Brazilian Journal of Biology®

ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Original Article

Pathogenicity and control of infections caused by motile *Aeromonas* in freshwater fish: immunostimulation strategies

Patogenicidade e controle de infecções por *Aeromonas* móveis em peixes de água doce: estratégias de imunoestimulação

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Abstract

In Brazil, despite favorable edaphoclimatic and hydrobiological conditions, the consolidation of the aquaculture sector is constrained by significant sanitary challenges, particularly bacterial infections caused by *Aeromonas* spp., which adversely affect fish farming, especially native species. In response, the widespread and often indiscriminate use of antimicrobials has contributed to the emergence and spread of multidrug-resistant strains. This study presents a narrative review addressing the clinical aspects, sanitary challenges associated with *Aeromonas* infections, and prophylactic strategies, with an emphasis on immunostimulation in freshwater fish, focusing on products derived from *Saccharomyces cerevisiae*, such as nucleotides and mannan-oligosaccharides. Intrinsic and extrinsic factors, including the cultivated species, ontogenetic stage, environmental conditions, and supplementation protocols, modulate the immunophysiological responses to these bioactive compounds and require specific scientific validation for each species. Therefore, there is an urgent need to advance research focused on Neotropical ichthyofauna, with particular emphasis on economically critical native species such as *Colossoma macropomum*, *Arapaima gigas*, *Brycon amazonicus*, *Piaractus mesopotamicus*, *Rhamdia quelen*, among others.

Keywords: immunostimulants, nucleotides, mannan oligosaccharides-MOS, fish farming, immune system.

Resumo

No contexto brasileiro, apesar das condições edafoclimáticas e hidrobiológicas favoráveis, a consolidação do setor aquícola permanece limitada por desafios sanitários significativos, em especial por infecções bacterianas causadas por *Aeromonas* spp., que impactam negativamente a piscicultura, especialmente de espécies nativas. Em resposta, o uso disseminado e frequentemente indiscriminado de antimicrobianos tem contribuído para o surgimento e disseminação de cepas multirresistentes. Este estudo apresenta uma revisão narrativa abordando os aspectos clínicos, os desafios sanitários associados às infecções por *Aeromonas* e as estratégias profiláticas, com ênfase na imunoestimulação em peixes de água doce, com foco em produtos derivados de *Saccharomyces cerevisiae*, como nucleotídeos e mananoligossacarídeos. Fatores intrínsecos e extrínsecos, incluindo a espécie cultivada, o estágio ontogenético, as condições ambientais e os protocolos de suplementação, modulam as respostas imunofisiológicas a esses compostos bioativos e requerem validação científica específica para cada espécie. Portanto, existe uma necessidade urgente de avançar na pesquisa sobre a ictiofauna neotropical, com ênfase em espécies nativas economicamente importantes, como *Colossoma macropomum*, *Arapaima gigas*, *Brycon amazonicus*, *Piaractus mesopotamicus*, *Rhamdia quelen*, entre outras.

Palavras-chave: imunoestimulantes, nucleotídeos, mananoligossacarídeos-MOS, piscicultura, sistema imunológico.

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Received: May 18, 2025 – Accepted: February 13, 2026
Editor: Takako Matsumura Tundisi

1. Introduction

Aquaculture is one of the fastest-growing sectors in animal production worldwide, driven by the rising global demand for aquatic protein sources (Mattos et al., 2021; Beg et al., 2024; Oliveira et al., 2025). According to the Food and Agriculture Organization of the United Nations (FAO, 2024), aquaculture production is projected to reach 111 million tons by 2032, with an average global fish consumption of 21.3 kg per capita. Despite its significant natural potential, Brazil still plays a modest role in this market (Pantoja-Lima et al., 2015; Aride et al., 2025; Liebl et al., 2025a, b; Santos et al., 2025a, b) with a national per capita consumption of only 10.5 kg (Agrimídia, 2024), lower than neighboring countries such as Chile and Ecuador. However, this figure is considerably higher in the Amazon region, reaching up to 150 kg per capita among riverine communities (Oliveira et al., 2010).

Among the sanitary challenges, motile *Aeromonas* septicemia is a disease caused by bacteria of the genus *Aeromonas* that has triggered epizootic outbreaks worldwide (Gallani et al., 2020; Pessoa et al., 2020; Mazumder et al., 2021). The immediate response, often based on the indiscriminate use of antibiotics, has led to serious issues such as antimicrobial resistance (AMR), residue accumulation in animal carcasses and the environment, as well as immunosuppression in the affected fish (Abdel-Latif et al., 2020; Leão et al., 2020; Sebastião et al., 2022).

In light of these limitations, research has focused on identifying safer and more sustainable alternatives, such as immunostimulants that promote activation of both innate and adaptive immune mechanisms in fish (Aride et al., 2016, 2018, 2020; Araújo et al., 2020; Hoshino et al., 2020; Nascimento et al., 2021; Furtado et al., 2025). These strategies involve enhancing leukocyte activity, lysozyme production, complement system activation, and improving intestinal integrity, supporting zootechnical performance and increasing fish resistance to pathogenic and environmental challenges (Hisano et al., 2018; Al-Ghamdi et al., 2023; Abd El-Naby et al., 2024; Moreira et al., 2024).

Among the main immunostimulants evaluated, derivatives of the yeast *Saccharomyces cerevisiae* Hansen, 1883, such as β-glucans, mannan oligosaccharides (MOS), and nucleotides, stand out. These compounds, obtained from the yeast cell wall or cytoplasm, have demonstrated efficacy in immune modulation and promoting intestinal health in farmed fish (Parapouli et al., 2020; Khanjani et al., 2022).

Such benefits have been widely documented in the literature, particularly over the past decade, especially in studies involving exotic species such as *Oreochromis niloticus* (Linnaeus, 1758), *Sander lucioperca* (Linnaeus, 1758), *Oncorhynchus mykiss* (Walbaum, 1792), *Ctenopharyngodon idella* (Valenciennes, 1844), *Megalobrama amblycephala* (Yih, 1955), *Ictalurus punctatus* (Rafinesque, 1818), *Betta splendens* (Regan, 1910), and *Clarias batrachus* (Linnaeus, 1758). In contrast, fewer studies have focused on native species such as *Rhamdia quelen* (Quoy and Gaimard, 1824), *Piaractus mesopotamicus* (Holmberg, 1887), *Arapaima gigas* (Schinz, 1822), and *Colossoma macropomum* (Cuvier, 1818) (Chagas et al., 2013; Sado et al., 2014; Zhao et al., 2015; Adorian et al., 2016; Azevedo et al., 2016; Özlüer-Hunt et al., 2016; Jarmołowicz et al., 2018; Hoshino et al., 2020; Mombach et al., 2020; Akter et al., 2021; Ding et al., 2022; Luo et al., 2024).

Thus, functional nutritional additives emerge as a promising alternative for developing more efficient, healthy, and environmentally sustainable aquaculture. This review examines the adverse effects of *Aeromonas* infections in aquaculture, with emphasis on the fish species farmed in Brazil. Additionally, it discusses the potential of dietary immunostimulants, such as mannan oligosaccharides (MOS), beta-glucans, and nucleotides, as prophylactic strategies to mitigate motile *Aeromonas* septicemia in production systems.

2. Motile *Aeromonas* Septicemia in Aquaculture

The genus *Aeromonas* comprises 36 species of Gram-negative, facultatively anaerobic, rod-shaped bacteria that primarily function as opportunistic pathogens possessing multiple virulence factors (Pessoa et al., 2019; Fernández-Bravo and Figueras, 2020; Yassen et al., 2021). Structural components, including flagella, pili, lipopolysaccharides (LPS), and membrane proteins, play crucial roles in tissue adhesion, invasion, and cellular recognition processes (Mendoza-Barberá et al., 2021). The capsule - an outer structure enveloping the bacterial cell membrane - protects host immune system defenses (Mendoza-Barberá et al., 2021).

Extracellular proteins, including enzymes and cytotoxins, contribute to bacterial pathogenicity and play distinct roles in the infectious process. Proteases degrade the fish epithelial mucosa, causing lesions in the skin and internal organs that facilitate infection (Figure 1A). Intestinal damage during *Aeromonas* infections is primarily mediated by secreted lipases that hydrolyze lipids in the outermost cellular layers (Figure 1B). *Aeromonas* hemolysins lyse erythrocytes through pore formation in cell membranes and are strongly associated with systemic host damage (Figure 1C). Furthermore, biofilm-forming capacity enhances strain virulence, leading to high mortality rates in culture systems (Pessoa et al., 2019). Notably, some strains are zoonotic and can cause gastrointestinal infections in humans (Fernández-Bravo and Figueras, 2020; Pérez et al., 2023).

Among the most well-known species of *Aeromonas* are *Aeromonas hydrophila* (Chester, 1901), *Aeromonas salmonicida* (Theodore and Pfennig, 1890), *Aeromonas caviae* (Van Damme et al., 1966), *Aeromonas sobria* (Sakazaki et al., 1959), *Aeromonas veronii* (Hickman-Brenner et al., 1987), and *Aeromonas jandaei* (Carnahan et al., 1991a).

Among them, *A. jandaei* and *A. hydrophila* are emerging as some of the most problematic bacterial pathogens (Mielke et al., 2022; Pellin et al., 2023; Rimal et al., 2026). These species are associated with significant mortality in economically important fish species in aquaculture (Figure 2A-F) (Samayanpaulraj et al., 2020).

The latter was first isolated and associated with human disease; its negative profile for fermentation of esculin, sucrose, and cellobiose, along with resistance to colistin, distinguishes *A. jandaei* from other *Aeromonas* species. This pathogen has recently been isolated from freshwater crocodiles (Pu et al.,

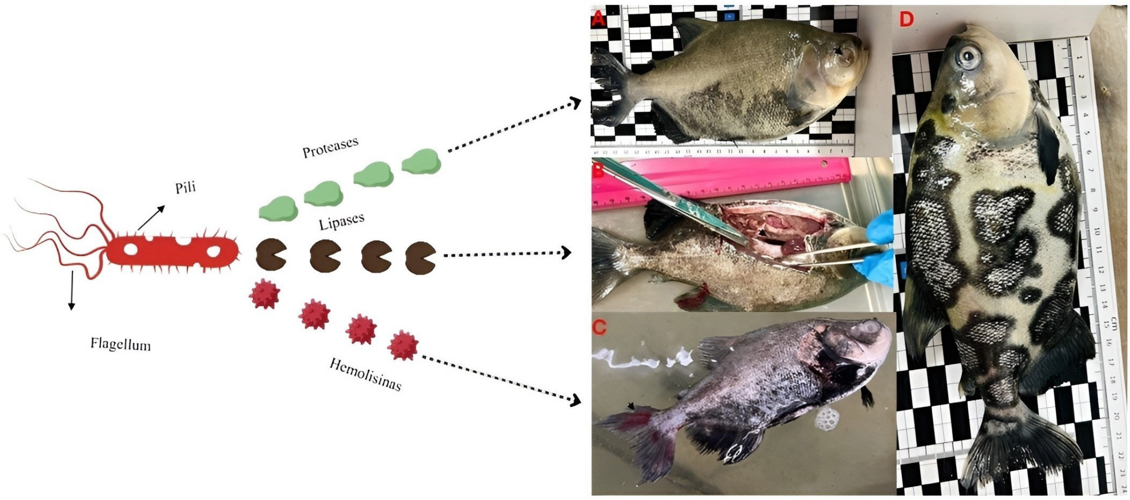

Figure 1. Clinical signs in *Colossoma macropomum* infected with *Aeromonas jandaei*, showing (A) ocular loss due to protease activity, (B) hemorrhagic and necrotic internal organs caused by enzymatic and cytotoxic damage, (C) fin hemorrhages, and (D) darkened skin lesions resulting from systemic *A. jandaei* infection.

Figure 2. Clinical signs observed in tambaqui (*Colossoma macropomum*) infected with *Aeromonas jandaei*. A – Tambaqui with eroded caudal fin and hemorrhagic pelvic fin; B – Individual exhibiting ascites and anal distension; C – Tambaqui presenting exophthalmia; D – Tambaqui with focal discoloration; E – Tambaqui with hemorrhagic eyeball; and F – Liver showing a pale and vascularized appearance.

2019) and fish (Pessoa et al., 2019; Mielke et al., 2022; Pellin et al., 2023). *A. jandaei* may be misidentified as *A. caviae*, *A. hydrophila*, or *A. veronii* (Carnahan et al., 1991b; Martinez-Murcia et al., 1992) due to their high genetic similarity, showing 99.5%, 99.0%, and 98.3% similarity, respectively. These species are also associated with mass mortality outbreaks in fish farming systems (Medina-Morillo et al., 2023).

The biochemical characterization revealed that *A. jandaei* are Gram-negative, short, motile rods that are positive for catalase and oxidase (Kumar et al., 2015). Additional tests demonstrated that the strains are positive for citrate utilization, Voges-Proskauer (VP) reaction, methyl red test, ortho-nitrophenyl-β-galactopyranoside (ONPG) activity, and lysine and arginine decarboxylase activity, but negative for ornithine decarboxylase activity (Kumar et al., 2015).

The key differentiating characteristics between *A. jandaei* and *A. hydrophila* were observed in esculin hydrolysis and sucrose fermentation (Abbott et al., 2003). While *A. hydrophila* (Chester, 1901) tested positive for both reactions, *A. jandaei* was negative for both biochemical tests (Kumar et al., 2015).

3. Occurrence of Aeromonosis in Fish and Experimental Evidence of Virulence

A. jandaei was isolated and characterized during mortality outbreaks in *Pangasianodon hypophthalmus* (Sauvage, 1878) aquaculture operations in Maharashtra, India (Kumar et al., 2015). Experimental challenges were conducted via intraperitoneal injection with bacterial concentrations ranging from 10^3 to 10^8 CFU/fish to fulfill Koch's postulates. The study determined an LD_{50} of 8.84×10^5 CFU/fish. Infected fish exhibited characteristic clinical signs, including hemorrhaging in fins and the ventral region, loss of secondary gill lamellae with progressive hyperplasia, accompanied by mild congestion, along with other tissue damage caused by the bacterial infection.

Mazumder et al. (2021) first isolated and characterized bacteria of the genus *Aeromonas*, specifically *A. hydrophila* and *A. jandaei*, from an outbreak of hemorrhagic septicemia in commercial farms of *Anabas testudineus* Bloch, 1792, in the Assam region of India during the winter season of 2018-2019 (November to January). The outbreak recorded 50% mortality, with affected individuals showing clinical signs including ulceration and fin rot in *A. testudineus*. For experimental infection, fish were inoculated with 1.3×10^4 and 2.5×10^4 colony-forming units (CFU)/fish, which confirmed clinical signs similar to those observed in natural infections: excessive mucus secretion, followed by gradual development of white-grayish lesions progressing toward the posterior half of the body that later extended to the caudal fin. The anal region showed scale loss that progressed to ulcers, and the fins exhibited reddish discoloration that later developed into conspicuous rot. A 100% mortality rate was recorded within 48 hours after artificial infection for both species at higher doses (3.4×10^6 and 4.2×10^6 CFU/fish), powerfully demonstrating that *A. hydrophila* and *A. jandaei* are equally pathogenic to *A. testudineus*. The authors also detected cytotoxic enterotoxin in both isolates and found only the aerolysin gene in *A. jandaei*.

Outbreaks of hemorrhagic septicemia caused by *A. jandaei* in Nile tilapia (*Oreochromis niloticus* Linnaeus, 1758) were recorded at the Aquaculture Center of UNESP (CAUNESP) in Jaboticabal, São Paulo, Brazil (Assane et al., 2021). Two distinct outbreaks were documented. The first outbreak occurred between August and September 2017 (winter season) in 340 healthy juveniles obtained from a commercial fish farm. This episode resulted in 90% cumulative mortality from the first to the tenth day post-stocking, following transport-induced stress. The second disease outbreak occurred between April and May 2019 (autumn season) at a commercial fish farm in Panorama (São Paulo State, Brazil), where cumulative mortality reached 50% by day 30 post-stocking, following a one-week acclimation period in earthen ponds.

Several *Aeromonas* species have been isolated from commercial and ornamental Amazonian fish species, with *A. jandaei* being identified in *Arapaima gigas* (Schinz, 1822). Like other infected fish species, affected specimens exhibited characteristic clinical signs and behavioral alterations, including hemorrhaging, fin erosion, and erratic swimming patterns (Medina-Morillo et al., 2023). Virulence characterization of *A. jandaei* demonstrated the presence of *fla* and *ahyB* virulence genes along with positive hemolytic, lipolytic, caseinolytic, and gelatinase activities, while testing negative for elastase activity despite possessing elastase genes. This apparent discrepancy between genetic potential and phenotypic expression may be explained by several factors, including non-amplifiable genetic variants with current primers, suboptimal incubation temperatures, and complex gene-regulatory mechanisms that affect protein expression, collectively demonstrating the multifactorial nature of virulence expression in these bacterial pathogens. In experimental challenge trials, inoculation of *Piaractus brachypomus* (Cuvier, 1818) with *A. jandaei* at a concentration of 10^8 CFU/fish resulted in 100% mortality, showing pathogenicity equivalent to *A. hydrophila* and *A. dhakensis* under identical infection conditions.

In both outbreaks, affected fish exhibited behavioral alterations and clinical signs including lethargy, anorexia, surface swimming, exophthalmia, cloudy eyes, hemorrhagic spots and skin redness beneath the opercula and at fin bases, fin rot, and body surface pallor. During the first outbreak, treatment with florfenicol (10 mg kg^{-1} body weight) and a thiamphenicol concentration of the same order of magnitude, administered via gavage, resulted in clinical signs resolving within 3 days post-medication. However, in the second outbreak, oxytetracycline administration (120 mg kg^{-1} body weight) failed to stop the mortality.

Proietti-Junior et al. (2021) reported the first mortality outbreak in a commercial *A. gigas* farm in Rio Branco, Acre state, Brazil, caused by a co-infection involving three bacterial species, including *A. jandaei*. The outbreak resulted in the mortality of 1,400 juvenile fish (8.2 ± 2.3 cm and 11.5 ± 3.8 g) within seven days of arrival. Affected fish exhibited clinical signs and behavioral alterations, including lesions of varying shapes, sizes and extent primarily located on the caudal fin; loss of equilibrium with erratic movements; reduced respiratory movements; and external body depigmentation with hemorrhagic foci. Necropsy findings revealed internal hemorrhagic-necrotic lesions in organs, including the kidney, liver, and modified swim bladder, along with splenomegaly (enlarged spleen), gallbladder distension, small hemorrhagic areas in the liver, ascites (fluid accumulation) with yellowish mucoid and bloody fluid in the intraperitoneal cavity, hyperemia, and abdominal cavity edema.

Consequently, the same authors evaluated experimental coinfection with *A. hydrophila* and *A. jandaei* strains isolated from the *A. gigas* outbreak. Challenge tests demonstrated that fish inoculated with 3.0×10^7 CFU/mL of either *A. hydrophila* or *A. jandaei* developed moderate infection from the third day post-challenge. After 96 hours, euthanized fish revealed mild localized hyperemia in organs, including kidneys, liver, and modified swim bladder, during necropsy, with no mortality observed during the experiment. However, simultaneous inoculation with both *A. hydrophila* and *A. jandaei* resulted in severe infection with 100% mortality within 48-72 hours, accompanied by clinical signs and behavioral alterations similar to those observed in the natural *A. gigas* outbreak. Genetic analysis confirmed that both strains carried virulence genes encoding cytotoxic exotoxins (*hlyA* and *aerA*), protease (*gcat*), deoxyribonuclease (*dnase*), and lipase (*lip*).

In another native Amazonian species, *C. macropomum*, researchers first reported the genetic diversity and virulence assessment of *Aeromonas* isolates. Among 34 characterized strains, the distribution was *A. hydrophila* (41.2%), *A. dhakensis* (20.6%), *A. caviae* (17.6%), *A. veronii* (11.8%), and *A. jandaei* (8.8%). The *A. jandaei* strains predominantly produced multiple extracellular enzymes (Pessoa et al., 2020). Phenotypic analysis revealed 23.5% of strains showed the HEM+/PROT+ pattern (hemolytic and proteolytic activity), followed by 20.5% with PROT+/LIP+ (proteolytic and lipolytic activity). All isolates demonstrated lipophilic potential and tested positive for hemolytic and protease activities, which correlated with the presence of *ser+* and *lip+* genes, though the *y-hemol* gene was not detected. Notably, this phenotypic hemolytic profile on blood agar was similarly observed in *A. dhakensis* and *A. caviae* strains. The authors attributed this hemolytic activity to alternative virulence factors not specifically investigated in the study, particularly aerolysin, a potent pore-forming hemolysin that lyses blood cells by forming membrane pores (Janda and Abbott, 2010).

Pellin et al. (2023) investigated the presence of *Aeromonas* in farmed *C. macropomum* from Amazonas State, Brazil, along with the occurrence of key virulence genes, including aerolysin (*aerA*), cytotoxic enterotoxin (*act*), and cytolytic enterotoxin (*ast*), to assess their pathogenic potential. Among 24 bacterial strains isolated from 153 tambaqui juveniles, 91.7% were identified as *A. jandaei*, indicating the high prevalence of this species in northern Brazilian aquaculture systems. Virulence gene detection revealed significant results, with eight isolates (33.3%) showing positive amplification for *act* (seven *A. jandaei* and one *A. hydrophila*). These virulence factors in *A. jandaei* enable bacterial invasion, colonization, and destruction of host cells by overcoming fish immune defense mechanisms (Assane et al., 2021).

Kim et al. (2019) reported that the *act* gene is the most frequently detected virulence factor, along with *aerA*, which functions as a porin capable of causing degeneration of intestinal crypts and villi in fish. These genes play crucial roles in *Aeromonas* infections by initiating apoptosis signaling pathways in eukaryotic cells, meaning their presence alone indicates high pathogenic potential. In a related study, Mielke et al. (2022) documented natural mortality outbreaks affecting 4,000 *C. macropomum* juveniles caused by co-infection with *A. jandaei* and *Flavobacterium columnare* following transport from Amazonian fish farms located in Presidente Figueiredo (n=1 farm; mean transport time: 108 min), Iranduba (n=1; 52 min), and Rio Preto da Eva (n=2; 76 min) to Manaus. Nearly 100% mortality occurred within 72 hours. Experimental challenges using 0.1 mL of inoculum per 10 g of body weight (10^9 CFU/fish) in healthy fish, followed by re-isolation from recently dead specimens, confirmed the presence of the same bacterial pathogens.

4. Challenges in the Therapeutic Control of *Aeromonas* Infections and the Emergence of Antimicrobial Resistance

Pathogen control in aquaculture has traditionally relied on the metaphylactic or prophylactic use of antibiotics. This practice has contributed to the emergence and spread of antimicrobial resistance among treated organisms (Bondad-Reantaso et al., 2023). Within the genus *Aeromonas*, all identified strains of *A. hydrophila* and *A. jandaei* have been reported to harbor antibiotic resistance genes, underscoring the high potential for antibiotic resistance in this bacterial group (Piotrowska and Popowska, 2014). The dissemination of multidrug-resistant bacteria in aquaculture is recognized as a global threat by the World Health Organization (WHO), the World Organisation for Animal Health (WOAH), and the Food and Agriculture Organization of the United Nations (FAO), which emphasize responsible antibiotic use and good management practices as key measures for sustainable aquaculture (Arthur et al., 2019).

Several studies have documented antimicrobial resistance among *Aeromonas* isolates recovered from cultured tilapia (*Oreochromis* spp.). For example, research on red hybrid tilapia farms found that *A. hydrophila* isolates exhibited resistance to multiple antibiotics, including novobiocin, ampicillin, spiramycin, and chloramphenicol, with many isolates showing a high multiple antibiotic resistance (MAR) index, indicating widespread resistance to antibiotics commonly used in aquaculture systems (Lee and Wendy, 2017).

Another study isolated 15 *A. hydrophila* strains from red *Oreochromis* spp., of which 100% were resistant to ampicillin, followed by oxytetracycline (26.7%), tetracycline (26.7%), trimethoprim (26.7%), and oxolinic acid (20.0%). The predominant resistance gene detected in *A. hydrophila* was *mcr-3* (20.0%), while 13.3% of the isolates harbored the *floR*, *qnrS*, *sul1*, *sul2*, and *dfrA* genes (Thaotumpitak et al., 2023).

The treatment of these bacterial infections poses significant challenges, as only two antimicrobial drugs are approved by the Brazilian Ministry of Agriculture, Livestock and Food Supply (MAPA) for treating bacterial infections in fish: oxytetracycline (used for salmonids and catfish) and florfenicol (used for trout and tilapia). According to recommendations from the National Union of Animal Health Products Industries (Sindan, 2018), both drugs are administered orally through medicated fish feed.

Among these medications, florfenicol is the most widely used antimicrobial in aquaculture systems to treat various bacterial diseases in fish (Zhang et al., 2020). However, these pharmaceuticals are often misused in fish farms, thereby selecting for resistant bacteria and disseminating corresponding antimicrobial resistance genes.

A recent study by Silva et al. (2024) analyzed 114 bacterial strains of *Aeromonas* spp. Isolated from *C. macropomum*, revealing widespread resistance to penicillin, high resistance rates to oxacillin, cefepime, cefadroxil, and azithromycin. The most effective antimicrobials were ampicillin-sulbactam, neomycin, and ofloxacin. Notably, 34.21% of isolates were classified as multidrug-resistant (MDR) phenotypes. These findings demonstrate that, despite the lack of approved antimicrobials for *C. macropomum* aquaculture in Brazil, significant antimicrobial resistance is present among *Aeromonas* isolates.

Sebastião et al. (2022) reported that all seven *Aeromonas* strains isolated from *C. macropomum* were resistant to ampicillin, whereas 28% showed resistance to erythromycin and sulfonamides. In addition, all isolates exhibited minimum inhibitory concentration (MIC) values above the tested range for amoxicillin, penicillin, novobiocin, tylosin tartrate, and clindamycin, and 85% of the strains were resistant to erythromycin. These findings indicate a high prevalence of antimicrobial resistance among *Aeromonas* isolates associated with *C. macropomum* and underscore the need for greater awareness among fish farmers and stronger regulatory oversight of veterinary drug use in aquaculture. The adoption of good management practices is essential to discourage the indiscriminate prophylactic and systemic use of antimicrobials.

5. Yeast-Derived Immunostimulants from *Saccharomyces cerevisiae*

Immunostimulants are biological substances that beneficially enhance both specific and nonspecific defense mechanisms in animals. These effects include: increased leukocyte counts and phagocytic activity, elevated lysozyme production, and enhanced complement system activity. When administered through feed, these compounds have been shown to improve zootechnical performance, stress resistance, antioxidant activity, inflammatory responses, and resistance to bacterial, viral, and parasitic infections, while also accelerating wound healing processes in fish (Campos et al., 2020; Hoshino et al., 2020; Pinheiro et al., 2024; Pan et al., 2024). The aquaculture industry utilizes various immunostimulants, including vitamins, bacterial derivatives, polysaccharides, plant and animal extracts, synthetic chemicals, and yeast-based products (Dias and Yoshioka, 2020).

The yeast cell wall of the genus *Saccharomyces* is a key determinant of its health-promoting properties, primarily due to its structural components, including mannan oligosaccharides (MOS) and β-glucans (Liu et al., 2021). These compounds have demonstrated efficacy in: enhancing growth performance (Campos et al., 2020); promoting intestinal integrity and modulating gut flora composition (Dobrianska et al., 2021; Sá et al., 2024) and skin microbiota (Pan et al., 2024); increasing mucin secretion and production of bactericidal proteins such as lysozyme (Medagoda et al., 2023); acting as cortisol modulators in stressed fish (Hoshino et al., 2020); improving carcass quality (Sverinciuc et al., 2018); stimulating angiogenic biosynthesis and wound healing processes in fish skin (Pan et al., 2024); and enhancing resistance against viral, parasitic, and bacterial pathogens (Zhao et al., 2015; Dias et al., 2019; Pinheiro et al., 2024).

β-glucans can be obtained from various sources and are classified by the type of glucose linkage. Cereal-derived β-glucans predominantly contain β (1,3) and β (1,4) glycosidic bonds without β (1,6) branching (Nakashima et al., 2018). Bacterial β-glucans consist exclusively of linear chains with β (1,3) linkages and lack branches. In contrast, fungal and algal β-glucans display a characteristic structure of linear β (1,3)-linked chains with β (1,6) branches, which confers a helical conformation. Immune system components specifically recognize this distinct structural configuration, triggering immune activation and establishing these compounds as among the most promising functional supplements for aquaculture applications (Machuca et al., 2022).

Solubility is a physicochemical parameter influenced by molecular weight, bond type, and degree of molecular branching (Nakashima et al., 2018). In practice, β-glucans exhibit considerable variation in solubility depending on the raw material source and the extraction conditions/methods employed (Hino et al., 2020).

Studies have identified multiple β-glucan receptors on macrophages, including scavenger receptors, complement receptor 3 (CR3), lactosylceramides, dectin-1, and Toll-like receptors. Dectin-1 emerges as the most efficient phagocytic receptor for yeast-derived β-glucans (Figure 3). However, the exact mechanisms of action remain incompletely understood (Goodridge et al., 2009), and numerous carbohydrate receptors remain to be discovered (Lee and Kim, 2014).

The innate immune system recognizes pathogen-associated molecular patterns (PAMPs) derived from infectious agents or from components of the commensal microbiota, including lipopolysaccharides, peptidoglycans, bacterial DNA, viral RNA, and other molecules present in the membranes of multicellular organisms ('non-self'). This system does not recognize host components ('self') because the genes encoding these pattern recognition receptors (PRRs) are encoded in the genome of the organism (Lee and Kim, 2014).

The β-1,3/1,6-glucan derived from *S. cerevisiae* Hansen, 1883 (Beta G® Nutribem) supplemented in the diet of channel catfish *I. punctatus* Rafinesque, 1818) juveniles induced a significant increase in leukocyte counts (Sanchez-Martinez et al., 2017). Elevated leukocyte levels

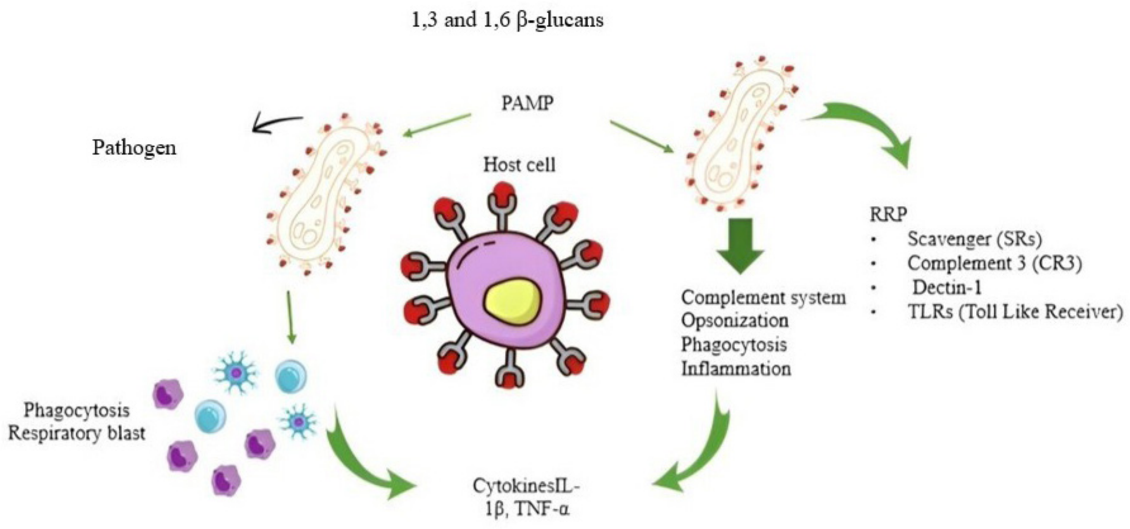

Figure 3. 1,3 and 1,6 β-glucans are recognized by immune system components. PRRs (Scavenger, Complement 3, Dectin-1, Toll-Like Receptor) identify a PAMP, activating intracellular signaling pathways, which result in the production of pro-inflammatory cytokines (such as IL-1β, TNF-α), complement system activation, and recruitment of immune cells to fight the infection.

are associated with improved health status, as these cells mediate immune responses. β-glucans promote leukocyte receptor activity, enhancing cellular functions that improve phagocytosis and increase cytokine secretion, thereby stimulating leukopoiesis (Zhang et al., 2022).

Studies evaluating commercial immunostimulants derived from yeast extract and dried brewer's yeast (Aquate Fish™®) demonstrated that following *A. hydrophila* infection, respiratory burst activity, leukocyte counts, and lymphocyte numbers were significantly increased in *A. gigas* fed diets supplemented with 12 g kg^{-1} of the product, indicating that this concentration is optimal for immune enhancement in this species (Dias et al., 2019). In a subsequent investigation, the same research team examined growth performance and immune responses in pirarucu receiving *S. cerevisiae* based immunostimulants under stress conditions. Dietary supplementation with 6-8 g kg^{-1} significantly improved final biomass, body length, body weight gain, daily weight gain, feed intake, specific growth rate, and reduced cholesterol levels, establishing these concentrations as effective growth promoters for the species (Dias and Yoshioka, 2020).

Studies using β-glucan (Betamune®, Biorigin) at a 0.2% dietary supplementation for 60 days in *C. macropomum* demonstrated significant increases in lysozyme concentration and activity compared with other treatments and controls. Furthermore, reduced mortality rates were observed at concentrations of 0.1% and 0.2% following challenge with *A. hydrophila* (Chagas et al., 2013). Recent research with *S. cerevisiae*, based immunostimulant (Aqute Fish™®) in *A. jandaei*-challenged *C. macropomum* identified 12 g kg^{-1} as the optimal concentration, showing 75% survival rates post-challenge (Fernandes, 2023). *S. cerevisiae* supplemented diets for *A. gigas* juveniles not only improved survival rates against *Trichodina* spp. Parasites also enhanced weight gain, final biomass, feed intake, and apparent feed conversion ratio (Pinheiro et al., 2024).

Mannan oligosaccharides (MOS) are complex carbohydrates composed of mannose sugar units specifically recognized by pathogenic bacteria during adhesion processes (Gainza and Romero, 2017). This recognition mechanism occurs in numerous pathogenic strains that significantly impact aquaculture systems. The use of MOS as pathogen colonization blockers is based on the concept that specific sugars, such as mannose, can inhibit lectin-mediated bacterial adhesion via fimbrial proteins (Figure 4). These bacterial lectins bind to complementary carbohydrate components of glycoproteins or glycolipids on host tissue surfaces. Research suggests that this adhesion interference reduces pathogenic colonization of the digestive tract, as pathogens are excreted in feces, thereby enhancing intestinal epithelial barrier integrity and function (Jana et al., 2021).

MOS has demonstrated significant benefits for nutrition and health across various animal species, including poultry, swine, and aquaculture species (Sharma, 2025). Research shows that MOS supplementation enhances both nonspecific and specific immunity, improves intestinal health, and increases pathogen resistance across multiple species (Ren et al., 2020; Ding et al., 2022). Furthermore, it can boost antioxidant capacity, modulate immune-related gene expression, and promote beneficial gut microbiota (Ren et al., 2020).

In aquaculture systems, MOS has shown positive effects on fish growth performance, survival rates, and immune responses (Ding et al., 2022). Its mechanism blocks pathogen adhesion to intestinal cells while maintaining gut barrier integrity (Gainza and Romero, 2017). Additionally, MOS supplementation can suppress excessive intestinal inflammation and improve feed conversion ratios (Ding et al., 2022). These findings underscore MOS's potential as a functional feed additive and immunostimulant in animal nutrition, particularly in antibiotic-free feeding programs.

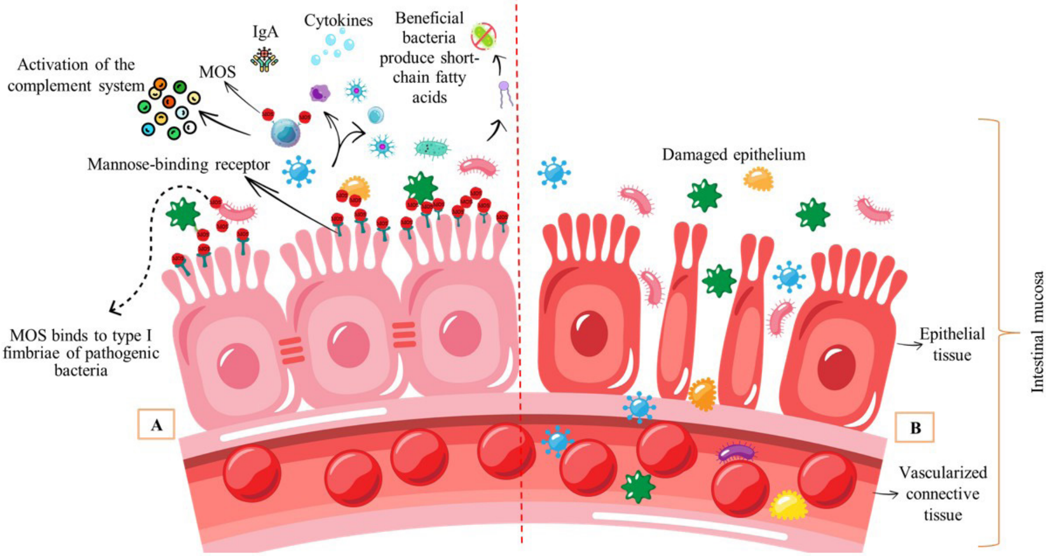

Figure 4. Schematic representation of the mechanism of action of mannan oligosaccharides (MOS) in the intestinal mucosa, involving the activation of humoral and cellular immune responses. A – In the presence of MOS, these compounds bind to the type I fimbriae of pathogenic bacteria, preventing their adhesion to the intestinal epithelium. Mannose-binding receptors (MBRs) on immune cells of the gut-associated lymphoid tissue (GALT recognize mannose-rich structures, triggering immune responses such as complement system activation, immunoglobulin A (IgA) production, and cytokine release. In addition, MOS promote the growth of beneficial bacteria capable of producing short-chain fatty acids, contributing to gut health and immune modulation. B - In the absence of MOS, pathogenic microorganisms can adhere to and colonize the intestinal epithelium, leading to epithelial damage, disruption of the mucosal barrier, and activation of inflammatory responses in the intestinal mucosa.

Nucleotides play a central role in nucleic acid biosynthesis (DNA and RNA) and serve as precursors for adenosine triphosphate (ATP) and key coenzymes that regulate essential metabolic reactions (Rossi et al., 2007). Although nucleotides are not traditionally classified as essential nutrients because they are endogenously synthesized, dietary nucleotide deficiency can impair liver, heart, intestinal, and immune functions (Grimble and Westwood, 2001).

Nucleotide biosynthesis occurs through precursor amino acids or the salvage pathway, which recycles existing nucleotides (Grimble and Westwood, 2001). The salvage pathway is energetically efficient, requiring only 1 mole of adenosine triphosphate (ATP) compared to 5 moles for de novo synthesis (Carver and Walker, 1995; Li and Gatlin III, 2006) (Figure 5). However, during periods of high metabolic demand, such as infections, physiological stress, or rapid growth phases, endogenous production may become insufficient to meet organismal requirements (Hess and Greenberg, 2012). Under these conditions, dietary nucleotide supplementation effectively compensates for limitations in endogenous synthesis (Hossain et al., 2020), thereby classifying nucleotides as semi-essential nutrients (Cruz et al., 2020).

In olive flounder (*Paralichthys olivaceus* Temminck and Schlegel, 1846), diets containing 1.5% nucleotides combined with β-glucan, vitamin A, and E significantly enhanced growth performance, immune parameters, intestinal histomorphology, and anti-inflammatory gene expression (Medagoda et al., 2023). The commercial products NuPro® and Bio-Mos® were tested in common carp (*Cyprinus carpio* Linnaeus, 1758) fry at 2% inclusion, increasing biomass by 24.3% and 28.6%, respectively, and survival by 9.3% and 16.7%, respectively (Vachko et al., 2020).

However, the effects on fish zootechnical performance show considerable variability, influenced by multiple factors including: the type of nutritional additive employed, target species characteristics, administered dosage, supplementation duration, environmental conditions, and water quality parameters (Leite et al., 2025; Bussons et al., 2021; Liebl et al., 2022, 2021). Similarly, physiological responses are highly species-dependent, making these elements crucial for achieving consistent improvements in the health, welfare, and growth parameters of aquatic organisms (Khanjani et al., 2022).

6. Mannan Oligosaccharides - MOS (Actigen®)

Mannan oligosaccharides contain mannose, a carbohydrate that mimics the adhesion receptors on epithelial cells and serves as a decoy substrate for the elimination of pathogenic bacteria (Pan et al., 2024). The immunomodulatory mechanism of MOS involves activating the fish's nonspecific immune system through Toll-like receptors (TLRs) on the membranes of blood cells, tissues, and immune cells. These receptors recognize pathogen-associated molecular patterns (PAMPs) on exogenous substances, triggering targeted immune responses against pathogens (Torrecillas et al., 2014).

In channel catfish *I. punctatus*, supplementation with Actigen® - a concentrated source of yeast cell wall-

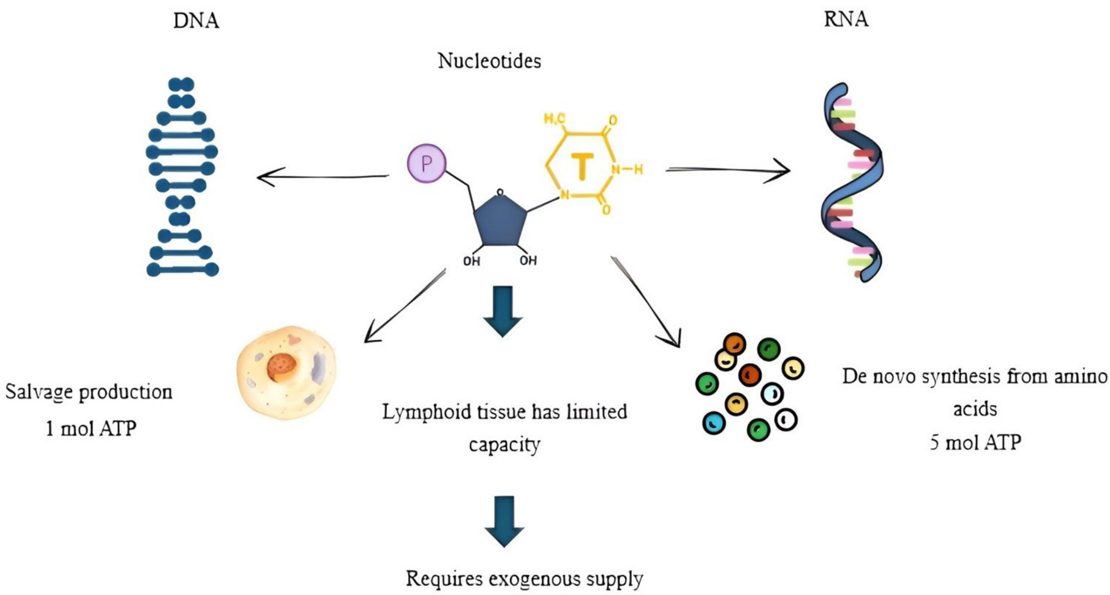

Figure 5. Illustrative model of nucleotide biosynthesis through the salvage pathway and amino acid synthesis.

derived material rich in active mannose and beta-glucan - demonstrated: upregulated expression of mannose receptors 1 and 2 (CD206 and CD280), increased production of various chemokines and pro-inflammatory cytokines, and improved health status and survival rates (Zhao et al., 2015).

In juvenile turbot, *Scophthalmus maximus* Linnaeus (1758), dietary supplementation with 0.16% MOS (Actigen®) promoted epithelialization and inflammatory cell recruitment while stimulating extracellular matrix (ECM) biosynthesis and angiogenesis (new blood vessel formation). The treatment also modified the skin microbiota composition and enhanced wound-healing processes (Pan et al., 2024).

Actigen® effectively increased parasite resistance in greater amberjack (*Seriola dumerili* Risso, 1810) during a 90-day supplementation trial. The 2 g kg^{-1} dietary dose protected *Neobenedenia girellae* Hargis, 1955, reducing parasite load and total length. This protective effect correlated with upregulation of pro-inflammatory cytokines in skin and intestinal tissues and with enhanced serum bactericidal activity (Fernandez-Montero et al., 2021). However, the combined use of immunostimulants led to excessive immune stimulation, diminishing therapeutic efficacy (Fernandez-Montero et al., 2021).

Using a distinct dietary protocol for *O. niloticus,* supplementation with MOS at 0.04%, 0.06%, and 0.08% concentrations for 60 days significantly enhanced: lysozyme activity, globulin levels, hematocrit, mean corpuscular volume, erythroblast counts, total leukocytes, lymphocytes, and monocytes - even without antigenic stimulation (Ha et al., 2017).

In *Clarias gariepinus Burchell*, 1822, dietary supplementation with Bio-Mos® at 2 g kg^{-1} of diet for 92 days resulted in increased weight gain, improved feed conversion ratio, and higher survival rates, in addition to enhanced health indicators, including elevated leukocyte counts and improved biochemical parameters, such as reduced glucose levels and a lower activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratio (Genç et al., 2020). When the same product was incorporated into *O. niloticus* diets under different supplementation protocols, similar beneficial effects were observed. Dietary inclusion of Bio-Mos® at 10%, 15%, and 20% kg^{-1} of diet for 60 days increased final body weight, improved protein efficiency, and enhanced innate immune responses, including lysozyme activity and complement system parameters, particularly at the highest inclusion level (Antonio-Cisneros et al., 2022). Likewise, in *O. niloticus*, supplementation with mannan oligosaccharides (MOS) at 2, 4, and 8 g kg^{-1} of diet for 45 days improved feed conversion ratio, feed intake, and protein efficiency, with 4 g kg^{-1} identified as the optimal dietary level (Al-Ghamdi et al., 2023).

In *P. mesopotamicus*, dietary supplementation with Glucan-MOS® at 1 g kg^{-1} of diet for 30 days improved weight gain, feed conversion ratio, and protein efficiency ratio compared with the control diet. In addition, inclusion levels of 2 and 4 g kg^{-1} were sufficient to enhance leukocyte respiratory burst and lysozyme activity, and to increase circulating thrombocytes, neutrophils, and monocytes following stressful handling and experimental challenge with *A. hydrophila*. Supplemented fish also exhibited attenuated stress responses, as evidenced by lower cortisol and glucose levels than in the control group. These results reinforce the benefits of dietary strategies incorporating β-1,3/1,6-glucans and mannans as functional supplements before periods of intensive management in aquaculture (Soares et al., 2018).

7. Nucleotídeos (NuPro®)

NuPro® is a yeast-based product derived from the cytoplasmic contents of *S. cerevisiae* cells, containing approximately 5% nucleotides by dry weight (Kowalska et al., 2015; Berto et al., 2016). The benefits of NuPro® supplementation in feeds encompass nutritional and functional properties (Ozkan-Yilmaz et al., 2018). Dietary nucleotide supplementation has been tested across various aquatic species, demonstrating multiple benefits including: enhanced growth performance and weight gain, improved resistance to parasitic and bacterial diseases, superior carcass quality, modulated immune responses, stress regulation, and accelerated wound healing in fish (Özlüer-Hunt et al., 2016; Hoshino et al., 2020; Yassen et al., 2021).

Channel catfish juveniles can tolerate dietary incorporation of NuPro® up to 100 g kg^{-1} without performance impairment (Peterson et al., 2012). In pikeperch *S. lucioperca*, NuPro® supplementation at 40-60 g kg^{-1} demonstrated immunomodulatory properties by stimulating non-specific immunity and potentially improving hepatic function, though without significant growth effects (Jarmołowicz et al., 2012). For the same species, yeast extract (NuPro®) significantly enhanced growth at all tested concentrations (2%, 4%, and 6%) during a 60-day trial. These treatments resulted in reduced alanine aminotransferase (ALT) activity. Histological analysis revealed dose-dependent improvements in intestinal morphology, including increased enterocyte height and expansion of the supranuclear absorption zone. The 2% inclusion level was identified as optimal (Jarmołowicz et al., 2018).

Using the same concentration protocol for pikeperch but over a shorter 56-day period, researchers observed improved blood biochemical parameters, increased cellular immune activity and lysozyme levels, and reduced ALT, AST, and alkaline phosphatase activity (Kowalska et al., 2015).

In *O. niloticus*, dietary supplementation with NuPro® (0, 10, 20, 40, 60, and 80 g kg^{-1}) for 75 days improved growth performance, nutrient utilization, hematological and immunological responses, and resistance to experimental *A. hydrophila* infection. The data revealed a linear increase in feed intake with increasing NuPro® levels, resulting in 28.8% weight gain, improved survival rates, better feed conversion efficiency, and increased counts of thrombocytes, leukocytes, and monocytes (Berto et al., 2016).

A feeding trial evaluated the effects of dietary nucleotide supplementation (Nucleoforce™) on growth performance and on hematological, biochemical, and immunological parameters, as well as disease resistance, in *Pangasianodon hypophthalmus*. Fish were fed control or nucleotide supplemented diets (250 or 500 g t^{-1}) for eight weeks. Nucleotide supplementation significantly improved weight gain and specific growth rate, enhanced hematological and immune responses, and increased antioxidant and serum protein levels, particularly at 500 g t^{-1}. Following experimental challenge with *Pseudomonas aeruginosa*, fish receiving nucleotide-supplemented diets exhibited lower cumulative mortality, indicating improved health status and increased resistance to bacterial infection (Yassen et al., 2021).

The combined supplementation of functional immunomodulators, including β-glucans (1000 mg kg^{-1}), nucleotides (150 mg kg^{-1}), ascorbic acid (1000 mg kg^{-1}), and α-tocopherol (20 mg kg^{-1}), was evaluated in juvenile *O. niloticus* fed diets with reduced animal protein and increased soybean meal content. The supplemented diet significantly improved growth performance, feed efficiency, protein retention, intestinal morphology, and gut microbiota diversity, without affecting hematological or immunological parameters, indicating no immune overstimulation. These findings demonstrate that functional additives can enhance growth and gut health, supporting sustainable dietary formulations with lower inclusion of animal protein (Sá et al., 2024).

In the Amazonian native pirarucu, dietary supplementation with *S. cerevisiae* extract (NuPro®) for 30 days enhanced innate immune responses at all tested concentrations (0, 10, 40, and 80 g kg^{-1}). The treatment also increased thrombocyte counts following handling stress and reduced blood glucose levels, thereby establishing this additive as an effective immunostimulant at the 40 g kg^{-1} inclusion level (Hoshino et al., 2020).

8. Effects on Intestinal Health

Intestinal health is fundamental to growth, productivity, and immune function in aquatic animals, as enhanced nutrient absorption correlates with increased intestinal villus height. These factors contribute to improved zootechnical indices in fish. Numerous studies have conducted histomorphological characterizations of the gastrointestinal tract following dietary supplementation to better the nutritional effects of feed ingredients in fish nutrition (Adorian et al., 2016; Azevedo et al., 2016; Jarmołowicz et al., 2018; Cavalcante et al., 2020; Ding et al., 2022; Sá et al., 2024).

Dietary supplementation with an immunostimulant blend containing nucleotides, β-glucans, ascorbic acid, and α-tocopherol (0.1%, 0.15%, and 0.2%) in *O. niloticus* juveniles resulted in increased intestinal fold number, greater fold length, expanded total absorptive surface area, and higher goblet cell counts compared to control groups. These findings demonstrate that the immunostimulant promoted intestinal growth and enhanced mucosal morphology (Sá et al., 2024). In pikeperch *(S. lucioperca)*, yeast extract supplementation (2%, 4%, and 6%) over 60 days significantly increased enterocyte height, supranuclear absorption zone dimensions, and body weight gain, and improved daily growth indices in a dose-dependent manner (Jarmołowicz et al., 2018).

When MOS was supplemented in striped catfish (*Pangasianodon hypophthalmus*) diets at concentrations of 0.2%, 0.4%, 0.6%, and 0.8% for 90 days, significant intestinal morphological changes were observed: anterior and mid-intestinal villi length increased at 0.6-0.8% concentrations, while anterior villi width was significantly reduced at 0.2-0.4% compared to both control and higher MOS groups. Posterior intestinal width remained unaffected. These results demonstrate the beneficial effects of MOS on intestinal morphology in striped catfish juveniles (Akter et al., 2021).

A combination of MOS and β-glucan demonstrated positive effects when supplemented at 0.1% and 0.2% in pacu (*P. mesopotamicus*) diets for 30 days. The results showed increased villus height and perimeter, which correlated with improved growth performance and feed efficiency at these concentrations (Hisano et al., 2018). The dual polysaccharide supplementation enhanced growth responses, feed utilization, and intestinal morphology in pacu, indicating a synergistic nutritional effect (Hisano et al., 2018).

The combined dietary supplementation of nucleotides and β-glucans positively affected growth performance and intestinal morphology in *Ctenopharyngodon idella*. Fish fed diets containing nucleotides (0.01%) and/or β-glucans (0.10%) for 60 days exhibited increased villus height and width, as well as greater intestinal wall thickness, indicating improved intestinal structure and absorptive capacity (Luo et al., 2024).

These findings underscore the critical importance of balanced nutrition and demonstrate the potential benefits of nucleotide and mannan oligosaccharide compounds for maintaining intestinal health and promoting growth in aquatic species, particularly in intensive aquaculture systems.

9. Perspectives

Applying yeast-derived immunostimulants from *S. cerevisiae*, particularly next-generation commercial products such as NuPro® and Actigen®, has demonstrated significant potential as a strategic approach to fish health management. Scientific evidence confirms that these additives positively modulate innate immune responses through enhanced phagocytic activity, upregulation of antibacterial and antioxidant enzymes, activation of the complement system, increased cytokine production, improved intestinal morphology, beneficial modulation of the gut microbiota, and elevated resistance to bacterial and parasitic pathogens, as well as reduced handling stress. Consistent reports also document improvements in zootechnical parameters, including weight gain, feed conversion ratios and survival rates. Furthermore, carcass quality enhancements - particularly in total saturated/unsaturated fatty acid composition, free amino acid profiles, chewiness, and elasticity - confirm their role as multifunctional feed additives in modern aquaculture.

The nucleotides in NuPro® and the mannan oligosaccharides in Actigen® have demonstrated efficacy in promoting both intestinal development and immune function, with measurable benefits for aquatic organisms' health, particularly under intensive farming conditions. However, immunostimulant responses vary significantly depending on: species specificity, ontogenetic stage, environmental conditions, exposure duration, and administered concentration. These factors require careful evaluation in supplementation protocols, as research documents that overdosing or prolonged exposure may yield antagonistic effects, including suppression of key immunological parameters.

Thus, *S. cerevisiae*-derived products have established themselves as sustainable and effective alternatives for aquaculture intensification, enhancing animal welfare, biosecurity, and production efficiency. However, the mechanisms underlying this remain poorly understood, and exposures are based on assumptions derived from experimental trials in higher vertebrates, given the similarity of immune system components. Additional studies are recommended to explore further the mechanisms of action of these compounds, including the identification of the types of receptors present in host cells that identify exogenous compounds, such as those derived from yeast, the determination of ideal concentrations for different species, intermittent application strategies, such as adjuvants in vaccine protocols and treatment, and validation on a commercial scale. In addition, it is essential to research Brazilian native species such as *C. macropomum*, *A. gigas*, *B. amazonicus*, *P. mesopotamicus*, and *R. quellen*, given the significant knowledge gap for these species of great socioeconomic importance.

Acknowledgements

This study was supported by CAPES (Brazilian Federal Agency for Support and Evaluation of Graduate Education) through a doctoral scholarship. JPFR is a postdoctoral fellow of the National Council for Scientific and Technological Development CNPq, process 150531/2024-9. PHRA is a productivity grant recipient from the Amazonas State Research Support Foundation FAPEAM, process 01.02.016301.02472/2025-05. ATO (process 310966/2025-6) is the beneficiary of a research productivity grant from CNPq and Post-Doctoral studies at the Amazonas State University (UEA). The Project PDPG CAPES/FAPEAM Notice N.018/2020.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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