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Review Article

The anti-microbial and immune boosting effects of milk lactoferrin in the fish

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ABSTRACT

Lactoferrin is a glycoprotein from the transferrin family and contains N- and C- lobe which bind Fe^{3+} ion. It is detected in milk of cow, buffalo, camel and other livestock. However camel milk contains highest amount of lactoferrin. Lactoferrin boosts the immune system by protecting the host cells against bacterial and viral infections and inflammations. Activation, proliferation and regulation of the phagocytic action of immune cells are also done by the lactoferrin. The antiviral actions of lactoferrin are against both DNA and RNA viruses and inhibit viral adhesion and entry into cells and binds viral particles. The boosting host immune system by nutritional supplements such as lactoferrin prevents microbial infection into the host cells. It's proved that immune-stimulants in fish culture are useful because they can improve the immune responses and disease resistance through improving the phagocytic cells function and bactericidal and fungicidal activities. Growth promotion of lymphocytes and the production of macrophages, granulocytes, neutrophil and leucocytes is regulated by lactoferrin. Milk lactoferrin can modulate immune responses to infections; and may be a novel preventative treatment for more infections in human, animal and fish. However, it needs more researches on dosage to confirm its effects against infections in fish.

Keywords: Milk lactoferrin, anti-microbial, fish health

INTRODUCTION

Lactoferrin has the ability to chelate with two Fe^{3+}, reversibly (El-Agamy et al., 2006). It is found in high quantity in mature and colostral milk of cow, camel, sheep and goat (Berlutti et al., 2011). Its reported that lactoferrin content in bovine milk ranges from 0.02 to 0.35 mg/mL, however camel milk lactoferrin is higher than bovine milk (0.7-2.1 mg/mL) (Zhang et al., 2005). Alhaj et al. (2020) reported that the amount of camel milk lactoferrin is 10 times higher than cow's lactoferrin. Iron withholding ability of lactoferrin lead to inhibiting of the microbial growth and immuno-modulation properties (Berlutti et al., 2011). Moreover, without iron binding ability, lactoferrin interact with

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bacteria and viruses and inhibits their attachment to the cell receptors. No significant difference was seen in the anti-microbial activity of iron and non-iron binding forms of lactoferrin (Valenti and Antonini, 2005). Moreover, lactoferrin is also produced in considerable amounts by neutrophils and mucosal epithelial cells in cows, goats, horses and humans (Okubo et al., 2016). Some physiological functions of lactoferrin are including regulation of iron absorption, protection against microbial infections, anti-inflammatory and immuno-modulator properties (Gonzalez-Chavez et al., 2009), thus lactoferrin is regarded as a nutraceutical supplement. Most of the anti-microbial actions of camel milk are due to lactoferrin and immunoglobulins (Mohammadabadi et al., 2018). Lactoferrin has immuno-modulatory activities by binding to microbial particles or cell receptors and able to inhibit the infections (Kell et al., 2020).

Few studies revealed *in vitro* effects of lactoferrin on fish macrophages or the effect of the dietary lactoferrin on suppressing of stress responses and the enhancement of disease resistance in fish (Esteban et al., 2005). Lactoferrin enhances resistance against infections with *Ichthyophthirius multifiliis* in goldfish (Kakuta, 1996) and bacterial infections in rainbow trout (Sakai et al., 1993). In some other studies, dietary bovine lactoferrin could not reduce mortality in Atlantic salmon infected with *Aeromonas salmonicida* or infectious anaemia virus (Lygren et al., 1999). Positive effects of bovine lactoferrin on growth and resistance against infection with *Ichthyophthirius multifiliis* (Kakuta, 1996) in goldfish were reported. The aim of this recent review is exploring anti-microbial and immune boosting effects of camel milk lactoferrin against infections in the fish.

The anti-microbial function and immune stimulatory of milk lactoferrin: Iron withholding ability of lactoferrin is effective in inhibition of biofilm production of pathogens (Berlutti et al., 2011). The bacteriostatic activity of lactoferrin is due to binding the Fe3+, as Fe3+ for bacteria growth at the infection site will be limited and virulence, motility and biofilm formation of pathogenic bacteria will be inhibited (Gonzalez-Chavez et al., 2009) Lactoferrin has direct interaction with LPS of bacterial surfaces and damages membrane of Gram-negative bacteria (Gonzalez-Chavez et al., 2009) and lysozyme action and antibiotics drugs will be enhanced (Ellison and Gieh, 1991). Lactoferrin effects toward Gram-positive bacteria are due to binding to lipoteichoic acid and hindering the adhesion of bacteria to the cell surfaces (Serrano, 2006). The antiviral activity of lactoferrin in particular camel lactoferrin is against many viruses including enveloped and naked viruses (Berlutti et al., 2011). It inhibits the virus attachment and entry into host cells, binds virus particles and prevents infections (Queiroz et al., 2013). Lactoferrin interfere the viruses in the early phase by preventing of viral replication in the target cells (Serrano, 2006). Lactoferrin boosts the immune response and protects host cells against bacterial and viral infections (Kell et al., 2020). Also it regulates production of cytokines, chemokines and reactive oxygen species (Britigan et al., 2001), modulates activation, proliferation and motility of immune cells, induces the lytic activity and phagocytosis (Legrand, 2012) and strengthens the migration of neutrophils and leukocytes (Gonzalez-Chavez et al., 2009) thus control inflammation and immunity (Embleton et al, 2013).

The action mechanism of milk lactoferrin on immune system of fish: Immuno-stimulants enhance the immune response and disease resistance in fish culture. The most important effect of immune stimulants is modulating the phagocytic cells and increase bactericidal and fungicidal activities in the fishes (Esteban et al., 2005). Milk lactoferrin as immune regulatory agent control inflammation and immunomodulation functions (Brook, 1995) such as promotion of leucocyte growth, enhancing of hydroxyl radical production by neutrophils and increasing of phagocytosis action of monocyte and macrophage (Esteban et al., 2005).

Intensive fish culture systems cause to highly stressful environment and suppression of the immune responses in fish, thus results in increase of susceptibility to diseases (Kumari et al., 2003). Lactoferrin receptors detected on activated T and B cells, monocytes, intestinal cells, platelets cells and possess immunotropic properties with maturation of T and B cells (Adamik and Walszczyk, 1996). Lactoferrin controls growth of lymphocytes, production of macrophages, granulocytcs and neutrophil leucocytes and increase killing of intracellular parasite by murine macrophages and human monocytes (Sakai et al., 1993).

Is milk lactoferrin effective in the different fishes?

Antibiotics cause to the antibiotic resistant strains and the risks of antibiotic residues in cultured species for human (Sahu et al., 2007). Prevention of fish diseases through stimulation of the immune system is a promising approach in aquaculture (Ardo et al., 2008). Esteban et al. (2005) reported although the presence of lactoferrin in fish is still unknown, but it will have same effects to mammals. Lactoferrin suppress stress responses and enhances disease resistance in the fish. Some other studies reported that dietary bovine

lactoferrin not able to reduce mortality in Atlantic salmon infected with *Aeromonas salmonicida* (Lygren et al., 1999) and had no any effect on the specific immunity of vaccinated Asian catfish (Kumari et al., 2003). Bovine lactoferrin enhances phagocytes activation (Sakai et al., 1993, 1995) in rainbow trout and increased mucus production and leucocytes in red seabream (Kakuta et al., 1996). Positive effects of oral bovine lactoferrin were reported on goldfish growth and increased granulocytes and lymphocytes numbers in blood (Kakuta *et al*., 1996). Also disease protective effects and immuno-stimulatory of bovine lactoferrin in goldfish, seabream and rainbow trout have been reported by several researchers (Sakai et al., 1993, 1995).

Milk lactoferrin effects against bacterial infections in tilapia: Esteban et al. (2005) reported oral administration of bovine lactoferrin inhibits bacterial infection in tilapia and elevates survival after bacterial infection. Tilapia was fed diets with 10, 50, 100, and 150 mg bovine lactoferrin/Kg feed for 60 days, and then were infected with *Streptococcus agalactiae*. Lactoferrin supplementation leads to higher survival rate and suppression of bacterial growth at 24–96 h in organs. Peroxidase activity and content of leukocytes at 24 h was reduced. Moreover, after supplementing lactoferrin, it was detected in the small intestines mucosa of tilapia and due to immunomodulatory properties of lactoferrin, tilapia mortality reduced.

Milk lactoferrin effects on disease resistance in Asian catfish: Asian catfish were fed diets containing 50, 100 and 200 mg bovine lactoferrin/kg feed for 2 weeks. The results showed that supplementing lactoferrin particularly at 100 mg, significantly enhanced serum lysozyme level, decreased oxidative radical production and increased protection against *A. hydrophila* challenge. The lactoferrin not influenced specific immunity but 100 mg lactoferrin for 1 week efficiently enhanced the non-specific immunity and disease resistance in catfish. Thus it provides a useful way for protecting cultured catfish against infectious diseases. According to this study lactoferrin is one immuno-stimulant for farmed catfish and potentially combats infections and reduces mortality (Kumari et al., 2003).

Milk lactoferrin effects on immuno-modulatory properties in Atlantic salmon: Atlantic salmon were fed commercial diets with 140 mg bovine lactoferrin /kg feed for 19 days. Then fishes were challenged with *Aeromonas salmonicida* ssp. *salmonicida* or infectious salmon anaemia virus. Result indicated lysozyme activity in serum and head kidney and cumulative mortality were unaffected by inclusion of lactoferrin. It's proved under the condition of this experiment, effects of lactoferrin supplementing on non-specific immunity or disease resistance in Atlantic salmon for a short period cannot detected (Lygren et al., 1999).

Milk lactoferrin effects on resistance to bacterial infection in rainbow trout: Orally administration of bovine lactoferrin for 3 days prior to challenging with *V. anguillarutn* caused to increase survival rates and enhance resistance against *Streptococcits* sp. In lactoferrin-treated fish, significant increase in phagocytic activities of pronephros cells against *V. anguillarum* was observed. However, no *in vitro* bactericidal activities against *anguillarum* or *Streptococcus* sp. were observed. Therefore, the Iactoferrin enhanced the resistance of the rainbow trout against bacterial infection by the activation of phagocytes (Sakai et al., 1993). Sasaki et al (95) also reported 100mg/kg bovine lactoferrin (25 % Fe saturated) in rainbow trout fishes increased phagocytic activity of kidney cells.

Milk lactoferrin effects on non-specific immune responses in rainbow trout: In one study, rainbow trout fishes were fed diets containing 0, 50, 100, 200 and 400 mg bovine lactoferrin/kg diet twice daily for 8 weeks. Dietary lactoferrin had not significant effect on growth performance. But lysozyme activity and antiprotease activity increased significantly in fishes fed 100, 200, or 400 mg lactoferrin but not serum peroxidase. Thus feeding of rainbow trout with 100 mg or higher amounts enhances the non-specific immune response (Rahmatinegad et al., 2018).

CONCLUSION

Milk lactoferrin with properties of immunomodulatory, anti-microbial and antiviral may have unique potential in prevention and treatment of infections. Immuno-stimulants such as milk lactoferrin cause to increase the phagocytic cells function and improve the immune responses and disease resistance in fish culture. Milk lactoferrin may be a novel preventative treatment against infections in fish-farming industry, but it needs more researches to confirm its efficacy against infections.

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