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Review

Effect of *Bacillus* Probiotics on the Immunological Responses of Nile Tilapia (*Oreochromis niloticus*): A Review

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Abstract: The use of antibiotics and therapeutics for Nile tilapia has increased along with its increased production and intensification. Probiotics have been studied as an alternative to the excessive use of antibiotics in fish diets. Studies have demonstrated that dietary *Bacillus* probiotic inclusion promotes faster growth and disease resistance in farmed fish species. Despite advances in research, there is still uncertainty about the mechanisms controlling the immune response of fish. In this review, we summarize and discuss recent research on the immune responses of Nile tilapia to *Bacillus* probiotics. Through the use of immunological information including phagocytosis, lysozyme activity, respiratory activity, antioxidant proteins, complement activity, and immune-related gene expression, researchers hope to develop effective strategies for successfully using *Bacillus* probiotics in *Oreochromis niloticus* farming.

Keywords: Nile tilapia; *Bacillus* probiotics; gut microbiota; immune response

Key Contribution: The key aspect highlighted in the review is the effects of *Bacillus* probiotics on Nile tilapia's immune system.

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1. Introduction

Over the last few decades, aquaculture has grown in popularity as a method of producing seafood for human consumption [1]. It has been a key part of many regions of the world's food supply and has been rising tremendously as the demand for seafood increases [2]. However, in recent years, aquaculture has been plagued by a variety of infections, resulting in massive economic losses [3].

The use of antibiotics in commercial aquaculture has been a common practice for many years. While this practice has been effective in combating infectious diseases, it has also caused several significant problems [4,5]. In recent years, indiscriminate pesticide and antibiotic usage has led to the emergence of antibiotic-resistant bacteria, and residual antibiotics can be detected in aquatic products. Using pesticides and antibiotics to control disease outbreaks is no longer encouraged due to their detrimental effects on the environment, including the creation of mutagenic microbial strains and harming fish, including Nile tilapia [6,7].

As a result, the use of environmentally acceptable feed additives, such as probiotics, to improve the physiology, growth performance, and immune responses of aquaculture-related species has grown in popularity in recent years [8,9]. It is known that live bacteria, also known as probiotics, can have a variety of physiological effects on the hosts [10].

One of the primary benefits of *Bacillus* probiotics is their ability to regulate mucosal and systemic immunity, thus reducing inflammation and improving the body's ability to fight off infection [11,12].

Bacillus probiotics have been found to help improve the absorption of vitamins and minerals from food and help break down proteins, carbohydrates, and fats to ensure that the body is obtaining the nutrients it needs for optimal health [13,14]. However, choosing the right probiotics is crucial because the wrong ones can negatively impact nutrient metabolism, immunomodulation, colonization resistance, and pathogen resistance. Critical considerations include the ability to be cultured on a larger scale and survive until reaching the gastrointestinal tract (GIT) of the host by being able to resist acidic conditions in the stomach [14].

Incorporating *Bacillus* probiotics, such as *B. coagulans* ATCC 7050 and *B. subtilis* WB60, into aquatic animals' diets has improved their development, growth, immunity, and disease resistance [15,16]. As a result, *Bacillus* probiotic supplementation has been noted to be effective in improving fish health, including Nile tilapia [17,18].

Although *Bacillus* probiotics have gained increased attention, their mechanism of action, optimal dosage, and administration techniques remain poorly understood [19,20]. The Nile tilapia is a species of freshwater fish that is widely farmed throughout the world. Its hardiness, fast growth rate, and high nutritional value make it an attractive choice for farmers, and its efficient farming systems make it a more sustainable option for the environment. With landings of farmed Nile tilapia reaching an all-time high, it is clear that this species will continue to be an important part of the aquaculture industry for years to come [21–23].

Extensive Nile tilapia farming has been a profitable agricultural activity for many years. However, in recent years, the sector has been challenged by several disease outbreaks caused by pathogenic bacteria, resulting in a high rate of Nile tilapia mortality and morbidity [24,25]. The immunomodulatory activity of *Bacillus* probiotic (*Bacillus cereus*) administered to Nile tilapia is essential [26]. This is because *Bacillus* probiotics can assist in boosting the fish's immune system, minimize disease risk, and reduce the number of antibiotics used in farming [27–31]. Therefore, this review emphasized recently discovered information concerning the immunomodulatory activity of recent *Bacillus* probiotics studies that influence the immunomodulatory potency via Nile tilapia diets. The reasonable identification of knowledge gaps in this field has emphasized the necessity for future research on efficient fish health management systems and advancing the aquaculture sectors.

2. Common *Bacillus* Probiotics Used in Nile Tilapia Rearing and Farming

Several *Bacillus* species have been identified as potential probiotics for aquaculture (including *B. subtilis, B. clausii, B. velezensis, B. cereus, B. coagulans, B. licheniformis, B. pumilus, B. mojavensis, and B. megaterium*) [32–35]. Using *Bacillus* species in tilapia farming is common and effective, primarily as feed or water additives [36–39]. The most common way to give fish probiotics is through the use of feed.

Encapsulating the probiotic in feed allows it to be released slowly over a more extended period, creating a sustained-release effect. This allows the probiotic to remain in the fish's intestines longer, interacting with the immune system and developing a positive effect [30,40,41]. Probiotics are administered to fish through live food, either by packaging the probiotic in the live food or by adding it to the water where the live feed is grown.

Because the probiotic is included in the live feed, it may be promptly and directly absorbed by the fish, having an immediate impact [41]. To increase their benefits, *Bacillus* probiotics can be combined with prebiotics or other substances (fructooligosaccharide combined with *B. licheniformis*, *Astragalus extracts* combined with *B. subtilis*) [42–44]. Prebiotics are non-digestible food elements that promote the growth and activity of beneficial bacteria in the gut and can aid in boosting probiotic effectiveness [45]. In addition, vitamins, minerals, and enzymes can also be added to the probiotic to enhance its benefits.

As a result, the carrier may influence immune system regulation [46]. Nile tilapia have been discovered to benefit from *Bacillus* probiotics (*B. safensis, B. subtilis, B. licheniformis*) which offer several health advantages [20,47,48]. *Bacillus* probiotics can contribute to the health and growth of Nile tilapia by encouraging the growth of beneficial bacteria in the gut, enhancing feed conversion effectiveness, and increasing disease resistance [49,50]. Nile tilapia have been reported to benefit from *Bacillus* probiotics, although the exact method of action and dosage may vary from fish to fish [51–53].

3. *Bacillus* Probiotics and Gut Microbiota

The gut microbiota consists of bacteria found in the gastrointestinal tracts of humans and other animals that live in symbiotic relationships with them [54]. The gut microbiota of Nile tilapia has been noted to be primarily dominated by the phyla Fusobacteria, Proteobacteria, and Bacteroidetes [55,56]. Nile tilapia's skin, eggs, gills, and digestive system are home to numerous natural kinds of bacteria [57].

The gut microbiome controls the intestinal epithelium's morphology, function, host physiology, and immunological responses, which significantly impact digestion and homeostasis [58,59]. Adeoye et al. [60] studied the effects of *Bacillus* probiotics (*B. subtilis*, *B. licheniformis*, and *B. pumilus*) on the gut microbiota of Nile tilapia.

Adding *Bacillus* probiotics to Nile tilapia feed increased the levels of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, while decreasing the levels of pathogenic bacteria. Han et al. [20] investigated the effects of *Bacillus* probiotics (*B. licheniformis*) on Nile tilapia growth performances. *Bacillus* probiotics were found to increase the growth rate of Nile tilapia when added to their feed. Hence, *Bacillus* probiotics may benefit Nile tilapia, as they can help improve the gut microbiota. Magda et al. [61] investigated the viability of *Bacillus* probiotics in influencing immunity in Nile tilapia. Their study found that adding *Bacillus subtilis* to the Nile tilapia diet significantly improves the immune system.

Studies have shown that using *Bacillus* probiotics can significantly increase the number of beneficial bacteria in the gut of Nile tilapia. These beneficial bacteria can help promote better digestion and absorption of nutrients and reduce the risk of disease [62]. For example, dietary administration of a *Bacillus* probiotic (*Bacillus cereus*) increased beneficial bacteria such as *Lactobacillus, Bifidobacterium*, and *Enterococcus* species and decreased pathogenic bacteria such as *Aeromonas* and *Vibrio* species [26], as well as several immune-related genes, such as interleukin-1β, tumor necrosis factor-α, and interferon-γ.

As shown in a study by Wu et al. [48], *Bacillus safensis* NPUST1 supplementation appears to be effective in regulating the gut microbiota within Nile tilapia. It provides a potential solution to aluminum-induced imbalances within the gut microbiota of Nile tilapia. In addition, *Bacillus* probiotics (*B. velezensis, B. cereus,*) increased the production of short-chain fatty acids, which are beneficial for gut health [63]. Based on the data provided by Hassaan et al. [64], *Bacillus pumilus* significantly enhanced Nile tilapia growth, immunity, and gut microbiota. A probiotic *Bacillus* strain improved Nile tilapia's growth performance significantly. Results showed that the fish gained weight, were more fed, and had a higher specific growth rate. Additionally, the use of *Bacillus* probiotics (*B. coagulans*) significantly improved the total serum protein level, lysozyme activity, and total immunoglobulin E (IgE) level in Nile tilapia [11].

Similarly, Yaqub et al. [65] found that dietary supplementation with *Bacillus licheniformis* SB3086 improved growth performance, immunological parameters, intestinal morphology, and resistance to challenge infections in *Oreochromis mossambicus.* The growth performance, immunological parameters, intestinal morphology, and resistance of *O. mossambicus* were significantly improved by *B. licheniformis* SB3086.

The colonization dynamics of the gut microbiota in Nile tilapia are largely determined by environmental factors (such as temperature, pH, and salinity) [66–69]. It has been shown that Nile tilapia's diet also influences gut microbiota colonization dynamics [70–72].

Also, certain dietary components, including carbohydrates, proteins, lipids, and vitamins, may influence gut microbiome composition [66,73]. Fish's age, diet, and health status also affect the colonization dynamics of their gut microbiota, with some bacteria becoming more abundant as they age [56,74].

The composition of the gut microbiome of Nile tilapia may also be influenced by environmental toxins, such as heavy metals [75].

4. Mode of Action of *Bacillus* Probiotics in Nile Tilapia

Bacillus probiotics (*B. subtilis*) have the potential to protect the intestines against diseases, make the environment inhospitable for pathogens, compete for vital nutrients, restrict epithelial adhesion sites, and alter immune responses at the physiological and molecular levels (Figure 1) [76].

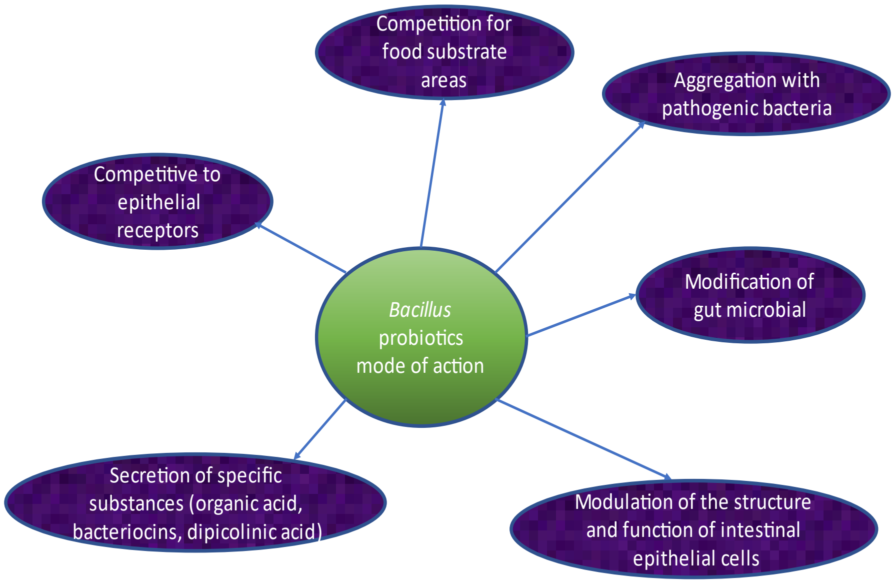

Figure 1. Scheme demonstrating the *Bacillus* probiotics' mode of action, *Bacillus* probiotics protect the intestines against diseases, by making the environment inhospitable for pathogens, compete for vital nutrients and restrict epithelial adhesion sites.

Probiotics from the genus can be consumed in various ways, including as food supplements, bio-encapsulated *Bacillus* particles, and water additives [77]. *Bacillus* probiotics (such as *B. amyloliquefaciens*) are known to create both organic acids and short-chain fatty acids, which can enhance the operation of the digestive system to aid in food digestion (proteins, carbohydrates, and lipids) [78,79].

As a result of enhancing the production of digestive enzymes, such as lipase, amylase, and protease, *Bacillus* probiotics (*B. subtilis and B. licheniformis*) improve feed digestibility [80]. Two host-associated *Bacillus* species (*B. amyloliquefaciens* and *B. licheniformis*) were fed to Nile tilapia, and high lipase activity was seen in *B. subtilis* in their intestines [49,50].

Bacillus probiotics (such as *Bacillus* sp. KUAQ1 and *Bacillus* sp. KUAQ2, *B. subtilis* C-3102, *B. subtilis*, and *B. velezensis* LF01) have been shown to compete for adhesion sites with pathogens on the gastrointestinal epithelium of Nile tilapia [81–84].

According to Bidhan et al. [30], *Bacillus clausii* produces several inhibitory substances (proteases) that can aid in the inhibition of pathogen adherence to the mucosal epithelium.

A range of *Bacillus* species, including *B. cereus*, *B. subtilis*, and *B. amyloliquefaciens*, can compete with pathogens for adhesion sites, protecting Nile tilapia from diseases [85]. For instance, *Vibrio* sp. (*V. harveyi* and *V. parahaemolyticus*, *V. alginolyticus*) and *Mycobacterium* species were suppressed from growing in Nile tilapia when *B. pumilus*, *B. firmus*, *B. subtilis*, and *B. cereus* were utilized as probiotics [86].

By inhibiting intestinal absorption and hepatic accumulation of aluminum, *Bacillus* probiotic bacteria like *Bacillus cereus* and *Bacillus subtilis* can alleviate aluminum-induced oxidative stress and tissular damage caused by aluminum [87].

Among the most commonly used aquaculture probiotics, *Bacillus subtilis* promotes multiple protective mechanisms such as synergistic mechanisms, antagonistic mechanisms, competitive exclusion, and immune stimulation [88]. Intestinal cell and microvillus density were boosted by adding *B. subtilis* and *B. cereus* to tilapia's diet, boosting disease resistance via changes in the intestinal microbiota [17].

Kuebutornye et al. [50] reported that the increase in density of microvilli in fish intestines could minimize pathogenic microorganisms' colonization rate. Microvilli are minute, finger-like protrusions that line the surface of the intestines, and their density has been found to influence the intestine's absorptive surface area [89].

A higher density of microvilli enhances the absorptive surface area, allowing for better absorption of nutrients and other substances. Because there are fewer surfaces for the pathogenic microbes to attach and colonize as a result of the increased absorptive surface area, the rate at which they cling and colonize also decreases [90].

Activating and altering the fish's immune response with dietary *Bacillus* probiotics has been found to increase the resistance of Nile tilapia to various infections (Table 1) [91].

Table 1. The effect of different *Bacillus* probiotics on the immune response in Nile tilapia.

Probiotic Name	Probiotic Source	Dose (CFU/g)	Feeding Duration (Days)	Immunological Effects	Country of Investigation	Reference
B. subtilis HAINUP40	Natural pond water	10^8	56	LYZ (↑ after 2 weeks), RB (↑ after 2 weeks), SOD (↑ after 14 weeks), T-AOC (↑ after 14 weeks)	Hainan, China	[92]
B. subtilis NZ86	Commercial	Individual 10^7	51	LYZ (↓), PG (↔), RB (↔), IL-1β (↔), TNF-α (↔), AH50 (↑ NZ86), LYZ (↑ NZ86)	Miami, IL, USA	[37]
Bacillus spp.	*O. niloticus* gastrointestinal tract	10^8	28	NO (↑), IgM (↑), LYZ (↑), AKP (↑), CAT (↑), SOD (↑)	Gaozhou, China	[49,50]
B. velezensis TPS3N, *B. subtilis* TPS4, *B. amyloliquefaciens* TPS17	*O. niloticus* gastrointestinal tract	10^8 individual, $10^8 + 10^8 + 10^8$ combined	28	NO (↑), IgM (↑), LYZ (↑), AKP (↑), ACP (↑), SOD (↑), CAT (↑), MDA (↓)	Gaozhou, China	[49,50]
B. subtilis	Commercial	1×10^8 and 1×10^{10} CFU/kg	56	IL-1β, TNF-α, IFN-γ, and hsp-70 in the live (↑)	Greentech Aquaculture Co. Ltd., Nonthaburi, Thailand	[93]
B. subtilis E20	Culture collection strain	0.3 mL of 10^8 cells/mL	95	Non-specific immunity parameters including LYZ, PG (↑)	Cairo, Egypt	[94]
B. subtilis	Commercial	10^{10} individual	180	Serum TP (↑), WBCs (↑), LYZ (↑)	Sagana, Kenya	[38]
B. amyloliquefaciens	Culture collection strain	2.1×10^9	60	LYZ (↑), RB (↑), PG (↑), SOD (↔)	Pingtung, Taiwan	[52]
B. pumilus	*O. niloticus*	10^7–10^9	120	Peripheral blood leukocyte (↑), RB (↑), PG (↑)	Bangkok, Thailand	[53]
B. subtilis	Commercial	3 g kg^{-1}	42	TLR-2 (↑), TNF-α (↑), IL-1β (↑), IL-10 (↑), TGFβ (↑), HSP70 (↑)	Plymouth, UK	[51]
B. amyloliquefaciens	Commercial	10^9	60	Blood TP (↑), IgM (↑), TNF-α (↑), HSP70 (↓), SOD (↔)	Kafr El-Sheikh farm, Kafr al-Shaykh, Egypt	[95]
B. licheniformis HGA8B	Anabas testudineus gastrointestinal tract	10^6, 10^8	60	MUC 2 (↑), SOD (↑), TLR-2 (↑), IL-10 (↑), TNF-α (↔), IL-8 (↔) GSH-Px (↑), CAT (↑), MPO (↑)	Panagad, Kerala, India	[96]
B. cereus	*O. niloticus* intestinal tract	10^7, 10^8 via water	42	LYZ (↑), peroxidase activity (↑), ACP (↑), SOD (↑)	Guangzhou, China	[26]
B. subtilis, *B. megaterium*, and *B. licheniformis*	Culture collection strain	10^6	120	TNF-α (↑), HSP70 (↑), LYZ (↔)	Khon Kaen, Thailand	[97]
B. velezensis H3.1	*O. niloticus* intestinal tract	10^8	15	LYZ (↑ mucus) (↔ serum)	Chiang Mai, Thailand	[98]
B. cereus NY5	*O. niloticus* intestinal tract	10^4 CFU mL^{-1} individual via water	90	SOD (↑ skin)	Guangzhou, China	[99]
B. subtilis WB60	*Anguilla japonica* intestine	10^8 individual	56	LYZ (↑), SOD (↑), HSP70 (↑), MPO (↑), IL-1β (↑), IFN-γ (↑), TNF-α (↑)	Busan, Republic of Korea	[100]

CFU: colony forming unit, LYZ: lysozyme, RB: respiratory burst, SOD: superoxide dismutase, PG: phagocytic activity, NO: nitric oxide, IgM: immunoglobulin M, AKP: alkaline phosphatase, CAT: catalase, ACP: acid phosphatase, MDA: malondialdehyde, WBCs: white blood cells, serum TP: serum protein, blood TP: blood total protein, GHS-Px: glutathione peroxidase, MPO: myeloperoxidase. Symbols are used to explain whether or not the immunological activities were highly significant; i.e., ↑: significant increase, ↓: significant decrease, ↔: no significant changes.

5. *Bacillus* Probiotics and Fish Immunological Response

The Nile tilapia is an important species of fish due to its well-developed innate immune system [101]; this system is composed of physical barriers, humoral components, and cellular components [102]. The physical barriers of the Nile tilapia include the skin made up of several layers of cells that provide a protective barrier against infection. The mucus layer of the fish helps trap any foreign particles that may enter the body [103]. The humoral components of the Nile tilapia's immune system are made up of proteins and other molecules that are produced by the fish's body to fight off any potential pathogens [92,104]. The cellular components of the Nile tilapia's immune system are composed of several different types of cells that are responsible for recognizing and attacking any foreign particles that may enter the body [105,106].

Epithelial cells are a type of cell that forms the outer layer (skin, mouth, digestive tract, respiratory system) of tissue in organs and other structures of the body; these cells are important for protection, absorption, secretion, and transport [107]. In addition to protecting the body from infection and disease, mucous secretions are made up of immune system cells (mucosa-associated lymphoid tissue (MALT)). Based on its location, MALT can be divided into three types: gill-associated lymphoid tissue (GALT), skin-associated lymphoid tissue (SALT), and gut-associated lymphoid tissue (GALT) [108].

In the gut mucosa, probiotic organisms interact with numerous immune-competent cells [109]. Pathogen pattern recognition receptors (PRRs) are gene-encoded proteins that detect molecular patterns of pathogens and inform the host whether or not the pathogen is pathogenic [110]. *Bacillus* probiotic species (*B. amyloliquefaciens*, *B. subtilis*) interact with several immune-competent cells in the gut mucosa of the host (Nile tilapia). A host can identify pathogenic bacteria using pathogen pattern recognition receptors (PRRs), which are germline encoded proteins that recognize pathogen-specific molecular patterns [95,111]. Molecular patterns associated with damage or pathogens (PAMPs or DAMPs) recognized by PRRs include lipopolysaccharides, lipoic acid, peptidoglycan, and viral intracellular signatures.

The host recognizes microbe-associated molecular patterns (MAMPs) found in pathogens and nonpathogenic microorganisms. *Bacillus* probiotics (*B. subtilis, B. fragilis*) are examples of PAMPs on nonpathogenic microorganisms [112,113]. In response to pathogens, the innate immune system is alerted by signaling molecules generated when MAMPs and PRRs interact on host cells [38,96]. MAMPs from *Bacillus licheniformis* HGA8B interacted with PRRs of antigen-presenting cells and epithelial cells via toll-like receptors (TLRs) and nucleotide oligomerization domain receptors (NLRs), increasing complement activity in Nile tilapia fed diets containing *Bacillus licheniformis* HGA8B [96].

MAMPs, such as peptidoglycans, are found in the cell walls of *Bacillus* species (*B. subtilis*) and other bacteria [114,115]. MAMPs increase the transcription of pro-inflammatory cytokines and chemokines, which recruit innate immune cells when *Bacillus probiotics* (*B. subtilis*) interact with the immune system [71,115]. Several studies have shown that *Bacillus* probiotics (*B. velezensis* TPS3N, *B. subtilis* TPS4, *B. amyloliquefaciens* TPS17) can improve tilapia's local and systemic immunity (Figure 2 summarizes the effects of *Bacillus* probiotics on fish immunological responses) [39,49,50].

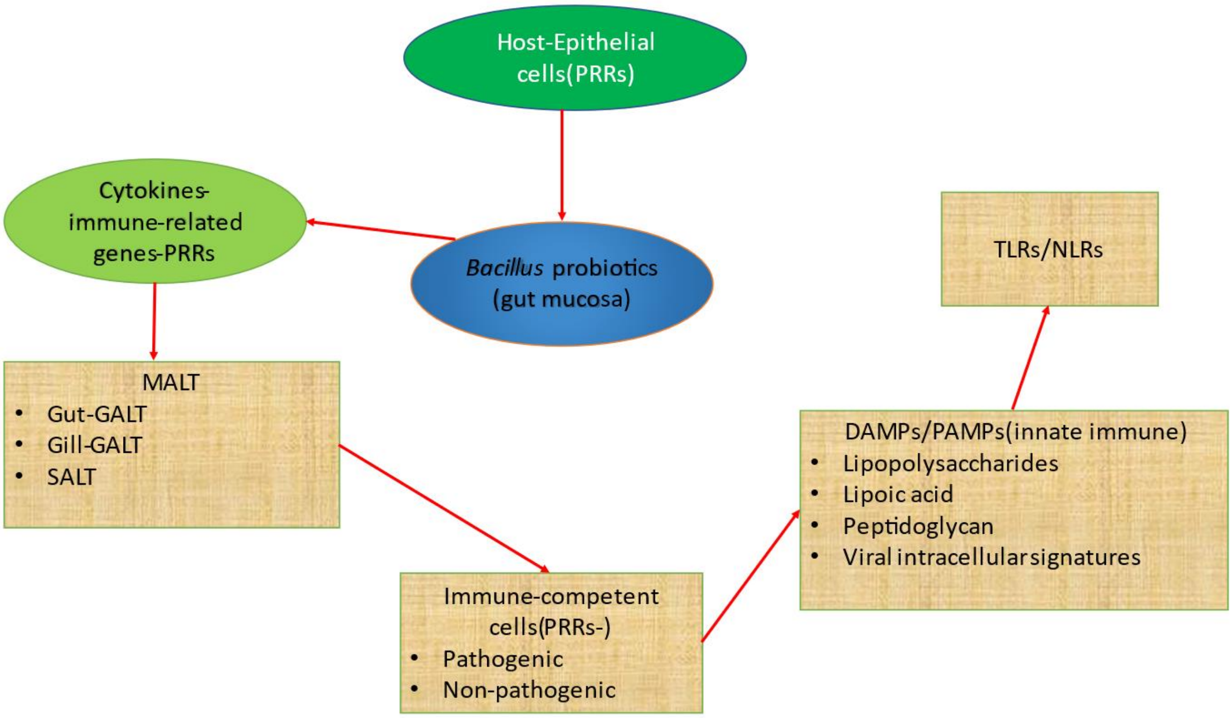

Figure 2. Interactions between host and microbe in the fish mucosal immune system, host recognizes microbe-associated molecular patterns (MAMPs) found in pathogens and nonpathogenic microorganisms, innate immune signaling molecules generated when MAMPs and PRRs interact on host cells.

5.1. Bacillus Probiotics Improve Immune Response

Several types of immune system cells can interact with probiotic bacteria (*Bacillus subtilis*). These cells include monocytes, macrophages, lymphocytes, granulocytes, neutrophils, and natural killer cells [116]. Through signaling from the cell surface pattern recognition receptors or by activating lymphoid cells, Nile tilapia can enhance their innate immune response to threats as a result of etiological agents [117].

Activation of immune cells by *Bacillus* probiotics (*B. coagulans, B. licheniformis*, and *B. subtilis*) can alter the intestinal mucosa by detecting DAMPs contained in stressed or wounded cells' biomolecules [10,118]. Opiyo et al. [119] found that *Bacillus subtilis* can increase white blood cells in Nile tilapia when administered as a probiotic. For instance, a study of Nile tilapia fed *Bacillus pumilus*-containing diets showed greater peripheral blood leukocyte counts [53]. Acidophilic granulocytes and intraepithelial lymphocyte proliferation were increased in Nile tilapia fed diets containing *Bacillus subtilis* and *Bacillus licheniformis* [120].

In Reda and Selim's study, the use of *Bacillus amyloliquefaciens* in fish feed improved intestinal function and mucosal immunity in Nile tilapia by increasing villous height in the proximal and middle intestines [121]. In fish and higher vertebrates, serum immunoglobulins are a crucial component of the humoral immune system and help to provide disease resistance. B lymphocytes create antibodies that bind to an antigen when it is encountered.

This binding procedure aids in preventing disease-causing antigens from entering the body [61]. Several *Bacillus* probiotics such as *B. amyloliquefaciens* and *Lactobacillus* sp., *B. velezensis* TPS3N, *B. subtilis* TPS4, and *B. amyloliquefaciens* TPS1, whether administered separately or in combination, have been shown to increase immunoglobulin levels and leukocyte counts [49,50,122].

5.2. Bacillus Probiotics Modulate Phagocytic Activity

The innate immune system acts as the first line of defense against infection [123], and *Bacillus* probiotics (*B. amyloliquefaciens*, *B. subtilis*, *B. licheniformis*, and *B. pumilus*) have been shown to enhance phagocytosis in Nile tilapia [124]. *Bacillus subtilis* probiotics ameliorated Nile tilapia's phagocytic index despite the fish being raised at high stocking density, demonstrating that *Bacillus* probiotics can relieve the stress associated with intensive rearing [47].

In the study conducted by Fath El-Bab et al. [125], it was found that feeding *Bacillus coagulans*-containing diets increased phagocytic activity in Nile tilapia farming. Pei-Shan Wu et al. [48] also observed an increase in phagocytosis in Nile tilapia fed diets containing *Bacillus safensis* NPUST1 against Aeromonas hydrophila. In addition, another study by Telli et al. [47] discovered that adding *Bacillus* probiotics to fish feed caused Nile tilapia to increase phagocytic activity. Similarly, adding *Enterococcus faecium* to the tilapia diet increased immunity when exposed to *A. hydrophila*, indicating an immunological resistance [126].

5.3. Bacillus Probiotics Regulate Lysozyme Activity

Bacillus amyloliquefaciens and *Bacillus subtilis* have both demonstrated lysozyme stimulation in Nile tilapia [52,92,100]. Saurabh et al. [101] suggest that the increased lysozyme levels in Nile tilapia could be attributed to an increase in phagocytes that secrete lysozyme or an increase in lysozyme-producing cells. The type, quantity, and time of *Bacillus* probiotics (*B. velezensis* H3.1) that are administered may affect lysozyme activity [59]. In Nile tilapia exposed to the pathogenic bacteria *Streptococcus agalactiae*, *Bacillus amyloliquefaciens* was found to increase lysozyme levels [52]. Lysozyme is a multifunctional enzyme present in many animals, plants, and microbes; lysozyme, on the other hand, attacks chitin, a significant component of fungal cell walls [101].

In Nile tilapia challenged with hypoxic conditions, *Bacillus pumilus* administered as a probiotic significantly improved various humoral and cellular immune activities, including lysozyme activity [92]. Furthermore, *Bacillus subtilis* controls lysozyme activity and reduces the negative effects of salinity stress on Nile tilapia [127].

5.4. Bacillus Probiotics Modulate the Respiratory Burst Process

Bacillus probiotics can modify the respiratory burst process in Nile tilapia; the respiratory burst process is a natural defense mechanism used by fish to defend themselves against pathogens and other environmental stressors [82]. *Bacillus* probiotics can influence the respiratory burst process in Nile tilapia by generating antioxidant molecules.

These molecules help to reduce reactive oxygen species (ROS) production by cells, hence minimizing the amount of oxidative damage that occurs [52]. Compared to the control group, Nile tilapia fed a diet containing *Bacillus subtilis* strain NZ86 for 51 days displayed increased respiratory burst activity [37]. However, the period of *Bacillus* probiotic feeding required to boost particular immunological parameters varies between *Bacillus* probiotic strains and aquatic species. When tilapia juveniles were fed *Bacillus pumilus* AQAHBS01 (1×10^7–10^9) for 14 days, respiratory burst activity was significantly enhanced [53], but no differences were found during feeding with *Bacillus safensis* NPUST1 strains for 8 weeks [48].

Furthermore, Liu et al. [92] found that no significant differences in respiratory burst activity were detected between two strains of *Bacillus subtilis* and *Bacillus licheniformis* during the feeding of Nile tilapia over 4 weeks. To decide the optimal feeding duration for Nile tilapia probiotics, further research is required to determine the benefits of short- and long-term administration, as well as the attributes and dosage of cultured strains.

5.5. Bacillus Probiotics Improve Complement Activity

Complement activity is a type of immune response triggered when the body detects the presence of a foreign substance, such as a virus or pathogenic bacteria [128,129]. In Nile tilapia, *Bacillus* probiotics have been found to improve complement activity by increasing the production of proteins (complement factors), which help to identify and target foreign substances [130]. Nile tilapia diet containing *B. amyloliquefaciens*, *B. licheniformis*, *B. pumilus* AQAHBS01, and *Pediococcus pentosaceus* PKWA-1 and *B. subtilis* BA04 showed increased complement-mediated hemolysis [20,82].

In multiple investigations, tilapia fed diets containing *B. amyloliquefaciens*, *B. licheniformis*, *Bacillus pumilus* AQAHBS01, and *Pediococcus pentosaceus* PKWA-1 and *B. subtilis* BA04 showed higher complement-mediated hemolytic activity [53]. Nevertheless, feeding *Bacillus subtilis* O14VRQ and *Bacillus* spp. KUAQ1 to Nile tilapia failed to increase serum complement levels [37,82].

A two-experiment study by Ridha and Azad [131] found that only adult Nile tilapia had high serum complement activity after consumption of *Bacillus subtilis* in the diet; thus, divergent findings highlight the value of thoroughly investigating how probiotics affect Nile tilapia's immune response and growth.

5.6. *Bacillus Probiotics Stimulate Immune-Related Gene Expression*

The effects of *Bacillus* probiotics on the expression of immune-related genes in Nile tilapia have been studied in various studies [98]. A significant increase in cytokine and chemokine expression was observed in Nile tilapia fish treated with *Bacillus* probiotics (*B. amyloliquefaciens*, *B. subtilis*, and *B. licheniformis*) [132–134]. Nile tilapia express immune-related genes in response to multiple pathogens, including pro-inflammatory and anti-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-8 (IL-8), interferon (IFN), tumor necrosis factor (TNF), and interleukin-10 (IL-10) [99,135]. Pro-inflammatory and anti-inflammatory cytokines are proteins released by various cells in the fish parts that contribute to defense in the presence of bacteria colonization or invasion.

The balance of cytokine expression is a major component in determining the immune response to *Bacillus* probiotics [135]. In Nile tilapia fed diets containing both *B. subtilis* and *B. licheniformis*, C-lysozyme, heat shock protein 70 (HSP70), transforming growth factor beta (TGF-), defensin and small body size decapentaplegic homolog 3 (SMAD3) were upregulated in the mid-intestine and head kidney [54,103,136,137].

DAMPs also promote the host's defense mechanisms, as shown by elevated HSP70, IL-1, IFN-gamma, and tumor necrosis factor (TNF) expression in Nile tilapia fed diets containing *Bacillus subtilis* WB60 or *Lactococcus lactosis* [100]. In Nile tilapia diets containing *Bacillus licheniformis* HGA8B, IL-10 demonstrated anti-inflammatory effects, suggesting that the host may have developed tolerance to the probiotic as it is not perceived as a threat [99].

A study in Nile tilapia showed increased cytokine IL-10 in the intestine after administration of *Bacillus* probiotics (*B. licheniformis* and *B. subtilis*) [51,54,135]. As molecular chaperones, heat shock proteins (HSPs) (HSP60, HSP70, and HSP90 families) interact with proteins to prevent them from aggregating, refold polypeptides, and repair or denature proteins in altered or denatured states [10,138]. In aquatic species, HSP70s are considered the most helpful biomarkers of infection due to their wide range of expression [139].

During stressful conditions, fish secrete significant amounts of HSP70, which may boost protein integrity and reduce apoptosis [81,98,138]. Fish have been found to express less HSP70 in some studies, but Nile tilapia exhibit the opposite trend in numerous in-vivo studies. In general, suppression of HSP70 gene expression by probiotics is associated with a reduction in growth rate and survival [137,140].

6. *Bacillus* Probiotics Regulate Antioxidant Enzyme Activity

Bacillus probiotics (such as *B. subtilis*) have been proven to help regulate the antioxidant enzyme activity of Nile tilapia farm operations. The antioxidant enzymes in fish help break down the hazardous compounds in the water and prevent the detrimental effects of free radicals (Table 1) [141]. It has been shown that *Bacillus* probiotics can significantly reduce oxidative stress in various health problems that are exacerbated by oxidative stress [142].

Many aerobic cellular functions generate reactive oxygen species, and their concentration is determined by their synthesis and elimination by the antioxidant system [143]. Numerous antioxidants are found in cells and are involved in maintaining ROS levels at low levels, preventing oxidative damage, and preventing the onset of several diseases [144]. A variety of fish species, including Nile tilapia, contain antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [100,145]. Antioxidant enzyme activities are frequently utilized as functional criteria for assessing Nile tilapia immune responses [26].

Bacillus subtilis, *Bacillus coagulans* [139], and *Bacillus cereus* [26] added to Nile tilapia rearing systems increased SOD activity. A similar rise in SOD activity was seen when *Bacillus paralicheniformis* SO1 was added to tilapia diets [140]. In the fish's liver and intestines, SOD, CAT, and GPx levels are increased, indicating an enhanced ability to fight disease. Fish probiotics, including *Bacillus* spp., have been linked to an increase in antioxidant enzymes in various fish, including tilapia [99,142,146–148].

7. Conclusions and Future Perspectives

This review summarizes current knowledge about the beneficial effects of *Bacillus* probiotics on Nile tilapia (*Oreochromis niloticus*) immunity at various life stages, highlighting several areas in need of further investigation. This review provides compelling evidence that the administration of *Bacillus* probiotics can alter Nile tilapia's immunity by strengthening the gut barrier's defense mechanisms, thereby preventing the development of several diseases. According to the findings, probiotic bacteria can modify and strengthen Nile tilapia's immune system through a variety of mechanisms. Academicians, scientists, producers, and fish industry owners must investigate the specific aspects of bacteria–host interactions conferring favorable changes in diverse immune responses to offer clinically effective, bacteria-based strategies to support aquaculture's health, production, and economic growth. There is also potential for future research to investigate the co-administration of *Bacillus* probiotics with prebiotics, multiple-species probiotics, pulse-feeding tactics, and encapsulating techniques to preserve *Bacillus* probiotics throughout treatment.

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