

Immune Enhancement Strategies as Alternative to Antibiotics in Aquaculture

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ABSTRACT

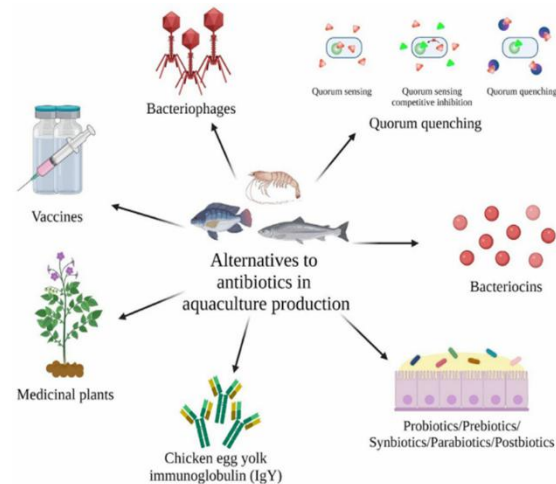
Aquaculture is a rapidly growing food industry that serves as an important source of protein worldwide. However, disease outbreaks continue to pose a major threat to production, often leading to economic losses and increased reliance on antibiotics for disease control. The excessive use of antibiotics in aquaculture has raised serious concerns due to its negative impacts on the environment, disruption of fish metabolism, and the emergence of antibiotic-resistant microorganisms that threaten public health. Various antibiotic alternatives, such as medical plants, Probiotics, Prebiotics, Aquatic organism products, organic acids, vaccines, bacteriophages, bacteriocins, quorum quenching, and chicken egg yolk immunoglobulin (IgY) have been explored as alternative strategies. These alternatives offer promising solutions to enhance disease resistance and maintain fish health while minimizing environmental impact. Hence, the adoption of such innovative and eco-friendly practices is essential for promoting sustainable aquaculture, ensuring animal welfare, and safeguarding human health.

INTRODUCTION

Antibiotics are antimicrobial agents primarily used to inhibit or kill pathogenic bacteria by disrupting cell membranes, interfering with protein or DNA synthesis, or inhibiting essential enzyme activity. Their effectiveness is largely due to their selective toxicity toward prokaryotic cells. However, many antibiotics are non-biodegradable and can persist in the body and environment long after excretion. Antibiotics are widely used as therapeutic or prophylactic agents in aquaculture. The continuous and excessive use of antibiotics has raised serious concerns for both aquatic organisms and human health. Residues of these drugs in edible tissues can lead to allergic reactions, toxic effects, disturbances in intestinal microflora, and the development of antibiotic resistance.

A significant proportion of antibiotics administered through feed are not fully absorbed by fish or shrimp and instead enter the surrounding environment. These compounds can accumulate in sediments, disrupt natural ecological processes, and adversely affect aquatic ecosystems. Antibiotic contamination has also been reported in farmed species such as tilapia (Bortolotte *et al.* 2021), Rainbow trout (Adel *et al.* 2017) and salmon (Miranda *et al.* 2018) across different regions (Almashhadany *et al.* 2024). Moreover, antibiotic residues have led to the rejection of a notable percentage of aquaculture exports by major markets such as the US and EU (FAO 2020). Together, these concerns highlight the urgent need for more responsible and sustainable antibiotic use in aquaculture to minimize environmental impact and combat antimicrobial resistance.

Immunity-Based Strategies in Modern Aquaculture



1. Medicinal plants

Medical plants are natural immunostimulants that have gained attention in aquaculture as natural alternatives to synthetic chemicals and antibiotics. They contain a variety of bioactive compounds, such as tannins, alkaloids, phenolics, flavonoids, terpenoids, saponins, and glycosides, which can be extracted using solvents or used directly in raw form. These compounds promote growth and appetite, enhance immunity, and provide antimicrobial, antioxidant, and anti-stress effects in fish (Bondad-Reantaso *et al.*, 2023). Some of the commonly used medical plants in aquaculture are garlic bulb, ginger root, onion leaf, fenugreek seed, basil leaf, and peppermint leaf.

2. Probiotics

Probiotics are live, non-pathogenic microorganisms, mainly bacteria and yeast, such as *Lactobacillus* and *Bifidobacterium*, that confer health benefits to the host when administered in sufficient amounts. In aquaculture, probiotics are recognized as a sustainable alternative to antibiotics because of their effectiveness in maintaining gut health and preventing diseases. They are amplified by dynamic interactions between the host,

microbiota, and surrounding environment (Tong *et al.*, 2023).

3. Prebiotics

Prebiotics are a group of carbohydrates, typically oligosaccharides, that are non-digestible to the host but digestible to specific bacterial populations residing in the gut. They act as selective substrates for specific intestinal bacteria, which stimulate the growth and activity of beneficial microorganisms in the gut, boosting host health. In aquaculture, immunosaccharide-based prebiotics have gained considerable attention due to their ability to enhance growth, feed efficiency, and immune responses. Common prebiotics used in freshwater fish include fructooligosaccharides (FOS), mannanoligosaccharides (MOS), inulin, galactooligosaccharides (GOS), xylooligosaccharides (XOS), and β -glucans.

4. Aquatic organism product

The use of aquatic products to enhance fish immunity has become an important focus in aquaculture. Compounds such as chitin, chitosan, and seaweed improve both humoral and cellular immune responses, boost antioxidant defenses, and regulate immune-related gene expression, thereby increasing disease resistance and stress tolerance. Chitin and chitosan, commonly derived from crustaceans, are effective at low inclusion levels (0.5–1%) but may cause metabolic or digestive issues at higher doses. Chitin functions as a PAMP, activating immune receptors (e.g., TLR2, dectin-1, and mannose receptors) and signaling pathways such as NF- κ B, leading to cytokine production. Seaweeds, including red (*Asparagopsis taxiformis*) and brown (*Dictyota intermedia*) species, also enhance immunity and antioxidant capacity of fish. However, the optimal dosage and duration vary across species, and excessive use may result in oxidative stress, reduced

digestion efficiency, immune suppression, or toxicity. Therefore, careful application and further research are needed to maximize their benefits.

5. Organic acid

Organic acids, such as citric, lactic, benzoic, and formic acid, are short-chain fatty acids with antimicrobial properties that can enhance growth, nutrient utilization, and disease resistance in aquatic animals. Studies in carp, tilapia, salmon, and rainbow trout have shown that dietary organic acids improve growth performance, feed efficiency, and immunity (Reda *et al.* 2016; Ng and Koh 2017). Salts of formic acid, such as potassium diformate (KDF), further enhance growth, feed utilization, and nutrient digestibility in tilapia (Lim *et al.* 2010). Additionally, organic acids inhibit gram-negative bacteria and modulate gut microbiota, highlighting their potential as natural alternatives to antibiotics in aquaculture.

6. Vaccine

Vaccines are prepared from pathogens, such as bacteria or viruses, or their products that are weakened, inactivated, or modified pathogens or their components to prevent diseases. In aquaculture, they can be administered orally, by injection, or through immersion, and can stimulate both humoral and cell-mediated immune responses. While antibodies are effective against extracellular pathogens, intracellular bacteria such as *Salmonella*, *Listeria monocytogenes*, and *Mycobacterium* require strong cell-mediated immunity. This involves Th1 cytokines, macrophage activation, and cytotoxic T lymphocytes (CTLs) that destroy infected cells. Live-attenuated vaccines are particularly effective in inducing this response, although inactivated vaccines can also be effective depending on the adjuvant used.

7. Bacteriophages/Phages

Bacteriophages are viruses that infect and kill bacteria, making them promising alternatives to antibiotics in aquaculture. Naturally abundant in aquatic environments, they replicate inside host bacteria and destroy them, particularly during the lytic cycle. Phage therapy primarily uses lytic phages and can be applied through water, feed, injection, or topical methods, with bath treatments being effective for external infections and oral delivery suitable for gut-related infections. Phages produce lytic enzymes that break bacterial cell walls and biofilms and may also stimulate fish immunity. They are highly specific, environmentally safe, self-replicating, and stable under various conditions. Phage therapy can be applied as active (replicating) or passive (high dose) treatment and may use single phages or phage cocktails, the latter being more effective and reducing resistance. It has shown success against key fish pathogens, such as *Vibrio*, *Aeromonas*, *Flavobacterium*, *Edwardsiella*, *Streptococcus*, and *Lactococcus garvieae*.

8. Quorum Quenching (QQ)

Quorum quenching (QQ) is an innovative biocontrol strategy that disrupts bacterial communication systems via quorum sensing (QS). QS allows bacteria to coordinate activities such as virulence, biofilm formation, and host invasion through signaling molecules called autoinducers. QQ interferes with these signals by blocking or degrading them, thereby reducing the ability of pathogens to cause diseases. QQ agents include beneficial bacteria, enzymes, and natural compounds. *Bacillus* species are key producers of QQ enzymes, with strains such as *Bacillus licheniformis*, *B. velezensis*, *B. subtilis*, *B. lentus*, and *B. firmus* showing strong effectiveness against pathogens such as *Aeromonas hydrophila* and *Vibrio* spp. and significantly improving survival rates in fish

and shrimp. Additionally, natural compounds, such as curcumin and coumarin, can inhibit QS. Overall, QQ is a promising and sustainable alternative to antibiotics for aquaculture.

9. Bacteriocins

Bacteriocins are ribosomally synthesized antimicrobial peptides produced by bacteria such as *Bacillus* and *Lactococcus* and are considered eco-friendly alternatives to antibiotics in aquaculture. They act by disrupting bacterial cell walls, inhibiting cell wall synthesis, forming pores, and interfering with DNA, RNA, and protein metabolism, leading to rapid pathogen death. Some bacteriocins also stimulate the immune system of fish. They are effective against key pathogens, including *Lactococcus garvieae*, *Aeromonas* spp., *Pseudomonas* spp., and *Vibrio* spp. However, their use is limited by their potential toxicity to beneficial gut microbiota, disruption of ecological balance, and the risk that bacteriocin-producing bacteria may revert to pathogenic forms, requiring careful and controlled application.

10. Chicken egg yolk immunoglobulin (IgY)

Chicken egg yolk immunoglobulin (IgY) is an effective passive immunization tool in aquaculture because hens produce high levels of pathogen-specific antibodies that can be easily extracted from the egg yolk. Compared to IgG, IgY is more stable, cost-effective, and suitable for large-scale use. It can be administered as purified IgY, egg yolk extract, or powder via injection, immersion, or oral routes. IgY has shown strong protective effects in various species, including fish and shrimp, against pathogens such as *Vibrio* spp. and *Aeromonas salmonicida*. It improves survival rates through injection, immersion, and oral delivery, with immersion being particularly effective against infections entering through the skin and gills. Despite these advantages,

IgY remains a safe, versatile, and antibiotic-free approach for disease prevention and control in aquaculture.

CONCLUSION

A comprehensive and integrated approach is essential to reduce antibiotic dependence and effectively address antibiotic resistance in aquaculture while maintaining fish health and productivity. This involves combining preventive measures, such as improved farm management and vaccination, with targeted therapeutic strategies. Several effective alternatives to antibiotics are available, including medicinal plants, probiotics, aquatic organism products, vaccines, QQ, bacteriophages, bacteriocins, and IgY, which enhance the natural immune response of fish and improve disease resistance. Additionally, advances in biotechnology have enabled the development of innovative solutions, such as phage therapy and other bio-based treatments that specifically target pathogens. To ensure the successful adoption of these alternatives, further research is required to evaluate their efficacy, cost-effectiveness, and environmental impacts across different aquaculture systems. Collaboration among scientists, industry stakeholders, and regulatory authorities is crucial for refining these approaches, establishing proper guidelines, and promoting their responsible use. Together, these efforts will support a sustainable, ethical, and resilient aquaculture industry.

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