



Review Article

***Vibrio parahaemolyticus*: Exploring its Incidence in Malaysia and the Potential of *Streptomyces* sp. as an Anti-*Vibrio* Agent**

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Abstract: As the world recovers from the COVID-19 pandemic, concern remains for future potential outbreaks because of the persisting effects of climate change, including the proliferation of infectious diseases. The frequent isolation of *Vibrio parahaemolyticus* in the surrounding environment is of concern as it can cause infections in marine animals and transmitted to humans. *V. parahaemolyticus* is the leading cause of foodborne gastroenteritis worldwide. Malaysia is one of the top seafood consumers and this places us at a higher risk of exposure to *V. parahaemolyticus* infections. Over the years, this foodborne pathogen has been isolated from various sources in Malaysia, mainly from seafood such as shellfish, shrimps, and fish. To make matters worse, there has been an emergence of antibiotic-resistant *V. parahaemolyticus* worldwide, which is attributed to the uncontrolled use of antibiotics in aquaculture to prevent and treat vibriosis. Therefore, it is vital to utilize alternatives such as probiotics to control *V. parahaemolyticus* to prevent further propagation of antibiotic-resistant strains of the bacteria. A potential candidate for probiotics is *Streptomyces* sp., a class of filamentous, Gram-positive bacteria that produce a variety of bioactive compounds during their life cycle, which can be useful in drug discovery. The bioactive compounds produced by *Streptomyces* sp. have been proven to have microbiota-modulating and stimulatory effects on the host, enhancing immunity and providing protective effects against *V. parahaemolyticus* infections. With the application of *Streptomyces* sp. as probiotics in aquaculture, the efficacy of the available antibiotics can be preserved, and the further spread of antibiotic resistance in the environment can be reduced.

Keywords: *Vibrio parahaemolyticus*; anti-*Vibrio*; *Streptomyces*; prevalence; probiotics

1. Introduction

The fear of an endemic or pandemic will always linger since we are slowly recovering from the COVID-19 pandemic. This zoonotic-transmitted disease was discovered in China and moved rapidly from person to person [1, 2]. As we scrambled to find the treatment for this pneumonia-like infection, the virus continued to travel to other countries worldwide [3, 4]. COVID-19 infected millions, causing a rise in death cases and paralysis of the healthcare system [3, 5-7]. Although vaccination programs were initiated, infection cases are still being reported due to emerging new variants of concern (VOC) [8-14]. We have yet to be entirely freed from the COVID-19 pandemic and have already started addressing another primary public concern; climate change.

Climate change is a pressing global challenge impacting the environment, ecosystems, and human health [15, 16]. Among the many consequences of climate change, the proliferation of infectious diseases is a growing concern [17]. Recently, the rise of *Vibrio parahaemolyticus* infections in animals and humans has gained attention [18-20]. The situation is further worsened by the spillover of antibiotic-resistant *V. parahaemolyticus* to animals and humans.

Vibrio parahaemolyticus is a halophilic, Gram-negative bacteria that naturally reside in bodies of water such as estuaries, rivers, and oceans [21-23]. As they share a natural habitat with aquatic animals, *V. parahaemolyticus* can infect these animals and cause a disease known as vibriosis. Symptoms of vibriosis in marine animals can manifest as skin ulcerations, exophthalmia, necrosis of the appendages, and death in severe cases [24]. Vibriosis has significantly impacted the aquaculture industry as it causes high mortality rates in farmed marine life, thus reducing the production of farmed marine fish and shrimp, leading to severe economic losses [24-26]. Most notably, *V. parahaemolyticus* is responsible for acute hepatopancreatic necrosis disease (AHPND) in shrimps, which causes death in the early stages of the life of shrimps [27, 28]. Outbreaks of AHPND have significantly reduced the production of shrimps worldwide; for example, in Thailand, there was a decrease in approximately 30% of shrimp production in 2013 compared to 2012 [29]. It is estimated that AHPND costs the shrimp aquaculture industry about USD 1 billion annually [30].

Moreover, these pathogenic bacteria can be transmitted to humans via consumption or exposure to contaminated seafood, resulting in gastroenteritis in humans which manifests as fevers, nausea, stomach cramps, diarrhea, and vomiting [31-34]. Mild cases of gastroenteritis caused by *V. parahaemolyticus* is generally self-limiting, with rehydration being the focus for recovery. With severe cases of gastroenteritis due to the foodborne pathogen, antimicrobial therapy is guided by comparable clinical syndromes caused by other *Vibrio* species, such as *Vibrio cholerae*. Thus, the antibiotic of choice is doxycycline, fluoroquinolones, and macrolides [35]. However, due to the uncontrolled use of antimicrobials for prophylaxis and management of diseases in aquaculture farms [36, 37], the environmental pressure from antimicrobial residues enables the emergence of antibiotic-resistant strains of *V. parahaemolyticus*. The pathogen has since developed antimicrobial resistance against a myriad of antibiotics such as penicillin, cephalosporins, aminoglycosides, tetracyclines, macrolides, quinolones, fluoroquinolones, sulfonamides, and carbapenems [38-45]. The rapid emergence of antimicrobial resistance in *V. parahaemolyticus* decreases the efficacy of antibiotics in treating its infections. Thus, to better manage *V. parahaemolyticus* infections, alternatives to antibiotics need to be explored to prevent the further spread of antibiotic resistance genes within the environment.

Recently, probiotics have gained popularity in their application in managing *V. parahaemolyticus* infections [46-49]. Probiotics are live microorganisms that can benefit the host when administered adequately [50, 51]. They modulate the host microbiota to promote growth and increase disease resistance [48, 52]. Studies have also reported that probiotics can have many functionalities in aquaculture. For instance, they can act as growth promoters, stimulate the production of inhibitory compounds, improve nutrient digestion in the host, strengthen immune response, and improve water quality [53, 54]. The microorganisms which are commonly known to be probiotics are *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bacillus* sp., *Bifidobacterium bifidum*, *Lactococcus lactis*, and *Saccharomyces cerevisiae* [47, 49]. However, recent studies point to *Streptomyces* sp. as a potential probiotic to be used in aquaculture due to its ability to produce many secondary metabolites, which can elicit

beneficial effects in the host [55-57]. They are potential probiotics for the prophylaxis and treatment of vibriosis in aquatic animals.

Continuous monitoring and surveillance on the prevalence of *V. parahaemolyticus* remain crucial to ensure the microbial load in the seafood supplied to consumers is safe for consumption. In addition, consistent efforts to monitor the prevalence of *V. parahaemolyticus* in our surrounding environment can prevent gastroenteritis outbreaks and maintain public health. The exploration of alternatives to antibiotics is also essential to preserve the efficacy of the currently available antibiotics and prevent the spread of antibiotic-resistance genes. Probiotics, such as *Streptomyces* sp., help to prevent and manage *V. parahaemolyticus* infections in farmed marine animals, reducing the probability of disease transmission from seafood to humans. In addition, probiotics can promote the growth of farmed marine animals and produce safe-to-consume seafood products for the general public. This review aims to provide insight into the prevalence of *V. parahaemolyticus* in Malaysia and the anti-*Vibrio* properties of *Streptomyces* sp., which make them potential agents in managing *V. parahaemolyticus* infections.

2. Incidence of *Vibrio parahaemolyticus* in Malaysia

Seafood is a nutrient-rich source of food that is vital in maintaining a healthy, balanced diet as they provide protein, unsaturated fatty acids, minerals, and vitamins [58]. The consumption of seafood has also been associated with reduced cholesterol levels and the prevention of cardiovascular diseases due to omega-3 fatty acids in seafood [59]. In Malaysia, seafood consumption has been consistently on an upwards trend. For instance, seafood consumption increased from 42.7kg per capita in 2020 to 43.38kg per capita in 2021 [60]. The high seafood consumption in Malaysia puts Malaysians at risk of foodborne diseases from seafood, given there is an increased risk of transmission and/or exposure to *V. parahaemolyticus*. Moreover, the foodborne pathogen has been frequently isolated from various sources such as seafood and the water environments in Malaysia [39, 43, 44, 61-63] (Table 1).

V. parahaemolyticus are halophiles Gram-negative bacterium that favor warm, brackish waters as their natural habitat [64, 65]. It has been reported that *V. parahaemolyticus* thrive in warmer seawater temperatures where the expression of virulence factors is upregulated, thus promoting the propagation of pathogenic bacteria [66, 67]. The tropical climate in Malaysia makes it hot and humid year-round, thus resulting in higher temperatures in bodies of water around the country. This creates a favorable environment for *V. parahaemolyticus* to grow and increases the risk of transmission to marine animals and humans. Therefore, studies have been done to determine the prevalence of these foodborne pathogens in Malaysia. A quick search was performed across three databases, Embase, Medline, Scopus, and Google Scholar, using the keywords: “prevalence OR incidence OR occurrence AND *Vibrio parahaemolyticus* AND Malaysia” to determine relevant original articles published between 2005 and 2023. Results from the search found that *V. parahaemolyticus* are most commonly isolated from seafood such as shellfish [39, 41, 43, 62, 68-

76], shrimps [42, 63, 68-70, 77-81], squids [68, 69, 72], fishes [40, 44, 61, 69, 72, 75, 82-90], and sea cucumber [91]. The pathogen has also been isolated from vegetables [92, 93] and environmental sources such as seawater [44, 94], coastal waters [73, 74, 95], and water from shrimp farms [63, 77].

In a study done to determine the prevalence of *V. parahaemolyticus* in shellfish in Selangor, Malaysia, 450 shellfish samples were screened, and based on colony morphology, all these samples were positive for *Vibrio* sp. Upon further confirmation via the *toxR* gene polymerase chain reaction assay [96], 44.4% (200/450) of the samples were confirmed to have *V. parahaemolyticus* [39]. Tan et al. also reported 61/75 shellfish samples were positive for *V. parahaemolyticus* [68], indicating a high prevalence of the foodborne pathogen in shellfish. Moreover, a study done in Kuala Terengganu, Malaysia, where 80 shellfish samples, including mussels, carpet clams, cockles, and scallops, were obtained, found that more than half (57.5%, 46/80) of the samples were contaminated with *V. parahaemolyticus* [71]. The high prevalence of *V. parahaemolyticus* in shellfish can be attributed to their natural habitat and filter feeding. Shellfish typically reside on the sea floors, and due to their filter feeding, they can garner a higher concentration of *V. parahaemolyticus* up to 100-fold higher than their surrounding waters [97].

In shrimps, Letchumanan et al. reported a prevalence of 57.8% (185/320) for *V. parahaemolyticus* isolates found in samples obtained from retail supermarkets [42]. In comparison, Tan et al. reported 88.57% (31/35) of shrimp samples were positive for the marine pathogen [68]. A prevalence study on cultured shrimps reported that over half (55%) of the 225 samples tested positive for *V. parahaemolyticus*, with the rest testing positive for other species in the *Vibrio* family [41]. The high prevalence of *V. parahaemolyticus* is of concern as these bacteria can cause AHPND in the shrimps, which primarily targets the hepatopancreas of the shrimp in the early stages of life, resulting in early mortality [98]. Outbreaks of AHPND in Malaysia have caused a reduced production of shrimp and cost the industry a loss of approximately USD 0.49 billion from 2011 to 2014 [99]. *V. parahaemolyticus* has also been isolated from fish; for example, the pathogen has been isolated from 116 of 130 short mackerel samples, indicating that 89.2% of the fish samples were contaminated with bacteria [61]. Meanwhile, Noorlis et al. reported that 49 isolates of *V. parahaemolyticus* were found in 300 freshwater fish purchased from retail levels [82]. In a separate study, 120 finfish samples were tested, and the results show that *V. parahaemolyticus* was present in 48.33% of the samples [84]. Researchers also studied the occurrence of *V. parahaemolyticus* in cultured groupers in Peninsular Malaysia, whereby they found that 25% of the 270 grouper samples were contaminated with *V. parahaemolyticus*. The foodborne pathogen can also be isolated from environmental sources such as seawater; for instance, 50 water samples, including river water, seawater, and water from a waterfall in Kelantan were tested and 25 of the samples were positive for *V. parahaemolyticus* [100]. Besides, 21 *V. parahaemolyticus* isolates were also detected from 21 coastal seawater samples from three beaches in peninsular Malaysia [94]. The incidence of *V. parahaemolyticus* is unavoidable in aquatic environments, hence marine life such as fishes and shrimps can accumulate *V. parahaemolyticus* before being harvested. The high

prevalence of *V. parahaemolyticus* detected in Malaysia shows the need for constant surveillance of the microbial load of this foodborne pathogen in seafood and the environment. This is to ensure the seafood supplied to consumers is safe for consumption, and gastroenteritis outbreaks can be avoided. Moreover, by monitoring the microbial load of *V. parahaemolyticus* in the aquaculture system, vibriosis outbreaks can be detected earlier to prevent high mortality, reduce economic losses and increase seafood production to meet supply demands.

Table 1. Sources of *V. parahaemolyticus* in Malaysia.

Source	References
Aquatic animals	
Blood clams	[68, 69]
Fish	[40, 44, 69, 72, 75, 82-90]
Oyster	[69]
Prawn	[69]
Sea cucumber	[91]
Shellfish	[39, 41, 43, 62, 70-76]
Short mackerels	[61]
Shrimps	[42, 63, 68-70, 77-81]
Squids	[68, 69, 72]
Surf clams	[68]
Vegetables	
Cabbage	[92, 93]
Carrot	[92, 93]
Cucumber	[92, 93]
Four-winged bean	[92]
Indian pennywort	[92]
Japanese parsley	[92]
Lettuce	[92, 93]
Long bean	[92]
Sweet potato	[92]
Tomato	[92, 93]
Wild cosmos	[92]
Environmental	
River water	[100]
Sea water	[44, 73, 74, 94, 95, 100]
Shrimp farm water	[63, 77]

3. Harnessing the Anti-*Vibrio* properties of *Streptomyces* sp.

There is a dire need for antibiotic alternatives because of the rapid emergence of antibiotic-resistant genes and antibiotic-resistant *V. parahaemolyticus* in the environment [38, 101, 102]. In aquaculture, the uncontrolled use of antibiotics has further accelerated the development of antibiotic resistance within these bacteria, thus rendering the effects of antimicrobial agents in these systems useless [36]. Henceforth, researchers are looking for alternatives to antibiotics to be used in the aquaculture industry to better combat diseases caused by *V. parahaemolyticus*. By finding alternatives to antibiotics, the efficacy of the currently available antibiotics can be preserved, and they can remain effective in treating infections caused by the pathogen. In recent years, *Streptomyces* sp. has been the microorganism of interest for aquaculture use as a probiotic [48, 49, 54, 103].

In 1943, *Streptomyces* sp. was first discovered as the source of the antibiotic streptomycin by Waksman et al. [104], and to date, over 700 known species have been isolated from the environment [105, 106]. *Streptomyces*, belonging to the Actinobacteria class [107, 108], is a group of complex filamentous, sporulating, Gram-positive bacteria which resemble fungi in their morphology [109-112]. They are highly abundant in soils and are also found in the sediments of marine environments, as they play a vital role in the ecosystem due to their broad range of metabolic processes [113-115]. Their ability to produce a variety of secondary metabolites and bioactive compounds makes them essential microorganisms in drug discovery [116-123]. The metabolites are typically produced during the life cycle of *Streptomyces* sp. driven by environmental factors [124], and over 10,000 bioactive compounds have been retrieved from these species [125]. The bioactive compounds produce possess a multitude of functionalities, including antibacterial [126-128], anticancer [129-131], antioxidant [132-134], and antifungal properties [135-137].

Moreover, the potential of cultured *Streptomyces* in producing bioactive secondary metabolites is yet to be fully realized, as environmental factors such as pH, temperature, and incubation times can affect metabolite production [138, 139]. Studies have shown that co-cultivation with other bacterium produces secondary metabolites that would otherwise not be found when culturing *Streptomyces* under standard lab conditions [140-142]. Furthermore, genome mining studies on *Streptomyces* have shown that they possess biosynthetic gene clusters that are not known to produce any secondary metabolites, and they are also commonly called cryptic clusters. Nonetheless, these cryptic biosynthetic clusters may not be cryptic in a second species of *Streptomyces* [143]. Therefore, it is suggested that a good fraction of undiscovered secondary metabolites may potentially become therapeutic agents [144]. This makes *Streptomyces* sp. and its bioactive compounds good candidates in drug discovery, as its potential has yet to be fully exploited.

From the plethora of bioactive compounds produced by *Streptomyces*, several have been identified as a source of antibacterial agents, specifically against *Vibrio* species [145]. This group of bacteria has been identified as potential candidates for probiotics to be used in aquaculture [48]. Marine *Streptomyces* sp. isolated by Yang et al. demonstrated strong

antagonistic activity towards pathogenic *V. parahaemolyticus*. By using the agar diffusion method, they reported clear inhibition zones of 33 mm and 15 mm in diameter after 96 hours of incubation in both solid and liquid cultures of the selected *Streptomyces* sp. strain, S073, against pathogenic *V. parahaemolyticus* ^[56]. The antagonistic activity of the chosen *Streptomyces* sp. could be attributed to its production of carboxylate-type siderophore to create a lethal iron-limiting condition for *V. parahaemolyticus* isolates ^[56]. In a follow-up study with the same strain of *Streptomyces* sp., the researchers identified dibutyl phthalate (DBP) as another compound that elicits inhibitory effects against *V. parahaemolyticus*. It was concluded that the antagonistic effects of S073 were dependent on the synergistic effects of DBP-mediated antagonism and siderophore-governed iron competition with *V. parahaemolyticus* ^[146]. The vibriocidal activity of *Streptomyces* sp. was also discovered when an inhibition zone of 20mm was observed during the agar well diffusion method when tested against pathogenic *V. parahaemolyticus* isolated from fish ^[147].

In India, *Streptomyces rubrolavendulae* M56 isolated from the sediments of the Bay of Bengal also showed antagonistic effects towards *V. parahaemolyticus*. Co-culture experiments with medium-sized biogranules produced by M56 and *V. harveyi*, *V. parahaemolyticus*, *V. alginolyticus*, and *V. fluvialis* showed a gradual decline in viable vibrio count. Upon day three of the co-culture experiment, no viable *Vibrios* were detected in the water tanks. In addition, M56 was reported to be non-pathogenic to post larvae shrimp under experimental setup, making them a safe option for use in aquaculture ^[55]. It is suggested that the enzymes produced by M56, including protease, amylase, lipase, DNase, and phosphatase could inhibit the growth of *Vibrio* sp. In addition, competition for colonization between M56 and *Vibrio* sp. in the natural system also reduces the *Vibrios* available to invade the post-larvae ^[55]. A separate study reported that supplementation of *Streptomyces* sp., RL8, as a probiotic stimulated the growth of *Bacteriovorax*, a group of predator bacteria ^[57]. They can invade the periplasmic space of Gram-negative bacteria such as *V. parahaemolyticus*, and alter the *Vibrio* cell wall to consume their cytoplasmic content, resulting in cell lysis ^[148]. RL8 also stimulated the antimicrobial producers, which protected the white shrimps by preventing them from *V. parahaemolyticus* infections ^[57]. When RL8 was used with other probiotics, such as *Bacillus* sp., higher bacterial diversity and significant stimulation of *Bacteriovorax* population were also reported ^[57]. This indicates that RL8 is a potential candidate to be used in synergy with other commonly known probiotics to produce beneficial effects on the host.

Given the current evidence of the anti-*Vibrio* properties of *Streptomyces* sp. in animal model studies, *Streptomyces* sp. possesses the excellent potential to become probiotics that can be utilized in aquaculture to prevent and control *Vibrio* infections. In addition, *Streptomyces* sp. can stimulate diversity in the gut microbiome of aquatic animals such as shrimp, leading to increased antimicrobial producers within the gut, thereby providing a protective effect against infections ^[57]. Furthermore, *Streptomyces* sp. has also been shown to enhance the growth of red swordtail fish via the production of indoleacetic acid, a growth-promoting hormone ^[149]. Supplementation of *Streptomyces* sp. in oral shrimp feed also promoted the growth rates of post-larval shrimp ^[150]. Moreover, in aquaculture systems, the

accumulation of organic waste, such as ammonia and nitrite can cause water quality problems, making the farmed animals susceptible to diseases and infections^[151]. Studies have shown that the administration of *Streptomyces* sp. within these culture systems increased the population of heterotrophic bacteria, thereby increasing the decomposition rate of organic waste, and the ammonia levels were reduced, ultimately improving the water quality^[150, 152, 153]. The multi-faceted beneficial qualities of *Streptomyces* sp., including its capabilities in *Vibrio* inhibition, gut modulation, water quality improvement, and growth promotion, can be harnessed to develop probiotics that can be used in aquaculture systems. The synergistic effects of *Streptomyces* sp. can protect populations of farmed animals within culture systems from infections, thereby preserving the stability and sustainability of the aquaculture industry.

4. Conclusion

In conclusion, the prevalence of *V. parahaemolyticus* in Malaysia's seafood and the environment remains of concern as the pathogen is frequently isolated from these sources. However, to cause disease in humans, the *V. parahaemolyticus* isolates would have to express the virulence genes such as the thermostable direct hemolysin (*tdh*) gene and the TDH-related hemolysin (*trh*) gene to cause symptoms of gastroenteritis^[154]. The isolates must express the *Photobacterium* insect-related (*Pir*) toxin genes, *PirA* and *PirB* genes to cause AHPND in shrimps^[63, 155]. Nevertheless, these foodborne pathogens are still frequently detected in our surroundings, thus increasing the probability of disease transmission, which could have detrimental effects on the aquaculture industry and the country's public health. In addition, the rapid emergence of antibiotic resistance among *V. parahaemolyticus* isolates has reduced the efficacy of the available antibiotics. The process of developing a new antimicrobial agent is lengthy and time-consuming. Thus, alternatives such as probiotics are being explored to replace antibiotics to prevent vibriosis in aquatic animals. *Streptomyces* sp. has been a focal point of drug discovery in aquaculture, as it produces many bioactive compounds during its life cycle that could be useful in modulating the microbiota of farmed marine life. The various bioactive compounds produced can have antagonistic or vibriocidal effects on *V. parahaemolyticus*, which can be useful in deploying them in aquaculture. *Streptomyces* sp. has been found to stimulate growth and provide protective effects in shrimps. However, further studies and trials need to be done to determine the most effective dosage for administration to other species of aquatic animals. Currently, animal models of the effects of *Streptomyces* sp. as a probiotic have been producing promising results. Thus researchers are optimistic that these beneficial effects can be proven in clinical trials so that *V. parahaemolyticus* infections in humans can also be prevented with the application of *Streptomyces* sp.

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