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Bioactive immunostimulants as health-promoting feed additives in aquaculture: A review

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A B S T R A C T

Bioactive immunostimulants could be derived from different sources like plants, animals, microbes, algae, yeast, etc. Bioactive immunostimulants are the most significant role to enhance aquatic production, as well as the cost of this method, which is effective, non-toxic, and environment-friendly. These immunostimulants are supportive to increase the immune system, growth, antioxidant, anti-inflammatory, and disease resistance of aquatic animals' health and also improve aquatic animal feed. Diseases are mainly targeted to the immune system of aquatic organisms in such a way that different processes of bioactive immunostimulants progress are considered imperative techniques for the development of aquaculture production. Communicable infections are the main problem for aquaculture, while the mortality and morbidity connected with some outbreaks significantly limit the productivity of some sectors. Aquaculture is considered the mainly developing food production sector globally. Protein insists is an important issue in human nutrition. Aquaculture has been an exercise for thousands of years, and it has now surpassed capture fisheries as the most vital source of seafood in the world. Limited study reports are available to focal point on bioactive immunostimulants in aquaculture applications. This review report provides information on the nutritional administration of bioactive immunostimulants, their types, functions, and beneficial impacts on aquatic animals' health as well as for the feed quality development in the aquaculture industry. The scope of this review combined to afford various kinds of natural derived bioactive molecules utilization and their beneficial effects in aquaculture applications.

1. Introduction

Bioactive immunostimulants have been utilized to improve aquatic animal health, a broad spectrum of bioactive active molecules are used to enhance aquatic animals' health in many ways such as antimicrobial, antioxidant, immunostimulant, growth-promoting, and anti-inflammatory properties as well as bioactive molecules applied in aquatic feed is the novel technique, this bioactive immunostimulant approach reliable and reproducing methods to enhance the feed quality [1–3]. In addition, dietary administration of various bioactive immunostimulants namely FOS, butyric acid, propionic acid, polyphenol, chitosan, soybean isoflavones, lentinan, lipoteichoic acid, lactoferrin, and fucoidan have several positive effects such as immune system enhancement, growth, survival and disease confrontation against harmful microbes in aquatic organisms, natural bioactive immunostimulant dietary additive technique is the new way to enhance aquatic productions [4–8]. Microbial disease (bacteria, fungi, and viruses) outbreaks are considered the most imperative problem of aquaculture production, which can eventually lead to devastating financial losses [11]. The modes of action of immunostimulants are boosting the

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immune system of aquatic animals and also improving the immunity level against harmful microbes, bioactive immunostimulants are already been used to control pathogens in shrimp and fish including bacteria (*Aeromonas hydrophila, Aeromonas salmonicida, Vibrio anguillarum, Vibrio vulnificus, Vibrio salmonicida, Streptococcus* sp., *Yersinia ruckeri*) and viruses, which cause diseases such as *hematopoietic necrosis*, *yellow head virus*, viral *hemorrhagic septicemia* and the parasite *Ichthyophthirius multifiliis*, these kinds of immunostimulants are supportive to boost survival and reduced mortality rate in aquatic animals [9,10]. Aquaculture is a vital and rapidly developing sector as it performs a very important responsibility to attain widespread protein foodstuff demands. The responsibility of aquaculture to expand the socio-economic implication of some places is mainly obvious since it's not only able to provide essential nutrients but also a variety of employment opportunities are created [12]. This review provides information about dietary administration, functions, and doses of different bioactive immunostimulants to increase healthy aquatic production and also enhance feed quality levels in the aquaculture industry.

2. The roles of bioactive immunostimulants in aquaculture

2.1. Bioactive immunostimulants improve growth and digestive

Bioactive immunostimulants are present in plants, animals, and microbes or can be synthetically produced; the natural derived bioactive immunostimulants have various biological actions such as antioxidant, antitumor, cytotoxic, an inducer of apoptosis and cell cycle arrest, antimicrobial, larvicidal, chemotactic, antifouling, antimelanogenic, and anti-inflammatory activities [13]. Bioactive immunostimulants can be classified into two types such as macromolecules (carbohydrates, proteins, nucleic acids, lipids, and polysaccharides) and micro molecules (natural products, primary and secondary metabolites), both the biomolecules play a major role in aquaculture. Bioactive immunostimulants are complex organic molecules, which are present in all living organisms, while such bioactive immunostimulant substances maintain the metabolic process of all living organisms [15]. Moreover, bioactive immunostimulants are shaped in the body and maintain the structure and growth, while they could be characterized as necessary for body functions [16]. The bioactive immunostimulants contain numerous positive responses such as the immune system strengthening, antioxidant activity, mediation of hormones, and butyric acid production in the colon as well as combination and/or dilution of structure in the gut, the small intestine is not only the fatal position for nutrient digestion and absorption but also strongly connected with a different region of intestinal antigens and bacteria to control gut and whole-body health [14]. Similarly, Ashraf et al. (2020) defined bioactive immunostimulant substances as the material that can cause stimulating effects on living tissue [17].

2.2. Bioactive immunostimulants modulate gut microbiota

Dietary immunostimulants feed additives were described as of quite chemical characteristic nature, containing nutritional and non-nutritional possessions as well as bioactive immunostimulants, which may connect with direct or indirect physiological responses of fish species [18]. Moreover, dietary feed additives of carvacrol, and/or thymol koi carp (*Cyprinus carpio*) [20] from (*Allium sativum*) garlic rainbow trout (*Oncorhynchus mykiss*) [21] have revealed noteworthy possessions on gut health, digestive enzyme activity, intestinal immunity, and extra supportive photogenic targets for the progress of aquatic feed, the dietary immunostimulant additive stimulates and modifies the intestinal microbiota conferring health benefits of the host, but notably down-regulated the relative manner of tumor necrosis factor α (TNF-α) ($P = 0.0002$) and transforming enlargement factor β (TGF-β) and remarkably decreased malonaldehyde (MDA) levels in fish species. Heterogeneous groups of functional feed additives, such as essential oils (derived from aromatic plants) are widely used to enhance animal nutrition since these bioactive immunostimulants are applied in livestock nutrition as well as in animal feed. Essential oils are an important bioactive immunostimulant group; as such molecules are potential chemotherapeutic alternatives without side effects like immunostimulant, antimicrobial, anti-stress, antioxidant, and growth-stimulating effects while there is no ecological or harmful side effects linkage. Additionally, essential oils may exhibit a positive impact on the gut health of livestock as well as fish species [22]. Additionally, the colonization of gut microbiota has an important function in the regulation of non-specific and specific pathways of the immune system [24]. The intestinal microbiota of fish has an extremely imperative responsibility due to gastrointestinal growth, higher digestive enzyme action, mucosal tolerance maintenance, immunoregulation, and infection treatment enhancement [25–28]. Similarly, the gut microbial composition changes in the host's microbiota through the utilization of bioactive immunostimulants from various sources [23]. Different types of dietary functional feed additives such as probiotics, prebiotics, phytogenics, and immunostimulants are used to enhance healthy aquatic animals' production and also enhance the feed quality in aquaculture, the dietary immunogen additive increased growth performance, feed utilization, protein efficiency, and also decrease feed conversion ratio consequently, dietary immunogen additive increased higher body protein content [19].

2.3. Bioactive immunostimulants improve immunity

The nutritional additives of β-glucan, chitosan, or raffinose have been used to improve the non-specific immune system of koi (*Cyprinus rubrofuscus*) by amplifying various resistant criteria such as phagocytic activity, respiratory burst activity, lysozyme action, WBC, and SOD action, finally, the bioactive immunostimulants are supportive to get better the immune system of aquatic animals [31]. MyD88 signaling pathway is directly triggered by MAMPs of intestinal microbiota strains. Different kinds of substances (lysozyme, protease, complements, lectins, and immunoglobulins) are significant for skin mucosal immunity and also for disease resistance in fish [29]. For example, the MyD88 signaling pathway plays a major part in the innate immune system control, while on other hand some microbial components controlled the adaptive immune system, increased digestive enzyme, protein content, and reduced lipid content level, there are no differences in immune gene expression those all the parameters confirmed by the control groups (IgM and IgT) of rainbow trout (*Oncorhynchus mykiss*) head kidney [30]. Fishes treated with bioactive immunostimulants have generally confirmed by phagocytic cell performance increase [32], as according to literature the phagocytic cell action can be better by bioactive immunostimulants due to the activation of a natural immune response, for example, the inflammatory reaction before adaptive response such as antibody production, excessive doses level of some immunostimulants provoke immunosuppression in fish. The side effects of immunostimulants have not been well-studied. The study concluded that immunostimulants are a vital role in to control of fish infections and the optimum dietary immunostimulants are helpful to improve the growth of farming fish culture [33]. Mendoza Rodriguez et al. (2017) examined that dietary additives of organic acids (polyhydroxy butyrate (PHB 2%), potassium diformate (KDF 0.6%)), other biomolecules (carrageenan (0.5%) and alginic acid (1%)) enhanced the immunological system of red drum (*S.ocellatus*), as well as feed efficiency and weight gain, was notably decreased in fish feed compared to the basal diet and together bioactive immunostimulants [34]. Consequently, the bioactive immunostimulant supplements have been shown to noticeably resilient structure stimulation of fish [35]. In aquaculture, bioactive immunostimulants and their derivatives enhanced non-specific immune responses against various diseases, while these molecules have exhibited effective immunostimulant properties in fish and shrimps [10].

2.4. Bioactive compoundsas immunostimulants in aquaculture

2.4.1. Plants derivedbioactive immunostimulants

Plant-based bioactive immunostimulants as supplements could show the potential impact in aquatic organisms like enhanced gut health, immune system, antimicrobial action and act as appetite stimulators, the herbal bioactive immunostimulants only give positive effects; they cannot be suggested owing to their remaining and other side effects in aquatic animals [36]. Similarly, the active dietary supplementation of herb and spices were capable to provoke and release intestinal enzymes, mucosal serum immunities, and antioxidant response that will stimulate the appetite; thus, rising food consumption and subsequently improving the efficiency in Nile tilapia (*Oreochromis niloticus*), this dietary additive has no significant changes in feed conversion ratio and also dietary inclusion was not affected to fish health [37]. In addition, various plants derived bioactive elements such as flavonoids, alkaloids, phenolics, terpenoids, tannins, steroids, glycosides, saponins, and essential oils have been described to show positive effects namely immunostimulation, growth promotion, anti-pathogenic, appetite stimulation, and anti-stress in fish species, this study pointed out that dietary additives of herbal bioactive immunostimulant as helpful to enhanced physiological and hematological responses in fishes [36]. The plant-based bioactive immunostimulants were commonly tonics for the release of digestive enzymes and have a direct effect on intestinal microflora, while according to literature these compounds can increase the digestibility, feed conversion, and protein synthesis of the rainbow trout (*Oncorhynchus mykiss*) [38]. Different types of plant bioactive immunostimulants have been added to feed supplements, demonstrating significant impacts in farmed animals, while such dietary additives are safe for animals, consumers, and the environment [39]. Abha and Abhisweta (2020) reported that the animal feed industry utilized plant bioactive immunostimulants to develop animal nutrition and health [40]. Additionally, Baleta et al. (2022) suggested that dietary additives of 1% ethanolic katuk extract bioactive immunostimulant enhanced growth, appetite, and improved food utilization in Orange-spotted grouper (*Epinephelus coioides*) [41].

2.5. Polyphenols

The polyphenols group is one of the major classifications of bioactive immunostimulants produced by plants to defend against different pathogenic bacteria, fungi, and viruses and also defend response to various types of abiotic stress [42]. Therefore, polyphenols are suggested as alternative options for the (partial) replacement of chemicals and antibiotics in aquaculture development [43,44]. In addition, polyphenol dietary additive (tannins from 2.5 to 20.0 g/kg) was used for immunological parameters enhancement in rohu (*Labeo rohita*) fingerlings, while these supplements have shown numerous positive effects such as resistance against oxidative stress improvement, reproductive performance, growth performance and infection resistance in different fish species such as European sea bass (*Dicentrarchus labrax*), black carp (*Mylopharyngodon piceus*), Wuchang bream (*Megalobrama amblycephala*), common carp (*Cyprinus carpio*), convict cichlid (*Amatitlania nigrofasciata*) and beluga sturgeon (*Huso huso*) [10,45–51]. Dietary polyphenol supplement (0.2%) was extracted from chestnut and olive mill wastewater, this polyphenol additive improved the growth performance, immunological parameters, and antioxidant status, and also feed conversion ratio of fish-fed polyphenols notably diminished and differentiated from the control groups in common carp (*Cyprinus carpio*) fingerlings [52]. Dietary *Clarius lazera* phenol additives have been used in various concentrations (35, 75, 150, and 300 mg/L) and enhanced hematological parameters and also elevated LDH, glucose, and cortisol, and significantly reduced serum cholesterol concentration in catfish (*Siluriformes*). The dietary polyphenol was supportive to improve the fish's immune system [53]. In addition, dietary tannins polyphenol additive (0.1%) was derived from chestnut wood and were in various analyzes such as growth parameters, growth gene expression, enzymatic activity, and hematological and non-specific immune parameters in beluga under experimental conditions. Finally, the optimum level of 0.1% dietary polyphenol was supportive to improve fish health [51].

2.6. Flavonoids

Flavonoids are the most important ingredients of plants [54]. Dietary *Allium mongolicum Regel* flavonoids (AMRF) supplement (40 mg/kg) enhanced the immune system, antioxidant status, regulation of gene activation, and infection resistance of *Cephalopholis argus* (Peacock hind) against *Aeromonas hydrophila* as well as considerably decreased in serum cortisol, liver MDA content, serum ALT and AST activity [55]. Dietary supplementation of *R. verniciflua* extract flavonoids enhanced feed quality level and fish production, exhibiting also a significant impact on antiviral effects in fish viral diseases like infectious *hematopoietic necrosis virus* (IHNV) and *viral hemorrhagic septicemia virus* (VHSV) [56].

2.7. Alkaloids

Alkaloids are found in plant tissues as a type of water-soluble salts of organic acids, esters, or sugars rather than as free bases [57]. Moreover, alkaloids contain different types of protein bands, which have a significant role in immune system enhancement and infection resistance against various pathogens in fish [58]. Subsequently, dietary additives of *Gelsemium elegans* alkaloids (40 mg/kg) increased intestinal villus length, villus number, muscle growth, antioxidant activity, intestinal immune activity, cytokine-related genes expression, and also to improved the disease resistance of Wuchang bream (*Megalobrama amblycephala*), while firmicutes abundance was reduced at phylum level after the alkaloid feeding [59]. Zhou et al. (2016) reported that dietary additives (25 g/kg) of the fibrous root of *Rhizoma Coptidis* containing alkaloids could enhance the immune system and disease resistance in common carp (*Cyprinus carpio*) [60].

2.8. Fructooligosaccharides

FOS is derived from blue agave plants, vegetables, fruits, cereals, and grains [61], composed of D-fructans, in which fructose is attached by b-(2–1) glycosidic connections and associated with an end glucose unit. Additionally, FOS may be linked via tolls like receptors (TLR2) pointing to macrophages [62] and stimulating the expression of antimicrobial peptides (Leap), which have a significant role in natural immune protection and disease resistance in fish (*Megalobrama amblycephala*) [63]. Likewise, dietary supplementation of FOS (1%,2%, and 3%) increased lysozyme action, salinity stress resistance, leukocyte production, and elevated digestive enzyme function in Caspian roach fry (*Rutilus rutilus*) [64]. Similarly, our research group described that diet containing (5 g/kg) FOS improved intestinal enzyme activity, and lysozyme action, and also decreased triglyceride (TG) levels compared to the control diet in Japanese flounder (*Paralichthys olivaceus*) [59,65]. Dietary supplementation of FOS (0.3 and 0.6%) has shown a beneficial effect on the innate immune response of Nile tilapia (*Oreochromis niloticus*), confirmed by the major progress of serum lysozyme action and IgM level and also both plasma and phenoloxidase performance were noticeably ($P < 0.05$) affected only by dietary FOS levels with the maximum standards experiential in fish fed 0.6 and 0.3% FOS, respectively [66].

2.9. Galactooligosaccharides

Galactooligosaccharides (GOS) incorporate 2–20 different prebiotic substances of galactose and glucose and are generally formed by the enzymatic hydrolysis of lactose [67]. GOS has a small point of polymerization, which improves its metabolization rate by probiotics [68]. The use of GOS (1% and 2%) dietary supplement enhanced humoral and mucosal immune response, survival rate, and increased salinity resistance in Caspian roach (*Rutilus rutilus*) fry as well as there is no negative impacts in the experimental condition [69]. Nutritional management of GOS as an immunostimulant in rockfish (*Sebastes schlegeli*) presented that feeding rockfish with (1%) of GOS for 8 weeks, notably improved skin mucus as well as humoral immune criteria, and also this bioactive immunostimulant not affected to the physiological and hematological responses in fish species [70]. Yukgehnaish et al. (2020) reported that the dietary supplement of GOS (10 g/kg^{-1}) acted as a significantly important prebiotic for the Atlantic salmon (*Salmo salar*) and also this bioactive immunostimulant affected protein concentration in the wet body and protein retention were reduced by 6 and 9%, respectively, relative to the basal fish [71], Caspian roach (*Rutilus rutilus*) [72], rainbow trout (*Oncorhynchus mykiss*) [73], common carp (*Cyprinus carpio*) [25,74], Caspian white fish (*Rutilusfrisii kutum*) [75], narrow-clawed crayfish (*Astacusleptodactylus Leptodactylus*) [76], and rockfish (*Sebastes schlegelii*) [70].

2.10. Inulin

Inulin exists in several fruits, vegetables, and cereals, like leeks, onions, chicory, bananas, wheat, garlic, and artichokes. It is reported that dietary inulin supplement (5 g/kg) could improve hematocrit and NBT activity levels and lysozyme activity as well as there is no negative impact on physiological and hematological response in Nile tilapia (*Oreochromis niloticus*) [77]. Gupta et al. (2020) stated that dietary inulin additives can control the hematological and/or serum biochemical parameters (erythrocyte counts, mean corpuscular volume (MCV), hematocrit, mean corpuscular hemoglobin (MCH), hemoglobin, mean corpuscular hemoglobin concentration (MCHC), leukocyte counts, serum glucose or serum total protein levels, differential leukocyte counts and serum cholesterol); thus this indicator has a prominent role in fish health [78]. Furthermore, Mo et al. (2015) presented that dietary inulin additive (2%) improved growth action and the natural immune system of grass carp (*Ctenopharyngodon Idella*) [79]. Another study about inulin supplement (15–20 g/kg) in Barramundi (*L.calcarifer*) juveniles; reported significant effects in histology, biochemical parameters, and immunohistology [80].

2.11. Salidroside

Salidroside is a glucoside of tyrosol, which is present in the plant species of *Rhodiola Rosea*. It has been considered, along with rosavin, as one of the most significant factors responsible for the known antidepressant and anxiolytic actions of this plant [81]. Zhang et al. (2021) reported that salidroside was found not only in the plant *Rhodiola Rosea* but also in a few Chinese herbs like *Angelica root* [82], *Ganoderma lucidum* [83], *Prunella vulgaris*, etc., as well as this bioactive immunostimulant enhanced the immune system and antiviral effects challenging against *coxsackievirus* B3 and *dengue virus* [84]. Xie et al. (2020) pointed out that salidroside (0.1% and1.0%) components were highly present in *Prunella vulgaris* extracts, and these factors enhanced non-specific immune activity, respiratory burst activity, phagocytic activity reduced mortality rate, and treat Olive flounder (*Paralichthysolivaceus*) challenge with *Uronema marinum*. Finally [4], Yang et al. (2020) mentioned that dietary additive of salidroside improved the immune system in crucian carp (*Carassius carassius*) and enhanced the defense action against harmful microbes, main at the concentration of 100 mg/kg for four weeks. The protective effect of salidroside on crucian carp (*Carassius auratus*) might be considered as an alternative to antibiotics for controlling fish infections in aquaculture as well as the quantity of *A. hydrophila* in the kidney and spleen was considerably decreased in salidroside additive diet groups ($P < 0.05$).

2.12. Geniposide

Geniposide is a bioactive iridoid glycoside; it is present in different types of medicinal herbs, namely *Gardenia jasminoides* (fruits). Geniposide showed a variety of pharmacological responses both *in vitro* and *in vivo* applications, such as antidiabetic, anti-inflammatory, neuroprotective, hepatoprotective, analgesic, antidepressant-like, cardioprotective, antioxidant, immune-regulatory, antithrombotic, and antitumor activity. Geniposide is derived from *Gardenia jasminoides Ellis*, a Chinese herbal medicine [85]. Nevertheless, few studies demonstrate the efficacy of geniposide as an immunostimulant in fish species, dietary administration of geniposide 400–800 mg/kg increased total collagen and alkaline-insoluble collagen content in grass carp (*Ctenopharyngodon Idella*) muscle than control and also fish fed diet containing geniposide notably reduced muscle crude lipid content compared to control groups [86]. Geniposide was shown as an efficient diet supplement to control the apoptosis-related factor, reduce WSSV (*white spot syndrome virus*) simulation and increase the survival rate of WSSV-challenged red swamp crayfish (*Procambarus clarkii*) [87]. Similar beneficial effects of lysozyme reaction were also observed in crucian carp (*Carassius carassius*) [88], and Nile tilapia (*Oreochromis niloticus*) [66] feeding geniposide-containing food. According to the literature, the use of 100 mg geniposide/kg was proved positive effects on immune reaction improvement and infection resistance in crucian carp (*Carassius carassius*), one of the most (freshwater) cultivated fish species in China. Furthermore, this dietary supplement was tested for innate immune response improvement, upregulated resistant connected gene exhibition, and infection resistance against *Aeromonas hydrophila* in crucian carp (*Carassius carassius*) [89].

2.13. Lectins

Lectins are carbohydrate-binding proteins, present in most plants and some animals [90]. Lectins are considered as a carbohydrate detection domain, mainly binding sugars while there are different classifications of animal lectins namely C-type, I-type, F-type, L-type, P-type, M-type, R-type, F-box lectins, chitinase-like lectins, galectins, intelectins, calnexin, and ficolins. Lectins play a major role in intracellular and extracellular, extracellular lectins are vital for cell signaling and pathogen recognition while intracellular lectins play a major part in the convey of proteins movement throughout the cells and in protein sorting [91]. C- type lectins, which are responsible for stimulating the immune system, are particularly linked with PAMPs on the surfaces of several harmful microbes, providing them the ability to detect a broad diversity of pathogens [92]. Several classifications of lectins have been recognized in rainbow trout serum through calcium ion chains to *A. salmonicida* lipopolysaccharide [93]. On the other hand, opsonizing lectins, which are present in fish serum, may be beneficial for fish health, as are considered for the immune mechanism and prevention of aquatic animal diseases. The components play an imperative function in protecting the host by identifying pathogens and then increasing their elimination and appearance in phagocytic cells of the immune system. The mammalian mannose-associated lectin can opsonize in different types of organisms such as yeasts, bacteria, and surrounded viruses, like HIV or influenza [94]. Similarly, the potential function of lectins as non-recognized substances in all living organisms' immunity [95]. Likewise, the crucial role of lectins in molecular biology and immunological analysis in animals [96], while the importance of lectins in the innate immune reaction of mammals is well known [97]. In addition, Liang et al. (2020) pointed out that lectins from immune cells of marine invertebrates were effective in improving disease resistance against *V. vulnificus* and *V. pelagicus* in aquatic animals and also reduced mortality rate in aquatic animals [98].

2.14. Carotenoids

Carotenoids are natural pigments, with a significant role in all living organisms like plants, algae, fungi, bacteria, and animals. Animals cannot synthesize carotenoids, so they obtain them from their diet [99]. Shrimp-extracted carotenoid supplements of 100 and 200 mg/kg could lead to immune system enhancement and infection resistance of Carp against *A. hydrophila* [100]. The addition of carotenoids in feed exhibited a beneficial role in both fish and fishery products as pathogenic organisms' inhibition was achieved. Carotenoids' dietary additives range (50 and 100 mg/kg) varies from species to species [101]. Many researchers exhibited that a dietary additive of 100 mg carotenoids/kg can boost the immune system, survival, and growth as well as avoid harmful effects of lipid peroxidation in different species such as rainbow trout (*Oncorhynchus mykiss*), giant tiger prawn (*Penaeus monodon*) and European bullhead (*Cottus gobio*) [102–104]. Natural immunostimulants, namely dietary supplements of carotenoids boosted the immune system, disease resistance, and antioxidant function of aquatic animals and also downregulated in superoxide dismutase but high catalase activity compared to the control one [105]. The function of plants based bioactive compounds as immunostimulants in aquatic animals has been summarised in Table 1.

2.15. Animal originated bioactive immunostimulants

2.15.1. Chitosan

Chitosan is a type of alkaline polysaccharide existing in the shell of aquatic organisms namely crabs, shrimps, and shellfish. Chitosan is a conventional non-toxic, safe, bio-compatible, and bio-degradable polymer substance. The main effect of chitosan molecule progression is to significantly increase the growth of aquatic species [106], reduce the growth of harmful microbes [107], purify the aquaculture water [108], and improve the resistance of aquatic organisms to infections [106]. Chitosan can chelate metal ions via the role of amino acid groups and hydroxyl substances and might decrease the heavy metal ions in water; thus chitosan is considered a major defender factor for the aquatic species [109]. In addition, immunostimulants are responsible for the improvement of inflammatory cell function namely polymorphonuclear leucocytes, cytokine, and macrophages [110]. In aquaculture, dietary chitosan improved the protective effect against bacterial infections and enhanced the immune response in hybrid striped bass (*Morone saxatilis*) [111], while recently, chitosan was presented as an effective immunostimulant in different fish species [112]. Dietary supplement of chitosan enhanced non-specific immune response under experimental conditions of healthy control, and additionally, chitosan was tested against the immune response modulation in rohu (*Labeo rohita*) [113]. Diets with chitosan for rainbow trout (*Oncorhynchus mykiss*) [114], olive flounder (*Paralichthys olivaceus*) [115], koi (*Cyprinus rubrofuscus*) [116], and kelp grouper (*Epinephelus bruneus*) [107] demonstrated that such a bioactive immunostimulant could improve growth, natural immunity, infection, stress resistance, enhance immunological criterion and increase water quality. The mechanism of chitosan action as an immunostimulant in fish has not been fully established yet. Similar studies showed that chitosan additives might increase the innate immune system response of various fish species [117]. Oushani et al. (2020) reported the action of chitosan as an immunostimulant in rainbow trout (*Oncorhynchus mykiss*), as they observed that a chitosan (2.5 g/kg) diet was favorable on immunological criteria and increased the survival rate of rainbow trout (*O. mykiss*) against environmental stress [114]. Wu et al. (2020) reported that the immunostimulatory feature of chitosan for olive flounder (*Paralichthys olivaceus*) activates the innate immune system of fish species, thus this action exhibits a defense role in the fish body through amino moieties [115].

2.16. Lactoferrin

Lactoferrin is a globular glycoprotein with a molecular mass of about 80 kDa that is widely represented in different secretory fluids namely milk, saliva, tears, and nasal secretions. Lactoferrin is one of the significant bioactive mechanisms of the immune system in the body; it has

Table 1
Plants originated bioactive compounds as immunostimulants in aquaculture.

Origin	Bioactive immunostimulants	Aquatic organisms	Immune response	References
Plant	**Fructooligosaccharides**	Caspian roach	↑lysozyme function, improvement of IgM level, No significant different ACP and increases PO	[63,65]
		Common carp Nile tilapia		
		Japanese sea bass	↑growth, digestion and immune activities	[190]
		Tambaqui	Promote growth and improved healthiness	[191]
		Juvenile grouper *Epinephelus coioides*	Improved immune system and intestinal morphology	[192]
	Galactooligosaccharides	Caspian roach Rainbow trout Narrow-clawed Crayfish	↑ Humoral and mucosal immune reaction	[69,71,72,75]
		Common Carp	Controlled innate immune response in skin mucosa	[193]
		Pacific white shrimp	Modulate gut microbiota composition, reduce stress and enhanced immune system	[194]
	Inulin	*L. calcarifer* *Rainbow trout*	↑ hematocrit, NBT and lysozyme activity, biochemical parameters and immuno-haematology	[63,79]
		common carp	↑growth performance, innate immune response and antioxidant activity	[195]
		Nile tilapia	Improved fish health under salinity stress condition	[196]
	Salidroside	Crucian carp Paralichthysolivaceus	↑ immune related gene and non specific immune system	[4,105]
	Geniposide	Crucian carp Nile tilapia	↑ innate immune response, upregulated immune gene expression, RPA	[65,188]
		Crayfish	Anti inflammatory, antioxidant and antiviral activity	[197]
	Polyphenols	Common carp fingerlings	↑haematological parameters(erythrocytes and haemoglobin), anti oxidant status	[51]
		Amatitlania nigrofasciata	Improved humoral and mucosal response and antioxidant activity	[198]
		Lates Calcarifer	Improved growth, mucosal immune response and liver oxidative status	[199]
	Flavonoids	*C.argus* *Trachinotusovatus*	↑immune system, antioxidant activity, regulation of immune gene expression	[7,54]
		Ctenopharyngodon idella	↑Antioxidant, anti inflammatory and immune response	[200]
	Alkaloids	*Megalobramaamblycephala* common carp	↑antioxidant activity, Intestinal immune activity, RPA	[58,59]
		Pacific white shrimp	Improved growth response, survival rate, immune response and antibacterial activity	[201]

↑- Enhance or Increase or Improve.

antimicrobial activity (bacteriocide, fungicide) and is part of the innate defense, mainly against mucose. Lactoferrin connects with DNA and RNA, polysaccharides, and heparin, and performs the biological response in complexes with these ligands [118]. The dietary additive of 100 mg/kg Lf enhanced the immune response, respiratory burst, leukocytes peroxidase content, and phagocytic index in gilthead sea bream (*Sparus aurata*) [119]. [120] Morshedi et al. (2020) observed that the dietary supplement (1200 mg/kg) of Lf could enhance low salinity stress, tolerance of air exposure, natural immune response, and mucus secretion of juvenile orange-spotted grouper (*Epinephelus coioides*), as well as dietary LF, did not affect the growth rate of this species under the condition applied in this study. Similarly [35], Luna-Castro et al. (2021) represented that the nutritional additive of Lf at a level of 100 mg/kg increased the innate immunity and infection resistance of sea bream (*Pagrus major*) and Asian catfish (*Siluriformes*), as well as this study, described that support the possible use of Lf as an immunostimulant for farmed fish species. Several Lactoferrin (Lf) products have been classified and evaluated, but bovine lactoferrin (BLf) has received attention for its potential for animal protection. Owing to its immunoregulatory function, BLf may stimulate antiviral, antifungal, and antibacterial functions and subsequently may activate efficient defense against different microbial infections in some fish species according to the dose and administration methods [121]. Additionally, dietary Lf supplementation of 100 mg/kg for 1 week the immune system improvement of diverse fish species such as goldfish (*Carassius auratus*), rainbow trout (*Oncorhynchus mykiss*), Atlantic salmon (*Salmo salar*), red sea bream (*Pagrus major*) and Asian catfish (*Siluriformes*) [122]. The function of animals-base bioactive compounds as immunostimulants in aquatic animals has been summarised in Table 2.

2.17. *Bacterium originated bioactive immunostimulants*

2.17.1. *Peptidoglycan*

Peptidoglycan or murein is a polymer consisting of sugars and amino acids that forms a mesh-like peptidoglycan layer outside the plasma membrane of most bacteria, forming the cell wall. The sugar component consists of alternating residues of β-(1, 4) linked N-acetyl glucosamine (NAG) and N-acetylmuramic acid (NAM), and attached to the NAM is a peptide chain of three to five amino acids. Peptidoglycan performs the structural function, strengthens the bacterial cell wall, and prevents the osmotic pressure of the cytoplasm. Peptidoglycan was also involved in the binary division during bacterial cell reproduction [123]. Oral dietary supplements of peptidoglycan (0.2 mg/kg) extracted from *Bifidobacterium thermophilum* could act against *vibriosis* and white spot syndrome in kuruma shrimps (*Marsupenaeus japonicas*) as well as reduce mortality and increase the survival rate in shrimp [124]. Likewise, dietary additives of cellular components like cell wall (CW), peptidoglycan (PG), and lipoteichoic acid (LTA) enhanced physiological and immunological response, while notably decreased feed conversion ratio (FCR) was noticed in all the treatments compared with the control group in orange-spotted grouper (*Epinephelus coioides*) [125]. [126] Kondo et al. (2021) demonstrated that dietary additives of A3a-PG (8 g A3α-PG/kg) led to the immune system enhancement, disease resistance, and growth performance of Japanese flounder (*Paralichthys olivaceus*) as well as the highest dose explored in the previous report, (16 g A3α-PG/kg), also failed to show any significant influences, although no obvious pathology was observed. Another case of dietary additive of peptidoglycan (0.18 g/kg for5 days/week) exhibited an increase in the immune system and infection resistance of black tiger shrimp (*Penaeus monodon Fabricius*) and there is no significant changes to the growth [127]. The immunostimulatory effect of microbial peptidoglycan is acknowledged from the laboratory verification process, which can stimulate innate immune responses, phagocytic index, and survival rate and infection resistance against aquatic pathogens in aquatic animals [128].

Table 2
Animal originated bioactive compounds as immunostimulants in aquaculture.

Origin	Bioactive immunostimulants	Aquatic organisms	Immune response	References
Animal	**Chitosan**	Rainbow trout Olive flounder Koi kelp grouper	↑haematological parameters, RPA	[105, 112–114]
	Lactoferrin	Asian catfish Atlantic salmon gilthead sea bream	↑non specific immune response, respiratory burst, leukocytes peroxidase content and phagocytic index, RPA	[34,117, 118]
	Carotenoids	Carp rainbow trout giant tiger prawn European bullhead	↑antioxidant activity, RPA. immune system response, Disease resistance	[98, 100–102]

↑- Enhance or Increase or Improve.

2.18. *Lipopolysaccharides*

Lipopolysaccharides (LPS) are huge molecules incorporating a lipid and a polysaccharide controlled of O-antigen, outer core, and inner core connected with a covalent bond, while they are attending in the outer layer membrane of the Gram-negative bacteria. LPS are the components of the gram-negative bacteria cell wall and also turn on B cell proliferation. LPS injected into red sea bream (*Pagrus major*) exhibited improved macrophage phagocytic action [129]. The LPS are very effective even in extremely low doses; while they can be derived from bacteria by chemical extraction methods and present better immunostimulating properties during their use in fish species [130]. Ali et al. (2021) suggested that LPS (1250 μg) played a significant role in rainbow trout (*Oncorhynchus mykiss*) and carp fish (*Cyprinus carpio*) species, as they are good immunomodulators and beneficial response in the disease resistance of fish species, the lipopolysaccharides improved phagocytic activity, total serum Ig and get better mucus lysozyme compared to untreated fishes mortality level is increased [32,131]. Abd El-Kader et al. (2021) recommended that dietary supplement of LPS (50 and 100 μg of LPS/fish) was injected intraperitoneally and successfully activated innate cellular and secondary immune response as well O-specific linkage for activating the adaptive immune system and disease resistance against *A. hydrophila* [132]. In contrast, oral consumption did not alter any of the aforementioned criteria. Similarly [133], Holen et al. (2021) reported that dietary additive of lipopolysaccharides was derived from *Salmonella Typhimurium*. The lipopolysaccharide component enhanced better immunostimulant, phagocytic activity, and disease resistance against *Escherichia coli* and *A. salmonicida* disease in trout (*Oncorhynchus mykiss*). In addition [134], Mohammadi et al. (2020) reported that a nutritional LPS additive of 0.1 mL was derived from *Aeromonas hydrophila* enhanced disease resistance against *A. hydrophila* in (*Oreochromis niloticus*) Nile tilapia as well as for disease prevention during unfavorable environmental conditions.

2.19. *Lipoteichoic acid*

Dietary supplementation of lipoteichoic acid (LTA) was derived from probiotics and is used to regulate immune gene expression as well as in ligand binding connections. Since LTA can stimulate the immune response in fish, it might be favorable for the control of disease in Gram-positive bacteria such as *Streptococcus iniae* and *Streptococcus agalactiae*

[135]. Similarly [136], Yang et al. (2019) observed that dietary additives of both peptidoglycan and LTA extracted from *B. pumilus* SE5 can stimulate TLRs/MyD88 signal pathway and the condition of antibacterial agents and thus form the gut microbiota in orange-spotted grouper (*E. coioides*). Additionally, dietary additive of LTA extracted from probiotic *B. pumilus* SE5 was utilized to uncontrolled three antibacterial peptides genes (epinecidin-1, hepcidin-1, and β-defensin) and immune gene expression (TLR2, NOD2, IL-8, IgM) in the head kidney of Grouper (*Epinephelus coioides*) [137]. Earlier studies have revealed that LTA is the main cell wall element of Gram-positive bacteria, can associate with the TLR-2 receptor, and triggers a cascade of responses. *L. Plantarum* LTA extensively improved the feature of TLR2 and *V. anguillarum* flagellin particularly improved TLR5. It is differentiated that LTA, flagellin, and LPS bacterial components are mainly stimulated by TLR2, TLR5, and TLR9 receptor pathways [138,139]. [140] Gao et al. (2016) suggested that dietary LTA enhanced the natural immune system of silver pomfret (*Pampus argenteus*). Probiotic dietary additives of LTA can regulate the activation of several inflammatory factors and provoke apoptosis to a lower level, as might also be determined by the physiological characterization of the bacterium. Dietary supplements of LTA an imperative function in the host cell TLR and also enhanced immune response, probiotic colonization, and decreased pathogenic load while sustaining a strong and active strength among the host and its gut bacteria.

2.20. Levan

Levan is a naturally occurring fructan, the homopolymer of fructose. The molecular weight and degree of branching of levan differ depending on the production organism. Moreover, the molecular weights of bacterial levan are much higher than the plant levan due to the multiple branching [141]. Levan is the component of natural polymeric chain linkages, which are mainly present in the microbial extracellular products of *Bacillus subtilis*, *Bacillus polymyxa*, *Zymomonas mobilis*, *Acetobacter xylinum,* and a few plant species [78]. Similarly, dietary additives (25 g/kg) of microbial levan exhibited beneficiary effects in aquatic animals like improved non-specific immune response, disease resistance, growth, survival, and enhanced tolerance to thermal stress, and also levan additive diets notably reduced the count of total viable aerobic bacteria and *Vibrio* spp. in the gut region of orange-spotted grouper (*Epinephelus coioides H.*) [142]. Moreover, the dietary additive of microbial levan (1.25%) enhanced the immune response and thermal stress tolerance effect of rohu (*L. rohita*) juveniles, this optimum dietary additive can confer protection against thermal stress tolerance in fish species [143].

2.21. Fungal originated bioactive immunostimulants

Higher fungi are considered important sources of natural products and have also exhibited various biological properties like anti-microbial, anti-oxidant, immunostimulation, hypoglycaemic activities, and anti-cancer [144]. Numerous higher fungi (*Pleurotus ostreatus*, *Lentinula edodes*, *Grifola frondosa*, *Coriolus Versicolor*, *Ganoderma lucidum*, and *Schizophyllum commune*) have bioactive polysaccharides in their fruiting bodies; mycelium and broth culture [145]. Consequently, polysaccharides can significantly improve the growth and natural immune response of fish and shrimp species [146–148].

2.22. Lentinan

Lentinan is a biological active transformer, which is shown to be effective in protecting the host from oxidative damage without obvious adverse activity and also diet additives of lentinan were used to modify the gastrointestinal microbiota, which would be useful to sustain the epithelial barrier role and enhance intestinal immunity. Lentinan is a type of β-glucans with safe and pharmacological properties as well as immunomodulatory, anti-oxidant, anti-inflammatory, anti-microbial, and metabolic regulatory functions [147,149]. The nutritional additive of lentinan (100 μg/ml) has notably increased the intestinal anti-oxidant, and inflammatory capacity by enhancing the performance of SOD, CAT, and GSH-Px, and suppressing lipid peroxidation and also lentinan may be effective for the treatment of gut inflammation including IBD in juvenile taimen (*Hucho taimen*) [148,149]. [150]. Galindo-Villegas et al. (2016) reported that lentinan can induce anti-microbial activity and stimulate the immune system through *in vitro* methods. Moreover, dietary additives of lentinan (100–1000 μg/ml) increased the immune system and disease resistance in Common carp (*Cyprinus carpio*) by *in vitro* methods [151].

2.23. Mannan oligosaccharides

Mannan oligosaccharides (MOS) are extracted from the cell wall of yeasts and recently researchers indicated the beneficial properties of MOS in fish and shrimp species [152]. The possible effect of MOS (0.6%) in aquaculture content is determined by the mannose receptor (endocytic receptor), while these receptors communicate with macrophages and endothelial cells to be identified together with individual glycoproteins and microbial glycan ligands [153]. MOS (0.6%) presented a related consequence on the function of lysozyme in Nile tilapia (*Oreochromis niloticus*), Japanese flounder (*Paralichthysolivaceus*), Rainbow trout (*Oncorhynchus mykiss*), and Channel catfish (*Ictalurus punctatus*), while the dietary additives of MOS were not affected in fish growth and immune system [154]. MOS as feed supplements (6 g/kg) in aquaculture of fish and shellfish may demonstrate to be supportive to the host by increasing innate immunity, although more studies described that it is needed to infer the appropriate level of MOS addition to diverse fish species and also MOS dietary supplement was significantly decreased lipogenic enzymes response in liver and resulted in a lower lipid vacuolization and more regular-shaped morphology of hepatocytes approximately the sinusoidal spaces, which could be associated to better energy and good feed utilization because of the improvement of feed utilization and the decrease of feed intake found in the current experiment [155]. The dietary additive of MOS (0.4%) notably activated hemolytic and phagocytic reactions in rainbow trout (*Oncorhynchus mykiss Walbaum*) [156], while an amount of 2 g MOS/kg for 60 days was used to evaluate certain immune components and immuno-associated enzymes in red sea bream (*Pagrus major*) as well as the specific immunostimulatory activity of MOS in the gastrointestinal tract of fish and also the performance of lysozyme, bactericidal and peroxidase in serum and mucus of fish fed MOS diets improved over the control [157]. Similarly, the dietary feed supplement of MOS (0.6%–1%) was experienced to increase blood protein levels in rohu (*Labeo rohita*) and Nile tilapia (*Oreochromis niloticus*), and also dietary additive of MOS at a 0.6% and 1% dietary level stimulates growth and survival in rohu (*Labeo rohita*) and Nile tilapia (*Oreochromis niloticus*). In difference, elevated addition levels of immunostimulants led to an immunosuppressive effect in rohu (*Labeo rohita*) and Nile tilapia (*Oreochromis niloticus*) [158].

2.24. β-Glucans

Glucans are primarily present in the cell walls of bacteria, fungi, algae, lichens, and yeasts they obtain a helical or spiral backbone suitable to specific intra-factor hydrogen bonding. These β-glucans (10 mg/kg) have been commonly expressed to control the immune function as well as blood neutrophils, oxidative radical production, and superoxide anion production in stimulated macrophages of *Litopenaeusvannamei* juveniles [159]. The main component of β glucans is high-quality immunostimulating factors. The abundance and nature of side chains strongly affect the capability of the glucans to interfere with binding to external receptors on the particular cells influencing the reaction of the glucans as an immunostimulant [160]. These changes may indicate the way to a mortality rate reduction of fish species against various pathogens. Innovative β–glucan receptors namely Dectin-1 and Toll-like receptors on leukocyte surfaces of vertebrates have provided various insights into the functions of immune responses induced by β-glucans [161]. Oral dietary administration of yeast-derived beta-glucans was showed that numerous positive affects such as enhance phagocytosis, lysozyme levels, respiratory burst activity, and resistance against bacterial pathogens in several cultured fish species. The function of glucans have been extensively studied in aquatic animals and the findings indicate that β -glucans improved growth and significantly reduced mortality rate in certain species of aquatic animals [162,163]. β-glucans have been mentioned for their valuable role in several fish species such as red sea bream (*Pagrus major*) [164], Atlantic Salmon (*Salmo salar* L.) is utilized to improve growth, survival, immune system, disease resistance against aquatic pathogens and reduced mortality rate in aquatic animals [165].

The function of microbial-based bioactive compounds as immunostimulants in aquatic animals has been summarised in Table 3.

2.25. Algal bioactive immunostimulants

2.25.1. Alginate

Alginate was derived from brown seaweed, and it is a polysaccharide component controlled by β-1, 4-D-mannuronic acid (M), and C5-epimer a-L-glucuronic acid (G). A dietary additive of sodium alginate was used to increase the non-specific immune system and infection resistance in Tilapia (*Oreochromis niloticus*) [125,166]. In addition, a nutritional additive of sodium alginate (2 g/kg) enhanced the survival of grouper *E. coioides* by increasing its phagocytic activity, respiratory bursts, lysozyme activity, alternative complement activity, and SOD activity, disease resistance against *Streptococcus* sp. and iridovirus infection in grouper [167]. It has been reported that the nutritional additive of sodium alginate (2 g/kg) could improve phagocytic activity, respiratory bursts, lysozyme activity, alternative complement activity, SOD activity, and disease resistance against *V. alginolyticus* but decreased GPX activity in Pacific white shrimp (*L. vannamei*) [168].

2.26. Alginic acid

Alginic acid (or algin) is a naturally occurring, edible polysaccharide, present in brown algae. Such compound is hydrophilic and forms a viscous gum when hydrated. Accompanied by different metals such as calcium and sodium, forms salts, which are recognized as alginates. Its color ranges from white to yellowish-brown. Concerning its beneficial results through consumption; previous studies demonstrated that alginic acid could be used to enhance the nonspecific immune response in fish species [125]. Dietary supplements of alginic acid (1 g/kg) improved immune response, growth performance, and infection resistance against WSSV disease in *P. monodon*, suitable dietary level of alginic acid is protecting immune system response against WSSV infection in juvenile *P. monodon* [169]. Similarly, ergosan is an algal derivative with alginic acid (2 g/kg), which could be used to improve innate immune response and infection resistance in different types of fish species [170]. Additionally, ergosan containing (0.5% and 1%) alginic acid derived from *Laminaria digitata*, could enhance the immune response, phagocytic activity, respiratory activity, and expression of interleukins and less response in a humoral immune parameter in rainbow trout (*Oncorhynchus mykiss*) [171]. The dietary additive of ergosan (5 g/kg) enhanced growth performance, protease, esterase activities, alkaline phosphatase, lysozyme actions, and disease resistance against *Yersinia ruckeri* in rainbow trout (*Oncorhynchus mykiss*) (110 g) [172].

2.27. Fucoidan

Fucoidan is a complex long-chain sulfated polysaccharide, present in different species of brown algae. Commercially available fucoidan is usually derived from the different seaweed species namely *Fucus vesiculosus, Cladosiphon okamuranus, Laminaria japonica, and Undaria pinnatifida*. Fucoidan (3% and 6%) promotes several biological effects like immunostimulation, disease resistance improvement, growth, and survival, whereas serum Albumin/Globulin (A/G) ratio and blood glucose level exhibited decreasing trend in diverse fishes and shrimps [173]. Saeed et al. (2021) reported that dietary fucoidan (200 mg/kg of body weight, group 12–15 g) boosted phagocytic activity and disease resistance of shrimps as well as overdoses of several immunostimulants to induce immunosuppression in fish [174]. The side effects of immunostimulants have not been well-studied. Dietary supplements of fucoidan (1 g/kg) increased the immune system (circulating hemocytes, PO activity, RBs, phagocytic activity) and disease resistance against *V. alginolyticus* in shrimps. The study reports concluded that dietary fucoidan's most important role is to enhance the immune system of shrimp species [175]. Finally, oral administration of fucoidan (15 g/kg) derived from *Sargassum polycystum* could reduce the infection of *White Spot Syndrome Virus* (WSSV) and reduce mortality rate, increase survival level in black tiger shrimp *P. monodon* [176].

Table 3
Microbial bioactive compoundsas immunostimulants in aquaculture.

Origin	Bioactive immunostimulants	Aquatic organisms	Immune response	References
Microbes (Bacteria and fungi)	**Peptidoglycan**	kuruma shrimps Japanese flounder *Penaeus monodon*	↑immune system response, RPA, antibacterial and antiviral effects	[122,124,125]
		sea cucumber	Potential immunomodulatory factor Regulation of innate immune response	[202]
		spotted sea bass		[203]
	Lipopolysaccharides	Red sea bream trout	↑phagocytic activity and disease resistance against antibacterial activity	[127,131]
		Channa argus	Induced antioxidant and immune response	[204]
	Exopolysaccharides	Zebrafish	↑immune system response, antibacterial effects, higher expression of TLR1 and TLR 2	[189]
		Pacific white shrimps	Good immune modulator and preventive factor against vibriosis	[205]
		Zebrafish	Modification changes of gut microbiota but not affected SCFAs	[206]
	Lipoteichoic Acid	Silver pomfret	↑TLR, RPA	[137]
	Levan	Labeo rohita	↑Lys, TP, A: G, RBA, RPA	[140]
		common carp	Potent nutraceutical and immuno additive agents	[207]
		Cyprinus carpio	Growth promoter and antibacterial agents	[208]
	Lentinan	juvenile taimen	↑TGF-β, TNF-α, IL-1β, IL-6 and IL-8, ↑SOD, CAT, and GSH-Px, RPA	[148,149]
		Senegalese sole	Modulate immune system and regulate gut microbiota	[209]

↑- Enhance or Increase or Improve.

2.28. Laminarin

Laminarin is the most significant component derived from plants and seaweeds; Laminarin has a lot of bio-functional performances such as antitumor, anti-apoptotic, anti-inflammatory, anticoagulant, and antioxidant activity. The biological activities of laminarin can be improved after appropriate chemical modifications, sulphation, and novel processing techniques. Studies on feeding laminarin-rich extracts to animals point out its suitability as an efficient component for food applications [177,178]. Laminarin is generally low molecular weight (e.g., 5 kDa) and their inter-chain linkages with glucans residues are of great importance [179]. [180] Cui et al. (2021) demonstrated that laminarin injection can change the expression of Arginine kinase (AK), and antioxidant activity, and reduced the activity of *Staphylococcus aureus, Listeria monocytogenes, Escherichia coli, and Salmonella typhimurium*. Similarly [181], Shanmugavel and Krishnamoorthy (2021) reported that laminarin may act as an immunostimulant and the energy source of crustaceans [179]. Meng et al. (2020) demonstrated that dietary laminarin of 1 g/kg enhanced growth activity, feed efficiency, and the nonspecific immune reaction of *E. coioides* and also The levels of Creatinine (CREA) and UREA, as well as the action of alkaline phosphatase (ALP), were lower than of the control. There was no major difference in the levels of alanine aminotransferase (ALT) and, aspartate aminotransferase (AST) between control groups and treated groups. This study recommended that laminarin regulates the immune response and induces growth of the fish.

2.29. Ulvans

Ulvans are derived from the cell wall of green seaweeds; they contain sulfated polysaccharides, *Ulva* was elevated in dietary fiber which stimulates gastrointestinal health and is linked to a reduction in the incidence of chronic diseases as well as biological activities of dietary ulvans contains several positive responses such as immunomodulating, antiviral, antioxidant, antihyperlipidemic and anticancer activity in human and animals (including fish) [181,183]. In literature, it was reported for the first time that dietary supplementation (1 g/kg) of ulvans component could enhance immune system response and disease resistance against bacterial and parasitic infection and there was no significant difference in growth performance among fish for any of the diets tested of Nile tilapia (*Oreochromis niloticus*) [184]. [185] Ponce et al. (2020) suggested that *U.ohnoi* containing ulvans element was nontoxic and potential application as a vaccine adjuvant and/or nutraceuticals in aquaculture. Ulvans (0.5 mg/fish) was used to enhance immune gene expression and regulate immune pathways in flatfish (*Senegalese sole*) juveniles. Dietary supplements of ulvans as sulfated polysaccharide elements contain numerous health-beneficial effects such as anticoagulant, antiviral, antioxidative, anticancer, and immunomodulating activities. In addition, dietary additives of ulvans help improve aquatic animal health and there is no negative impact on aquatic animals [186]. Dietary supplementation range of ulvans (0.05%) improved immunological parameters (respiratory burst, total hemocyte count, and phenoloxidase activities) of shrimps and also survival and challenging tests in giant tiger prawn (*P. monodon*) and Pacific white shrimp (*L. vannamei*), The dietary administration of ulvan was an effective immunostimulant for *L. vannamei* and *P. monodon* [187]. The function of other original bioactive compounds as immunostimulants in aquatic animals has been summarised in Table 4.

3. Conclusion

This review is based on the last few years' literature data analysis and provides an enlightening direction for bioactive immunostimulant improvement in the aquaculture industry. As a comprehensive study was needed to improve bioactive immunostimulants, this review concluded that bioactive immunostimulants sources, types, functions, and administration methods are beneficial for the improvement of healthy aquatic production and also for the increase of feed quality levels. Due to this review report, information was presented about bioactive immunostimulants, which are beneficial with a decreased negative impact on aquatic animal health. Thus, such a report mainly focused on positive responses analysis. The utilization of plant, animal, bacterial, fungal, and algal-originated bioactive immunostimulants is strongly recommended for improved aquatic animal health and aquatic environment enhancement. Biomolecules' functional feed additives improve healthy aquatic productions and enhanced aquatic feed quality levels and are also less toxic, cost-effective, and environmentally friendly. The next steps of our research group will focus on the extraction, characterization, and identification of biomolecules from different natural sources, biomolecules interaction analysis from the body, identification of novel bioactive immunostimulants, able to improve functional nutritional supplements in the modern aquaculture industry. This study information is enlightening to the future research direction of novel bioactive immunostimulants in the aquaculture industry.

Declaration of competing interest

Authors have no conflict of interest to declare for the publication of

Table 4
Various bioactive compounds as immunostimulants in aquaculture.

Origin	Bioactive immunostimulants	Aquatic organisms	Immune response	References
Algae	**Alginic acid**	Penaeus monodonRainbow trout	↑ immune system, growth and antiviral activity	[169,172]
Yeast	**β-Glucans**	Litopenaeusvannamei Red sea bream Atlantic Salmon	↑phagocytic activity, RPA, resistance against bacterial pathogens	[164,165]
	Mannanoligosaccharides	Rainbow trout Nile tilapia	↑TLC ↑ blood protein, RPA	[154,156]
Seaweed	**Alginate**	Tilapia GrouperE. Coioides	PA, PoA, RBA	[166,167]
	Fucoidan	*P. monodon*	↑ immune system, RPA	[176]
	Laminarin	*E. coioides*	↑ non specific immunity, RPA	[179]
	Ulvans	*P. monodon* L. vannamei Nile tilapia	THC, RBA, PoA ↑immune response, RPA	[184,187]

↑- Enhance or Increase or Improve.
Abbreviations of immunological parameters: ACP- Acid phosphatase; RPA-reduce pathogenic activity; IgM-ImmunoglobulinM; TLC-Total leukocyte count, THC-Total haemocyte count; SOD-Superoxide dismutase; GSH-Px, Glutathione-peroxidase; CAT-Catalase; TAC - Total antioxidant capacity; Lys- Lysozyme activity; PA-Phagocytic activity; PI- Phagocytic activity PoA-phenoloxidase activity; TP-Total protein; A:G, Albumin/Globulin; RBA- Respiratory burst activity; SOD- Super oxide dismutase; RBC- Red blood cell; WBC - White blood cell; IL-1a; Interleukin 1a; TNF-a, Tumor Necrosis Factor a; TAS-Total antioxidant status; ACP- the alternative complement pathway; PO activities-total peroxidase enzyme concentration; ACPA-the alternative complement pathway activity.

the present work.

Data availability

Data will be made available on request.

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