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Fish disease

Effects of Glucans and Nucleotides on the Immunity, Health, and Growth of Fish. A Review with Special Reference to the Egyptian Situation

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ABSTRACT

β-glucan and nucleotides have beneficial impacts on aquaculture species' health and growth. Studies on fish dietary nucleotides have revealed that may alter the structure of the intestines, increase resistance to stress, enhance the quality of the larvae by fortifying the brood supply, and promote growth. In the early phases of development and modify both innate and adaptive immunity. Nucleotides and β-glucan supplementation have demonstrated very constant positive effects on a variety of fish species, despite sporadic variability in physiological responses. Despite the fact that research on fish nutrition based on nucleotides is just getting started, and there are a lot of fundamental questions have not yet been addressed, observations to date have supported the idea that fish require nucleotides as contingent or semi-essential nutrients, and that further study is required to improve fish culture by supplementing the diet with nucleotides. Scientists have demonstrated that β-glucan can alter some significant immunological (lysozyme, phagocytic, oxidative burst and phenoloxidase activities) and biochemical (serum hemoglobin, serum protein, and total hemocyte count) characteristics, giving fish and aquatic organisms a more effective immune profile. These beneficial effects are thought to be caused by the supply of physiologically necessary amounts of nucleotides by diet because some tissues have a restricted capacity for synthesis (e.g. lymphoid). Fish feed on diet supplemented with β-glucan exhibited decreased susceptibility to genes linked to acute inflammatory reactions. Research has demonstrated that fish's immune defense is enhanced by β-glucan of fish and other aquatic creatures, strengthening their resilience to disease by boosting beneficial responses and lowering harmful ones.

Key words: β-glucan, nucleotides, Immune response, Fish, Immunostimulant

INTRODUCTION

Natural or synthetic substances known as immunostimulants are used to alter and strengthen an organism's immune response to diseases that usually come via disease-causing agents (Manoppo et al., 2015). These days immune-stimulating agents are frequently used since they are inexpensive, safe, and cause minimal environmental contamination. Extracts from plants, microbial byproducts, and polysaccharides are examples of immunostimulants which are incorporated into the diets of aquaculture creatures. To safeguard fish from contagious diseases, it is essential to make choices about the most appropriate and potent immune-stimulating agent. One of the well-researched immunostimulants, β-glucans, is frequently utilized to enhance animal and human health (Fusté et al., 2019). Aquaculture is growing in most emerging countries to fulfill the yearly increase of need for aquatic food products. However, it is well known that one of the major obstacles that fish farmers encounter is the occurrence of disease outbreaks brought on by harmful organisms. Aquaculture is expected to rise by 62% between 2010 and 2030, meeting more than two-thirds of worldwide demand for fishes and crustaceans and Mollusca, as a result of changing eating habits and population expansion (Verdegem et al., 2023). A significant barrier is the prevalence of aquatic animal diseases, which are made worse by international trade, system intensification, and climate change (Singh and colleagues, 2023). Farmers are forced to use antibiotics and disinfectants due to the ease with which pathogen evolution and disease outbreaks are facilitated by high-density cultures and intensified systems (Li et al., 2024). However, excessive use of these substances weakens animal immune systems and encourages the growth of microorganisms resistant to antibiotics, endangering human health worldwide (Devadas et al., 2024)

Furthermore, the usage of antibiotics has led to major issues, including the degradation of aquatic ecosystems and aquatic environments, the lingering presence of residues of antibiotics in fish meat, as well as the detrimental effects on human health. (Sumon et al., 2022). Alternative methods of disease prevention, like as vaccination and functional feed supplements that have been suggested in this area (Noman et al., 2024). Functional feed supplements, including immunostimulants and probiotics, have gained traction for their potential to enhance fish performance, immune systems, and feed utilization (Noman et al., 2024). Incorporating such supplements into fish diets could not only improve disease prevention but also contribute to better resource utilization, fostering sustainable aquaculture development (Mathan et al., 2024). The primary emphasis of this review is effect of dietary usage of β-glucan and nucleotides on the immunity, health and growth of fish and other aquatic species and current data on the applications in advanced aquaculture and the investigations that based on using of β-glucan and nucleotides in Egypt in different species of fish.

The origins and properties of β-glucans

The main structural components of the cell wall the β-glucans that store carbohydrates and provide defense against invasive infections. They can be present in cereal grains like barley and oats. fungi such as *Pneumocystis carini* and *Agaricus subrufesuns*, and baker yeast, *Saccharomyces cerevisiae*(Shah et al., 2017). Additional sources of β-glucans include certain bacteria species that belong to the Rhizobiaceae family and edible mushrooms like shiitake, lingzhi, and oyster mushrooms (Khan et al., 2017). The content of β-glucan varies based on the source. The amount of β-glucan in barley and oats and varies around 2% to 8%, but it makes up 50% to 60% of the entire polysaccharides found in the cell wall of the yeast (Nishantha et al., 2018). Additionally, the amount of β-glucan in various species of mushroom ranges from 8.608 g to 60.788 g/100 g Mass that is dry; wild-growing mushroom species such as bracket fungus have a larger amount of β-glucan (Sari et al., 2017).

β-glucans' size, shape, and solubility can all influence their activity and, consequently, their immunomodulatory effects. As indicated by Suchecka et al. (2016), Higher molecular weight β-glucans (like zymosan) are believed to have more significant cellular effects, such as activating leucocyte cells, the activity of phagocytes, antimicrobial properties, action of antioxidants, and activity of respiratory bursts, Conversely, β-glucans having a smaller molecular weight, such as glucan phosphate, have less influence on cells.

Mechanism of action of β-glucans

Both innate and acquired immune activity activation is significantly influenced by β -glucan. In addition to acting on invasive pathogens, b-glucan-stimulated innate immune responses also support the activity and function of developed immunity (Sakai, 1999).

β-glucans are responsible for several functions that fortify and safeguard the immune system and provide the best defense against possible health risks due to their ability to directly bind and activate macrophage cells and other white blood cells such as the cells of neutrophils and natural killer (NK) cells (Herre et al., 2004).

Numerous vertebrate and invertebrate organisms have been the focus of a lot of study. On β-glucan as an immunostimulant; Soltanian et al. (2009) provided great details about this topic. When β-glucan was given to Atlantic salmon *(Salmon salar)* through diet, the activity of respiratory burst was stimulated. According to several studies, administration of β-glucan through diet temporarily boosts the ability to withstand infection in gilthead sea bream, (Ortuno et al., 2002), *Clarias gariepinus* (Yoshida et al., 1995), Catla catla, Rohu (Sahoo and Mukherjee, 2002), and *Oncorhynchus tshawytscha* (Nikl et al., 1993).

Resistance to the microsporidian developed by rainbow trout Salmonae Loma is significantly influenced by the timing of b-glucan administration (Guselle et al., 2007). Lysozyme activity, HSP concentrations of gill, and liver were increased at thirty days, However, sea bass fed glucans and alginic acid at 15 days showed a significant increase in serum complement activity. According to Bagni et al. (2005), who recorded the effect of dietary glucan that is depending on duration. Only fish fed the Ergosan diet showed increased complement activity. The parameters of innate and specific immunity, survival rate, performance of growth, the conversion index in fish under treatment and fish under control did not change substantially over time. A key factor in boosting immune responses is the purity of the immunostimulant agent (β-glucan) that is provided.

Usage of β glucan as an adjuvant (substances that enhance immune response) and/or immunostimulant (biologically active compounds) to strengthen the fish immune system has grown (Filho et al., 2019). As stated by Bagni et al. (2005), β-glucan, which is derived from yeasts, mushrooms, seaweeds, and cereal plants, is the most beneficial bioactive component utilized in aquaculture. Scientists have demonstrated that β-glucans mainly strengthen fish's non-specific defenses, making them more resistant to infectious diseases. Fish have also shown signs of evolving specific defense, according to several research (Siwicki et al., 2004).

The immunological functions (lysozyme, complement, phagocytic, and serum bactericidal activity) of rohu *(Labeo rohita)* fed a diet containing 250 mg of β-glucan/kg peaked after 42 days of feeding, according to Misra et al. (2006), while the indices began to increase on day 28 of the trial. The experimental diet also increased phagocytic activity and lymphocyte proliferation. Chang et al. (2013) found that *(Epinephelus coioides*) exhibited significantly increased the lysozyme activity and complement activity against *Vibrio alginolyticus* when add in its diet mushroom β-glucan at 1 g and 2 g per kg diet. Beginning on day six and continuing until day thirty, the activities increased. According to Kaisa et al. (2018), the microbiota of the intestine plays essential function in preserving the shape of the intestine and barrier function; disturbances may result in inflammatory reactions (Przewł´ocka et al., 2020).

Prior studies have shown that inclusion of β-glucan in the diets of fish can affect gut microbiota's makeup. The composition of microbiota Solea senegalensis was altered by feeding β-glucan, for instance, with a reduction in the intestinal Vibrio proportions (Carballo et al., 2019). Likewise, when sea bass were fed diets enriched with β-glucan, the prevalence of the dysgonomonas species within the Bacteroidetes phylum was significantly lower. (Carda-Di´eguez et al., 2014). In a different study, β-glucan inclusion in the diet was associated with a reduction in the species richness and OTU count of the carp microbiota (Kühlwein et al., 2013). All these results are consistent with the findings of our ongoing study.

<u>Research on β-glucan's effects in Egypt</u>

The species of fish	Dose used	Time of experiment	Findings	Challenge with pathogen	The References
Oreochromis niloticus	**0.5 g/kg**	**One month**	Lysozyme activity ↑, increasing phagocytic activity and phagocytic index and interleukin 8↑, No change in Interleukin 1 beta	Deltamethrin	Dawood and others (2020)
Oreochromis niloticus	**0.5 g/kg**	**2 months**	Lysozyme activity ↑, increasing phagocytic activity and phagocytic index and *Tumor necrosis factor-alpha* Interleukin 1 beta ↑,	Crowding stress	Dawood, Metwally, et al. (2020)
Oreochromis niloticus	**1 BG and 0.5 BG g kg and 1 ASP, or 0.5 ASP**	**60 days**	Enhanced *Immunoglobulin M*, lysozyme, antioxidant enzymes, bactericidal, and phagocytosis which indicated improved immunity	Effect on Growth rate, Oxidative response and Immune Response	Dawood, Eweedah et al., (2020)
Oreochromis niloticus	**50 mg/kg)**	12 weeks	hematocrit values increased, hemoglobin, and white blood vessels, expression of genes and growth rate	Genetically Improved Farmed Tilapia	Dawood, Magouz et al., (2020)

Oreochromis niloticus	**0.5 g/kg**	**2 weeks**	Lymphocytes↑, ↑ *Immunoglobulin M* Lysozymes↑, Nitric oxide↑, Interleukin-8↔	Atrazine, *Aeromonas sobria*	Neamat-Allah et al. (2020)
Oreochromis niloticus	**5 g/kg**	**2 weeks**	Phagocytic activity↑, Phagocytic index↑, *Respiratory burst activity*↑, *Tumor necrosis factor-alpha*↑	*Aeromonas hydrophila*	Sherif and Mahfouz (2019)
Oreochromis niloticus	**0.5 & 1 g/kg**	**Eighty-four days**	↑*Immunoglobulin M*, serum Nitric oxide↔, Lysozyme activity increased↔	*Aeromonas hydrophila*	Hosseny et al. (2018)
Oreochromis niloticus	**2 g/kg**	**21 days**	Interleukin-8↔↑, *Tumor necrosis factor-alpha* ↑, *Toll-like receptor*↑, and ↑*Immunoglobulin M*	*Streptococcus iniae*	Salah et al. (2017)
Oreochromis niloticus	**1 g/kg**	**Twenty-one days**	Respiratory burst activity ↑, Phagocytic activity ↑,Bactericidal activity ↑, Lysozyme activity↑, Nitric oxide↑	*Aeromonas hydrophila*	El-Boshy et al. (2010)
Oreochromis niloticus	**β-glucans + mannan oligosaccharides**		killing ↑, Phagocytic activity ↑, ↑, Lysozyme activity↑, Nitric oxide↑↑, Lymphocytes ↑, Survival↑ against Yersinia ruckeri		Selim & Reda, (2015)
Pagrus major	**β-glucan + Vitamin C**		*Respiratory burst activity* ↑, ↑Lysozyme Alternative complement activity ↑, Peroxidase activity ↑, Bactericidal activity ↑		Dawood et al. (2017)
Pagrus major	**β-glucan + *Lactobacillus plantarum*(heat-killed)**		Bactericidal activity ↑, Alternative complement activity ↑, Lysozyme activity↑, Peroxidase activity ↑		Dawood et al. (2015)

Increasing (↑), decreasing (↓), and no significant changes were seen in the experimental fish when compared to the controls.

Nucleotides: Structure

Nucleotides are important metabolites which are significant for structural, metabolic, energetic, and regulatory processes (Rudolph, 1994). According to several studies, dietary nucleotide supplementation improved several physiological processes in numerous species, particularly in the early stages of life (Gil, 2002). It has been suggested that during periods of rapid development or high metabolism, particular organs, such as cells of immune system and cells of gastrointestinal system, may require more nucleotides than others.

Nucleotides (NT) are low molecular weight compounds composed of a nitrogenous base, one to three phosphate groups, and a pentose sugar. (Cosgrove, 1998). The nucleobases are categorized as either pyrimidines, which include cytosine (C), thymine (T), and uracil (U), or purines, which include adenine (A) and guanine (G). Ribose and deoxyribose are examples of pentose sugars. A nucleoside (NS) is made up of a pentose sugar connected to a purine or pyrimidine base, whereas an NT is a phosphate ester of NS (Li and Gatlin, 2006). NTs are the structural units used in the synthesis of DNA and RNA.

The impact of dietary NTs on performance of growth rate and the gastrointestinal tract

NT inclusion in diets is crucial for the establishment of healthy gastrointestinal (GI) tract functions in various species. For instance, the proximal, mid, and distal intestines of Commercially NT additions are added to the diet of Atlantic salmon. The mean fold heights of the fish fed the control diet were substantially lower than those of the fish fed ("Optimum" 0.03% of the overall feed). This could have resulted in a larger surface area of the gut (Burrells et al., 2001). Additionally, NT inclusion in diets may have an impact on the flora that lives in the gastrointestinal tract. After weaning pigs exposed to stresses, Sauer et al. (2010) found that NT additions in diets could alter the composition of gastrointestinal microbiota (Moore et al., 2011). According to the authors, dietary NTs may be a viable substitute for antimicrobial growth enhancers in piglets. Dietary NTs have an impact on the performance of growth of some species some species particularly during the early stages of growth, like in Atlantic salmon. (Burrells *et al*., 2001), *Oreochromis niloticus* (Ramadan *et al*., 1994), rainbow trout (Mohebbi *et al*., 2013), grouper (Lin *et al*., 2009), Pacific white shrimp (Li *et al*., 2007), weanling pigs (Li *et al*., 2015) and mice (Xu *et al*., 2013). Even though nucleotide supplementation was previously demonstrated to enhance weaned rats' development on low-protein diets (Gyo¨rgy, 1971), it has been accepted that under typical circumstances, de novo nucleotide synthesis is sufficient to sustain the growth rate. (Cosgrove, 1998). An outside source of nucleotides may stimulate fish growth and crustaceans to achieve their high rate of cell reproduction in their early phases, according to Borda et al. (2003), who evaluated data on application of nucleotides in the diets of to sea bream larvae. Additionally, Person-Le Ruyet et al. (1983) found that following 55-day feeding study, turbot larvae (around 100 mg/fish) fed supplemented diet with inosine- (1.3% of diet for 6 days, 0.13% for 45 days) showed considerably improve the growth and survival rate. According to their later research, giving turbot larvae diet contained 0.77% inosine for 10 or 20 days also markedly boosted their weight gain (approximate beginning weight of 230 mg/fish). According to Me´tailler et al. (1983), the enhancement of growth of inosine was thought to be caused by increased feed consumption at the beginning of weaning, which encouraged quicker consumption of food and reduced water-borne nutrient leaching, or it might have had a role in metabolism. Along with inosine, combinations of nucleotides and metabolites (such Ascogen R, Chemoforma Co., Basal, Switzerland) have additionally been demonstrated to occasionally increase growth in fish, including young rainbow trout (Adamek et al., 1996) and tilapia larvae (Ramadan and Atef, 1991). On the other hand, most fish that are young or subadults seem to have a negligible growth-enhancing impact (Li et al., 2004).

The effect of dietary NTs on immune function

Dietary NT may be necessary to maintain adequate immunological function. (Carver et al., 1990). Li et al. (2005) investigated that Growth, stress tolerance (measured by plasma cortisol after confinement), and in situ challenge by co-habitation with A. ocellatum in juvenile red drums were not significantly impacted by the dietary addition of 0.2% NT (Optimum).The potential impact of pure NT mixes on juvenile red drums was also examined by Li et al. (2007). They discovered a brief growth-enhancing effect that lasted for the first week before disappearing. However, the immune system function was improved by dietary supplementation of 0.5 or 1% NT (Ascogen), as indicated by the secretion of superoxide anion by head kidney macrophages, intestinal fold, and microvillus height in the same fish species. (Cheng et al., 2011). Burrells et al. (2001) found that adding dietary NT (0.03%, Optimum) increased the survival rates of rainbow trout after challenging the infectious salmon anemia virus and V. anguillarum.

According to Leonardi et al. (2003), dietary NT (Optimum) enhanced the number of B lymphocytes and decreased the release of plasma cortisol. It also improved the cells' resistance to the infectious pancreatic necrosis virus. Tahmasebi-Kohyani et al. (2012) recently discovered that feeding fingerling rainbow trout 0.15-0.2% NT supplementation improved their performance in handling and crowding stress (plasma cortisol, glucose, and ion concentration), immune function, lysozyme activity, and IgM level), as well as their resistance to *S. iniae*.

Studies on the immunostimulatory effects of Nucleotides in Egypt

Nucleotide used	**Dose incorporated in diet** (kg−1 diet)	**Period of administration**	**Species**	**Results**	**Authors**
Ascogen	2 and 5 g	4 months	Hybrid tilapia	↑growth and survival	Ramadan and Atef (1991)
Ascogen	5 g	4 months	Hybrid tilapia	↑ antibody titer after vaccination and mitogenic response of lymphocyte	Ramadan et al., (1994)
nucleotides and/or beta-glucan	(200 mg/kg diet)		Broiler chicken	Improving parameters growth of, morphology of intestine, and a number of biochemical parameters of broiler chicken	Aya et al., (2024)
Nucleotides	0.05%, 0.15%, and 0.25% NTs	30 days	Nile tilapia	improved cytokine gene expression, leukocyte cells, antioxidant activity, non-specific immunity, and resistance to disease in addition to blood proteins.	Reda et al., (2018)
nucleotide	0.5, 1.5 and 2.5 g	60 days	Nile tilapia	highest growth performance, as well as the expression of the genes for Ghrelin, insulin-like growth factor, and growth hormone	Selim et al. 2020
a commercial nucleotide Nucleoforce Fish™	250mg/kg or 500mg/kg	150 days	Gilthead seabr eam	**Enhancement** of the mitochondrial enzyme in the liver **activity,** state of antioxidants**,** expression of immune genes**, and gut microbial ecology**	El-Nokrashy Et al., (2021)

The consequences of combining nucleotides and β-glucan on aquaculture

It has been demonstrated that using two or more supplements together has a synergistic effect that produces better results than using them separately (Hany et al., 2024). According to earlier studies, pigs' growth performance might be enhanced by applying nucleotides and β-glucan together (Huang et al., 2023).

Nucleotides and β-glucan have prebiotic and anti-inflammatory benefits by strengthening fish's resilience to stress and boosting their immune systems. (Pogue et al., 2021).Numerous physiological and metabolic processes depend on nucleotides. (Krüger and van der Werf, 2018). In periods of rapid growth or when certain disorders are present, endogenously produced nucleotides may not be enough to meet the needs of tissues and cells with high metabolic activity, even if they can typically meet the needs of a normal metabolism. (Norton et al., 2001). As a result, more nucleotides are necessary to promote the best possible cellular growth and function. It has been demonstrated that dietary nucleotides improve the growth of fish and utilization of feed. (Liu, 2016), immune response and stress resistance (Reda et al., 2018), health of the intestine (Cheng et al., 2011), particularly the gut microbiota's homeostasis (El-Nokrashy et al., 2021), and quality of flesh (Tie, 2018). Numerous natural sources contain the chemically diverse and highly conserved carbohydrate known as β-glucan. Several research have documented more beneficial effects for fish due to of β-glucan addition, such as improving health of intestine (Carballo et al., 2019), enhancing immunological response (Ching et al., 2021), increasing stress tolerance (Salah et al., 2017), and promoting growth (Song et al., 2020). Furthermore, it has been discovered that dietary glucan enhances the quality of pig meat by raising intramuscular fat content and muscle pH, decreasing muscle drip losses, and altering the ratio of saturated to unsaturated fatty acids. (Luo et al., 2019), However, it is unclear how β-glucan supplementation affects the quality of fish meat. Fish flesh quality is determined by several physicochemical factors as pH, water-holding capacity, and the texture of the flesh (Jiang et al., 2016). Previous research has demonstrated that supplements containing β-glucan and nucleotides can both enhance the quality of flesh. For example, it has been discovered that feeding broilers β-glucan improves the quality of their flesh. (Cho et al., 2013) and pigs (Luo et al., 2019) by lowering the amount of cooking loss. In a similar way it has been observed that dietary nucleotides enhance the quality of grass carp flesh by preventing the decrease in muscle pH and minimizing muscle cooking loss. (Tie, 2018). As a strong adjuvant, β-glucan can successfully elicit host immunological responses, both innate and adaptive. (Qi et al., 2011). Additionally, it can lessen the inflammatory response by inhibiting TLRs and lowering the synthesis and release of proinflammatory cytokines such as IL-1β and tumor necrosis factor-α (TNF-α). (Kankkunen et al., 2010). Nucleotides' immunomodulatory qualities have also been demonstrated in fish, as demonstrated by their capacity to reduce intestinal inflammation in zebrafish when taken as supplements. (Guo et al., 2017), as well as suppress the grass carp's TNF-α mRNA expression level. (Tie et al., 2021).

CONCLUSIONS AND PERSPECTIVES

It is widely acknowledged that the use of immunostimulants in fish trials results in positive outcomes like protection against diseases because they boost humoral and cellular responses. However, care must be given regarding problems like tolerance, undesirable side effects like immunosuppression from using excessive amounts of immunostimulants, or undesirable effects brought on by long-term usage of such substances. The use of β -glucan and nucleotides in aquaculture may improve financial outcomes and lower production costs (volume of investment).The cost-benefit analysis of these feed additives needs to be conducted for other commercially significant marine species as well as in a broader perspective across the production cycle. Combined application of nucleotides and β-glucan might provide more advantages than supplementing with β-glucan or nucleotides alone. It is hoped that several difficulties, focusing especially on the immunological response polarization following binding of immunostimulants to receptors, would become public knowledge following the development of proteomic and genomic methods for several fish species.

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