

# Impact of Ecotoxins on Innate Immunity of fishes: A Review

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**ABSTRACT:** Immune response in fishes is an important aspect for studying fish health. Heavy metals are constantly reported by researchers to be present in water bodies and are causing damage to both flora and fauna inhabiting these water bodies. Fishes with weak immune response against pollutants or any other identifiable pathogen should be studied to give details of its immunological status. Certain parameters like excessive mucus secretion, hyperactivation of goblet cells, dermal melanosis, dermal granuloma, altered lysozyme activity and many others have been reported. Studies have been done either in cells in vitro, in laboratory and microcosms and also the fish in field. The present review gives details about the studies done with varying degree of immunological alterations and has also suggested new ways of studying immune response in fishes due to environmental pollutants found to cause damage.

**KEYWORDS:** Heavy metal, Innate immunity, melanomacrophage centres, lysozyme.

## I. INTRODUCTION

In the recent decades, reduced mortality rate, better medical facilities has led to a tremendous increase in population but at the cost of depletion of resources. World population is expected to increase by over a third or 2.3 billion people between 2009 and 2050 [52]. It is not easy to feed such a huge population, hence agriculture faces certain challenges. There is a need to look for some other sustainable production methods which can help overcome this problem of overpopulation. One such production method is aquaculture. Aquaculture has got a promising role in dealing with food crisis. Fish being a potential source of animal protein will continue to solve the problem of hunger in future. Fish is highly nutritious, it possesses non saturated fatty acids and omega 3 which helps in reduction in blood cholesterol and helps prevent heart disease [14].

The overall status of a living organism is determined by the environment in which it resides. Similarly the body functions of a fish are closely related with their aquatic habitat. There are different parameters of water, which, in their certain optimal ranges are important for survival of fish. Any change in these parameters might disturb the normal functioning of fish or even prove fatal. These parameters include dissolved gases like oxygen and carbon dioxide, pH, hardness, salinity, alkalinity, total dissolved solids etc. The fluctuations in these parameters is attributed to addition of certain materials called pollutants. When large quantities of pollutants are added to an aquatic environment it may either lead to heavy mortality of fish or cause long term effects such as immune-suppression, reduced metabolism and damage to gills and epithelia [2]. Also the adverse water quality leads to increase in the number of pathogens and makes their infiltration easier in the body of fishes. Pollutants can be of organic nature or inorganic. Organic pollutants include detergents, insecticides and herbicides, chlorinated solvents, petroleum hydrocarbons, disinfection by-products and fuel combustion by-products. Inorganic water pollutants include fertilizers containing nitrates and phosphates, ammonia from food processing waste and heavy metals. Organic pollutants are biodegradable whereas inorganic pollutants incapable of getting degraded, get accumulated in the organisms at various trophic levels of a food chain. In polluted aquatic ecosystems transfer of metals through food chains can be high enough to bring harmful concentrations in fish [10]. Several metals are crucial to metabolism of cells at low concentration but are toxic at higher concentrations [30]. Heavy metals cannot be degraded chemically beyond their chemical state. They can only be redistributed between

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biotic and abiotic components and interact with them, hampering their normal functioning. Heavy metals get accumulated in the tissues of fish and this accumulation depends on concentration of metal, time of exposure, metal uptake method, temperature, pH, hardness and salinity of water, fish age and feeding habits [22]. Generally higher the metal concentration, more of it will be taken up and accumulated by the fish. They are more likely to be deposited in organs like liver, kidney and gills and the least in muscle tissue. They are mostly introduced into water due to effluents from industries, consumer waste or even from acidic rain which breaks down soil and releases heavy metals into streams, rivers and ground waters. Heavy metals have been correlated to alterations in immune system of fish and the incidence of infectious diseases [42]. These infectious diseases may lead to increased mortality. It is therefore essential to investigate the effect of heavy metals on immune system of fish.

## II. HEAVY METALS AND IMMUNE RESPONSE IN FISHES

Heavy metals are the elements with higher atomic weight and a density 5 times greater than that of water [46]. Heavy metals occur naturally in earth's crust and are emitted during mining and processing. These metals are then carried off to the sea. Water bodies are markedly polluted during mining activities [18]. Lead is the most prevalent heavy metal contaminant. Lead levels in the aquatic environment of industrial societies have increased 2-3 times to those of pre-industrial times. Lead is used in vehicles as an anti-knocking agent, in toys as stabilizers, color enhancer and anti-corrosive agent. Arsenic is another heavy metal which gets accumulated in tissues of fish. It is used in tanning industry to remove hair from hides. Cadmium is released into environment into water as a mining by-product. Manganese is released into freshwater ecosystem through industries like textiles, dyes, steel, paints, ceramics, pesticides and fertilizers. Copper is used for parasite control in aquatic environments in the form of copper sulphate. The usage of mercury is very widespread in industrial processes and products like lamps, thermometers, batteries. The major source of mercury is degassing of earth's crust. It is also used in dentistry as amalgam. Zinc is introduced into water bodies through urban run-off, being released from paint industries and surface cleaner chemical industries.

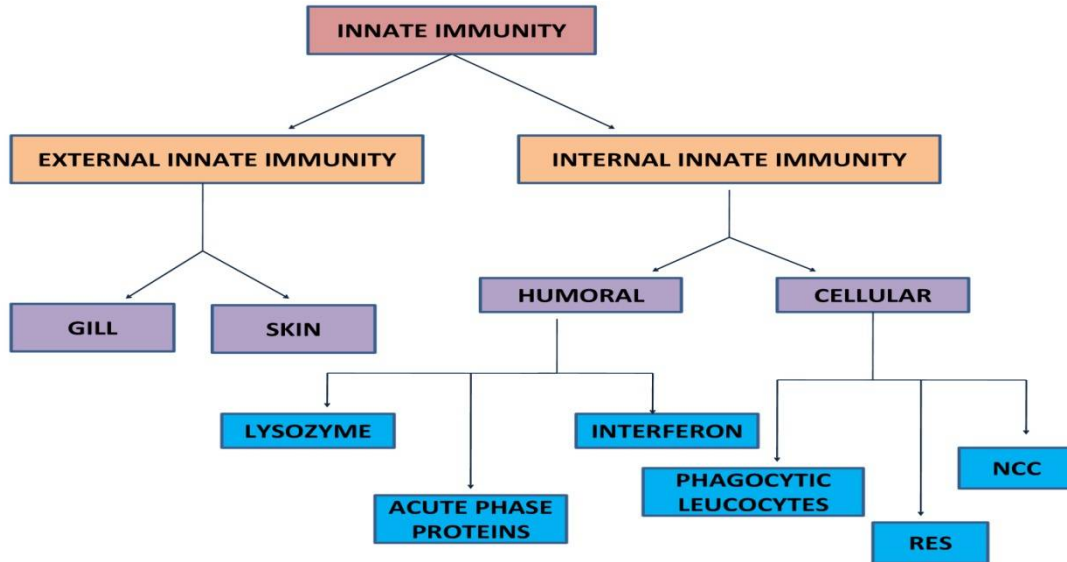
Immune system is a host defense system which comprises many biological structures within an organism and protects it against disease. All organisms possess immune system which is either rudimentary or more complex as in humans [4]. A rudimentary or basic immune system involves certain physical barriers that provide immediate but non-specific response [3]. If innate immune system fails to stop the entry of pathogen, adaptive immune response gets activated. This system is more efficient and adapted because of immunological memory it develops [31]. Fishes possess both innate and adaptive immunity; however the innate response is much significant in them. Fishes possess almost all the secondary lymphoid organs present in mammals except the lymphatic nodules and bone marrow [15]. The kidney, thymus and spleen comprise the largest lymphoid organs in teleosts [53]. In fish, the immune cells are contained in their whole kidney, however immunologically active portion is the head kidney or pronephros. It is the main immune organ which is responsible for phagocytosis [50]. Pronephros is formed by 2 Y arms which penetrate underneath gills. Macrophages are the main cells found in the anterior kidney which aggregate into structures called melanomacrophage centers (mmcs), and the lymphoid cells, which are found at all developmental stages and mostly exist as Ig<sup>+</sup> cells (B cells). Pronephros is the central organ for immune-endocrine interactions and major site of antibody production [35]. Thymus is homogeneous, bilobed and is represented by a thin sheet of lymphoid tissue that is arranged subcutaneously in the dorsal commissure of the operculum and is lined by mucous tissue of the pharyngeal epithelium [12]. It was found that the thymus is responsible for the production of T cells. Thymus develops in lamina propria of GIT in pouches that are located at the base of gill arches. During development it migrates to underlying mesenchyme. So, in most teleosts it is located near gill cavity, associated with pharyngeal epithelium. Another immune organ spleen consists of a system of splenic ellipsoids, mmcs and lymphoid tissue [47]. In addition to these immune organs there are other external and internal components of innate immunity (fig. 1).

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(Fig.1) Various components of innate immunity.  
NCC: Non-specific cytotoxic cells, RES: Reticulo-endothelial system

The external components provide physical barriers to the entry of pathogens while as humoral components or the non specific defense components are present in serum, mucus and eggs of fish. They inhibit the growth of microbial pathogens non-specifically. These are predominantly proteins and glycoproteins. In ecotoxicology these components have been studied since decades however the examination is confined to few classes viz lysozyme, interferons and acute phase proteins. Non-specific cellular defenses include phagocytic leucocytes, NCC (non-specific cytotoxic cells) and RES (Reticulo-endothelial system). Various studies have shown alterations in these cells and humoral components as a consequence of the ecotoxicants present in the surrounding water. The table below gives a glance of work reported on the issue of heavy metal accumulation and immune response elicited because of it. (Table 1)

**TABLE 1: STUDIES ON HEAVY METAL EXPOSURE ON IMMUNE PARAMETERS OF FISHES**

Country	Year	Heavy Metals	Fish	Organ	Immune Parameters	References
USA	1979	Motor exhaust emissions	<i>Carassius auratus</i>	gills	Excessive mucus secretion	[6]
Netherlands	1981	Mercuric chloride	<i>Salmo gairdneri</i>	gills	Excessive mucus secretion	[26]

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<b>United Kingdom</b>	1981	Cadmium	<i>Pleuronectes platessa</i>	Skin	Altered production of glycoprotein in mucus	[16]
<b>United states</b>	1983	Arochlor 1254, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) , 3 Methylcholanthrene	<i>Salmo gairdneri</i>	blood	Increased serum CRP levels (10-20 folds)	[51]
<b>Canada</b>	1984	Crude oil	<i>Gadus morhua</i>	gills	Mucous cell no. increases	[24]
<b>United Kingdom</b>	1986	Mercury	<i>Pleuronectes platessa</i>	plasma	Reduction in lysozyme activity	[17]
<b>United States</b>	1986	Cadmium	<i>Morone saxatilis</i>	Peritoneal exudate cells	Increased migration of peritoneal macrophages, Enhanced antibody titre	[38]
<b>United states</b>	1986	Copper	<i>Salmo gairdneri</i>	pronephros	Inhibition of respiratory burst of leucocytes	[13]
<b>France</b>	1987	Manganese	<i>Cyprinus carpio</i>	Pronephric & splenic macrophages	Stimulates respiratory burst	[9]
<b>Canada</b>	1987	Benzo[a]pyrene, Benza[a]anthracene, 7,12-dimethylbenzanthracene (DMBA)	Rainbow trout	blood	Reduction in phagocytosis by BaP Remained unchanged by BaA	[49]
<b>Israel</b>	1988	Cadmium, Organic fertilizer, lead	<i>Cyprinus carpio</i>	skin	Necrosis and apoptosis of pavement cells Leucocyte infiltration in epidermis, increase in fibroblasts	[21]
<b>India</b>	1988	Dodecyl benzene sodium sulfonate	<i>Rita rita</i>	gills	Decline in goblet no. followed by increase after 72 hrs	[40]
<b>USA</b>	1989	Malathion	<i>Lepomis macrochirus</i>	gills	Excessive mucus secretion	[37]

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France	1991	Trichlorophan, Dichlorvos	<i>Cyprinus carpio</i>	Blood, Headkidney phagocytes	Reduced lysozyme activity, Inhibition of respiratory burst	[11]
India	1992	Hg, Cd, NH <sub>3</sub> , phenol metacid-50 or carbaryl	<i>Channa punctatus</i>	blood	Increased serum CRP levels (2-4 folds)	[20]
United kingdom	1992	Sewage sludge	<i>Limanda limanda</i>	Kidney,spleen	Increase in no. of MMC	[44]
Hungary	1993	Cadmium	<i>Cyprinus carpio</i>	gills	Decrease in goblet cell number	[45]
Netherlands	1994	TCDD & chromium	<i>Cyprinus carpio</i>	Kidney, spleen	Increase in no. of MMC	[48]
United states	1994	pentachlorophenol	<i>Fundulus heteroclitus</i>	pronephros	Inhibition of phagocytosis of yeast by macrophages & eosinophils	[39]
United States	1994	Nickel	<i>Onchorhynchus mykiss</i>	peritoneum	Increase in random migration of peritoneal macrophages	[5]
United states	1994	Cadmium	Rainbow trout	Peritoneum	Enhancement of phagocytic activity of peritoneal macrophages at low doses; inhibition at high doses	[55]
United states	1995	Copper	<i>Carassius auratus</i>	pronephros	Enhancement of respiratory burst	[32]
United Kingdom	1995	Cadmium	<i>Dicentrarchus labrax</i>	Pronephros macrophages	Enhanced respiratory burst activity	[25]
United states	1995	PCB 126	<i>Ictalurus punctatus</i>	Peripheral blood	Non-specific cytotoxic cell activity reduced, reduction in phagocytic oxidative burst activity	[36]
USA	1997	<i>1-Naphthyl-N- Methylcarbamate</i>	<i>Carassius auratus</i>	gills	Excessive mucus secretion	[8]

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Singapore	1998	Mercury	<i>Trichogaster trichopterus</i>	kidney	Increased lysozyme activity	[27]
India	1998	Hg, Cd, Phenol, hexachlorocyclohexane	<i>Catla catla</i>	blood	Increased serum CRP levels (3-4 folds)	[33]
Canada	1999	Cadmium, Mercury, zinc	<i>Onchorhynchus mykiss</i>	Serum, pronephros	Increased lysozyme activity, Decreased phagocytic ingestion in macrophages	[41]
Switzerland	2000	Nonylphenol	Rainbow trout	skin	Irregularly shaped mucosomes	[7]
Canada	2000	Benzopyrene	Rainbow trout	liver	Hepatocyte toxicity	[43]
Canada	2008	Polyaromatic Hydrocarbons (PAH)	<i>Mya arenaria</i>	haemolymph	Interfering with maturation of haemocytes	[34]
KSA	2014	Heavy metal pollution	Tilapia	skin	Hyperactivation of goblet cells, dermal melanosis, dermal granuloma	[54]

### III. HISTOPATHOLOGICAL STUDIES OF IMMUNE ORGANS

Prolonged exposure of fish to pollutants especially heavy metals has been reported to induce histological, morphological and biochemical alterations in the tissues even at low concentrations which may influence the quality of fish [23]. The BAF (Bioaccumulation Factor) is used to evaluate the concentration of a heavy metal accumulated in tissues of organism with respect to its concentration present in the environment. The histological alterations can be observed and evaluated by Histopathological studies. The stereological analysis provide quantitative data on pathological lesions that helps to establish correlation with other biomarkers hence increasing the probability of identifying cause (stressor) and effect (biomarker) relationship. Histopathological investigations also have the capability to differentiate between organ lesions which are induced by diseases and other environmental factors (food, temperature) from those lesions which are caused due to pollutant exposure. A high concentration of heavy metals will lead to suppression of immune system eventually inviting a pathogenic attack which in turn affects cellular and humoral components of immune system. This might lead to severe deformities in functioning of vital organs that have an eminent immunological role. Kidneys in addition to providing hematological and immunological functions release corticosteroids and catecholamines (stress hormones). ACTH causes an elevation in TNF-alpha and interleukins, showing a link between neuroendocrine and immune system of fish. A study by F Salim (2015) on different organs of fresh water fish residing in rivers close to power station shows reduced haemopoietic tissue, vaculation & peritubular odema in kidney. Moreover perirenal adipose tissue was infiltrated with inflammatory cells. Study on spleen of same fish showed depletion of follicular aggregation & lymphoid tissue. Red pulp had turned haemorrhagic. Viscottivoeth

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(1999) showed that there is an evidence of nephrotoxic effect on fish caused by pesticides leading to tubular and glomerular lesions in kidney. A study on farmed and wild European sea bass showed glomerular atrophy and lysis of glomerular tuft of kidney. Inflammatory changes were caused due to accumulation of mono nuclear cells. Other studies have also shown by vacuolar degeneration in the epithelium of renal tubules, focal hemorrhage between the renal tubules and edema in Bowman's capsules with atrophy in the glomeruli. Spleen also showed mild to moderate splenic congestion. The cellular damage is more pronounced in fish exposed to completely polluted stream than those fish which are exposed to a moderately polluted stream. Most severe effects were obtained in the fish treated with ammonia, thereby strongly affecting renal corpuscle, where basal laminae were heavily thickened and glomeruli often completely destroyed [19]. A study on the effect of sewage sludge on immune response of *Lemanda lemanda* showed an increase in number of MMC [44]. MMC's are physiological features of fish spleen and kidney which are believed to be functional equivalents of germinal centres of spleen and lymph nodes in mammals. Degree of MMC aggregation is proved to show a positive co-relation with water temperature [29]. Similarly, morphometric evaluation made on seasonal changes affecting number of lymphocytes in thymus, spleen and pronephros of *Salmo trutta* showed their highest emergence in summers as compared to winters [1]. Seasonal changes affect not only affect the structure but also the function of immune system in all ectothermic vertebrates. It is stated that the innate parameters of immune system are more sensitive to temperature changes as compared to acquired ones, innate being active at low temperature range while acquired are more effective at higher temperatures. In cod, spontaneous haemolytic and protease activity was more active at 1°C- 7°C than at 14°C, opposite being the case of IgM concentration [28]. Rainbow trout acclimatized at different temperatures showed lower phagocytic and complement activity at 5°C than at 20°C which shows the adverse effect of low temperature on innate parameters of fish. Non specific or innate response has been considered as an essential component in combating pathogens due to limitations of adaptive immune system, limited repertoire of antibodies and slow proliferation, maturation and memory of lymphocytes. The need of the hour is to evaluate immune system and the stressors that cause fluctuations in its normal functioning because the intake of healthy fish is directly related to the health of humans.

#### IV. CONCLUSION

It is quite evident that ecotoxicants especially heavy metals have an adverse impact on innate immunity but the mechanisms which are responsible for it are still ambiguous. This needs to be understood whether these toxicants affect stress hormone levels or have a direct impact. Many times scientists have induced the fish with different doses/concentrations of heavy metals to study their impact on immune response of fish but they haven't been able to explain the net effects on innate immunity as some changes have opposite effects e.g, a certain heavy metal might elevate level of lysozyme but decrease the phagocytic activity. Different mechanisms of bioaccumulation are yet to be studied; the mechanisms that cause the release of free radicals are yet to be uncovered. Toxicant induced alterations by natural stressors could be better explained by assessing the alterations in leucocyte number, alterations in lysozyme activity, c-reactive protein and alkaline phosphatase in addition to histopathological studies of various immune organs. These provide reliable assessment of various biomarkers that are indicators of quality of environment. Moreover, the species which is severely affected or is sensitive to even smaller concentration of heavy metal could prove a better environmental bioindicator.

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