Fenneropenaeus indicus)*	[75]
	Streptomyces sp. VITSDK1	Sahul Indian Grouper Eye (SIGE) cell lines	[98]
	Streptomyces sp.	*P. monodon*	[76]
	Streptomyces fradiae	*Penaeus monodon*	[78]
Bioremediation	*Streptomyces coelicoflavus* (A6) *Streptomyces diastaticus* (A44) *Streptomyces parvus* (A56) *Streptomyces champavatii* (R32)	*Penaeus monodon*	[103]
	Streptomyces sp. MOE6	*In vitro* experiment	[104]
	Streptomyces sp. SH5	*In vitro* experiment	[105]
In vivo protection during challenge experiment	*Streptomyces* CLS-28 *Streptomyces* CLS-39 *Streptomyces* CLS-45	*Artemia* *P. monodon* (Post Larvae)	[77]
	Streptomyces sp. N7 *Streptomyces* sp. RL8	White shrimp *(Litopenaeus vannamei)* juvenile	[81]
	Streptomyces sp. VITNK9	n/a	[82]

	Streptomyces sp. VITNK9	*In vitro* experiment	[106]
Competitive exclusion of pathogens	*Streptomyces rubrolavendulae* M56	*In vitro* experiment *P. monodon* (Post Larvae)	[29]
	Streptomyces sp. RL8	*Artemia franciscana* nauplii	[80]
Enzymatic activities	*Streptomyces chartreusis* KU324443	*Common carp (Cyprinus carpio)*	[111]
	Streptomyces CLS-28 *Streptomyces* CLS-39 *Streptomyces* CLS-45	*Artemia* and *P. monodon* (Post Larvae)	[77]
Stimulation in growth and survival	*Streptomyces virginiae* W18	*Carassius auratus*	[115]
	Streptomyces sp.	Red swordtails *(Xiphophorus helleri)*	[79]
Protein source	*Streptomyces* sp.	*Xiphophorus maculatus* (Juvenile)	[83]
	Streptomyces sp.	*Xiphophorus maculatus*	[116]
Modification in gut microbiota	*Streptomyces* sp. RL8	White shrimp *(Litopenaeus vannamei)*	[30]

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4. Biotoxicity of *Streptomyces* strains

García-Bernal et al. [31] evaluated the toxicity of *Streptomyces* sp. RL8 and N7 in *Artemia salina* nauplii adopting the method used by Rajabi et al. [117]. The experiment was conducted using *Streptomyces* spp. RL8 and N7 cell mass in five different concentrations 1, 5, 10, 50, and 100 g/L accordingly in 96-well polystyrene plates by adding 200 µL in each well. Ten (10) nauplii of *Artemia salina* were added per well for each concentration in triplicate and incubated at room temperature. Negative control was prepared using 10 nauplii of *Artemia salina* and artificially produced seawater. The toxicity of probiotic bacteria was determined by comparing the survival outcome of *Artemia salina* to the control group after the interval of 24, 48, and 72 hours of the experiment. The addition of these concentrations in feed and oral administration caused no mortality to *Artemia salina* indicating the nontoxic behavior of mentioned *Streptomyces* strains. In the same study, he also performed the toxicity assay of the RL8 and N7 towards the postlarvae of *Litopenaeus vannamei* with an average weight of 0.24 ± 0.04 g. *Streptomyces* suspension cultures were equally sprayed on feed concentrations of 1×10^8, 1×10^9, and 1×10^{10} CFU g^{-1} and administered ad libitum. Ten (10) shrimps were cultured per experimental unit per treatment in triplicate according to the experimental design previously used by Purivirojkul et al. [118] for controlling pathogenic bacteria in fairy shrimp *Branchinella thailandensis* culture. Survival of *Litopenaeus vannamei* was determined by comparing the results of this experiment with the control group after three intervals of 24, 48, and 72 hours. Both strains were found innocuous to *Litopenaeus vannamei* as no mortality was caused during the experiment. Another experiment revealed that *Streptomyces* sp. MAPS15 was innocuous and nontoxic and caused no infection or mortality in *Penaeus monodon* [119].

Das et al. [77] have analyzed the biotoxicity of *Streptomyces* strains towards both nauplii and adults of *Artemia salina*. The toxicity test used harvested wet cell mass from three *Streptomyces* strains (CLS-28, CLS-39, and CLS-45). The experiment was carried out in sterile polystyrene 12-well cell culture plates. Artemia was counted and stored in five separate wells each containing 5 ml of sterile seawater with cell mass suspension concentrations of 0.1%, 0.5%, 1%, 5%, and 10%. After 72 hours of incubation at 28°C, the mortality rate was determined at 24, 48, and 72 hour intervals. The increase in cell mass concentration of *Streptomyces* strain CLS-39 resulted in a notably high mortality rate (F=69.71, P0.01) for both nauplii (67.7%) and adult (64.3%) artemia.

To test, whether the *Streptomyces* treated fish/shellfish pose any threat to human consumers, García-Bernal et al. [120] evaluated *Streptomyces* strain V4 to determine its toxigenicity using the hemolytic assay. The strain was inoculated on agar plates (Cat. # 211728, BD-Bioxon, Franklin Lakes, NJ, USA) prepared with 5% of human blood and 2.5% of sodium chloride (NaCl); the plates were then incubated for 7 days at 30°C. Hemolytic activity was examined using a hemolytic *Vibrio parahaemolyticus* strain as a control. No hemolytic or toxic activity was observed during the experiment, however, *In vivo* testing in fish/shellfish is necessary for further clarity.

5. Drawbacks of using *Streptomyces* as probiotics in aquaculture and possible solutions

The possible limitations of using *Streptomyces* as probiotics in aquaculture are as follows:
(1) Some *Streptomyces* strains are found in extreme environments and thus are difficult to extract.
(2) Culturing *Streptomyces* is laborious and challenging.
(3) Several compounds produced by *Streptomyces* have an unpleasant odor and taste.
(4) There is a risk of lateral gene transfer associated with *Streptomyces*.

Extreme and untapped environments are considered a hotspot of novel bacterial and fungal species with unique properties and applications, thus, attracting researchers from all around the globe. Several *Streptomyces* species are also extremophiles [121–124] possessing distinctive characteristics favorable to aquaculture [18, 25, 77, 125, 126]. Modern mechatronic collection devices are used to collect samples from extreme habitats [127]. For example, Remote-Operated Submarine Vehicle (ROVs) [128], Robotic Sampling Systems (RSS), Unmanned Ground Vehicles (UGVs), Unmanned Aerial Vehicles (UAVs) [129], and Autonomous Underwater Vehicles (AUVs) [130] are often used.

Culturing *Streptomyces* can be challenging due to a lack of standardized media and culturing methods. *Streptomyces* also have a slow growth rate; thus, identification requires extensive culture-dependent studies [28]. Additional experiments are needed to develop suitable and standardized laboratory procedures.

Geosmin (GSM, *trans*-1,10-dimethyl-*trans*-9-decalol) and 2-methylisoborneol (MIB (1-R-exo)-1,2,7,7-tetramethyl-bicyclo[2.2.1]heptan-2-ol) are two saturated bicyclic terpenoids produced as secondary metabolites by *Streptomyces* [131]. These compounds have a muddy/earthy taste and unpleasant odor [132, 133] which reduces the palatability of feed, consequently reducing the feed intake of cultured fish and shellfish [134]. Both GSM and MIB can be accumulated or absorbed in the gills, skin, and flesh up to 200–400 folds, reducing the commercial value of the fish [135]. Several techniques have been used for the remediation of these compounds from rearing water such as the use of powdered activated carbon, ozonation, and biofiltration [136]. In the case of *Streptomyces*, ozonation is more effective as it eradicates GSM and MIB from the rearing system via oxidation [137].

Additionally, various bacterial species are used for the biodegradation of MIB and GSM such as *Pseudomonas* spp., *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Enterobacter* spp., *Candida* spp., *Flavobacterium multivorum*, *Flavobacterium* spp., *Slaviensisbacillus* spp., *Bacillus subtilis*, and *Bacillus cereus*, *Bacillus subtilis*, *Arthrobacter atrocyaneus*, *Arthrobacter globiformis*, *Rhodococcus moris*, *Chlorophenolicus* strain N-1053, *Rhodococcus wratislaviensis* respectively.

Inducing genetic mutation in *Streptomyces* and Polymerase Chain Reaction (PCR)-targeted *Streptomyces* gene replacement are other techniques used to eliminate the odorous soil geosmin.

Research shows that the Cyc2 protein in *Streptomyces* (specifically the N-terminal domain), required for geosmin biosynthesis can be made to be inactive or even eliminated by PCR or a double crossover [28, 138].

Lastly, the possibility of lateral transfer of antibiotic resistance genes could be another limitation of using *Streptomyces* as probiotics in aquaculture. Various other probiotics which are often used in aquaculture may also develop antibiotic resistance such as several species of *Enterococcus* [139], *Lactobacillus* sp. [140], and *Bacillus* sp. [141]. Therefore, it is suggested that preference should be given to strains that do not possess any virulence or antibiotic-resistant genes. Systematic analysis should be carried out to determine the potential risks associated with antibiotic resistance genes in the *Streptomyces* genome. Remedial techniques could be opted to eliminate the genetic factor from the relevant probiotic strains which facilitate antibiotic resistance. For example, protoplast formation is used as a method to eliminate resistance gene-carrying plasmids from the *Lactobacillus reuteri* (ATCC55730) without affecting the therapeutic characteristics of the probiotic [142].

6. Future prospects

Despite several bacterial species being extensively analyzed and utilized in aquaculture practices as probiotics, members of the class Actinomycetes are rarely considered [81, 143, 144]. A Few experiments in the recent past have highlighted the potential and prospects of species belonging to the class Actinomycetes, especially, *Streptomyces* in promoting the overall health of aquaculture species. Most of the previously conducted experiments focused on the use of single or multi-strain *Streptomyces*-based probiotics and overlooked the aspects of using multi-species *Streptomyces*-based probiotics. Several recently published original articles indicated the importance of multi-species probiotics as an eco-friendly growth stimulator in aquaculture [145, 146]. Thus, the use of *Streptomyces* in combination with other bacterial species could induce promising health benefits in aquaculture and requires further consideration.

Several other non-bacterial products such as prebiotics, mushrooms, microalgae, and yeast also benefited aquaculturists in maintaining healthy and sustainable aquaculture practices. Recently, postbiotics, phytobiotics, and paraprobiotics have also emerged and gained research attention by virtue of their long shelf life, safety, and potential health-promoting benefits on the host. *Streptomyces* incorporation with these products may synergistically confer greater health benefits which may result in better production and growth rate in both fish and shellfish aquaculture. Therefore, further experimentation on the use of *Streptomyces* as a probiotic candidate in a non-conventional manner is needed to better ascertain its potential in aquaculture.

7. Conclusion

Maintaining a sufficient food supply for an increasing global population is an expensive and strenuous task. Sustainable aquaculture has provided an alternative to meet market demands and global trade, reducing the overexploitation of natural resources by capture fisheries.

Additionally, the recent diversification and intensification of aquaculture also necessitated the development of new technological innovations to mitigate the effects of viral epizootics prevalent in aquaculture practices and to produce high-quality livestock with lower production time. An innovative approach to using live biotherapeutics for sustainable aquaculture has emerged in recent decades.

This review focuses particularly on the role of *Streptomyces* strains as potential probiotics in aquaculture. Studies have revealed numerous beneficial effects of *Streptomyces* on reared fish and shellfish. The secondary metabolites, antagonistic, and siderophore compounds produced by *Streptomyces* strains exerted antimicrobial, antibiofilm, antiviral, antifungal, and antioxidative effects on the cultured species. *Streptomyces* also enhance disease resistance, survival, growth, enzymatic activities, bioremediation of pond water, and modify the gut microflora.

There are also limitations and uncertainties associated with the use of some *Streptomyces* strains in aquaculture. To avoid undesired results, following a standardized, experimentally proven procedure of strain selection is mandatory. Further research is required for a comprehensive understanding of *Streptomyces* strains as probiotics before their use in aquaculture practices, especially those causing adverse effects and those with the possibility of gene transfer to the gastrointestinal microflora of fish, and later to human consumers.

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