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Vijayaram Srirengaraj , Hary L. Razafindralambo * , Holy N. Rabetafika , Huu-Thanh Nguyen , Yun-Zhang Sun *

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Review

Sustainable Biotic Agents in Aquaculture: Concepts, Action Mechanisms and Applications

Vijayaram Srirengaraj [1], Hary L. Razafindralambo [2,3,*], Holy N. Rabetafika [2], Huu-Thanh Nguyen [4] and Yun-Zhang Sun [1,*]

1 Fisheries College, Jimei University, Xiamen 361021, China; SV: vijayarambiotech@gmail.com; Y-ZS: jmusunyunzhang@163.com
2 ProBioLab, Namur, Belgium; probiolab@europe.com
3 BioEcoAgro Joint Research Unit, TERRA Teaching and Research Centre, Sustainable management of bio-aggressors & Microbial Technologies, Gembloux Agro-Bio Tech/Université de Liège, Gembloux, Belgium; h.razafindralambo@uliege.be
4 An Giang University, An Giang, Vietnam; nhthanh@agu.edu.vn
* Correspondence: HLR: h.razafindralambo@uliege.be; Y-ZS: jmusunyunzhang@163.com

Simple Summary: Aquatic animals are consistently exposed to the threats of environmental deterioration and infection outbreaks due to the excessive use of antibiotics and synthetic drugs. This practice leads to the accumulation of residues in aquatic systems and the development of antimicrobial resistance among pathogens. Nature-based solutions, such as functional feeds containing probiotics, prebiotics, postbiotics, and synbiotics, play a crucial role in maintaining a healthy environment and promoting the well-being of animals in aquaculture. Drawing upon a thorough literature survey and experimental evidence, these agents have been shown beneficial to aquatic animals and its ecosystem. Consequently, these biotic agents emerge as promising natural alternatives to traditional synthetic drugs and antibiotics in aquaculture.

Abstract: Aquaculture is a fast-emerging food-producing sector in which fishery production plays an imperative socio-economic role, providing ample resources and tremendous potential worldwide. However, aquatic animals are exposed to the deterioration of the ecological environment and infection outbreaks, which represent significant issues nowadays. One of the reasons for these threats is the excessive use of antibiotics and synthetic drugs that have harmful impacts on the aquatic atmosphere. It is not surprising that functional biotic feeds such as probiotics, prebiotics, postbiotics, and synbiotics have been developed as natural alternatives to sustain a healthy microbial environment in aquaculture. These functional feed additives possess several beneficial characteristics, including gut microbiota modulation, immune response reinforcement, resistance to pathogenic organisms, improved growth performance, and enhanced feed utilization in aquatic animals. Nevertheless, their mechanisms in modulating the immune system and gut microbiota in aquatic animals are largely unclear. This review discusses current research advancements to fill research gaps and promote effective and healthy aquaculture production.

Keywords: probiotics; prebiotics; synbiotics; gut microbiota; fishes; aquaculture

1. Introduction

Aquaculture is a fast-emerging food manufacturing sector worldwide, with Asia currently contributing to 90% of the total production. This sector involves the culture of tilapia, carp fishes, catfishes (non-air breathing and air-breathing), pangasius fishes, and prawns. Tilapia, in particular, is one of the main farmed fish globally and has seen a quadrupling in production over the past few decades due to its suitability for aquaculture, market demand, and stable market prices [1]. Among the major socio-economic sectors in the world, aquaculture generates numerous employment opportunities and fulfills a vital need for nutrients [2]. China is one of the largest seafood producing country in the world, alongside others like India, Vietnam, Bangladesh, Indonesia, Norway, and Egypt. In 2018, China alone produced 62.2 million tons of fish, representing more than 60% of the total fish production [3].

Aquatic animals, especially fishes, are exposed to adverse conditions due to the deterioration of the ecological environment. Disease outbreaks pose a significant challenge for aquaculture, impacting both the financial status and the economic development of communities in the Asia-Pacific region. Various types of aquatic microbial pathogens (such as *Aeromonas hydrophila*, *Aeromonas salmonicida*, *Vibrio anguillarum*, *Vibrio vulnificus*, *Vibrio salmonicida*, *Streptococcus* sp., *Yersinia ruckeri*), viruses (causing diseases like hematopoietic necrosis, yellow head virus, viral hemorrhagic septicemia), and parasites (e.g., *Ichthyophthirius multifiliis*) can cause different types of diseases in aquatic animals, including luminous vibriosis, filamentous bacterial disease, shell disease, larval mycosis, protozoan infections white spot, velvet disease, fungal infections, and dropsy [4–6].

The aquaculture production sector typically relies on traditional methods that involve the use of antibiotics (e.g., chloramphenicol, fluoroquinolones, nitrofurans, quinolones, florfenicol, sufamerazine, chorionic gonadotropin, oxytetracycline dihydrate, oxytetracycline hydrochloride) and synthetic chemicals (e.g., nitrofurans, formalin, malachite green, potassium permanganate, copper sulfate, and Neguvon) to control diseases. However, some of these chemotherapeutic applications have been widely criticized due to their negative impacts on aquaculture such as marine debris gathering, the rise of drug resistance and immunosuppressant activity. The intensive use of these traditional practices leads to the buildup of antibiotic and chemical residues, not only in aquatic animals but also in consumers, resulting in side effects such as diarrhea, vomiting, and stomach problems. Moreover, these traditional methods mainly affecting aquatic productions have been reported to be ineffective in controlling diseases in large-scale aquaculture processes [7–12].

In fish, the gastrointestinal tract (GIT) microbiota plays several vital functions. These microbial consortia increase digestive action, enhance the immune system, protect against harmful microbes, and improve intestine development [13]. In recent years, some gnotobiotic (germ-free) animal models have been developed as wonderful tools for studying host-microbe interaction. Moreover, gnotobiotic models have been used to investigate the role of gut microbiota in xenobiotic metabolism [14,15]. Using zebrafish (*Danio rerio*) model, researchers observed that the presence of alkaline phosphatase in the brush border intestine plays a vital function in gut epithelium division, as well as in the modulation of gene expression in bacteria, which possesses various functional properties (e.g., epithelial maturation, hormone-secreting endocrine organs and mucous secreting goblet cells in the gastrointestinal tract in *D. rerio* larvae [16,17]. Recently, it was reported that TLR2/MyD88 signaling played an essential role in innate immune recognition and activation during the colonization of two indigenous bacteria (*Chryseobacterium* ZOR0023 and *Exiguobacterium* ZWU0009) in zebrafish [18]. Indigenous probiotic microbes have significant functions such as developing the immune system (nonspecific and specific immunity) and inducing different types of cytokines, namely TNF-a, interleukins (IL-6, IL-10, IL-12), and IFN-c [19]. Indigenous probiotic *Bacillus pumilus* SE5 activates the expression of TLR2 signaling and antibacterial peptides genes in the intestine of grouper (*Epinephelus coioides*) The enhanced TLR2 signaling may result from the interaction of the host with the probiotic cell components [20,21]. In addition to enhancing the immune system in fish, the gut microbiota also provides important protection against pathogenic organisms [22,23].

Functional feed additives of probiotics, prebiotics, and/or synbiotics in diets have been extensively recommended to maintain a healthy GIT microbial community, improving infection resistance, and consequently promote the health of cultured aquatic organisms [24–26]. These biotic-based ingredients, consisting in live microorganisms, inert substrates, and the combination of both, possess a wide range of multiple functionalities They represent alternative nature-based solutions for improving aquatic animal health and production [23,27,28]. This review provides insights into the current developments in the utilization of probiotics, prebiotics, postbiotics, and synbiotics in aquaculture applications. It also presents a new way to develop the healthy and modern aquaculture industry.

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2. Probiotics

2.1. Definition, and characteristic features

The Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) defined probiotics as "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [29]. Recently, the term probiotics is associated with microbial feed additives, when controlled in enough amounts, conferring health and beneficial impact on the host of aquatic animals [28].

Probiotics act as a defense system for the host against harmful microbes or foreign substances [30–33]. They also produce beneficial bioactive molecules such as enzymes, proteins, lipids, organic acids, and others. Some of these bioactive molecules improve adherence to probiotics and reduce therefore the activity of pathogens in the gut region through the surface competition mechanism [34]. Probiotics play a significant responsibility in strengthening the immune system of the host [35]. While earlier studies have noted the utilization of probiotics in pigs, poultry, cattle, and humans, their application in aquaculture is a relatively new idea [36,37]. Probiotics might be managed in two ways in aquaculture. They can be supplemented with feed to modulate the gut microbes, or they can be managed by direct addition into the water, thereby inhibiting the growth of pathogens. These modes of administration are very critical in the utilization of probiotics in finfish and shrimp aquaculture ([38,39]. Probiotics could be alive, dead, or microbial cell components, and provide benefits to the host when administered via the feed or to the rearing water. This is achieved at least in part via improving the microbial balance of the host or ambient environment [39]. Figure 1 summarizes the different entryways of probiotics and their benefits in the aquaculture system.

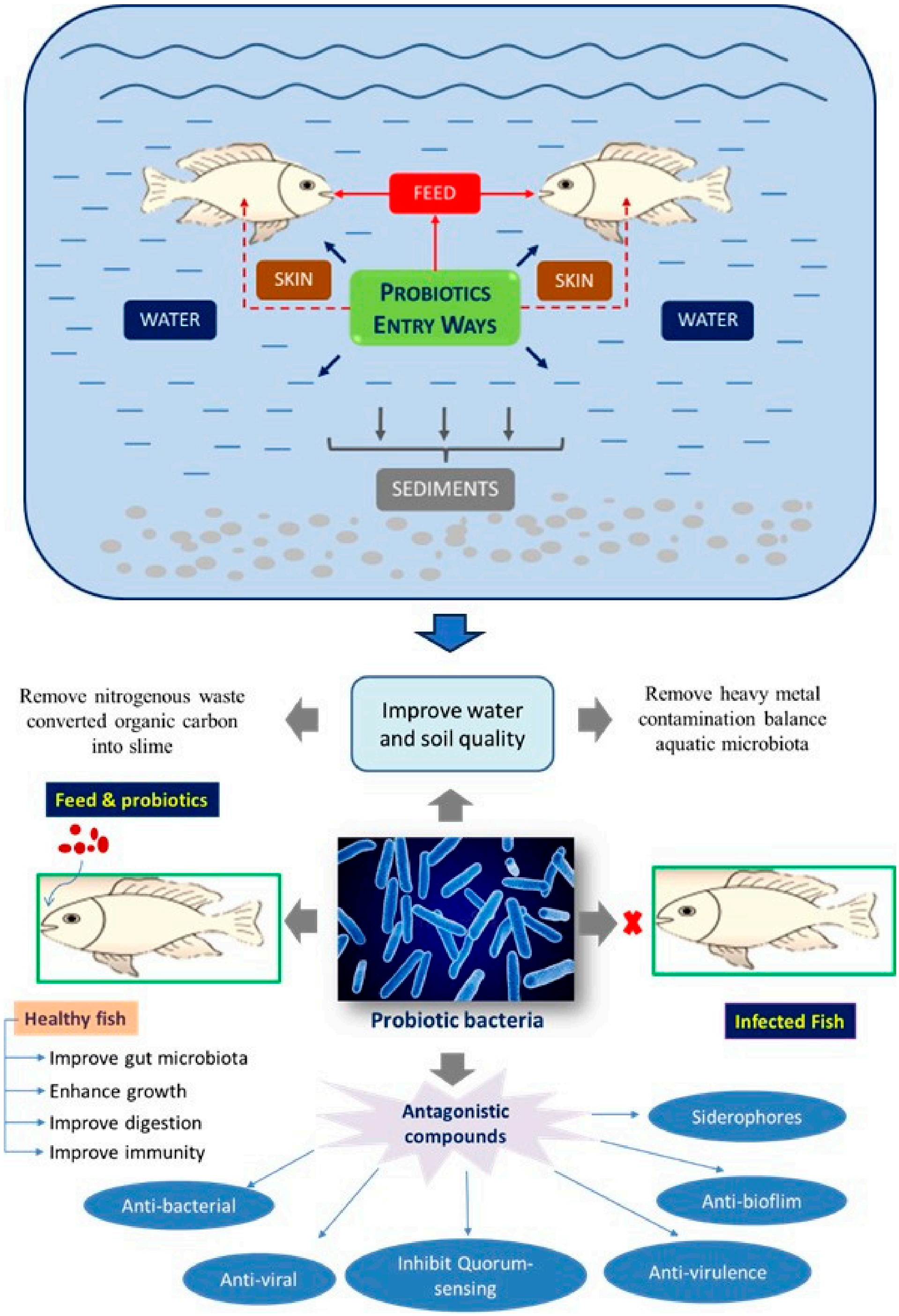

Figure 1. Illustration of the use and impact of probiotics in aquaculture systems.

Probiotics appear a new element agent for the development of aquaculture systems by exerting several favorable effects on growth activity, immune system, digestion, water quality, inhibition of pathogens, and regulation of gut microbes of aquatic animals. The utilization of probiotics in aquaculture is a modern trend, although its effectiveness in the aquatic ecosystem has not been considered comprehensively. Probiotics are ubiquitous, commonly present in aquatic animals, and play an important protective role throughout the digestive system [40,41]. Mainly represented by Lactobacilli, these beneficial microorganisms are vital to prevent illnesses and improve the aquatic animal GIT functions by excreting secondary metabolites such as lactic acid and other bioactive compounds [42,43]. These biomolecules synthesized by probiotics protect against the inhibitory molecules from predators [44]. They also can be extracted from probiotics in terrestrial plants and marine life forms, and then utilized to enhance disease resistance, develop the immune system, reduce environmental stress, and increase feed quality levels [45,46]. Advanced studies in this field have reported microbial by-product biomolecules such as enzymes, lipids, proteins, and immune toxins [47]. Nowadays, there exist some probiotic products commercially available, which are already used in aquaculture as feed additives [48]. These microbial by-products are beneficial and are mainly helpful in enhancing the health status of aquatic animals.

The characterization and identification of potential probiotics are based on various criteria such as acid and bile tolerance, no hemolytic activity, inhibition of pathogens, no pathogenicity, survivable in storage and field, cultivable on a big scale, competent to adhere to the epithelial liner of the gut, free of plasmid-encoded antibiotic resistance genes, safe for use as a feed additive, acting as a growth promoter, anti-inflammatory, antimutagenic, immunostimulatory, and beneficial effects on host animals. Every new strain used for probiotic expansion should contain all the aforesaid features [27,49,50].

2.2. Possible modes of action of probiotics in aquaculture

Significant effects of probiotic, e.g. *Bacillus* sp. as feed supplements, include the improvement of growth performance, digestive enzyme activity, infection resistance, and immune response in aquatic animals [51,52].

2.2.1. Probiotics act as a growth enhancer in aquaculture

One of the mechanisms, which regulates the metabolism of amino and fatty acids, is the capacity of various probiotic strains in producing vitamin B12, as revealed by a study on carp gut [53,54]. In addition, this is helpful to enhance fish growth and eradicate vitamin B12 deficiency in fish [55]. Also, essential macronutrients are usually supplied through feeds. Various micronutrients such as amino acids, vitamins, and fatty acids are very important for physiological functions as nutrients in aquatic animals [56–58]. For instance, diverse fish species such as carp (*Cyprinus carpio*), rainbow trout (*Oncorhynchus mykiss*), channel catfish (*Ictalurus punctatus*), and tilapia (*Oreochromis niloticus*) are identified to synthesize vitamin B12 [59–61]. The growth and survival rates of juvenile black tiger shrimp (*Penaeus monodon*) were enhanced when these were fed for 100 days with a combination of *Lactobacillus* sp., previously isolated from the GIT of chicken [62]. In fact, probiotics improve the digestive function of aquatic animals by producing or inducing the secretion of different kinds of extracellular enzymes such as proteases, amylases, and lipases. They also provide various growth nutrients such as vitamins, fatty acids, and amino acids [63]. The function of probiotics results in abridged feed cost, which accounts for 60-70% of the contribution cost of fish production [64,65]. Both the maximum growth performances and most excellent feed conversion ratio were detected when *O. niloticus* was fed with probiotic *Micrococcus luteus* [66,67]. *Bacillus subtilis* improved feed digestibility, enhanced weight gain, feed conversion, and significantly increased the survival rate of Bullfrog (*Lithobates catesbeianus*) fed with different doses (2.5, 5.0, and 10.0 g/kg) [68,69]. Bacillus species aid in the digestion of aquatic animals by supplying exoenzymes (proteases, lipases, and amylases) that enhance digestive enzymatic [70]. It was observed that *Streptococcus faecium* and Lactic acid bacteria (LAB) improved the growth and feed competence of Israeli carp and juvenile carp, respectively [71].

2.2.2. Biocontrol of bacterial diseases in aquaculture

In the past decades, numerous studies have stated that probiotics synthesize different types of inhibitory substances responsible for the antagonistic activity against pathogens. Two probiotic strains of LAB (*Lactococcus lactis* MM1 and *Enterococcus faecium* MM4) isolated from the intestine of orange-spotted grouper (*E. coioides*) can secrete several inhibitory substances such as hydrogen peroxide and bacteriocin-like substances. These can be utilized to induce antimicrobial activity against different pathogens such as *Staphylococcus aureus*, *V. harveyi*, and *V. metschnikovi* that affect grouper (*E. coioides*) [72,73]. Probiotic *B. pumilus* H2 had strong inhibitory activity against *Vibrio* sp

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through its main mechanism of amicoumacin production to involve disrupting the cell membrane and cell lysis, thus showing anti-*Vibrio* activity [74,75]. Probiotic *Bacillus velezensis* cell-free supernatant contained different types of bioactive molecules against *A. salmonicida* infection [76]. The lipopeptides N3 synthesized by the probiotic *Bacillus amyloliquefaciens* M1 have strong antibacterial activity in the whole-cell membrane, which can exhibit significant effect of ion-conducting channels in the whole-cell membrane as well as membrane-active properties [77,78]. The probiotic species *Clostridium butyricum* culture supernatant included different types of inhibitory substances, lowered the pH in the intestine, and thus decreased the growth of pathogens in fish intestinal epithelial cells [79]. Probiotic *E. faecium* was supplemented to the diets of Olive flounder and can enhance the antibacterial activity [80].

2.2.3. Biocontrol of viral diseases in aquaculture

Microorganism strains with potential probiotic effects in aquaculture such as *Pseudomonas* spp., *Vibrios* spp., and *Aeromonas* spp. induce antiviral effects against hematopoietic necrosis virus (IHNV) infection [81,82]. Similarly, the potential probiotic strain *Pseudoalteromonas undina* VKM-124 was used to improve Yellow Jack (*Carangoides bartholomaei*) larval survival and enhance the antiviral effect against Neuro Necrosis Virus (SJNNV) infection [83,84].

2.2.4. Immunostimulant agents in aquaculture

Immunity development and modulation are amongst the various health benefits of probiotics in aquaculture. The majority of the earlier studies have dealt with the health-boosting capability of probiotics in aquatic organisms. Currently, probiotics are very much focused on the immunological development properties of the piscine system [19]. Different types of probiotics improve various immunological properties, and notably several fishes use the efficiency of probiotics to vitalize teleost immunity in both in situ and ex-situ conditions [85]. Although hopeful findings were reported in previous studies, most of immunostimulants did not progress to large-scale function for fish. Since various immunostimulants in aquaculture produce similar effects, researchers have demonstrated the utilization of probiotics to enhance disease resistance and the immune system of carp fish species [86,87]. Several carp fishes showed an increase in the production of total serum protein, nitric oxide, lysozyme, albumin, phagocytic activity by blood leucocytes, and the expression of IL-1b, superoxide anion, and myeloperoxidase content, respiratory burst activity, and globulin levels, complement C3, TNF-α, and lysozyme-C [86,88]. Current study reports indicate that probiotics (either single or mixed type) could enhance the immunological development of fish [89]. Those reports have emphasized the immunomodulating properties of beneficial living cell organisms and the factors to facilitate the optimal induction of defense responses in the fish community. The probiotic strain *B. pumilus* SE5 isolated from the intestine of fast-growing grouper *E. coioides* [90,91] and subsequent studies demonstrated that both the viable and heat-inactivated *B. pumilus* SE5 could shape the intestinal immunity and microbiota [92], and improve the growth performance and systemic immunity in *E. coioides* [93]. The dietary supplementation of the cell wall (CW), peptidoglycan (PG), and lipoteichoic acid (LTA) of probiotic *B. pumilus* SE5 and their effect on intestinal immune-related genes expression and microbiota have been evaluated in 60 days of feeding trial. PG and LTA of probiotic *B. pumilus* SE5 were more effective than CW in shaping the intestinal immunity and microbiota in *E. coioides* [20], even if the mechanisms are largely unclear and need further study.

2.2.5. Interference of quorum sensing in aquaculture

Quorum sensing (QS) is a communication system among bacterial cells, which is very useful in controlling different kinds of biological macromolecule expressions like the virulence agents in a cell thickness-dependent comparative performance [94]. In this process, control of bacterial cells in gene expressions by generative, loosening and conceiving tiny marker molecules are called auto-inducers [95]. Disruption of the QS process of pathogenic organisms has been a probable anti-infective strategy, and different types of methods have been used to investigate the analysis of QS. These

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include the inhibition of signal molecule biosynthesis, application of QS antagonists, chemical inactivation of QS signals by oxidized halogen antimicrobials, signal molecule biodegradation by bacterial lactonases and by bacterial and eukaryotic acylase, and application of QS agonists in aquaculture [96,97]. N-Acyl homoserine lactones (AHLs) are the most important family of QS auto-inducers utilized in Gram-negative bacteria, and their biodegradation showed as a potential method to interrupt QS [98]. *Bacillus* sp. QSI-1 is a quorum quencher on virulence agent production and biofilm arrangement of the fish pathogen (*A. hydrophila*). The fish fed with QSI-1 was experimentally performed to have a relative percentage survival of 80.8%. The results indicate those AHLs degrading bacteria should be contemplated as an alternative to antibiotics in aquaculture for the biocontrol of bacterial fish infections [98,99]. In a biofilm system, bacteria are resistant to high temperatures, phagocytic cells, surfactants, antibiotics, and antibodies, and could alter their vital transmissions by quorum sensing signaling [100]. Probiotic *Bacillus* strains can effectively secrete quorum quenching enzymes and could reduce the pathogenic activity of *A. hydrophila* YJ-1 and control gut microbiota [101,102]. However, the form of action for this strain is still limited. Dietary supplementation of probiotics with quorum quenching activity such as *Bacillus cereus* QSI-1 has been shown to increase the intestinal barrier function and enhance the immune system of crucian carp against *A. hydrophila* infection. The quorum quenching bacteria increased the expression of tight junctions (TJ) proteins, ZO-1 and Occludin, which control the permeability and absorption of the intestinal mucosal barrier of crucian carp [103].

2.2.6. Stress improvement in aquaculture system

Stress in a fish's life cycle disrupts the entire production. The culture species may be weakened and averse to taking food. This is called food irrational fear. In this condition, probiotics in culture farms can decrease stress levels as well as help to enhance the innate immune system against pathogens and environmental stressors [6,104]. Probiotic treatment is very helpful in increasing the production of fish within the given time and it also reduces the stress level in normal aquaculture practice.

Studies have concluded that the use of some probiotic strains increased chronic stress resistance in zebrafish (*D. rerio*) [105,106]. An experimental nutritional probiotic *Lactobacillus delbrueckii* ssp. Delbrueckii supplementation of sea bass led to a decrease in cortisol levels from 25 to 59 days, which in fish tissue is a stress indicator since it is directly engaged with the host's reaction to stress [107]. One more approach evaluated that fishes treated with probiotics exhibited increased flexibility in stress tests when compared with the control group [65]. Antioxidative properties of probiotic *Lactobacillus fermentum* induce protective action in the intestinal microbial ecosystem and help to overcome exo- and endogenous oxidative stress [108]. The probiotic strain *Bacillus coagulans* SCC-19 alleviates the non-specific immune damage induced by cadmium in common carp while relieving oxidative stress induced by cadmium in fish [109].

2.2.7. Reducing heavy metals in aquaculture

Heavy metals (e.g., lead, cadmium, silver, chromium, mercury, cobalt, zinc, iron, and copper) are present in the soil, water, and atmosphere [110–112]. These metals can cause toxic effects on all organisms and pose a huge risk to food quality, crops, and environmental quality. Heavy metals are mainly connected with anthropogenic action in the ecosystem [113]. Aqueous release from metal industries (steel, mining, and electroplating) contains elevated levels of heavy metals that locate their system into water bodies which are also utilized for aquaculture action [114,115]. These heavy metals get accumulated in fish tissue, and thereby is a matter of great concern in human consuming via the food chain breathing. Their elimination is very helpful in reducing the toxic effect of the aquatic environment and outflow is subsequently imperative [116]. Among all recommended methods for eliminating heavy metal is the process of utilizing microbes, which is cost-effective [117]. Bacterial metabolic action activates the heavy metals via the production of organic and inorganic acids, complex formation with organic ligands, or oxidation reactions [118]. Microbes and microbial by-products can accumulate separate minute particles in the form of dissolved metals [119]. Generally,

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heavy metals activate the sporulation development of *Bacillus* species and thus decrease the heavy metal absorption [114,120]. In addition, probiotic microbes from aqua farming sediments can be utilized as a dietary supplement and helps to remove heavy metals, metal-resistant, and antibiotic-resistant categories from the intestine of aquatic organisms, particularly fish, to control the progress of heavy metals accumulation [121].

2.3. Major probiotic genera as biocontrol agents in aquaculture

The major probiotic genera used in aquaculture are Lactobacillus and Bacillus [122]. Most in case, Bacillus, Lactobacillus, Lactococcus, Leuconostoc, Pediococcus and Weissella have been isolated from fish and shellfish gut [123–127]. Supplementation in aquaculture feed is achieved using single-strain probiotics or association of various bacteria as multi-strain probiotics (MSP), which are reported to have more beneficial effects to host, owing to synergistic effects among various strains [128]. Table 1 lists some examples of probiotic-based functional feed additives for aquatic animals.

Table 1. Functional feed additives of major probiotics in aquatic animals.

Probiotics organisms	Functions	Aquatic organisms	References
Bacillus			
B. licheniformis HGA8B	↑growth performances and feed conversion ratio Up-regulation of immune genes	*O. niloticus*	[129]
B. cereus G19 *B. cereus* BC-01	↑ growth and immunity	*Apostichopus japonicus*	[130]
B. cereus EN25	Immunity and resistance against *Vibrio splendidus*	*A. japonicus*	[131]
B. pumilus SE5	↑ growth and immunity	*L. vannamei*	[132]
B. subtilis AB1	Bactericidal activity against *Aeromonas* infection	*O. mykiss*	[133]
Bifidobacterium			
Bifidobacterium animalis PTCC-1631	↑growth performance, digestion and nutrient utilisation	*O. mykiss*	[134]
B. lactis PTCC-1736	↑growth,nutrient digestability and carcass composition	*O. mykiss*	[134]
Carnobacterium			
C. divergens *C. maltaromaticum*	Antagonistic effects against *V. anguillarum*, *V. viscosus* and *A. salmonicida*	-	[135,136]
Lactobacillus			
L. plantarum CLFP	↓mortalities against harmful strain *L. garvieae*	*O. mykiss*	[137]
L. acidophilus	Against *Staphylococcus xylosus*, *Aeromonas hydrophila* gr.2 and *Streptococcus agalactiae* infection	*Clarias gariepinus*	[138]
L. pentosus	↑growth performances and feed conversion ratio ↑survival against *Vibrio* species	*L. vannamei*	[139]
Lactococcus			
Lactococcus lactis BFE920	Activation of non-specific immune system Bactericidal activity against *S. iniae*	*Paralichthys olivaceus*	[140]

Leuconostoc			
Lc. Mesenteroides CLFP 196	↑survival against *A. salmonicida* infection	*Salmo trutta*	[141]
Pediococcus			
P. pentosaceus HN10	↑ feed utilization, digestive enzyme activity and antivibrio activity	*L. vannamei*	[142]
Enterococcus			
E. casseliflavus CGMCC1.2136	↑growth performances, immunity and digestive enzyme activity	*Rutilus rutilus caspicus*	[143]
E. casseliflavus	↑growth performances and disease resistance against *S. iniae*	*O. mykiss*	[144]
E. durans	↑growth performances and survival rate	*O. mykiss*	[145]
Clostridium			
C. butyricum	↑antibacterial activity against *Vibriosis* infection	*O. mykiss*	[146]
C. butyricum	↑ immunity, regulate gut microbiota, antagonistic effects against *Aeromonas* sp., *Vibrio* sp., *Pseudomonas* sp.	*C. carpio*	[147]
Weissella			
W. confusa	↑growth performances	*O. mykiss*	[148]
W. confusa	↑growth performances, antibacterial activity *against A. hydrophila*	*Lates calcarifer*	[149]
Other strains			
A. veronii BA-1	↑immune system and antibacterial activity	*C. carpio*	[150]
Micrococcus luteus	↑growth performances and feed conversion ratio	*O. niloticus*	[151]
Pseudoalteromonas undina VKM-124	↑survival and antiviral activity	*Carangoides bartholomaei*	[83]
Yeast			
S.cerevisiae	↑growth performances and resistance into waterborne Cu toxicity	*Sarotherodon galilaeus*	[152]
S. cerevisiae	↑ immunity and ↓ mortality against *P. fluorescens*	*Mystus cavasius*	[153]
Yarrowia lipolytica	↑ immune response, antioxidant status, and disease resistance against *V. parahaemolyticus* infection	*Lutjanus peru*	[154]
Multi-strain			
B. subtilis and *Bacillus licheniformis* (BioPlus2B)	↑ resistance against *Y. ruckeri*	*O. mykiss*	[155]
Lactobacillus delbrueckii *Lactobacillus rhamnosus* *L. plantarum* *B. bifidum*	↑growth performances and immunity	*Acipenser baerii*	[156]

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Lactobacillus plantarum (STBL1), *Saccharomyces cerevisiae* (STBS1), *and Bacillus safensis* (SQVG18)	↑growth, antioxidant capacity, digestion, and gut microflora	*P. vannamei*	[157]

↓Decrease or reduce, ↑Increase or improve

3. Prebiotics

Prebiotics are "non-digestible sugars, which helpfully influence the host by specifically enhancing the development of health-encouraging strains in the gut" [158,159]. Prebiotics improve the synbiotic association amid the gut microbiota of the host [160], and are also known as immunosaccharides. There are various types of prebiotic compounds, including mannan oligosaccharides (MOS), fructooligosaccharides (FOS), and arabinooligosaccharides (AOS), which play a significant role in improving the natural immune system [161]. MOS is most frequently used in animal diets. This prebiotic improves growth activity, feed utilization, survival rate, development of immune reaction, and antagonistic activity against aquatic pathogens [162–164]. Oligosaccharide-type components have been connected with the development of immunity [165,166], and were used extensively in diverse fish species such as *Psetta maxima* [12], *Larimichthys crocea* [167], *Paralichthys olivaceus* [168], *Rutilus rutilus* [169], *Piaractus mesopotamicus* [170] and *Acipenser Persicus* [171]. Previous study reports have examined the function of prebiotics in cultured finfish and shellfish, explaining that these compounds have significant effects on gut microbial composition, immune system, and infection resistance against pathogenic organisms in fishes [172,173]. Previous studies have also verified the health beneficial effects of prebiotics on growth, and physiological status [174]. Prebiotics can improve the capability and feasibility of aquaculture production. The most frequently used prebiotics, including xylooligosaccharide (XOS), FOS, transgalactooligosaccharide (TGOS), glucooligosaccharide (GOS), soybean oligosaccharide (SBOS), polydextrose, inulin, and Lactosucrose, enhance the aquaculture production [175]. Natural sources of prebiotics in vertebrates include onion, garlic, tomato, honey chicory, leek, and so on [176].

3.1. Action in the gastrointestinal tract of aquatic animals

Prebiotics exert possible effects on host biological response, protecting fish species against harmful microbes and thus decreasing their mortality. However, the evaluation of the intestinal microbiota of important commercial fishes like hybrid striped bass, channel catfish, salmonids and tilapia is necessary to infer if there are any particular bacterial species to be enhanced by the utilization of prebiotics. By increasing the production of volatile fatty acids (VFA) in the GIT, the host's advantage is the inhibition of potentially pathogenic organisms [177,178]. The synthesis of VFA in the aquatic organisms' GIT indicates the presence of microbial communities [179]. The herbivorous fish were the first species (*Kyphosus cornelii* and *K. sydneyanus*) shown to contain VFA synthesized by the intestinal bacterial community [180]. Another fish species tilapia (*Oreochromis mossambicus*) was established to have VFA produced by intestinal bacterial communities [181]. Prebiotics have numerous favorable effects in aquatic animals by enhancing disease resistance and improving nutrient accessibility [182]. Recently, our group evaluated the effects of FOS on growth performance and predominant autochthonous intestinal microbiota of shrimp (*L. vannamei*) fed diets with fish meal partially replaced by soybean meal. The results showed that a dietary supplement of 2-4 g/kg FOS could improve the growth performance, and survival rate, and exert a beneficial effect on the intestinal microbiota of shrimp. A dose adding 2-4 g/kg FOS in shrimp diets with fish meal partially replaced by soybean meal was recommended [183,184].

3.2. Regulation in the immune system of aquatic animals

In the past decades, prebiotics has been used to regulate intestinal microbiota, modulate immunity, control pathogens, and increase the survival ability of aquatic animals. Fishes are a diverse

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group of organisms that include sharks, rays, and bony fishes [195]. Similar to all vertebrates, fishes rely fully on their natural immunity against pathogens due to the restrictions in their adaptive immune function [187]. There are various cellular and soluble components primarily concerned with the immune responses including phagocytes, leukocytes, and auxiliary cells, which are organized in tissues and organs with leukocytes being the most functional. The impacts of prebiotics on immunity are indirect and involve the modification of the gut microbes, thereby enhancing the immune system. Thus, these beneficial components assist in supply change effectiveness, enhance fish growth, and induce inhibitory activity against pathogens through the viable prohibition of linkage sites, synthesis of natural organic acids (e.g., formic acid, lactic acid, acetic acid), hydrogen peroxide, and numerous other compounds like bacteriocins, siderophores, lysozyme, and antibiotics. This also causes a change in physiological and immunological responses in fish's spleen, kidney and thymus, which are major lymphoid organs [48,188]. The prebiotic components act as growth promoter for commensal microbes to inhibit the adhesion and assault of harmful microorganisms in the epithelial cells. A beneficial effect of monosaccharide components arises from enhancing immune function and acting as a protection system for lymphoid organs as well.

3.2.1. Phagocytosis

Phagocytosis is the process by which immune cells like macrophages and neutrophils, engulf and digest foreign cells or particles, such as bacteria, viruses, or cellular debris [189]. FOS (0.5%) is used to enhance phagocytosis, respiratory burst, and phenoloxidase activity of sea cucumber coelomocytes and infection resistance against *V. splendidus* infection [190]. The phagocytic capability of inhabitant and obtained trout macrophages are related to the circumstances (i.e., in suspension versus attached and spread) of the cells at the time of particle treatment. Substrate binding and cells spreading may play a very important function in controlling the overall phagocytic capability of macrophages. Since the host's resistance against infectious agents depends upon the phagocytic ability of the cells, the finding that obtained trout macrophages can surround larger numbers of activity latex particles than inhabitant cells provides a better understanding of immune regulatory mechanisms in fish [191]. Dietary supplementation of FOS significantly improved lysozyme activity compared to control diet group. However, there were no significant effects of the phagocytic percentage of the phagocytic index. In addition, a combination of FOS and MOS (5.0 g/kg) showed a significant difference in phagocytic activity of Japanese flounder [171].

3.2.2. Macrophages activation

Macrophages play a very imperative function in the nonspecific and specific connection of the immune function to synthesize the highest level of immune reaction and eliminate harmful microbes. Macrophages are stimulated to produce diverse inflammatory cytokines like tumor necrosis factor (TNF), IL-1, IL-12, etc. [80]. The alterations in the physiology of macrophages as a result of environmental signals can benefit them with improved antimicrobial activity. Nevertheless, ecosystem signals do not always cause changes that improve macrophage immune activity. Both nonspecific and specific immune responses can result in macrophages that are more vulnerable to harmful infections and less prepared to generate cytokines that enhance immune system response [192].

3.2.3. Respiratory burst activity

A respiratory burst is the fast release of reactive oxygen substances namely superoxide anions, hydrogen peroxide, and hydroxyl radicals. These reactive oxygen compounds are generally used to defend the capability of the host organism to counter harmful microbes. They are synthesized by activated phagocytes that are responsible for destroying microbes [193]. Respiratory burst analyses were performed in naturally resistant cells and blood neutrophils using NBT (nitro blue tetrazolium) or MPO (myeloperoxidase) methods. Inulin (5 g kg-1) was utilized as a dietary nutrient supplement

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for Nile tilapia and improved lysozyme and hematocrit NBT action. It also significantly enhanced the natural immune system and increased the survival rate against *A. hydrophila* infection [194,195].

The marine invertebrates contain enzymes such as tyrosinases, laccases, and catecholases which can be modified to complement the system of prophenoloxidase. This enhancement improves antagonistic activity through processes like phagocytosis and respiratory burst via opsonization. In a study conducted on red swamp crayfish, supplementation of a prebiotic nutrient diet with 8 and 10 g kg^{-1} FOS over a 30-day trial period significantly enhanced phenoloxidase reaction, stimulated immune-related genes (lysozyme, crustin 1, SOD), and increased the survival rate and antibacterial activity against *A. hydrophila* infection [196].

3.2.4. Synthesis of antibodies

B lymphocytes could produce special antibodies for recognizing specific microbial antigens and these antibodies could neutralize the antigens by surface binding and attaching to the target cells. Antibodies could also perform phagocytosis activity through the activated complement system, and antibody-dependent cellular cytotoxicity (ADCC). The hematocrit or total hemocyte was analyzed to count the total number of blood cells including WBC, RBC, and platelets. The hematocrit analytical methods are used for macro immune system analysis in fish [197]. These methods are used for the enhancement of immune cells (neutrophils, basophils, eosinophils, lymphocytes, and monocyte) in fish blood. The dietary supplementation of MOS and β-glucans were used to enhance the immune system of carp fry [198,199].

3.3. Major prebiotics with biocontrol capabilities in aquaculture

3.3.1. β-glucans

There is enough evidence available regarding their positive effects on immune responses, disease resistance, and growth performance upon oral delivery to a variety of farmed animals such as salmonids [200], sea bream [201], and shellfish [202]. Supplementation of β-glucans as prebiotic enhances the growth activity and higher resistance action against pathogens in *P. vannamei* [203]. Prebiotic administration of β-glucans in diet is used to increase disease resistance; its efficiency depends on their origin and structure [204]. The Glucan substance extracted from the cell wall of yeast (*S. cerevisiae*) has the ability to enhance the non-specific immune system and disease resistance in the Atlantic salmon [205].

3.3.2. Oligosaccharides

The oligosaccharide components are crucial for the modulation of immune responses in fish species. The positive results of monosaccharide products have encouraged the development of various immunomodulating, environmentally friendly nutrient diet supplements for fish species [206]. The diet supplementation of MOS from 1 to 1.5g kg-1 was capable to get better the growth activity and the feed efficiency of common carp fingerlings, as well as their antibacterial ability against *A. hydrophila* infection [207]. The nutrient feed additives (FOS) in beluga (*Huso huso*) juveniles had numerous beneficial effects such as gut microbiota modulation, immune response, and digestive enzyme action and growth performance [208]. They also presented a 7-week study report in common carp with dietary supplementation of FOS at (0%, 0.5%, and 1%) different levels which proved to have significant effects on intestinal microbiota modulation and physiological response [209]. The dietary supplementation of MOS at 0.4% improved the growth performance and non-specific immune response of Asian catfish (*Clarias batrachus*) juvenile's [210]. The prebiotics FOS, when used as feed additives in juvenile large yellow croakers was found to improve growth action and digestive enzyme action [12,211].

Not all the prebiotic substances have immunostimulant properties, only a few references are available regarding the effects of isomalto-oligosaccharides (IMO), which consist of a combination of isomaltotriose, isomaltose, panose, and isomaltotetraose, on aquatic animals. No clear statement was recorded regarding immune responses [212].

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3.3.3. Chitosan

Chitosan is a linear polysaccharide component of β-(1–4) linked D-glucosamine and is synthesized through alkaline deacetylation. It is a major component of arthropods' exoskeleton like shrimps, crabs, insects, and lobsters. In aquaculture, chitosan induces immunostimulation effects in various species namely rainbow trout [213], olive flounder (*Paralichthys olivaceus*) [214], and salmonids [215]. The administration of chitosan in the nutrient feed of *C. carpio* koi for 75 days resulted in significant effects such as enhanced immune response, improved lipid metabolism, enhanced growth performance, and modulated intestine microbiota, thereby protecting the fish from pathogen invasion [216].

3.3.4. Inulin

The prebiotic component inulin, a soluble plant fiber, is used in the fish diet and plays a crucial role in enhancing the immune system in both mammals and fish. In aquaculture, tinulin finds significant use by activating the beneficial bacteria, inhibiting the pathogens, and boosting immune system activity [217]. Inulin has the potential to mitigate inflammation induced by a high-carbohydrate diet, thereby enhancing pathogen resistance in fish. Additionally, supplementing with inulin led to changes in gut microbiota composition and their metabolites. These alterations likely contribute to alleviating the metabolic syndromes induced by a high-carbohydrate diet in fish. [218].

Figure 2 summarizes the main components of prebiotics from natural sources as well as their main action modes in improving host health. The functional feed additives of prebiotics in aquatic animals are summarised in Table 2.

Table 2. Functional feed additives of prebiotics in aquatic animals.

Prebiotics	Functions	Aquatic species	References
FOS	↑growth, survival and gut microbiota section	*L. vannamei*	[184]
β-glucans	↑growth, survival and immune system	*Sparus aurata*	[201]
MOS	↑growth, immune system, antioxidant capacity and intestinal health	*Cyprinus carpio*	[219]
Chitosan	↑growth, feed utilization, lipid metabolism, gut microbiota composition and immune system	*Cyprinus carpio koi*	[216]
Inulin	↑growth, antioxidant capacity, immunity, and gut microbiota at low salinity	*L. vannamei*	[220]

↓Decrease or reduce, ↑Increase or improve.

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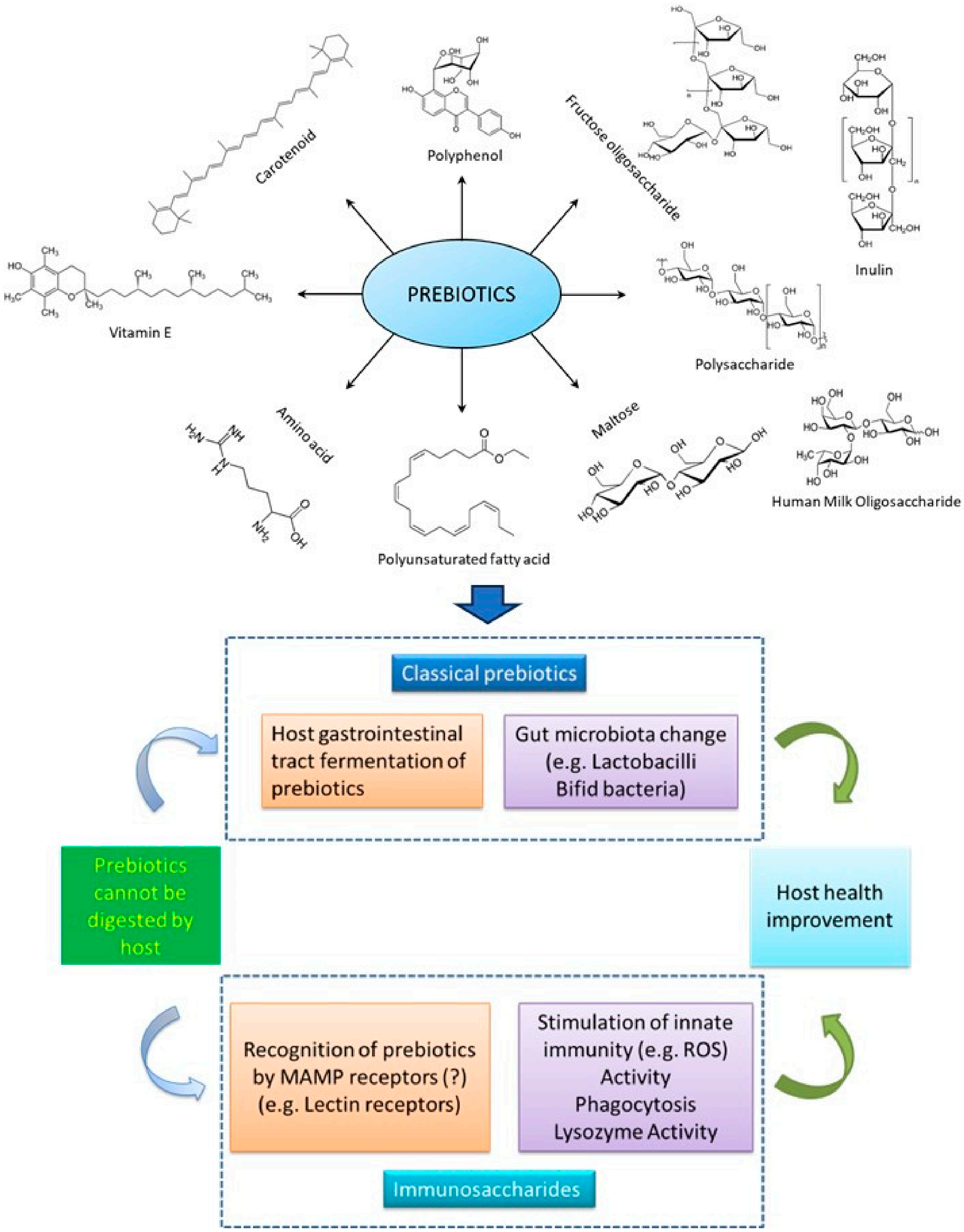

Figure 2. Main chemical components of prebiotics from natural sources and their action modes in improving host health.

4. Postbiotics

4.1. Concept, definition and major components of postbiotics

The use of live microorganisms as probiotics may have potential concerns associated with the gene resistance acquisition and translocation, and depends on their viability [221]. Likewise, it has been recognized that non-viable microorganisms as well as their components and metabolites can provide positive effects on health leading to the apparition of postbiotic concept [222]. Postbiotics are defined by consensus panels as a preparation of inactivated microorganisms and/or their components (cell fragments, cell walls, metabolites) that have beneficial health effects on host [223]. This definition does not include purified metabolites in the absence of cells and cells components. One defined postbiotics as dead microbes and/or cell structures or metabolites that are produced by bacterial lysis or secreted during fermentation process [224].

Postbiotics include inactivated probiotics called paraprobiotics, metabolites like short chain fatty acids (SCFAs), vitamins, and phenolic acids, secreted proteins and peptides, functional proteins and enzymes, cell wall components like LTAs and peptidoglycan (PG)-derived muropeptides, secreted and extracellular polysaccharides (EPS), cell lysates, cellular components (glycans, enzymes), microbial fraction, and surface molecules such as pili [225,226].

Figure **3** outlines main postbiotics components.

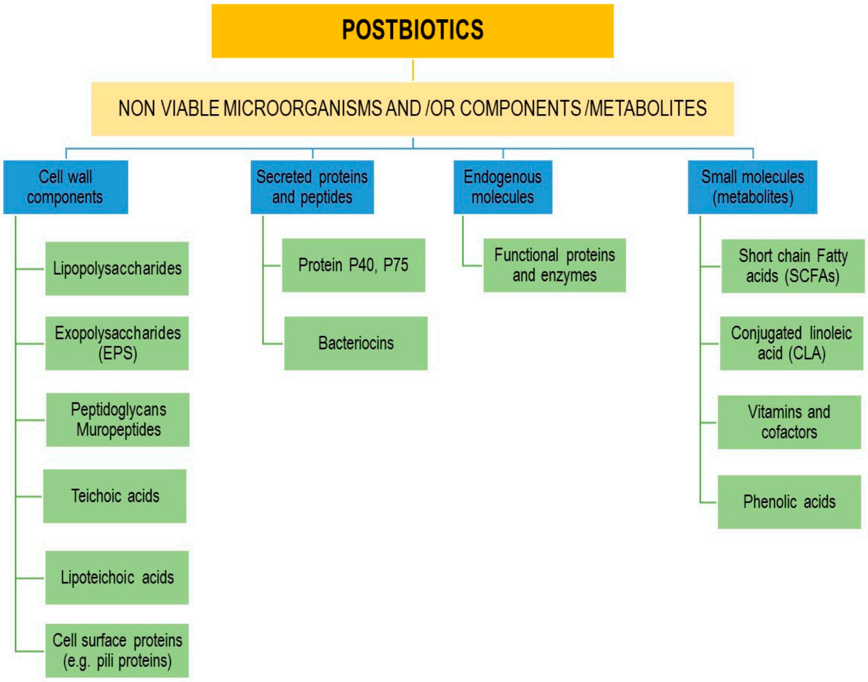

Figure 3. Postbiotic main components and molecules.

4.2. Action modes and applications of postbiotics in aquaculture

The action mechanisms of postbiotics are still unclear but it has been generally assumed that they are similar to those of live probiotics [227]. Three main mechanisms are involved in postbiotics action modes.

4.2.1. Immunomodulation by microbial compounds

Postbiotics act on the immune system through two signaling pathways, namely nuclear factor -kB (NF-kB) and mitogen-activated protein kinases (MAPK), which are involved in the immune and inflammatory responses. Postbiotics stimulate the innate and adaptive immune systems via external Toll-like receptors (TLRs) that recognize associated pathogens and bind to specific patterns such as LTAs and PGs. They also interact with intracellular nucleotide-like receptors (NLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors, which can bind to molecules like lipopolysaccharides (LPS), PG, and flagellin, thereby activating innate immune signaling pathways [224,226]. The role of PG recognition proteins in innate immune responses against pathogens has been demonstrated in fish [228,229]. PG-derived muropeptides from bacterial cell walls have been shown to boost the immune system of fish [230] and shrimp [231]. For instance, muropeptides isolated from *Bifidobacterium thermophilum* have been proven to enhance shrimp immunity by increasing phagocytic activity or activating immune genes [231,232].

Additionally, postbiotics can enhance epithelial barriers protection via cell surface molecules such as pili and secreted protein P40 [233]. For example, the role of *Lactobacillus pentosus* surface protein on immune response has been demonstrated in shrimp (*L. vannamei*) infected with *Vibrio parahaemolyticus* [234].

4.2.2. Antagonizing pathogens by antimicrobial activities

Postbiotics exhibit antimicrobial activities against various pathogens due to the presence of metabolites like peptides and organic acids [235]. Bacteriocin JFP2 isolated from *B. amyloliquefaciens* exhibits antimicrobial activity against fish pathogen *A. hydrophila* [236]. The dietary addition of postbiotic containing LAB (strain *Lactobacillus*) has been reported to protect rainbow trout (*O. mykiss*) against the bacterial fish pathogen *L. garvieae* after 30 days feeding [237].

4.2.3. Inhibition of oxidation by antioxidant enzyme systems and metabolites

Various postbiotics obtained from LABs have been shown to exhibit antioxidant activity mainly attributed to phenolic compounds [238]. *L. plantarum* postbiotics have been documented to enhance antioxidant activity in animals [239]. In aquaculture applications, the overall antioxidant status of shrimp fed with diets supplemented with *C. butyricum* postbiotics was improved regarding the increase of alkaline phosphatase, acid phosphatase, total nitric oxide synthase, lysozyme, peroxidase, superoxide dismutase activities, total antioxidant capacity, and phenoloxidase content in the serum [240].

In aquaculture, postbiotics have been used as growth promoters instead of antibiotics, as immune system stimulation and as disease control [197,233,241]. Recently, the potential application of postbiotics in aquaculture water quality to modulate bacterioplankton communities and to influence nutrient cycling and bacterial pathogen abundance has been reported [242]. Figure 4 illustrates potential applications of probiotics in aquaculture. Table 3 shows some recent potential applications of postbiotics in aquaculture.

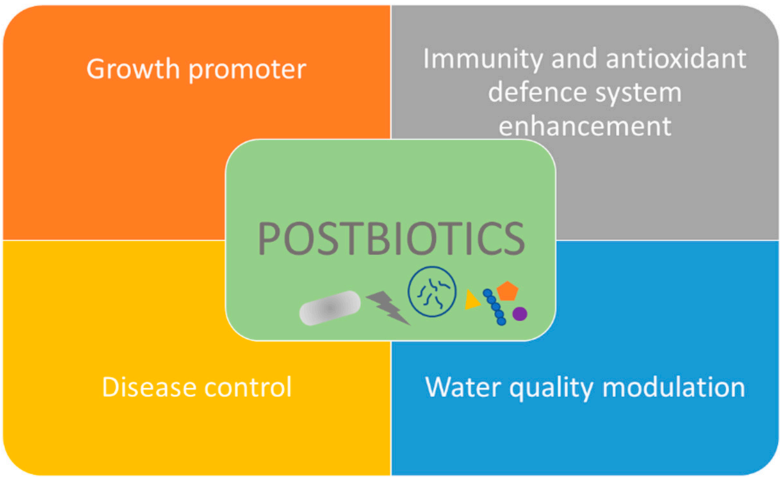

Figure 4. Postbiotics in aquaculture.

Table 3. Some recent potential applications of postbiotics in aquaculture.

Postbiotics	Microorganism producer	Aquatic species	Applications	References
Exopolysaccharides	*Lactococcus lactis* Z-2	Common carp (*C. carpio*)	Immunity enhancement Resistance against *A. hydrophila*	[243]
Cell surface proteins	*L. pentosus*	Shrimp (*Litopenaeus vannamei*)	Immune response improvement	[234]

Cell wall components (PGs and LTA)	*B. pumilus* SE5	Grouper (*E. coioides*)	Growth performance improvement Innate and adaptive immunity amelioration	[93]
Lipoteichoic acids	*L. plantarum* LTA	Silvery pomfret (*Pampus argenteus*)	Against *V. anguillarum*-caused vibriosis	[244]
Non live microorganisms				
	S. cerevisiae, *B. velezensis* and *Cetobacterium somerae*	Common carp (*C. carpio*)	Gut microbiota improvement Enhance non specific immunity Antioxidant status improvement	[245]
	Dried autolyzed yeast	Gilthead sea bream (*Sparus aurata*)	Intestinal microbiota improvement	[246]
	Rhodotorula minuta and *Cetobacterium somerae*	Hybrid sturgeon (*Acipenser baerii* x *Acipenser schrencki*)	Growth performance improvement Non-specific immunity improvement	[197]
	Heat killed *L. plantarum* L-137	Nile tilapia (*O. niloticus*)	Growth performance stress resistance and immunity enhancement	[247]

5. Synbiotics

Synbiotics refer to dietary additives that blend probiotics and prebiotics in a synergistic combination, thereby enhancing their beneficial effects. When either dietary additives or supplements are used, the resulting positive effects typically follow one of three patterns: ingredient effects, synergism, or potentiation. Supplementation outcomes occur when the combined effects of both additives used together approximate the sum of the effects of the individual supplements. In the case of synergism, the amalgamated result of the two products is significantly greater than the sum of the effects of each factor administered alone. The term potentiation is used differently; some pharmacologists interchange it with synergism to describe a result that is better than that of a supplement alone, while others use it to describe an outcome that is only present when both substances are used simultaneously [248,249].

5.1. Possible modes of action of synbiotics in aquaculture

5.1.1. Synbiotics enhance digestive enzyme and growth performance

Dietary administration of synbiotics is helpful in enhancing the digestive enzyme action of fish, allowing the host to degrade more nutrients. This dietary method increases digestive action and likely enhances the weight gain rate and/or feed efficiency [250]. Nutrient diet supplementation with a mixture of probiotics and monosaccharides enhances feed efficiency and overall health in carp. However, limited data is available in aquaculture regarding the function of nutrient diet supplementation of synbiotics in carp [23]. Nutrient diet administration of synbiotics enhances the lymphocyte and white blood cells in carp [251]. Synbiotics (IMBO), a combination of probiotics (*E. faecium*) and prebiotics (FOS), have been used to enhance the growth performance, survival rate, and digestive enzyme function of common carp fingerlings [252]. Dietary supplementation of FOS, MOS, and *B. clausii* can improve growth performance and health benefits of the Japanese flounder more than the control diet [168]. Dietary supplementation of FOS and 1.35×10^7 CFU g-1 *B. subtilis* (single or mixed) increases the specific growth rate (SGR) and feed efficiency ratio (FER) compared to the groups without *B. subtilis* additives in juvenile large yellow croaker (*Larimichthys crocea*) [211]. Figure 5 illustrates the possible modes of action of synbiotics in aquaculture.

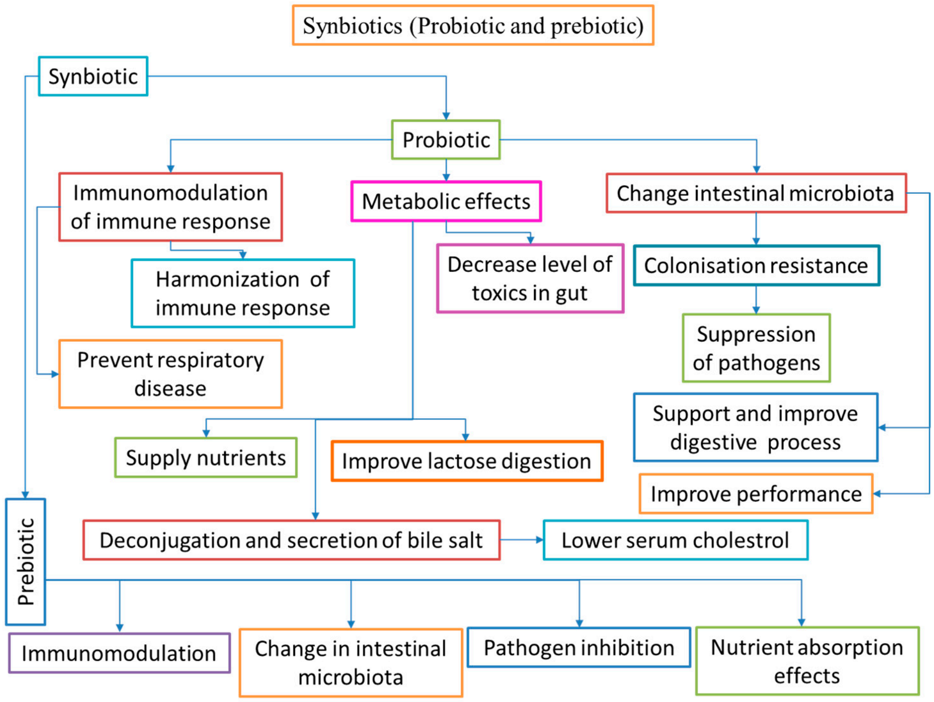

Figure 5. Illustration of modes of action of synbiotics in aquaculture.

5.1.2. Synbiotics improve immune response and disease resistance

An amalgamation of probiotics and prebiotics feed supplements is mainly helpful to enhance the survival of beneficial organisms, as the presence of prebiotics protects well-organized fermentation. Finally, this rewards the host with a suitable approach [253]. The nutritional additives of probiotics and prebiotics (MOS, FOS, and inulin) enhance the fish immune system via GIT [23,254,255]. A synbiotic composed of *Pediococcus acidilactici* and galactooligosaccharides improved immune parameters and antagonistic activity against *S. iniae* when administered to rainbow trout fingerlings for 8 weeks [256]. The combination of probiotic *Bacillus* sp. and 0.2% of prebiotic isomaltooligosaccharide has been used to improve immune functions in shrimp (*Penaeus japonicas*) against *V. alginolyticus* infection [257]. In addition, the blended use of *Bacillus* and molasses improved the microbial population, enhanced the development of the probiotic community, and inhibitory activity against pathogens in pacific white shrimp [258]. The effectiveness of synbiotic treatment in conditions of defense against infectious factors could be evaluated by a confrontation examination due to its regulatory power over harmful microbes and its capability to resist infections [259]. The functional feed additives of synbiotics in aquatic animals are summarised in Table 4.

Table 4. Functional feed additives of synbiotics in aquatic animals.

Synbiotics	Functions	Aquatic organisms	References
P.acidilactici + GOS	↑growth, survival and digestive enzyme function	*Labidochromis lividus*	[260]
B. clausii + FOS,MOS	↑growth, survival and digestive enzyme function	*Paralichthys olivaceus*	[261]
P.acidilactici + GOS	↑immunity and antagonistic activity against *S. iniae* infections	*Oncorhynchus mykiss*	[262]
B. subtilis + *L. acidophilus* + *S. cerevisiae* + FOS	↑growth, and feed efficiency ratio	*Eriocheir sinensis*	[263]

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P.acidilactici + IMO	↑growth, immune response, and antioxidant capacity	*C. carpio*	[264]

↓Decrease or reduce, ↑Increase or improve.

6. Limitations of the use of biotic agents in aquaculture

The use of biotic agents in aquaculture instead of antibiotics has recently gained significant interests [265]. Probiotics have been shown to be effective in promoting growth, increasing immunity, and improving resistance to infections in aquatic animals [266]. The major limitation of their use comes from the problem of possible gene resistance acquisition and translocation, as well as the question of their viability and/or ability to colonize the fish gut [221]. The use of multi-strain probiotics increases the possibility of strain survival rates and therefore improves the beneficial effects on growth, immunity and infection resistance of aquatic animals [128]. Postbiotics present an advantage over probiotics because they do not have viability problems and are less susceptible to environmental conditions [221,267]. Additionally, they generally have a complex composition made up of several compounds that play multiple roles and provide numerous beneficial effects on aquatic animals. However, their use to manage infectious disease is still in its early stages [235].

Prebiotics, as inert biotic agents, are relatively safe and cost-effective alternative to probiotics. Several studies on their immunostimulant properties and growth promotion in fish and shellfish have shown some evidence for their interest in aquaculture [268]. Nevertheless, studies on the optimal dose should be carried out, as inadequate dose may lead to detrimental effects on aquatic animals [182,208]. Synbiotics improve the colonization of microorganisms in the intestines and are generally more effective than probiotics or prebiotics alone [267]. For example, Nile tilapia (*O. niloticus*) fed with synbiotic showed the highest increase in the specific growth rate compared to the group fed with probiotics or prebiotics alone [251,269]. Extensive studies are still needed to specify the role of prebiotics, probiotics, postbiotics, and synbiotics in growth performance, intestinal health, and immune aspects with a focus on the mechanisms underlying the synbiotic diet in aquatic animals against various pathogens. The mode of administration and dose of the biotic agents are also important and have certainly an impact on their effectiveness [270].

7. Concluding remarks and future perspectives

Aquaculture is one of the fastest-growing food manufacturing sectors in the world. Disease outbreaks pose significant problems for aquaculture, impacting the financial status and economic development of people in the Asia-Pacific region as a whole. Globally, most researchers have analyzed and concluded that functional feeds (probiotics, prebiotics, and synbiotics) or immunostimulants are potential alternatives for the development of the modern aquaculture industry. These methods are particularly useful in enhancing aquaculture production as they offer numerous health benefits, such as the modulation of gut microbiota and immune systems, enhancement of disease resistance and survival rates, improvement of growth performance, and efficient feed utilization.

While several study reports are available regarding probiotics, prebiotics, and synbiotics, these are not sufficient to drive the development of the aquaculture industry. Extensive studies are needed at different levels, corresponding to the role of prebiotics, probiotics, and synbiotics in growth performance, intestinal health, and immune aspects. Additionally, there is a need for a deeper understanding of the mechanisms underlying synbiotic diets in aquatic animals against various pathogens.

This review concludes that functional feed additives, such as probiotics, prebiotics, and synbiotics, are utilized to enhance the immune system, disease resistance, gut microbiota survival rates, growth performance, and feed utilization in numerous commercially available fish species. However, data from zebrafish modeling studies are very limited. In the future, not only probiotics, prebiotics, and synbiotics but also various other beneficial substances, such as functional amino acids, fatty acids, enzymes, organic acids, and herbs, can be added or substituted to enhance the innate immune system, disease resistance, and growth and survival rates in the zebrafish model. These additions can also improve feed quality levels in aquaculture. Furthermore, postbiotics, which are components or metabolites from dead probiotic microorganisms, show promise as functional feed components."

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