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# Probiotics and paraprobiotics in aquaculture: a sustainable strategy for enhancing fish growth, health and disease prevention—a review

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This review delves into the increasing interest in probiotics and paraprobiotics as a viable alternative to antibiotics in aquaculture, highlighting their potential to enhance fish health and prevent diseases. As the aquaculture industry continues its global expansion, addressing the challenges associated with disease outbreaks in high-density fish populations becomes imperative. The review underscores the promising role of probiotics and paraprobiotics as a sustainable strategy to mitigate these challenges. The diverse positive impacts of various probiotic strains such as *Arthrobacter*, *Bacillus*, *Lactobacillus*, *Bifidobacterium*, *Clostridium*, and others emphasize their roles in enhancing growth, resistance to diseases (including bacterial, viral, and parasitic infections), stress reduction, water quality management, and environmental sustainability. Challenges such as stability, host specificity, and regulatory considerations must be addressed to optimize the use of probiotics in aquaculture. Additionally, paraprobiotics, or non-viable microbial cells, present a safer alternative to the criticized antibiotics and even live probiotics in environments where microbial viability poses a risk. These inactivated cells retain the ability to modulate the immune system and improve gut health, offering a promising complementary approach to fish disease prevention. The review advocates for a systematic approach combining research, innovation, and collaboration to effectively integrate probiotics and paraprobiotics into fish farming practices. Furthermore, the mechanisms by which probiotics and paraprobiotics modulate gut microbiota, produce antimicrobial compounds, and strengthen fish's immune system have been elucidated. Moreover, the practical applications of probiotics in fish farming, including optimal administration methods and the challenges and limitations faced by the industry, have been discussed. Emphasis on the importance of continued research to explore new probiotic and paraprobiotic

strains and develop innovative delivery systems to ensure the sustainability of aquaculture has been discussed. By enhancing fish health, reducing the need for antibiotics, and improving water quality, probiotics, and paraprobiotics contribute to more sustainable and environmentally responsible aquaculture operations.

#### KEYWORDS

probiotics, paraprobiotics, bacteriocins, disease resistance, probiogenomics, sustainable aquaculture, gut microbiota modulation

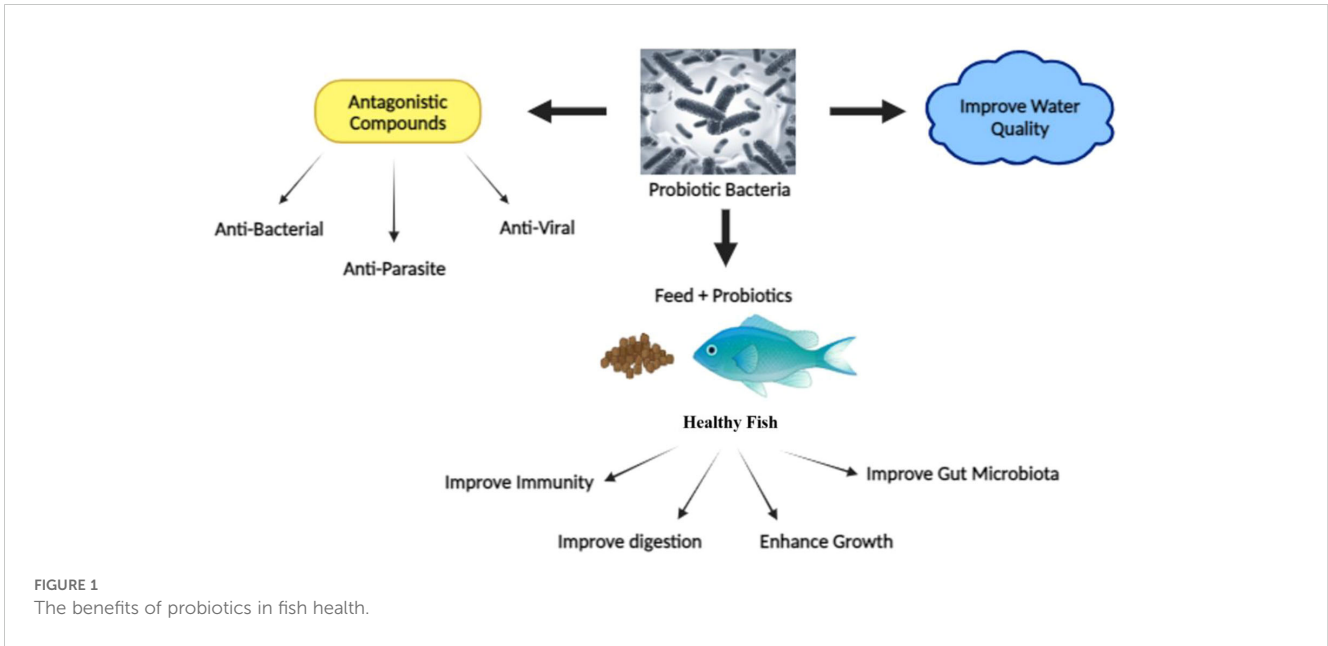
## 1 Introduction

Aquaculture stands as the swiftest expanding sector in animal production globally, trading around 160 million tons of farmed fish valued at US\$80 billion annually (Loh et al., 2020). This trend accelerates, notably with high-value demersal fish species such as grouper, barramundi, snapper, and pompano (FAO, 2014). The aquaculture industry faces a significant setback due to disease outbreaks among aquatic species, resulting from the necessity of high stocking densities to meet the escalating fish demand (Abarike et al., 2018). Antibiotics, vaccines, and other prophylactic mechanisms have been widely employed for disease management in aquaculture. The widespread use of antibiotics in treating infections creates selective pressure for antibiotic resistance, a trait that could be transferred to other bacteria. It is widely acknowledged that administering antibiotics to finfish and shellfish potentially causes adverse effects on the host organisms and humans. This understanding led the European Union to prohibit antibiotic use in 2003. As an alternative approach to using antibiotics, vaccines, and chemicals in treating diseases, probiotics and paraprobiotics have emerged due to their eco-friendly and immune-based prevention attributes in aquaculture (Ringo, 2020). As antibiotics face limitations as growth promoters in the livestock and aquatic industries across many countries, the utilization of probiotics is rising, emerging as a viable alternative (Kwoji et al., 2021).

Probiotics are recognized for their positive impacts on health and have become established as dietary supplements, well-known for their multitude of health benefits (Mishra et al., 2015). The World Health Organization (WHO) and Food and Agricultural Organization (FAO) defines probiotics as “live microorganisms that, when taken in sufficient quantities, provide health advantages to the host (Wang et al., 2019). Over time, a range of probiotic species from the bacteria genus *Arthrobacter*, *Bacillus*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Micrococcus*, *Pediococcus*, *Aeromonas*, *Burkholderia*, *Enterobacter*, *Pseudomonas*, *Rhodopseudomonas*, *Roseobacter*, *Shewanella*, and *Clostridium butyricum* have been identified and applied to boost the growth and immune capabilities of various aquaculture species (Kuebutornye et al., 2019; Tran et al., 2020a). Probiotics encompass nonpathogenic species like those from the

*Saccharomyces*, *Streptococcus*, and *Lactococcus* classes. Their beneficial effects on the host can be either direct or indirect, involving improved barrier function, modulation of the mucosal immune system, synthesis of antimicrobial substances, bolstered food digestion and absorption, and changes to the intestinal microflora (Hemaiswarya et al., 2013). Meanwhile, microbial organisms employed as probiotics or under assessment as potential probiotics in Chinese aquaculture hail from diverse taxonomic divisions, encompassing Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, and yeast (Wang et al., 2019). Probiotics have shown an ardent ability to improve fish’s health and welfare by aiding disease resistance, enhancing growth, reducing stress, managing water quality, and improving reproduction (Indriyani Nur, 2019) (Figure 1). The effectiveness of probiotics in fish can vary based on factors such as the specific probiotic strain used, fish species, environmental conditions, dosage, and method of administration (Nayak, 2010).

Probiotics’ beneficial effects are not limited to their living cells. Alongside probiotics, paraprobiotics (also known as ghost probiotics) are non-viable microbial cells that confer health benefits to the host (Taverniti and Guglielmetti, 2011; Monteiro et al., 2023). They have recently gained much attention due to their potential role in aquaculture. Paraprobiotics are considered a safer alternative to live probiotics, especially in environments where the viability of microorganisms may pose a risk. They retain the ability to modulate the immune system, produce bioactive compounds, and improve gut health, similar to live probiotics (Taverniti and Guglielmetti, 2011; Vallejo-Cordoba et al., 2020; Monteiro et al., 2023). The use of paraprobiotics can be particularly advantageous in aquaculture settings where the stability and safety of microbial supplements have critical concerns (Nayak, 2010). Paraprobiotics are defined as “inactivated (non-viable) microbial cells, which, when administered in sufficient amounts, confer benefit to consumers.” This description resembles that of probiotics defined by the FAO/WHO with slight adjustments (Aguilar-Toalá et al., 2018; Siciliano et al., 2021). Numerous studies have demonstrated that dead probiotic cells can also elicit various biological responses. Research has consistently shown that products containing both viable and non-viable cells can produce beneficial biological responses (Thakur et al., 2016; Bajpai et al., 2018). Paraprobiotics, derived from heat-



inactivated cells, can be utilized to boost immune responses and exhibit immunomodulatory activities. The components of dead cells have been found to exhibit anti-inflammatory properties in the gastrointestinal tract (GIT). Interestingly, both live and dead probiotics have been shown to exert specific actions (Adams, 2010; de Almada et al., 2016; Akter et al., 2020). Probiotic bacteria can be rendered inactive using various techniques, including sonication, heat, chemicals, and gamma or ultraviolet (UV) radiation. The most commonly used technique among them is heat inactivation. In some circumstances, the heat-inactivation method may be safer than other inactivation techniques like UV-inactivation. These techniques kill microorganisms, and each one has a unique inactivation mechanism. The probiotic microorganisms' beneficial qualities ought to be preserved in paraprobiotics through the inactivation process (Choudhury and Kamilya, 2019; Tran et al., 2022). Paraprobiotics' health-promoting benefits are illustrated in Figure 2.

Probiotics and paraprobiotics stand out as safe supplements that enhance host health by boosting growth, offering nutrition, regulating microbial presence, fortifying immune responses, optimizing feed utilization, bolstering digestive enzyme activity and efficiency, reducing stress, refining water quality, and managing diseases (Selim and Reda, 2015) (Figure 1). Both probiotics and paraprobiotics offer sustainable, environmentally friendly solutions for enhancing fish health and disease resistance, making them essential components in modern aquaculture practices (Indriyani Nur, 2019).

The application of probiogenomics in aquaculture represents a cutting-edge approach to enhance the effectiveness of both probiotic and paraprobiotic strategies in fish health management. This emerging field combines genomic technologies with probiotic and paraprobiotic research to elucidate the molecular mechanisms underlying probiotic-host interactions, facilitating the development of more potent and targeted probiotic strains (Pérez-Sánchez et al., 2014). Probiogenomics enables researchers to identify and screen

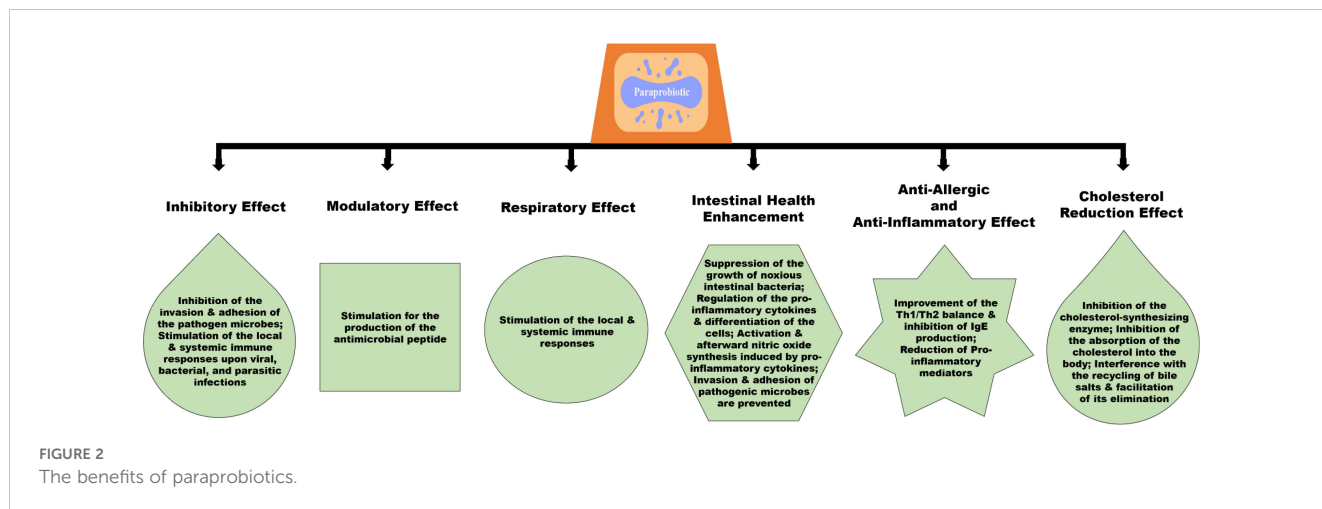
potential probiotic candidates more efficiently, focusing on strains with specific genetic traits that confer beneficial effects on fish health and growth (Ringø et al., 2018). This approach has also revolutionized the development of commercial probiotics/paraprobiotics by allowing for the selection of strains with enhanced stability, functionality, and host-specificity. Then, probiogenomics provides valuable insights into optimizing probiotic dosages and formulations for different fish species, as the efficacy of probiotics in disease prevention can vary significantly depending on the concentration and the target species (Hoseinifar et al., 2018). By leveraging probiogenomic approaches, aquaculturists can develop more effective, species-specific probiotic/paraprobiotic solutions to improve fish health, growth performance, and disease resistance in aquaculture systems.

This review aims to explore the protective effects of probiotics and paraprobiotics in fish, outline some of the main functions performed by these beneficial microorganisms in aquaculture, and discuss the advancements in probiogenomics that are shaping the future of biotic applications in the aquaculture industry.

## 2 Candidate probiotics and paraprobiotics and screening methods

### 2.1 Bacterial candidates commonly used as probiotics and paraprobiotics

Probiotic candidates in fish are typically isolated from the fish's digestive system, rearing water, sediments in culture tanks, or other sources. These candidates are then evaluated for their probiotic properties via *in vitro* (such as antimicrobial activity, acid and bile tolerance, and adhesion ability) and *in vivo* functional assays (Ringø et al., 2018). The selection of probiotics varies greatly from one fish species to another to properly maintain the good-to-bad ratio of bacteria in the gut mucosal surface (Han et al., 2015). Unlike live



probiotics, paraprobiotics do not pose the same risks associated with live bacteria, such as the potential for gene transfer or environmental persistence. Paraprobiotics have been shown to elicit similar beneficial effects as probiotics, including immune modulation, enhancement of barrier function, and production of bioactive compounds (Taverniti and Guglielmetti, 2011). These properties make paraprobiotics a viable alternative, especially in conditions where the stability and safety of live microorganisms might be compromised. Several bacterial candidates have been tested for probiotic and paraprobiotic potential, including *Bacillus* sp., *Micrococcus* sp., *Enterococcus* sp., *Phaebacter* sp., *Shewanella* sp., *Lactobacillus* sp., and *Pseudomonas* sp (Lobo et al., 2014). These microorganisms have been shown to improve fish health, growth performance, and survival rates, as well as enhance the expression of several immunological factors and reduce the pathogen load to the gut mucus layer (Banerjee and Ray, 2017). They can also contribute to nutrient enhancement in the host, such as increasing crude lipid, total protein, and body weight in Nile tilapia (*Oreochromis niloticus*) fed with the probiotic strain of *Lactobacillus* sp (Hamdan et al., 2016). These microorganisms, whether viable or non-viable, have beneficial effects on the gut of aquatic animals in the digestion of dietary nutrients as well as in the production of energy (Ringø et al., 2018). The integration of paraprobiotics into aquaculture is still emerging, but their potential to control different physiological activities of aquatic organisms and provide similar benefits to live probiotics is promising. Several probiotics, such as *Aeromonas media* (e.g., strain A199), *B. subtilis*, *Lactobacillus helveticus*, *Enterococcus faecium*, *Carnobacterium inhibens*, are considered to be significantly effective at present (Lakshmi et al., 2013). Apart from these discussed laboratory-based probiotics, various experimentally approved commercial probiotics, and paraprobiotics are also available on the market that is also effective in aquaculture (Table 1).

## 2.2 Screening methods used in the determination of potential probiotics

Screening probiotics for use in fish aquaculture is a crucial process involving multiple steps to ensure the safety and efficacy of

the potential probiotic strains. The initial phase typically begins with isolating microorganisms from various sources, including the GIT of healthy fish, aquatic environments, and fermented products (Amoah et al., 2024; Merrifield et al., 2010). These isolates are then subjected to a series of *in vitro* tests to evaluate their potential probiotic properties. Common screening criteria include the ability to survive and grow under conditions similar to those found in the fish gut, such as low pH and the presence of bile salts (Vine et al., 2004). Additionally, potential probiotics and paraprobiotics should exhibit antagonistic activity against known fish pathogens, which is often assessed through methods like agar well diffusion or co-culture assays (Newaj-Fyzul et al., 2014). Screening *in vitro* involves evaluating the adherence capacity of the potential probiotics to fish intestinal mucus or cell lines, as this property is considered essential for colonization and persistence in the host gut (Balcázar et al., 2008). In the case of paraprobiotics, the focus is on their ability to modulate immune responses and produce bioactive compounds even in their non-viable state (Adams, 2010). The production of beneficial compounds, such as digestive enzymes, vitamins, or antimicrobial substances, is also assessed during this stage. Safety considerations are paramount, and potential probiotics are screened for antibiotic resistance to ensure they do not contribute to the spread of antibiotic-resistance genes in aquatic environments (Pérez-Sánchez et al., 2014). The absence of virulence factors and toxin production is verified to guarantee the safety of the probiotic candidates for the host fish and human consumers.

Following successful *in vitro* screening, promising probiotic and paraprobiotic candidates undergo *in vivo* evaluation in target fish species. These trials assess their effects on fish growth performance, feed utilization, immune response, and disease resistance (Ringø et al., 2018). Growth parameters such as weight gain, specific growth rate (SGR), and feed conversion ratio (FCR) are commonly measured. Immune parameters, including lysozyme activity, phagocytic activity, and expression of immune-related genes, are evaluated to determine their immunomodulatory effects (Hoseinifar et al., 2015b). Challenge tests against common fish pathogens are conducted to assess the protective effects of the probiotic treatment. Additionally, the impact of the probiotic on gut microbiota composition and intestinal morphology is often

TABLE 1 Commercial probiotics and paraprobiotics available on the market for aquaculture production.

Product Name	Company (Country)	Composition	Beneficial Effects	References
<b>•Paraprobiotics</b>				
Hilyses®	ICC (Brazilia)	<i>Saccharomyces cerevisiae</i>	Enhanced immune response, improves digestive health, boosts growth performance, reduces stress, increases disease resistance, and supports gut microbiota balance in fish	(Araújo et al., 2015)
LAC-Shield™	Morinaga Milk Industry (Japan)	Heat-killed <i>Lactocaseibacillus paracasei</i> MCC1849	Modulated the fish's immune system and helps fight bacterial infections.	(Murata et al., 2018; Lensch et al., 2024)
Staimune®	Ganeden (United States)	Heat-killed <i>Heyndrickxia coagulans</i> (previously <i>Bacillus coagulans</i> )	Enhanced growth, immune response, and disease resistance in fish	(Endres et al., 2009; James et al., 2021; Lensch et al., 2024; Omar et al., 2024)
Lacteo® diarrhEase™	Lacteol (French)	Heat-killed <i>Lactobacillus acidophilus</i> LB cells	Improved growth performance, increased antioxidant capacity, and strengthen the immune system in various fish species	(Lievin Moal, 2016; Ringo et al., 2018; Barui et al., 2024; Lensch et al., 2024)
<b>•Probiotics</b>				
Epicin	Epicore Bionetworks Inc (United States of America)	<i>Bacillus</i> spp., <i>Pediococcus</i> spp., <i>Enterococcus</i> spp.	Improved water quality, enhanced growth, better disease resistance	(Balcázar et al., 2006)
AlCare	Alpharma Inc (United States of America)	<i>Bacillus licheniformis</i> , <i>B. subtilis</i>	Enhanced growth, improved feed conversion, better disease resistance	(Merrifield et al., 2010)
Levucell	Lallemand Animal Nutrition (France)	<i>Saccharomyces cerevisiae boulardii</i>	Improved growth, enhanced immune response, better stress tolerance	(Tovar-Ramírez et al., 2010)
Sanolife PRO-F	INVE Aquaculture (Belgium)	<i>Bacillus subtilis</i> , <i>B. licheniformis</i> , <i>B. pumilus</i>	Improved feed conversion, enhanced survival rates, better water quality	(van Hai and Fotedar, 2010)
EcoProAqua	Keeton Industries (United States of America)	<i>Bacillus subtilis</i> , <i>B. licheniformis</i> , <i>B. megaterium</i> , <i>Pediococcus acidilactici</i>	Improved growth, enhanced immune function, better water quality	(Nayak, 2010)
Bioplus	Chr. Hansen (Denmark)	<i>Bacillus subtilis</i> , <i>B. licheniformis</i>	Enhanced growth performance, improved feed utilization, better disease resistance	(Ridha and Azad, 2012)
Protexin Aquatech	Probiotics International Ltd (United Kingdom)	Multi-strain mix including <i>Bacillus subtilis</i> , <i>Lactobacillus rhamnosus</i> , <i>Enterococcus faecium</i>	Enhanced growth, improved disease resistance, better water quality	(Mohapatra et al., 2012)
AquaStar	Biomin (Austria)	<i>Bacillus subtilis</i> , <i>Enterococcus faecium</i> , <i>Lactobacillus reuteri</i> , <i>Pediococcus acidilactici</i>	Improved larval survival, enhanced immune response, better growth performance	(Azimirad et al., 2016)
Bactocell	Lallemand Animal Nutrition (France)	<i>Pediococcus acidilactici</i>	Improved feed efficiency, enhanced immune response, better digestibility	(Hoseinifar et al., 2015a)
Efinol	Bentoli Agrinutrition (United States of America)	<i>Bacillus subtilis</i> , <i>Pediococcus acidilactici</i> , <i>Saccharomyces cerevisiae</i>	Enhanced growth, improved feed efficiency, better stress tolerance	(Hauville et al., 2016)
Ecobiol	Evonik (Germany)	<i>Bacillus amyloliquefaciens</i> CECT 5940	Improved gut health	(Casillas-Hernández et al., 2023)

(Continued)

TABLE 1 Continued

Product Name	Company (Country)	Composition	Beneficial Effects	References
<b>•Probiotics</b>				
Biogut	Varsha Group (India)	<i>Lactobacillus sporogens, Lactobacillus acidophilus, Bacillus subtilis, Bacillus licheniformis and Saccharomyces cerevisiae</i>	Improves survival, resistance to disease, and immune system against white muscle disease.	(Pavadi et al., 2018)
Toyocerin	Rubinum (Spain)	<i>Bacillus cereus var. toyoi</i>	Encourage growth, boost specimen homogeneity, and enhance intestinal mucosa	(Abdulmawjood et al., 2019)
Agrimos	Lallemand Animal Nutrition (Denmark)	<i>Saccharomyces cerevisiae</i>	Enhanced animal performance and balance of microbiota while preserving gut integrity.	(Mohamed et al., 2017)

examined using molecular techniques and histological analysis (Carnevali et al., 2017).

The final stages of probiotic screening involve assessing the technological properties of the selected strains, such as their ability to survive processing conditions, storage stability, and ease of administration in aquaculture settings (Merrifield et al., 2010). Factors like temperature tolerance, oxygen requirements, and compatibility with feed ingredients are considered to ensure the practical application of the probiotic in fish farming. It is important to note that the efficacy of probiotics can vary depending on factors such as fish species, developmental stage, and environmental conditions. Comprehensive evaluations under different scenarios are necessary to determine the most suitable

probiotic strains for specific applications in aquaculture (Dawood et al., 2018). Some studies have demonstrated that the heterogeneous expression of probiotic bacteria in fish can increase intraepithelial lymphocytes, acidophilic granulocytes, and bactericidal activity specific to fish. As research advances, new screening methodologies, including high-throughput sequencing and omics approaches, are being incorporated to provide a more comprehensive understanding of probiotic-host interactions and identify novel probiotic candidates with enhanced benefits for fish health and aquaculture production. The strategy for selecting probiotics for commercial use is shown in Figure 3. A list of probiotics and paraprobiotics currently available on the market has been provided in Table 1.

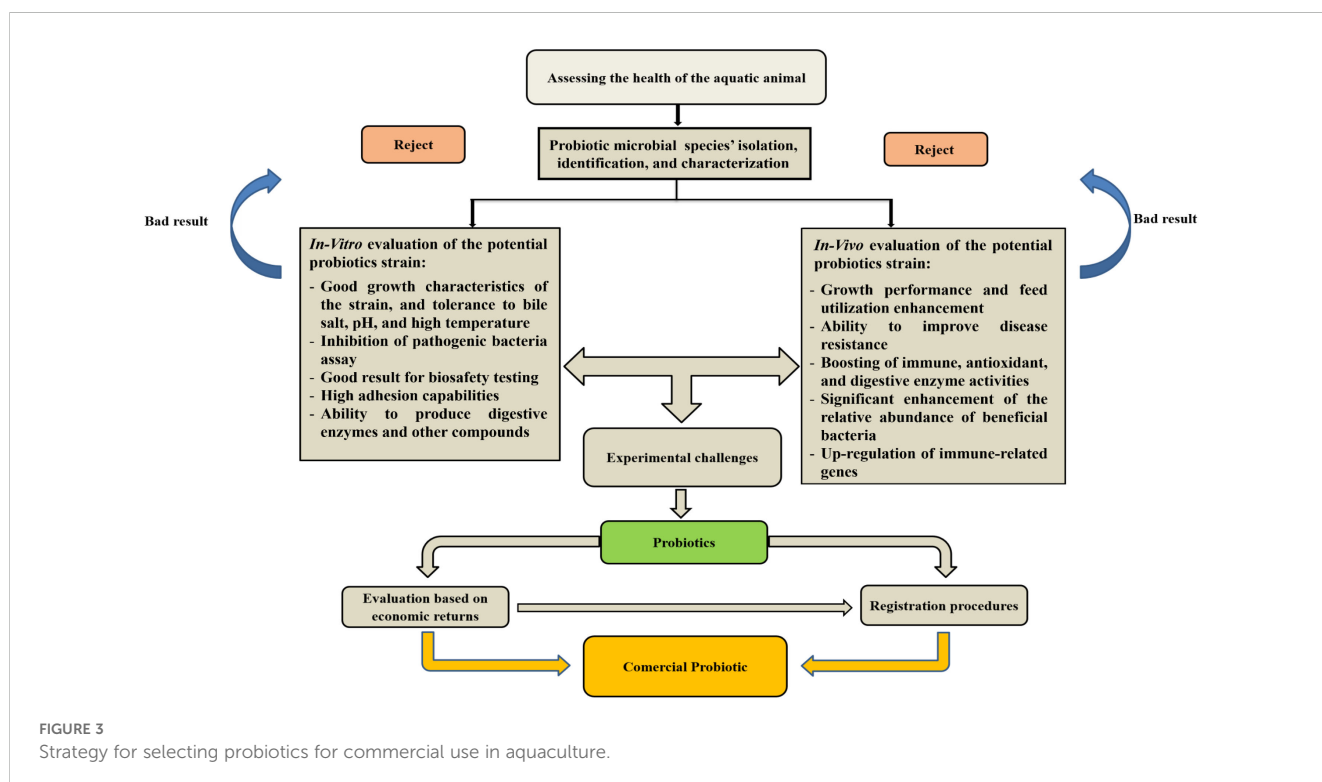


FIGURE 3 Strategy for selecting probiotics for commercial use in aquaculture.

## 3 Mechanisms of action of probiotics and paraprobiotics in fish

### 3.1 Gut microbiota modulation

Gut microbiota modulation refers to the alteration or management of the microorganisms residing in the GIT to achieve a desired outcome. This modulation can be achieved through various means, including supplementing probiotics and paraprobiotics. The supplementation of *Bacillus cereus* and *Geotrichum candidum* probiotics in *Labeo rohita* fish resulted in the detection of a lower relative abundance of *Trichosporon* and *Cryptococcus* and even an absence of opportunistic pathogenic strains (*Staphylococcus saprophyticus* and *Sporobolomyces lactosus*) in the gut as compared to the control group (Ghori et al., 2022). Using paraprobiotics as a food carrier in a carbohydrate matrix can be a far more promising way to enhance gut modulation than incorporating them directly into foods or protein-rich diets. Adding paraprobiotics increased the prevalence of beneficial bacterial genera, including *Lactobacillus*, *Bifidobacterium*, and *Ruminococcus*, which are known for their positive roles in gut health. In contrast, the genera *Corynebacterium* and *Plesiomonas*, which are less associated with gut health benefits, were less prevalent after paraprobiotic supplementation (Yolmeh et al., 2024).

Fish share a notably intimate connection with their surrounding environment. Contrasts between land and water species are evident in how their intestinal microbiota interacts with their surroundings. Different fish species also have a wide range of GIT morphology differences (Denev et al., 2009). Aquatic animals regularly encounter potential pathogens during osmoregulation and feeding. Unlike terrestrial animals, the bacterial makeup in the GIT of aquatic animals spurred the development of the probiotic concept. While humans and land-based livestock undergo embryonic development protected within an amnion, fish and shellfish release their larvae into the external environment early in their life cycle. These vulnerable larvae, despite their underdeveloped digestive tracts, begin feeding at an earlier age, exposing them to a heightened risk of gastrointestinal microbiota-related issues (Lara-flores, 2011). An imbalanced fish gut microbiota with heightened bad bacteria can result in decreased metabolism, stunted growth, stress, and the onset of diseases. The influence of gut microbiota on fish physiology heavily relies on the specific composition of microbial communities within the gut, largely shaped by their diet (Ghori et al., 2022). In tilapia, alterations in the gastrointestinal microbiota corresponded with the stimulation of the endocrine system, leading to intensified expression of insulin-like growth factor system genes, showcasing the microbiota's influence on fish development by regulating gene expression and organ function in intestinal epithelial cells (Haque et al., 2022; Luan et al., 2023). Understanding the intricate bacterial makeup through advanced sequencing techniques is pivotal in precisely modifying these communities and enhancing fish health and productivity. Manipulating fish gut microbiota using prebiotics, antibiotics, and probiotics offers a further exploration of their role. Emerging dietary elements, particularly prebiotics, and synbiotics as

supplementary feeds aside from probiotics and paraprobiotics, regulate fish physiology, growth, and overall health. Researchers are increasingly focusing on these additives due to their direct impact on the gut microbiome in fish (Ghori et al., 2022).

Some researchers have suggested that combining probiotics and paraprobiotics might offer synergistic benefits to animals, including fish. For example, a recent work by Yuhana et al. (2024) explored the effects of euryhaline probiotic and paraprobiotic *B. cereus* BR2 on African catfish. The experiment, which involved the supplementation of 1% (w/w) dose of probiotics and paraprobiotics at a cell density of  $10^8$  and  $10^{10}$  CFU/mL revealed a significant enhancement in the growth performance (survival rate, final weight, FCR, and SGR), digestive enzyme (protease, amylase, and lipase) activities, immune-related genes (IL-1 $\beta$  and MHC-2 $\beta$  expression), and resistance to *Edwardsiella tarda* ETS1.1 in the treated group contrast to the results obtained in the control group. Another study by Meng et al. (2023) showed that combining live and inactivated *Lactobacillus rhamnosus* enhanced gut microbiota diversity and nutrient absorption in common carp (*Cyprinus carpio*).

Probiotics actively colonize the gut and interact with the host's microbiome and immune system, whereas paraprobiotics modulate the gut environment through their cellular components, such as peptidoglycans, lipoteichoic acids, and metabolites, without colonizing the gut.

### 3.2 Production of antimicrobial compound

In general, microbial populations release substances that can kill or slow the growth of other microbes, shaping how they compete for resources like chemicals and energy (Verschuere et al., 2000). These substances in the host's gut, surfaces, or environment create a defense against opportunistic pathogens. The antibacterial effect of bacteria is attributed to several factors, including the production of antibiotics (Williams and Vickers, 1986), siderophores (Sugita et al., 2012), bacteriocins (Vandenbergh, 1993), and changes in pH through the release of organic acids (Sugita et al., 1997). For example, according to Sugita et al. (2012), probiotic strains such as *Photobacterium leiognathi*, *Vibrio scophthalmi*, and *Enterovibrio norvegicus* were noted to produce siderophore inhibitory substances against some pathogenic bacteria. Again, Banerjee and Ray (2017) also reported that *Bacillus subtilis* strain LR1 produces bacteriocins that inhibit pathogens, including *Aeromonas hydrophila*, *Aeromonas salmonicida*, *Bacillus mycoides*, and *Pseudomonas fluorescens*. Also, Feliatra et al. (2018) reported that *Bacillus thuringiensis* as a probiotic strain H4, produces bacteriocins that inhibit pathogens, including *Pseudomonas stutzeri* (Feliatra et al., 2015). As shown in laboratory studies, bacteriocins (Table 2) can inhibit pathogen replication using small-molecule compounds (Cavera et al., 2015; Heilbronner et al., 2021; Soltani et al., 2021; Retnaningrum, 2024). Leading this category are short-chain fatty acids (SCFAs) like lactic acid, alongside hydrogen peroxide, showing similar inhibitory effects. Within Lactobacilli, both low-molecular-weight bacteriocins (LMWB) and high-molecular-weight bacteriocins (class III) are produced. LMWB, classified as

TABLE 2 Classes of bacteriocins.

Classes	Characteristic features	Bacteriocins produced	Common producer organism	References
<b>Class I</b>	<b>Post-translationally modified peptides</b>			
Subclass I.1	Single-peptide, elongated lantibiotics	Subtilin, ericin S, ericin A	<i>B. subtilis</i>	(Parisot et al., 2008)
Subclass I.2	Other single-peptide lantibiotics	Sublancin 168, mersacidin, paenibacillin	<i>B. subtilis</i>	(Dubois et al., 2009)
Subclass I.3	Two-peptide lantibiotics	Haloduracin, lichenicidin	<i>B. halodurans</i>	(Lawton et al., 2007)
Subclass I.4	Other post-translationally modified peptides	Subtilosin A	<i>B. amyloliquifaciens</i>	(Sutyak et al., 2008)
<b>Class II</b>	<b>Non-modified peptides</b>			
Subclass II.1	Pediocin-like peptides	Coagulins, SRCAM 37, SRCAM 602, SRCAM 1580	<i>B. coagulans</i>	(Le Marrec et al., 2000)
Subclass II.2	Thuricin-like peptides	Thurincin H, thuricin S, thuricin 17, bacthuricin F4, cerein MRX1	<i>B. thuringiensis</i>	(Gray et al., 2006)
Subclass II.3	Other linear peptides	Cerein 7A, cerein 7B, lichenin, thuricin 439	<i>B. cereus</i>	(Osc�ariz and Pisabarro, 2000)
Class III	Large proteins	Megacin A-216, megacin A-19213	<i>B. megaterium</i>	(Kiss et al., 2008)
Class IV	circular structure, unique and versatile antimicrobial peptides	AS-48, Gassericin A, Reuterin 6, Acidocin B, Butyriovibriocin AR10, Uberolysin, Circularin A	<i>Enterococcus faecalis</i> S-48, <i>Lactobacillus gasseri</i> LA39, <i>Lactobacillus reuteri</i> LA6, <i>Lactobacillus acidophilus</i> M46, <i>Butyriovibrium fibrisolvans</i> AR10, <i>Streptococcus uberis</i> 42, <i>Clostridium beijerinckii</i> ATCC 25752	(Galvez et al., 1986; Toba et al., 1991; Leer et al., 1995; Kalmokoff and Teather, 1997; Kawai et al., 1998; Kawulka et al., 2003; Kemperman et al., 2003; Wirawan et al., 2007)

antimicrobial peptides, fall into three categories: class I lantibiotics (featuring posttranslationally modified peptides with unique amino acids like lanthionine), class II (heat-stable non-lantibiotics), and class IV (cyclic antimicrobial peptides) (Maqueda et al., 2008; Oelschlaeger, 2010). Acetic and lactic acid, among other organic acids, exhibit potent inhibition against gram-negative bacteria, making them key antimicrobial components in probiotics. These acids penetrate bacterial cells in their undissociated form, where they later dissociate within the cytoplasm. This process may cause a decrease in intracellular pH or accumulation of the acid’s ionized form, potentially resulting in pathogen death (Bermudez-Brito et al., 2012). Several bacterial species including *Blautia* spp., *Bifidobacterium* spp., and *Clostridium* spp. (*Clostridium butyricum* and *Clostridium lactatifermentans*) are reported to be involved in SCFA production (organic acids such as propionic and butyric acid), significant in enhancing the growth performance, intestinal health (enhancing the morphology (intestinal mucosal thickness, goblet cell counts, villi length), and gut microbial community and diversity), immune responses, and antioxidant activities (such as increase in total-superoxide dismutase, superoxide dismutase, glutathione peroxidase, and catalase) (Tran et al., 2020b; 2023).

Lactic acid bacteria, known for producing bacteriocins, often inhibit the growth of other microorganisms, primarily gram-positive ones (Timothy et al., 2021; Fernandes and Jobby, 2022). While most pathogens associated with aquaculture are gram-

negative, research has explored the potential role of lactic acid bacteria as probiotics in aquaculture (Vandenbergh, 1993). So, considering lactic acid bacteria’s minimal presence in fish gut microbiota and their typically nonpathogenic nature, it’s uncertain if their inhibition of related species significantly contributes to the overall health of the host organism (Verschuere et al., 2000).

While paraprobiotics do not produce active antimicrobial compounds like live probiotics, they can still contribute to antimicrobial effects through various mechanisms. First, the cell wall components of paraprobiotics, such as peptidoglycan and lipoteichoic acids, can stimulate the host’s immune system, indirectly contributing to antimicrobial defense (de Almada et al., 2016). Additionally, some paraprobiotics may contain preformed antimicrobial compounds, such as bacteriocins or organic acids, that were produced before inactivation, which can still exert their effects despite the cells being non-viable (Nataraj et al., 2020). Although they are not alive, paraprobiotics can occupy space in the gut, potentially preventing the adhesion of pathogenic bacteria to the intestinal epithelium, a mechanism known as competitive exclusion (Zommiti et al., 2018). Certain studies have demonstrated that paraprobiotics can disrupt existing biofilms formed by pathogenic bacteria, indirectly contributing to antimicrobial effects (Sharma et al., 2020). Lastly, they are known to modulate the composition of the gut microbiota, potentially favoring the growth of beneficial bacteria that produce antimicrobial



compounds, thus supporting overall gut health (Chuah et al., 2019). These mechanisms illustrate the multifaceted role of paraprobiotics in enhancing host defenses against pathogens, even in the absence of live cells.

While the mechanisms of action differ between probiotics and paraprobiotics, both can contribute to antimicrobial effects in the host. Probiotics primarily act through the direct production of antimicrobial compounds, while paraprobiotics exert their effects through preformed compounds, immune modulation, and physical interactions with the gut environment.

### 3.3 Strengthening the immune system and nutrient utilization

Probiotics, those beneficial microorganisms found in various supplements or naturally in the environment, play a crucial role in bolstering a fish's immune system against diseases. A recent review by Shija et al. (2023) showed that *Bacillus* probiotics offer a key advantage by regulating mucosal and systemic immunity, leading to decreased inflammation and heightened infection-fighting capabilities. They play a significant role in enhancing the absorption of essential vitamins and minerals from food, aiding in the breakdown of proteins, carbohydrates, and fats, and ensuring that the body receives vital nutrients for optimal growth and health (Peng et al., 2020). When administered to fish, probiotics interact with the fish's gut microbiota, fostering a balanced and healthy environment within the GIT. Selecting the appropriate probiotics is critical, as incorrect choices can detrimentally affect nutrient metabolism, immune regulation, resistance against colonization, and defense against pathogens (Butt and Volkoff, 2019). Serum immunoglobulins play a vital role in the humoral immune system of fish and higher vertebrates, contributing significantly to disease resistance (Sahoo et al., 2021). B lymphocytes produce antibodies that attach to encountered antigens, effectively blocking disease-causing agents from entering the body (El-Ezabi et al., 2011). Other immune parameters, including lysozyme, acid phosphatase (ACP), alkaline phosphatase (AKP), and catalase (CAT), play influential roles in enhancing the immune response of fish. Various *Bacillus* probiotics, including *B. amyloliquefaciens*, *B. coagulans* ATCC 7050, *B. licheniformis* ATCC 11946, *B. tequilensis* GPSAK2, *B. velezensis* TPS3N, *B. velezensis* GPSAK4, *P. polymyxa* ATCC 842, *B. subtilis* TPS4, *B. subtilis* GPSAK9, and *B. amyloliquefaciens* TPS1, whether used independently or in combination, demonstrate the ability to elevate immunoglobulin levels, bolster leukocyte counts, and enhance lysozyme, ACP, AKP, and CAT levels (Amoah et al., 2021, 2023; Shija et al., 2023).

Probiotics play a significant role in improving nutrient utilization in fish. Producing digestive enzymes is one of the primary mechanisms by which probiotics enhance nutrient utilization. Several probiotic strains can synthesize enzymes such as amylases, proteases, and lipases, complementing the host's digestive capabilities (Merrifield et al., 2010). For example, a report by Mohapatra et al. (2012) found that rohu (*L. rohita*) fingerlings fed with a multi-strain probiotic supplement showed significantly higher intestinal amylase,

protease, and lipase activities compared to the control group. This enhanced enzymatic activity can lead to improved digestion and absorption of nutrients from the feed, resulting in better growth performance and feed conversion ratios. Probiotics and paraprobiotics also contribute to nutrient utilization by modifying the gut microbiota composition and metabolism. Beneficial bacteria can create a more favorable gut environment for nutrient absorption and even synthesize certain beneficial nutrients for the host. For example, some probiotic strains have been shown to produce SCFAs through fermentation of non-digestible carbohydrates. These SCFAs serve as energy sources for intestinal epithelial cells and have various beneficial effects on fish health (Hoseinifar et al., 2018). So, by improving nutrient utilization, probiotics and paraprobiotics not only promote better growth and health outcomes for fish but also contribute to more efficient and sustainable aquaculture practices. Table 3 shows examples of the beneficial effects of probiotics and paraprobiotics on the immune system and nutrient utilization in various fish species.

## 4 Strategies used by probiotics and paraprobiotics in tackling disease pathogens

### 4.1 Competitive exclusion

Probiotics and paraprobiotics deal with pathogens through competitive exclusion, a mechanism where beneficial microorganisms outcompete pathogens for resources and attachment sites. This process involves the production of antimicrobial compounds, competition for nutrients, and colonization of sites on the host's mucosal surfaces (Rahman et al., 2021). Similarly, heat-killed *Lactobacillus plantarum* (a paraprobiotic) has demonstrated the ability to adhere to intestinal mucus, potentially blocking pathogen attachment sites in fish (Soltani et al., 2024). The competitive exclusion effect has also been observed with probiotic yeasts, such as *Saccharomyces cerevisiae*, which can reduce the colonization of *A. hydrophila* in the intestines of Nile tilapia (de Moraes et al., 2022). Multi-strain probiotic formulations have also shown enhanced competitive exclusion effects compared to single-strain probiotics in various aquaculture species (Dawood et al., 2018).

### 4.2 Modulation of the immune system

Probiotics and paraprobiotics play a crucial role in modulating the immune system of aquatic organisms, enhancing their resistance to pathogens. These beneficial microorganisms stimulate innate and adaptive immune responses, increasing immune cell production, antibodies, and cytokines (Bruce and Brown, 2017). For example, dietary supplementation with *B. amyloliquefaciens* has been shown to upregulate the expression of immune-related genes in the liver and intestine of Nile tilapia, improving their resistance to *Streptococcus agalactiae* infection (Van Doan et al., 2021). Paraprobiotics, such as heat-killed

TABLE 3 Effects of Probiotics and Paraprobiotics on Immune System and Nutrient Utilization in Various Fish Species.

Probiotics				
Probiotic Used	Fish Species	Immune System Effects	Nutrient Utilization Effects	References
<i>Bacillus subtilis</i>	Asian seabass ( <i>Lates calcarifer</i> )	Upregulation of immune-related genes (IL-1 $\beta$ , TNF- $\alpha$ )	Enhanced apparent digestibility of dry matter and protein	(Adorian et al., 2019)
<i>Lactobacillus plantarum</i>	Nile tilapia ( <i>Oreochromis niloticus</i> )	Increased lysozyme and phagocytic activity	Improved protein efficiency ratio and feed conversion ratio	(Abou-El-Atta et al., 2019)
	Common carp ( <i>Cyprinus carpio</i> )	Enhanced lysozyme and complement activity, Enhancement of immune cell activity, and increased production of antibodies and cytokines	Increased weight gain and performance, enhanced digestibility, improved feed conversion ratio	(Zhang et al., 2020)
	Grouper ( <i>Epinephelus coioides</i> )	Reduction of inflammatory responses, Enhancement of immune gene expression, improved antioxidant activity	Improved digestibility and absorption, enhanced growth performance, improved protein utilization	(Liu et al., 2021)
<i>Lactobacillus rhamnosus</i>	Rainbow trout ( <i>Oncorhynchus mykiss</i> )	Enhanced immune cell activity, upregulation of immune-related genes, increased cytokine production, and improved lysozyme and complement activity	Enhanced protein utilization, improved liver function and detoxification, and improved feed conversion ratio	(Hajirezaee and Khanjani, 2023)
	Red sea bream ( <i>Pagrus major</i> )	Increased resistance against <i>Edwardsiella tarda</i>	Enhanced nutrient digestibility and feed utilization	(Dawood et al., 2015a)
<i>Lactobacillus acidophilus</i>	Zebrafish ( <i>Danio rerio</i> )	Increased serum lysozyme and complement activity	Improved growth performance and feed efficiency	(Hoseinifar et al., 2015a)
<i>Pediococcus acidilactici</i>	Atlantic salmon ( <i>Salmo salar</i> )	Modulation of intestinal microbiota and improved barrier function	Improved feed efficiency and growth performance	(Vasanth et al., 2015)
<i>Shewanella putrefaciens</i>	Gilthead seabream ( <i>Sparus aurata</i> )	Increased lysozyme activity, Stimulation of innate immune responses, enhanced cytokine, modulation of mucosal immunity	Improved digestive enzyme activity, Enhanced growth performance, gut microbiota modulation	(Cámara-Ruiz et al., 2020)
Heat-killed <i>Lactobacillus plantarum</i>	Nile tilapia ( <i>Oreochromis niloticus</i> )	Increased lysozyme activity, enhanced complement activity, and a boost in respiratory burst activity	Increased protein efficiency ratio and improved apparent digestibility of dry matter.	(Van Doan et al., 2020)
Heat-killed <i>Lactobacillus acidophilus</i>	Asian seabass ( <i>Lates calcarifer</i> )	Increase in serum lysozyme levels, enhanced alternative complement activity, and improved phagocytic activity	Increased apparent protein digestibility and improved apparent energy digestibility.	(Nguyen et al., 2017)
Heat-killed <i>Lactobacillus rhamnosus</i>	Zebrafish ( <i>Danio rerio</i> )	Increased expression of immune-related genes, including il1 $\beta$ , tnfr $\alpha$ , and il10, as well as enhanced neutrophil activity	Increased expression of nutrient transporter genes and a greater intestinal villi height.	(Zang et al., 2019)
Heat-inactivated <i>Bacillus coagulans</i>	Common carp ( <i>Cyprinus carpio</i> )	Increased serum lysozyme activity, higher complement C3 levels, and enhanced superoxide dismutase activity	Increased apparent digestibility of dry matter and crude protein, as well as enhanced intestinal protease and lipase activities.	(Xu et al., 2016)
Heat-killed <i>Lactococcus lactis</i>	Olive flounder ( <i>Paralichthys olivaceus</i> )	Increased lysozyme activity, enhanced myeloperoxidase activity, and a boost in respiratory burst activity	Improved growth performance and enhanced feed efficiency.	(Beck et al., 2015)
Heat-inactivated <i>Psychrobacter</i> sp.	Yellow croaker ( <i>Larimichthys crocea</i> )	Elevated serum lysozyme activity, higher complement C3 and C4 levels, and increased IgM levels.	Increased weight gain rate, enhanced specific growth rate, and improved protein efficiency ratio.	(Sun et al., 2011)
Heat-inactivated <i>Lactobacillus casei</i>	Atlantic salmon ( <i>Salmo salar</i> )	Increased expression of immune-related genes in the intestine and head kidney, along with enhanced serum lysozyme activity	Increased apparent digestibility coefficients for dry matter and protein, as well as enhanced intestinal fold height.	(Vasanth et al., 2015)

*Enterococcus faecalis*, have demonstrated the ability to enhance the activity of phagocytes and increase the production of lysozyme in rainbow trout, leading to improved survival rates when challenged with *Aeromonas salmonicida* (Rodríguez-Estrada et al., 2013). Probiotic mixtures containing *Lactobacillus* and *Bacillus* species have been reported to stimulate the production of pro-inflammatory cytokines and enhance the activity of natural killer cells in various fish species, contributing to improved disease resistance (Van Doan et al., 2021). Additionally, the immunomodulatory effects of probiotics and paraprobiotics have been noted to extend beyond direct pathogen interactions, influencing aquaculture species' overall health and stress resistance (Dawood et al., 2020).

### 4.3 Production of antimicrobial compounds

One of the key mechanisms by which probiotics and paraprobiotics fight against disease pathogens is through the production of antimicrobial compounds. These substances include organic acids, hydrogen peroxide, bacteriocins, and biosurfactants, which can directly inhibit or kill pathogenic microorganisms (Banerjee and Ray, 2017). For example, *B. subtilis* isolated from a healthy fish gut produced various antimicrobial peptides that effectively inhibited the growth of *V. anguillarum* and *A. hydrophila* (Kuebutornye et al., 2019). Lactic acid bacteria, such as *Lactobacillus plantarum*, produced organic acids that lowered the pH of the intestine, creating unfavorable conditions for pathogen growth (Giri et al., 2018). Even in their non-viable form, paraprobiotics can retain the ability to produce or release antimicrobial compounds. Heat-killed *L. acidophilus* has been found to maintain its antibacterial activity against fish pathogens due to the presence of stable antimicrobial peptides (Ringo et al., 2018). The synergistic effects of multiple antimicrobial compounds produced by probiotic consortia have shown enhanced pathogen inhibition compared to single-strain applications in various aquaculture systems (Puvanendram et al., 2021).

### 4.4 Biofilm formation and disruption

Probiotics and paraprobiotics deal with pathogens through the formation of beneficial biofilms and the disruption of pathogenic biofilms. Biofilms are complex communities of microorganisms attached to surfaces, and their formation can significantly impact the colonization and persistence of both beneficial and pathogenic bacteria in aquaculture environments (Cai and Arias, 2017; Muhammad et al., 2020). *Bacillus* species have been shown to form protective biofilms on fish skin and intestinal surfaces, creating a barrier against pathogen colonization (Benhamed et al., 2014; Elsadek et al., 2023). These beneficial biofilms can also produce extracellular polymeric substances (EPS) that have antimicrobial properties and enhance the host's immune response (Watters et al., 2016; Singh et al., 2021). Conversely, probiotics and paraprobiotics can disrupt existing pathogenic biofilms. For

example, cell-free supernatants from *L. plantarum* have demonstrated the ability to inhibit and disperse biofilms formed by *V. parahaemolyticus* (Knipe et al., 2021; Shangguan et al., 2021). Heat-killed *B. subtilis* paraprobiotic strain has also shown the capacity to interfere with quorum sensing systems of pathogens, thereby reducing their biofilm formation capabilities (Rajesh and Rai, 2016; Mayer and Kronstad, 2017; Arjes et al., 2022). The interaction between probiotics, paraprobiotics, and biofilms represents a complex and dynamic process that plays a crucial role in pathogen control in aquaculture systems (Cai and Arias, 2017; Arunkumar et al., 2020).

### 4.5 Host microbiome modulation

Probiotics and paraprobiotics significantly tackle disease pathogens by modulating the host microbiome, which plays a crucial role in maintaining aquatic organisms' health and disease resistance. By introducing beneficial microorganisms or their components, these supplements can alter the composition and diversity of the gut microbiota, creating an environment less favorable for pathogen colonization (Choudhury and Kamilya, 2019; Vargas-Albores et al., 2021). For example, dietary supplementation with *L. rhamnosus* has been shown to increase the abundance of beneficial bacteria while reducing potentially pathogenic species in the intestines of zebrafish, leading to improved resistance against *A. hydrophila* infection (Zhong et al., 2022; Zhou et al., 2022). Heat-killed *Enterococcus faecium* paraprobiotics have demonstrated the ability to modulate the gut microbiota of rainbow trout, promoting the growth of lactic acid bacteria and inhibiting potential pathogens (Rodríguez-Estrada et al., 2013; Ringø et al., 2018; Zhong et al., 2022; Zhou et al., 2022). The modulation of the host microbiome by probiotics and paraprobiotics extends beyond the gut, influencing the microbial communities on the skin and gills of aquatic animals, which serve as important barriers against pathogen invasion (Yeşilyurt et al., 2021; Goh et al., 2023; Szydłowska and Sionek, 2023). Consequently, the interaction between probiotics, paraprobiotics, and the host microbiome has been shown to influence metabolic processes and nutrient absorption, indirectly improving the host's ability to resist pathogen infections (Karthika Parvathy et al., 2022; Zawistowska-Rojek and Tyski, 2022).

### 4.6 Quorum sensing interference

Probiotics and paraprobiotics deal with pathogens via the interference with quorum sensing (QS) systems, which are cell-to-cell communication mechanisms used by many pathogenic bacteria to coordinate virulence factor production and biofilm formation (Lazar et al., 2023; Rawal and Ali, 2023; Che et al., 2024). By disrupting these communication systems, probiotics and paraprobiotics can effectively reduce pathogens' virulence and colonization ability in aquaculture environments. For example, certain strains of *B. subtilis* have been found to produce enzymes that degrade acyl-homoserine lactones

(AHLs), key signaling molecules in the QS systems of many Gram-negative pathogens like *Vibrio* species (Garg et al., 2014; Singh, 2015; Shaheer et al., 2021; Monzón-Atienza et al., 2024). Probiotic *Lactobacillus* strains have demonstrated the ability to inhibit the QS-regulated production of virulence factors in *A. hydrophila*, a common fish pathogen (Lu et al., 2023; Zhang et al., 2023). Heat-killed *Lactobacillus plantarum* paraprobiotics have shown the capacity to interfere with QS systems even in their non-viable state, suggesting that cell components or metabolites play a role in this interaction (Vallejo-Cordoba et al., 2020; Siciliano et al., 2021). The QS interference mechanisms of probiotics and paraprobiotics extend beyond direct pathogen interactions, influencing the overall microbial ecology of aquaculture systems and potentially reducing the spread of antibiotic resistance genes (Hernández, 2021; Srirengaraj et al., 2023; Che et al., 2024). So, combining QS interference with other probiotic mechanisms, such as competitive exclusion and immunomodulation, has shown synergistic effects in pathogen control, highlighting the multifaceted nature of probiotic and paraprobiotic interactions in aquaculture.

## 5 Effects of probiotics on fish health

The protective benefits of probiotics on fish health have gained significant attention. These beneficial bacteria enhance fish immunity to diseases, promote growth, and help reduce stress. Below is an illustrative table demonstrating the protective impacts of probiotics on fish health (Table 4).

### 5.1 Improved growth performance

Probiotics are vital in aquaculture, fostering enhanced growth, increased feed efficiency, and overall health across diverse fish species (El-Saadony et al., 2021). Probiotics also significantly enhance growth performance in aquaculture by influencing several key mechanisms. One primary mechanism is the improvement of nutrient digestion and absorption. Probiotics can enhance the digestive enzyme activity in the fish gut, leading to a more efficient breakdown of feed components and increased nutrient availability (Singh et al., 2011). This efficiency in nutrient utilization translates into improved growth rates. Another crucial mechanism is the modulation of gut microbiota. By promoting a balanced microbial community, probiotics reduce the prevalence of harmful bacteria that can compete with fish for nutrients (Dawood et al., 2019). This balance helps maintain a healthier gut environment, which supports better growth. A balanced microbiota can also improve immune function, bolster disease resistance, and promote overall health, consequently fostering improved growth and performance (Tan et al., 2019; Wang et al., 2020; Han et al., 2024).

Probiotics also contribute to improved feed conversion ratios by optimizing nutrient absorption and reducing waste. This enhanced feed utilization reduces feed conversion ratios and lowers production costs (Hasan et al., 2023). Additionally, probiotics

may mitigate stress responses by improving gut health, which helps the fish allocate more energy toward growth rather than coping with stress (Rueda-Robles et al., 2022).

Probiotics play a multifaceted role: they foster a healthier gut environment, mitigating the impact of environmental stressors on fish health and growth. This support frequently enhances growth rates and overall performance (Ntakirutimana et al., 2023). Improving digestion and absorption, probiotics can reduce excess nutrient release into the water, thus aiding in the reduction of environmental pollution associated with aquaculture practices (Nathanailides et al., 2021). Overall, the enhanced growth performance observed with probiotic use can be attributed to their role in optimizing digestion, maintaining a balanced gut microbiota, and improving feed conversion efficiency.

### 5.2 Stress reduction

Environmental changes or handling stress can significantly affect fish's health and overall well-being (Andrews et al., 2021; Menon et al., 2023). Investigating the potential of probiotics in mitigating these stress responses is a progressive approach. Probiotics, known for their beneficial effects on gut health and immunity, have shown promising results in various animal studies, including fish, in reducing stress and enhancing resilience to environmental stressors (Mohapatra et al., 2014). In fish, stress responses often manifest through behavior, physiology, and immune function changes. Probiotics might help modulate these responses by promoting a healthy gut microbiota, which is crucial to the fish's overall health and stress tolerance (Luan et al., 2023).

Research indicates that the administration of specific probiotic strains may enhance stress tolerance in fish through various mechanisms, such as the regulation of stress hormones (Schreck and Tort, 2016). In fish, the hypothalamic-pituitary-interrenal (HPI) axis is the primary mediator of stress as it controls the release of cortisol, a major stress hormone (Zhang et al., 2015). According to Chowdhury et al. (2020), probiotics have been demonstrated to affect this endocrine axis by modifying the release and regulation of cortisol, which helps to promote a more balanced and under-control stress response. For example, by improving gut-brain axis communication, some probiotic strains may lower cortisol levels, which in turn may lessen the activation of the HPI axis during stressful situations (Herrera et al., 2019). Studies have previously highlighted probiotics' immunity boost mechanisms (Ashaolu, 2020) and enhanced gut health mechanisms (Hasan and Banerjee, 2020). A healthy gut microbiome can improve the immune system, potentially making fish more resistant to immunosuppression due to stress, and can help nutrient absorption and reduce inflammation, which can indirectly reduce stress levels in fish. As probiotics can potentially alleviate stress-induced alterations in fish behavior by fostering a healthier internal environment, the mitigation of behavioral change mechanisms is significant (Naiel et al., 2022).

Despite promising initial results, further research is essential to comprehend the specific mechanisms, identify the most effective

TABLE 4 Protective effects of probiotics on fish health.

Aquatic Species	Probiotic species	Dose	Duration	Beneficial Effects	Reference
<i>Danio rerio</i> , <i>Oncorhynchus mykiss</i>	<i>B. subtilis</i> and <i>B. licheniformis</i> (Bioplus2B)	$2.24 \times 10^9$	4 weeks	Improved growth performance (FCR, SGR, and PER) and enhanced haematological parameters (haemoglobin, RBC, and haematocrit values)	(Raida and Buchmann, 2009; Taherpour et al., 2023)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>B. licheniformis</i> (Biogen)	3 g Kg <sup>-1</sup>	14 weeks	Significant improvement in growth parameters (weight gain, AWG, ADG, SGR, and FCR) and haematological parameters (haemoglobin, RBC count, PCV, blood platelets, and WBC count, plasma proteins)	(El-Haroun et al., 2006; Mehrim, 2009)
<i>Epinephelus fuscoguttatus</i> ♀ × <i>Epinephelus lanceolatus</i> ♂	<i>Bacillus velezensis</i> GPSAK4, <i>Bacillus subtilis</i> GPSAK9, and <i>Bacillus tequilensis</i> GPSAK2	$1.0 \times 10^9$ CFU/g	6 weeks	Enhanced growth performance, whole fish-body proximate composition, blood haematological parameters, serum, liver, intestinal biochemical indexes, intestinal health (morphology and microbiota), and protection against <i>V. harveyi</i> pathogen	(Amoah et al., 2024)
<i>O. niloticus</i>	Biogen ( <i>Bacillus</i> based) hydrolytic enzymes)	0.5%, 1.0%, 1.5% and 2.0%	12 weeks	Improved growth parameters (weight gain, specific growth rate, feed utilization, food conversion ratio, and protein efficiency ratio)	(Soltan and El-L, 2008; Ibrahim, 2013; Nayak, 2021)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>Lactobacillus acidophilus</i>	<i>B. subtilis</i> ( $0.5 \times 10^7$ ) + <i>Lactobacillus acidophilus</i>	60 days	Enhanced blood indices (MCV, MCH, and MCHC), improved growth parameters (weight gain), and boosted immunity (gut immunity)	(Aly et al., 2008b; Ibrahim, 2013; Nayak, 2021)
<i>Labeo rohita</i>	<i>B. subtilis</i> and <i>Lactobacillus lactis</i> / <i>B. subtilis</i> , <i>L. lactis</i> and <i>S. cerevisiae</i>	$10^{11}$ CFU g <sup>-1</sup>	60 days	Improved growth parameters (growth, protein efficiency ratio, nutrient retention and digestibility, lower feed conversion ratio), and microecology of gut	(Kumar et al., 2006; Mohapatra et al., 2012)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>B. licheniformis</i>	3 g kg <sup>-1</sup> ; 5 g kg <sup>-1</sup> ; 7 g kg <sup>-1</sup> & 10 g kg <sup>-1</sup>	4 weeks	Enhanced immunity ( <i>lysozyme</i> , <i>protease</i> , <i>antiprotease</i> , SOD, immunoglobulin M level in both serum and skin mucus, upregulation of <i>C-lysozyme</i> , HSP-70, b-defensin, transforming growth factor-b in mid-intestines and head kidney)	(Abarike et al., 2018)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>L. plantarum</i>	$10^7$ CFU g <sup>-1</sup>	60 days	Improved immunity ( <i>phagocytic</i> , <i>lysozyme</i> , <i>phenoloxidase</i> , <i>phosphatase activities</i> and immunoglobulin)	(El-Ezabi et al., 2011)
<i>O. niloticus</i>	<i>B. subtilis</i> and Biogen	–	–	Improved growth performance	(Soltan and El-L, 2008)
<i>Oncorhynchus mykiss</i>	<i>Bacillus</i> species and <i>Aeromonas sobria</i>	$2 \times 10^8$	2 weeks	Enhanced protection against multiple pathogens ( <i>Aeromonas salmonicida</i> , <i>Streptococcus iniae</i> , <i>Yersinia ruckeri</i> , <i>Vibrio ordalii</i> , <i>Vibrio anguillarum</i> , and <i>Lactococcus garvieae</i> )	(Brunt et al., 2007)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>Lactobacillus acidophilus</i>	<i>B. subtilis</i> ( $0.5 \times 10^7$ ) + <i>Lactobacillus acidophilus</i>	60 days	Boosted immune system function	(Aly et al., 2008b; Ibrahim, 2013; Nayak, 2021)
<i>O. niloticus</i>	<i>B. subtilis</i> and <i>S. cerevisiae</i>	1.5 g kg <sup>-1</sup>	6 weeks	Improved growth performance (weight gain, feed conversion ratio, and protein efficiency ratio)	(Marzouk et al., 2008)
<i>Lates calcalifer</i>	<i>B. licheniformis</i> , <i>B. subtilis</i> and <i>B. amyloliquefaciens</i>	$1 \times 10^3$ , $1 \times 10^6$ and $1 \times 10^9$ CFU g <sup>-1</sup>	56 days	Enhanced immune response (leucocytes, lysozyme, and liver oxidative stress-related genes), improved growth performance, and reduced oxidative stress	(Adorian et al., 2019)
<i>Lates calcalifer</i>	<i>B. subtilis</i> and <i>Bacillus</i> species	<i>B. subtilis</i> ( $14.2 \times 10^7$ CFU mL <sup>-1</sup> ), <i>Bacillus</i> sp. ( $2.9 \times 10^7$ CFU mL <sup>-1</sup> ) (1:1)	30 days	Improved growth performance (weight gain, survival), enhanced gut microbiota (amylolytic and cellulolytic microbes), and boosted immunity	(De et al., 2015)

Where: FCR (feed conversion ratio); SGR (Specific Growth Rate); PER (Protein Efficiency Ratio); AWG (Average Weight Gain); ADG (Average Daily Gain); PCV (Packed Cell Volume); MCV (Mean Corpuscular Volume); MCH (Mean Corpuscular Hemoglobin); MCHC (Mean Corpuscular Hemoglobin Concentration); SOD (Superoxide Dismutase); HSP-70 (Heat Shock Protein 70).

probiotic strains for different fish species, determine appropriate dosages, and establish optimal administration methods (Cai et al., 2022). Environmental stressors vary widely, so investigating probiotics' efficacy across different stressors (temperature changes, pollutants, handling stress) would be crucial to determining their broader applicability (Bajagai et al., 2016). The potential use of probiotics to reduce stress responses in fish holds significant promise for aquaculture, fisheries, and conservation efforts (Vine et al., 2006). It could lead to more sustainable practices and healthier fish populations, ultimately benefiting the industry and the environment.

### 5.3 Disease resistance

Research on probiotics and paraprobiotics in fish has shown promising results in resistance to various diseases, including bacterial, viral, and parasitic infections. In a review by Pandiyan

et al. (2013), the effects of probiotics in preventing common bacterial infections in farmed fish were detailed. It was demonstrated that specific probiotic strains, when added to the fish diet, reduced the incidence of bacterial infections (Table 5) by promoting a healthy gut microbiota, thus enhancing fish's immune response. Also, another research conducted by Kuebutornye et al. (2019) provided important information on using probiotics to fight bacterial infections in different fish species. The findings highlighted that certain probiotic supplementation effectively suppressed the growth of pathogenic bacteria in the fish gut, thereby lowering infection rates. Infections caused by parasites, although very limited regarding their information to researchers, have caused tremendous damage to the aquaculture sector. Abdel-Aziz et al. (2020) research on the impact of probiotics on parasitic infections in fish highlighted that certain probiotic supplements altered the gut environment, making it less favorable for parasite survival and development, leading to a decrease in parasite infestation and improved overall fish health. Mohapatra et al. (2013) also

TABLE 5 Probiotics' role in the prevention of bacterial, parasitic, and viral infections in fish.

Probiotic	Fish Species	Diseases or Causative pathogenic agent	Effectiveness	Reference
<i>Lactobacillus acidophilus</i>	Nile tilapia	<i>Pseudomonas fluorescens</i> , <i>Streptococcus iniae</i>	Improve immune function and disease resistance	(Al-Dohail et al., 2011)
<i>Lactobacillus sakei</i>	Rock bream	<i>Edwardsiella tarda</i>	A non-significant decrease in the cumulative mortality	(Harikrishnan et al., 2011)
<i>Lactococcus lactis</i>	Olive flounder	<i>Streptococcus iniae</i>	Activated the innate immune system and protection against pathogen infection	(Kim and Austin, 2006)
<i>Bacillus subtilis</i>	Red hybrid tilapia	<i>Streptococcus agalactiae</i>	Reduced mortalities	(Ng et al., 2014)
<i>Bacillus licheniformis</i>	Tilapia	<i>Streptococcus iniae</i>	Improved the disease resistance	(Han et al., 2015)
<i>Pseudomonas aeruginosa</i>	Zebrafish	<i>Vibrio parahaemolyticus</i>	Protect fish by inhibiting biofilm formation and enhancing defense mechanisms	(Vinoj et al., 2015)
<i>Flavobacterium sasangense</i>	Common carp	<i>A. hydrophila</i>	Enhance immune response and disease resistance	(Chi et al., 2014)
<i>Lactobacillus rhamnosus</i>	Rainbow trout	Furunculosis	Immune modulation, pathogen inhibition	(Nikoskelainen et al., 2003)
<i>Lactobacillus plantarum</i>	Indian major carp	<i>Motile Aeromonas Septicemia</i>	Competitive exclusion, immune enhancement	(Nayak, 2010)
<i>Bacillus subtilis</i>	Nile tilapia	Streptococcosis	Competitive exclusion, immune enhancement	(Aly et al., 2008a)
<i>Pseudomonas fluorescens</i>	Atlantic salmon	Enteric redmouth disease	Competitive exclusion, pathogen inhibition	(Gram et al., 1999)
<i>Carnobacterium maltaromaticum</i>	Rainbow trout	Lactococcosis	Immune response stimulation, pathogen inhibition	(Kim and Austin, 2008)
<i>Lactobacillus casei</i>	Rainbow trout	Infectious pancreatic necrosis virus	Reduces viral load	(Mohammadi and Tukmechi, 2015)
<i>Bacillus subtilis</i>	Tilapia	Spring viremia of carp virus	Enhances immune response	(Tang et al., 2021)
<i>Lactobacillus plantarum</i>	Catfish	Viral hemorrhagic septicemia virus	Improves survival rate	(Hai, 2015a)
<i>Saccharomyces cerevisiae</i>	Carp	Infectious hematopoietic necrosis virus	Reduces mortality rate	(Nayak, 2010)
<i>Bacillus spp</i>	Tilapia	Tilapia lake virus (TiLV)	Strengthen tilapia immunity and resistance against TiLV infections.	(Waiyamitra et al., 2020)

concluded that by modulating the host's immune response and gut microbiota, probiotics played a crucial role in preventing and managing parasitic diseases among different fish species. Besides that, several viral infections have been recorded in aquaculture, stampeding the growth and development of the sector. In the works of [Chattaraj et al. \(2022\)](#), where the role of probiotics in preventing viral infections in aquaculture was elucidated, they observed that probiotics containing specific strains enhanced antiviral immunity in fish, reducing the susceptibility to viral pathogens and lessening the severity of infections. [Mondal et al. \(2022\)](#) also explained the efficacy of probiotics in controlling viral outbreaks in fish farms. Their work indicated that regular administration of probiotics reduced viral loads and enhanced the immune defense mechanisms in the fish, lowering viral infection rates significantly. [Table 5](#) displays some other examples of the function of probiotics in preventing bacterial, parasitic, and viral infection in fish.

These studies collectively emphasize the potential of probiotics as a preventive measure against common diseases in fish, demonstrating their effectiveness in reducing the incidence and severity of bacterial, viral, and parasitic infections through their beneficial effects on the fish's immune system and gut health.

## 5.4 Promoter of reproduction

Probiotics have emerged as a promising area of aquaculture research, particularly in their role in promoting reproduction in fish. These beneficial microorganisms have been found to influence various aspects of fish reproduction, from gamete quality to larval survival. Applying probiotics in fish reproduction is a broader trend towards more sustainable and environmentally friendly aquaculture practices.

One of the primary ways probiotics promote fish reproduction is by improving broodstock's overall health and immune function. [Gioacchini et al. \(2010\)](#) demonstrated that probiotic supplementation in the zebrafish (*Danio rerio*) diet increased fecundity and egg quality. The researchers observed higher fertilization and hatching rates in eggs from probiotic-fed females compared to the control group. They attributed these improvements to the probiotics' ability to modulate the expression of genes related to reproduction and metabolism. Probiotics have also been shown to enhance sperm quality in male fish. A study by [Hoseinifar et al. \(2015b\)](#) on common carp (*Cyprinus carpio*) found that dietary supplementation with *Lactobacillus plantarum* significantly improved sperm motility, viability, and concentration. The researchers suggested that these improvements were likely due to the probiotics' antioxidant properties and ability to enhance nutrient absorption.

Beyond gamete quality, probiotics have been found to impact larval development and survival positively. Research by [Carnevali et al. \(2017\)](#) on European sea bass (*Dicentrarchus labrax*) showed that probiotic treatment of larvae resulted in higher survival rates, which could be linked to enhanced reproductive success in later stages. The study also noted accelerated immune system development in probiotic-treated larvae, which could benefit fish health and reproduction in the long term. The mechanisms by which probiotics influence fish reproduction are multifaceted. One key

pathway is through the modulation of the gut-brain axis. [Falcinelli et al. \(2016\)](#) demonstrated that probiotic administration in zebrafish altered gene expression in appetite control and reproduction in the brain, suggesting probiotics' ability to influence reproductive processes through neuroendocrine pathways.

Probiotics also play a role in enhancing the nutritional status of fish, which indirectly supports reproductive processes. A study by [Mohammadian et al. \(2019\)](#) on rainbow trout (*Oncorhynchus mykiss*) found that probiotic supplementation improved protein digestibility and amino acid absorption. This enhanced nutritional status could improve gamete production and overall reproductive performance. The impact of probiotics on fish reproduction extends to stress reduction, which is crucial for optimal reproductive performance. Stress can negatively affect reproductive processes in fish, leading to reduced gamete quality and spawning success. Research by [Dawood et al. \(2020\)](#) on Nile tilapia (*O. niloticus*) showed that probiotic supplementation reduced cortisol levels and oxidative stress markers, potentially creating a more favorable physiological state for reproduction.

## 5.5 Improvement of water quality

Probiotics have emerged as a promising tool in aquaculture for improving water quality via the reduction of harmful nitrogenous compounds accumulation in aquatic environments. According to [Zhou et al. \(2009\)](#), a mixture of *Bacillus* sp. has the capacity of reducing the total nitrogen and phosphorus in grass carp culture water. [Verschuere et al. \(2000\)](#) reviewed probiotics in aquaculture and highlighted their potential to improve water quality by competing with harmful bacteria for nutrients and space. [Laloo et al. \(2007\)](#) showed that multi-species probiotics could effectively reduce ammonia, nitrite, and nitrate levels in ornamental fish systems. As reviewed by [Martínez Cruz et al. \(2012\)](#), probiotics maintain water quality through the decomposition of undesired organic substances. [Gatesoupe \(1999\)](#), in his discussion on probiotics, also emphasized that they have the capacity to alter the microbial composition in both the water and the digestive tract of cultured aquatic species. [Kesarcodi-Watson et al. \(2008\)](#) reviewed the use of probiotics in aquaculture and highlighted their potential to inhibit the growth of pathogenic bacteria, thereby improving water quality. [Xie et al. \(2013\)](#) found that a probiotic mixture could significantly reduce the abundance of potential pathogens in the water of grass carp culture systems. Thus, the ability of probiotics to modulate microbial communities in aquatic environments significantly contributes to improving water quality.

Soil probiotics have emerged as a promising approach to improve water quality in aquaculture systems, indirectly benefiting fish health and productivity ([Flegel, 1998](#)). These beneficial microorganisms, typically applied to the sediment or water column, can significantly impact water quality parameters crucial for fish welfare. One of the primary ways soil probiotics improve water quality is by reducing harmful nitrogenous compounds. *Bacillus* species are noted to reduce ammonia and nitrite levels in aquaculture ponds effectively. The researchers found

that these probiotics enhanced the nitrogen cycle by promoting the growth of nitrifying bacteria, thereby improving water quality and creating a healthier environment for fish (Zhou et al., 2009). Similarly, Kumar et al. (2016) reported that soil probiotics containing *B. subtilis* significantly reduced ammonia levels in carp ponds, improving fish growth and survival rates. Using probiotics in aquaculture and highlighting their potential to break down organic waste, minimize sludge accumulation, and improve overall water clarity (Verschuere et al., 2000). This process enhances water quality and helps maintain optimal dissolved oxygen levels, which are critical for fish health. A group of *Bacillus* species applied to pond soil was noted to effectively reduce organic matter and improve water transparency in tilapia culture systems (Laloo et al., 2007). Soil probiotics were noted to maintain a balanced microbial community in aquaculture environments, suppressing the growth of pathogenic organisms that can deteriorate water quality. Probiotics added to soil indirectly improved water quality by reducing the bacterial load contributing to poor water conditions (Martinez Cruz et al., 2012).

## 5.6 Immune system enhancement

Probiotics have been shown to enhance the innate immune response in various fish species. A study by Nayak (2010) demonstrated that probiotic administration could stimulate the production of antimicrobial peptides and increase phagocytic activity in fish. Pérez-Sánchez et al. (2011) found that dietary supplementation with *Shewanella putrefaciens* improved the innate immune response in gilthead seabream. Giri et al. (2013) reported that *B. subtilis* supplementation could enhance lysozyme and respiratory burst activity in rohu fish (*L. rohita*). Hoseinifar et al. (2015a) observed increased complement and lysozyme activities in beluga (*Huso huso*) juveniles fed with *L. acidophilus*. The adaptive immune system of fish can also be modulated by probiotic supplementation. Research by Panigrahi et al. (2007) showed that dietary *L. rhamnosus* supplementation could enhance antibody production and expression of cytokine genes in rainbow trout. Abid et al. (2013) found that a multi-strain probiotic mixture increased serum immunoglobulin levels in tilapia. Salinas et al. (2008) demonstrated that *L. delbrueckii* enhanced T-cell mediated immunity in gilthead seabream. Again, Standen et al. (2013) reported that probiotic *Pediococcus acidilactici* stimulated intestinal T-cell proliferation and modulated cytokine expression in tilapia.

There are several incidences recorded where probiotics improved disease resistance in fish after enhancing their immune status. Newaj-Fyzul et al. (2007) found that rainbow trout fed with *B. subtilis* showed increased resistance against *A. hydrophila* infection. Aly et al. (2008b) demonstrated that a mixture of *B. subtilis* and *L. acidophilus* improved survival rates of tilapia challenged with *A. hydrophila* and *Pseudomonas fluorescens*. Nikoskelainen et al. (2003) reported enhanced resistance against *A. salmonicida* in rainbow trout fed with *L. rhamnosus*. Zorriehzaha et al. (2016) reviewed the immunomodulatory effects of probiotics in fish and shellfish, highlighting their

potential for disease prevention. The positive effects on disease resistance was achieved via the probiotic's ability to enhance fish immunity. The impact of probiotics on fish immune systems extends to stress tolerance and overall health. Taoka et al. (2006) showed that probiotic-fed tilapia exhibited lower cortisol levels and improved stress resistance. Carnevali et al. (2006) found that *L. delbrueckii* supplementation enhanced growth and reduced stress-related gene expression in sea bass larvae. Mohapatra et al. (2012) demonstrated that probiotic supplementation improved rohu's growth performance and immunological parameters. Lastly, Merrifield et al. (2010) reviewed the application of probiotics in aquaculture, emphasizing their role in enhancing fish health and immune function.

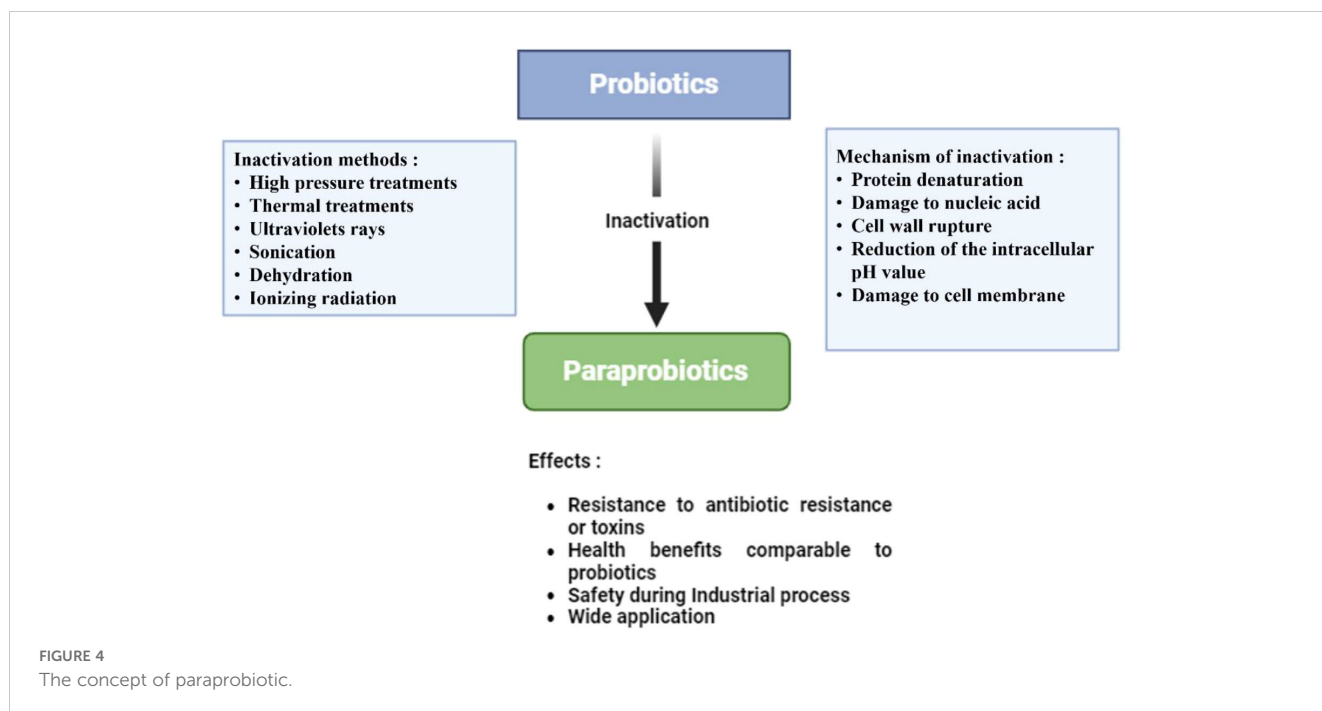
## 6 Beneficial effects of paraprobiotics

Paraprobiotics, as highlighted earlier, are nonviable microbial cells, and using these bacteria has several benefits over using live microorganisms (de Almada et al., 2018). The application of paraprobiotics has not gained the same traction as the well-established usage of probiotics in aquaculture (Choudhury and Kamilya, 2019). Many paraprobiotic preparations have been tested in fish and shellfish following the work of Villamil et al. (2002), who reported the immunostimulatory potential of heat-killed *Lactococcus lactis* in turbot. These investigations mainly aimed to discover how paraprobiotics affect immunological responses, growth, and disease resistance. According to numerous research studies, paraprobiotics can modulate immunity and provide disease resistance just as well as their viable counterparts (Dash et al., 2015; Dawood et al., 2015a). Conversely, compared to their non-viable counterparts, viable microorganisms have been shown to offer greater health advantages (Muñoz-Atienza et al., 2015; Choudhury and Kamilya, 2019). Paraprobiotics are derived from probiotics that have been inactivated through methods such as heat, pressure, or radiation (Lee et al., 2023). Although these cells are no longer viable, they still offer important health benefits, including resistance to antibiotic-resistant pathogens, promoting immune health, and ensuring safety in industrial applications (Abd El-Ghany, 2020; Siciliano et al., 2021). With stability and effectiveness similar to live probiotics, paraprobiotics have a wide range of uses in the food and pharmaceutical industries (Cuevas-González et al., 2020; Vallejo-Cordoba et al., 2020) (See Figure 4).

### 6.1 Improved growth performance

The Indigenous microbiota is thought to play a crucial role in maintaining the metabolic functions of the digestive tract in aquatic animals (Choudhury and Kamilya, 2019). Feed probiotics, which are viable beneficial microbes, have been shown to improve the appetite of aquatic animals by enhancing digestibility through various mechanisms. For example, they produce enzymes that break down complex nutrients, making them more accessible to the animal's digestive system, leading to better nutrient absorption and utilization and subsequently stimulating appetite (Dawood et al., 2015a).





Paraprobiotics have been found to enhance aquatic animal's growth performance and feed utilization. Several studies have demonstrated the positive impact of paraprobiotics on growth parameters in fish, including improved growth rate, feed efficiency, weight gain, SGR, feed grain, and protein efficiency ratio (Rodríguez-Estrada et al., 2013; Dawood et al., 2015a, 2015b; Yan et al., 2016). However, not all studies have reported positive results, as heat-killed probiotics (*B. subtilis*, *L. lactis*, and *S. cerevisiae*) added to the diet of rohu did not have a significant impact on growth, protein efficiency ratio, nutrient retention, digestibility, FCR, or gut colonization (Mohapatra et al., 2012). While paraprobiotics have been shown to positively impact various growth parameters in fish, the underlying mechanisms behind this beneficial effect remain unclear and require further investigation.

## 6.2 Disease resistance

Paraprobiotics are beneficial to the host because they increase the host's resistance to pathogenic infections. Although the exact mechanisms by which paraprobiotics inhibit pathogens are unclear, it is generally accepted that immunostimulation is the main mechanism through which the host resists pathogenic microorganisms (Fura et al., 2016; de Almada et al., 2018). Several studies have demonstrated the ability of paraprobiotics to enhance disease resistance in aquatic animals. For example, Villamil et al. (2002) found that heat-killed lactic acid bacteria inhibited the growth of pathogenic *V. anguillarum* *in vitro*. Feeding rainbow trout with formalin-killed paraprobiotics reduced mortality after *A. salmonicida* infection (Irianto and Austin, 2002; Rodríguez-Estrada et al., 2013). Other studies have shown that paraprobiotics can improve resistance to various pathogens, including *Edwardsiella tarda* in Nile tilapia (Taoka et al., 2006), *Aeromonas* sp. in rainbow trout (Newaj-Fyzul et al., 2007), *V. anguillarum* and *A. hydrophila* in Chinese Drum

(Leong, 2008; Pan et al., 2008), *V. harveyi* in Japanese pufferfish (Biswas et al., 2013b), *Flavobacterium psychrophilum* in rainbow trout (LaPatra et al., 2014), and *A. hydrophila* in *M. rosenbergii* (Dash et al., 2015). Most of these studies also found that paraprobiotics not only enhanced disease resistance but also stimulated the immune system, implying that the immunostimulatory effects of paraprobiotics contribute to their ability to protect against disease.

## 6.3 Stimulation of the immune system

The function of paraprobiotics in boosting the immune system has been thoroughly studied, especially in models of higher vertebrates (Taverniti and Guglielmetti, 2011; de Almada et al., 2016). Studies conducted *in vitro* have consistently shown how effective paraprobiotics are at boosting immune responses. For example, it has been demonstrated that exposure to paraprobiotic preparations dramatically increases the myeloperoxidase concentration, phagocytic activity, nitric oxide production, and respiratory burst activity in fish head-kidney leukocytes (Villamil et al., 2002; Kamilya et al., 2015; Choudhury and Kamilya, 2019). In response to paraprobiotic stimulation, the expression of several immune-related genes has been markedly up-regulated. This involves the overexpression of COX-2 and pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-17A/F-3, TNF- $\alpha$ , and TNF- $\beta$ . Furthermore, there has been an upregulation of TGF- $\beta$ 1, IL-2, IL-7, IL-15, IL-21, IL-10, and other regulatory cytokines, as well as cell-mediated immune regulators such as IL-12p35, IL-12p40, and IL-18, and antiviral cytokines such as IFN- $\alpha$  and IFN- $\gamma$ . There has been a notable up-regulation of defense and antibacterial genes, including granzyme A/K, g-type lysozyme, catalase, phospholipid-hydroperoxide glutathione peroxidase, non-specific cytotoxic cell receptor protein-1, and BPI/LBP, indicating a strong immune

response to paraprobiotic stimulation (Caipang et al., 2010; Lazado et al., 2010; Biswas et al., 2013a, 2013b; Román et al., 2013; Sun et al., 2014; Giri et al., 2016). The immune-stimulatory effects of paraprobiotics have been consistently demonstrated across various studies. The up-regulation of immune-related genes and defense genes suggests that paraprobiotics play a crucial role in enhancing the immune system's response to pathogens. Furthermore, the significant increase in respiratory burst activity, myeloperoxidase content, phagocytic activity, and nitric oxide production in fish head-kidney leukocytes exposed to paraprobiotic preparations *in vitro* highlights the potential of paraprobiotics as a therapeutic agent in disease prevention and treatment (Choudhury and Kamilya, 2019).

Paraprobiotics can cause a variety of humoral and cellular immunological responses in different fish species, according to *in vivo* research. Increased levels of serum and gut lysozyme activity, peroxidase content, oxygen radical production, myeloperoxidase activity, alkaline phosphatase activity, natural hemolytic complement activity,  $\alpha$ 1-antitrypsin, immunoglobulin levels, and total serum protein are among these reactions (Taoka et al., 2006; Dash et al., 2015; Dawood et al., 2015a, 2015b; Singh et al., 2017; Choudhury and Kamilya, 2019). Besides that, studies have demonstrated that dietary paraprobiotics improve neutrophil migration, plasma bactericidal activity, phagocytic activity, respiratory burst activity, and cytotoxic activity. They also increase the number of macrophages, lymphocyte populations, acidophilic granulocytes, and gut IgM+ cells (Taoka et al., 2006; Pan et al., 2008; Salinas et al., 2008; Choudhury and Kamilya, 2019). It has been discovered that paraprobiotics stimulate the expression of several immune-relevant genes, such as TLR2, C3, and iNOS genes, as well as pro-inflammatory cytokines, cell-mediated immune regulators, antiviral cytokines, and other regulatory cytokines (Biswas et al., 2013a, 2013b; Yan et al., 2016; Singh et al., 2017). Studies have shown that paraprobiotics can considerably improve immunological parameters in aquatic animals. These results imply that paraprobiotics may be advantageous for immunostimulation on a molecular and cellular level. Several structural elements of the bacterial cell, which have been demonstrated in earlier research to elicit immunological responses, may be responsible for the immunostimulatory qualities of paraprobiotics (Kataria et al., 2009; Adams, 2010; Taverniti and Guglielmetti, 2011; de Almada et al., 2016).

## 7 Probiogenomics in aquaculture

Probiogenomics, a term coined to describe the application of genomic technologies to probiotic research, has emerged as a powerful approach in aquaculture to enhance our understanding of probiotic mechanisms and to develop more effective probiotic strains. This field combines genomics, transcriptomics, proteomics, and metabolomics to elucidate the molecular basis of probiotic effects in aquatic organisms by enhancing host health (Pérez-Sánchez et al., 2014).

One of the primary applications of probiogenomics in aquaculture is the genomic characterization of potential probiotic strains. Whole-genome sequencing of probiotic candidates provides

valuable insights into their metabolic capabilities, stress resistance mechanisms, and potential for producing bioactive compounds (Elshagabee et al., 2017). For instance, a report by Pérez-Sánchez et al. (2011) utilized comparative genomics to identify genes related to adhesion factors, bacteriocin production, and immunomodulatory compounds in *L. plantarum* strains isolated from fish. This genomic information not only aids in enhancing our understanding of the molecular basis of probiotic effects but also facilitates the development of genetic markers for rapid screening and identification of promising probiotic strains in aquaculture settings.

Probiogenomics also enables the study of host-microbe interactions at a molecular level, providing insights into how probiotics influence fish health and physiology. Transcriptomic analyses of fish intestinal tissue following probiotic administration have revealed modulation of genes involved in immune response, metabolism, and stress tolerance (Hoseinifar et al., 2018). For example, a report by Giri et al. (2018) employed RNA-seq technology to investigate the effects of dietary *B. subtilis* on the intestinal transcriptome of rohu (*L. rohita*), identifying significant changes in the expression of genes related to innate immunity and lipid metabolism. Such studies contribute to understanding the mechanisms underlying probiotic benefits and help optimize probiotic applications in aquaculture.

The integration of multi-omics approaches in probiogenomics research is paving the way for a systems biology perspective on probiotic function in aquaculture. Combining genomics with proteomics and metabolomics allows for a comprehensive assessment of probiotic effects on host metabolism and the gut microbiome (Chauhan and Singh, 2019). For instance, Xia et al. (2018) employed a multi-omics approach to investigate *L. plantarum*'s effects on tilapia's intestinal health, revealing coordinated changes in microbial community structure, host gene expression, and metabolite profiles. The field of probiogenomics is an emerging field, and its relevance in aquaculture is yet to be established (Lazado and Caipang, 2014). As probiogenomics continues to advance, it promises to revolutionize aquaculture research by enabling next-generation probiotics with enhanced specificity and efficacy, ultimately contributing to improved fish health and growth, and the application of probiogenomics is poised to become a cornerstone in advancing the aquaculture industry. For example, studies have shown that probiotics such as *Lactobacillus* and *Bacillus* strains improve immune response and survival rates in fish like rainbow trout, shellfish and other finfish species, which transcends to enhancing their disease resistance (Pérez-Sánchez et al., 2014; Ringø et al., 2020). These advancements provide robust evidence of probiotically enhanced diets benefiting aquaculture (Hai, 2015).

## 8 Practical applications in fish farming

### 8.1 Optimal administration methods for probiotics and paraprobiotics in fish farming

Using probiotics and paraprobiotics in aquaculture requires effective administration methods to ensure they achieve the desired

outcomes. Various administration methods have been developed, including incorporating probiotics into fish feed for dosage control (Brunt and Austin, 2005), dissolving probiotics in water (Rakhfid et al., 2020), immersion or bath treatments for specific applications (Hang, 2021), injection (LaPatra et al., 2014), coating probiotics on fish feed pellets for controlled delivery (Zulhisyam et al., 2020), and encapsulation for prolonged release (Huang et al., 2021).

Incorporation into feed which is one of the most common and practical ways to administer probiotics in fish feed, allows for controlled dosing and ensures that fish receive the probiotics throughout the feeding process. Feed-based administration has been shown to improve growth performance, enhance gut health, and increase disease resistance (Liao and Nyachoti, 2017; Salaheen et al., 2017; Amit et al., 2022). Recent advancements include microencapsulation techniques that protect probiotics during feed processing and ensure their survival in the GIT (Liu et al., 2019; Yao et al., 2020). Microencapsulation also enables a more controlled release of the probiotic organisms, optimizing their effects over time (Sarao and Arora, 2017; Frakolaki et al., 2021; Kowalska et al., 2022). Then, dissolving probiotics into the water or using immersion/bath treatments is particularly effective for larval or juvenile stages of fish, where feeding routines may not be well established (Luz and Favero, 2021; Vargas-González et al., 2024). Recent studies suggest that water-based probiotic administration can enhance immune responses and reduce pathogen load in fish-rearing systems (Yazhiniprabha et al., 2022; Yaslikan et al., 2023). Immersion methods are often used during the early stages of fish development to prevent disease outbreaks (Mohd-Aris et al., 2019; Mondal and Thomas, 2022; Oliveira et al., 2022).

Paraprobiotics, being inactivated microbial cells or cell fractions, often leverage similar administration routes but with specific considerations. Recent studies have shown promising results with heat-killed probiotics incorporated into feed, demonstrating improvements in growth performance, immune function, and disease resistance in various fish species (Dawood et al., 2018; Van Doan et al., 2020). Novel techniques such as spray-drying have been employed to create stable, powder forms of paraprobiotics for easy incorporation into feed or water (Talpur et al., 2014). Importantly, research has begun to explore the co-administration of probiotics and paraprobiotics, revealing potential synergistic effects that could enhance overall fish health and productivity (Azimirad et al., 2016). As the field evolves, there is a growing focus on optimizing dosages, developing targeted delivery systems, and conducting long-term studies to fully understand the impacts of these microbial-based interventions on fish health, growth, and environmental sustainability in aquaculture settings (Hoseinifar et al., 2018).

Nonetheless, the effectiveness of each administration method can be influenced by factors such as the probiotic strain used, fish species, water quality, and environmental conditions (Sayes et al., 2018). So, further research is needed to determine the most appropriate and efficient administration method for a particular aquaculture operation. Several studies have shown that different probiotic administration methods can affect fish's immune response. For example, a study conducted by Simón et al. (2021) showed that administering probiotics through injection can improve the immune

response of fish better than administering probiotics through feed. On the other hand, Rodrigues et al. (2020) showed that encapsulation of probiotics can improve fish survival and reduce stress. In recent years, several new technologies for probiotic administration in aquaculture have been developed, such as using nanoparticles (Qiao et al., 2022) and microencapsulation (Gyawali et al., 2023). Nanoparticles, for example, allow for better bioavailability of probiotics and can target specific areas of the GIT, improving the overall health of fish (Gómez-Guillén and Montero, 2021; Nasr-Eldahan et al., 2021; Vijayaram et al., 2024). Another promising technology is the use of biofilms, where probiotics are embedded into biofilm matrices, allowing them to colonize surfaces in aquaculture systems and provide continuous probiotic effects (Ashrafudoulla et al., 2021; Li et al., 2022). These technologies can improve the effectiveness of probiotic administration and reduce production costs. Thus, further research is necessary to identify the most suitable and efficient probiotic administration methods for specific aquaculture operations, as well as to develop new technologies that can enhance the effectiveness of probiotic administration.

## 8.2 Challenges and limitations

Overcoming challenges in applying probiotics and paraprobiotics in fish farming involves addressing various issues, including stability (Terpou et al., 2019), host specificity, response, and regulatory considerations. Several challenges are associated with the application of probiotics in fish farming, each requiring distinct solutions (Ishtiaq et al., 2021).

First, ensuring probiotic and paraprobiotics stability is critical for their effectiveness, with factors like temperature, moisture, and oxygen sensitivity impacting their viability (Dinkçi et al., 2019). Formulating probiotics with stabilizers, employing encapsulation techniques, and storing them under optimal conditions, such as through microencapsulation, can enhance stability, safeguarding their viability until administration (Sun et al., 2023).

Another challenge lies in the host specificity of probiotics, where the efficacy of a particular strain in one fish species may not be replicated in others (Fontana et al., 2013). Research efforts are needed to identify probiotic strains with broad-spectrum benefits or species-specific formulations, tailoring applications to the unique microbiota of different fish species in aquaculture systems (Das et al., 2022). Variations in individual fish responses pose another challenge, stemming from differences in microbiota, genetics, and environmental conditions within a species (Adamovsky et al., 2018). Thorough trials and individual fish monitoring can help identify these variations. Customizing probiotic formulations or dosages based on individual or population-specific needs can enhance overall efficacy (Lowe et al., 2020).

The regulatory landscape presents challenges as the use of probiotics and paraprobiotics in fish farming is subject to varying frameworks across regions (Lulijwa et al., 2020). Engaging with regulatory authorities, staying informed about guidelines, and conducting research to provide scientific evidence on safety and efficacy are essential steps for navigating these challenges and obtaining regulatory approval. Concerns about the environmental

impact of releasing probiotics into aquatic environments, including ecological impacts and resistance development, present challenges. Mitigating risks involves implementing best management practices, such as targeted delivery methods and environmental impact monitoring. Responsible probiotic use, coupled with adherence to environmental regulations, is crucial in addressing these concerns (Hancz, 2022). While paraprobiotics may pose fewer environmental risks due to their inactivated nature, their long-term effects on aquatic ecosystems still need to be studied.

Optimizing dosage and application methods is another challenge, considering factors like feed conversion, water quality, and fish behavior (Yildiz et al., 2017). Conducting controlled studies to determine optimal dosage and application methods based on specific aquaculture conditions is crucial (Bregnballe, 2022). Tailoring probiotic administration to suit the feeding habits and environment of the fish species in question enhances overall efficacy (Wuertz et al., 2021). Addressing these challenges collectively will contribute to the sustainable and effective integration of probiotics in fish farming practices. By addressing these challenges systematically through scientific research, innovation in formulation and application methods, and collaboration with regulatory bodies, the effective integration of probiotics in fish farming can be realized, promoting sustainable and healthy aquaculture practices.

## 9 Future perspective

Research on the application of probiotics in fish has undergone significant advancements, with a notable evolution in approaches over the years. A thorough examination of published research on probiotics reveals several key trends: firstly, the use of probiotics has emerged as a viable and sustainable strategy for disease control; secondly, there is an ongoing quest to discover new probiotic candidates; and thirdly, the applications of probiotics have expanded beyond disease control, demonstrating a broader range of benefits (Lazado and Caipang, 2014). In certain situations when probiotics are harmed and/or rendered inert during processing and/or shelf life, the creation of paraprobiotics as supplements and their incorporation into meals and beverages provide a significant substitute. Paraprobiotics will, therefore, have several uses in situations where adding probiotics ought to solve a technological problem. Paraprobiotic products, as opposed to live probiotic goods, do enable the creation of safer and more stable products. Consequently, the use of paraprobiotics in food, medicine, supplements, and fodder is rapidly growing, and soon, their use will be widespread. Recent research has indicated that the biogenic and paraprobiotic properties of dead cells, microbial fractions, or cell lysates can preserve the host's health.

Envisioning the future of probiotics in fisheries necessitates comprehensively exploring research gaps, novel strains, and innovative delivery systems (Vieira et al., 2021). Addressing research gaps is pivotal in understanding fish microbiomes to identify bacterial strains beneficial for different species. The focus should extend to characterizing the gut microbiota of various fish and comprehending how probiotics interact with existing microbial

communities over time (Legrand et al., 2020). Investigating the long-term effects of probiotic administration is equally crucial, delving into sustained benefits, potential host microbiota adaptation, and any unintended consequences.

Exploring new strains is vital for enhancing the spectrum of benefits offered by probiotics. This involves isolating unique microbial strains with superior properties, including stress tolerance, antimicrobial activity, and positive effects on growth and immune responses (Kwoji et al., 2021). Customizing probiotic formulations for different fish species is essential, requiring research to understand species-specific requirements and preferences.

Innovative delivery systems play a key role in shaping the future of probiotics. Advancements in microencapsulation techniques can enhance stability and targeted delivery, with research exploring new materials and methods to improve probiotic survival in the digestive system (Vivek et al., 2023). Exploring nanotechnology applications offers innovative possibilities, as well as investigating nanoencapsulation methods to improve bioavailability and controlled release (Chadha, 2021). Developing precision delivery systems, such as smart feed formulations or site-specific administration, can optimize distribution, minimize environmental impact, and enhance overall effectiveness (Karunathilake et al., 2023).

Ecosystem-level studies are paramount for sustainable aquaculture practices. Assessing the broader ecological impact of probiotics on aquatic ecosystems is vital in understanding interactions with non-target species and environmental factors (Ibrahem, 2013). Investigating the potential for antibiotic resistance and horizontal gene transfer among probiotic strains and native microorganisms ensures responsible probiotic use (Rossi et al., 2014).

Integrating omics technologies (Kwoji et al., 2023), including genomics, metagenomics, and proteomics, provides comprehensive insights into the genetic makeup of probiotic strains, host responses, and microbial interactions. This integrative approach enhances our understanding of the mechanisms underlying probiotic functionality, paving the way for informed and sustainable advancements in probiotics within fisheries.

## 10 Conclusion

To summarize, probiotics and paraprobiotics are increasingly recognized as valuable alternatives to antibiotics in aquaculture, offering numerous benefits for fish health and disease prevention. These beneficial microorganisms help modulate the gut microbiota, enhancing digestion, nutrient absorption, and immune responses in fish. Probiotics, which are live microorganisms, produce antimicrobial compounds such as bacteriocins and organic acids that inhibit the growth of pathogens. At the same time, paraprobiotics, composed of inactivated cells, provide similar benefits through their bioactive components. Both probiotics and paraprobiotics strengthen the immune system, improving disease resistance against bacterial, viral, and parasitic infections. Additionally, probiogenomics enables the development of more targeted and effective probiotic strains tailored to specific fish

species and environmental conditions. Commercially available products utilizing these microorganisms already show promising results in improving fish growth, survival rates, and water quality, making them essential components in sustainable aquaculture practices.

## Author contributions

MF: Conceptualization, Data curation, Methodology, Validation, Writing – original draft. KA: Conceptualization, Data curation, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. YH: Methodology, Supervision, Writing – review & editing. JC: Project administration, Supervision, Writing – review & editing. AA: Writing – review & editing, Formal analysis. CN: Formal analysis, Writing – review & editing. VS: Formal analysis, Writing – review & editing. XJ: Formal analysis, Writing – review & editing. FB: Formal analysis, Writing – review & editing. HC: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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