Progress in Microbes and Molecular Biology

HH PUBLISHER

Review Article

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

Ke-Yan Loo[1], Loh Teng-Hern Tan[1,2], Jodi Woan-Fei Law[1,3], Priyia Pusparajah[4], Sunny Hei Wong[5,6], Kok-Gan Chan[1,7,8], Learn-Han Lee[1,9,10*], Vengadesh Letchumanan[1,10*]

Article History

Received: 13 April 2023;

Received in Revised Form: 28 May 2023;

Accepted: 6 June 2023;

Available Online: 10 June 2023

[1]Novel Bacteria and Drug Discovery Research Group (NBDD), Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Selangor Darul Ehsan, Malaysia; ke.loo@monash.edu (K-YL)

[2]Innovative Bioprospection Development Research Group (InBioD), Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru 80100, Malaysia; loh.teng.hern@monash.edu (LT-HT)

[3]Next-Generation Precision Medicine and Therapeutics Research Group (NMeT), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Selangor Darul Ehsan, Malaysia; jodi.law1@monash.edu (JW-FL)

[4]Medical Health and Translational Research Group (MHTR), Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, 47500, Selangor Darul Ehsan, Malaysia; priyia.pusparajah@monash.edu (PP)

[5]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232, Singapore; sunny.wong@ntu.edu.sg (SHW)

[6]State Key Laboratory of Digestive Disease, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

[7]Institute of Biological Sciences, Faculty of Science, University of Malaya, 50603, Kuala Lumpur, Malaysia; kokgan@um.edu.my (K-GC)

[8]International Genome Centre, Jiangsu University, Zhenjiang, China

[9]Sunway Microbiomics Centre, School of Medical and Life Sciences, Sunway University, Sunway City 47500, Malaysia

[10]Pathogen Resistome Virulome and Diagnostic Research Group (PathRiD), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Selangor Darul Ehsan, Malaysia

*Corresponding author: Vengadesh Letchumanan and Learn-Han Lee, Pathogen Resistome Virulome and Diagnostic Research Group (PathRiD), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Selangor Darul Ehsan, Malaysia; vengadesh.letchumanan1@monash.edu (VL); lee.learn.han@monash.edu (L-HL)

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 *Bacterivorax* 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, *Streptoymces* 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 *Photorhabdus* 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.

Author Contributions: K-YL conducted the literature search, critical data analysis, and manuscript wiring. LT-HT, JW-FL, PP, SHW, KCG, L-HL and VL provided proofreading, comprehensive editing and technical support. VL and L-HL conceptualized and founded this writing project. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Jeffrey Cheah School of Medicine and Health Sciences Strategic Grant 2021 (Vote Number: STG-000051).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ciotti M, Ciccozzi M, Terrinoni A, *et al*. The COVID-19 pandemic. Crit Rev Clin Lab Sci 2020; 57(6): 365-388.
2. Ang WS, Law JW-F, Letchumanan V, *et al*. COVID-19 Pandemic in Brunei Darussalam. Prog Microbes Mol Biol 2023; 6(1).
3. Loo KY, Law JW-F, Tan LTH, *et al*. South Africa's battle against COVID-19 pandemic. Prog Microbes Mol Biol 2022; 5(1).
4. Joseph RJ and Ser H-L. Stories from the East: COVID-19 situation in India. Prog Microbes Mol Biol 2021; 4(1).
5. Lau AWY, Tan LT-H, Ab Mutalib N-S, *et al*. The chemistry of gut microbiome in health and diseases. Prog Microbes Mol Biol 2021; 4(1).
6. Thye AY-K, Pusparajah P, Tan LT-H, *et al*. COVID-19: Gastrointestinal Manifestations and Complications. Prog Microbes Mol Biol 2021; 4(1).
7. El-Sadr WM, Vasan A, and El-Mohandes A. Facing the new Covid-19 reality. New England Journal of Medicine 2023; 388(5): 385-387.
8. Loo K-Y, Letchumanan V, Ser H-L, *et al*. COVID-19: Insights into potential vaccines. Microorganisms 2021; 9(3): 605.
9. Robinson PC, Liew DF, Tanner HL, *et al*. COVID-19 therapeutics: Challenges and directions for the future. Proc Natl Acad Sci 2022; 119(15): e2119893119.
10. Loo K-Y, Tan LT-H, Law JW-F, *et al*. COVID-19: An Update on the Latest Therapeutic Agents. Prog Microbes Mol Biol 2023; 6(1).
11. Loo K-Y and Letchumanan V. COVID-19: Understanding the New Variants of Concern. Prog Microbes Mol Biol 2022; 5(1).
12. McVernon J and Liberman J. WHO keeps covid-19 a public health emergency of international concern. BMJ 2023; 380: 1-2.
13. Edwin HV and Antony CS. An update on COVID-19: SARS-CoV-2 variants, antiviral drugs, and vaccines. Heliyon 2023.
14. Barouch DH. Covid-19 vaccines—immunity, variants, boosters. N Engl J Med 2022; 387(11): 1011-1020.
15. Pecl GT, Araújo MB, Bell JD, *et al*. Biodiversity redistribution under climate change: Impacts on ecosystems and human well-being. Science 2017; 355(6332): eaai9214.
16. Brumfield KD, Chen AJ, Gangwar M, *et al*. Environmental Factors Influencing Occurrence of Vibrio parahaemolyticus and Vibrio vulnificus. Applied and Environmental Microbiology 2023: e00307-23.
17. Ogden NH and Gachon P. Climate change and infectious diseases: What can we expect? Can Commun Dis Rep 2019; 45(4): 76-80.
18. Wang D, Flint SH, Palmer JS, *et al*. Global expansion of Vibrio parahaemolyticus threatens the seafood industry: Perspective on controlling its biofilm formation. LWT 2022; 158: 113182.
19. Baker RE, Mahmud AS, Miller IF, *et al*. Infectious disease in an era of global change. Nat Rev Microbiol 2022; 20(4): 193-205.
20. Ndraha N, Huang L, Wu VC, *et al*. Vibrio parahaemolyticus in seafood: Recent progress in understanding influential factors at harvest and food safety intervention approaches. Curr Opin Food Sci 2022; 48: 1-7.
21. Su Y-C and Liu C. Vibrio parahaemolyticus: A concern of seafood safety. Food Microbiol 2007; 24(6): 549-558.

22. Letchumanan V, Chan KG, and Lee LH. Vibrio parahaemolyticus: a review on the pathogenesis, prevalence, and advance molecular identification techniques. Front Microbiol 2014; 5: 705.
23. Letchumanan V, Loo K-Y, Law JW-F, *et al*. Vibrio parahaemolyticus: The protagonist of foodborne diseases. Prog Microbes Mol Biol 2019; 2(1).
24. Mohamad N, Amal MNA, Yasin ISM, *et al*. Vibriosis in cultured marine fishes: a review. Aquaculture 2019; 512: 734289.
25. Mancuso M, Genovese M, Guerrera MC, *et al*. First episode of vibriosis in wild specimens of Pagellus bogaraveo (Brünnich, 1768) in the Mediterranean Sea. Cah Biol Mar 2015; 56: 355-361.
26. Khouadja S, Lamari F, and Bakhrouf A. Characterization of Vibrio parahaemolyticus isolated from farmed sea bass (Dicentrarchus labrax) during disease outbreaks. Int Aquat Res 2013; 5(1): 13.
27. Santos HM, Tsai C-Y, Maquiling KRA, *et al*. Diagnosis and potential treatments for acute hepatopancreatic necrosis disease (AHPND): a review. Aquaculture International 2020; 28(1): 169-185.
28. Lai H-C, Ng TH, Ando M, *et al*. Pathogenesis of acute hepatopancreatic necrosis disease (AHPND) in shrimp. Fish Shellfish Immunol 2015; 47(2): 1006-1014.
29. Hong X, Lu L, and Xu D. Progress in research on acute hepatopancreatic necrosis disease (AHPND). Aquaculture International 2016; 24(2): 577-593.
30. Zorriehzahra M and Banaederakhshan R. Early mortality syndrome (EMS) as new emerging threat in shrimp industry. Adv Anim Vet Sci 2015; 3(2S): 64-72.
31. Austin B. Vibrios as causal agents of zoonoses. Vet Microbiol 2010; 140(3-4): 310-317.
32. Lee L-H, Loo K-Y, Tan LT-H, *et al*. *Exploring the gut microbiota variation in response to vibrio infection*, in *Gut*. 2021, BMJ Publishing Group.
33. Loo K-Y, Law JW-F, Tan LT-H, *et al*. Diagnostic techniques for rapid detection of Vibrio species. Aquaculture 2022: 738628.
34. Ong IJ, Loo K-Y, Law LN-S, *et al*. Exploring the impact of Helicobacter pylori and potential gut microbiome modulation. Prog Microbes Mol Biol 2023; 6(1).
35. Morris J. Vibrio parahaemolyticus infections. 2022 [Accessed 13 April]; Available from: https://www.uptodate.com/contents/vibrio-parahaemolyticus-infections.
36. Lulijwa R, Rupia EJ, and Alfaro AC. Antibiotic use in aquaculture, policies and regulation, health and environmental risks: a review of the top 15 major producers. Rev Aquac 2020; 12(2): 640-663.
37. Grudlewska-Buda K, Bauza-Kaszewska J, Wiktorczyk-Kapischke N, *et al*. Antibiotic Resistance in Selected Emerging Bacterial Foodborne Pathogens—An Issue of Concern? Antibiotics 2023; 12(5): 880.
38. Loo KY, Letchumanan V, Law JWF, *et al*. Incidence of antibiotic resistance in Vibrio spp. Rev Aquac 2020; 12(4): 2590-2608.
39. Letchumanan V, Pusparajah P, Tan LT-H, *et al*. Occurrence and Antibiotic Resistance of Vibrio parahaemolyticus from Shellfish in Selangor, Malaysia. Front Microbiol 2015; 6: 1-11.
40. Amalina NZ, Santha S, Zulperi D, *et al*. Prevalence, antimicrobial susceptibility and plasmid profiling of Vibrio spp. isolated from cultured groupers in Peninsular Malaysia. BMC Microbiol 2019; 19(1): 251.
41. Haifa-Haryani WO, Amatul-Samahah MA, Azzam-Sayuti M, *et al*. Prevalence, Antibiotics Resistance and Plasmid Profiling of Vibrio spp. Isolated from Cultured Shrimp in Peninsular Malaysia. Microorganisms 2022; 10(9): 1851.
42. Letchumanan V, Yin W-F, Lee L-H, *et al*. Prevalence and antimicrobial susceptibility of Vibrio parahaemolyticus isolated from retail shrimps in Malaysia. Front Microbiol 2015; 6: 1-11.

43. Venggadasamy V, Tan LT-H, Law JW-F, *et al*. Incidence, antibiotic susceptibility and characterization of Vibrio parahaemolyticus isolated from seafood in Selangor, Malaysia. Prog Microbes Mol Biol 2021; 4(1).
44. Faja OM, Sharad AA, Younis KM, *et al*. Isolation, detection of virulence genes, antibiotic resistance genes, plasmid profile, and molecular typing among Vibrio parahaemolyticus isolated in Malaysian seawater from recreational beaches and fish. Vet World 2019; 12(7): 1140-1149.
45. Letchumanan V, Chan KG, and Lee LH. An insight of traditional plasmid curing in Vibrio species. Front Microbiol 2015; 6: 735.
46. Goh JXH, Tan LT-H, Law JW-F, *et al*. Harnessing the potentialities of probiotics, prebiotics, synbiotics, paraprobiotics, and postbiotics for shrimp farming. Rev Aquac 2022; 14(3): 1478-1557.
47. Goh JXH, Tan LT-H, Law JW-F, *et al*. Probiotics: Comprehensive Exploration of the Growth Promotion Mechanisms in Shrimps. Prog Microbes Mol Biol 2023; 6(1).
48. Tan LT-H, Chan K-G, Lee L-H, *et al*. Streptomyces Bacteria as Potential Probiotics in Aquaculture. Front Microbiol 2016; 7: 1-8.
49. Hai NV. The use of probiotics in aquaculture. J Appl Microbiol 2015; 119(4): 917-935.
50. Hill C, Guarner F, Reid G, *et al*. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014; 11(8): 506-514.
51. Sánchez B, Delgado S, Blanco-Míguez A, *et al*. Probiotics, gut microbiota, and their influence on host health and disease. Mol Nutr Food Res 2017; 61(1): 1600240.
52. Rohani MF, Islam SM, Hossain MK, *et al*. Probiotics, prebiotics and synbiotics improved the functionality of aquafeed: Upgrading growth, reproduction, immunity and disease resistance in fish. Fish Shellfish Immunol 2022; 120: 569-589.
53. Defoirdt T, Boon N, Sorgeloos P, *et al*. Alternatives to antibiotics to control bacterial infections: luminescent vibriosis in aquaculture as an example. Trends Biotechnol 2007; 25(10): 472-479.
54. Martínez Cruz P, Ibáñez AL, Monroy Hermosillo OA, *et al*. Use of probiotics in aquaculture. Int Sch Res Notices 2012; 2012.
55. Augustine D, Jacob JC, and Philip R. Exclusion of Vibrio spp. by an antagonistic marine actinomycete Streptomyces rubrolavendulae M56. Aquaculture Research 2016; 47(9): 2951-2960.
56. Yang M, Zhang J, Liang Q, *et al*. Antagonistic activity of marine Streptomyces sp. S073 on pathogenic Vibrio parahaemolyticus. Fish Sci 2019; 85(3): 533-543.
57. Mazón-Suástegui JM, Salas-Leiva JS, Medina-Marrero R, *et al*. Effect of Streptomyces probiotics on the gut microbiota of Litopenaeus vannamei challenged with Vibrio parahaemolyticus. Microbiol Open 2020; 9(2): e967.
58. Bianchi M, Hallström E, Parker RWR, *et al*. Assessing seafood nutritional diversity together with climate impacts informs more comprehensive dietary advice. Commun Earth Environ 2022; 3(1): 188.
59. Lund EK. Health benefits of seafood; Is it just the fatty acids? Food Chem 2013; 140(3): 413-420.
60. Department of Fisheries Malaysia. Fisheries Statistics. 2021 [Accessed Available from: https://www.dof.gov.my/en/resources/fisheries-statistics-i/.
61. Tan CW, Malcolm TTH, Kuan CH, *et al*. Prevalence and Antimicrobial Susceptibility of Vibrio parahaemolyticus Isolated from Short Mackerels (Rastrelliger brachysoma) in Malaysia. Front Microbiol 2017; 8: 1-9.
62. Malcolm TTH, Cheah YK, Radzi CWJWM, *et al*. Microbial risk assessment of Vibrio parahaemolyticus in bloody clams in Malaysia: A preliminary model from retail to consumption. Microb Risk Anal 2016; 4: 43-51.

63. Yan CZY, Austin CM, Ayub Q, *et al*. Genomic characterization of Vibrio parahaemolyticus from Pacific white shrimp and rearing water in Malaysia reveals novel sequence types and structural variation in genomic regions containing the Photorhabdus insect-related (Pir) toxin-like genes. FEMS Microbiol Lett 2019; 366(17).
64. Urquhart EA, Jones SH, Yu JW, *et al*. Environmental Conditions Associated with Elevated Vibrio parahaemolyticus Concentrations in Great Bay Estuary, New Hampshire. PLoS One 2016; 11(5): e0155018.
65. Letchumanan V, Ser H-L, Tan W-S, *et al*. Genome sequence of Vibrio sp. SALL 6 isolated from shellfish. Prog Microbes Mol Biol 2019; 2(1).
66. Billaud M, Seneca F, Tambutté E, *et al*. An Increase of Seawater Temperature Upregulates the Expression of Vibrio parahaemolyticus Virulence Factors Implicated in Adhesion and Biofilm Formation. Front Microbiol 2022; 13.
67. Vezzulli L, Grande C, Reid PC, *et al*. Climate influence on *Vibrio* and associated human diseases during the past half-century in the coastal North Atlantic. Proc Natl Acad Sci 2016; 113(34): E5062-E5071.
68. Tan CW, Rukayadi Y, Hasan H, *et al*. Prevalence and antibiotic resistance patterns of Vibrio parahaemolyticus isolated from different types of seafood in Selangor, Malaysia. Saudi J Biol Sci 2020; 27(6): 1602-1608.
69. Paydar M, Teh CSJ, and Thong KL. Prevalence and characterisation of potentially virulent Vibrio parahaemolyticus in seafood in Malaysia using conventional methods, PCR and REP-PCR. Food Control 2013; 32(1): 13-18.
70. Letchumanan V, Ab Mutalib N-S, Wong SH, *et al*. Determination of antibiotic resistance patterns of Vibrio parahaemolyticus from shrimp and shellfish in Selangor, Malaysia. Prog Microbes Mol Biol 2019; 2(1).
71. Tang JYH, Wan-Rosli WF, Abdul-Razak NH, *et al*. Incidence and antibiogram of Vibrio parahaemolyticus in processed and frozen bivalve mollusks in Kuala Terengganu, Malaysia. Int Food Res J 2014; 21(4): 1349-1353.
72. Maurice Bilung L, Linang V, Apun K, *et al*. Application of Real Time PCR for the Detection and Enumeration of Vibrio parahaemolyticus from Seafood in Sarawak (Malaysia). Borneo J Resour Sci Technol 1970; 5: 70-78.
73. Al-Othrubi SM, Alfizah H, Son R, *et al*. Rapid detection and E-test antimicrobial susceptibility testing of Vibrio parahaemolyticus isolated from seafood and environmental sources in Malaysia. Saudi Med J 2011; 32: 400-406.
74. Al-Othrubi SMY, Hanafiah A, Radu S, *et al*. Molecular Analysis and Genetic Studies on *Vibrio parahaemolyticus* Isolated from Seafood and Costal Water in Malaysia. Arch Pharm Pract 2012; 3(1): 61.
75. Stratev D, Fasulkova R, and Krumova-Valcheva G. Incidence, virulence genes and antimicrobial resistance of Vibrio parahaemolyticus isolated from seafood. Microb Pathog 2023; 177: 106050.
76. Nakaguchi Y. Contamination by Vibrio parahaemolyticus and Its Virulent Strains in Seafood Marketed in Thailand, Vietnam, Malaysia, and Indonesia. Trop Med Health 2013; 41(3): 95-102.
77. Muthukrishnan S, Defoirdt T, Ina-Salwany MY, *et al*. Vibrio parahaemolyticus and Vibrio harveyi causing Acute Hepatopancreatic Necrosis Disease (AHPND) in Penaeus vannamei (Boone, 1931) isolated from Malaysian shrimp ponds. Aquaculture 2019; 511: 734227.
78. Saifedden G, Farinazleen G, Nor-Khaizura A, *et al*. Antibiotic Susceptibility profile of Vibrio parahaemolyticus isolated from shrimp in Selangor, Malaysia. Int Food Res J 2016; 23(6): 2732-2736.
79. Bakar P, Y R-A, Gan HM, *et al*. Detection of PirA/B Toxin Genes for Acute Hepatopancreatic Necrosis Disease (AHPND) and Vibrio parahaemolyticus in Penaeus vannamei Culture from Major White Shrimp Producing Farms in Malaysia. Pertanika J Trop Agric Sci 2022; 45: 171-186.
80. Amatul-Samahah M, Muthukrishnan S, Omar W, *et al*. Vibrio spp. associated with acute hepatopancreatic necrosis disease (AHPND) found in penaeid shrimp pond from the east coast of peninsular Malaysia. J Environ Biol 2020; 41: 1160-1170.

81. Ariyawansa S, Abdullah Sani N, and Munid L. Prevalence of toxic genes of Vibrio parahaemolyticus in shrimps (Penaeus monodon) and culture environment. Int Food Res J 2009; 16: 89-95.

82. Noorlis A, Ghazali FM, Cheah YK, *et al*. Antibiotic resistance and biosafety of Vibrio cholerae and Vibrio parahaemolyticus from freshwater fish at retail level. Int Food Res J 2011; 18(4): 1523-1530.

83. Lee L-H, Ab Mutalib N-S, Law JW-F, *et al*. Discovery on Antibiotic Resistance Patterns of Vibrio parahaemolyticus in Selangor Reveals Carbapenemase Producing Vibrio parahaemolyticus in Marine and Freshwater Fish. Front Microbiol 2018; 9: 1-13.

84. Bonny SQ, Hossain MAM, Lin TK, *et al*. Multiplex MPN-PCR for the enumeration of three major Vibrios in raw fishes in Malaysia. Food Control 2018; 90: 459-465.

85. Noorlis A, Ghazali FM, Cheah Y, *et al*. Prevalence and quantification of Vibrio species and Vibrio parahaemolyticus in freshwater fish at hypermarket level. Int Food Res J 2011; 18(2).

86. V M, Chan CSW, and Apun K. Molecular confirmation and characterization of Vibrio parahaemolyticus from retailed fish. Int Food Res J 2015; 22: 1705-1710.

87. Auzureen AMZ, Michael MS, Mohamed M, *et al*. Detection of pathogenic Vibrio species and antibiogram activity in Asian Seabass (Lates calcarifer) in Tumpat, Kelantan. Trop Biomed 2022; 39(4): 569-574.

88. Dewi RR, Hassan L, Daud HM, *et al*. Prevalence and Antimicrobial Resistance of Escherichia coli, Salmonella and Vibrio Derived from Farm-Raised Red Hybrid Tilapia (Oreochromis spp.) and Asian Sea Bass (Lates calcarifer, Bloch 1970) on the West Coast of Peninsular Malaysia. Antibiotics 2022; 11(2): 1-21.

89. Amalina NZ, Dzarifah Z, Amal MNA, *et al*. Recent update on the prevalence of Vibrio species among cultured grouper in Peninsular Malaysia. Aquaculture Research 2019; 50(11): 3202-3210.

90. Dewi RR, Hassan L, Daud HM, *et al*. On-Farm Practices Associated with Multi-Drug-Resistant Escherichia coli and Vibrio parahaemolyticus Derived from Cultured Fish. Microorganisms 2022; 10(8).

91. Chanderan M, Mazlan N, Weinheimer A, *et al*. Screening of vibrio spp. isolated from sea cucumber stichopus horrens. Int J Med Toxicol Leg Med 2019; 22: 130.

92. Tunung R, Margaret S, Jeyaletchumi P, *et al*. Prevalence and quantification of Vibrio parahaemolyticus in raw salad vegetables at retail level. J Microbiol Biotechnol 2010; 20(2): 391-396.

93. Tunung R, Jeyaletchumi, P., Margaret, S.P., Ubong, A., Elexson, N., Ghazali, F.M., Noranizan, M.A., Chandrika, M., Nakaguchi, Y., and Son, R. Detection and quantification of *Vibrio parahaemolyticus* in vegetables and environmental samples at farm level. Food Research 2022; 6(5): 9.

94. Tanil GB, Radu S, Nishibuchi M, *et al*. Characterization of Vibrio parahaemolyticus isolated from coastal seawater in peninsular Malaysia. Southeast Asian J Trop Med Public Health 2005; 36(4): 940.

95. You KG, Bong CW, and Lee CW. Antibiotic resistance and plasmid profiling of Vibrio spp. in tropical waters of Peninsular Malaysia. Environmental Monitoring and Assessment 2016; 188(3): 171.

96. Kim YB, Okuda J, Matsumoto C, *et al*. Identification of Vibrio parahaemolyticus strains at the species level by PCR targeted to the toxR gene. J Clin Microbiol 1999; 37(4): 1173-7.

97. Broberg CA, Calder TJ, and Orth K. Vibrio parahaemolyticus cell biology and pathogenicity determinants. Microbes Infect 2011; 13(12-13): 992-1001.

98. Khimmakthong U and Sukkarun P. The spread of Vibrio parahaemolyticus in tissues of the Pacific white shrimp Litopenaeus vannamei analyzed by PCR and histopathology. Microb Pathog 2017; 113: 107-112.

99. Kua BC, Iar A, Siti Zahrah A, *et al*. *Current status of acute hepatopancreatic necrosis disease (AHPND) of farmed shrimp in Malaysia*. in *Addressing Acute Hepatopancreatic Necrosis Disease (AHPND) and Other Transboundary Diseases for Improved Aquatic Animal Health in Southeast Asia: Proceedings of the ASEAN*

Regional Technical Consultation on EMS/AHPND and Other Transboundary Diseases for Improved Aquatic Animal Health in Southeast Asia, 22-24 February 2016, Makati City, Philippines. 2016. Aquaculture Department, Southeast Asian Fisheries Development Center.

100. Vimala B, Thong KL, and Chong V. Isolation, detection and genomic differentiation of Vibrio cholerae and Vibrio parahaemolyticus in Bachok, Kelantan. Malaysian J Sci 2010; 29: 1-10.

101. Letchumanan V, Ser H-L, Tan W-S, *et al*. Genome Sequence of Vibrio parahaemolyticus VP152 Strain Isolated from Penaeus indicus in Malaysia. Front Microbiol 2016; 7: 1-4.

102. Letchumanan V, Ser HL, Chan KG, *et al*. Genome Sequence of Vibrio parahaemolyticus VP103 Strain Isolated from Shrimp in Malaysia. Front Microbiol 2016; 7: 1496.

103. Law JWF, Tan LT-H, Letchumanan V, *et al*. Streptomyces griseiviridis sp. nov., A Novel "Modern Actinobacteria" isolated from Malaysia Mangrove Soil. Prog Microbes Mol Biol 2023; 6(1).

104. Jones D, Metzger H, Schatz A, *et al*. Control of gram-negative bacteria in experimental animals by streptomycin. Science 1944; 100(2588): 103-105.

105. Worsley SF, Newitt J, Rassbach J, *et al*. *Streptomyces* Endophytes Promote Host Health and Enhance Growth across Plant Species. Applied and Environmental Microbiology 2020; 86(16): e01053-20.

106. Komaki H. *Recent Progress of Reclassification of the Genus Streptomyces*. Microorganisms, 2023. **11**, DOI: 10.3390/microorganisms11040831.

107. Quinn GA, Banat AM, Abdelhameed AM, *et al*. Streptomyces from traditional medicine: sources of new innovations in antibiotic discovery. J Med Microbiol 2020; 69(8): 1040-1048.

108. Chater KF. *Streptomyces*, in *Brenner's Encyclopedia of Genetics (Second Edition)*, S. Maloy and K. Hughes, Editors. 2013, Academic Press: San Diego. p. 565-567.

109. Tan LT-H, Lee L-H, and Goh B-H. The bioprospecting of anti-Vibrio Streptomyces species: Prevalence and applications. Prog Microbes Mol Biol 2019; 2(1).

110. Ser H-L, Tan LT-H, Tan W-S, *et al*. Whole-genome sequence of bioactive streptomycete derived from mangrove forest in Malaysia, Streptomyces sp. MUSC 14. Prog Microbes Mol Biol 2021; 4(1).

111. Pusparajah P, Law JW-F, Chan K-G, *et al*. Whole-Genome Sequence of Streptomyces pluripotens strain MUM 16J, a Potential Resource of Glycopeptide Antibiotic and Biocontrol Agent against Biofilm-forming Bacteria. Prog Microbes Mol Biol 2023; 6(1).

112. Elsalam RM, Goh KW, Mahadi M, *et al*. The Antibacterial Activities of Secondary Metabolites Derived from Streptomyces sp. Prog Microbes Mol Biol 2022; 5(1).

113. Guerrero-Garzón JF, Zehl M, Schneider O, *et al*. Streptomyces spp. From the Marine Sponge Antho dichotoma: Analyses of Secondary Metabolite Biosynthesis Gene Clusters and Some of Their Products. Front Microbiol 2020; 11.

114. van der Meij A, Worsley SF, Hutchings MI, *et al*. Chemical ecology of antibiotic production by actinomycetes. FEMS Microbiol Rev 2017; 41(3): 392-416.

115. Bentley SD, Chater KF, Cerdeño-Tárraga AM, *et al*. Complete genome sequence of the model actinomycete Streptomyces coelicolor A3(2). Nature 2002; 417(6885): 141-147.

116. Law JW-F, Chan K-G, He Y-W, *et al*. Diversity of Streptomyces spp. from mangrove forest of Sarawak (Malaysia) and screening of their antioxidant and cytotoxic activities. Sci Rep 2019; 9(1): 1-15.

117. Lee L-H, Chan K-G, Stach J, *et al*. The search for biological active agent (s) from actinobacteria. Front Microbiol 2018; 9: 824.

118. Law JW-F, Ser H-L, Ab Mutalib N-S, *et al*. Streptomyces monashensis sp. nov., a novel mangrove soil actinobacterium from East Malaysia with antioxidative potential. Sci Rep 2019; 9(1): 3056.
119. Lee L-H, Zainal N, Azman A-S, *et al*. Mumia flava gen. nov., sp. nov., an actinobacterium of the family Nocardioidaceae. Int J Syst Evol Microbiol 2014; 64(Pt_5): 1461-1467.
120. Law JW-F, Pusparajah P, Ab Mutalib N-S, *et al*. A review on mangrove actinobacterial diversity: the roles of Streptomyces and novel species discovery. Prog Microbes Mol Biol 2019; 2(1).
121. Kemung HM, Tan LT-H, Chan K-G, *et al*. Streptomyces sp. strain MUSC 5 from mangrove forest in Malaysia: Identification, antioxidant potential and chemical profiling of its methanolic extract. Prog Microbes Mol Biol 2020; 3(1).
122. Law JW-F, Letchumanan V, Tan LT-H, *et al*. The rising of "modern actinobacteria" era. Prog Microbes Mol Biol 2020; 3(1).
123. Thye AY-K, Letchumanan V, Tan LT-H, *et al*. Malaysia's Breakthrough in Modern Actinobacteria (MOD-ACTINO) Drug Discovery Research. Prog Microbes Mol Biol 2022; 5(1).
124. Procópio REdL, Silva IRd, Martins MK, *et al*. Antibiotics produced by Streptomyces. Braz J Infect Dis 2012; 16: 466-471.
125. Law JW-F, Law LN-S, Letchumanan V, *et al*. Anticancer Drug Discovery from Microbial Sources: The Unique Mangrove Streptomycetes. Molecules 2020; 25(22): 5365.
126. Wu C, Du C, Ichinose K, *et al*. Discovery of C-Glycosylpyranonaphthoquinones in Streptomyces sp. MBT76 by a Combined NMR-Based Metabolomics and Bioinformatics Workflow. J Nat Prod 2017; 80(2): 269-277.
127. Nair S and Abraham J. *Natural Products from Actinobacteria for Drug Discovery*, in *Advances in Pharmaceutical Biotechnology: Recent Progress and Future Applications*, J.K. Patra, A.C. Shukla, and G. Das, Editors. 2020, Springer Singapore: Singapore. p. 333-363.
128. Maiti PK, Das S, Sahoo P, *et al*. Streptomyces sp SM01 isolated from Indian soil produces a novel antibiotic picolinamycin effective against multi drug resistant bacterial strains. Sci Rep 2020; 10(1): 10092.
129. Gui C, Yuan J, Mo X, *et al*. Cytotoxic Anthracycline Metabolites from a Recombinant Streptomyces. J Nat Prod 2018; 81(5): 1278-1289.
130. Han X, Liu Z, Zhang Z, *et al*. Geranylpyrrol A and Piericidin F from Streptomyces sp. CHQ-64 ΔrdmF. J Nat Prod 2017; 80(5): 1684-1687.
131. Sun C, Liu Z, Zhu X, *et al*. Antitubercular Ilamycins from Marine-Derived Streptomyces atratus SCSIO ZH16 ΔilaR. J Nat Prod 2020; 83(5): 1646-1657.
132. Cheng C, Othman EM, Reimer A, *et al*. Ageloline A, new antioxidant and antichlamydial quinolone from the marine sponge-derived bacterium Streptomyces sp. SBT345. Tetrahedron Lett 2016; 57(25): 2786-2789.
133. Weslati I, Simões L, Teixeira A, *et al*. Antibacterial and antioxidant activities of Streptomyces sp. strain FR7 isolated from forest soil. Lett Appl Microbiol 2023; 76(4): ovad036.
134. Ab Mutalib N-S, Wong SH, Ser H-L, *et al*. Bioprospecting of microbes for valuable compounds to mankind. Prog Microbes Mol Biol 2020; 3(1).
135. Wang W, Song T, Chai W, *et al*. Rare Polyene-polyol Macrolides from Mangrove-derived Streptomyces sp. ZQ4BG. Sci Rep 2017; 7(1): 1703.
136. Yang J, Yang Z, Yin Y, *et al*. Three novel polyene macrolides isolated from cultures of Streptomyces lavenduligriseus. J Antibiot 2016; 69(1): 62-65.

137. Jeon BJ, Kim JD, Han JW, *et al*. Antifungal activity of rimocidin and a new rimocidin derivative BU16 produced by Streptomyces mauvecolor BU16 and their effects on pepper anthracnose. J Appl Microbiol 2016; 120(5): 1219-1228.
138. Islam MR, Jeong YT, Ryu YJ, *et al*. Isolation, Identification and Optimal Culture Conditions of Streptomyces albidoflavus C247 Producing Antifungal Agents against Rhizoctonia solani AG2-2. Mycobiology 2009; 37(2): 114-120.
139. Alam K, Mazumder A, Sikdar S, *et al*. Streptomyces: The biofactory of secondary metabolites. Front Microbiol 2022; 13: 968053.
140. Kurosawa K, Ghiviriga I, Sambandan T, *et al*. Rhodostreptomycins, antibiotics biosynthesized following horizontal gene transfer from Streptomyces padanus to Rhodococcus fascians. J Am Chem Soc 2008; 130(4): 1126-1127.
141. Cho JY and Kim MS. Induction of antifouling diterpene production by Streptomyces cinnabarinus PK209 in co-culture with marine-derived Alteromonas sp. KNS-16. Bioscience, biotechnology, and biochemistry 2012; 76(10): 1849-1854.
142. Traxler MF, Watrous JD, Alexandrov T, *et al*. Interspecies interactions stimulate diversification of the Streptomyces coelicolor secreted metabolome. MBio 2013; 4(4): 1-12.
143. Onaka H. Novel antibiotic screening methods to awaken silent or cryptic secondary metabolic pathways in actinomycetes. J Antibiot 2017; 70(8): 865-870.
144. Doroghazi JR and Metcalf WW. Comparative genomics of actinomycetes with a focus on natural product biosynthetic genes. BMC Genomics 2013; 14(1): 611.
145. Tan LT-H, Lee L-H, and Goh B-H. Critical review of fermentation and extraction of anti-Vibrio compounds from Streptomyces. Prog Microbes Mol Biol 2020; 3(1).
146. Bi Y, Liu G, Yu Q, *et al*. Anti-Vibrio dibutyl phthalate from marine-derived Streptomyces sp. S073. Res Vet Sci 2021; 140: 198-202.
147. Kamarudheen N, George CS, Pathak S, *et al*. Antagonistic activity of Marine Streptomyces sp. on Fish pathogenic Vibrio species isolated from Aquatic Environment. Res J Pharm Technol 2015; 8(11): 1529-1533.
148. Crossman LC, Chen H, Cerdeño-Tárraga A-M, *et al*. A small predatory core genome in the divergent marine Bacteriovorax marinus SJ and the terrestrial Bdellovibrio bacteriovorus. ISME J 2013; 7(1): 148-160.
149. Dharmaraj S and Dhevendaran K. Evaluation of Streptomyces as a probiotic feed for the growth of ornamental fish Xiphophorus helleri. Food technology and Biotechnology 2010; 48(4): 497-504.
150. Aftabuddin S, Kashem MA, Kader MA, *et al*. Use of Streptomyces fradiae and Bacillus megaterium as probiotics in the experimental culture of tiger shrimp Penaeus monodon (Crustacea, Penaeidae). Aquac Aquar Conserv Legis 2013; 6(3): 253-267.
151. Dauda AB, Ajadi A, Tola-Fabunmi AS, *et al*. Waste production in aquaculture: Sources, components and managements in different culture systems. Aquac Fish 2019; 4(3): 81-88.
152. Das S, Lyla P, and Ajmal Khan S. Application of Streptomyces as a probiotic in the laboratory culture of Penaeus monodon (Fabricius). Israeli J Aquac 2006.
153. Das S, Ward LR, and Burke C. Screening of marine Streptomyces spp. for potential use as probiotics in aquaculture. Aquaculture 2010; 305(1): 32-41.
154. Wang H, Tang X, Su Y-C, *et al*. Characterization of clinical Vibrio parahaemolyticus strains in Zhoushan, China, from 2013 to 2014. PLoS One 2017; 12(7): e0180335.

155. Lin SJ, Huang JY, Le PT, *et al*. Expression of the AHPND Toxins PirA(vp) and PirB(vp) Is Regulated by Components of the Vibrio parahaemolyticus Quorum Sensing (QS) System. Int J Mol Sci 2022; 23(5).