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Marine-derived products as functional feed additives in aquaculture: A review

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ABSTRACT

The aquaculture industry is expanding to meet the daily requirements of humanity from high-quality seafood. In this regard, intensive aquaculture systems are suggested, resulting in high production but being challenged with immunosuppression and disease invaders. Antibiotics were used for a long time to protect and treat aquatic animals; however, continuous use led to severe food safety issues, reducing the natural immunity response and high resistance to harmful bacterial strains. Therefore, natural functional additives were introduced to reduce or even replace chemotherapies. More specifically, marine-derived substances showed effective immunostimulant and antioxidative roles when introduced to aquatic animals. Bioactive molecules derived from algae, crustaceans, and fish, including astaxanthin, carotenoids, chitosan, fucoidan, lectins, and polyunsaturated fatty acids (PUFAs), are the most applied additives in aquaculture. In addition, marine-derived biomolecules were introduced to several other sectors, such as nutraceuticals, pharmaceuticals, cosmetics, and agriculture. Marine-derived substances are lipid-soluble biomolecules known for their ability to cross the cellular membranes, thereby causing pigmentation roles. Consequently, marine-derived biomolecules are involved in antioxidative and immune activation effects and, thereby, high performances and productivity of aquatic animals. In the literature, there are available knowledge about the possibility of using marine-derived biomolecules in aquaculture. This article presents information about the sources, mode of action, and effects of marine-derived biomolecules on aquatic animals to fortify the scientific community with enough details about friendly natural substances for sustainable aquaculture.

1. Introduction

Aquaculture is a growing sector that produces high-quality animal protein (Van Doan et al., 2022). As global consumption of aquatic animals and the intensity of their production increase, producers face increasing pressure to maintain a high rate of growth and animal health while minimizing diseases (Dawood, 2021). Intensive aquaculture systems can result in a higher incidence of diseases in farmed fish due to

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favorable conditions for pathogen growth and spread, leading to reduced growth, productivity, and economic losses (Mugwanya et al., 2022; Wang et al., 2017). For a long time, antibiotics and chemical substances have been applied to prevent and control infection in aquaculture (Okeke et al., 2022). However, excessive use of antibiotics causes drug-resistant infections, immune system inhibition, environmental contamination, and accumulation in animal tissues, potentially harming humans (Gomez-Zavaglia et al., 2019; Ringø et al., 2012). The first ban on the use of subtherapeutic antibiotics in animals, including fish, in the European Union came into force in January 2006 [Regulation (EC) No. 1831/2003 of the European Parliament and the Council] (Zhou et al., 2021). There is a need to find sustainable alternative strategies to improve disease resistance in cultured fish (Dawood et al., 2018). Natural immunostimulants, such as prebiotics, synbiotics, probiotics, nutritional supplements, complex carbohydrates, hormones, herbs, and cytokines, may be helpful techniques for promoting development, stimulating the immune response, and controlling disease in aquatic animals (Al-Saif et al., 2014; Dawood et al., 2022; De Jesus Raposo et al., 2015).

The marine environment is a rich source of natural products including polysaccharides, oligosaccharides, peptides, vitamins, minerals, fatty acids, sterols, carotenoids, and phenolic compounds (Romano et al., 2017). Research has recently focused on marine-derived polysaccharides extracted from microalgae, macroalgae, crabs,shellfish, fungus, and corals that exhibit a broad spectrum of biological activity (Fig. 1) (Barzkar et al., 2019; Tarman et al., 2011). Polysaccharides can operate as prebiotics, where indigestible dietary components are absorbed by gut microbiota, potentially improving the host organism's intestinal immunity and health state (Li et al., 2010; Patil et al., 2018). In recent years, considerable efforts have been made to investigate the use of polysaccharides in fish and shrimp culture and its effects on the immune system (Abuelsaad, 2014; Lin et al., 2017). The marine-derived polysaccharides including alginate, galactan, fucoidan, agar, laminarin, carrageenan, chitin, ulvan, and chitosan have been used as feed additives in aquatic animals (del del del Rocío Quezada-Rodríguez and Fajer-Ávila, 2017; El Knidri et al., 2018). Research into the use of marine processing by-products, generally considered waste, has identified active compounds suitable for applications in aquaculture and humans (Ambati et al., 2014; Calder, 2015). In this review, we focus on the screening of marine by-products as bioactive compounds and their potential effects on the overall performances of fish species.

2. Sources of marine derived substances

Numerous marine organisms contain compounds of chemical and medicinal potential (Romano et al., 2017). In the marine environment, invertebrates represent the richest source of substances employed as functional compounds, in contrast to the terrestrial environment in which plants yield the majority of natural products, possibly since marine organisms are harder to collect and identify than terrestrial organisms (Al-Saif et al., 2014; De Jesus Raposo et al., 2015). Several materials derived from marine organisms have historically been used as feed ingredients, including the polysaccharides (carrageenan, alginate, and agar) (Murthy et al., 2017). Such compounds are commonly called immunostimulants (Mohan et al., 2019). It is found that bioactive compounds derived from algae, especially polysaccharides, account for the best source of immunostimulants (Vijayaram et al., 2022). Another well-known derivative from algae is carotenoids which are generally considered antioxidants (Aklakur, 2018).

3. Polysaccharides

3.1. Polysaccharides from marine sources

Red seaweed of the genera Gigartina, Hypnea, Eucheuma, Chondrus, and Iridaea contain sulfated polysaccharides in the amorphous sections of the cell walls known as carrageenan 8 (Pacheco-Quito et al., 2020). These polysaccharides have broad applications in food and other industries as thickening, gelling, stabilizing, and suspending agents (Mišurcová et al., 2012). Carrageenan provides phospholipids to aquatic animals and enhances the physical characteristics of many animals (Van Doan et al., 2019). The efficacy of carrageenan as a growth promoter in common carp was evaluated by Murthy et al. (2017). Compared to a control group, the lowest concentrations demonstrated superior outcomes in the case of specific growth rate, feed utilization, protein efficiency ratio, feed conversion rate, and survival. Seaweed is a source of bioactive compounds that can produce a variety of secondary metabolites with antifungal, antibacterial, and anthelminthic activity, especially green, brown, and red algae (Oumaskour et al., 2012). The Chlorophyceae macroalga *Caulerpa scalpelliformis* is abundant in warm water ecosystems of the Pacific, Atlantic, and Indian oceans. Immunostimulatory effects of quaternary alkaloids present in *C. scalpelliformis* were seen in *Channa striatus* (Balasubramanian and Michael, 2016). A specific alkaloid, caulerpin, was shown to have an antimicrobial effect against *Vibrio anguillarum* (Aiya Subramani et al., 2016).

Macrogard™, a yeast β-glucan polysaccharide, has been used as an immune modulator in fish for decades (Petit et al., 2019; Vetvicka et al., 2013). Sulphated polysaccharides derived from macroalgae, including heparin, alginate, fucoidan, and laminarin, have immunomodulatory effects in mammals (Rajauria, 2015). It can increase the complement

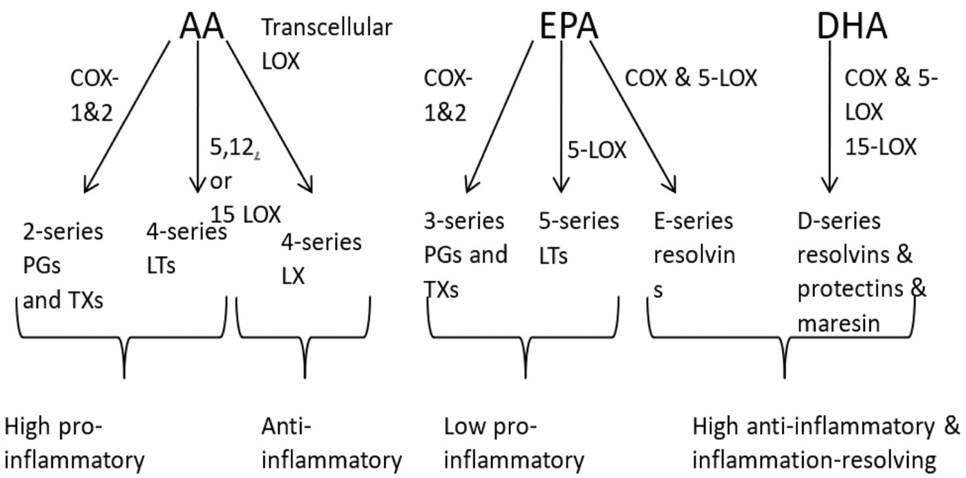

Fig. 1. Overview of the synthesis of lipid mediators from arachidonic acid (AA), eicosapentaenoic (EPA) acid, and docosahexaenoic acid (DHA) and their effects on inflammation. Cyclooxygenase (COX), lipoxygenase (LOX), prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), lipoxins (LXs).

activity in sea bass (*Dicentrarchus labrax*) to a greater extent than Macrogard™ (Bagni et al., 2005). A study evaluated the effects of polysaccharides derived from *C. scalpelliformis* compared to a yeast-derived commercial immunostimulant (Macrogard™) on Nile tilapia (*Oreochromis niloticus*) and concluded that polysaccharide administration stimulated the non-specific immune response, immune gene expression, and disease resistance (Yengkhom et al., 2018).

Green algae of the genus Ulva (formerly Enteromorpha) are common seaweeds distributed worldwide (Hayden et al., 2003; Wichard et al., 2015). Their content of sulfated polysaccharides, phenolic compounds, fatty acids, vitamins, and minerals has led to their use as functional foods (Gullón et al., 2020; Wichard et al., 2015). Ulva is used both as a condiment and nutritional supplement in China, Japan, and the USA (Fleurence and Levine, 2016; Mohamed et al., 2012; Wells et al., 2017) and has been investigated as an ingredient in aquafeeds (Guerreiro et al., 2019). Ulvan, a polysaccharide obtained from the green alga *Ulva clathrate*, positively affected the hematology, immunity, and growth of Nile tilapia (del Rocío Quezada-Rodríguez and Fajer Ávila, 2017). The results indicated that ulvan might affect the immunological response (phagocytic activity and white blood cell count) in tilapia.

Microalgae possessing a high level of essential fatty acids are in demand as enrichment of live food for fish larvae since commercial n-3 PUFA supplements exhibit a short shelf life (Ansari et al., 2021). Some microalgae are an excellent source of carbohydrates, lipids, and proteins and are used in hatchery feed for the larval stage of most cultured species (Nagarajan et al., 2021). They also contain pigments and sterols used as functional food additives (Krienitz and Wirth, 2006). *Chaetoceros* sp. is an optimal live feed for Artemia because of high levels of n3 LC-PUFA, especially eicosapentaenoic (EPA) acid (Lora-Vilchis et al., 2004). *Artemia nauplii*, with suitable biochemical composition, size, and easy acceptance by larvae, are the primary protein source in commercial shrimp culture (Sorgeloos et al., 1998). Their paucity of EFAs and nucleotides makes them an incomplete diet for marine finfish and crustacean larvae (Chakraborty et al., 2007). A study was conducted to evaluate the efficacy of *A. franciscana* enriched with *Chaetoceros gracilis* or *Saccharomyces cerevisiae* on growth, stress resistance, and fatty acid profile of *Litopenaeus vannamei* postlarvae (Ahmadi et al., 2017). Shrimp larvae were fed Artemia enriched with *S. cerevisiae* or *C. gracilis*, and newly hatched *A. franciscana* nauplii were provided to a control group. After 15 days, concentrations of EPA and DHA were higher in larvae fed Artemia enriched with *C. gracilis* than in other groups. The inclusion of marine microalgae *C. gracilis* and *S. cerevisiae* in live feed for *Litopenaeus* larvae could be an effective strategy in aquaculture.

Ulva rigida, a green macroalga seaweed widespread near submerged marine rocks, is a good source of carbohydrates, protein, ash, lipids, and low starch content (Zemke-White and Clements, 1999) and cellulose (Roesijadi et al., 2010). Water-soluble extracts of *U. rigida* can induce a significant increase in phagocytic respiratory burst activity of turbot *Psetta maxima* (Castro et al., 2004). Furthermore, the effects of different water-soluble polysaccharides extracted from *U. rigida* were investigated on the antioxidant enzyme activity, growth performance, innate immune parameters, and disease resistance in gray mullet (*Mugil cephalus*) challenged with *Photobacterium damselae* (Akbary and Aminikhoei, 2018). The fish were fed four concentrations of the extract over two months. It was shown to stimulate fish immunological parameters and was associated with a significant boost in growth performance. Compared to a control diet, mortality was reduced in fish receiving the supplement.

Fucoidan is a sulfated polysaccharide associated with immunostimulation, growth promotion, and disease resistance in crustaceans and fish (Chotigeat et al., 2004; Immanuel et al., 2012; Kitikiew et al., 2013; Traifalgar et al., 2010). The brown seaweed *Sargassum wightii* of the class Phaeophyceae contains bioactive compounds that include fucoidans. Gora et al. (2018) investigated the effects of *S. wightii* and its fucoidan-rich seaweed extract (FRSE) on non-specific immunological status, b-defensin 1, and hepcidin gene expression, and survival in *Labeo rohita* fingerlings challenged with *Aeromonas hydrophila*. The study tested diets containing 0%, 1%, 2%, 3%, and 6% FRSE for 60 days. The results show a significant increase in the survival rate and immune response, but no differences in growth performance were found.

Organic acids can influence the microbial composition of the digestive tract in fish, which plays a vital role in nutrition and health and enhances the immune system (Burr et al., 2005). The organic acids polyhydroxy butyrate (PHB), a natural short-chain fatty acid monomer (Najdegerami et al., 2012), and potassium diformate (KDF), along with carrageenan and alginic acid, were substituted for cellulose in feed to assess their immunostimulant properties in red drum (*Sciaenops ocellatus*) (Mendoza Rodriguez et al., 2017). The results showed a significant increase in the phagocytic activity in fish fed with a PHB diet. The study concluded that organic acids and alga extracts could boost red drum immune responses, with carrageenan demonstrating the most significant promise as an immunostimulant. In tilapia, KDF inclusion enhanced weight gain and resistance against *V. anguillarum* and was reported to be a valuable organic acid in aquaculture (Ramli et al., 2005). Alginic acid, an anionic polymer derived from brown seaweed, is present in *Undaria pinnatifida* and *Macrocystis pyrifera* intercellular mucilage and cell walls (Chapman, 2012).

Bolaños et al. (2017) investigated the antibacterial and antifungal activity of *Sargassum polycystum*, *Sargassum oligocystum*, *Sargassum crassifolium,* and *Sargassum cristaefolium* in vitro. Powdered seaweed extracts were prepared, and disc diffusion for antimicrobial activity was used with different organic solvents to increase the polarity. Action against 13 pathogens confirmed *S. polycystum* to exhibit the highest antimicrobial activity. The pathogenic bacteria included in the challenge were Gram-positive *Staphylococcus aureus*, *Streptococcus mutans*, *Micrococcus luteus*, *Bacillus subtilis*, and Gram-negative *A. hydrophila Escherichia coli*, *Pseudomonas aeruginosa*, and *P. fluorescence*. The fungi *Aspergillus parasiticus*, *A. niger*, *Candida tropicalis*, *Penicillium expansum*, and *Saccharomyces cerevisiae* were also tested (Bolaños et al., 2017). Diet supplementation with *Gracilaria* sp., a red seaweed, can prevent oxidation damage to packaged fish after freezing and increase its shelf life (Araújo et al., 2015). It is rich in bioactive compounds like polyphenols and sulfated polysaccharides and has applications in the agar industry (Porse and Rudolph, 2017). The presence of natural pigments chlorophyll, phycobilins, and carotenoids (M Cardoso et al., 2014) makes it suitable for inclusion in fish feeds to replace currently used artificial colorants (Nickell and Bromage, 1998). The effect of *Gracilaria* spp. on fillet quality, oxidative stress, and immune response in European seabass (*D. labrax*) (Peixoto et al., 2019) was investigated. They compared a basal diet (control) to one supplemented with a methanolic extract of *Gracilaria* spp. and one supplemented with the insoluble residue of *Gracilaria* spp. extraction. Growth indicators, digestive enzyme activity, immune parameters, oxidative stress responses, fillet pH and color (L*, a*, and b* values), and skin color were evaluated. With the exception of the alternative complement pathway, no differences were observed among diet groups.

3.2. *Commercially available polysaccharides in aquafeeds*

A plethora of research has introduced immunostimulants for sustainable aquaculture (Abdul Kari et al., 2021; Kari et al., 2022). Polysaccharides obtained from seaweed and crustacean shells are also recognized, including beta-glucan, Astragalus polysaccharides (APS), and chitooligosaccharide (COS) with potential defense responses (Wang et al., 2017). Chitin is a natural polymer abundant in crustaceans with a molecular structure similar to cellulose. The N-deacetylated polysaccharide from chitin is called chitosan (Elieh-Ali-Komi and Hamblin, 2016). Chemical and enzymatic hydrolysis of poly chitosan yield the commercially available polysaccharide chitooligosaccharide (Knaul et al., 1999). Different administration doses, duration of administration, and efficacy make COS a versatile immunostimulant (Xing et al., 2017). Its low molecular weight and solubility in water make COS the most widely used polysaccharide in health and immunity (Lin et al., 2017). Chitin and its derivatives are widely used as antimicrobials (Luo et al., 2017; Zhao et al., 2016) and antioxidant agents (Yang et al., 2017) with excellent wound-healing properties (Wang et al., 2011).

Polysaccharides derived from herbs serve as effective immunostimulants in fish. Astragalus, a traditional Chinese herbal medicine, is derived from APS and has effective immunostimulant roles in both humans and animals (Fu et al., 2014). An investigation of dietary supplementation with APS and COS on growth performance, immune parameters, and disease resistance was conducted in the largemouth bass (*Micropterus salmonids*). Lin et al. (2017) used plant-derived APS and commercial COS separately and combined. Disease resistance was assessed by challenge with *A. hydrophila*. Both applications resulted in the upregulation of phagocytic, lysozyme, and superoxide dismutase activity in fish. The administration of both APS and COS also significantly increased the growth performance and resistance against infection by *A. hydrophila* in a 50-day feeding trial in Nile tilapia (Meng et al., 2017). Chitosan's non-allergenic, biodegradable, and nontoxic characteristics make it a valuable active bioactive agent (Kurita, 1998). However, its poor solubility challenges its use in food and biochemical applications (Lodhi et al., 2014). Chitosan's low solubility in water could be overcome by employing COS which is highly soluble in water due to its short chain length and the free amino group in D-glucosamine units (Jeon et al., 2000).

4. Carotenoids

Carotenoids are the most abundant lipid-soluble pigments, accounting for about 750 naturally occurring carotenoids, including over 250 of marine origin (De Carvalho and Caramujo, 2017). Carotenoids are organic pigments that are found in the chloroplasts of photosynthetic organisms, such as plants and algae. However, carotenoids are not produced exclusively by photosynthetic organisms. They are also produced by some heterotrophic fungi and bacteria (Armstrong et al., 1989). They are tetraterpenes that include conjugated double bonds in their 40-carbon polyene chain. They generally differ in a) the number of oxygen atoms in the structure (non-oxygenated = carotenes, oxygenated = xanthophylls), b) hydrogenation of the polyene chain, c) cyclization of the ends of the molecule with ε- or βionone rings, or d) the length of the chromophore (McNulty et al., 2008). Carotenoids have different effects due to their double bond structure, which aids in camouflage, reproduction, photoprotection, and consumer acceptance for consumption and aquaria (de Carvalho and Caramujo, 2017).

The best-known carotenoids are astaxanthin (red), tunaxanthin (yellow), canthaxanthin (orange red), beta-carotene (orange), and doradexanthins (yellow), zeaxanthin (red,) and echinone (red). Most heterotrophic organisms, including crustaceans and fish, are incapable of carotenoid synthesis, and it is often kept in the integument and gonads in fish. Additionally, certain fish, particularly salmonids, store carotenoids in their muscle (Lim et al., 2018). Fish generally show no or limited capacity to metabolize carotenoids. Except for catfish, integumentary carotenoids are preserved as mono- or di-esters in most animals. Cyprinids can convert lutein or zeaxanthin to astaxanthin, whereas salmonids are unable to do so (Maoka, 2011). Specific carotenoids, primarily α-carotene, β-carotene, and β-cryptoxanthin have critical qualities as precursors to vitamin A (Weber and Grune, 2012). In Atlantic salmon (*Salmo salar*), astaxanthin and canthaxanthin showed provitamin A activity. In addition, in some freshwater fish, zeaxanthin, lutein, and astaxanthin are precursors to vitamin A2 (3,4-dehydroretinol) (Lim et al., 2018).

Carotenoids are frequently associated with cell membranes in biological systems. Nonpolar carotenoids such as lycopene and b-carotene appear to be encapsulated within the bilayer, whereas oxygenated carotenoids cross the membrane with their polar rings exposed to the environment (McNulty et al., 2008). Carotenoids are good in quenching free radicals and singlet oxygen, especially at low oxygen partial pressures. Antioxidative capacity varies with compound, but, in general, the presence of oxy-functional groups expands antioxidative properties (Ambati et al., 2014). In mammalian systems, carotenoids have been shown to have anti-inflammatory, anti-cancer, and anti-diabetic properties and a clear role in preventing cardiovascular diseases. Catalase and glutathione peroxidase are increased; pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α are decreased; and free radical species are generally suppressed. Much of these effects can be attributed to their antioxidative functions (Milani et al., 2017).

Astaxanthin is a common carotenoid pigment found in the flesh of carnivorous fish species, which gives it colorful characteristics (Lu et al., 2021). Astaxanthin has improved egg and sperm quality and hatching success in several fish species and possibly improves growth performance (Ambati et al., 2014). In aquatic animals, carotenoids enhance larval growth (Wang et al., 2018), enhance the performance of broodstock (Verakunpiriya et al., 1997), and enhance disease resistance (De Carvalho and Caramujo, 2017). A nine-week study was conducted in rainbow trout (*Oncorhynchus mykiss*) to examine the properties of naturally derived carotenoids in fish, using the marine alga *Dunaliella salina* as the β-carotene source and red yeast *Phaffia rhodozyma* as astaxanthin source. Amar et al. (2004) noticed a considerable increase in complement activity and phagocytic rate in fish serum. Superoxide anion production in head kidney and plasma total immunoglobulin levels remained unaffected.

The heterobasidiomycetous yeast *Xanthophyllomyces dendrorhous* and the green alga *Haematococcus pluvialis* are the main microorganisms producing astaxanthin (Barredo et al., 2017; Rodríguez-Sáiz et al., 2010). Yeast and yeast extracts have been used in pathogen-associated molecular pattern immunostimulant diets (Álvarez-Rodríguez et al., 2018; Vallejos-Vidal et al., 2016). The effects of *X. dendrorhous* extract and various plant extracts were investigated on the antioxidant and immunological status of cultured Atlantic salmon exposed to crowding stress (Reyes Cerpa et al., 2018). The results showed that the diets protected fish against oxidation and promoted the immune response.

Studies of rainbow trout have reported a reduction in oxidative stress via a decrease in the level of lipid peroxidase with a diet containing astaxanthin-rich red yeast (Nakano et al., 1999; Rahman et al., 2016). Attempts have been made to determine the effect of plant extract species as a dietary supplement on various health outcomes (Salomón et al., 2020). The study included extracts from Saint John's wort *Hypericum perforatum*, lemon balm *Melissa officinalis*, and rosemary *Rosmarinus officinalis* (Reyes-Cerpa et al., 2018). Feed containing immunostimulants was given for days, and during the last ten days, the fish were stressed due to overcrowding. The results confirmed that the dietary supplements boosted antioxidant status and gene expression associated with Th2-like responses, implying a protective effect (Reyes-Cerpa et al., 2018).

Pontogammarus, of the family Pontogammaridae, is an essential source of feed for fish (for example, Caspian roach (*Rutilus caspicus*)) in the Caspian Sea. Of the two species of the genus, *Pontogammarus maeoticus* is the most abundant and used as a feed source (Mirzajani, 2003). These amphipods are rich in free amino acids and beta-carotene (Baeza Rojano et al., 2010). They possess high antioxidant levels and could be incorporated into aquaculture feed as immunostimulants. The effect of *P. maeoticus* extract on immunological parameters, feed intake, growth performance, and stress resistance in Caspian roach (*Rutilus lacustris*) was reported by Rufchaei et al. (2017). Significant improvements in the resistance to salinity stress, innate immune parameters, and growth performance were observed.

5. Polyunsaturated fatty acids

Long-chain polyunsaturated fatty acids (LC-PUFA), including EPA, docosahexaenoic acid (DHA), and AHA, are essential fatty acids performing multiple functions in most organisms. They directly affect membrane fluidity and lipid rafts that affect the function and specificity of enzymes, surface receptors, transmembrane proteins, and ion channels (Pablo and Cienfuegos, 2000). Some fatty acids serve as signaling molecules directly modulating cellular processes and impacting immunity in aquatic animals. Elevation of arachidonic acid (ARA) in the diet results in increased prostaglandins, improving macrophage performance and white blood cell activity (Bell and Sargent, 2003). Arachidonic acid activates the transcription factor NFκB in monocytes and other cells, leading to direct transcription of pro-inflammatory mediators, including TNF-α, IL-1α, IL-1β, and COX-2 (Camandola et al., 1996). In addition, n-3 LC-PUFAs modulate inflammatory and immune responses through the eicosanoid cascade. This process is currently regarded as the primary pathway linking dietary lipid and inflammatory processes (Masoodi et al., 2015; Tallima and El Ridi, 2018).

The eicosanoid cascades through the production of numerous oxygenated derivatives of C20/22 LC-PUFA. They are short-lived (<1 s) and act on cells directly or indirectly by affecting the production of mediators like cytokines. Precursor LC-PUFAs are released from cell membranes by phospholipase A2 and converted to prostaglandins (PG) through COX-1 and −2 or leukotrienes (LT) via lipoxygenases (5-, 12-, or 15-LOX) (Fig. 1) (Calder, 2006a; Calder, 2006b).

In mammalian systems, eicosanoids produced from ARA are the predominant type of eicosanoids found in tissues, and many of these products are highly pro-inflammatory agents (Tallima and El Ridi, 2018). Prostaglandin E2 (PGE2) elevates the body's temperature, increases vascular permeability, and produces pain (Cheng et al., 2021). In comparison, leukotriene B4 (LTB4) enhances vascular permeability and is a potent chemoattractant for leukocytes. Further, it generates the release of lysosomal enzymes and free radicals by neutrophils and induces the production of pro-inflammatory cytokines like tumor necrosis factor TNF-α, leukocyte endogenous mediator IL-1β, and B cell differentiation factor IL-6 (Calder, 2009). High levels of dietary n-6 PUFA induce a robust and efficient inflammatory response, particularly to pathogens. However, this response has the potential to overshoot, becoming a problem rather than a solution. This is seen in sepsis and some microbial diseases mediated through exotoxins (Anderson and Fritsche, 2002). It is characterized by hyper-expression of endothelial and leukocyte adhesion molecules and high levels of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. If severe, the inflammatory process is life-threatening, and increased survival in many inflammatory-driven microbial (exotoxins) and parasitic infections has been attributed to a dampening of the primary inflammatory response. High levels of pro-inflammatory n-6 eicosanoids will suppress immunity (Sijben and Calder, 2007). For example, PGE2 suppresses cell-mediated immunity through inhibition of T-lymphocyte proliferation and reductions in Th1-type cytokines (IL-2 and IFN-γ) (Calder, 2015). This is significant in persistent inflammation, in which organisms are more susceptible to opportunistic infections.

Altering diet significantly impacts eicosanoid cascades, an effect usually attributed to the competitive production of PGs and LTs of the 3- and 5-series when the level of EPA in membranes increases (Bercea et al., 2021). As opposed to ARA-derived eicosanoids, EPA derivatives have low pro-inflammatory potential and will thus serve to inhibit the inflammatory responses competitively (Dyall et al., 2022). In recent years there has been considerable progress related to identifying three new families of eicosanoids from EPA and DHA: resolvins, protectins, and mares, all of which show inflammation-resolving action, mainly through inhibition of neutrophil infiltration and cytokine expression (Serhan, 2008). Increasing dietary intakes of fish oils, and thereby EPA and DHA, have been used to lower inflammatory load in humans. Producers of fish diets have been forced to replace fish oils with vegetable oils. As vegetable oils are deficient in EPA and DHA and rich in C18 n-6 PUFA, the dietary shift has reduced the n-3/n-6 ratio from 10 to less than 0.1 (Tocher, 2010). The synthesis of n-6 eicosanoids predominates over n-6 counterparts, a condition that has been proposed to contribute to viral heart and skeletal muscle inflammation (Martin and Król, 2017).

In Atlantic salmon, exposure to stress increased intestinal expression of COX along with levels of PGE2, PGF2α, and 6-keto-PGF1α (Oxley et al., 2010). The effect of eicosanoids and diet-caused shifts are, however, unclear. In general, PGE2 induces the synthesis of pro-inflammatory cytokines like IL-6 and IL-10 in leucocytes but suppresses the expression of TNFα and immunoglobulins (Gómez-Abellán and Sepulcre, 2016). Stable PGE2 injected into rainbow trout showed immunosuppressive action by reducing the number of plaque-forming cells following inoculation with *A. salmonicida* (Knight and Rowley, 1995).

In recent years, there has been significant development of new marine LC-PUFA, EPA, and DHA sources. The exploitation of lower trophic levels is feasible (Tocher, 2010), but the most significant potential is probably with microalgae, yeast, and transgene oil crops (Tocher et al., 2019). Using oils from algae and plant crops will be possible not only to increase the dietary LC-PUFA content but also to manipulate the relative content of LC-PUFA, providing the potential to optimize the immune response sufficiently to fight infections.

6. Marine yeasts

Yeasts are a polyphyletic group of basidiomycetous and ascomycetous fungi that share the unusual ability to grow in unicellular form. Yeasts are primarily used in the food sector to produce ethanol and carbon dioxide during baking, brewing, and wine fermentation. Marine yeasts participate in plant substrate decomposition, biodegradation of oils, parasitism, and nutrient recycling (Alamillo et al., 2017; Kutty and Philip, 2008). They can convert organic products from animal and plant debris to yeast biomass. Marine yeasts were first discovered in the Atlantic Ocean and are present in seawater, seaweed, and marine mammals. Most fermented forms are found in polluted water or muddy areas (Kutty and Philip, 2008). Non-pathogenic dimorphic ascomycetous yeasts are found in soils contaminated with oils and wastewater and in the marine environment. *Yarrowia lipolytica* is one of the most studied yeasts because of its unique biochemical and physiological properties (Zinjarde et al., 2014), which could be utilized in the food sector and in upgrading different types of food wastes.

An environment with a high concentration of particles, such as a hypersaline milieu, may be a prospective source of bioactive chemicals for animal feed supplements. Alamillo et al. (2017) reported that after a challenge with *V. parahaemolyticus*, a Y. lipolytic N-6 isolate derived from a hypersaline environment stimulated the non-specific immune response and antioxidant activity in the head-kidney and spleen of Pacific red snapper (Lutjanus Peru). The results showed a significant increase in the non-specific immune response, including respiratory burst, phagocytic activity, nitric oxide production, myeloperoxidase activity, and inhibition of leukocyte apoptosis.

Polyphenols are secondary metabolites of plants with a varied structure composed of several hydroxyl groups on aromatic rings (Quan et al., 2019). Researchers and food technologists have become interested in polyphenols because of their antioxidant properties and applications in preventing and treating conditions such as cancer and cardiovascular and neurodegenerative disease (Cory et al., 2018; Rasouli et al., 2017; Silva and Pogačnik, 2020). Polyphenols can modulate the activity of a wide range of enzymes and cell receptors and hence exert multiple biological actions in addition to antioxidant activity. Researchers have attempted to identify polyphenols and establish their therapeutic effects (Caban et al., 2019; Khan et al., 2019; Pavlova et al., 2019).

Intensive marine shrimp farming is a promising approach to expanding the aquaculture industry. As opposed to brackish pond culture, floating net cages confers several advantages. They do not require regular water replacement or aeration, and there is no accumulation of organic waste (Zarain-Herzberg et al., 2010). Despite the benefits, sea cage shrimp culture faces significant challenges. The natural environment and the existence of predators can cause physiological stress, adversely affecting the shrimp immune system and decreasing production (Peterson and Walker, 2002). An improved management protocol to prevent stress-related problems is to enhance immunity by using immunostimulants in feed. *Nodulisporium* sp. KT29 is a natural endophytic fungus, isolated from red algae, which contain polyphenols that are capable of boosting the shrimp immune system (Wahjuningrum et al., 2016) and increasing production (Saputra et al., 2016). Efianda et al. (2018) investigated the effects of *V. harveyi*–induced *Nodulisporium* sp. KT29 on bioactive compound concentration (β-glucan, saponin, polyphenol, and phytosterol) intestinal surface structure and production performance of Pacific white shrimp *L. vannamei* cultured in the sea. Bacterial induction is used to increase bioactive compound levels in fungi, in this case, to activate the bioactive compounds in *Nodulisporium* sp. KT29 using the pathogenic bacteria *V. harveyi*. The treatments included inoculation with killed *V. harveyi* cells, the inoculation of living *V. harveyi* cells, and no bacteria. The group receiving killed bacteria showed the highest levels of bioactive compounds. The study results reveal that introducing a foreign compound or bacteria can increase the concentration of secondary metabolites produced by a fungus as a defensive action (Calvo et al., 2002; Ipcho et al., 2016).

7. Conclusions

Incorporating dietary additives such as probiotics, prebiotics, vitamins, and crude plant extracts is a current strategy to mitigate problems related to the increased intensification of aquaculture and more frequent manifestations of pathogens. Marine organisms, including sponges, mussels, jellyfish, plants, alga seaweed, and crustaceans, yield bioactive compounds of high potential application in aquaculture. Many of these products confer specific benefits such as immune stimulation and consequently may reduce the risk of infectious diseases. Some marine products contain highly insoluble dietary fiber or non-digestible polysaccharides that serve as a rich source of prebiotics.

8. Future research

While using marine-derived compounds as antibiotics and immunostimulants in aquaculture is a promising alternative to combat low productivity and disease outbreaks, several areas still require further research. The optimal dosages and delivery methods for marine-derived compounds in aquaculture are yet to be determined. Besides, the long-term effects of marine-derived compounds on aquatic animal health and productivity still need to be fully understood. Therefore, further research is required to identify the most effective doses and modes of administration, including encapsulation and delivery systems.

Author contributions

Authors shared equally in this work. All authors have read and agreed to the published version of the manuscript.

CRediT authorship contribution statement

Conceptualization, Project administration, Writing – original draft, and Writing and editing the revised version were done equally by all authors.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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