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CONTROL OF YERSINIOSIS IN RAINBOW TROUT, *ONCORHYNCHUS MYKISS*: INNOVATIVE NON-ANTIBIOTIC FEED-BASED STRATEGIES – A REVIEW

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Abstract

Yersiniosis or enteric redmouth (ERM) is responsible for significant mortalities among rainbow trout and other salmonids. Hence, its prevention and/or control has become a research hotspot. Antibiotics are effective for control; however, accumulating evidence indicates that unrestricted use of antibiotics harms fish, human beings, and the environment. Thus, finding safe, efficacious, cost-effective, and environmentally friendly substitutes is of great interest. Reports showed that dietary supplementation with functional additives with health-promoting and immunostimulatory functions could be a promising strategy. Herein, we provide an overview of the non-antibiotic feed-based strategies for combating ERM in rainbow trout without resorting to antibiotic usage. For this issue, the uses and application of some vitamins, probiotics, prebiotics, synbiotics, quorum quenching probiotic strains, algae, or organic acids, are included in the article. The roles of phytobiotics (herbal supplements), their phytochemicals, and the essential oils extracted from them will also be elucidated. Some emerging nano-based feed supplements are also discussed. Considering their advantages, literature declared that the dietary supplementation of these supplements could enhance the overall health condition, hemato-immunity, and disease resistance and conferred high protection of trout experimentally infected with yersiniosis. Given this perspective, this article presents the current situation and the latest knowledge on these supplements, emphasizing not only their roles to support immunity and decrease the effects of ERM, but also to minimize antibiotic usage in aquaculture. Limitations and future perspectives on their effectiveness and efficacy are also discussed. This review will help enhance aquaculture sustainability and improve the health and welfare of rainbow trout.

Key words: probiotics, control, trout, non-antibiotic, phytobiotics, yersiniosis

Yersiniosis, or enteric redmouth disease (ERM), is among the bacterial diseases that threaten rainbow trout farming. It is a contagious septicemic bacterial disease caused by *Yersinia ruckeri* and is one of the main etiologies involved in economic losses in *O. mykiss* and other salmonids worldwide (Wrobel et al., 2019). *Y. ruckeri* is a Gram-negative rod-shaped bacterium with a vast range of susceptible hosts in marine and freshwater environments (Kumar et al., 2015). This disease was first identified and diagnosed in rainbow trout (Ross et al., 1966); however, its prevalence and pathogenicity spread rapidly worldwide (Bastardo et al., 2011). ERM disease is manifested by high mortality and morbidity rates, especially when fish are subjected to stress factors like poor water quality, high stocking densities, and poor management conditions (Timothy and Gregory, 2005). It is characterized clinically by hemorrhages and redness in the mouth, jaws, and at the base of all fins, protruded exophthalmic eyes with blood spots, and darkened skin (Kumar et al., 2015). Infection with *Y. ruckeri* may result in septicemia associated with hemorrhages scattered on the fish's body surfaces (Tobback et al., 2007). ERM was reported in all fish ages, although it mainly appears in chronic and acute forms in grow-out and fingerling fish, respectively (Barnes et al., 2016). This disease causes high mortalities; hence, the control and prevention of the disease is considered a critical need to reduce the losses obtained from this disease.

Beyond the uses and application of vaccination programs, it was found that using commercial antibiotics (e.g., florfenicol (FLO), enrofloxacin (ENR), oxytetracycline (OTC), and erythromycin) is considered a conventional and commonly used method employed by fish farmers against *Y. ruckeri* infection (Calvez et al., 2014; Rostang et al., 2021). Unfortunately, the antibiotic-resistant strains of *Y. ruckeri* have rapidly increased, and several strains can develop resistance against most commercially used antibiotics (Balta et al., 2010; Huang et al., 2014; Onuk et al., 2019). Several *Y. ruckeri* strains were recently identified and displayed resistance to 14 antibiotics with 39 resistance genes (Feng et al., 2022). On the other hand, vaccination is regarded as an effective strategy to prevent ERM outbreaks in fish farms, which was first licensed in 1976 for salmonids in the USA based on formalin-killed bacteria vaccines (Sommerset et al., 2005). Commercially available vaccines against the major serotypes of *Y. ruckeri* by intraperitoneal injection, oral, and immersion routes should be used according to the fish's age, size, and farm conditions (Bridle and Nowak, 2014). However, the effectiveness and efficacy of vaccines against ERM vary according to several factors, such as nutritional status, general health status, water quality, stock density, environmental conditions, and several serotypes of *Y. ruckeri* strains (Yang et al., 2021). Indeed, the positive role of vaccination against ERM in reducing antibiotic use cannot be ignored, but vaccination alone is insufficient to ensure high survival rates in dealing with contagious diseases. Moreover, the duration of protection obtained from the use of vaccines is not enough to cover the whole economic life of fish, which is the main reason for the continuous primary impetus for the ongoing need to produce and develop new and more efficient vaccines (Flores-Kossack et al., 2020). According to the literature above, finding natural, effective, and safe alternative solutions to combat ERM in aquaculture sectors seems more necessary. Indeed, the practical applications of non-antibiotic approaches will be considered effective strategies to minimize antibiotic use to combat bacterial diseases in the aquaculture industry (Dien et al., 2023). A variety of strategies have been used to combat ERM including stress reduction, water quality management and biosecurity controls, selective breeding, and others. Moreover, the use of non-antibiotic feed additives is an important strategy.

Given the vital roles of nutrition in boosting immunity and enhancing disease resistance in aquaculture, many feed supplements can be categorized as functional immunostimulants (Trichet, 2010). There is increasing research on using natural immunostimulants to boost immunity and resistance against diseases (Dawood et al., 2018; Encarnação, 2016). Phytobiotics are medicinal herbs and their derivatives, which have become a common method to control and/or prevent diseases by improving cellular, humoral, and skin mucosal immunity in aquatic animals (Li et al., 2022). Phytochemicals found in medicinal plants, include polyphenols, alkaloids, phenolic acids, terpenoids, lectins, flavonoids, terpenes, carotenoids, and polypeptides with diverse biological advantages (Harikrishnan et al., 2011). These beneficial molecules can significantly boost the defense mechanisms of fish and enable them to fight and combat the effects of diseases (Tadese et al., 2022; Zhang et al., 2022). There is extensive published literature on using a variety of herbal extracts (Adel et al., 2020, 2016; Awad et al., 2019, 2020), plant parts (Bektaş et al., 2019; Özil and Diler, 2023), or essential oils derived from medicinal plants (Acar et al., 2018; Salem et al., 2022) to augment the resistance of rainbow trout against ERM disease.

Reports also showed that several types of probiotics, prebiotics, and synbiotics have displayed encouraging outcomes in boosting immunity and providing effective control against ERM in *O. mykiss* (Capkin and Altinok, 2009; Kim and Austin, 2008; Villumsen et al., 2020 a). The successful use of organic acids and their salts (acidifiers) has been studied to upgrade the immune system of fish species (Ng and Koh, 2017). In addition, oral administration of organic acids can be an excellent candidate to provide protection against ERM due to the positive manipulation of autochthonous gut microbial communities by enhancing the growth of beneficially important bacteria and restraining the growth of intestinal pathogens in fish (Yılmaz et al., 2018 b; Yilmaz et al., 2018 a). Therefore, feed additives can positively increase the general health status and survival of farm-raised fish by elevating innate immune functions. This article reviews published literature that discusses the scope of the problems relating to antibiotic use in aquaculture and the possible alternatives. Hence, in this review, we present a comprehensive and state-of-the-art vision of knowledge, limitations, and future perspectives about the most used feed-based non-antibiotic approaches for enhancing the immunity and resistance of *O. mykiss* against ERM. The data presented in this article would help to improve the aquaculture sustainability, health, and welfare of rainbow trout.

Antibiotic use in the treatment and control of ERM disease

Several antimicrobial compounds were tested to control ERM disease. Earlier studies showed that potentiated sulfonamides can beneficially be helpful in the treatment of natural and experimental ERM in rainbow trout (Bullock et al., 1983). Oxolinic acid (OA) was also used to prevent and treat *Y. ruckeri* infection in *O. mykiss* (Rodgers and Austin, 1983). Even though *Y. ruckeri* was found to be sensitive to several antibiotics, resistance has also been reported. For instance, resistance of some *Y. ruckeri* isolates in the USA has been reported to therapeutic doses of OTC and sulfamerazine (Post, 1987). Resistance to tetracyclines and sulfonamides has also been detected (De Grandis and Stevenson, 1985). It was also found that *Y. ruckeri* strains showed that only one strain from 50 was resistant to FLO (Michel et al., 2003). Furthermore, it was demonstrated that *in vitro* testing reported that *Y. ruckeri* isolates promptly elaborate resistance against several antimicrobials such as OTC, OA, and potentiated sulfonamides (Rodgers, 2001). However, Calvez et al. (2014) mentioned that trimethoprim/sulfamethoxazole, followed by ENR and doxycycline, were the most active antibiotics against French *Y. ruckeri* biotypes 1 and 2 identified from rainbow trout.

In aquaculture, antibiotics are commonly used as prophylactic, chemotherapeutic, or growth promotors (Ibrahim et al., 2020). However, the misuse of antibiotics can result in several hazardous effects, such as increased opportunities for the permanency of residues in aquaculture products (fillets and other products), which can promote adverse reactions and provoke antibiotic-resistant mechanisms of significant bacterial pathogens in human beings (Alderman and Hastings, 1998; Cabello et al., 2013). In the same sense, this may also result in the emergence of antibiotic-resistant strains in aquatic environments, which can induce serious disease problems and mass kills among farmed fish (Preena et al., 2020). Besides, their negative consequences and detrimental effects on aquatic animal health and aquatic ecosystems (Cabello, 2006). Moreover, the non-selective and undesirable impacts of antibiotics will lead to getting rid of the beneficial intestinal microbiome of treated fish. They will, in turn, diminish and hamper the balance of the intestinal microbial ecosystem, especially the microbial community structure (Grenni et al., 2018). For the above reasons, global efforts are urgently required to encourage the well-judged application of antibiotics for prophylaxis in aquaculture. In addition, antibiotic overuse in aquaculture must also be ceased, and stakeholders and fish farmers should be encouraged to adopt and implement antibiotic alternatives and apply other disease-prevention and control measures (Santos and Ramos, 2018).

Feed-based non-antibiotic strategies to combat ERM in rainbow trout

This review article summarizes the content from 81 articles published up to September 2023, focusing on the possible non-antibiotic tools used to control and reduce the losses resulting from ERM in rainbow trout. The literature was accomplished using multiple search scientific engines, including Web of Science, Elsevier Scopus, Google Scholar, and PubMed. The keywords used during the investigation are rainbow trout, ERM, control, phytobiotics, herbal extracts, plants, *Yersinia ruckeri*, organic acids, probiotics, prebiotics, synbiotics, disease resistance, protection, vitamins, algae, nanomaterials, and immunity. References present in each paper were cross-checked for other articles that were relevant to the subject of the present review article. We reviewed many feed-based non-antibiotic therapies evaluated for possible control of ERM in rainbow trout. According to the published literature, they include herbal supplements, probiotics, prebiotics, synbiotics, essential oils (EOs), phytochemicals, organic acids, nanomaterials, vitamins, algae, and miscellaneous groups (Figure 1). The feed additive category and percentage (%) of papers published about this review are depicted in Figure 2. The highest abundance of studies was concentrated on the use of herbal supplements (extracts or plant parts) (32.10%), followed by probiotics (27.16%).

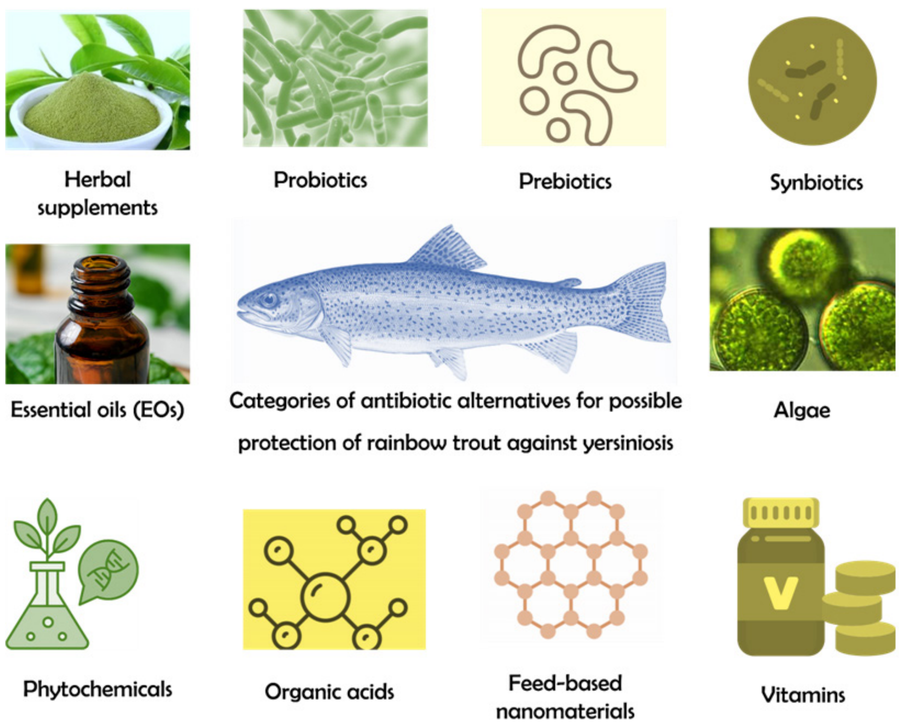

Figure 1. An illustrative diagram shows the different categories of feed-based non-antibiotic approaches used to combat yersiniosis in rainbow trout according to the published literature. These dietary supplements boost the immunity responses, improve the intestinal microbial communities (probiotics), enhance the resistance, and provoke protection against experimental *Y. ruckeri* infection

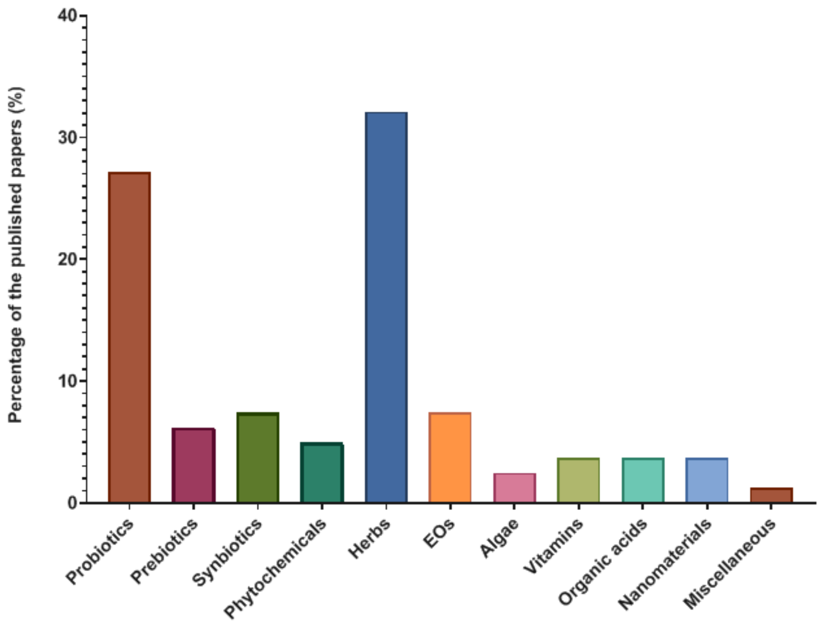

Figure 2. The feed additive category and percentage (%) of papers published on the non-antibiotic feed supplements for possible control of yersiniosis in rainbow trout according to the published literature. Probiotics (n = 22), prebiotics (n = 5), synbiotics (n = 6), phytochemicals (n = 4), essential oils (EOs; n = 6), herbal extracts and plants (n = 26), algae (n = 3), vitamins (n = 3), organic acids (n = 3), nanomaterials (n = 3) and miscellaneous (n = 1)

Phytomedicines

In aquaculture, phytomedicines have gained significant interest and popularity in formulated aquafeeds in the last decades because of their health benefits and potential applications (Abd-elaziz et al., 2023; Shohreh et al., 2024). Phytobiotics are plants, plant part(s), or extract(s) with several advantageous uses, such as enhancing growth, stimulating immunity, boosting antioxidant defense, and increasing the resistance of fish to diseases (Citarasu, 2010; Harikrishnan et al., 2011). These outcomes are not only restricted to the plant parts or their extracts but also their phytochemical composition (Li et al., 2022) and the essential oils extracted from them (Dawood et al., 2021). As a result, phytobiotics will be of great value in avoiding the risks of antibiotic use (Awad and Awaad, 2017). There is considerable interest in the dietary application of herbal extracts and medicinal plants due to their low cost, ease of preparation and application, and decreased environmental impacts.

Herbal extracts

Many investigations have evaluated several types of herbal extracts on the immune responses and resistance of *O. mykiss* against *Y. ruckeri* infection (Table 1). For instance, Sheikhzadeh et al. (2011) performed a short-term trial to evaluate the immunomodulatory impacts of decaffeinated green tea extract. Those researchers demonstrated that a diet of 20 mg/kg significantly enhanced the serum bactericidal activities (BA) against *Y. ruckeri* infection. Another study showed that applying an ethanolic extract of *Mentha piperita* in rainbow trout diets for eight weeks resulted in higher resistance and survivability against an experimental ERM. These observations were linked with significantly increased growth performance and hemato-immunological indices such as red blood cells (RBCs), white blood cells (WBCs), hematocrit (HCT), hemoglobin (Hb) contents, and respiratory burst (RBA) activity (Adel et al., 2016). Interestingly, dietary supplementation with ethanolic *Panax ginseng* extract for ten weeks resulted in slight increases in serum lysozyme activity (LYZ) and leukocytes RBA activities of rainbow trout associated with a reduction in mortality rates of fish experimentally challenged with *Y. ruckeri* (Bulfon et al., 2017). Moreover, administration of 3% *Urtica dioica* ethanolic extract in diets significantly improved the growth performance, stimulated immunity indices (immunoglobulin M (IgM), LYZ, complement components C3 and C4, and RBA of leukocytes), and reduced the cumulative mortality (CMR %) of rainbow trout after experimental challenge with *Y. ruckeri* (Saeidi asl et al., 2017). Furthermore, supplementation with 0.1% hydroalcoholic extract prepared from *Olea europea* leaves significantly increased the resistance of *O. mykiss* against *Y. ruckeri* infection, which was associated with higher expression levels of some immune-associated genes such as tumor necrosis factor-alpha (*TNF-α*), interleukin-1 beta (*IL-1β*), and *IL-8* genes (Baba et al., 2018).

Table 1. Dietary phytobiotics (plant parts and herbal extracts) used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Herbal extracts	Tested dietary doses	Period (days)	Hemato-immune effects[1]	Experimental infection with *Y. ruckeri*				References
				Infection dose	Period (days)	SR (%)		
						Control	Treated	
Panax ginseng extract	0.01, 0.2, 0.3 g/kg	70 d	Slight ↑ serum LYZ and leukocytes RBA No differences in TP, GLO, AP, and MPO	2.2×10^4 CFU/mL	15 d	7%	17%, 10% and 13%	(Bulfon et al., 2017)
Urtica dioica extract	1, 2 and 3%	56 d	↑ RBC, WBC, HTC, Hb, TP, IgM, LYZ, C3, C4, and RBA in 3% group	10^6 cells/mL	14 d	40%	50%, 60% and 80%	(Saeidi asl et al., 2017)
Olive leaf ethanolic extract	0.1, 0.25, 0.5, 1%	60 d	↑ expression of *TNF-α*, *IL-1β* and *IL-8* genes in 0.1% group	1.5×10^8 CFU/mL	20 d	Lowest SR (%)	Highest SR (%)	(Baba et al., 2018)
Zingiber officinale extract	1, 3, 6 and 10 g/kg	56 d	↑ TP, total Ig, LYZ, PA, BA, C3, and C4 in 10 g/kg group	10^6 cells/mL	14 d	41.6%	48.4%, 55.4%, 65.2%, 91.4%	(Soltanian et al., 2019)
Coriandrum sativum extract	0.5, 1 and 2%	56 d	↑ HCT, Hb, LYZ, and ACH50 in the 2% group	1×10^7 cells/mL	14 d	40%	60% in 2% group	(Naderi Farsani et al., 2019)
Hala extract	0.5, 1 and 2%	14 d	↑ TP, AP, MPO, BA in 2% group ↑ *TNF-α* and *IL-8* genes in 0.5% and 2% groups	10^3 cells/fish	10 d	33.3%	21.43% and 26.67%	(Awad et al., 2019)
Artemisia dracunculus extract	1, 2 and 3%	56 d	↑ RBCs, WBCs, HTC, Hb, LYZ, and RBA ↑ Mucosal immunity (TP, ALP, LYZ, and PA)	1.1×10^6 cells/mL	14 d	Lowest SR (%)	Highest SR% in 2% group	(Gholamhosseini et al., 2021)
Common mallow (*Malvae sylvestris*) extract	1%, 3% and 5%	56 d	↑ ALB, GLO, TP, total Ig, and ACH50 in 3% and 5% groups ↑ HCT, Hb, MCH, MCV, WBCs, RBCs, and LYZ in all treated groups	0.5×10^8 cells/fish	14 d	Lowest SR (%)	Highest SR% in 3% group	(Rashidian et al., 2020)
Polygonum minus (PM) extract	5, 10 and 15 mg/kg	56 d	↑ RBCs, WBCs, Hb, TP, ALB, and GLO ↑ LYZ, RBA, total Ig in PM15 ↑ skin mucus TP and esterase in PM15 ↑ expression of *IL-1β*, *IL-8*, *TNF-α*, and *lysozyme* genes in PM15	1.5×10^8	14 d	39.67%	48.79%, 57.34% and 69.69 %	(Adel et al., 2020)
Mentha longifolia extract	0.1, 0.2 and 0.3%	28 d	↑ WBCs, RBCs, Hb, HCT, TP, ALB, complement, LYZ, RBA, ACH50	10^8 cells/mL	10 d	Lowest SR (%)	Highest SR (%)	(Heydari et al., 2020)
Ziziphora clinopodioides extract	0.5, 1.5, 3 and 4.5 %	56 d	↑ LYZ, ACH50, IgM, mucus (LYZ and BA)	10^7 cells/mL	14 d	26%	36%, 43%, 46% and 56%	(Oroji et al., 2021)
Sumac (*Rhus coriaria* L.)	0.5, 2 and 5%	56 d	↑ WBCs, RBCs, ACH50, LYZ, expression of *TNF-α* and *IL-1β* genes in 2 and 5% groups	0.5×10^7 CFU/mL	15 d	Lowest RPS (%)	RPS (%) = 28.31%, 62.74% and 71.25%	(Gharaei et al., 2020)
Roseship (*Rosa canina*)	10, 20 and 30%	50 d	↑ RBCs, WBCs, Hb, HCT, NBT, and PA in 20% group	3×10^8 CFU/mL	10 d	20.83%	45.83%, 66.67% and 41.66%	(Şahan et al., 2017)

[1]ACH50: alternative complement pathway 50; ALB: albumin; AP: antiproteases; BA: bactericidal activity; C3: complement component C3; C4: complement component C4; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; Ig: immunoglobulin; IL-1β: interleukin-1 beta; IL-8: interleukin 8; lgM: serum immunoglobulin M; LYZ: lysozyme activity; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPO: myeloperoxidase; NBT: nitroblue tetrazolium activity; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBCs: red blood cells; SR%: survival rate percent; TNF-α: tumor necrosis factor alpha; TP: total protein; WBCs: white blood cells.

In the latest years, some publications have highlighted the importance of using herbal extracts as dietary supplements to reduce the risks of ERM in rainbow trout. For instance, Awad et al. (2019) declared that administration of 2% alcoholic extract prepared from *Pandanus tectorius* leaves in diets resulted in increased serum immune-related parameters (total protein, myeloperoxidase (MPO) content, antiproteases, and BA activities), expression of immune-related genes and reduced mortalities of rainbow trout after an experimental challenge with *Y. ruckeri*. Among the studies that used herbal extracts, Naderi Farsani et al. (2019) found that 2% dietary hydroalcoholic extract of *Coriandrum sativum* seed significantly increased innate immune responses of rainbow trout (serum LYZ and complement activities) and decreased mortality after *Y. ruckeri* infection. The same observation was reported in rainbow trout when fed diets supplemented by *Zingiber officinale* extract for 56 days, whereas fish exhibited higher resistance against *Y. ruckeri*, together with simultaneous higher immune responses (serum LYZ, phagocytic activity (PA), and BA activities) and antioxidant enzyme defense mechanisms (Soltanian et al., 2019).

Interestingly, it was found that a dietary supplement of *Alpinia officinarum* extract enhanced innate and adaptive immunity, expression of immune genes in the head kidneys, and resistance of *O. mykiss* against ERM (Awad et al., 2020). Bilen et al. (2021) described that oral administration of *Juniperus excelsa* methanolic extract at a daily dietary dose of 8 mg/kg body weight for 14 days significantly increased survival rates of *O. mykiss* post-infection with *Y. ruckeri*. Similarly, dietary ethanolic extract of *Polygonum minus* (15 mg/kg for eight weeks) improved growth performance, humoral and mucosal immune parameters, expression of *IL-1β*, *IL-8*, and *lysozyme* genes in rainbow trout, and conferred protection and highest survivals of rainbow trout after *Y. ruckeri* challenge (Adel et al., 2020). Gholamhosseini et al. (2021) found that 2% methanolic extract of *Artemisia dracunculus* supplementation in diets for eight weeks led to an elevation in growth rates and resistance of *O. mykiss* against *Y. ruckeri* infection. Those authors also reported the highest hemato-immunological parameters (WBCs count, alternate complement activity (ACH50), serum total protein, total Ig, LYZ, and mucus BA) in the fish group fed a diet with 3% extract supplementation. Of interest, it was found that 0.2% *Mentha longifolia* extract significantly improved the resistance and survival rates of rainbow trout against ERM (Heydari et al., 2020). These observations were associated with the highest RBCs, WBCs, hemoglobin, hematocrit, serum LYZ activity, RBA, and expression of immune-related (*lysozyme* and *TNF-α*) genes.

The positive effects of *Malvae sylvestris* aqueous extract were found when added to diets with a dose of 3% or 5% for eight weeks. Results revealed significantly increased innate and mucosal immunity and provided significant resistance and protection of rainbow trout against *Y. ruckeri* infection (Rashidian et al., 2020). Those authors supposed that the highest disease resistance was accompanied by improvement in growth rate, hematological indices (HTC, Hb, WBCs count, RBCs count, and lymphocytes), innate immune responses (ACH50), mucosal immune parameters (ACH50, total Ig and LYZ activity). Firouzbakhsh et al. (2021) found that dietary supplementation with 0.5% *Capsicum annuum* extract improved growth performance, hematological parameters, plasma total protein, albumin, serum LYZ, and ACH50 activities in rainbow trout juveniles accompanied by higher survivals post-infection with *Y. ruckeri*. Moreover, Ghafarifarsani et al. (2021) declared that administration of *Quercus brantii* extract in diets for eight weeks resulted in higher *in vitro* antibacterial activities of rainbow trout skin mucous against *Y. ruckeri*. Oroji et al. (2021) found an increase in resistance against ERM of rainbow trout following dietary administration of 3% hydroalcoholic extract of *Ziziphora clinopodioides* for eight weeks. Those authors declared that the highest disease resistance of fish was associated with the highest growth rates and serum non-specific immunological parameters (such as LYZ, BA, and total Ig). Likewise, Terzi et al. (2021) elucidated that aqueous methanolic extract of *Prunus domestica* significantly improved innate immunity and provoked higher survival of *O. mykiss* against *Y. ruckeri*. Latterly, it was found that the best immunocompetence of rainbow trout was found when fed diets supplied with *Glycyrrhiza glabra* extract (2 g /kg) for 56 days (Darvishi et al., 2022). Those authors reported higher skin mucosal immunity (LYZ activity, alkaline phosphatase activity, total Ig values, and mucus BA against *Y. ruckeri*) associated with increased transcription of immune-related (*TNF-α, IL-1β, IL-8*, and *IgM*) genes and higher survival of fish post-challenge with *Y. ruckeri* (Darvishi et al., 2022).

Plant-based feed supplements

Several studies reported enhanced immune responses and resistance of rainbow trout upon feeding plant-based feed supplements. For example, Mansouri Taee et al. (2017) showed that administering 1 or 1.5% *Myrtus communis* powder for 60 days in rainbow trout diets significantly increased the antimicrobial activities of skin mucus against *Y. ruckeri*. As indicated by Şahan et al. (2017), it was found that dietary administration of 20% *Rosa canina* meal improved hematological (RBCs, WBCs, Hb, HCT, and RBCs indices), non-specific immune indices (such as NBT and PA), antioxidant parameters (SOD, CAT, and GSH), and highest survival against *Y. ruckeri* infection in rainbow trout. Bektaş et al. (2019) also demonstrated that supplementation of rainbow trout diets with *Nigella sativa* seed powder (1 or 2.5 g/kg for 60 days) significantly increased the growth, hemato-immune parameters and provided significant protection against infection with *Y. ruckeri*. Another study showed that dietary administration of 2 or 5% *Rhus coriaria* meal powder significantly increased resistance of rainbow trout against *Y. ruckeri* infection along with higher RBCs and WBCs counts, serum LYZ and ACH50, and hepatic up-regulation in TNF-α and IL-1β genes (Gharaei et al., 2020).

Recently, Chekav et al. (2023) declared that administration of 1.5% *Heracleum persicum* meal powder for 60 days significantly increased hematological indices (RBCs and WBCs counts), boosted the non-specific immune indices (serum LYZ activity) and conferred higher protection against the survival of *O. mykiss* against *Y. ruckeri* infection. Similarly, 1.5% *Calendula officinalis* meal powder for two months positively impacted the growth, activities of digestive enzymes, antioxidant defensive mechanisms, serum and mucus immune indices, and resistance of rainbow trout against ERM caused by *Y. ruckeri* (Ghafarifarsani et al., 2023 a). Lately, Özil and Diler (2023) demonstrated that *Origanum onites* crude powder stimulated the non-specific immune responses (NBT, PA, serum LYZ activity, and IgM levels) and provided higher protection and survivability of rainbow trout against *Y. ruckeri* infection.

Functional phytochemicals

Phytochemicals are a group of beneficial plant chemicals such as flavonoids, phenolics, alkaloids, pigments, glucosinolates, anthocyanins, terpenoids, carotenoids, and isoflavonoids. These molecules have been considered functional supplements to promote growth and immunity, mitigate stress, boost antioxidant capacity, and improve disease resistance of fish and shrimp (Abdel-Latif et al., 2023; Naiel et al., 2023). Several researches declared the beneficial roles of phytochemicals in boosting the immunity and resistance of *O. mykiss* against ERM disease (Table 2). For example, Yılmaz and Ergün (2018) declared that the dietary application of a natural plant-derived polyphenolic acid known as trans-cinnamic acid in a supplementation dose of 250 or 500 mg/ kg significantly boosted the immunity responses of the treated rainbow trout manifested by significantly increased LYZ activity, IgM, PA, RBA, and potential killing activity along with a significant increase of the mRNA transcripts of immune-related genes (IL-1β, IL-8, TNF-α, TGF-β, and IgT) in the head kidney. Those authors further reported the potential role of trans-cinnamic acid (250 or 500 mg/ kg) in increasing the survival of *O. mykiss* (74.67%) experimentally infected with *Y. ruckeri* when compared with the control (49.33%) (Yılmaz and Ergün, 2018). Another study by Mişe Yonar (2019) found that dietary application of another plant-derived polyphenolic acid known as ellagic acid significantly enhanced the hemato-immunological indices and resistance of *O. mykiss* after being challenged to *Y. ruckeri* infection. In the same sense, Gültepe (2020) found that dietary supplementation with D-limonene obtained from orange peel essential oil significantly enhanced blood immunity and proved significant protection of *O. mykiss* against ERM caused by *Y. ruckeri* with high survival rates of the treated groups in comparison with the control group. Recently, Ghafarifarsani et al. (2023 b) demonstrated that the application of a plant-derived polyphenolic acid known as chlorogenic acid (200, 400, and 600 mg/ kg for 60 days) significantly increased the immunity of rainbow trout manifested by increased serum LYZ, immunoglobulin, and complement C3 and C4. Those authors also declared that chlorogenic acid significantly increased the survival rate % of the treated rainbow trout after experimental challenge with *Y. ruckeri*. From the studies mentioned above, it could be concluded that these phytochemicals can enhance the health status and immune responses of fish to combat the effects of challenging pathogens (Ahmadifar et al., 2021; Chakraborty and Hancz, 2011); thus, these chemicals could be considered an effective disease control strategy with possible application in aquaculture (Li et al., 2022).

Essential oils (EOs)

EOs extracted from medicinal plants have gained significant interest in aquafeed because of their well-known growth-promoting, antioxidant, immune stimulant, and disease-resistance effects (Dawood et al., 2022). Several recent studies were conducted on the role of EOs in augmenting the immunity and resistance of rainbow trout against ERM (Table 3). It was highlighted that *Thymus vulgaris* and *Foeniculum vulgare* EOs significantly increased the serum BA and resistance of rainbow trout to *Y. ruckeri* infection (Gulec et al., 2013). Similarly, the dietary application of *Ducrosia anethifolia* EO for eight weeks also increased the survival rate % of *O. mykiss* after experimental infection with *Y. ruckeri* (Dehghan et al., 2016). Moreover, a 60-day feeding trial also revealed that supplementation of pomegranate seed EO in diets significantly improved the resistance and decreased the cumulative mortalities of rainbow trout against yersinosis (Acar et al., 2018). Of interest, a commercial product containing a cocktail of *Thymus vulgaris*, *Origanum vulgare*, and *Eucalyptus* EOs (Mix-oil®) for 56 days boosted the hemato-immunity of rainbow trout manifested by significantly increased serum LYZ, total Ig, ACH50, complement C3 and C4, and total protein levels compared to the control (Bababaalian Amiri et al., 2020). Those authors further elucidated that the fish group that received an EOs mixture (400 ppm) had the highest relative percent survival (80%) after experimental infection with *Y. ruckeri* compared to 40% in the control group.

Salem et al. (2022) showed that *Sinapis alba* EO, as a dietary supplement, could significantly increase LYZ and MPO activities and the resistance of rainbow trout to ERM. Lately, it was demonstrated that dietary application of *Linum usitatissimum* EO for nine weeks significantly increased the innate immunity responses, potential killing activity of kidney phagocytes, MPO, LYZ activities, and survival rates of rainbow trout challenged experimentally with virulent *Y. rukeri* (Salem et al., 2023). Recently, it was found that *Origanum onites* EO (0.5 mL per kg diet) for eight weeks provoked higher survival rates (100%) of rainbow trout vaccinated against ERM with no reported cumulative mortalities compared with a vaccinated and non-supplemented group (Özil and Diler, 2023). It has been previously reported that the beneficial roles of EOs may be associated with their antibacterial and immunostimulatory effects (Alnahass et al., 2023; Dawood et al., 2021). These effects propose the potential application of EOs as a functional ingredient in aquafeed.

Table 2. Dietary functional bioactive phytochemical applications used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Phytochemicals	Tested dietary doses	Period (days)	Hemato-immune effects[1]	Experimental infection with *Y. ruckeri*				References
				infection dose	period (days)	SR% or RPS		
						control group	treated group	
Ellagic acid	50, 100 and 200 mg/ kg	56 d	No differences in MCV, MCH, and MCHC Significant ↑ RBCs, Hb, HCT, WBCs, NBT, PA, PI, TP, IgM, BA, LYZ, and MPO	1×10^5 CFU/mL	14 d	RPS = 40.00%	RPS = 56.67%, 70.00% and 73.33%	(Mişe Yonar, 2019)
D-limonene	0.5, 1 and 3 mL/kg	90 d	↑ RBCs, HCT, Hb, and MCHC in 0.5 and 1 mL/kg group Significant ↑ ALB	3×10^6 CFU/mL	15 d	SR% = 39%	SR% = 60%, 69 % and 69%	(Gültepe, 2020)
Trans-cinnamic acid	250, 500, 750, 1500 mg/ kg	60 d	↑ TP, GLO, LYZ, IgM, PA, RBA, and potential killing activity in 250 or 500 mg/ kg groups. ↑ expression of immune-related genes (*IL-8, IL-1β, TGF-β, TNF-α*, and *Ig*T) in the head kidney in 250 or 500 mg/kg groups	3×10^8 CFU /mL	20 d	SR% = 49.33%	SR% = 74.67%, 74.67%, 49.33% and 42.67%	(Yılmaz and Ergün, 2018)
Chlorogenic acid	200, 400, 600 and 800 mg/ kg	60 d	↑ LYZ, Ig, and C3 and C4 of 200, 400, and 600 mg/kg groups The highest TP and GLO in 400 mg/kg group	10^7 cells/mL	14 d	SR% = 35.34%	SR% = 51.16%, 64.46%, 75.60% and 60.02%	(Ghafarifarsani et al., 2023 b)

[1]ALB: albumin; BA: bactericidal activity; C3: components 3; C4: complement 4; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; Ig: immunoglobulin; IgM: immunoglobulin M; *IgT:* immunoglobulin T; *IL-1β:* interleukin-1 beta; *IL-8:* interleukin 8; LYZ: lysozyme activity; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MDA: malondialdehyde; MPO: myeloperoxidase; NBT: nitroblue tetrazolium; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBCs: red blood cells; RPS: relative percent survival; SR%: survival rate percent; *TGF-β:* transforming growth factor beta; *TNF-α:* tumor necrosis factor alpha; TP: total protein; WBCs: white blood cells.

Table 3. Dietary essential oils (EOs) applications used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

EOs tested	Tested dietary doses	Period (days)	Hemato-immune responses[1]	Experimental infection with *Y. ruckeri*				References
				infection dose	period (days)	CMR (%) or SR (%) or RPS		
						control	treated	
A mixture of *Thymus vulgaris* and *Foeniculum vulgar*e EOs	10 ml/100 g feed	7 d	↑ BA, TP, and ALB	3×10^7 CFU/mL	7 d	Lowest SR%	Highest SR%	(Gulec et al., 2013)
*Ducrosia anethifoli*a essential oil	0.001, 0.01 and 0.1%	56 d	No differences in LYZ and ALB Significant ↓ TP, BA, GLO	2.24 ± 10^6	10 d	CMR% = 55%	CMR% = 40%, 70% and 70%	(Dehghan et al., 2016)
Pomegranate seed oil	0.5, 1 and 2%	60 d	↑ RBCs, Hb, MCHC No differences in HCT, MCH, TP, ALB, GLO, LYZ, MPO	6.8×10^6 CFU/mL	20 d	SR% = 45.10%	SR% = 58.82%, 56.86% and 56.86%	(Acar et al., 2018)
A mixture of *Thymus vulgaris*, *Origanum vulgare* and *Eucalyptu*s sp. EOs	50, 200 and 400 ppm	56 d	↑ RBCs, HCT, LYZ, Ig, ACH50, C3, C4, and TP No differences in MCV, MCH, MCHC, and Hb	1×10^6 cells/mL	14 d	RPS = 40%	RPS = 80 % in 400 ppm group	(Bababaalian Amiri et al., 2020)
White mustard oil	0.5, 1 and 1.5%	63 d	↓ RBA and potential killing activity ↑ LYZ and MPO activities	1×10^7 CFU/mL	10 d	Lowest SR%	Highest SR%	(Salem et al., 2022)
Flaxseed oil	0.5, 1 and 1.5%	63 d	↑ innate immune parameters, potential killing activity, MPO, and LYZ activity	1×10^7 CFU/mL	10 d	Lowest SR%	Highest SR%	(Salem et al., 2023)

[1]ACH50: alternative complement pathway; ALB: albumin; BA: bactericidal activity; C3: complement component C3; C4: complement component C4; CMR: cumulative mortality; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; Ig: serum total immunoglobulin; LYZ: lysozyme activity; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPO: myeloperoxidase; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBA: respiratory burst activity; RBCs: red blood cells; RPS: relative percent survival; SR%: survival rate percent; TP: total protein; WBCs: white blood cells.

Table 4. Probiotic applications used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Probiotics	Tested dietary doses	Period (days)	Hemato-immunity responses[1]	Experimental challenge with *Y. ruckeri*				References
				infective dose	period (days)	SR%		
						control	probiotic	
Carnobacterium sp.	$5×10^7$ cells/g feed	28 d	The highest resistance against *Y. ruckeri*	$5×10^7$ cells/mL	14 d	36%	100%	(Robertson et al., 2000)
A mixture of *B. subtilis* and *B. licheniformis*	$4×10^4$ spores/g feed	42 d	No differences in HCT and plasma protein	$1.8×10^6$ CFU per fish	28 d	16.7%	41.7%	(Raida et al., 2003)
Carnobacterium maltaromaticum B26 and *Carnobacterium divergens* B33	10^7 cells/g feed	14 d	↑ PA of head kidney macrophages in B26 group ↑ RBA and LYZ in B33 group ↑ Gut mucosal LYZ activity	$1.6×10^7$ cells/mL	14 d	13%	73% and 80% in B26 and B33	(Kim and Austin, 2006)
Bacillus sp. JB-1 *Aeromonas sobria* GC2	$2×10^8$ cells/g feed	14 d	↑ TP, RBCs, WBCs, anti-protease activity, RBA, serum LYZ, mucus LYZ	$3×10^7$ cells/mL	14 d	20%	100% in JB-1 and 94% in GC2	(Brunt et al., 2007)
Saccharomyces cerevisiae extract and hydrolyzed powder	0.5 and 1%	60 d	No significant changes in HCT, RBCs, Hb Significant ↑ LYZ, ACH50, total serum antibody	$1.1×10^6$ CFU/mL	14 d	Lowest SR%	Highest SR%	(Tukmechi and Bandboni, 2014)
Lactobacillus casei *L. plantarum*	$5×10^7$ CFU/g feed	30 d	↑ LYZ, ACH50 and total immunoglobulin in *L. casei* group	$0.5×10^7$ CFU/mL	15 d	46.5%	76.7% and 63.5%	(Andani et al., 2012)
Pediococcus acidilactici (PA) *Enterococcus faecium* (EF)	PA= $2×10^6$ CFU/g feed EF = $2.5×10^8$ CFU/g feed	56 d	↑ RBCs, WBCs, HCT, IgM, RBA, TP, ALB, and GLO No differences in Hb, MCV, MCH, MCHC, LYZ, C3, and C4	$1.2×10^8$ cells /mL	10 d	26.7%	80% and 66.7% in PA and EF	(Abedian Amiri et al., 2017)
A mixture of *Bacillus subtilis* (BS) and trans-cinnamic acid (TA)	BS = 10^7 CFU/g TA = 25, 50, 75 and 150 mg/kg	60 d	↑ RBA, PA, PI, MPO and total antiprotease activity in all mixtures	$3×10^8$ CFU /mL	20 d	45.33%	73.33%, 72.00%, 66.67% and 78.67%	(Yılmaz et al., 2020)

[1]ACH50: alternative complement pathway 50; ALB: albumin; BA: bactericidal activity; C3: complement component C3; C4: complement component C4; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; IL-1β: interleukin-1 beta; IL-8: interleukin 8 receptor; lgM: serum immunoglobulin M; LYZ: lysozyme activity; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPO: myeloperoxidase; NBT: nitroblue tetrazolium activity; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBCs: red blood cells; TNF-α: tumor necrosis factor alpha; TP: total protein; WBC: white blood cells.

Notwithstanding the studies above, several limitations still may affect the obtained results. For example, phytochemical constituents and the quality of the plant extracts, dietary administration doses, feeding duration, and administration regime may affect the results, which require additional investigations. The possible mechanism underlying the effects of these phytomedicines warrants more and more experimentation. The optimal supplementation strategy of phytomedicines should be described in detail. Moreover, additional investigations are also necessary to uncover novel phytochemicals, plants, herbal extracts, and combinations between phytobiotics and probiotics to obtain promising results. Optimizing the extraction process and standardizing feed formulation are also required. Additional research studies to increase the stability and enhance the bioavailability of phytomedicines (herbs, EOs, phytochemicals, and extracts) using nanotechnological procedures and special encapsulation technology merit further research studies.

Probiotics

Probiotics are live microbial supplements administered adequately through the gastro-intestinal tract (GIT) to maintain the intestinal microbial balance for conferring health profits to the host (El-Saadony et al., 2021). These supplements can exert their characteristics through several mechanisms, such as secreting some inhibitory metabolites and competition for essential nutrients and adhesion sites (Yilmaz et al., 2022). There are several criteria for selecting probiotic strains, including their ability to colonize the intestinal epithelial surface (Balcázar et al., 2006). Several probiotic bacterial strains (Irianto and Austin, 2002) and probiotic yeast strains (Mahdy et al., 2022; Taha et al., 2023) can be beneficially used in aquaculture. Herein, several reports about the potential effects of probiotics to combat ERM in *O. mykiss* (Table 4).

Probiotic yeasts

Dietary supplementation of probiotic yeasts could greatly boost immunity and disease resistance in rainbow trout. For example, Tukmechi et al. (2011) revealed that *Saccharomyces cerevisiae* that was previously treated with beta-mercapto-ethanol (in a dietary dose rate of 5 $\times 10^7$ CFU/g feed for 30 days) considerably stimulated the immune system (particularly serum LYZ activity and complement system) and growth performance of *O. mykiss* juveniles and also thus enhanced their resistance against experimental infection with a pathogenic *Y. ruckeri* strain. Those authors proposed that this treated yeast strain was efficiently utilized in fish diets and thus improved the digestibility of diets. The inclusion of a commercial product composed of fermented *S. cerevisiae* (Hilyses®; 5 g/kg diet for 50 days) in diets effectively promoted the growth, skin mucosal immunity (LYZ, protease, alkaline phosphatase, and esterase enzyme activities) and significantly increased hemagglutination and antibacterial activities of rainbow trout against *Y. ruckeri* (Sheikhzadeh et al., 2012). An increase in the non-specific immunological capacity (serum LYZ, ACH50, and total serum antibody levels) was observed, together with simultaneous higher survival after experimental infection with *Y. ruckeri* when rainbow trout fed diets supplied with a combination of *S. cerevisiae* extract and hydrolyzed powder for 2 months (Tukmechi and Bandboni, 2014).

A further study revealed that rainbow trout fed diets supplied with the yeast *S. cerevisiae* var. *boulardii* strain CNCM I-3799 (10 g/kg diet for 60 days) presented higher growth, immunity, and survival of *O. mykiss* challenged with a pathogenic *Y. ruckeri* (Sheikhzadeh et al., 2016). The application of a commercial yeast product composed of two *Saccharomyces* yeasts known as *S. cerevisiae* and *S. elipsoedas* (Aqualase®) for eight weeks significantly increased the lactic acid bacteria population in the intestinal tracts and enhanced the growth of rainbow trout compared to the control (Adel et al., 2017). Those authors reported that this commercial yeast product also boosted the skin mucosal immunity of the treated fish, reflected by significant increases in LYZ activity and inhibitory potential of skin mucus against *Y. ruckeri*. Indeed, the yeast strains used have great potential as probiotics for enhancing the immunity and resistance of rainbow trout against ERM. The benefits and gains from using yeast-based probiotics include several items, such as the modulation of GIT microbiota, positive effects on the fish immune system, and boosted resistance against the challenged bacterium. These features affirm the significance of probiotic yeasts in recuperating health and advance the perspectives of using probiotic yeasts in aquaculture.

Probiotic bacteria

There is accumulating evidence that applying probiotic bacteria in diets significantly improved rainbow trout's immunity and resistance against ERM. For example, Robertson et al. (2000) isolated *Carnobacterium* sp. from the intestinal tract of Atlantic salmon and appraised its application as a potential probiotic for *O. mykiss*. Those authors found that dietary application of this probiotic bacteria for 14 days has effectively reduced the disease caused by *Y. ruckeri* infection after a cohabitation challenge of rainbow trout. Using a commercially purchased probiotic product (BioPlus2B®) comprising a combination of *Bacillus subtilis* and *B. licheniformis* for 42 days conferred protection of rainbow trout against ERM disease after exposure to *Y. ruckeri* infection (Raida et al., 2003). Moreover, dietary administration of *Bacillus* sp. JB-1 and *Aeromonas sobria* GC2 for 14 days considerably boosted the immunity such as anti-protease activity, RBA, and LYZ activity of rainbow trout, and increased the survival rates of fish after cohabitation challenge with *Y. ruckeri* (Brunt et al., 2007). Kim and Austin (2008) have evaluated the probiotic activity of two host-derived probiotic bacteria identified from the intestinal tracts of healthy rainbow trout and their potential role in protection against ERM disease in rainbow trout. Those authors found that the application of *Carnobacterium maltaro-*

maticum B26 and *C. divergens* B33 strains in the feeds of *O. mykiss* (10^7 cells/g feed for 14 days) significantly increased the gut mucosal LYZ activity and provided significant protection of fish after experimental challenge with *Y. ruckeri* infection when compared with the controls (Kim and Austin, 2008). Capkin and Altinok (2009) found that using host-derived probiotics known as *Enterobacter cloacae* and *B. mojavensis* that were previously isolated and defined from the gut of rainbow trout in a dose rate of 1×10^8 cells per g diet for 60 days provided considerable protection against ERM disease.

Among the pool of studies for a given probiotic supplement, Abbass et al. (2010) mentioned that administering subcellular components of two probiotic bacteria *A. sobria* GC2 and *B. subtilis* JB-1, improved the survival and conferred protection of *O. mykiss* against *Y. ruckeri* infection. Moreover, it was found that two host-derived lactic acid-producing bacteria (LAB) defined as *Lactobacillus casei* and *L. plantarum* isolated from the intestines of common carp provided considerable protection and enhanced survival of rainbow trout against ERM (Andani et al., 2012). Using *Pediococcus acidilactici* and *Enterococcus faecium* in feeds for 56 days significantly increased the survival of *O. mykiss* following exposure to *Y. ruckeri* infection (Abedian Amiri et al., 2017). In a context where *L. plantarum* strain 426951 was applied in feeds for 72 days, results revealed significantly boosted immune responses and growth performance and enhanced the efficacy of immersion vaccination of *O. mykiss* against *Y. ruckeri* (Soltanian et al., 2019).

A recent study has revealed that microencapsulated *L. rhamnosus* strain ATCC 7469 significantly upgraded the growth and immunity responses and conferred the highest resistance of rainbow trout against the *Y. ruckeri* challenge (Hooshyar et al., 2020). In a similar trend, results were also described that *Lactococcus lactis* subsp. *lactis* strain PTCC 1403 applied in *O. mykiss* feeds for eight weeks enhanced the feed efficiency, immunity biomarkers (serum LYZ activity and IgM levels), and resistance of *O. mykiss* to *Y. ruckeri* infection (Yeganeh et al., 2021). Further, the incorporation of a commercial product (DiPro Aqua®) composed of a combination of *B. subtilis* and *B. licheniformis* (2×10^8 CFU/kg for 56 days) in rainbow trout feeds significantly enhanced the growth, ameliorated intestinal histomorphology and increased the antibacterial activities of the skin mucus against *Y. ruckeri* (Naraghi et al., 2022). Although many investigations reported the benefits and promising results of probiotics to combat bacterial diseases such as ERM in rainbow trout, there are still gaps in explaining the probiotic mechanisms of action (Amenyogbe et al., 2020). Moreover, the hazards that may result from transferring antibiotic-resistant genes from probiotics to pathogenic bacteria should not be ignored (Wang et al., 2019).

On the other side, several indigenous host-derived probiotics from the intestines of *O. mykiss* were examined and investigated for their potential *in vitro* inhibitory activities against *Y. ruckeri* infection. For instance, an earlier study demonstrated that host-derived LAB probiotics, including *Lactococcus lactis* CLFP 101, *L. plantarum* CLFP 238, and *L. fermentum* CLFP 242 isolated from the microbiota of the intestines of *O. mykiss* significantly inhibited the adhesion of *Y. ruckeri* under *in vitro* circumstances (Balcázar et al., 2008). Similarly, Medina et al. (2020) isolated two host-derived probiotics known as *B. amyloliquefaciens* 131 and *Paenibacillus* spp from the intestinal tracts of healthy *O. mykiss*, investigated for their probiotic characteristics and demonstrated their potential inhibitory activities against *Y. ruckeri* with no pathogenic effects to *O. mykiss*. Furthermore, Mortezaei et al. (2020) have evaluated *in vitro* the probiotic properties of two indigenous LAB probiotic bacteria known as *Lactococcus lactis* and *Weissella oryzae* that were previously isolated and identified from the intestinal ecosystem of *O. mykiss* and reported that their antagonistic activities against *Y. ruckeri*. Although the results of the studies above, further research studies are still necessary to verify the effectiveness and efficacy of these probiotics to be applied in aquafeed.

Combination of probiotic bacteria with other supplements

Combining herbal supplements with probiotics in fish diets seems to produce a vast array of beneficial functions and synergistic outcomes resulting from both supplements. It was reported that dietary application of a mixture of a probiotic composed of *L. acidophilus* and *Bifidobacterium bifidum* (1 g/kg) in combination with resveratrol (800 mg/kg) for eight weeks significantly boosted the innate immunity biomarkers of rainbow trout manifested by significant increases in serum complement activity, LYZ activity and BA of treated rainbow trout (Naderi Farsani et al., 2021). Those authors further reported significant improvements in mucosal immunity (LYZ, BA, alkaline phosphatase, and total immunoglobulins) along with the highest survival rates in this group compared to the controls following experimental challenge with pathogenic *Y. ruckeri*, suggesting that supplementing diets with this combination could be an effective alternative to antibiotics use for controlling ERM than each one alone. It was supposed that the obtained results might be attributed to the impacts of this mixture in a faster stimulation of the innate immunity and antioxidant defense mechanisms in *O. mykiss* after four weeks of dietary administration (Naderi Farsani et al., 2021). Later, Jasim et al. (2022) reported that a combination of *L. fermentum* with *Cinnamomum* sp. powder resulted in enhancement of the growth, digestive enzyme activities, immune responses (LYZ, total immunoglobulins, complement C3, C4, ACH50, MPO, and RB activity), and resistance abilities of rainbow trout to the challenge with yersinosis disease under crowding stress when compared with the effect of each one alone. Those authors also suggest the synergistic effects obtained from probiotics and herbs on augmenting the immunity and disease resistance of treated fish. Another study showed that a combination of *B. subtilis* and trans-cinnamic acid also improved immune parameters like RBA, PA, phagocytic index, MPO, and total anti-protease and increased the survival of *O. mykiss* challenged by *Y. ruckeri* infection (Yılmaz et al., 2020). Moreover, a mixture of *L. casei* and potassium sorbate for 60 days increased the resistance of *O. mykiss* to *Y. ruckeri* infection in comparison with the controls (Jafarnodeh et al., 2020).

Quorum quenching (QQ) probiotics

The phenomenon of quorum quenching (QQ) or quorum-sensing (QS) inhibition can be accomplished via the enzymatic degradation of the virulence factors of pathogenic bacteria; hence, they could be used to control bacterial virulence (Chen et al., 2013; Defoirdt et al., 2004). It is well known that acylated homoserine lactone (AHL) is produced by many fish-associated pathogenic bacteria, including *Y. ruckeri*, which act as signal molecules in the QS system (Jesper et al., 2005; Kastbjerg et al., 2007); hence, evaluation of AHL degradation is considered as a method for QS inhibition (Kalia and Purohit, 2011). *In vitro* study showed that AHL-degrading QQ probiotic strains such as *B. cereus*, *B. thuringiensis*, *Citrobacter gillenii*, *Stenotrophomonas moltiphilia*, and *Enterobacter hormaechei* subsp. *hormaechei* can decrease biofilm formation in *Y. ruckeri* (Torabi Delshad et al., 2018). The same authors also observed that *in vivo* dietary administration of these QQ bacteria in diets of rainbow trout (10^8 CFU /1 g of feed) for 40 days could enhance the resistance of fish and provide a way to control ERM disease in rainbow trout, suggesting that these strains can act as probiotic candidates for combating ERM. From the authors' point of view, we can conclude that using AHL-degrading QQ probiotics could be considered a new trend for controlling ERM in rainbow trout. Nevertheless, the potential role of QQ strains in protecting rainbow trout after experimental challenge with *Y. ruckeri* remains unclear, as there is no direct physical contact between the dietary QQ strains and the challenged *Y. ruckeri*. Accordingly, further experimentations should be carried out to determine the AHL concentrations in the serum of the treated trout, methods of the clearance of the injected bacteria, and the roles of QQ strains to stimulate the fish's immune system against the challenged bacterium. These research points would give an ideal explanation for this phenomenon.

Prebiotics

Prebiotics are non-digestible fibers that usefully influence the host by selectively promoting the growth of some gut-associated microorganisms such as inulin, fructooligosaccharides (FOS), mannan oligosaccharides (MOS), β-glucan (BG), and several others (Song et al., 2014). Using a commercial product containing yeast BG derived from the cell wall of *S. cerevisiae* (with a dietary dose of 0.2%) promoted immune competence (total immunoglobulins, IgM, LYZ, and ACH50 levels) associated with enhanced resistance and relative level of survival of *O. mykiss* fries after an experimental challenge with *Y. ruckeri* (Ghaedi et al., 2015). Of interest, those authors further reported that dietary application of yeast β-glucan positively impacted the immunity status of brood fish and could transfer some maternal immune factors (such as ACH50) into oocytes to the offspring. However, Menanteau-Ledouble et al. (2022) declared that dietary administration of a commercially purchased β-glucan purified from the cell walls of *S. cerevisiae* for six weeks had limited effects on the resistance of *O. mykiss* to *Y. ruckeri*. These contradictory findings may be attributed to different dietary supplementation dosages, different feeding durations, life stages, and sources of β-glucan.

Poly-β-hydroxybutyrate (PBH) is a polymer compound that is produced by various microorganisms and can be hydrolyzed to β-hydroxybutyrate by enzymes secreted by the GIT of many aquatic animals and exhibits functions similar to short-chain fatty acids such as antibacterial activities (Abdel-Latif et al., 2020). Dietary PBH could be considered a prebiotic compound as it could promote the growth of healthy bacteria in the fish intestinal tract (Sui et al., 2016). The roles of dietary PBH in combating ERM in rainbow trout have been examined in many investigations (Table 5). The application of PBH for six weeks significantly enhanced the growth, digestive enzyme activities, immune functions, and resistance of *O. mykiss* fries experimentally challenged with *Y. ruckeri* (Najdegerami et al., 2017 a). Moreover, dietary applications of 2% PBH, 0.2% MOS, or their mixture for 60 days significantly increased the robustness, manifested by higher survival rates of *O. mykiss* fingerlings following their challenge with pathogenic *Y. ruckeri* (Najdegerami et al., 2017 b). Of interest, it was found that dietary 1% PBH for 70 days enhanced the serum total antibody levels and increased the survival rates of *O. mykiss* fingerlings challenged with *Y. ruckeri* infection (Najdegerami, 2020). Despite these promising results, more research is needed to clarify the timing, application schedule, and prebiotic regimens to induce adequate protection against ERM in rainbow trout.

Synbiotics

Synbiotics are a feed supplement that contains a cocktail of probiotics and prebiotics to exert synergistic effects (Abdel-Latif et al., 2022 a; Yilmaz et al., 2022). There are many investigations on the efficacy of synbiotics to boost the immunity and resistance of rainbow trout to ERM (Table 6). For example, the application of a commercial synbiotic composed of FOS, exogenous multi-enzymes, and probiotics (Probioenzyme® Px) considerably increased the mRNA transcripts of the TNF-α gene and enhanced disease resistance against *Y. ruckeri* infection in *O. mykiss* (Rastiannasab et al., 2017). Those researchers confirmed that the reported effects could be associated with the synergistic effects of the components in the tested synbiotic, which is the chief reason for stimulating the immune system to react strongly against the challenged bacterial pathogen. Similarly, it was found that a dietary supplement of 0.1% of a commercial synbiotic mixture (Celmanax®) of *S. cerevisiae* conjoined with MOS for two months considerably augmented immunity responses (serum LYZ activity and total serum antibodies) and resistance of *O. mykiss* against *Y. ruckeri* (Khodadadi et al., 2018, 2021). Another study by Ohtani et al. (2020) found that diets co-supplied with a combination of *P. acidilactici* and MOS improved the resistance towards experimental infection with *Y. ruckeri* in rainbow trout. Of interest, co-supplementation of a mixture of yeast cell wall extract, nucleotides, and vitamins to rainbow trout diets for four weeks decreased the mortalities following *Y. ruckeri* infection (Villumsen et al., 2020 a). Those researchers proposed that the prebiotic compounds indirectly helped induce the immune system by promoting the growth of probiotic bacteria in the gut. Despite this, a synbiotic cocktail comprised of *P. acidilactici* with citrus flavonoids or bacterial parabiotics did not significantly improve the ERM resistance in rainbow trout but only decreased the risk in treated groups when compared with the control group (Villumsen et al., 2020 b). Accordingly, we can conclude that synbiotic applications could augment immunity and enhance the resistance of rainbow trout against ERM. Indeed, the beneficial effects may be correlated to the synergistic effects of prebiotics and probiotics. Hence, selecting probiotics and the prebiotic substrate is essential to get the required values from synbiotics. Additionally, the interactive synergistic impact between probiotics and prebiotics should be studied in detail to determine accurate mechanisms of action for the synbiotic mixture. From the authors' point of view, colonization of the GIT of the treated fish by the probiotic and its effects on intestinal microbiota composition and intestinal immunological responses should be addressed and studied in future investigations.

Organic acids

At present, there is increasing awareness of the regular use of organic acids, salts, or their mixture in aquafeeds to enhance feed palatability, nutrient utilization, growth performance, gut health, immunity, antioxidant capacity, and disease resistance in a wide range of farmed finfish (Abdel-Latif et al., 2020; Ng and Koh, 2017). Early reports showed that dietary supplementation of immunostimulants and/or with a commercially purchased product (Mera™ Cid) containing organic acids (including propionic and formic acids) resulted in a change in the gut microbial communities in rainbow trout but induced slight protection of fish to ERM disease caused by *Y. ruckeri* infection (Jaafar et al., 2013). Some organic acids, as presented in Table 7, showed that dietary humic acid alone (0.6% humic acid for 60 days) (Yılmaz et al., 2018 b) or a combination of humic acid with other organic acids such as fulvic, ulmic, and fulfonic acids (Farmarin® XP) (Yilmaz et al., 2018 a) significantly increased serum lysozyme, phagocytic, antibacterial, and respiratory burst activities, and survival of rainbow trout after experimental challenge with *Y. ruckeri*. Consequently, Yilmaz et al. (2018 a) proposed that the dietary application of Farmarin® XP could be regarded as a possible dietary substitute for antibiotic usage to control ERM in *O. mykiss*. These effects may be associated with the impact of dietary organic acids in the modulation of the gut microbiota with the ability to reduce the viable count of the pathogenic bacteria in the gut; hence, they can increase the disease resistance abilities of the treated fish and highlighting their roles in mitigating disease outbreaks in aquaculture (Ng et al., 2015; Romano et al., 2015).

Algae

Microalgae play an essential role in the aquatic food chain and are commonly used in rearing several aquatic animals (Borowitzka, 1998). In aquaculture, they gained particular interest because of their high nutritional value, contents of bioactive ingredients such as β-carotene and astaxanthin, and their potential to replace protein sources (such as fish meal) in aquafeed (Abdel-Latif et al., 2022 b; Roy and Pal, 2015). Several microalgal species have been identified with possible applications in aquafeed (Abdel-Latif et al., 2022 c). On the other hand, macroalgae (seaweed) also gained special significance because they add nutritive value to the formulated aquafeed (Wan et al., 2019). Notably, brown seaweeds are commonly used owing to their immune-stimulating functions because of their contents of sulfated polysaccharides, which play a crucial role in enhancing the immunity and disease resistance of aquatic animals (Abdel-Latif et al., 2022 d).

Regarding the scope of the present article, there are two reports on the possible role of algal species in combating ERM in rainbow trout, as demonstrated in Table 8. It was found that dietary application of a hot water extract of the macroalga *Sargassum angustifolium*, particularly in a dose rate of 400 mg/kg diet for eight weeks, significantly increased hematological indices such as Hb, HCT, RBCs count, WBCs count, TP, and ALB content of rainbow trout (Zeraatpisheh et al., 2018). Those researchers reported the lowest CMR (46.66%) in this group compared to (80%) in the control group after the experimental challenge with *Y. ruckeri*. These results could be attributed to fucoidan in *S. angustifolium* with noticeable immunomodulatory and antioxidant effects (Borazjani et al., 2017). It seems that seaweed and its extracts and bioactive compounds are considered a vital source of several immunostimulant compounds, presenting possible advantages to the immune system of fish and their resistance against challenging pathogens (Thanigaivel et al., 2016), suggesting an alternative therapeutic strategy for controlling and managing fish diseases. In addition, sulfated carbohydrates from seaweed seem to have potential immunomodulatory effects (Wijesinghe and Jeon, 2012). The microalga *Spirulina platensis* (2.5% powder) significantly enhanced the mucosal immunity and increased the mRNA expression levels of some immune-associated genes such as *lysozyme* and *IgM* genes in rainbow trout after a 7-week feeding trial (Sheikhzadeh et al., 2019). Those authors also demonstrated the lowest CRM (32%) in spirulina-treated groups compared to 50% in the control group after the experimental challenge with *Y. ruckeri* infection. These effects could be correlated with spirulina's immunomodulatory and antioxidant roles when included in fish diets (Ragap et al., 2012; Watanuki et al., 2006).

Table 5. Prebiotic applications used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Prebiotics	Tested dietary doses	Period (days)	Hemato-immune effects[1]	Experimental infection with *Y. ruckeri* infection					References
				route	infection dose	period	Cumulative mortality (CMR; %)		
							control	treated	
Poly-β-hydroxybutyrate (PBH)	0.5, 1 and 2%	42 d	Not detected	Water bath	5.5×10^7 CFU/mL for 4 h at 14–15°C	14 d	Highest CMR%	Lowest CMR%	(Najdegerami et al., 2017 a)
PBH or mannan oligosaccharides (MOS)	(2% PHB), (0.2% MOS), or (2% PHB + 0.2% MOS)	60 d	Significant ↑ serum total antibody in PHB alone and PHB+MOS	IP injection	1.1×10^7 cells/mL	10 d	Highest CMR%	Lowest CMR%	(Najdegerami et al., 2017 b)
PBH	0.5, 1 and 2%	70 d	Significant ↑ total serum antibody titers	IP injection	1.1×10^7 CFU/mL	14 d	Highest CMR%	Lowest CMR%	(Najdegerami, 2020)

[1]MOS: mannan oligosaccharides; PHB: poly-β-hydroxybutyrate.

Table 6. Dietary synbiotic applications used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Prebiotics	Tested dietary doses	Period (days)	Hemato-immune effects[1]	Experimental infection with *Y. ruckeri* infection					References
				route	infection dose	period (days)	SR (%) or CMR (%)		
							control group	treated group	
Celmanax® (a mixture of *Saccharomyces cerevisiae* and MOS)	0.1, 0.5 and 1 %	60 d	The highest serum LYZ and total serum antibodies in 0.1% group	IP injection	1.1×10^7 CFU /mL	14 d	SR% = below 20%	SR% = 73.33% in 0.1% group	(Khodadadi et al., 2018, 2021)
Probioenzyme® (a mixture of multi-enzymes, FOS, and probiotics)	0.3 and 0.5 g/kg diet	60 d	Significant ↑ expression of TNF-α gene No differences in IL-1***β*** expression	Water bath	2×10^8 CFU /mL	20 d	CMR% = 44.9%	CMR% = 29.3% in 0.5 g/kg group	(Rastiannasab et al., 2017)

[1]CMR: cumulative mortality; IL-1β: interleukin-1 beta; LYZ: lysozyme activity; MPO: myeloperoxidase; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; SR%: survival rate percent; TNF-α: tumor necrosis factor alpha.

Table 7. Dietary organic acids used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Dietary supplements	Tested dietary doses	Period (days)	Hemato-immune responses[1]	Experimental infection with *Y. ruckeri*				References
				infection dose	period (days)	SR (%)		
						control group	treated group	
Humic acid	0.3%, 0.6% and 1.2%	60 d	No differences RBCs, Hb, HCT, TP, ALB, and GLO Significant ↑ potential killing activity, PA, PI, and LYZ	3×10^8 CFU/mL	20 d	41.18%	45.10%, 80.39% and 49.02%	(Yilmaz et al., 2018 a)
Farmarin® XP	0.1, 0.2 and 0.4%	60 d	No differences in RBCs, Hb, HCT, TP, ALB, GLO, PA, and MPO Significant ↑ RBA	3×10^8 CFU/mL	20 d	49.02%	54.90, 72.55% and 62.75%	(Yılmaz et al., 2018 b)

[1]ALB: albumin; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; lgM: immunoglobulin M; LYZ: lysozyme activity; MPO: myeloperoxidase activity; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBCs: red blood cells; SR%: Survival rate percent; TP: total protein; WBCs: white blood cells.

Table 8. Dietary algal species used to increase immunity and resistance against yersinosis caused by *Y. ruckeri* infection in rainbow trout

Algal supplement	Tested dietary doses	Period (days)	Hemato-immune responses[1]	Experimental infection with *Y. ruckeri*				References
				infection dose	period (days)	CMR (%)		
						control group	treated group	
Sargassum angustifolium	50, 100, 200 and 400 mg /kg	56 d	Significant ↑ Hb, HCT, RBCs, WBCs, TP, and ALB in 400 mg/kg group No differences in LYZ and complement system	10^8 cells /mL	10 d	80%	66.66% in 50 mg/kg group 46.66% in 400 mg/kg group	(Zeraatpisheh et al., 2018)
Spirulina platensis	2.5% and 5%	49 d	Significant ↑ expression of immune-related (*lysozyme* and *IgM*) genes	1×10^7 CFU/mL	12 d	50%	32% in both 2.5 and 5%	(Sheikhzadeh et al., 2019)

[1]ALB: albumin; CMR: cumulative mortality; GLO: globulin; Hb: hemoglobin; HCT: hematocrit; IgM: immunoglobulin M; LYZ: lysozyme activity; MPO: myeloperoxidase activity; PA: phagocytic activity; PI: phagocytic index; RBA: respiratory burst activity; RBCs: red blood cells; TP: total protein; WBCs: white blood cells.

Vitamins

Vitamins are considered functional nutrients that contribute positively to maintaining the sustainability of salmonid aquaculture by promoting health status and welfare, improving growth, and nutrient utilization, boosting immunity and disease resistance, and combating stressors (Liu et al., 2022). Earlier studies showed that dietary supplementation with vitamin E (806 mg/kg diet) for 22 weeks significantly reduced the cumulative mortalities of *O. mykiss* experimentally exposed to virulent *Y. ruckeri* (Furones et al., 1992). Those researchers proposed that dietary vitamin E positively enhanced innate immunity and the fish's resistance to bacterial infection. Moreover, it was noticed that the kinetics of specific immune antibody responses following vaccination against ERM disease caused by *Y. ruckeri* infection was significantly enhanced when *O. mykiss* were fed diets supplied with yeast glucan and vitamin C for two weeks and then returned to the control diet for four weeks (Verlhac et al., 1996), suggesting the immunomodulatory effects of these nutrients and their roles in maintaining fish health. Another study illustrated that combined dietary supplementation of vitamins C and E decreased the cumulative mortality of *O. mykiss* following the challenge with *Y. ruckeri* (Wahli et al., 1998). Of interest, those researchers highlighted that the highest mortalities were noticed in the fish group experimentally infected with *Y. ruckeri* and fed double-deficient or low diets of both vitamins, suggesting their positive effects on fish immunity and disease resistance.

Nanomaterials

In recent years, nanotechnology has utilized dietary nutrients to produce nanofood products. Nanotechnology presents an ample number of beneficial applications that can significantly transform aquaculture into a brilliant, well-developed industry (Fajardo et al., 2022). The topmost advantages that will be gained from the use of these materials in nutraceuticals and functional foods are their roles to i) increase the absorption and bioavailability, ii) enhance solubility and dispersion, and iii) improve stability against degradation, especially during processing (Chen et al., 2006; Pathakoti et al., 2017). Moreover, nanomaterials prepared from essential nutritional elements were more effective and valuable than traditional forms due to their high bioavailability, which will, in turn, facilitate nutrient utilization (El Basuini et al., 2016). On the other hand, several nanomaterials displayed potential *in vitro* antibacterial effectiveness against several fish-associated bacterial pathogens, including *Y. ruckeri*, such as chitosan nanoparticles (CHNPs) (Ahmed et al., 2020), green-synthesized silver nanoparticles using *Verbena officinalis* leaf extract (Sanchooli et al., 2018), and zinc oxide nanoparticles (Shaalan et al., 2017).

With particular emphasis, many investigations used nano-scale applications to enhance immunity and disease resistance; hence, they can be included in disease control strategies (Sabo-Attwood et al., 2021). In this concern, dietary administration of nano-chitosan-loaded clinoptilolite (especially at a dose of 0.05 g /kg diet) for 70 days noticeably upgraded the growth parameters and boosted the immune functions of rainbow trout manifested by the elevated serum bactericidal activities of *O. mykiss* against *Y. ruckeri* compared with the control (Khani Oushani et al., 2020). Another study by Ahmed et al. (2021) reported the potential immunomodulatory roles of dietary marine biosourced CHNPs after a short-term application of a dose rate of 5 g/kg dry feed for 21 days. The results of this study indicated that dietary CHNPs performed a significant role in enhancing the resistance of rainbow trout against ERM disease. Those researchers suggested that dietary CHNPs exerted their effects via modulating the antibacterial defensive mechanisms and intestinal immune responses of rainbow trout against *Y. ruckeri* infection. Recently, it was found that a combination of copper nanoparticles with vitamin C for 60 days in diets significantly increased growth performance, enzymatic antioxidant mechanisms, immune indices (serum LYZ activity and ACH50), and survival rates of rainbow trout after being experimentally challenged with *Y. ruckeri* infection (Delavari et al., 2022). Those authors proposed that this combination generated synergistic effects resulting in improved nutrient utilization, metabolic efficiency, and intestinal histoarchitecture and subsequently enhanced the antioxidant capacity and immune responses in rainbow trout. From our point of view, we found that nanotechnology demonstrated significant applications and promising results in improving immunity and disease resistance, which will play a vital role in aquaculture. However, more research studies are needed to evaluate different dietary dosages for a longer feeding duration. Moreover, the detailed antibacterial, growth-promoting, and immunomodulatory mechanisms of these materials warrant further investigations.

Miscellaneous group

Recent research found that the application of medicinal plants fermented with probiotic bacteria in aquaculture nutrition was beneficial not only to upgrading the nutritional quality and bioactive components of the formulated diets but also to improving the growth performance and immunity of fish with promising results (Wang et al., 2022). In this concern, Niazi et al. (2023) indicated that dietary application of 0.8% and 1% of the fermented medicinal plants such as *Curcuma longa* and *Camellia sinensis* with the probiotic bacterium known as *Lactobacillus brevis* significantly enhanced the growth performance, digestive enzyme activities and increased the serum BA, immunoglobulin, TP, GLO, and skin mucus alkaline phosphatase in rainbow trout compared to the control group, demonstrating its potential role in augmenting the growth and mucosal and serum immune functions of the treated fish. Of interest, those authors also reported increased resistance of *O. mykiss* challenged with *Y. ruckeri*, whereas the highest survival rate was 66.7% and 83.3% in groups fed 0.8% and 1% of the probiotic-fermented plants compared to the controls. The authors proposed that these results may be conjoined with the encouraging roles of combining probiotics and medicinal herbs on fish's immune system (Wei et al., 2022). Moreover, the high protection rate may also relate to the effective roles of herbal plants and probiotics in activating innate immunity and further promoting resistance to challenging pathogens (Wang et al., 2022). Another attribution is the role of probiotic-fermented plants in strengthening the functions of the fish's intestinal barrier via improving the intestinal histomorphology and modulation of the GIT microflora by inhibiting the development of harmful and pathogenic bacteria and boosting the colonization of beneficial gut flora, henceforth boosting intestinal health status, and consequently improving the host immunity responses (Meng et al., 2023). These hypotheses provide theoretical support for applying herbal plants fermented with probiotics in aquaculture. The prime fermentation technology of medicinal herbs could support the conversion of the functional bioactive compounds present in medicinal plants through probiotic bacteria (Niazi et al., 2023). Although promising results were obtained in this study, there is still a gap in illustrating the types of bioactive compounds that resulted in the fermentation procedure and their actual roles and effects in improving fish immunity and resistance, which will require additional future research studies and should not be underestimated.

Conclusions, limitations, and future perspectives

ERM is an important bacterial disease affecting rainbow trout and other salmonids, causing significant mortalities and economic losses. The use of antibiotics to control bacterial infections has been restricted and became illegal in aquaculture by several national and international regulations because of the problem of the development of antibiotic resistance, antibiotic residues in aquaculture products, and their negative impacts on aquatic environments. Therefore, finding alternatives is considered an essential step to pave the way for limiting antibiotic usage and endorsing sustainable aquaculture. During the last decades, great efforts and research studies have been conducted to find safe, effective, suitable, and environmentally friendly alternatives to antibiotics to develop feed-based non-antibiotic strategies for tackling the negative impacts of ERM in rainbow trout, such as vitamins, probiotics, prebiotics, synbiotics, phytobiotics, phytochemicals, EOs, algae (microalgae and macroalgae), organic acids, and some new feed-based nanomaterials. According to the literature, these feed supplements beneficially improved the functionality of aquafeeds prepared for feeding rainbow trout. Indeed, the published results declared that these supplements could ensure an antibiotic-free aquatic environment. Moreover, results elucidated that these approaches beneficially helped to boost immunity, enhance resistance, provide considerable protection, and reduce mortalities resulting from experimental ERM in rainbow trout.

Several limitations are still present. For instance, we found that future research studies are encouraged to declare in-depth the mechanisms by which these materials induced their effects to combat the negative impact of ERM. More field-based experiments are also needed to determine the possibility of large-scale applications of these materials. Field experiments might provide different findings than those presented in laboratory-based experiments. Limitations of these treatments, their commercial accessibility, or economic impacts in terms of cost-benefit ratios have not been discussed in the literature; however, their effects in the application of these strategic control methods are important and should not be ignored. Perhaps the most important limitation of nutritional control of ERM disease is the question of when to apply it to fish and how long the effect lasts. There is no discussion of when disease typically occurs on farms or how these prevention strategies would be implemented.

Future perspectives should be directed towards combining two or more feed supplements from the above categories to provide complementarity non-antibiotic approaches for building a strategic direction to combat ERM in rainbow trout. Moreover, innovative nanotechnology applications are also needed to improve the protection of rainbow trout via more relatively safe, applicable, practical, and cost-effective materials. Besides, more and more functional feed supplements with immunostimulatory effects should be explored to diversify the types of feed supplements used to enhance the functionality of aquafeed used for farming rainbow trout. Lastly, new non-antibiotic approaches should also be tested in various fish farms, such as ozone-nanobubbles (Dien et al., 2023), which could oxygenate rearing waters, help to improve fish growth, reduce the pathogen loads in aquaculture facilities, and consequently ensure antibiotic-free and pathogen-free aquaculture.

Author contributions

All authors have read and agreed to the published version of the manuscript. All authors have contributed equally and substantially to the work reported.

Data availability statement

Data in the present review article is available from the corresponding author under reasonable request.

Conflicts of interest

The authors declare no conflict of interest.

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