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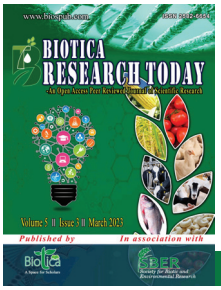

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Immunostimulants as an Aquatic Animal Health Management Perspective

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Abstract

The majority of medications, chemicals, and vaccinations are only partially effective, but immunostimulants overcomes these drawbacks. It can be found in both biological and synthetic forms. It is used in aquaculture as a prophylactic agent to prevent disease from occurring. It stimulates the host's immune response and strengthens the immune system. It improves the survival and disease resistance of cultured organisms while also being cost effective. In this paper, we briefly reviewed about the immunostimulant's perspectives in the fisheries sector, especially in larval rearing. This review sheds light on different immunostimulants categories, significance during rearing and their role in aquaculture.

Keywords: Aquaculture, Disease management, Immune system, Immunostimulants

Introduction

In India, the fisheries sector is one of the fastest-growing animal food productions in recent decades it has increased its production from 0.75 million metric tons in 1950-1951 to 16.24 million metric tons in 2021-2022 (Handbook of Fisheries Statistics, 2022). This increased production is possible because of the use of prophylactic and therapeutic agents in aquaculture. Chemotherapeutics have been used to treat bacterial infections in cultured fish. However, the prevalence of drug-resistant bacteria has become a major issue in fish farming. A vaccine is the best method against infectious disease due to a highly expensive and highly skilled person is required; farmers are not using the vaccine to control the disease. Immunostimulants are a farmer and eco-friendly disease-preventive alternative technique and one of the most promising alternative techniques to strengthen fish immune systems. To decrease the pathogen affecting aquatic animals the use of immunostimulants will stimulate and strengthen the host immune response. The use of immunostimulants in aquaculture is the most advisable and more advantageous prophylactic measure.

Immunostimulants and Their Classification

An immunostimulant is a naturally occurring compound that modulates the immune system by increasing the host's resistance against diseases that in most circumstances are caused by pathogens (Bricknell and Dalmo, 2005).

Categories of Immunostimulants

1. **Specific immunostimulants**: It will provide antigenic specificity in immune response such as vaccines or any antigen.

2. **Non-specific immunostimulants**: It acts irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immunostimulators.

Types of Immunostimulants based on Origin

1. **Synthetic Chemicals**: Levamisole, FK-565 (Lactoyltetrapeptide from *Streptomyces olvaceogriseus*), Quaternary ammonium compounds (QAC).

Article History

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2. **Biological Substances**

• Bacterial derivatives: MDP (Muramyl dipeptide from *Mycobacterium* species), Lipopolysaccharide (LPS), Freund's complete adjuvant (FCA), EF203.

• Yeast derivatives: b-1,3 glucan, b-1,6 glucan.

• Nutritional factors: Vitamin C and E, n-3 fatty acid.

• Hormones: Growth hormone, Prolactin, tri-iodothyronine.

• Cytokines: Interferon, Interleukin.

• Polysaccharides: Chitosan, Chitin, Lentinan, Schizophyllan, Oligosaccharide.

• Animal and plant extracts: Ete (tunicate), Hde (Abalone), Glycyrrhizin, Firefly squid, Quillaja, Saponin (Soap tree).

• Others: Lactoferrin, Soyabean protein, Quil A, Spirulina, *Achyranthes aspera* (Herb), *Mucor circinelloides* (Fungi).

Methods of Administration

1. Injection

The most common and effective injection route is intraperitoneal which is the least stressful to fish compared to other injection methods. This method is mostly used in intensive culture techniques because it consumes lots of time and it requires intensive labor as well as the costliest method too. It is applicable only for large-size fishes of more than 10-15 g in body weight. The major advantage of this method is it produces a strong non-specific immune response. *E.g.*: Glucan injected to channel catfish intraperitoneally shows an increase in phagocytic activity and reduces fish mortality challenge with *Edwardsiella ictaluri*.

2. Immersion

The immersion method of administration is cost-effective and it is the least stressful to fish compared to the injection method. It is widely used for small-size fish, where the injection is impractical. This method is very effective during the acclimatization of juveniles to ponds in field conditions. *E.g.*: Using immersion of levamisole showed an increase in circulating leukocytes, phagocytic rate and increased protection against *P. damselae* sub sp. *piscicida* in *European seabass*.

3. Oral Uptake

It is the most cost-effective method with economically viable. It is widely used in extensive aquaculture systems. Immunostimulants powders are mixed with feed using a fish oil coating as a binder. The bioencapsulation method is also followed to immunize the fish larvae during their early larval stages with live feed organisms.

Mode of Action

Immunostimulants work by activating organisms' immune systems, boosting their resistance to infections (Figure 1). It is dependent on the type, dosage, mode of administration, timing, and length of exposure. Immunostimulants increase the ability of macrophages, complements, lymphocytes and non-specific cytotoxic cells to phagocytose and kill the bacteria. Various immunostimulants and their mode of action listed in the (Table 1), immunostimulatory effect on fish and shrimp is listed in the (Table 2).

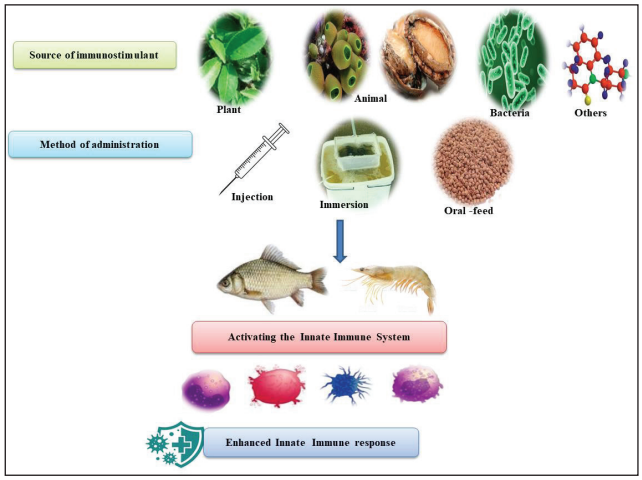

Figure 1: Overview of Immunostimulant in aquaculture

Table 1: Various Immunostimulants and their mode of action

Immunostimulants	Mode of action
Levamisole, Freund's Complete Adjuvant (FCA), Glucans, Muramyl dipeptide, FK-565 (Lactoyltetrapeptide from *Streptomyces olivaceogriseus*)	Stimulators of T-lymphocytes
Bacterial endotoxions, Lipopolysaccharides	Macrophage activator
Glucans, Chitin and Chitosan	Macrophage activator, Stimulation of B-cells
Chemotoxins	Inflammatory
Detergents and Sodium dodecyl sulphate, Quaternary ammonium compounds (QAC), Saponins	Cell membrane modifiers
Vitamin C and E, n-3 fatty acids	Nutritional factors
Animal and fish extracts	Mitogens

(Source: Mastan, 2015)

List of Pathogens that are Effectively Controlled using Immunostimulants

Bacteria: *Aeromonas hydrophila*, *Aeromonas salmonicida*, *Edwardsiella tarda*, *Edwardsiella ictaluri*, *Vibrio anguillarum*, *Vibrio vulnificus*, *Vibrio salmonicida*, *Yersinia ruckeri*, *Streptococcuss* sp., *C. butyricum*, *E. seriolacida*.

Virus: Infectious hematopoietic necrosis (IHN), Yellowhead virus (YHV), Viral hemorrhagic septicemia (VHS).

Parasite: *Ichthyophthirius multifiliis, Crytocaryons* (Sakai, 1999).

Significance of Immunostimulants in Larval Rearing

Immunomodulation of larval fish has been offered as a possible approach for boosting larval survival by increasing the developing animals' innate responses until their adaptive immune response is adequately developed to support an

Table 2: Imunostimulatory effect on fish and shrimp

Agent	Fish	Administration	Results
Levamisole	Carp	ip	Increased phagocytosis
		oral	Increased NBT
		im	Increased phagocytosis and CL
	Trout	in vitro	Increased phagocytosis and NBT
		ip	Increased phagocytosis and CL
		im	Increase complement
FK-565 (Lactoyl tetrapeptide from *Streptomyces olivaceogriseus*)	Trout	ip	Increased phagocytosis
		in vitro	Increased antibody
MDP (Muramyl-dipeptide)	Trout	ip	Increased phagocytosis and CL
LPS (Lipopolysaccharide)	Catfish	in vitro	Increased interleukin 1
	Plaice	ip	Increased macrophage migration
	Redseabream	ip	Increased phagocytosis
	Gold fish	in vitro	Increased macrophage activating factor
	Salmon	in vitro	Increased phagocytosis and NBT
FCA	Coho salmon	ip	Increased phagocytosis
	Brook trout		
	Trout		
	Yellow tail		
Vibrio bacteria	Trout	im	Increased phagocytosis
	Prawn	ip, im	
	Shrimp	Im, ip, oral	
Chitin	Trout	ip	Increased phagocytosis
EF203 (Fermented products of chicken egg)	Trout	oral	Increased phagocytosis,NBT and CL
Chitosan	Trout	Oral	Increased phagocytosis and NBT
		ip	Increased NBT
		im	Increased killing
Yeast glucan	Salmon	ip, oral	Increased complement and lysozyme
	Catfish	ip	Increased phagocytosis, killing and antibody production
		oral	Increased NBT
	Trout	ip	Increased lysozyme, killing, production of superoxide anion
	Shrimp	im	Inceased phenoloxidase
		in vitro	Increased NBT, CL
	Turbot	oral	Increased lysozyme, CL
Tunicate	Eel	ip	Increased phagocytosis
	Catfish		
Abalone	Trout	ip	Increased CL, phagocytosis and natural killer cell
Firefly squid	Trout		Increased mitogen. NBT and killing
Vitamin C	Catfish	oral	Increased complement, phagocytic index,

Table 2: Continue...

Agent	Fish	Administration	Results
	Salmon		Increased complement, macrophage activating factor, NBT
	Trout		Increased proliferation and macrophage activating factor
Vitamin E	Salmon	oral	Increased Phagocytosis
	Turbot		
Vitamin A	Salmon	oral	Increased antiprotease activity and migration

(Source: Sakai, 1999)

[Abbrevations: ip - intra peritoneal route, im - intramuscular route, CL - chemiluminescent response, FCA - Freund's Complete Adjuvant, LPS - Lipopolysaccharide, MDP - Muramyl-dipeptide, NBT - Nitroblue tetrazolium reaction]

effective response to the pathogen. When treated with an immunostimulant, larval fish have the potential to boost their innate defense mechanisms prior to pathogen exposure or to improve survival after pathogen exposure. Larval fish can be bathed in a solution of an immunostimulant or it can be incorporated into their diet to provide improved protection through crisis periods such as the end of yolk sac/ first feeding or metamorphosis (Bricknell and Dalmo, 2005).

Evaluating the Efficacy of Immunostimulants

There are two main procedures for evaluating the-

1. in vivo, such as a challenge test using fish pathogens, and

2. in vitro, such as the measurement of the efficiency of cellular and humoral immune mechanisms.

Conclusion

This study concludes that immunostimulant plays a prominent role in aquaculture and aquatic animal health management sector. It increases the survival of larval fish rearing and increase disease resistance in cultured fish and shrimp. The use of immunostimulants can protect fish from several infectious diseases and decrease mortality rates. It can also promote recovery from immunosuppression states caused by stress. Even vaccination is not effective against Bacterial kidney disease and some viral infection; improper handling, overuse of chemotherapeutic agents leads to antimicrobial resistance to aquaculture. To overcome these limitations immunostimulant is the best option. Immunostimulants are thought to be safer than chemotherapeutics and their range of efficacy is wider than vaccination. The combination of vaccination and immunostimulant administration may also increase the potency of vaccines. Hence, it is expected that immunostimulants are the most dependable and promising strategy to control the emerging disease in aquaculture in the near future.

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