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Microalgae-Derived Bioactives as Immunonutrients in *Litopenaeus vannamei* Aquaculture: Mechanisms, Efficacy, and Future Prospects

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ABSTRACT

Shrimp aquaculture, particularly the farming of *Litopenaeus vannamei*, has experienced rapid growth over the past two decades. However, this intensification is frequently challenged by disease outbreaks, environmental stressors, and the overuse of antibiotics, which have raised serious concerns regarding antimicrobial resistance (AMR) and environmental degradation. Immunonutrition—the strategic use of functional dietary components to modulate immune responses—has emerged as a sustainable alternative to conventional chemotherapeutic interventions. Among various immunonutrients, microalgae have gained increasing attention due to their rich profile of bioactive compounds, including polyunsaturated fatty acids (PUFAs), pigments such as astaxanthin and fucoxanthin, sulfated polysaccharides, vitamins, and antioxidant peptides. This review highlighted the immunomodulatory mechanisms and efficacy of microalgae-derived compounds in enhancing the innate immune response of *L. vannamei*, including increased phenoloxidase activity, total hemocyte count (THC), and the expression of key immune genes. Comparative insights with other immunonutrients, including probiotics, β-glucans, phytogenics, and vitamins, were provided to position microalgae as a multifunctional and promising solution. Finally, current limitations and future directions for the development, application, and commercial integration of microalgae in shrimp aquafeeds were discussed. This review underscores the potential of microalgae-based immunonutrition to support disease-resilient and environmentally responsible shrimp aquaculture.

INTRODUCTION

Shrimp aquaculture faces persistent challenges related to disease outbreaks, antibiotic resistance, and environmental stressors. *Litopenaeus vannamei*, or the whiteleg shrimp, dominates global shrimp production due to its high market value, rapid growth, and adaptability **(Zhang *et al.*, 2024)**. The global production of *L. vannamei* increased significantly from 158 thousand tonnes in 2000 to 5.8 million tonnes in 2020, with an estimated value rising from USD 854.38 million to USD 35.45 billion over the same period **(FAO, 2023)**. However, the intensification of farming practices has led to frequent episodes of infectious diseases, necessitating innovative strategies to improve shrimp health and resilience.

Immunonutrition, which integrates nutritional science with immunological outcomes, offers a promising approach. The concept involves using specific dietary components to enhance immune function and disease resistance, thereby reducing the need for chemical agents. The overuse of antibiotics in aquaculture has become a major concern due to the emergence of antimicrobial resistance (AMR), residual contamination in aquatic environments, and potential human health risks through the food chain **(Ahmed *et al.*, 2024; Agbabiaka *et al.*, 2025; Yi *et al.*, 2025)**.

Functional feeds based on immunonutrition offer a natural and sustainable alternative by strengthening shrimp's innate immune defenses, thereby decreasing reliance on antibiotics and contributing to responsible aquaculture practices **(Vasquez-Moscoso *et al.*, 2025; Zhang *et al.*, 2025)**. This review explored how functional feeds, particularly those containing microalgae and nano-formulated bioactive compounds, can be employed to strengthen the immune systems of *vannamei* shrimp.

IMMUNONUTRITION AND ITS ROLE IN SHRIMP AQUACULTURE

Immunonutrition is grounded in the principle that diet can influence immune competence **(Gianotti *et al.*, 2024)**. In aquatic species like shrimp, where adaptive immunity is absent, the innate immune system serves as the primary defense mechanism. Dietary components or specific nutrients, whether individually or in combination, that have the capacity to activate or regulate this system are referred to as immunonutrients **(Grimble, 2009; Ferreira *et al.*, 2024; Gianotti *et al.*, 2024;)**. In shrimp farming, where infectious diseases and environmental stressors often lead to significant production losses, immunonutrition offers a promising alternative to maintain shrimp health and farm productivity.

In *L. vannamei* aquaculture, the importance of immunonutrition is underscored by the growing challenges of disease outbreaks, environmental stress, and the overuse of antibiotics. Traditionally, antibiotics have been widely used in aquaculture to control bacterial infections and improve growth performance. However, their overuse has led to the development of antimicrobial resistance (AMR), which poses a serious threat to both human health and the sustainability of aquaculture systems **(Henriksson *et al.*, 2018; Mitchell *et al.*, 2024)**. Additionally, antibiotics often leave residues in the aquatic environment and shrimp products, potentially causing long-term ecological damage **(Bengtsson & Kautsky, 2002)**.

Given these concerns, immunonutrition has gained attention as a sustainable strategy for enhancing shrimp health. By incorporating specific bioactive compounds, such as microalgae-derived bioactives, vitamins, polysaccharides, and omega-3 fatty acids, immunonutrition can stimulate the immune system, improve shrimp resilience to pathogens, and reduce the need for antibiotic treatments **(Pakravan *et al.*, 2017; Feng *et al.*, 2020)**. These nutrients help strengthen the innate immune system, which plays a critical role in the first line of defense against pathogens. The innate immune system of shrimp relies on various immune cells, enzymes, peptides, and proteins that can recognize and respond to microbial invaders **(Li & Xiang, 2013; Tassanakajon *et al.*, 2013; Feng *et al.*, 2020)**.

One of the key benefits of immunonutrition in shrimp aquaculture is the improvement in disease resistance. Studies have shown that dietary supplementation with immunonutrients, such as omega-3 fatty acids and carotenoids, enhances the shrimp's immune response, increasing its ability to combat bacterial and viral infections. For instance, compounds like astaxanthin from microalgae are known to exhibit antioxidant properties, helping to reduce oxidative stress in shrimp and supporting immune cell function. Additionally, nutrients like β-glucans and polysaccharides have been shown to stimulate immune cell activity, increase phenoloxidase (PO) levels, and enhance overall immune defense mechanisms **(Zhou *et al.*, 2021; Wang *et al.*, 2023)**.

MICROALGAE AS A SOURCE OF BIOACTIVE COMPOUNDS

Microalgae are a rich source of bioactive compounds and have been extensively studied for their immunostimulatory properties in aquaculture. Species such as *Chaetoceros gracilis*, *Nannochloropsis* spp., and *Tetraselmis* spp. are known for their high content of EPA, DHA, carotenoids (such as astaxanthin and fucoxanthin), and essential amino acids **(Pratiwi *et al.*, 2009; Tachihana *et al.*, 2020; Moser *et al.*, 2022; Paterson *et al.*, 2023)**. These compounds contribute to enhanced immune responses by modulating antioxidant activity, reducing oxidative stress, and promoting cellular immune defense.

Studies have demonstrated that the inclusion of microalgae in shrimp feed leads to increased survival rates, improved hemolymph quality, and enhanced expression of immune-related genes such as *prophenoloxidase* and *crustin* **(Zhang *et al.*, 2025)**. Notably, *Chlorella pyrenoidosa* and *Dunaliella salina* have shown promise in silver-nanoparticle form by increasing shrimp resistance to disease and accelerating their growth process **(Mishbach *et al.*, 2024)**.

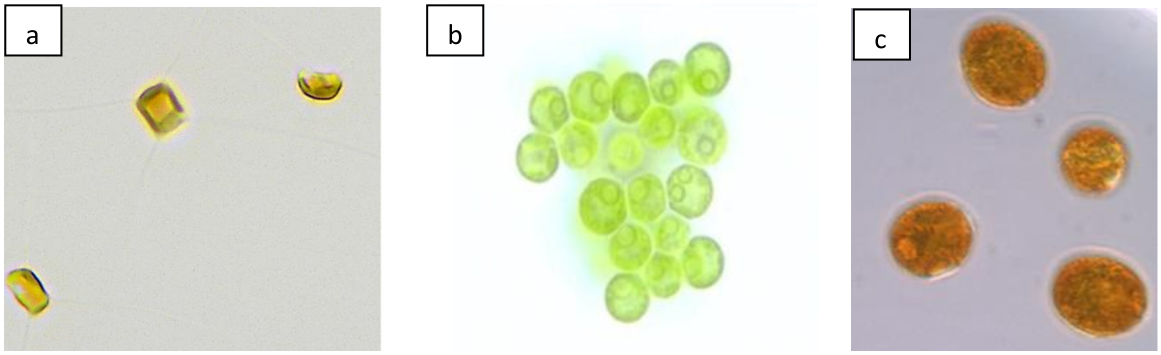

Fig. 1. Several species of potential microalgae. a. *Chaetoceros gracilis*; b. *Chlorella* sp.; c. *Dunaliella salina* **(Olmos *et al.*, 2015; Bhuyar *et al.*, 2020; Tachihana *et al.*, 2020)**

Table 1. Immunonutrients in microalgae and their effects

Immunonutrients	Bioactivities	Possible mechanisms
ω-3 PUFAs (e.g. DHA and EPA)	Anti-inflammatory, immunomodulatory, antioxidant, growth promotion **(Zhang *et al.*, 2024)**	• Activating the G-protein-coupled receptor GPR120, which downregulates NF-κB signaling and suppresses the transcription of inflammatory genes **(Robertson *et al.*, 2013)** • Incorporated into cell membranes, influencing membrane fluidity and signaling **(Ayee *et al.*, 2020)** • Reducing reactive oxygen species (ROS) **(Ambrozova & Lojek, 2010)**
Carotenoids (e.g. astaxanthin, fucoxanthin, and beta-carotenes)	Antioxidant, immunomodulatory, photoprotective, coloration and reproductive enhancement **(Marcoval *et al.*, 2020; Tomas *et al.*, 2020; Cichoński & Chrzanowski, 2022)**	• Scavenging free radicals and protects tissues from oxidative damage **(Pérez-Gálvez & Roca, 2020)** • Reducing inflammation by inhibiting the downstream production of pro-inflammatory cytokines • Reducing oxidative stress caused by light exposure **(Marcoval *et al.*, 2020)** • Astaxanthin bound in

		carotenoproteins (e.g., crustacyanin) produces coloration ranging from purple and blue to blue-black and yellow, contributing to crustacean camouflage and mate selection. **(De Carvalho & Caramujo, 2017)**
Polysaccharides (e.g., β-glucans)	Antioxidant, antimicrobial, immune cell stimulation **(Costa *et al.*, 2021; Shen *et al.*, 2023)**	• Enhance the innate immune system of *Litopenaeus vannamei* **(Raa, 2015; Martínez-Porchas & Vargas-Albores, 2017)** • Enhancing the intestinal health of white shrimp by maintaining gut microbiota balance, reducing intestinal inflammation, and strengthening immune and antioxidant defenses **(Shen *et al.*, 2023)**
Peptides	Antioxidant, antimicrobials **(Fernando *et al.*, 2024; O'Connor *et al.*, 2022)**	• Mitigate oxidative stress created by ROS (**Fernando *et al.*, 2024)** • Blocking bacterial protein production by attaching to ribosomal subunits **(Zuorro *et al.*, 2024)**
Vitamins (e.g. vitamin C and E)	Antioxidant **(Koyande *et al.*, 2019)**	• Counteract free radicals, safeguard cellular components, and minimize oxidative stress-induced damage **(Koyande *et al.*, 2019)**
Minerals (e.g. zinc, phosphorus, selenium)	Antioxidant **(Prates, 2025)**	• Protection against cellular oxidative stress **(Prates, 2025)**
Polyphenols	Antioxidant, anti-inflammatory, anti-microbial, anti-adipogenic **(Ferreira *et al.*, 2024)**	• Increasing catalase and peroxidase activities in scavenging reactive oxygen species/ ROS **(Jahazi *et al.*, 2020)** • Damaging the outer cell membrane of Gram-

	negative bacteria through porin pores **(Mandal and Domb, 2024)** • Inactivate microbial adhesins, enzymes, cell envelope transport proteins **(Kumar and Pandey, 2013)** • Modulating multiple inflammation - associated cell signaling pathways **(Jantan *et al*., 2021)** • Altering the expression of adipokines **(Herranz-López *et al.*, 2012)**

Microalgae-derived immunonutrients modulate the immune system of *L. vannamei* through diverse and complex mechanisms that enhance both the cellular and humoral components of the shrimp's innate immune response. Unlike vertebrates, shrimp rely almost entirely on innate immunity to combat pathogens, making dietary immunostimulants a crucial strategy for health management in aquaculture. The key mechanisms of immunomodulation by microalgae bioactives can be grouped into several interrelated actions, including immune cell activation, antioxidant defense enhancement, modulation of signaling pathways, and promotion of gut microbial balance **(Kaur *et al.*, 2023)**.

One of the primary immunomodulatory actions involves stimulation of hemocyte activity. Hemocytes are the main immune cells in shrimp, responsible for phagocytosis, encapsulation, and the production of antimicrobial peptides. Bioactives such as β-glucans and sulfated polysaccharides from microalgae (e.g., *Chaetoceros*, *Porphyridium*) are recognized as pathogen-associated molecular patterns (PAMPs) by shrimp pattern recognition receptors (PRRs), triggering a cascade of immune responses. This includes increased total hemocyte count (THC), enhanced phagocytic index, and upregulated activity of phenoloxidase (PO)—a key enzyme in the melanization pathway that helps immobilize and kill invading pathogens **(Campa-Córdova *et al.*, 2002; Azhar *et al.*, 2020)**.

Enhancement of antioxidant defense is another crucial mechanism. Oxidative stress, often induced by high-density farming, poor water quality, or pathogen infection, leads to cellular damage and immune suppression. Microalgal carotenoids such as astaxanthin and β-carotene, as well as polyphenols and PUFAs, act as potent antioxidants by scavenging reactive oxygen species (ROS). Their dietary inclusion upregulates antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which protect immune cells from oxidative damage and sustain immune function during stress **(Yu *et al.*, 2021; Wang *et al.*, 2022)**.

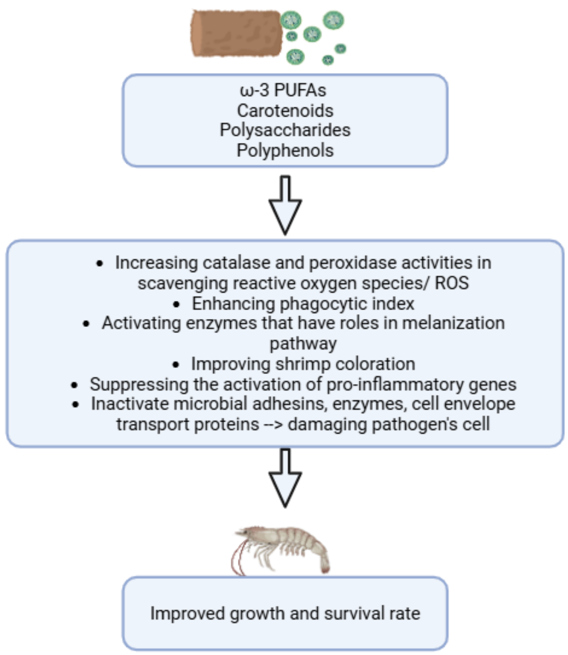

Fig. 2. General actions of microalgae-derived immnonutrients in improving shrimp's growth and survival rate

Microalgae bioactives also modulate intracellular signaling pathways involved in immune responses. For instance, polysaccharides and fatty acids may influence the NF-κB and MAPK signaling pathways, which regulate the transcription of genes encoding pro-inflammatory cytokines, antimicrobial peptides (AMPs), and stress-related proteins. Upregulation of immune-related gene expression, such as those for *prophenoloxidase*, *crustin*, *lysozyme*, and interleukin-like molecules, has been observed in *L. vannamei* fed microalgae-supplemented diets, suggesting a direct immunostimulatory effect at the molecular level **(Robertson *et al.*, 2013)**.

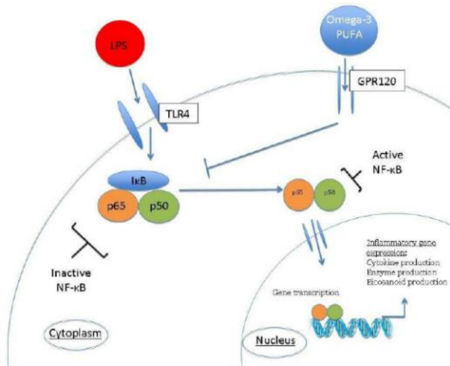

Fig. 3. Mechanism of PUFA suppressing the transcription of pro-inflammatory genes **(Robertson *et al.*, 2013)**

CHALLENGES AND LIMITATIONS

Despite the promising potential of microalgae-derived bioactives in enhancing shrimp health and immunity, several challenges and limitations remain that may hinder their widespread application in commercial aquaculture settings. These challenges span across scientific, economic, and practical domains and highlight the need for more integrative research and development efforts.

One of the primary challenges in utilizing microalgae as a source of bioactive compounds is the high variability in their biochemical composition. This variability not only occurs among different microalgae species but also within the same species when grown under different environmental conditions or culture media **(Curcuraci *et al.*, 2022)**. Factors such as cultivation conditions, harvesting time, and processing methods can significantly influence the concentration and efficacy of bioactive compounds such as carotenoids, fatty acids, and polysaccharides **(Sui *et al.*, 2020; Ampofo & Abbey, 2022; Uguz & Sozcu, 2023; Su, 2024)**. This inconsistency makes it difficult to standardize microalgae products and ensure uniform immune-modulating effects in shrimp.

Another significant limitation is the lack of precise dosage guidelines. While numerous studies have reported the benefits of microalgae supplementation, the optimal inclusion levels of different species and compounds in shrimp diets are still unclear. Excessive or suboptimal dosages may lead to inefficient immune stimulation, poor feed conversion, or even negative physiological effects. Standardized protocols are needed to determine species-specific and stage-specific dietary requirements for *L. vannamei*.

From a practical standpoint, the cost and scalability of microalgae production present economic challenges. Although microalgae cultivation can be sustainable, large-scale production requires controlled conditions, high-quality water sources, and energy inputs that can increase operational costs. Drying, extraction, and formulation of bioactive compounds further add to production expenses, making them less accessible for small- and medium-scale shrimp farmers **(Usman *et al.*, 2022)**. In addition, limited regulatory frameworks and commercial formulations impede the integration of microalgae-derived immunonutrients into mainstream aquafeeds. In many regions, feed additives of biological origin must undergo extensive safety assessments and regulatory approvals, which can be time-consuming and costly. Moreover, commercial feed manufacturers may be hesitant to adopt novel ingredients without robust, large-scale efficacy data and long-term performance evaluations **(Paterson *et al.*, 2023)**.

Scientific limitations also exist in terms of understanding the mechanisms of action. While many studies report immune-enhancing effects, the cellular and molecular pathways through which microalgae bioactives interact with the shrimp immune system remain only partially understood. This lack of mechanistic clarity hampers targeted feed development and may limit the predictive power of experimental results across different environmental conditions and pathogen types.

Lastly, the integration of microalgae-based feeds with other farm management strategies (e.g., water quality control, biosecurity, vaccination) is not yet fully optimized. The multifactorial nature of disease resistance in aquaculture demands a holistic approach, and over-reliance on dietary immunonutrients alone may not provide adequate protection in high-risk scenarios **(Pérez-Gálvez & Roca, 2020)**.

FUTURE PROSPECTS

The incorporation of microalgae-derived bioactives in shrimp aquaculture represents a rapidly evolving field with significant potential to revolutionize health management in *L. vannamei* farming. As sustainability and antibiotic-free practices gain global traction, microalgae-based immunonutrition is poised to become a cornerstone of functional feed strategies. However, realizing its full potential requires continued scientific innovation, interdisciplinary collaboration, and translational efforts.

A key future prospect lies in the identification and characterization of novel microalgae strains with superior immunostimulatory properties. While commonly used genera such as *Spirulina*, *Chlorella*, and *Chaetoceros* have been extensively studied, the vast diversity of marine and freshwater microalgae remains largely untapped. Advanced screening methods, including omics technologies (e.g., transcriptomics, metabolomics), can be utilized to discover new strains rich in bioactive compounds such as polysaccharides, polyunsaturated fatty acids (PUFAs), and pigments like astaxanthin and β-carotene.

Moreover, precision nutrition approaches will play a crucial role in optimizing feed formulations. Research should aim to determine the ideal combinations, dosages, and timing of microalgae-derived immunonutrients to match the specific immune needs of shrimp at various developmental stages and under different environmental or pathogenic stress conditions. Such studies should also help unravel the molecular mechanisms by which these bioactives modulate gene expression in shrimp immune pathways.

In the realm of product development, efforts should focus on scaling up cost-effective and stable microalgae-based feed formulations that retain bioactivity during processing and storage. Technologies such as encapsulation and cold-press drying can be refined to preserve sensitive bioactives without compromising feed quality. Industry–academia partnerships will be vital in transitioning lab-scale findings into commercially viable products.

In addition, there is a need for large-scale, long-term trials under commercial farming conditions to validate the efficacy, safety, and economic feasibility of microalgae-based immunonutrients. These trials should consider multiple health indicators, growth performance, survival rates, and cost–benefit analyses to generate robust data that can support regulatory approval and farmer adoption.

Indonesia, with its extensive coastal resources, favorable tropical climate, and status as one of the world's leading *L. vannamei* producers, holds significant potential as a development hub for this innovation. Its rich biodiversity of marine and freshwater microalgae, combined with an expanding aquaculture industry and growing interest in sustainable feed alternatives, positions the country as a strategic location for pilot projects, commercial trials, and large-scale production. Leveraging these advantages, alongside supportive policy and regulatory frameworks, could accelerate the adoption of microalgae-based immunonutrition in both domestic and export-oriented shrimp farming.

Finally, policy and regulatory frameworks must evolve to accommodate and encourage the use of bio-based immunonutrients. Clear guidelines for registration, labeling, and claims related to microalgae-derived feed additives will facilitate market access and consumer trust, especially in regions with stringent food safety standards.

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