*Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231– 6345 (Online)*
*An Open Access, Online International Journal Available at http://www.cibtech.org/jls.htm*
*2017 Vol. 7 (3) July-September, pp. 10-17/Kabita*
***Review Article***

# AN OVERVIEW OF FISH IMMUNE SYSTEM WITH SPECIAL EMPHASIS OF TELEOST FISHES

***Sk Kabita**
*Department of Zoology, Raja Peary Mohan College (University of Calcutta)*
**Author for Correspondence: skkabita123@gmail.com*

## ABSTRACT
Like mammals, fish's immune system is built with two divisions i.e., non-specific or innate immunity and specific or adaptive immunity. The non-specific immune system in fish is the second line of defence which responds non-specifically against pathogensbefore the specific immune system takes command of the defence mechanism. Both specific and non-specific immune responses are complementary to each other to prevent infection in fish. The overview of fish immunity with a focus on teleost fishes (largest infraclass of fresh water ray finned bony fishes) was discussed in this study.

***Keywords:*** *Fish Immune System, Innate Immunity, Adaptive Immunity, Defence Mechanism, Pathogens, Teleost Fishes*

## INTRODUCTION
The members of Teleost fishes (The ray-finned fishes) belong to the largest infraclass Teleostei under the class Actinopterygii. They have some unique characteristics in terms of immunity. The fishes depend on the immune system as their fundamental defence mechanism like invertebrates but along with the innate immune system they have several components of the specific immune system like all vertebrates.
The mucus and epithelial cells that line the skin, gills, and stomach act as a physical barrier and it is part of the non-specific immune system. Monocytes, macrophages, and granulocytes (neutrophils and eosinophilic granulocytes), which are non-specific cellular immune defence cells, are drawn to the infected region when pathogens penetrate the physical boundaries and utilize a variety of non-specific molecular and cellular processes to destroy the microorganisms (Corbel, 1975). To stop the pathogenic proliferation, the humoral components of the innate immune response through the generation of several proteins and glycoproteins, including lysozyme, complement, C-reactive proteins, lectins, interferons and transferrins (Firdaus-Nawi & Zamri-Saad, 2016). Leucocytes, such as macrophages or monocytes, granulocytes, macrophages, non-specific cytotoxic cells (NCCs), toll-like receptors (TLRs), and dendritic cells are the main cell types and receptors involved in non-specific cellular immunity. These cells are produced from pluripotent stem cells in the lymphoid tissue of fish, such as the head kidney, thymus, spleen, and gut-associated mucosal tissue (GALT) (Takahashi *et al.,* 2014). The production of innate humoral soluble acute phase molecules such as C-reactive protein, anti-protease, complement components, transferrin, lectin, and serum amyloid A in the liver and head kidney is also found. The humoral innate response depends heavily on these acute-phase proteins. These also influence the head kidney and promote leukocyte differentiation (Firdaus-Nawi & Zamri-Saad, 2016). Fish immunity has a core process that focuses on the surface parts that are connected to their environment, such as their gills, guts, gastrointestinal tracts, and skin. These mucosal tissues are the primary receptors of foreign stimuli and they release a variety of molecules such as tiny peptides, cytokines, and hormones that start the general physiological response and stimulate the non-specific immune response that occurs at the systemic level (Gomez *et al.,* 2013).
The main cellular components of specific immunity are B and T lymphocytes. B lymphocytes are developed in the head kidney of fish considered as primary lymphoid organ like the bone marrow of mammals (Parra *et al.,* 2015). Spleen is considered as secondary lymphoid organ because B lymphocytes are activated and differentiated into plasma memory cells within it (Fig 1). By responding to pathogens by activating T lymphocytes with the help of the class-II MHC, macrophages and dendritic cells bridge non-

specific and specific immunity (Fig. 1). The maturation of T cells takes place in the thymus of fish (Takahashi *et al.*, 2014; Firdaus-Nawi & Zamri-Saad, 2016). Fish have a simpler immune system than mammals, yet it nonetheless offers the required defence against noxious environmental infections. Understanding the fish immune system is crucial for determining the health of the fish. Haematopoiesis and cytokine generation are crucial factors that the majority of studies have concentrated on in order to better understand fish immunological health. Both innate and adaptive immunity depend on hemopoiesis since the defence cells are made from hemopoietic pluripotent cells in lymphoid organs and tissue. Therefore, it is considered as a major parameter in fish immunity. Since the production of these defence cells is regulated by cytokines that bind the receptors present on the surface of these pluripotent stem cells (Zapata *et al.*, 2006), cytokines production is also recognized as one of the important parameters of fish immunity. It would be overoptimistic to study the role of each component of teleost fish immunity since there is limited information available in the literature.

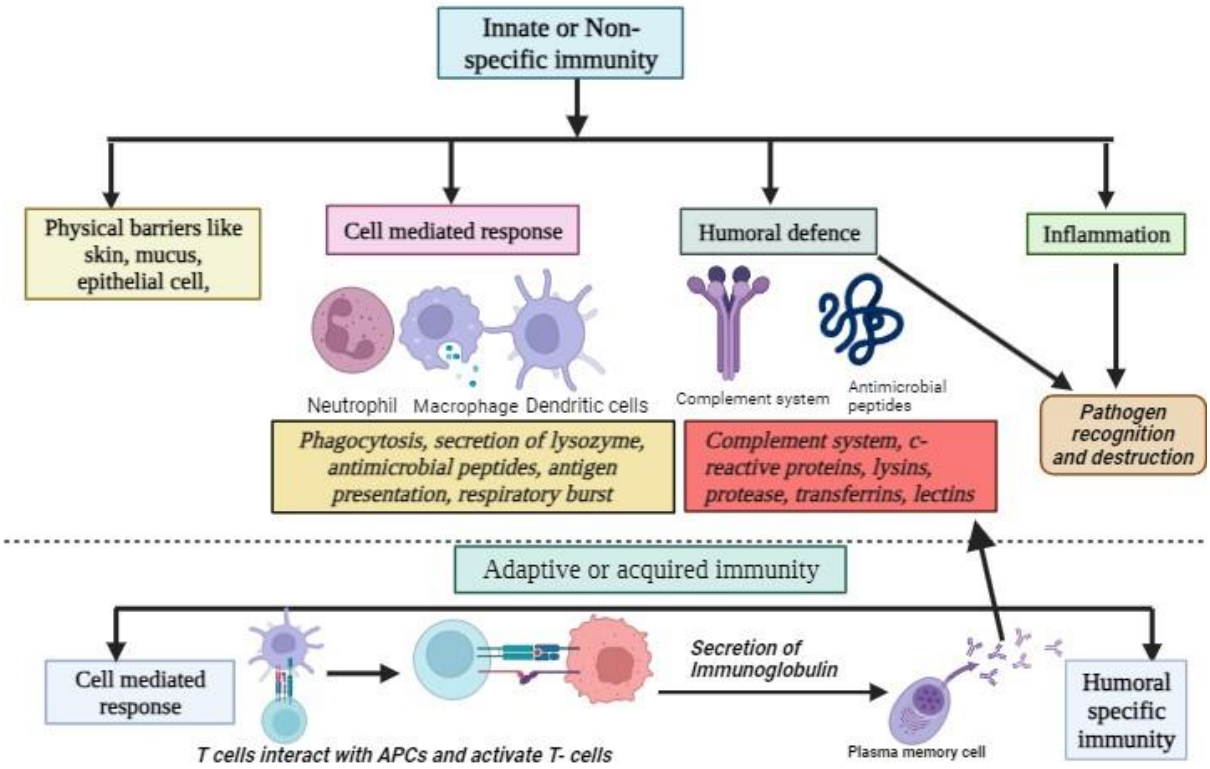


**Fig 1: Overview of Immune System in Fish**

**IMMUNE SYSTEM OF FISHES**

Fish immune system is broadly categorised into divisions i.e., non-specific or innate immunity, and specific or adaptive immunity. In this section we will discuss the fish immunity with a focus on teleost fishes (largest infraclass of fresh water ray finned bony fishes).

***Non-specific Immunity***

The non-specific immune response is categorised into cellular and humoral immune system. The non-specific immune system composed of mucus and epithelial cells that line the skin, gills and stomach imparts a physical barrier to identify and restrict the invasion of pathogenic microorganisms into the body in a general manner. When pathogens breach the physical barriers, the components of non-specific cellular immune defence cells such as monocytes, macrophages, granulocytes (neutrophils and eosinophilic granulocytes) are recruited to the invaded inflamed site and neutralize the microbes by

applying various type of non-specific molecular and cellular mechanism (Corbel, 1975; Firdaus-Nawi and Zamri-Saad, 2016). The innate immune response recruit various proteins and glycoproteins such as lysozyme, the complement, C-reactive proteins, lectins, interferons, transferrins to prevent the pathogenic growth (Firdaus-Nawi and Zamri-Saad, 2016). These humoral components work with the cellular components in an integral manner at the initial stage to prevent pathogen invasion. In the next sections, the non-specific cellular and humoral immune systems are discussed separately.

***Non-specific Cellular Immunity***

As already mentioned, that the major cell types involved in non-specific cellular immunity are leucocytes including macrophages or monocytes, granulocytes, macrophages and non-specific cytotoxic cells (NCCs), toll-like receptors (TLRs) and dendritic cells.

*Macrophages or Monocytes*

These cells are mobile phagocytes produced through the process of haematopoiesis and matured in fish head kidney and thymus and migrate from bloodstream to tissue (Hodgkinson *et al.*, 2015). Both of them act in inflammatory reaction indifferently to any pathogenic invaders or tissue injuries. Macrophages produce nitrogen oxide species (NOS) and reactive oxygen species (ROS) to destroy exogenous pathogens (Secombes, 1996).

*Granulocytes*

These cells have a unique structural feature and are known as the polymorphonuclear (PMN) white blood cells. Fine granules are present in the cytoplasm of these cells which named them granulocyte and they are classified into the three types namely neutrophils, basophils and eosinophils with specific functions in innate cellular fish immunity. The neutrophil reacts after the bacterial infection and migrates from vessels into the infected site to phagocytose bacteria. Eosinophil that involves in allergic inflammation followed by killing of internal parasites. Eosinophilic granular cells present in mucosa like skin, gill, gut are less mobile phagocytic cells which destroy helminths. Similarly, Fish non-specific cytotoxic cells (NCCs) target and destroy protozoa and virus affected host cells in skin or gill mucosa, blood and lymphoid organ through the process like apoptosis or necrotic mechanisms similar to the natural killer cell of mammal (Secombes, 1996). These cell population is produced from pluripotent stem cells in the lymphoid tissue of fish like head kidney, thymus, spleen, and gut-associated mucosal tissue (GALT) (Abdel-Aziz *et al.*, 2010; Chettri *et al.*, 2011; Metcalf and Nicola, 1995)

Both neutrophil and macrophages produce reactive oxygen species, hydrolytic proteins to engulf and to destroy microbes. When tissue is injured or infected with pathogens the infected tissue releases chemotaxis agent such as chemokines and complement anaphylatoxin to attract and promote migration of neutrophils and monocytes from blood to inflamed tissue. The damaged tissue generates chemotactic agents such as fibrinopeptides, fibrin, plasmin, complement anaphylatoxins, prostaglandins, leukotrienes which facilitate the extravasation and migration of these cells from bloodstream to site of infection. After arriving, these phagocytes phagocytose the invading microbes generate and secrete mediators like chemokines, TNF-α, IL-1β which cause inflammation and these mediators in turn increase the migration of macrophage and neutrophils. These mediators also act on liver and head kidney. The hepatocytes produce innate humoral soluble acute phase molecules such as C-reactive protein, anti-protease, complement components, transferrin, lectin, serum amyloid A. These acute phase proteins are integral part of humoral innate response. These also act on head kidney and increase the differentiation of leukocytes. The granulocyte basophil does not have any significant role in fish innate immunity. (Firdaus-Nawi and Zamri-Saad, 2016)

*Toll-like Receptors (TLRs)*

TLRs are another important component of innate cellular immunity in fish. They are small proteins capable of recognizing the specific conserved molecule of pathogen. Macrophages and neutrophils contain Toll-like receptor and TLR has been found in fish species such as goldfish *Carassius auratus* (Stafford *et al.*, 2003), zebrafish, *Danio rerio* (Jault *et al.*, 2004), Japanese flounder, *Paralichthys*

*olivaceus* (Takano *et al.*, 2011). TLR binds with pathogen associated molecular pattern (PAMPs) and activate signalling pathway that induce the expression of inflammatory cytokines IL-1β and TNF-α gene.

*Dendritic Cells*

They also take part in cell mediated innate immunity act as potent antigen presenting cells (APCs) and connect the innate and adaptive immunity as they are involved in phagocytosis and antigen presentation. (Inbaraj *et al.*, 2016)

***Non-specific Humoral Immunity***

Fish has several soluble or humoral defence components like complement (mainly alternative pathways), lectin, transferrin, lysozyme, C-reactive protein and several other substances. Inflammatory mediators like cytokines(Interferon, Interleukin and macrophage activating factors) are also considered as soluble or humoral components (Mehana *et al.*, 2015). They play crucial roles in fish immunity (Saurabh and Sahoo, 2008).

*Complement System (Alternative Pathways)*

The complement system is an important defence mechanism of the soluble component of the fish immune system which is associated with initiating of innate immune response as well asawaking upthe adaptive immune response(Alvarez-Pellitero, 2008) involving its various soluble proteins(Gasque, 2004). This system is activated by alternative pathway in fish which involves in lytic activity, opsonisation, chemotactic and pro-inflammatory function (Boshra *et al.*, 2006; Ellis, 1999; Iwama and Nakanishi, 1996; Nonaka *et al.*, 1981). The alternative pathway activated by pathogen associated molecular patterns (PAMPs). In this system, two complement product C5a and C3b produced through protease activity act as chemotactic agents that lure neutrophils and monocytes/macrophage to inflammatory site. These two proteins help in opsonisation, phagocytosis and killing by formation of membrane attack complex. The complement system is used to get information about fish health condition (Bayne and Gerwick, 2001a; Boshra *et al.*, 2006).

*Lysozyme*

Lysozyme in fish is secreted by leucocytes and present in mucus and blood plays a different role more compared to in mammals (Demers and Bayne, 1997). Fish lysozyme is present in leucocytes rich organs, especially head kidney, gill, skin, gut epithelium where pathogen invasion occurs frequently (Lie *et al.*, 1989; Murray and Fletcher, 1976). Lysozyme prevents some bacterial attack of fish as it shows antibiotic effect by cleaving the glycosidic bond of bacterial cell wall and it is a good indicator of innate immune condition (Demers and Bayne, 1997; Saurabh and Sahoo, 2008).

*Alkaline Phosphatase*

Alkaline phosphatase (AP) is an indispensable enzyme of non-specific immunity in fish and it is secreted in mucus, serum, gastrointestinal tract (Nigam *et al.*, 2012). When fish remains in pollutant environment or infected by pathogens, stress level increase, the secretion of AP also increases; that is why it is an important stress indicator (Ross *et al.*, 2000).

*Transferrin*

It is a glycoprotein which is involved in iron transport and is important part of immune system (García-Fernández *et al.*, 2011).After getting stimulated by cytokines liver produces transferrin and it creates limitation in microbial growth by making low iron concentration in body (Chen *et al.*, 2009; Jurecka *et al.*, 2009; Lambert *et al.*, 2005; Suzumoto *et al.*, 1977). Transferrin has been found in about 100 bony fish species (Jamieson, 1990).

*Lectin*

Lectin is the most primordial molecules and also very important pattern recognition receptor, present in mucus, blood, egg (Iwama and Nakanishi, 1996). It has high affinity for carbohydrate derived from pathogens and promote agglutination in several fish species from Chondrichthyes to teleost (Bayne and Gerwick, 2001b; Ewart *et al.*, 2001; Russell and Lumsden, 2005; Tsutsui *et al.*, 2003).

*Cytokines*

In fish there is a network of signalling polypeptides called cytokines and chemokines like other vertebrate which are involve inregulating and coordinating the innate and specific immune response. (Magnadóttir, 2006) When pathogen causes injury in tissue TNF-α, IL-6,IL-1β which are the main inflammatory cytokine secreted by the tissue macrophages (Huising *et al.,* 2004; Whyte, 2007)and these cytokines also stimulate liver to secrete acute phase protein. Chemokines are small cytokine that help in trafficking of neutrophils, macrophages to the site of infection have been found in fish. When fishes are infected with virus a potent glycoprotein called interferon is produced and secreted. Interferon inhibits viral replication in infected cell (Iwama and Nakanishi, 1996).

*C-reactive Proteins (CRP)*

CRP appears first after the tissue damage, infection and inflammation in most animals. It belongs to pentraxin family found in blood, mucus, eggs in response to tissue damage caused by infection, inflammation. CRP was first discovered in the serum of *Pneumococcus* bacteria infected patient which react with C-polysaccharide of cell wall of this pathogen, so it is called C-reactive protein (CRP). (Du Clos, 2000) CRP has been isolated from many fish species such as Channel catfish *Ictalurus punctatus* (Szalai *et al.,* 1994), tilapia, *Tilapia mossambica* (Ramos and Smith, 1978), rainbow trout, *Salmo gairdneri* (Winkelhake and Chang, 1982), *Channa punctatus.* (Mitra and Bhattacharya, 1992) CRP promotes opsonisation, phagocytosis and complement activation. Liver secretes CRP getting stimulated by cytokines produced by tissue macrophage (Magnadottir *et al.,* 2011; Nakanishi *et al.,* 1991; Salinas *et al.,* 2011; Szalai *et al.,* 1994).

*Mucosal Immunity*

One fundamental process of fish immunity focused on the doorway of pathogenicity that means the superficial part which is associated with surroundings: gill, gut, gastrointestinal tract and skin. Foreign stimuli are received primarily by these mucosal tissues and produce many substances which are messenger like small peptides, cytokines, hormonesthat will initiate the overall physiological retort fostering the non-specific immune response which occur at systemic level (Parra *et al.,* 2015).

***Specific Immunity***

Along with non-specific immunity, specific immunity is also a vital component in fish immune system. When a pathogen passes the physical barrier and non-specific immunity, specific immune response, the third line defence activated by cellular and humoral components of non-specific immunity (Firdaus-Nawi and Zamri-Saad, 2016). Highly specialised exclusive systemic cells and humoral components as well as processes are involved in specific immune system to control or eliminate pathogenic growth. Specific immunity composed of two major components: the lymphocytes and immunoglobulins (antibodies) known as cellular and humoral immunity respectively (Firdaus-Nawi and Zamri-Saad, 2016).

The main cellular components of specific immunity are B and T lymphocytes. B lymphocytes develop in head kidney of fish considered as primary lymphoid organ similar to the bone marrow of mammal (Zapata *et al.,* 2006). Spleen is considered as secondary lymphoid organ because B lymphocytes are activated and differentiated into plasma memory cells within it (Bromage *et al.,* 2004). The connection between non-specific and specific immunity is mediated by macrophage and dendritic cells as they respond to pathogens to activate T lymphocytes using the class-II MHC (Fig. 1B). The maturation of T cells takes place in the thymus of fish (Biller-Takahashi and Urbinati, 2014).

Specific humoral immunity involves antibody production and secretionand other accessory processes. These include the T cell activation, cytokine release and production. The antibodies are secreted from B lymphocyte lineage or the B cells and bind with the antigens present on the surface of invading microbes to eradicate it. Furthermore, B cells are stimulated by the interaction with activated T cells and B cells are differentiated into plasma memory cells which produce immunoglobulins.The immunoglobulins of fish are tetrameric IgM (pentameric in mammal), IgD, IgZ and secretory IgT (Firdaus-Nawi and Zamri-Saad, 2016). They are found in fish body fluid, serum, mucus, eggs, gastrointestinal mucosa.

The process of fish immunity is not as complex as mammals, but it provides necessary protection against antagonistic pathogens from the environment. To know the fish health condition, it is essential to get idea

about fish immune system. To have a better understanding of fish immune health the important parameters focused on most studies are Haematopoiesis and cytokine production. Haematopoiesis is essential for both innate and adaptive immunity where the defence cells are produced in lymphoid organs and tissue from haematopoietic pluripotent cells. Therefore, it is considered as a major parameter in fish immunity.Since the production of these defence cells is regulated by Cytokines that bind the receptors present on the surface of these pluripotent stem cells (Hanington *et al.,* 2009), cytokines production is also recognised as one of the important parameters of fish immunity. It would be overoptimistic to write the function of *Spirulina* on each component of fish immunity, since there is no such information are available in literature. Thus, we reviewed the importance of *Spirulina* on fish health and immunity in the followingfour major headings.

## CONCLUSION

Fish, like all living organisms, possess immune systems to defend against pathogens. Their immune responses are two types, innate and adaptive. Innate immunity includes physical barriers like scalesand mucus, as well as cells like phagocytes such as macrophages, neutrophils, and dendritic cells thatengulf pathogens. These cells also produce various types of antimicrobial peptides like lysozyme, lectins, complement elements, and protease to combat infections. Adaptive immunity develops afterexposure to pathogens, involving specialized immune cells such as T and B cells. Fish lack lymphnodes, but immune cells aggregate in various tissues. Mucosal surfaces, like gills and intestines, playa vital role in immune defence due to constant exposure to waterborne pathogens. Understanding fishimmunity aids in both conservation of wild populations and sustainable aquaculture practices. There are lots of literatures available in mammalian immune system, in compare to that the area on fish immune system is under-explored. The study on immune system of this important aquaculture candidate will be worthy of exploration and helpful to mitigate the gap area.

## REFERENCES

**Abdel-Aziz ESH, Abdu SBS, Ali TES and Fouad HF (2010).** Haemopoiesis in the Head Kidney of Tilapia, *Oreochromis Niloticus* (Teleostei: Cichlidae): A Morphological (Optical and Ultrastructural) Study. *Fish Physiology and Biochemistry* 36(3) 323–336.

**Alvarez-Pellitero P (2008).** Fish Immunity and Parasite Infections: From Innate Immunity to Immunoprophylactic Prospects. *Veterinary Immunology and Immunopathology* 126 (3-4) 171–198.

**Bayne CJ and GerwickL (2001).** The Acute Phase Response and Innate Immunity of Fish. *Developmental and Comparative Immunology* 25 (8-9) 725–743.

**BoshraH, Li J and Sunyer JO (2006).** Recent Advances on the Complement System of Teleost Fish. *Fish and Shellfish Immunology*20 (2) 239–262.

**Bromage ES, Kaattari IM, Zwollo P and Kaattari SL (2004).** Plasmablast and Plasma Cell Production and Distribution in Trout Immune Tissues. *Journal of Immunology* 173 (12) 7317–7323.

**Chen J, Wang J, Meyers KR and Enns CA (2009).** Transferrin-directed Internalization and Cycling of Transferrin Receptor 2. *Wiley Online Library* 10 (10), 1488–1501.

**Chettri JK, Raida MK, Holten-Andersen L, Kania PW and Buchmann K (2011).** PAMP Induced Expression of Immune Relevant Genes in Head Kidney Leukocytes of Rainbow Trout (Oncorhynchus Mykiss). *Developmental and Comparative Immunology* 35 (4) 476–482.

**Corbel MJ (1975).** The Immune Response in Fish: A Review. *Journal of Fish Biology* 7 (4) 539–563.

**Demers NE and Bayne CJ (1997).** The Immediate Effects of Stress on Hormones and Plasma Lysozyme in Rainbow Trout. *Developmental and Comparative Immunology* 21 (4) 363–373.

**Du Clos T (2000).** Function of C-reactive Protein. *Annals of Medicine* 32 (4) 274–278.

**Ellis AE (1999).** Immunity to Bacteria in Fish. *Fish and Shellfish Immunology* 9 (4) 291–308.

**Ewart KV, Johnson SC and Ross NW (2001).** Lectins of the Innate Immune System and their Relevance to Fish Health. *ICES Journal of Marine Science* 58 (2) 380–385.

**Firdaus-Nawi M and Zamri-Saad M (2016).** Major Components of Fish Immunity: A Review. *Pertanika Journal of Tropical Agricultural Science* 39 (4) 393–420.
**García-Fernández C, Sánchez JA and Blanco G (2011).** Characterization of the Gilthead Seabream (*Sparus Aurata L.*) Transferrin Gene: Genomic Structure, Constitutive Expression and SNP Variation. *Fish and Shellfish Immunology*. 31 (4) 548–556.
**Gasque P (2004).** Complement: A Unique Innate Immune Sensor for Danger Signals. *Molecular Immunology* 41 (11) 1089–1098.
**Gomez D, Sunyer JO and Salinas I (2013).** The Mucosal Immune System of Fish: The Evolution of Ttolerating Commensals while Fighting Pathogens. *Fish and Shellfish Immunology* 35 (6) 1729.
**Hanington PC, Tam J, Katzenback BA and Hitchen SJ, Barreda DR and Belosevic M (2009).** Development of Macrophages of Cyprinid Fish. *Developmental and Comparative Immunology* 33 (4) 411–429.
**Hodgkinson J, GrayferL and Belosevic M (2015).** Biology of Bony Fish Macrophages. *Biology* 4 (4) 881–906.
**Huising MO, Stet RJM, Savelkoul HFJ and Verburg-Van Kemenade BML (2004).** The Molecular Evolution of the Interleukin-1 Family of Cytokines; IL-18 in Teleost Fish. *Developmental and Comparative Immunology* 28 (5) 395–413.
**Inbaraj S, Sejian V, Bagath M and Bhatta R (2016).** Tropical Agricultural Scicene Impact of Heat Stress on Immune Responses of Livestock: A Review. *Pertanika Journal of Tropical Agricultural Science* 39 (4) 459–482.
**Iwama GK and Nakanishi T (1996).** *Fish Immune System: Organism, Pathogen and Environment*, Vol. 15, 1st edn, edited by Hoar WS, Randall DJ (Academic Press) 380.
**Jamieson A (1990).** A Survey of Transferrins in 87 Teleostean Species. *Animal Genetics* 21(3) 295–301.
**Jault C, Pichon L and Chluba J (2004)**. Toll-like Receptor Gene Family and TIR-domain Adapters in *Danio Rerio*. *Molecular Immunology* 40 (11) 759–771.
**Jurecka P, Irnazarow I, Stafford JL, Ruszczyk A, Taverne N, Belosevic M, Savelkoul HFJ and Wiegertjes GF (2009).** The Induction of Nitric Oxide Response of Carp Macrophages by Transferrin is Influenced by the Allelic Diversity of the Molecule. *Fish and Shellfish Immunology* 26 (4) 632–638.
**Lambert LA, Perri H, Halbrooks PJ and Mason AB (2005).** Evolution of the Transferrin Family: Conservation of Residues Associated with Iron and Anion Binding.*Comparative Biochemistry and Physiology. Part B, Biochemistry & Molecular Biology* 142 (2) 129–141.
**Lie Ø, Evensen Ø, Sørensen A and Frøysadal E (1989).** Study on Lysozyme Activity in Some Fish Species. *Disease of Aquatic Organism* 6, 1–5.
**MagnadóttirB (2006).** Innate Immunity of Fish (Averview). *Fish and Shellfish Immunology* 20 (2) 137–151.
**Magnadottir B, Audunsdottir SS, Bragason BT, Gisladottir B, Jonsson ZO, Gudmundsdottir S (2011).** The Acute Phase Response of Atlantic Cod (Gadus Morhua): Humoral and Cellular Response. *Fish and Shellfish Immunology*. 30 (4-5) 1124–1130.
**Mehana E, Rahmani AH and Aly SM (2015).** Immunostimulants and Fish Culture: An Overview. *Annual Research and Review in Biology* 5 (6) 477–489.
**Metcalf D and Nicola N (1995).** The Hemopoietic Colony-stimulating Factors: From Biology to Clinical Applications. The Hemopoietic Colony-stimulating Factors. https://doi.org/10.1017/CBO9780511663376
**Mitra S and Bhattacharya S (1992).** Purification of C-reactive Protein from *Channa punctatus* (Bloch). *Indian Journal of Biochemistry and Biophysics* 29 (6) 508–511.
**Murray CK and Fletcher TC (1976).** The Immunohistochemical Localization of Lysozyme in Plaice (*Pleuronectes Platessa* L.) Tissues. *Journal of Fish Biology* 9 (4) 329–334.
**Nakanishi Y, Kodama H, Murai T, Mikami T and Izawa H (1991).** Activation of Rainbow Trout Complement by C-reactive Protein. *American Journal Veterinary Research* 52 (3) 397–401.
**Nigam AK, Kumari U, Mittal S and Mittal AK (2012).** Comparative Analysis of Innate Immune

Parameters of the Skin Mucous Secretions from Certain Freshwater Teleosts, Inhabiting Different Ecological Niches. *Fish Physiology and Biochemistry* 38 (5) 1245–1256.

**Nonaka M, Yamaguchi N, Natsuume-Sakai S and Takahashi M (1981).** The Complement System of Rainbow Trout (*Salmo Gairdneri*). I. Identification of the Serum Lytic System Homologous to Mammalian Complement. *The Journal of Immunology*. 126(4) 1489-94.

**Parra D, Royes-Lopez L, Tort L (2015).** Mucosal Immunity and B Cells in Teleosts: Effect of Vaccination and Stress. *Frontiers in Immunology* 6 (JUN).

**Ramos F, Smith AC (1978).** The C-reactive Protein (CRP) Test for the Detection of Early Disease in Fishes. *Aquaculture* 14 (3) 261–266.

**Ross NW, Firth KJ, Wang A, Burka JF and Johnson SC(2000).** Changes in Hydrolytic Enzyme Activities of Naïve Atlantic Salmon Salmo Salar Skin Mucus Due to Infection with the Salmon Louse *Lepeophtheirus Salmonis* and Cortisol Implantation. *Disease of Aquatic Organism* 41(1) 43–51.

**Russell S and Lumsden JS (2005).** Function and Heterogeneity of Fish Lectins *Veterinary Immunology and Immunopathology* 108 (1-2) 111–120.

**Salinas I, Zhang YA and Sunyer JO (2011).** Mucosal Immunoglobulins and B Cells of Teleost fish *Developmental and Comparative Immunology* 35 (12) 1346.

**Saurabh S and Sahoo PK (2008).** Lysozyme: An Important Defence Molecule of Fish Innate Immune System. *Aquaculture Research* 39 (3) 223–239.

**Secombes CJ (1996).** The Nonspecific Immune System: Cellular Defenses. *Fish Physiology* 15 (C) 63–103.

**Stafford JL, Ellestad KK, Magor KE, Belosevic M, Magor BG (2003).** A Toll-like Receptor (TLR) Gene that is Up-regulated in Activated Goldfish Macrophages. *Developmental and . Comparative Immunology* 27 (8) 685–698.

**Suzumoto BK, Schreck CB and McIntyre JD (1977).** Relative Resistances of Three Transferrin Genotypes of Coho Salmon (*Oncorhynchus Kisutch*) and Their Hematological Responses to Bacterial Kidney Disease. *Journal of the Fisheries Research Board of Canada* 34 (1) 1–8.

**Szalai AJ, Bly JE and Clem LW (1994).** Changes in Serum Concentrations of Channel Catfish (*Ictalurus Punctatus Rafinesque*) Phosphorylcholine-reactive Protein (PRP) in Response to Inflammatory Agents, Low Temperature-shock and Infection by the Fungus Saprolegnia sp. *Fish and Shellfish Immunology* 4 (5) 323–336.

**Takano T, Kondo H, Hirono I, Endo M, Saito-Taki T and Aoki T (2011).** Toll-like Receptors in Teleosts. *Diseases in Asian Aquaculture VI*. 385197–208.

**Takahashi JD and Urbinati EC(2014).** Fish Immunology. The Modification and Manipulation of the Innate Immune System: Brazilian Studies. *Anais da Academia Brasileira de Ciencias* 86 (3) 1483–1495.

**Tsutsui S, Tasumi S, Suetake H and SuzukiY (2003).** Lectins Homologous to those of Monocotyledonous Plants in the Skin Mucus and Intestine of Pufferfish, *Fugu Rubripes*. *Journal of Biological Chemistry*278 (23) 20882–20889.

**Whyte SK (2007).** The InnateIimmune Response of Finfish – A Review of Current Knowledge. *Fish and Shellfish Immunology* 23 (6) 1127–1151.

**Winkelhake JL and Chang RJ (1982).** Acute Phase (C-Reactive) Protein-Like Macromolecules From Rainbow Trout (Salmo Gairdneri). *Developmental and Comparative Immunology* 6 (3) 481–489.

**Zapata A, Diez B, Cejalvo T, Gutiérrez-De Frías C and Cortés A (2006).** Ontogeny of the Immune System of Fish. *Fish and Shellfish Immunology* 20 (2) 126–136.