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Mechanisms and the role of probiotic *Bacillus* in mitigating fish pathogens in aquaculture

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Abstract Diseases are natural components of the environment, and many have economic implications for aquaculture and fisheries. Aquaculture is a fast-growing industry with the aim to meet the high protein demand of the ever-increasing global population; however, the emergence of diseases is a major setback to the industry. Probiotics emerged as a better solution to curb the disease problem in aquaculture among many alternatives. Probiotic *Bacillus* has been proven to better combat a wide range of fish pathogens relative to other probiotics in aquaculture; therefore, understanding the various mechanisms used by *Bacillus* in combating diseases will help improve their mode of action hence yielding better results in their combat against pathogens in the aquaculture industry. Thus, an overview of the mechanisms (production of bacteriocins, suppression of virulence gene expression, competition for adhesion sites, production of lytic enzymes, production of antibiotics, immunostimulation, competition for nutrients and energy, and production of organic acids) used by *Bacillus* probiotics in mitigating fish pathogens ranging from *Aeromonas*, *Vibrio, Streptococcus*, *Yersinia*,

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Pseudomonas, *Clostridium*, *Acinetobacter*, *Edwardsiella*, *Flavobacterium*, white spot syndrome virus, and infectious hypodermal and hematopoietic necrosis virus proven to be mitigated by *Bacillus* have been provided.

Keywords *Bacillus* · Aquaculture · Diseases · Immunity · Mechanism

Introduction

Aquaculture is a fast-growing industry aimed at meeting the high protein demand of the ever-increasing global population (Plant and LaPatra 2011). Fish and fishery products are sources of important proteins and micronutrients that are essential for human health (Carbone and Faggio 2016). The emergence of diseases, however, has been a setback to the aquaculture industry. Diseases are natural components of the environment, and many have economic implications for aquaculture and fisheries industry (Plant and LaPatra 2011; Lafferty et al. 2015; Carbone and Faggio 2016).

Diseases in aquaculture are caused by bacterial, viral, and parasites (Carbone and Faggio 2016; Bastos Gomes et al. 2017). Most of the pathogenic diseases in aquaculture are often associated with the genus *Aeromonas*, *Vibrio*, *Streptococcus*, *Yersinia*, *Acinetobacter*, *Lactococcus*, *Pseudomonas*, and *Clostridium* (Santos et al. 2018; Yi et al. 2018). Massive mortality events have been associated with one or more of the pathogens mentioned above, and many efforts have been made to mitigate the occurrence of fish diseases. These efforts initially included the use of antibiotics which later failed its purpose due to the issue of antibiotic resistance (Pérez-Sánchez et al. 2014). Moreover, the use of antibiotics in systems with large water volume is relatively expensive (Harikrishnan et al. 2011); therefore, subsequent measures including the use of vaccines, probiotics, prebiotics, paraprobiotics as well as medicinal plants were employed (Pérez-Sánchez et al. 2014; Van Hai 2015a, b; Abarike et al. 2018b; Choudhury and Kamilya 2018; Kuebutornye et al. 2019). Among all the alternatives to antibiotics, probiotics have gained much attention due to their ability to create an unfriendly atmosphere for pathogens as well as the production of compounds with inhibitory properties and immunostimulation among other benefits (Balcázar et al. 2006; Merrifield et al. 2010).

Lactic acid bacteria (LAB) and *Bacillus* species family are the most commonly used probiotic candidates (Banerjee and Ray 2017). *Bacillus* as probiotics have been proven experimentally over the years to combat diseases (Balcázar et al. 2006; Kavitha et al. 2018; Ramesh and Souissi 2018; Yi et al. 2018), to improve feed utilization which in turn enhances growth (Aly et al. 2008; Zhou et al. 2010; Gobi et al. 2016; Goda et al. 2018), to enhance the immunity of aquaculture fish species (Nayak 2010; Abriouel et al. 2011; Buruiană et al. 2014), and to improve the quality of the rearing water (Camargo and Alonso 2006; Nimrat et al. 2012; Zokaeifar et al. 2014) as well as stress reduction (Shaheen et al. 2014; Abdollahi-Arpanahi et al. 2018; Eissa et al. 2018). *Bacillus* has a long history of being used in the pharmaceutical industry and medicine to mitigate many diseases in humans, animals, and as a biological control agent in plants due to their ability to produce a wide range of metabolites with antagonistic activity against microbes (McKeen et al. 1985; Silo-Suh et al. 1994). Also, the sporulation ability of *Bacillus* species makes them very important probiotic candidates (Meidong et al. 2018; Kuebutornye et al. 2019). Endospore formation enables them to withstand extreme stresses and also provides biological solutions to the preservation and formulation problems thus can be produced on a large scale (Yi et al. 2018).

Many researchers have proven that *Bacillus* could be used to mitigate diseases in the fish farming industry. This review provides an overview of published scientific studies in which *Bacillus* have been investigated as effective agents for controlling diseases in the aquaculture sector. This review mainly focuses on the possible mechanisms used by *Bacillus* in fighting diseases as well as the various diseases proven experimentally to be mitigated by *Bacillus* in the aquaculture industry.

The role of *Bacillus* in mitigating fish pathogens

Bacillus species are essential as they synthesize antibiotics/metabolites which are antagonistic against pathogens and also possess immunostimulatory abilities (Al-Ajlani and Hasnain 2010; Amin et al. 2015) thus have been used to control various diseases (McKeen et al. 1985; Silo-Suh et al. 1994). The use of *Bacillus* as probiotics in aquaculture is relatively recent; nevertheless, their role in mitigating pathogenic microorganisms in aquaculture is overwhelming (Table 1). The following are classes of pathogenic microbes which

Table 1 Summary of *Bacillus* species used in mitigating pathogenic microbes in aquaculture

Pathogen	*Bacillus* species	Mechanism/portion used for antagonism	Source	Host	Reference
A. hydrophila *A. salmonicida* *A. bivalvium* *A. veronii*	*B. subtilis*	Antimicrobial compounds	*Sparus aurata*, *Diplodus sargus*, and *Dicentrarchus labrax*	NA	Santos et al. (2018)
A. hydrophila	*B. subtilis*	Immunostimulation	Commercial	Nile tilapia	Addo et al. (2017a)
A. hydrophila	*B. subtilis*	Immunostimulation	Commercial	Nile tilapia	Iwashita et al. (2015)
A. hydrophila	*B. subtilis*	Immunostimulation	Grass carp	Grass carp	Tang et al. (2019)
A. hydrophila	*B. licheniformis*	Live suspension/immunostimulation	*L. rohita*	*L. rohita*	Ramesh et al. (2015)
A. hydrophila	*B. pumilus*	Live suspension/immunostimulation	*L. rohita*	*L. rohita*	Ramesh et al. (2015)
A. enteropelogenes	*B. pumilus*	Live suspension/immunostimulation	*L. rohita*	*L. rohita*	Ramesh et al. (2015)
A. enteropelogenes	*B. licheniformis*	Live suspension/immunostimulation	*L. rohita*	*L. rohita*	Ramesh et al. (2015)
A. hydrophila	*Bacillus* sp. MVF1	Immunostimulation	*Mystus vittatus*	*L. rohita*	Nandi et al. (2017a)
A. salmonicida	*B. velezensis* V4	Cell-free supernatant/immunostimulation	Marine recirculating aquaculture system	Rainbow trout	Gao et al. (2017a)
A. salmonicida	*B. velezensis* V4	Immunostimulation	Marine recirculating aquaculture system	Atlantic salmon	Wang et al. (2019)
Aeromonas sp.	*B. subtilis* AB1	Immunostimulation	Rainbow trout	Rainbow trout	Newaj-Fyzul et al. (2007)
A. hydrophila	*Bacillus* sp. *QSI-1*	Quorum quenching	*Carassius auratus gibelio*	Goldfish (*Carassius auratus*)	Zhou et al. (2016b)
A. hydrophila	*Bacillus* sp. YB1701	Antimicrobial activity/immunostimulation/-quorum quenching	Ponds	*Carassius auratus gibelio*	Zhou et al. (2018)
A. hydrophila	*Bacillus* sp. QSI-1	Quorum quenching	*Carassius auratus gibelio*	Zebrafish	Chu et al. (2014)
A. hydrophila	*B. subtilis*	Immunostimulation	Juvenile prawns	*Macrobrachium rosenbergii*	Keysami and Mohammadpour (2013)
V. parahaemolyticus	*B. licheniformis*	Immunostimulation	Culture pond	*Pangasius hypophthalmus*	Gobi et al. (2016)
29 *Vibrio* strains	*Bacillus pumilus* H2	Bacteriocin (amicoumacin A)	Marine sediment	NA	Gao et al. (2017b)
V. parahaemolyticus	*B. subtilis*	Antimicrobial peptides/immunostimulation	Fermented soybeans	*Litopenaeus vannamei*	Cheng et al. (2017)
V. parahaemolyticus	*B. subtilis*	Antimicrobial compounds		NA	Santos et al. 2018

Table 1 (continued)

Pathogen	*Bacillus* species	Mechanism/portion used for antagonism	Source	Host	Reference
			Sparus aurata, *Diplodus sargus*, and *Dicentrarchus labrax*		
V. harveyi	*B. subtilis*	Antimicrobial compounds	*Sparus aurata*, *Diplodus sargus*, and *Dicentrarchus labrax*	NA	Santos et al. (2018)
V. vulnificus	*B. subtilis*	Antimicrobial compounds	*Sparus aurata*, *Diplodus sargus*, and *Dicentrarchus labrax*	NA	Santos et al. (2018)
V. harveyi	*B. coagulans*	Immunostimulation	Commercial	*M. rosenbergii*	Gupta et al. (2016)
V. splendidus	*B. licheniformis* TC22	Immunostimulation	Sea cucumber	*Apostichopus japonicas*	Zhao et al. (2017)
V. anguillarum	*B. subtilis* WB60	Immunostimulation	Japanese eel	*Anguilla japonica*	Lee et al. (2018)
V. harveyi	*Bacillus* sp. D2.2	Immunostimulation	Tiger shrimp farm	*L. vannamei*	Harpeni et al. (2018)
S. iniae	*B. amyloliquefaciens*	Immunostimulation	NM	*O. fasciatus*	Kim et al. (2017)
S. agalactiae	*B. velezensis* JW	Metabolites/immunostimulation	Carp	*Carassius auratus*	Yi et al. (2018)
S. agalactiae	*B. subtilis* and *B. licheniformis*	Immunostimulation	Commercial	Nile tilapia	Abarike et al. (2018a, b)
S. agalactiae	*B. amyloliquefaciens* R8	Immunostimulation	NM	Zebrafish	Lin et al. (2019)
S. parauberis *S. iniae* *L. garvieae* *Lactococcus piscium*	*Bacillus* sp. CPB-St	Metabolites	Edible part of the shellfish	NA	Lee and Kim (2014)
Y. ruckeri	*B. subtilis* and *B. licheniformis*	Immunostimulation	Commercial	Rainbow trout	Raida et al. (2003)
Y. ruckeri	*B. subtilis* JB-1	Cellular components	NM	Rainbow trout	Abbass et al. (2010)
Y. enterocolytica	*B. proteolyticus*	Lytic enzyme (alkaline protease)	Fish processing wastes (fresh water and marine)	NA	Bhaskar et al. (2007)
P. fluorescens	*Bacillus* sp. CCF7 and *B. amyloliquefaciens*	Metabolites	*Catla catla*, *Labeo bata*, *Labeo rohita* and *Puntius javanicus*	NA	Nandi et al. (2017b)
P. fluorescens	*B. subtilis* LR1	Bacteriocins	*Labeo rohita*	Indian major carps	Banerjee et al. (2017)
Pseudomonas sp.	*B. velezensis*	Immunostimulation	Soil and catfish	Channel catfish	Thurlow et al. (2019)
Pseudomonas sp.	*B. circulans* *B. cereus*	Intracellular/extracellular products	*Osteochilus melanopleurus*	NA	Prayitno et al. (2018)
C. perfringens	*B. amyloliquefaciens*	Immunostimulation	Commercial	Nile tilapia	

Table 1 (continued)

Pathogen	*Bacillus* species	Mechanism/portion used for antagonism	Source	Host	Reference
					Selim and Reda (2015)
Acinetobacter sp. *A. tandoii*	*B. amyloliquefaciens*	Cell-free supernatants	*Labeo calbasu*	NA	Kavitha et al. (2018)
E. tarda	*Bacillus* species	Antimicrobial compounds	*Sparus aurata*, *Diplodus sargus*, and *Dicentrarchus labrax*	NA	Santos et al. (2018)
E. ictaluri	Mix of *B. amyloliquefaciens* 54A and *B. pumilus* 47B	Immunostimulation	Striped catfish	*P. hypophthalmus*	Thy et al. (2017)
E. ictaluri	*B. velezensis*	Immunostimulation	Soil and catfish	Channel catfish	Thurlow et al. (2019)
E. ictaluri	*B. subtilis* AB01	Immunostimulation	Channel catfish	Channel catfish	Ran et al. (2012)
E. tarda	*B. amyloliquefaciens*	Immunostimulation	Indigenous fermented fish product ‘Shidal’	*C. catla*	Das et al. (2013)
E. ictaluri	*B. subtilis*	Live cells	*Ctenopharynodon idellus*	*Ctenopharynodon idellus*	Guo et al. (2016a)
E. piscicida	*B. mojavensis*	Cell-free culture supernatants (organic acids)	Nile tilapia	NA	Etyemez and Balcazar (2016)
F. columnare	*B. subtilis*	Immunostimulation	NM	Nile tilapia	Mohamed and Refat (2011)
F. columnare	*Bacillus*	Metabolites (supernatants)	Channel catfish	Channel catfish	Ran et al. (2012)
WSSV	*Bacillus* PC465	Immunostimulation	*Fenneropenaeus chinensis*	*L. vannamei*	Chai et al. (2016)
WSSV	*Bacillus* OJ	Immunostimulation	*Litopenaeus vannamei*	*L. vannamei*	Li et al. (2009)
WSSV	*B. subtilis*	Immunostimulation	NM	*P. monodon*	Pham et al. (2017)
WSSV	*Bacillus* sp. Mk22	Immunostimulation	Saltpan	*P. monodon*	Sekar et al. (2016)
IHHNV	Mix *B. licheniformis* MAt32, *B. subtilis* MAt43, and *B. subtilis* subsp. *subtilis* GAtB1	Immunostimulation	*Anadara tuberculosa*	*L. vannamei*	Sánchez-Ortiz et al. (2016)

NM not mentioned, *NA* not applicable

threaten the aquaculture industry and the contribution of *Bacillus* to their mitigation.

Aeromonas

The genus *Aeromonas* includes various groups of straight coccobacillary to bacillary gram-negative bacteria that occur commonly in aquatic ecosystems and are sometimes isolated from food products (Hatje et al. 2014). *Aeromonas* are disease-causing pathogens of fish and other cold-blooded species and are as well regarded as the etiologic agents for a variety of infectious complications in both immunocompromised and immunocompetent persons (Janda and Abbott 2010; Fečkaninová et al. 2017). Members of this genus include *A. hydrophila*, *A. caviae*, *A. veronii*, *A. salmonicida*, *A. bivalvium*, *A. allosaccharophila*, *A. sobria*, *A. jandaei*, and *A. bestiarum* (Noga 1996; Fečkaninová et al. 2017; Santos et al. 2018). They are important pathogens in aquaculture due to high mortality and morbidity in a variety of fish species (salmon, trout, *Macrobrachium rosenbergii*, turbot, *Labeo rohita*, Atlantic cod, Nile tilapia, rockfish, wolfish, seabream) resulting in significant economic losses worldwide (Noga 1996; Ariole and Oha 2013; Keysami and Mohammadpour 2013; Dallaire-Dufresne et al. 2014; Addo et al. 2017a; Nandi et al. 2017a; Duarte et al. 2018). They can be detected in both marine and freshwater environments. Some members of the genus *Aeromonas* (*A. veronii*, *A. sobria*, *A. bivalvium*) however have been used to enhance the immunity of some fishes against other pathogenic microbes (Abbass et al. 2010; Hao et al. 2014, 2017; Giri et al. 2018).

As indicated by Cruz et al. (2012), probiotics can reduce mortality caused by *Aeromonas* species. Research findings from both in vitro and in vivo methods have proven that *Bacillus* species either inhibits the proliferation of *Aeromonas* species or enhances the host's immunity to withstand the virulence of *Aeromonas* species. For instance, natural antimicrobial compounds (NACs) produced by *Bacillus subtilis* were antagonistic against *A. hydrophila*, *A. salmonicida*, *A. veronii*, and *A. bivalvium* (Santos et al. 2018). *B. subtilis* was reported to confer protection on Nile tilapia (Iwashita et al. 2015; Addo et al. 2017a) and grass carp (Tang et al. 2019) against *A. hydrophila* infection. *Bacillus* species were also reported to reduce the susceptibility of *L. rohita* to *A. hydrophila* infection (Ramesh et al. 2015; Nandi et al. 2017a). With regards to *A. salmonicida*, *Bacillus velezensis* V4 was reported to reduce mortality up to 81.86% in rainbow trout and in Atlantic salmon after its infection (Gao et al. 2017a; Wang et al. 2019) through the modulation of immune parameters. In rainbow trout, *B. subtilis* AB1 was reported to be effective in inhibiting disease caused by highly virulent *Aeromonas* sp. (Newaj-Fyzul et al. 2007). The quorum quenching ability of *Bacillus* species against *A. hydrophila* has also been demonstrated (Zhou et al. 2016b; Zhou et al. 2018). Many more evidence (Keysami and Mohammadpour 2013; Chu et al. 2014; Iwashita et al. 2015) have proven that *Bacillus* can be used to protect fish against the adverse effects of *Aeromonas* species.

Vibrio

Vibrio species are found in aquatic environments, and most species namely *V. parahaemolyticus*, *V. alginolyticus*, *V. vulnificus*, *V. anguillarum*, *V. harveyi*, and *V. splendidus* have been reported to be responsible for many diseases in aquaculture (Jayasree et al. 2006; Letchumanan et al. 2015; Igbinosa 2016; Rasmussen et al. 2018). Interestingly, *Vibrio* species can be sporadically transmitted to humans through unhygienic food animals or contaminated water sources (Igbinosa 2016) suggesting that more attention needs to be paid to this group of pathogens. *Vibrio* species cause vibriosis which is a major epizootic disease that impacts wide and cultured fish species worldwide (Gao et al. 2017b). Clinical signs of Vibriosis in fish include fin erosion, skin haemorrhages, circular ulcerative lesions along the sides, and general congestion of the internal organs (liver and spleen) and pale yellow serous liquid in the gut (Breuil 1991). Disease outbreaks are usually detected when fish are immunocompromised or under stress due to overcrowding (Kumari 2013).

As indicated by Gao et al. (2017b), probiotics offer a promising approach to the prevention of *Vibrio* diseases in aquaculture. Many researches have demonstrated that *Bacillus* species are effective at mitigating the adverse effects caused by *Vibrio* species in aquaculture. Gobi et al. (2016) demonstrated the immunostimulatory potentials of *Bacillus licheniformis* in *Pangasius hypophthalmus* against *V. parahaemolyticus* infection. Gao et al. (2017b) reported that the cell-free supernatant of *Bacillus pumilus* H2 containing amicoumacin A was effective at inhibiting the growth of all 29 *Vibrio* strains tested. Antimicrobial peptides produced by *B. subtilis* exhibited antimicrobial activity against *V. alginolyticus* and *V. parahaemolyticus* and protected white shrimp, *Litopenaeus vannamei* against *V. parahaemolyticus* infection (Cheng et al. 2017). Similarly, supernatants (metabolites) of *B. subtilis* showed antibacterial activity against *V. parahaemolyticus*, *V. harveyi*, and *V. vulnificus* (Santos et al. 2018). Other studies in freshwater prawn, *M. rosenbergii* (Gupta et al. 2016), sea cucumber, *Apostichopus japonicas* (Zhao et al. 2017), Japanese eel, *Anguilla japonica* (Lee et al. 2018), and Pacific white shrimp, *L. vannamei* (Harpeni et al. 2018) in addition to the above evidences are indications that *Bacillus* species can be used to protect cultured fish from Vibriosis.

Streptococcus

Streptococcal diseases caused by *Streptococcus* species (*S. agalactiae*, *S. parauberis*, *S. dysgalactiae*, *S. iniae*, *L. garvieae*, and *Vagococcus salmoninarum*) occur in all parts of the world (Nho et al. 2009; Pereira et al. 2010; Abdelsalam et al. 2013; Mishra et al. 2018). Streptococcosis has resulted in substantial financial losses to the aquaculture industry (both marine and freshwater) especially in tilapia aquaculture with *S. agalactiae* and *S. iniae* being the main pathogens (Hernández et al. 2009; Suebsing et al. 2013; Nguyen et al. 2016; Leigh et al. 2018). It is notable that *Streptococcus* species are zoonotic and cause diseases in humans and other vertebrates hence need much attention (Addo et al. 2017b; Leigh et al. 2018; Mishra et al. 2018). Some symptoms of streptococcal diseases of fish include hemorrhage, lesions (liver, kidney, spleen, and intestine), erratic swimming, and swollen abdomen (Mishra et al. 2018).

Enhancement of immune parameters such serum antioxidant and lysozyme activity, serum protein and glucose level of *Oplegnathus fasciatus* by *Bacillus amyloliquefaciens* resulted in the fish's increased survival after *S. iniae* infection (Kim et al. 2017). Metabolites from *B. velezensis* JW inhibited the growth of *S. agalactiae* (Yi et al. 2018). Abarike and colleagues (Abarike et al. 2018a, b) reported the combined effects of *Bacillus* species and Chinese herbs as well as a mix of *Bacillus* species on the immunity of Nile tilapia, translating into its resistance against *S. agalactiae* infection. A similar observation was made in zebrafish after dietary *B. amyloliquefaciens* R8 supplementation (Lin et al. 2019). *Bacillus* sp. CPB-St was reported to be antagonistic against a variety of *Streptococcus* species (*L. garvieae*, *S. parauberis*, *Lactococcus piscium*, and *S. iniae*) (Lee and Kim 2014).

Yersinia

Yersinia ruckeri (a gram-negative rod-shaped enterobacterium) causes enteric red mouth disease (ERM) or yersiniosis in salmonid fish species, rainbow trout, channel catfish, sturgeons, and white fish (Tobback et al. 2007; Kumar et al. 2015; Ormsby and Davies 2017). *Y. ruckeri* infections have impacted dramatically on the aquaculture industry (Ohtani et al. 2019). Another member of this species *Yersinia enterocolitica* has been reported to cause infections in brown trout (*Salmo trutta* L.) (Kapperud and Jonsson 1976).

A few researchers have demonstrated that *Bacillus* species can be used to fight ERM in aquaculture. For example, immunostimulatory effects in rainbow trout instead of growth inhibition of *Y. ruckeri* by *B. subtilis* and *B. licheniformis* were observed in an experiment by Raida et al. (2003). It was concluded from this experiment that *Bacillus* could confer some protection against ERM. Intraperitoneal injection of rainbow trout with lipopolysaccharides (LPS), cell wall proteins, whole-cell proteins, outer membrane proteins, and live cells of *B. subtilis* JB-1 resulted in survival between 80 and 100% after being experimentally infected with *Y. ruckeri* (Abbass et al. 2010). This indicates that both cellular components and whole cells of *Bacillus* can be used in reducing the virulence of *Y. ruckeri*. In another study, a lytic enzyme, an alkaline protease produced by *Bacillus proteolyticus* inhibited the growth of pathogenic *Yersinia enterocolytica* (Bhaskar et al. 2007). These few pieces of evidence indicate that *Bacillus* has the potential to be used in mitigating diseases caused by *Yersinia*; therefore, more research in this direction is recommended.

Pseudomonas

Pseudomonas infections have been implicated as the most common bacterial infection in fish and mostly stress related and occur in freshwater, brackish, and marine farmed fish (Kholil et al. 2015; Wiklund 2016). Although some are used as probiotics (Korkea-Aho et al. 2011; Giri et al. 2012), few have been reported to cause diseases in fish. *P. fluorescens* and *P. aeruginosa* are regarded as opportunistic pathogenic microbes in aquaculture (Altinok et al. 2006). Reports indicate that *Pseudomonas* causes diseases in diverse fish species. For instance, *P. anguilliseptica* in eel, *A. japonica*, ayu (*Plecoglossus altivelis*), striped beakperch (*O. fasciatus*), cod (*Gadus morhua*), lumpsucker (*Cyclopterus lumpus*), *P. chlororaphis* in amago trout, *Oncorhynchus rhodurus*, *P. plecoglossicida* in ayu, *P. altivelis* and *P. putida* in rainbow trout, and *P. baetica* in wedge sole (*Dicologoglossa cuneata*) (Park et al. 2000; Altinok et al. 2006; Wiklund 2016; López et al. 2017).

A few studies have elucidated the role of probiotics in combating pathogenic *Pseudomonas* species. The few available demonstrates that *Bacillus* species can be considered as potential probiotics in combating *Pseudomonas* infections. For instance, in an experiment by Nandi et al. (2017b), dead cells of *Bacillus* sp. and *B. amyloliquefaciens* effectively inhibited the growth of *P. fluorescens*. Similarly, bacteriocins synthesized from *B. subtilis* LR1 showed inhibitory activity against *P. fluorescens* (Banerjee et al. 2017). Furthermore, feeding channel catfish with *B. velezensis* supplemented diet resulted in reduced *Pseudomonas* sp. in its intestines (Thurlow et al. 2019). Extracellular and intracellular products from *Bacillus circulans* and *Bacillus cereus* were reported to inhibit the growth of pathogenic *Pseudomonas* sp. (Prayitno et al. 2018). It is obvious that the role of probiotics especially *Bacillus* in combating other pathogenic *Pseudomonas* sp. such as *P. anguilliseptica*, *P. plecoglossicida*, and *P. putida* is less explored; meanwhile, available evidence indicates that *Bacillus* can be used to curb the adverse effects of *Pseudomonas* sp. in aquaculture. More researches in this regard are recommended.

Clostridium

It was shown that *Clostridium butyricum* could be used as probiotics (Song et al. 2006; Pan et al. 2008; Nayak 2010; Gobi et al. 2018; Sumon et al. 2018) while *Clostridium botulinum* and *Clostridium perfringens* have been reported to be pathogenic to fish and zoonotic (Novotny et al. 2004; Panigrahi and Azad 2007; Wani et al. 2018). Regarding the role of *Bacillus* in mitigating pathogenic *Clostridium* species in fish, a record is available. Immunostimulation of Nile tilapia *Oreochromis niloticus* by *B. amyloliquefaciens* spores resulted in higher survival after *C. perfringens* infection (Selim and Reda 2015). In nonfish species such as chicken (Jayaraman et al. 2013; Geeraerts et al. 2016; Zhou et al. 2016a) and mice (Fitzpatrick et al. 2011; Colenutt and Cutting 2014), *Bacillus* species have been reported to reduce the deleterious effects of pathogenic *Clostridium* species indicating the potential of *Bacillus* to be as well used as a control mechanism against pathogenic *Clostridium* in aquaculture.

Acinetobacter

The genus *Acinetobacter* includes gram-negative, nonfermentative, strictly aerobic, rod-shaped bacteria (Nemec et al. 2010). It was mentioned that this group of bacteria could infect a wide range of animals including fishes (Behera et al. 2017). Recent reports indicated the emergence of diseases in fish caused by *Acinetobacter* species. *A. baumannii*, *A. tandoii*, *A. junii*, *A. lwoffii*, *A. johnsonii*, *A. schindleri*, and *A. calcoaceticus* have been reported to cause diseases in rainbow trout, Indian major carp, common carp, blunt snout bream, *Dawkinsia filamentosa*, *Pangasius* fingerlings, and channel catfish (Reddy and Mastan 2013; Kozińska et al. 2014; Cao et al. 2016, 2017; Dadar et al. 2016; Behera et al. 2017; Kavitha et al. 2018). Despite all these incidences of *Acinetobacter* infections and the renowned role of probiotic *Bacillus* in fighting diseases in aquaculture, only one report of *Bacillus* species inhibiting the growth of *Acinetobacter* species has been reported (Kavitha et al. 2018). In their study (Kavitha et al. 2018), cell-free supernatants of *B. amyloliquefaciens* showed high antagonistic activity against *Acinetobacter* sp. and *A. tandoii.* With the rising incidence of *Acinetobacter* infections, more research geared towards probiotic *Bacillus* use is recommended.

Edwardsiella

The genus *Edwardsiella* have been associated with diseases in many economic fish species (Griffin et al. 2017; Buján et al. 2018a). *E. ictaluri* and *E. tarda* are pathogens of cultured channel catfish (*Ictalurus punctatus*), tilapia (*Oreochromis* sp.), Japanese flounder (*Paralichthys olivaceus*), mullet (*Mugil cephalus*), seabass (*Dicentrarchus labrax*), red seabream (*Pagrus major*), sole (*Solea senegalensis*), turbot (*Scophthalmus maximus*), yellowtail (*Seriola quinqueradiata*), and striped bass (*Morone saxatilis*) (Hawke et al. 1981; Mohanty and Sahoo 2007; Castro et al. 2012; Soto et al. 2012; Buján et al. 2018a). Other species such as

E. piscicida (Buján et al. 2018b; Choe et al. 2017) and *E. anguillarum* (Reichley et al. 2018) have also been reported to cause diseases in fish.

E. tarda was reported to be inhibited by antimicrobial compounds synthesized by *Bacillus* species (Santos et al. 2018). Studies by Thy et al. (2017) revealed that a mix of *B. pumilus* 47B and *B. amyloliquefaciens* 54A could stimulate the immune system (respiratory bursts, phagocytic activity, and lysozyme activity) of striped catfish (*P. hypophthalmus*) thereby increasing its resistance against *E. ictaluri* infection, likewise *B. velezensis* AP193 in channel catfish (Thurlow et al. 2019). Immunostimulation of catfish after probiotic *Bacillus* diet supplementation was observed, which translated into its resistance against *E. ictaluri* (Ran et al. 2012). Similarly, *B. amyloliquefaciens* increased Catla survival rates after being challenged with *E. tarda* by enhancing the immunity of the fish (Das et al. 2013). Live cells of *B. subtilis* exhibited inhibitory activities against *E. ictaluri* in an experiment by Guo and colleagues (Guo et al. 2016a). This inhibition could be attributed to competition for energy and nutrients resulting in the starvation and exclusion of *E. ictaluri.* Regarding pathogenic *E. piscicida*, in vitro studies by Etyemez and Balcazar (2016) revealed that cell-free culture supernatants of *Bacillus mojavensis* were antagonistic against *E. piscicida.* They proposed that antibacterial activity was as a result of the production of organic acids or pH-dependent compounds by the *Bacillus* species. These findings are evidence that *Bacillus* species can be used to control pathogenic *Edwardsiella* in aquaculture.

Flavobacterium

Flavobacterium spp. are dominant in freshwater environments (Laanto et al. 2017) and are known to be pathogenic. *F. branchiophilum* and *F. succinicans* are known for bacterial gill disease (BGD), a common and occasionally devastating disease that affects many farmed fish species worldwide (Good et al. 2015). *F. columnare* causes columnaris disease in both farmed and wild fish (Patra et al. 2016; Evenhuis et al. 2017). *F. columnare* has caused remarkable economic losses in fish such as *O. niloticus* (Eissa et al. 2010), *I. punctatus* (Shoemaker et al. 2008), *Catla catla* (Verma and Rathore 2013), *Clarias batrachus* and *L. rohita* (Dash et al. 2009), *Anabas testudineus* (Rahman et al. 2010), *Carassius auratus* (Verma et al. 2015), and *Oncorhynchus mykiss* (LaFrentz et al. 2012). *F. psychrophilum* is the etiological agent of rainbow trout fry syndrome as well as bacterial cold-water disease in older salmonid fish and hampers the productivity of salmonid farming worldwide (Chettri et al. 2018; Duchaud et al. 2018).

Mohamed and Refat demonstrated that *B. subtilis* in water or diet is effective in ameliorating the lesions of *F. columnare* disease in Nile tilapia (Mohamed and Refat 2011). In another experiment, metabolites (supernatants) of *Bacillus* species isolated from soil or channel catfish intestines successfully inhibited the growth of *F. columnare* using the agar well diffusion method (Ran et al. 2012). The available few evidence is indicative that *Bacillus* could be explored for their use against *Flavobacterium* infections.

White spot syndrome virus

One of the most virulent pathogenic and devastating viruses affecting the shrimp aquaculture industry as well as other crustaceans is white spot syndrome virus (WSSV), the causative agent of white spot disease (Ahmad et al. 2017). WSSV has been responsible for major economic loss worldwide to shrimp aquaculture since the 1990s (Jeena et al. 2018). Among the strategies developed by researchers to curb the damaging effects of WSSV, probiotic *Bacillus* emerged as one of the safe ways mainly through stimulation of the shrimp immunity. Typically, feeding *Bacillus* PC465 to *L. vannamei* increased its survival against WSSV challenge (Chai et al. 2016). Synergistic effects of *Bacillus* OJ and isomaltooligosaccharides resulted in higher immune titers in *L. vannamei* thus a higher survival against WSSV (Li et al. 2009). Many other studies (Sánchez-Ortiz et al. 2016; Sekar et al. 2016; Pham et al. 2017) have shown the ability of probiotic *Bacillus* to enhance the immunity of shrimp to withstand the pathogenicity of WSSV.

Infectious hypodermal and hematopoietic necrosis virus

Runt-deformity syndrome and stunted growth usually found in shrimps are caused by infectious hypodermal and hematopoietic necrosis virus (IHHNV) (Chen et al. 2017; Dewangan et al. 2017). Recent advancements have proven that IHHNV infests a wide range of crustaceans including crab, freshwater crayfish, *Procambarus clarkia*, and freshwater shrimps, *M. rosenbergii* (Nita et al. 2012; Rai et al. 2012; Chen et al. 2017) resulting in massive economic losses. Like WSSV, probiotic *Bacillus* has been reported to reduce infections caused by IHHNV through the enhancement of the host's immunity. For example, feeding *L. vannamei* with a diet containing a mix of *Bacillus* species resulted in reduced prevalence of IHHNV due to improved immunity (Sánchez-Ortiz et al. 2016). This single evidence demonstrates the potential of *Bacillus* species in the mitigation of runt-deformity syndrome in aquaculture. More research, however, is required to ascertain and elucidate the role of *Bacillus* in mitigating IHHNV.

Mechanisms used by *Bacillus* in protecting fish against pathogenic microbes

Understanding the various mechanisms used by *Bacillus* in combating diseases will help improve their mode of action hence yielding better results in their fight against pathogens in the aquaculture industry. As mentioned by Urdaci and Pinchuk (2004), the antimicrobial activity of a particular bacterial strain is dependent on their ability to produce diverse substances as well as compounds with very specific spectrums and modes of action such as bacteriocins, bacteriolytic enzymes, and antibiotics. The following are overviews (Fig. 1) of the possible mechanisms used by *Bacillus* in fighting pathogens in aquaculture.

Production of bacteriocins

Bacteriocins are bioactive antimicrobial peptides produced in the ribosome of many bacteria and released extracellularly. Bacteriocins are capable of killing or inhibiting the growth of prokaryotes and can be used against pathogenic bacteria and antibiotic-resistant strains of bacteria as well (Riley and Wertz 2002; Zou et al. 2018). Bacteriocins are different from traditional antibiotics and have been discussed in detail by Cavera et al. (2015) and Zou et al. (2018) and are considered alternatives to antibiotics (Bierbaum and Sahl 2009).

Genome sequencing has revealed the genus *Bacillus* as a source of antimicrobial compounds (Grubbs et al. 2017). A review on the antimicrobial substances produced by *B. subtilis* by Stein (2005) indicated that the antimicrobial active compounds synthesized by *B. subtilis* include ribosomally synthesized and post-translationally modified peptides (lantibiotics and lantibiotic-like peptides) and nonribosomally generated, as well as nonpeptidic compounds such as polyketides, aminosugars, and phospholipids. In another study by Urdaci and Pinchuk (2004), it was indicated that *Bacillus* species produce bacteriocins and bacteriocin-like inhibitory substances (BLISs) which are effective in inhibiting pathogens.

Collective literature showed that *Bacillus* species used in aquaculture have antimicrobial properties, specifically bacteriocin production. In a study by Yi et al. (2018), three PKS gene clusters (bacillaene, difficidin, macrolactin), four bacteriocins gene clusters, and five NRPS gene clusters (fengycin, bacilysin, surfactin, bacillibactin, and an unknown NRPS) which are bacteriocins and antimicrobial secondary metabolite–related genes were detected in *B. velezensis* isolated from carp. This has resulted in the ability of the *B. velezensis* to fight various fish pathogenic bacteria including *Aeromonas hydrophila*, *Vibrio parahemolyticus*, *Lactococcus garvieae*, *Aeromonas salmonicida*, and *Streptococcus agalactiae*. *B. amyloliquefaciens* isolated from the marine fish *Epinephelus areolatus* was reported to produce novel bacteriocin named CAMT2 which inhibited *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, and *V. parahaemolyticus* (An et al. 2015). Other studies also highlighted bacteriocin production by *Bacillus* species (Teixeira et al. 2009; Abriouel et al. 2011; Compaoré et al. 2013; Al-Thubiani et al. 2018). Aside from the traditional use of bacteriocins produced by *Bacillus* species, they are also used in food preservation as reported by Gálvez et al. (2007) to be good candidates as food preservatives, shelf life extenders, and ingredients. For instance, a novel bacteriocin Coagulin produced by *Bacillus coagulans* was proved to elongate the shelf life of large yellow croaker during storage at 4 °C (Fu et al. 2018). A similar observation was made by Teixeira et al. (2009) and Guo et al. (2016b) who concluded that bacteriocins produced by *Bacillus atrophaeus* and *B. licheniformis* could be useful against pathogens in the food industry thus could be used as preservatives. It could therefore be said that *Bacillus* species produce bacteriocins which exhibit both pathogenic and spoilage bacteria hence could be used in fighting diseases as well as in the preservation of fish food.

Quorum quenching (suppression of virulence gene expression)

Quorum sensing (QS) is a bacterial regulatory mechanism in which bacteria coordinate gene expressions in a

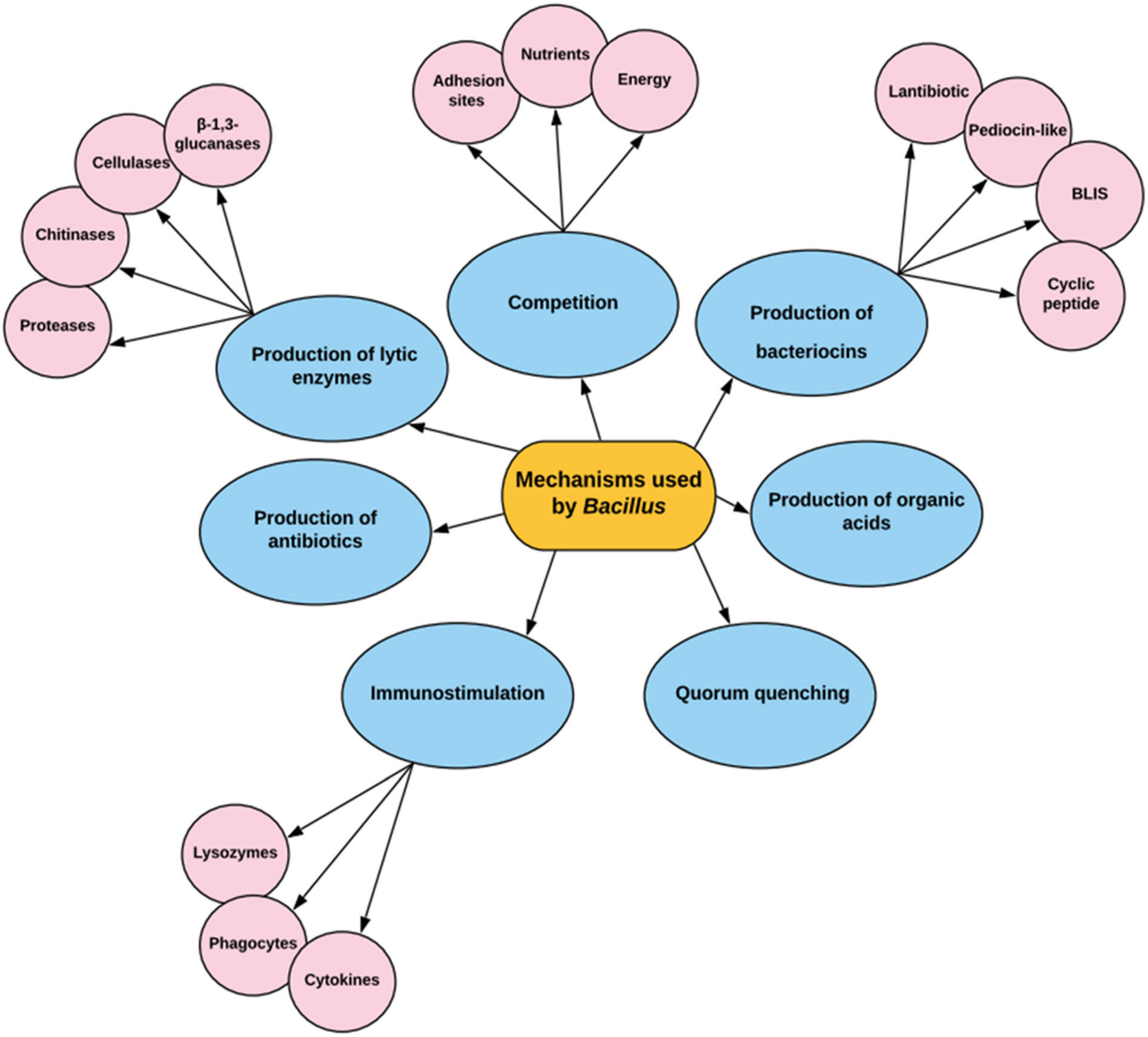

Fig. 1 Summary of the mechanisms used by *Bacillus* in mitigating pathogens in aquaculture

cell density–dependent manner by producing, releasing, and recognizing small signal molecules called autoinducers (Suga and Smith 2003; Defoirdt et al. 2004; Chu et al. 2014). N-acyl homoserine lactone (AHL) signals are used by bacteria to monitor their population density and synchronize target gene expression (Zhang and Dong 2004). QS regulates several bacteria phenotypes such as bioluminescence (Miller and Bassler 2001; von Bodman et al. 2008), biofilm formation (Cvitkovitch et al. 2003; Merritt et al. 2003), swarming (Shrout et al. 2006; Tremblay et al. 2007), and virulence factors (Mellbye and Schuster 2011) which contribute to bacterial pathogenesis.

Since QS controls the pathogenicity traits of bacteria, disruption of QS has been suggested and proven as a strategy to control pathogenic bacteria in the field of animal husbandry and aquaculture (Defoirdt et al. 2004; Boyen et al. 2009; Piewngam et al. 2018). Quorum quenching (QQ) therefore is the disruption of QS (Roy et al. 2011); thus, the destruction of AHLs is an efficient way to interrupt QS (Musthafa et al. 2011; Cao et al. 2014; Chu et al. 2014). Many microorganisms have been reported to produce enzymes which can degrade AHLs (Christiaen et al. 2011; Tang et al. 2013) of which *Bacillus* is no exception. In aquaculture, many researchers have proven that *Bacillus* species possess

QQ ability as one of its mode of suppressing the virulence of pathogenic microbes. For instance, a study by Musthafa et al. (2011) revealed that *Bacillus* sp. SS4 isolated from marine source interfered with the activities of AHL in *Chromobacterium violaceum* and *Pseudomonas aeruginosa* hence reducing their pathogenicity and biofilm production. In another study, AHL lactonase produced by *Bacillus* species was responsible for QQ in *A. hydrophila* and decreased the mortality of common carp after the challenge test (Chen et al. 2010). In another experiment, AiiO-AIO6 gene from *Bacillus* degraded the signal molecules of *A. hydrophila* and inhibited the expression of the virulence factors of *A. hydrophila* (Zhang et al. 2011). A similar observation was made by Reimmann et al. (2002) who concluded from their study that the introduction of an AHL degradation gene (aiiA gene) from *Bacillus* into *P. aeruginosa* can block cell-cell communication and exoproduct formation hence inhibiting its pathogenicity. Also, the supplementation of $AiiA_{AI96}$ into fish feed by oral administration decreased *A. hydrophila* infection in zebrafish significantly (Cao et al. 2012, 2014). Many other studies have reported the QQ ability of *Bacillus* (Chu et al. 2014; Torabi Delshad et al. 2018; Wee et al. 2018) in aquaculture; hence, *Bacillus* species produce enzymes (using aiiA gene) that interfere with the QS of pathogens thereby inhibiting their virulence.

Production of lytic enzymes

The genus *Bacillus* is known to produce various hydrolytic enzymes which have different substrate specificity and possess antimicrobial properties (Urdaci and Pinchuk 2004). These lytic enzymes have antibacterial and antifungal activities (Kim et al. 1999; Biziulevièius and Þukaitë 2002). The hydrolytic enzymes excreted degrade the cell wall components of pathogenic microbes. For instance, chitinases, proteases, cellulases, and β-1,3-glucanases are lytic enzymes which play a significant role in the lysis of the cell wall of pathogens since proteins, chitins, cellulose, and β-1,3(1,6)-glucans are important components of the cell walls of these pathogenic microbes (Urdaci and Pinchuk 2004; Jadhav et al. 2017).

The excretion of the above mentioned enzymes by the genus *Bacillus* has been reported by many researchers in the field of aquaculture. Although these enzymes are mostly linked with digestion, they may also be involved in the fight against pathogens which in turn results in the overall resistance of the reported fishes against the challenged pathogenic microbes. Protease (Liu et al. 2009; Ramesh et al. 2015; Thankappan et al. 2015; Mitra et al. 2018; Zaineldin et al. 2018; Cai et al. 2019), cellulase (Doroteo et al. 2018; Kavitha et al. 2018; Midhun et al. 2018), and glucanase (Kim et al. 2013) of *Bacillus* species have been reported in relation to fish; hence, attention needs to be paid to their ability to lyse the cell walls of pathogenic microbes instead of their traditional role as digestive enzymes. Also, the potential adverse effects of these lytic enzymes on other beneficial microorganisms need to be investigated since it is not clear whether these enzymes act against only the pathogenic microbes.

Production of antibiotics

As indicated by Stein (2005), *B. subtilis* devotes approximately 4–5% of the genome to antibiotic production. In earlier studies by Béahdy (1974), it was observed that 167 antibiotics were produced by *Bacillus* genus, including 23 from *B. brevis* and 66 different peptide antibiotics from *B. subtilis.* Afterward, many other antibiotics have been isolated from *Bacillus* and applied in pharmacology and veterinary as well as the food industry (Urdaci and Pinchuk 2004). For example, *B. subtilis* 2335 has been demonstrated to synthesize the antibiotic amicoumacin which was effective against *Helicobacter pylori* (Pinchuk et al. 2001). Common antibiotics produced by the genus *Bacillus* were summarized in Pinchuk et al. (2001).

Antibiotics synthesized by *Bacillus* species exhibit wide range of antimicrobial properties against gram-positive (bacitracin, laterosporin, gramicidin, and tyrocidin) and gram-negative (polymyxin) bacteria as well as against fungus (mycobacillin and zwittermicin) including antiviral properties (surfactin, subtilin, ericin A, and ericin S) (Urdaci and Pinchuk 2004; Suva et al. 2016). Antibiotic production by genus *Bacillus* is well elucidated by Urdaci and Pinchuk (2004). However, yet to be understood is whether these antibiotics synthesized by *Bacillus* could result in antibiotic resistance or not. Perhaps there is lesser chance of antibiotic resistance since *Bacillus* uses diverse ways to combat pathogenic microbes. Nonetheless, research in this area is recommended.

Stimulation of the host's immune system

Another mechanism used by *Bacillus* in protecting the host against pathogenic microbes is the stimulation of the host's nonspecific and specific immunity. Immunostimulatory effects of *Bacillus* have been reported in many studies in relation to aquaculture. Regardless of the form, whether vegetative cells or spores, *Bacillus* trigger the humoral and cell-mediated immune response of fish. The main components of specific and nonspecific immunity of fish are well elucidated (Tort et al. 2003; Magnadóttir 2006; Uribe et al. 2011; Thompson 2017; Wilson 2017).

Some studies have provided strong evidence that the administration of *Bacillus* species stimulates the immune (specific and nonspecific) system of fish. The interaction between *Bacillus* species and phagocytic activity of fish has been reported. For example, higher phagocytic activity has been reported in striped catfish (*Pangasianodon hypophthalmus*) after a mixture of *B. amyloliquefaciens* and *B. pumilus* diet supplementation (Thy et al. 2017). In parrotfish (*O. fasciatus*), decreased mortality was recorded after *Vibrio alginolyticus* challenge which was attributed to increased phagocytic activity after feeding with a diet supplemented with *B. subtilis* E20 (Liu et al. 2018). Enhanced phagocytic activity in *Haliotis discus hannai* Ino, *Epinephelus coioides*, and *L. rohita* was also observed after *B. licheniformis*, *B. pumilus* SE5, and *Bacillus aerophilus* diet supplementation, respectively (Yan et al. 2016; Ramesh et al. 2017; Gao et al. 2018). Lysozymes which are known for the destruction of the cell walls of certain bacteria have also been reported to be enhanced after *Bacillus* supplementation in *L. rohita* (Nandi et al. 2017a), *O. niloticus* (Abarike et al. 2018b, a), red sea bream (Zaineldin et al. 2018), and European sea bass (*D. labrax*) (Acosta et al. 2016). Other immune parameters of fish such as IgM (Nandi et al. 2017a; Ramesh et al. 2017), respiratory burst (Ramesh et al. 2017; Thy et al. 2017), pro-inflammatory cytokines (IL-8 and IL-1β) (Yan et al. 2016), and the modulation of genes related to immunity (He et al. 2011, 2013; Abarike et al. 2018a; Midhun et al. 2019) have been implicated with *Bacillus* diet supplementation in fish. He et al. (2013) also related the immunostimulatory effects of their *B. subtilis* C-3102 to the production of β-glucan and bacteriocins. Components of the innate and the adaptive immune system play crucial roles in the host's defense against infectious agents (Esteban et al. 2014; Munir et al. 2016); thus, enhancement of these components by *Bacillus* species suggests that *Bacillus* helps fish fight infectious agents by enhancing the immunity of the fish.

Competition for adhesion sites

Although pieces of evidence are available, competition for adhesion sites is another generally proposed mechanism by which probiotics inhibit the proliferation of pathogens (Sahu et al. 2008; Ige 2013; Addo et al. 2017b). In vitro methods have been used to support this claims but yet to be supported with in vivo methods (Kesarcodi-Watson et al. 2008).

Adhesion of bacteria to tissue surface is significant during the early stages of pathogenic infection. Competition for adhesion receptors with pathogens may be an inherent probiotic characteristic thus depriving pathogenic microbes of adhesion to cause infections (Addo et al. 2017b). Colonization of the gut and other tissue surfaces and competition for space for adhesion is one of the mechanisms used by probiotics to fight against harmful pathogens (Ringø et al. 2007). Many studies have proven the ability of probiotics to adhere to intestinal mucus using in vitro methods, but the competitive exclusion effects of these probiotics are not well elucidated (Kesarcodi-Watson et al. 2008). Lalloo et al. (2010) indicated that the basis of competitive exclusion by probiotics is through competition for available energy or chemicals or by the higher growth rate of the probiotics compared with the pathogenic microbes. They drew this conclusion from their experiment where *B. cereus* outcompeted *A. hydrophila* and inhibited its growth. In another study by Brunt and Austin (2005), it was demonstrated that the inhibition of pathogenic *L. garvieae* and *Streptococcus iniae* by their *Bacillus* species was not as a result of antibiosis or production of antimicrobial compounds. This supports Luis-Villaseñor et al. (2011) who indicated that *Bacillus* spp. possess higher adhesion abilities. Hence, competition for adhesion sites leading to the exclusion of pathogenic microbes is partially due to the higher growth rate of the probiotic microbes relative to the pathogenic microbes. Nevertheless, many factors such as adhesins, lipoteichoic acids, passive forces, hydrophobic, steric forces, and electrostatic interactions play a significant role in the adhesion capacity of microbes (Lara-Flores and Aguirre-Guzman 2009; Mohapatra et al. 2013).

Competition for nutrients and energy

Probiotic bacteria, as well as pathogenic microbes, use a similar source of energy and nutrients; thus, probiotic effects are attributed to competition for nutrients and energy sources (Verschuere et al. 2000a; Hassanein and Soliman 2010). Heterotrophs, which are abundant in the aquatic ecosystems, contest for organic substrates such as carbon and other energy sources (Mohapatra et al. 2013). Probiotics utilize nutrients available for pathogenic microbes thus starving the pathogenic microbes. *Bacillus* species show higher organic carbon utilization and are capable of synthesizing siderophores (low molecular weight chelating compounds) which expedite competitive uptake of iron for growth (Verschuere et al. 2000b; Winkelmann 2002; Lalloo et al. 2010). Iron and carbon are important requirements for the growth of most microbes; hence, limiting their availability can result in growth suppression (Braun and Killmann 1999). Under iron-limiting conditions, siderophore-producing probiotics deprive pathogens of iron (Kesarcodi-Watson et al. 2008). In a glucose and iron uptake studies, it was revealed that *B. cereus* had significantly higher growth in limited glucose or iron than pathogenic *A. hydrophila* which was attributed to siderophore production by the *B. cereus* isolates (Lalloo et al. 2010). Several *Bacillus* species have been shown through in vitro methods to use a variety of carbon sources for energy (Ramesh et al. 2015; Lee et al. 2017; Meidong et al. 2017; Kavitha et al. 2018) indicating their ability to deprive pathogens of these energy sources. It is notable that competition for nutrient and energy leads to competitive exclusion.

Production of organic acids

Inhibition of pathogenic microbes has been associated with the production of organic acids by probiotic LAB (González et al. 2007; Maeda et al. 2014). These organic acids are produced during lactic fermentation, and the type of organic acids produced is dependent on the type and strain of the LAB (Lindgren and Dobrogosz 1990). The production of organic acids by LAB results in antimicrobial effects through the reduction of pH, as well as the undissociated form of the molecules. The low pH causes acidification of the cell cytoplasm, and the undissociated acid diffuses passively across the membrane to collapse the electrochemical proton gradient or to modify the cell membrane permeability resulting in disruption of substrate transport systems (Ammor et al. 2006; Musikasang et al. 2009). Therefore, organic acids have strong inhibitory activity against pathogenic bacteria (Musikasang et al. 2009). Recently, Etyemez and Balcazar (2016) proposed that antibacterial activity of *B. mojavensis* against *Edwardsiella piscicida* was as a result of the production of organic acids or pH-dependent compounds by the *Bacillus* species. This suggests that like LABs, *Bacillus* species also produce organic acids which are antagonistic against fish pathogens.

Conclusion and future perspectives

Beneficial use of *Bacillus* in aquaculture has been well established. Mitigation of pathogenic microbes is one of the most important benefits of probiotic *Bacillus*. Reducing the incidence of diseases leads to healthy production and less mortality thus higher yields and more income to the farmer. Quorum quenching, production of bacteriocins, antibiotics and lytic enzymes, stimulation of immunity, competition for adhesion sites, nutrients and energy, and improvement of the rearing water quality are known mechanisms used by *Bacillus* in the mitigation process. It has been shown that probiotic *Bacillus* is useful in curbing the adverse effects of pathogens ranging from bacterial to viral infections in aquaculture. Other antipathogenic benefits of *Bacillus* include prevention of food spoilage thereby increasing shelf life and less wastage. This, in turn, results in the consumption of healthy fish by the consumer and also saves energy used for storage thus more income.

Although research in the use of *Bacillus* species against pathogens in aquaculture is advancing, other groups of equally significant aquatic pathogens namely *Yersinia*, *Flavobacterium*, *Edwardsiella*, *Acinetobacter*, *Clostridium*, WSSV, and IHHNV are less explored; therefore, much research in this direction regarding the use of *Bacillus* is recommended. The use of *Bacillus* to protect fish against viral infections and the production of antibiotics which have antiviral effects have been reported; nonetheless, this has not been fully exploited in fish. Also, probiotic *Bacillus* use to confer protection in fish against tilapia lake virus (Tattiyapong et al. 2017; Senapin et al. 2018), a newly emerging virus threatening tilapia culture can be explored. More research into the mechanisms employed by *Bacillus* against fish pathogens should be carried out to better understand and improve their efficacy. Finally, the relationship between antimicrobial compounds produced by *Bacillus* in in vitro studies and their in vivo immunostimulation must be well investigated, and the exact mechanism underlying the antiviral effects of *Bacillus* must be explored.

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Compliance with ethical standards

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

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