Review Article

Probiotic, Paraprobiotic, and Postbiotic as an Alternative to Antibiotic Therapy for Lactococcosis in Aquaculture

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ABSTRACT

Studies describing antagonistic activity and disease resistance efficacy of potential probiotics towards lactococcosis caused by *Lactococcus garvieae*, *Lactococcus lactis*, *Lactococcus piscium*, and *Lactococcus raffinolactis* are limited. Most studies have focused on lactic acid bacteria (LAB), and less attention has been paid to *Bacillus* probiotics or other gram-positive or gram-negative members. *Lactobacillus*, *Lactococcus*, *Leuconostoc*, and *Enterococcus* are the most common genera of LAB tested towards *L. garvieae* either in in vitro or in vivo assays, and the obtained results are promising. Although strains of *Flavobacterium*, *Pseudomonas*, *Aeromonas*, and *Vibrio* genera have shown antibacterial activity against *L. garvieae*, further work is required to confirm such inhibition activity, particularly by disease resistance bioassays. recently, gram-positive or gram-negative bacteria strains have demonstrated antimicrobial inhibition towards *L. garvieae* in postbiotics, but details of their mode of action warranted further studies. This review addresses the probiotic therapy for lactococcosis in aquaculture and discusses the present gaps.

Keywords: Probiotic, Lactococcosis, Aquaculture, Postbiotic, Paraprobiotic

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1. Introduction

Developing new and complex culture systems has increased the frequency of disease outbreaks in aquaculture (Abarike et al., 2018). Therefore, environmentally-friendly solutions have emerged as an alternative to antibiotic therapy (Kavitha et al., 2018). Probiotic therapy has been recognized as a perfect environmentally-friendly alternative to antibiotic therapy in medicine and veterinary medicine, and for aquaculture, numerous studies have been carried out to assess possible efficacy and potency of various bacterial species of both gram-positive and gram-negative members against pathogenic bacteria in aquaculture (Ringø et al., 2018; Soltani et al., 2019; Ringø et al., 2020; James et al., 2021; Nayak, 2021; Van Doan et al., 2021). Fish lactococcosis, particularly caused by *Lactococcus (L.) garvieae*, has become a serious recurring bacterial disease in farmed fish, and due to the disease pathogenesis, its treatment is often temporary and, in some cases, ineffective. Thus, probiotics or medicinal herbs can be considered a suitable replacement tool for reducing morbidity and mortality in farmed fish (Soltani et al., 2021). This review addresses an overview of published data on the efficacy of probiotics against aquaculture lactococcosis, particularly caused by *L. garvieae*, and discusses the present gaps. Table 1 presents detailed information for a quick study of the available data.

The disease

To avoid the overlap, we encourage the readers to refer to a comprehensive review on the pathogenesis of lactococcosis entitled "lactococcosis a re-emerging disease in aquaculture: disease significant and phytotherapy" conducted by Soltani et al. (2021). Lactococcosis is a systemic bacterial disease inducing a general hemorrhagic sign in susceptible fish species such as rainbow trout, tilapia, Asian sea bass, and grouper. The affected fish exhibit anorexia, darkening of the skin, sluggish movement, and abnormal behaviors like erratic and spiral swimming, swollen abdomen, anal prolapsus, lateral or bilateral exophthalmia, cataracts, congestion of the internal organs, and accumulation of turbid ascitic fluid in the peritoneal cavity (Figures 1).

Probiotic therapy for lactococcus garvieae infection

Lactic acid bacteria (LAB)

When strains of potential probiotics, including *L. lactis* subsp. lactis CLFP 100, *L. lactis* subsp. *cremoris* CLFP 102, *Lactobacillus (Lb.) curvatus* CLFP 150, *Leuconostoc (Leu.) mesenteroides* CLFP 196, and *Lb. sakei* CLFP 202 obtained from salmonid fish were assessed for their abilities of adhesion reduction (%) of *L. garvieae* in fish mucus by a competitive exclusion assay; the first three strains demonstrated more adhesion reduction than the last two strains (Balcazar et al., 2007). Of these 5 LAB, only *Leu. mesenteroides* CLFP 196 (Spain type collection), however, exhibited an antagonistic activity towards *L. garvieae* under in vitro assay. In addition, strains of *L. lactis* subsp. *cremoris* DSM 20069 (Braunschweig, Germany) revealed an inhibitory function towards *L. garvieae* under in vitro challenge.

Of 53 LAB strains isolated from silverside (*Odontesthes platensis*) intestine, only 4 isolates were inhibitory against *L. garvieae* under in vitro assay, with the strongest inhibition activity seen by *L. lactis* TW34 that could be in part due to its acidification and hydrogen peroxide production as well as its highly thermostable and pH tolerated secreted bacteriocin (Sequeiros et al., 2010). However, the correlation between the in vitro work and the in vivo data is necessary to judge the level of efficacy and or the potency of the *L. lactis* strain against pathogenic agents, such as *L. garvieae.* Of 335 endogenous bacterial strains isolated from rainbow trout intestine, only strains of *Lactobacillus*, *Lactococcus*, and *Leuconostoc* genera exhibited antagonistic activity against *L. garvieae* by agar spot assay (Pérez-Sánchez et al., 2011a). Although these strains revealed good survival at low pH and high bile concentration conditions plus a good adhesion character, they require further evaluation in in vivo challenge with *L. garvieae* infection.

Using a disk diffusion assay, *Enterococcus (Ent.) thailandicus* B3-22 isolated from the intestine of grey mullet (*Mugil cephalus*) was inhibitory against four strains of *L. garvieae* (strains E-9, E-10, 4103, 1–4, cb3-4) giving 7.5-85 mm zone of inhibition (Lin et al., 2013), but further research is required to elucidate the probiotic efficacy under in vivo disease resistance bioassay.

Among diverse bacterial isolates with different origins, including fish and shellfish, the following species demonstrated antagonistic activity towards fish pathogenic *L. garvieae* through their bacteriocin productions: *Ent. faecium* (isolated from sardine, *Sardina pilchardus* and Albacore, *Thunnus alalunga*), *Weissella cibaria* (isolated from cod, *Gadus morhua*), *Ent. faecalis* (isolated from Atlantic salmon, *Salmo salar*, European seabass, *Dicentrarchus labrax*, rainbow trout, *Oncorhynchus mykiss*, swimcrab, *necora puber*, and Norway lobster, *Nephrops norvegicus*), *Lb. sakei* subsp. *carnosus* (isolat-

Figure 1. Clinical signs of lactococcosis in various commercial fish species

A) Rainbow trout with typical bilateral exophthalmia and beginning of skin pigmentation

B) Explosion of the eye and darkening of the body (Soltani et al., 2021)

C) Nile tilapia with exophthalmia, hemorrhage, and cloudiness in the eyes, skin erosion and scale detachment (Abu-Elala et al., 2020)

ed from common ling, *Molva molva*), *Pediococcus pentosaceus* (isolated from common cockle, *Cerastoderma edule*, European squid, *Loligo vulgaris*), *Lb. curvatus* subsp. *curvatus*, *Ent. faecium* (isolated from common octopus, *Octopus vulgaris*, megrim, and *Lepidorhombus boscii*), *L. lactis* subsp. *cremoris*, and *Leu. mesenteroides* subsp. *cremoris* (with unknown origin) (Muñoz-Atienza et al., 2013). An autochthonous *Lb. plantarum* FGL0001 originally isolated from the hindgut of olive flounder, was inhibitory against *L. garvieae* with a 14-mm inhibitory zone (Beck et al., 2015). However, further research is needed to confirm the disease-resistance ability of this probiotic against lactococcosis infection. While *Lb. rhamnosus* isolated from the intestine of diseased fish exhibited no antagonistic activity against *L. garvieae* (Akayl et al., 2020), *L. lactis* RBT18, obtained from cultured rainbow trout exhibited antagonistic activity against *L. garvieae* (Contente et al., 2020). However, the disease resistance data for these LAB warranted future work to show a correlation between in vitro and in vivo results. Six autochthonous bacterial strains with probiotic potential, including *Ent. faecalis*, *Ent. hirae*, *L. lactis*, *Ped. pentosaceus*, *Staphylococcus (Staph.) hominis*, and *Staph. saprophyticus* isolated from the intestine of tambaqui (*Colossoma macromum*) can inhibit the growth of the pathogenic *L. garvieae* under in vitro assay as well as adhesion to the fish intestinal mucosa of tambaqui (Kotzent et al., 2021). However, further research is required to demonstrate their clinical efficacy measured by disease resistance against lactococcosis caused by *L. garvieae*.

It has been shown that the host-derived LAB with activity against fish pathogens has potential probiotic ability in some fish farming, such as rainbow trout, as an alternative or balancing strategy to antibiotics and vaccines for disease prevention or protection. In their research work by Araújo et al. (2015a), 55 isolates of *L. lactis* originally obtained from rainbow trout intestine and the rearing environment exhibited antibacterial activity against four virulent strains of *L. garvieae*, suggesting trout and its rearing environment as potential sources for the isolation of LAB with activity towards fish pathogenic *L. garvieae*.

There are limited reports about in vivo effectiveness of LAB bacteriocin (nisin Z) production as a mechanism to protect fish against *L. garvieae* infection. The bacteriocin nisin Z produced by *L. lactis* TW34 isolated from marine fish (*O. platensis*) could inhibit the growth of fish pathogenic *L. garvieae* at 5 and 10 AU/mL as minimum inhibitory concentration and minimum bactericidal concentration, respectively (Sequeiros et al., 2015). The bacteriocin could reduce the viable cell counts of *L. garvieae* by 6 times, indicating its bactericidal mode of action. In their study by Araújo et al. (2015b), the bacteriocinogenic strain of *L. lactis* subsp. *cremoris* WA2-67 isolated from rainbow trout intestine was more protective than non-bacteriocinogenic strain against infection by *L. garvieae*, indicating the relevance of nisin Z production as an anti-infective mechanism. When rainbow trout fed bacteriocinogenic strain *L. cremoris* WA2-67 (10^6 CFU/g feed) for 3 weeks and challenged with *L. garvieae*, survival in treated fish was 30% higher than fish fed with non-bacteriocinogenic knockout isogenic mutant strain (80% vs 50% survival). The control fish revealed 27.5% survival (Araújo et al., 2015b).

When the inhibitory activity of enterocin AS-48 obtained from *Ent. faecalis* UGRA10 was tested against 3 strains of *L. garvieae* exhibited in minimum bactericidal concentrations of 7.81-15.62 µg/mL (Baños et al., 2019). The enterocin at 25-100 µg/mL amount could also reduce 10^8 CFU/mL of *L. garvieae* within 2-10 hours post-exposure, but it showed no side effect on the rainbow trout cell line. One-month feeding rainbow trout with probiotics at 10^8 CFU/g feed made 50% survival, significantly higher than control fish. Interestingly, when intraperitoneally infected fish with *L. garvieae* were subjected to a regular bath treatment with the probiotic enterocin, they demonstrated higher survival (60%), suggesting a feasible protective effect by the *Ent. faecalis* and its bacteriocin towards *L. garvieae* infection. Thus, it could be considered an alternative to antibiotics for disease control in aquaculture.

Of 98 LAB isolated from rainbow trout intestines, only 10 isolates demonstrate satisfactory survival at low pH, high bile concentration, and adhesion character inhibitors against *L. garvieae*. However, only strains of *L. lactis* subsp. *lactis* M17 2-2 and *Lb. sakei* 2-3 were assessed for disease resistance where rainbow trout fed these probiotics at 10^8 CFU/g feed for 3 weeks. In other words, a significant increase was seen in the survival rates, i.e. 89.3% and 75% after the challenge with *L. garvieae* infection, compared to 46.4% survival in control fish (Didinen et al., 2017).

Strains of *Lb. acidophilus* and *Lb. bulgaricus* originally isolated from Barbus (*Barbus grypus*) exhibited an antagonistic activity towards *L. garvieae* (Mohammadian et al., 2019), and when rainbow trout were fed with these autochthonous probiotics each at 5×10^7 CFU/g feed demonstrated significantly higher protections of 63.71% and 51.56%, respectively, after being challenged with *L. garvieae* infection compared to 26.7% survival in the control fish. Such protection was partly due to an enhancement in innate immune responses, including serum lysozyme and complement activities, and upregulation of cytokine and growth genes measured by the authors. In addition, an improvement in growth performance and better probiotic colonization in fish intestines, plus an increase in the activity of fish digestive enzymes (amylase, trypsin, lipase, and alkaline phosphatase), were seen in the fish fed both probiotics.

One-month feeding rainbow trout with *Leu. mesenteroides* CLFP 196 and *Lb. plantarum* CLFP 238 isolated from salmonids at 10^6 CFU/g feed individually revealed no significant difference in fish growth between treated and control fish, but these LAB could increase fish survival up to 46% and 54% after *L. garvieae* challenge, respectively, compared to 22% survival rate in the control group (Vendrell et al., 2008). However, it is uncertain whether such protective efficacy was due to bacterial competition in the host gut or stimulation of the fish immune system.

Feeding rainbow trout with Lb. plantarum, *L. lactis*, and *Leu. mesenteroides* each at 10^6 CFU/g feed for 36 days demonstrated protections of 87.5%, 77.5%, and 67.5%, respectively, against *L. garvieae* infection compared to 67.5% survival in the control fish, suggesting host-specific probiotic is one of the factors that can influence the probiotic efficacy and or potency in target host as the diet containing Lb. plantarum exhibited only significantly higher protection to *L. garvieae* challenge than the other two LAB. This finding was supported by a significant up-regulation of *interleukin (IL)-1b, IL-10*, and *TNF-α* genes, plus higher mRNA levels of IL-10, IL-8, and IgT in the fish-fed *Lb. plantarum* post-*L. garvieae* challenge indicating a good stimulation of the fish immune responses (Pérez-Sanchez et al., 2011b). The author's data also showed that direct probiotic host interactions with the intestine are not always essential to stimulate fish immune responses to induce disease resistance in fish.

Olive flounder (*Paralichthys olivaceus*) intraperitoneally (IP) injected with *Ent. faecium* at 10^8 cells/fish as a potential probiotic before IP challenge with *L. garvieae* demonstrated an improvement in the fish immune responses measured by activities of lysozyme, complement, and protease, and up-regulation of *TNF-α* and *IL-1β* genes (Kim et al., 2012), showing *Ent. faecium* ability to protect fish from lactococcosis caused by *L. garvieae* through enhancing the fish immune responses. However, the disease-resistance bioassay warranted further research to confirm probiotic efficacy in the host.

There is little information regarding the efficacy of LAB in the form of a combination of lactococcosis caused by *L. garvieae*. Five weeks of feeding rainbow trout kefir (containing *Lb. kefiranofaciens*, *Lb. kefiri*, *Lb. parakefiri*, *Lb. acidophilus*, *Lb. helveticus*, *Lb. casei*, *Lb. bulgaricus*, *Bifidobacterium* spp., as well as *Saccharomyces* and *Kluyveromyces*) at 2%, 5%, and 10% enhanced total leukocytes, serum lysozyme activity, total serum protein, and IgM, especially in fish fed with higher dosage (10%) (Uluköy et al., 2016). When treated fish were challenged with *L. garvieae* infection, higher survivals (28%-52% survival rate) were obtained against *L. garvieae* challenge than *Yersinia ruckeri* infection (7.69% survival rate).

According to the literature, there is only one report demonstrating the anti-*L. garvieae* activity by the potential LAB isolated from the shrimp gut. In the study by Ben Braïek et al. (2017), a thermostable and an enterocin P producer *Ent. lactis* Q1 with a bactericidal mode of action isolated from fresh shrimp samples (*Penaeus vannamei*) exhibited antibacterial activity against *L. garvieae* but there are no data on its clinical efficacy in lactococcosis either in fish or in crustaceans.

Bacillus

In a study by Li et al. (2019), under in vitro challenge, *Bacillus velezensis* strain K2 isolated from the intestinal tract of hybrid grouper (*Epinephelus lanceolatus*×*E. fuscoguttatus*) inhibited the growth of *L. garvieae*, but no data on the in vivo experience work is available. Similarly, a strong inhibitory activity (3-4.3 cm in diameter) by *Bacillus subtilis* was seen against *L. garvieae* isolates obtained from the internal organs of the diseased fish (Akayl et al., 2020). *B. velezensis* strain JW isolated from carp intestine was inhibitory against *L. garvieae* and modulated goldfish immunity at various concentrations. Still, more studies are required to assess the disease resistance of treated fish to lactococcosis caused by *L. garvieae* (Yi et al., 2018). A two-week oral administration of *Bacillus* sp. JB-1 isolated from rainbow trout in the same fish species at various doses (10^3, 10^6, 10^8, 10^{10} cells/g feed) exhibited 88%, 84%, 100%, and 100% survival rates, respectively, in *L. garvieae* challenge compared to 20% survival rate in the control fish (Brunt et al., 2007). The *Bacillus* sp. was, however, more protective at higher doses than lower ones, indicating the dosage optimization effectiveness of the probiotics in disease resistance towards *L. garvieae* infection in fish. Such increased protections induced by probiotic *Bacillus* sp. in the treated trout could be partly due to the enhancement of the fish's innate immune responses, i.e. phagocytosis, respiratory burst, and lysozyme activity of serum and mucus and total protein.

Other potential probiotics

Among various gram-positive and gram-negative bacterial strains isolated from intestine of juvenile Japanese flounder (*Paralichthys olivaceus*), their live diets (*Artemia nauplii*), and rearing water, strains of *Flavobacterium*, *Pseudomonas*, *Aeromonas*, and *Vibrio* genera exhibited antibacterial activity against *L. garvieae* ATCC in a double-layer assay (Sugita et al., 2002). However, there is no data regarding the clinical efficacy of these gram-negatives towards lactococcosis caused by *L. garvieae* and, thus, warranted further research. In a report by Brunt and Austin (2005), rainbow trout fed probiotic *Aeromonas sobria* GC2 obtained from carp intestine (*Cyprinus* sp.) at 5×10^7 cells/g feed for 2 weeks stimulated the fish immune responses, including an increase in leucocyte population and enhancement in phagocytosis and respiratory burst measured by the authors. After challenging the treated fish with *L. garvieae* infection, a 98%-99% survival rate was obtained in the treated fish compared to a 10% survival rate in the control group. The higher (10^{10} cells/g feed) or lower (10^3 cells/g feed), however, presented lower survival rates (39%-60%) in the treated fish compared to fish fed *A. sobria* at 106-10^8 cells/g feed. In the subsequent research by Brunt et al. (2007), oral administration of the same strain of *A. sobria* GC2 at 2×10^8 cells/g feed in rainbow trout for 2 weeks again resulted in complete protection (100% survival rate) from *L. garvieae* challenge compared to 8% survival rate in the control fish, suggesting a dose optimization efficacy of *A. sobria* in the form of probiotic at concentrations ranged from 10^7 to 10^8 cells/g feed as an

Table 1. Probiotics, paraprobiotics, and postbiotics used as an alternative to antibiotic therapy for lactococcosis in aquaculture

Probiotics	Microbial Supplementation	Origin/Source	Efficacy	References
Gram-positive probiotic (LAB)	*Leuconostoc Mesenteroides* (CLFP 196)	Salmonidae	Antagonistic activity	Balcazar et al., 2007
	Lactococcus lactis subsp. *cremoris* (DSM 20069)	Salmonidae	Inhibitory function	Balcazar et al., 2007
	Lactococcus lactis (TW34)	Silverside (*O. platensis*)	Inhibition activity	Sequeiros et al., 2010
	Lactobacillus, Lactococcus and *Leuconostoc* spp.	Rainbow trout	Antagonistic activity	Pérez-Sánchez et al., 2011a
	Enterococcus thailandicus (B3-22)	Grey mullet (*M. cephalus*)	Inhibition activity	Lin et al., 2013
	Enterococcus faecium	Sardine (*S. pilchardus*) and albacore (*T. alalunga*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Weissella cibaria	Cod (*G. morhua*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Enterococcus faecalis	Atlantic salmon (*S. salar*), European seabass (*D. labrax*), rainbow trout (*O. mykiss*), Swimcrab (*N. puber*), and Norway lobster (*N. norvegicus*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Lactobacillus sakei subsp. *carnosus*	Common ling (*M. molva*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Pediococcus pentosaceus	Common cockle (*Cerastoderma edule*) and European squid (*L. vulgaris*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Lactobacillus curvatus subsp. *Curvatus* and *Enterococcus faecium*	Common octopus (*O. vulgaris*) and megrim (*L. boscii*)	Antagonistic activity	Muñoz-Atienza et al., 2013
	Lactococcus lactis subsp. *cremoris* and *Leu. mesenteroides* subsp. *cremoris*	Unknown	Antagonistic activity	Muñoz-Atienza et al., 2013
	Lactobacillus plantarum (FGL0001)	Olive flounder	Inhibition activity	Beck et al., 2015
	Lactococcus lactis (RBT18)	Rainbow trout	Antagonistic activity	Contente et al., 2020
	Enterococcus faecalis, *Enterococcus hirae*, *Lactococcus lactis*, *Ped. pentosaceus*, *Staphylococcus hominis* and *Staphylococcus saprophyticus*	Tambaqui (*C. macromum*)	Inhibition activity	Kotzent et al., 2021
	Lactococcus lactis	Rainbow trout	Antibacterial activity	Araújo et al., 2015a
	Lactococcus lactis (TW34)	*O. platensis*	Inhibition activity	Sequeiros et al., 2015
	Lactococcus lactis subsp. *cremoris* (WA2-67)	Rainbow trout	↑Survival rate	Araújo et al., 2015b
	Enterococcus faecalis (UGRA10)	Rainbow trout	Inhibition activity and ↑survival rate	Baños et al., 2019
	Lactococcus lactis subsp. *lactis* (M17 2-2) and *Lactobacillus sakei* 2-3	Rainbow trout	Disease resistance	Didinen et al., 2017

Probiotics	Microbial Supplementation	Origin/Source	Efficacy	References
Gram-positive probiotic (LAB)	*Lactobacillus acidophilus* and *Lactobacillus bulgaricus*	Barbus (*B. grypus*)	Antagonistic activity and disease resistance	Mohammadian et al., 2019
	Leuconostoc mesenteroides (CLFP 196) and *Lactobacillus plantarum* (CLFP 238)	Salmonidae	↑Survival rate	Vendrell et al., 2008
	Lactobacillus plantarum, *Lactococcus lactis* and *Lactococcus Mesenteroides*	Rainbow trout	Disease resistance	Pérez-Sanchez et al., 2011b
	Enterococcus Faecium	Olive flounder (*P. olivaceus*)	↑ lysozyme, complement, and protease, and up-regulation of *TNF-α* and *IL-1β* genes	Kim et al., 2012
	Lactobacillus kefiranofaciens, *Lb. kefiri*, *Lb. parakefiri*, *Lb. acidophilus*, *Lb. helveticus*, *Lb. casei*, *Lb. bulgaricus*, *Bifidobacterium* spp., *Saccharomyces* spp., and *Kluyveromyces* spp.,	Unknown	↑Total leukocytes, serum lysozyme activity, total serum protein, IgM, and ↑Survival rate of rainbow trout	Uluköy et al., 2016
	Enterococcus lactis Q1	Shrimp (*P. vannamei*)	Antibacterial activity	Ben Braïek et al., 2017
Gram-positive probiotic (Bacillus)	*Bacillus velezensis* (K2)	Hybrid grouper (*E. lanceolatus×E. fuscoguttatus*)	Inhibition activity	Li et al., 2019
	Bacillus subtilis (ATCC 6633TM)	Unknown	Antagonistic effect	Akayl et al., 2020
	Bacillus velezensis (JW)	Grass carp	Inhibition activity and immune modulation	Yi et al., 2018
	Bacillus sp. JB-1	Rainbow trout	↑Survival rate	Brunt et al., 2007
Gram-negative Probiotic	*Flavobacterium*, *Pseudomonas*, *Aeromonas*, and *Vibrio genera*	Juvenile Japanese flounder (*P. olivaceus*)	Antibacterial activity	Sugita et al., 2002
	Aeromonas sobria GC2	Carp (*Cyprinus* sp.)	↑ Leucocyte population, phagocytosis and respiratory burst, and ↑survival rate	Brunt & Austin, 2005
	Citrobacter farmer	Common carp (*C. carpio*)	↑ Lysozyme, complement, leucocytes population, and up-regulation of *IGF-1 FATP*, *γ-GTP*, *IL-1B*, *IL-8* and *IL-10* genes	Mohammadian et al., 2019
	Metschnikowia bicuspidata (MB58 and MB550)	Freshwater prawn (*M. rosenbergii*)	↑Survival rate	Sung et al., 2017
Parabiotic and postbiotic	*Aeromonas sobria*	Rainbow trout	↑Survival rate	Brunt & Austin, 2005
	Pediococcus pentosaceus (SL001)	Soil	Antibacterial activity, and ↑immune responses and ↑growth in gross carp	Gong et al., 2019
	Lactococcus lactis (RBT18)	Rainbow trout	Antimicrobial activity	Contente et al., 2020
	Lactobacillus sp. and *Leuconostoc* sp.	Rainbow trout	↑Growth, diversity of the bacterial community in the fish intestine, and survival rate	Pérez-Sánchez et al., 2020

effective dosage against *L. garvieae* infection in trout. In their study by Mohammadian et al. (2019), 2 months of oral administration of *Citrobacter farmeri* isolated from common carp (*Cyprinus carpio*) intestine in rainbow trout at 5×10^7 CFU/g feed revealed no significant difference in survival of treated fish after *L. garvieae* challenge compared to the control group. On the contrary, compared to control fish, the treated fish showed a higher enhancement in immune responses, including lysozyme, complement, leucocytes population, and up-regulation of *IGF-1*, and *FATP*, *γ-GTP* and *IL-1B* intestine genes as well as *IL-8* and *IL-10* genes. Such findings strongly suggest that evaluating the efficacy and potency of a specific probiotic is essential.

Five days feeding of *Metschnikowia bicuspidata* strains MB58 and MB550 isolated from the hepatopancreas of giant freshwater prawn (*Macrobrachium rosenbergii*) individually at MB58 and MB550 and also in combination form (both strains) induced 70.6%, 73.4%, and 100% survivals rates, respectively after challenge with *L. garvieae* infection compared to no survival in the control prawn. The findings suggest a higher efficacy of the mixed probiotics than split ones against lactococcosis in giant freshwater prawns, which could be partly due to higher activation of phenoloxidase and the total phenoloxidase level measured in the prawn-fed mixed probiotic strains (Sung et al., 2017). When the probiotics were orally used as encapsulation by alginic acid individually for 5 days, they exhibited higher survival rates in the animals fed with MB58 and MB550, i.e. 89.7% and 88% rates, respectively, than non-encapsulated ones. It is, however, essential to know such a higher survival was due to the protection of probiotics by the encapsulation or the stimulation of the animal immune system by the alginic acid (Kumar et al., 2017). Under in vitro assay, only strain MB550 was inhibitory to *L. garvieae*.

Paraprobiotics and postbiotics

In addition to the probiotics, applying paraprobiotics and postbiotics may be a viable alternative for preventing and controlling infectious diseases in aquaculture (Yao Ang et al., 2020). Paraprobiotics are prepared by inactivating bacterial/yeast biomass using high pressure, chemical agents, sonication, ionizing radiation, heat, ultraviolet radiation, chemical agents, and sonication (Vallejo-Cordoba et al., 2020). Postbiotics refer to soluble substances, including products or metabolic byproducts produced by live bacteria or secreted after bacterial lysis that can induce an immune-physiological advantage in the target host (Aguilar-Toalá et al., 2018). Besides the evidence of mechanisms that enhance the health status of fish/shellfish intestinal bacteria or probiotics, it has been shown that the viability of the bacteria may not be an essential factor in improving the health condition of the target animal (Aguilar-Toalá et al., 2018; Wegh et al., 2019). The application of paraprobiotics or postbiotics instead of probiotics has, thus, been arose as a new route to increase the health condition of the target host. However, more research is still essential to compare the benefits of probiotics, paraprobiotics, and postbiotics in aquaculture species. Limited data report the antagonistic effect or clinical efficacy of paraprobiotics or postbiotics against lactococcosis agents. Two weeks oral administration of rainbow trout with A. sobria paraprobiotic (formalin inactivated cells at 1×10^7 cells/g feed) and postbiotic (cell-free supernatant and sonicated cells each at 0.05 mL/g) exhibited survival rates of about 35% and 60%, respectively in *L. garvieae* infection compared to 30%-35% rate in the control groups (Brunt & Austin 2005), that was significantly lower than the administration of *A. sobria* in the form of probiotic measured by the same authors. This finding suggests a significant role of bacterial competitive exclusion by the live probiotic cells for adhesion reduction of the pathogenic microorganisms.

Also, cell-free supernatant (postbiotic) of *Ped. pentosaceus* SL001 isolated from soil samples was used in grass carp and demonstrated high antibacterial activity against *L. garvieae* by agar diffusion assay (Gong et al., 2019). Although this probiotic bacterium stimulated the grass cap immune system and enhanced the fish growth, further work is required to assess its efficacy in the form of postbiotic or para-probiotic in fish towards *L. garvieae* infection.

In a recent work by Contente et al. (2020), extracellular products of *L. lactis* RBT18 obtained from cultured rainbow trout gut exhibited antimicrobial activity against *L. garvieae*, suggesting the involvement of a thermostable antimicrobial compound (i.e. bacteriocin responsible for the extracellular antimicrobial activity exerted by *L. lactis)*. More in vitro and in vivo works are, however, needed to show the efficacy and safety of *L. lactis* RBT18 in the form of a probiotic in aquaculture as well as the optimization of the environmental conditions to decrease the bacteriocin oxidation and hence, bacterial pathogen resistance.

In addition, the effect of a LAB-based postbiotic, *Lactobacillus* sp., and *Leuconostoc* sp. originally isolated from rainbow trout on intestinal bacterial communities of rainbow trout and its capacity against *L. garvieae* infection demonstrated that its use at 3.0 mg/g feed for 4 weeks was superior in terms of growth, diversity of the bacterial community in the fish intestine, and survival rates (87.5% in the treatment vs 72.8% the control fish) after challenging fish with *L. garvieae* infection (Pérez-Sánchez et al., 2020). The postbiotic was obtained as a fermented food product composed of soy and alfalfa flour, in which two LAB were added in similar concentrations. Under in vitro assay, these LAB were also antagonistic towards *L. garvieae*. In the next study, a 30-day dietary paraprobiotic, *Lactobacillus* sp., previously isolated from rainbow trout, exhibited an increase in diversity and composition of the bacterial community (increase in phyla Tenericutes, Spirochaetes, and Bacteroidetes and a decrease in Fusobacteria) in the intestine of treated rainbow trout than in the control fish (Mora-Sa'nchez et al., 2020). Furthermore, significantly higher survival (75%) was seen in treated fish challenged with *L. garvieae* compared to control fish (52.5%), suggesting an eco-friendly strategy for the prevention and control of infection by *L. garvieae* in aquaculture through the application of dietary para-probiotic supplementation. The ability of paraprobiotics or postbiotics to modify the intestinal microbiota, modulation of animal immune functions, and increase disease resistance to infectious diseases suggest that their dietary supplementation may be a desirable alternative to probiotics, thus, avoiding potential hazards use of probiotics that are live microorganisms. In other words, some criteria, including cell viability in feed, shelf-life, the efficacy of gut colonization, antibiotic resistance due to horizontal gene transfer, or level of virulence, are some major matters associated with the application of probiotics that have minimum or no application for paraprobiotics or postbiotics. In addition, paraprobiotics can be considered safer (e.g. in the case of the immunosuppressed host) and require minimum regulatory requirements than probiotics (Teame et al., 2020). Despite the use of paraprobiotics raising a promise in improving aquaculture practices, more research is required to show their efficacy and potency in modulating commercial aquatic animal gut microbiomes at different life stages, especially early developmental stages. Thus, a question is whether the effectiveness and potency of a paraprobiotic or postbiotic of *L. garvieae* are similar to the inactivated whole-cell vaccine. Using inactivated whole cells in vaccines is one of the best ways to reduce finfish morbidity and mortality by *L. garvieae* infection (Vendrell et al., 2008; Zaheri-Abdevand et al., 2021). Such inactivated vaccines are considered postbiotic or paraprobiotic. It is, however, notable that there may be a large difference between postbiotic *L. garvieae* strains and *L. garvieae* strains used in the form of whole-cell inactivated vaccine because the efficacy and potency of the killed cell vaccines are associated with the level of immunogenicity criteria (e.g. antigens with the immunogenicity features) of the *L. garvieae* strains that are used for vaccine preparation. The study of the immunogenicity and virulence level of the bacterial strains are, thus, very important during the paraprobiotic selection process.

Probiotic therapy for infections by other lactococcal members

To our knowledge, no in vitro or in vivo works have reported probiotics' antibacterial activity against infections by *L. lactis*, *L. piscium*, and *L. raffinolactis* in aquaculture. Thus such a topic warranted future research works.

L. garvieae in the form of probiotic

Despite its severity as a serious aquaculture pathogen, some strains of *L. garvieae* with different origins have been assessed as potential probiotics. Of two strains of *L. garvieae* orally used in post-larvae of giant tiger prawn (*Penaeus monodon*), one strain could reduce the growth of shrimp, and another strain was not comparable to other probiotics in terms of growth and survival post-challenge with *Vibrio harveyi* and *V. parahemolyticus* (Swain et al., 2009). There are few reports of using *L. garvieae* with dairy origin as a potential probiotic for disease control against aquaculture pathogens. In a study conducted by Abdelfatah and Mahbouh (2018), a strain of *L. garvieae* of raw cow milk origin was inhibitory to *Staphylococcus aureus* under in vitro assay that could be in part due to bacteriocin (garvicin) production specifically active against other fish pathogenic strains of *L. garvieae* (Maldonado-Barragán et al., 2013). Oral application of this milk-origin *L. garvieae* strain in Nile tilapia (*Oreochromis niloticus*) at 10^7 cells/g feed for 10 days exhibited a higher survival rate (50%) in treated fish after the challenge with *Staph. aureus* infection compared to a 10% survival rate in the control one. Before the challenge test, no evidence of the disease was also seen in the fish-fed probiotic strains of *L. garvieae* isolated from giant freshwater prawn gut was inhibitory to *V. parahaemolyticus*, *V. alginolyticus*, and *A. hydrophila* by diffusion assay (Azahar et al., 2018). Still, no data on its in vivo disease resistance against these aquaculture pathogens is available.

The recent idea of using different types of agro-industrial waste as a cheap and fermentable carbon source for LAB, e.g. *L. garvieae,* has induced a new source of feed supplements for aquaculture. No data is available on the symbiotic potential of *L. garvieae* with carbohydrates from organic waste. In a recent work conducted by Patel and Patel (2020), 4 strains of *L. garvieae* isolated from tilapia (*O. niloticus*) (strains B2 and B3) and Japanese threadfin bream (*Nemipterus japonicus*) (R4 and R5) with ability to tolerate 7% sodium chloride, 3% bile salt, and broad range of pH (2–9) demonstrated the fermentation of the indigestible polysaccharides of peels of pineapple, orange, lemon, sugarcane, pomegranate, and sweet lemon. The symbiotic combination of the probiotic and prebiotic demonstrated that *L. garvieae s*trains gave a better fermentation efficiency with orange, sweet lemon, and pineapple than with lemon, sugarcane, and pomegranate (Patel & Patel, 2020). However, the efficiency of such symbiotics on the fish's immune-physiological status and disease resistance to lactococcosis warranted future research.

2. Conclusion

Fish lactococcosis, particularly caused by *L. garvieae*, is a major recurring bacterial disease in aquaculture worldwide. Disease treatment is often temporary or ineffective; thus, probiotics can be a suitable tool for reducing morbidity and mortality in infected aquaculture farms. From the available data, probiotic therapy for fish/shellfish lactococcosis is promising. However, more research is still required to evaluate the in vitro inhibitory activity and in vivo efficacy of different available probiotics to lactococcal agents, particularly virulent strains of *L. garvieae*. Also, fish/shrimp species and size, probiotic type and preparation method, dosage optimization of probiotics, and route of probiotic administration and duration application are major factors that require more attention for probiotic therapy towards lactococcosis in aquaculture. In addition, a detailed mode of action, e.g. probiotic colonization in animal gut mucosal surfaces and its competition with potential pathogens in animal intestine plus modulation of immunity of target animal are necessary before prescribing a specific commercial product as anti-lactococcosis in aquaculture.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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مقاله مروری

پروبیوتیک، پاراپروبیوتیک و پست بیوتیک جایگزینی برای درمان‌های آنتی‌بیوتیک علیه بیماری لاکتوکوکوزیس در آبزی پروری

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چکیده

مطالعات درزمینه قدرت ضدمیکروبی و کارآیی مقاومت به بیماری‌ها در مورد پروبیوتیک‌ها بر علیه بیماری لاکتوکوکوزیس با عوامل لاکتوکوکوس گارویه، لاکتوکوکوس لاکتیس، لاکتوکوکوس پسیوم و لاکتوکوکوس رافینولاکتیس اندک بوده است. در میان مطالعات انجام‌شده بیشترین تمرکز بر پروبیوتیک‌های اسید لاکتیک بوده و توجه کمتری به پروبیوتیک‌های باسیلی و سایر پروبیتیک‌های متعلق به گرم مثبت‌ها و گرم منفی‌ها شده است. جنس‌های لاکتوباسیل، لاکتوکوکوس، لوکونوستوک و انتروکوکوس متداول‌ترین جنس‌های باکتری‌های اسید لاکتیک هستند که از آن‌ها به‌عنوان پروبیوتیک علیه لاکتوکوکوس در هر دو شرایط برون‌تنی و درون‌تنی استفاده شده و نتایج امیدوارکننده‌ای داشته است. گونه‌هایی از جنس‌های آئروموناس، سودوموناس، فلاوباکتریوم و ویبریو خاصیت ضدلاکتوکوکوس گارویه داشته‌اند، اما مطالعات بیشتری به‌ویژه آزمایشات درون‌تنی نیاز می‌باشد تا خواص پروبیوتیکی آن‌ها مشخص شود. اخیراً نژادهایی از باکتری‌های گرم مثبت و گرم منفی در شکل پست بیوتیک با خاصیت ضدلاکتوکوکوس گارویه گزارش شده است، اما مکانیسم عمل آن‌ها نیازمند مطالعات بعدی است. در این مقاله مروری، خواص پروبیوتیک‌تراپی علیه لاکتوکوکوزیس در آبزی پروری بررسی شده است و نکات نیازمند مطالعه، مورد توجه قرار گرفته است.

کلیدواژه‌ها: پروبیوتیک، لاکتوکوکوزیس، آبزی پروری، پست بیوتیک، پاراپروبیوتیک

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