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Review

Multidisciplinary haematology as prognostic device in environmental and xenobiotic stress-induced response in fish

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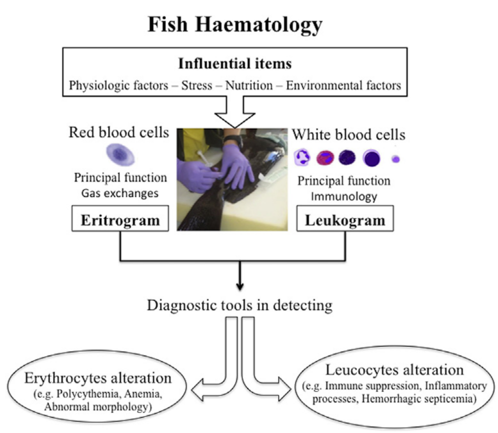
HIGHLIGHTS

- Haematology can evaluate normal blood cells variation by intrinsic or extrinsic factors.
- Fish blood cells alteration can be observed through eritrogram and leukogram.
- Haematological parameters can be indicator of environmental quality.
- Haematologic evaluation may assist the veterinary staff with detecting disease in fish.
- Mitochondrial activity can be a good indicator of fish health state.
- Mitochondria dysfunction may be associated with anemia development.

GRAPHICAL ABSTRACT



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ABSTRACT

The variations of haematological parameters hematocrit, hemoglobin concentration, leukocyte and erythrocyte count have been used as pollution and physiological indicators of organic dysfunction in both environmental and aquaculture studies. These parameters are commonly applied as prognostic and diagnostic tools in fish health status. However, there are both extrinsic and intrinsic factors to consider when performing a blood test, because a major limitation for field researchers is that the "rules" for animal or human haematology do not always apply to wildlife. The main objective of this review is to show how some environmental and xenobiotic factors are capable to modulating the haematic cells. Visualizing the strengths and limitations of a haematological analysis in the health assessment of wild and culture fish. Finally, we point out the importance of the use of mitochondrial activities as part of haematological evaluations associated to environment or aquaculture stress.

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Contents

1. Introduction

Haematological evaluation in fish has been done for more than 70 years (Katz, 1951; Hesser, 1960; Blaxhall and Daisley, 1973). Notwithstanding, for a correct interpretation of fish blood cells health status is necessary to contemplate a sum of variants, such as reproductive cycle, age, sex, feeding behavior, stress, nutritional status, and water quality as well as the habitat of species, since being poikilothermic animals are under the influence of environmental changes (Bastardo and Díaz-Barberán, 2005; Gabriel et al., 2004, 2007; Satheeshkumar et al., 2012a, 2012b). Furthermore, in aquaculture it is also necessary to consider the sampling technique, transportation, type of culture system, acclimation procedure, and water quality (Ezeri et al., 2004; Gabriel et al., 2004, 2007, 2011; Rey Vázquez and Guerrero, 2007; Correa-Negrete et al., 2009; Faggio et al., 2014a, 2014b, 2014c). On the other hand, factors such as blood collection, handling and storage time of blood samples can strongly influence the results obtained from a haematological analysis, recommending carrying out the haematological evaluations immediately after blood collection because long-term storage can modifies the results of the analyses, probably due to storage-related degenerative changes that may occur (Faggio et al., 2013; Fazio et al., 2014a).

Haematological paramters in fish including hematocrit (Hct), hemoglobin concentration (Hb), Red Blood Cell (RBC) and White Blood Cell (WBC) account, platelet count (PLT), Packed cell volume (PCV), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and sedimentation rate (Grant, 2015; Neelima et al., 2015). All these blood parameters can be influenced by intrinsic and external factors (Table 1) affecting the appearance of cells and the quantitative values obtained (Clauss et al., 2008). Differential blood cells (DBC) account, including RBC and WBC concentration, is one of the best haematological indicators of fish health because it can indicate the presence of an infectious disease (Blaxhall and Daisley, 1973; Grant, 2015) providing data for studies of defense mechanisms disease and pathogenesis (Fijan, 2002a, 2002b). This approach has been employed in monitoring the fish health status under conditions of reproduction, nutrition, and density (Palíková et al., 1999; Pavlidis et al., 2007; Zexia et al., 2007; Burgos-Aceves et al., 2010, 2012; El-Naggar et al., 2017), or after drug administration, parasite infestations, or environmental stress (Ranzani-Paiva et al., 2008; Dias et al., 2011; Seriani et al., 2015a, 2015b; Ventura et al., 2015; Corrêa et al., 2017; Grzelak et al., 2017; Valero et al., 2018). A comparative study in three cyprinid species Prussian carp *Carassius gibelio*, common bleak *Alburnus alburnus* and common rudd *Scardinius erythrophthalmus* showed that there were no differences in their haematological indices evaluated. Probably due to the similar living conditions of the studied species, such as their nutrition and habitat type (Nikolov and Boyadzieva-Doichinova, 2010). Therefore, the application of haematological indices is inexpensive and rapid to perform, allowing anticipating the clinical manifestations of diseases

Table 1
Main haematological parameters in fish blood studies influenced by intrinsic and external factors.

	Haematological parameter	Symbol	Derivation[a]	Exogenous factor	Endogenous factor	Hematologic abnormalities[b]
Red cell indices	Red blood cell counts	RBC	$\times 10^6$/mm^3	Season	Sex	Anemia
	Hematocrit	Ht	%	Temperature	Age	Polycythemia
	Hemoglobin	Hb	gHb/100 mL of blood	Photoperiod	Gender	Abnormal morphology
	Packed cell volume	PCV	Ht	Salinity	Nutrition	Stress
	Mean corpuscular volume	MCV	Ht × 100/RBC	pH	Reproduction	Iron deficiency anemia
	Mean corpuscular hemoglobin	MCH	Hb × 10/RBC	Water quality	Health	Anemia
	Mean corpuscular hemoglobin concentration	MCHC	Hb × 100/Ht	Pollutants	Disease	Iron deficiency anemia
White cell indices	White Blood Cell	WBC	$\times 10^3$/mm^3	Capture		Immunodeficiency
	Lymphocytes	L	%	Handling		
	Monocytes	M	%	Blood collection		Inflammatory
	Neutrophils	N	%	Density		Inflammatory
	Eosinophils	E	%			Phagocytosis
	Basophils	B	%			Phagocytosis

[a] Sarma (1990), Grant (2015).
[b] Clauss et al. (2008).

by monitoring the physiological, nutritional and health status of fish (Burgos-Aceves et al., 2010; Zorriehzahra et al., 2010). The blood and its constituents may reflect many diseases, the abnormalities of erythrocytes, leukocytes, thrombocytes, and clotting factors are considered primary blood disorders. Such aberrations in function or structure of the blood cells may result in anemia, leukopenia, leukocytosis, neutropenia, thrombocytopenia, and other blood cell abnormalities (Clauss et al., 2008). Then, to have a basic knowledge of haematology represents a valuable guide to assess the condition within the fish long before there is an outward manifestation of diseases (Rey Vázquez and Guerrero, 2007; Maheswaran et al., 2008), once reference values are established under standardized conditions (Faggio et al., 2013).

2. Haematological indices as biomarker of environmental variations and stress

Seasonality dominates the life cycle of fish. It coordinates several physiological activities and is believed to influence the blood parameters (Bromage et al., 2001). Temperature is one of main environmental variables associated with changes in haematological parameters, and its seasonal variations can induce compensatory metabolic changes at cellular and molecular level that may be associated with significant changes in blood chemistry (Kapila et al., 2002). Therefore, the effect of temperature seasonality has been studied in several fish species (Basu et al., 2001; Kapila et al., 2002; Lermen et al., 2004; Yang and Yeo, 2004; Gollock et al., 2006; Hur and Habibi, 2007; Jeong et al., 2012; Cho et al., 2015). Photoperiod is another environmental factor that seems to affect on the physiological and haematological condition of fish (Solomon and Okomoda, 2012a). Then, use of hematic tools to study fish blood composition in environmental and toxicological stress studies, as a possible indicator of physiological and pathological changes, is more recurrent (Zutshi et al., 2010; Rodrigues et al., 2018). Due to this high blood sensitivity, several blood studies have been carried out in order to understand the possible influence of seasonal changes that may have on these parameters (Folmar, 1993; Faggio et al., 2014a). Moreover, day and the season must be considered as key factors when blood parameters are used as biomarkers for disease and/or environmental alterations (de Pedro et al., 2005).

A study conducted by Faggio et al. (2014a) showed that gilthead seabream *Sparus aurata* and sea bream *Dicentrarchus labrax* presented similar monthly variations trends in RBC WBC, Htc and Hb, being mainly photoperiod and temperature-dependent. Both species showed an increase in values of RBC and Htc during cold-water season, which may be associated with water dissolved oxygen concentration disposal (Pascoli et al., 2011). During warm-dry seasons the concentration of dissolved oxygen tends to decrease and may be due to the intense decomposition of organic matter (Seriani et al., 2011). While, the amount of RBC and WBC in red garra *Garra rufa* was found to increase in summer and decreased in winter. This as an effect to an immunological response of fish activated by the increase in the microbiological activity in the warming waters in summer and the increase in the microorganisms density in water (Duman and Şahan, 2017). Significant monthly fluctuations of Hb, Hct, RBC, WBC, MVC, MCH and MCHC were also reported in the Nile tilapia *Oreochromis niloticus* in an lake that experiences two seasonal period: the rainy and dry seasons (Kefas et al., 2015). The highest level of Hb, RBC, and WBC were associated to dry season, which mighty be as a result of low volume of water during this period. Whereas, MVC, MCH, and MCHC fluctuated in both rainy and dry seasons probably as consequence of wide chemical used for agriculture discharged into the lake (Kefas et al., 2015). The relationship between the physical-chemical parameters water toxicity, low oxygen dissolved, ammonia and conductivity suggests that contaminants associated to sewage affected the water quality. Where conductivity seems to play a key role in the toxic action of chemical agents. In dry season conductivity is higher than in rainy season, which suggests that temporal variations in this variable can be attributed to pluviometric precipitation rates (Seriani et al., 2011). While a study done by Örün et al. (2003) in three cyprinid fish species Transcaucasian Sprilin *Alburnoides bipunctatus fasciatus*, Mossul bleak *Chalcalburnus mossulensis*, and kangal fish *Cyprinion macrostomus* indicates that, in addition to temperature and photoperiod, factors such as gender and water quality can influence the levels of blood parameters RBC, WBC, Hct, and Hb, adding to species factor. The three species presented significantly higher haematological indices in the warm months that in cold months. While the hematic values of Transcaucasian Sprilin were higher compared to those of Mossul bleak and kangal fish that were similar among them. Finally, the values of RBC, Hct, Hb, were higher in males, while a higher WBC index was reported in females, expressly during the reproductive stage. This same behavior, higher RBC values in male and higher WBC values in female, was observed in adult individuals of marine species Leopard grouper *Mycteroperca rocasea* during the reproductive season (Burgos-Aceves et al., 2010). This increment in WBC quantity or Leukophilia in females coincided with high plasma concentrations of oestradiol (E2) and testosterone (T), while the RBC increment or erythropoietic activity in males can be associated with an increased levels of 11-ketotestosterone (11-kt) in plasma, which suggests a coordination of endocrine-immune activity (Pottinger and Pickering, 1987). In addition, it has been postulated that leukocytes can infiltrate the gonad tissue from the peripheral blood to aid with immune surveillance and phagocyte activity and, may also aid in gonad reabsorption during post-spawning. Moreover, both mature male and female presented lower levels of RBC and Hct compared to the levels reported in immature individuals, demonstrating that age is another factor that can modulate the blood parameters (Burgos-Aceves et al., 2012). While, Fazio et al. (2015) report that both haematological parameters RBC and WBC were higher in male than female of Sea trout *Salmo trutta macrostigma* postulating that the reason for having higher haematological and even biochemical values in males is due to the high energy cost that females present in ovary development (Vijayakumari and Murali, 2012). Otherwise for Nile Green Tilapia *Tilapia zilli*, the nest mates presented lower levels in RBC, WBC, and Hct but without becoming significant compared with nest females (El-Naggar et al., 2017). According to a study conducted by Docan et al. (2016) some haematological parameters, such as the RBC, Hb, and MCHC are related to endogenous factors such as gender and reproductive state.

In a comparative study, the seawater flathead grey mullet *Mugil cephalus* and the freshwater goldfish *C. auratus* presented significant haematological variations. Higher values of RBC and Hct, associated with reduction in MCV, MCH and MCHC were reported in the grey mullet in respect to goldfish. Whereas, values of WBC and Thrombocytes (TC) count were lower in the grey mullet with respect to goldfish (Parrino et al., 2018). According to previous works, high RBC values are usually associated with species of fast movement and high activity (Fazio et al., 2013a). Moreover, a high value of Hct and concomitant reduction in their volume is due to an adaptive process to salinity of seawater habitat. While, the lower levels of WBC in the seawater species could be associated to feeding habits (Satheeshkumar et al., 2012a, 2012b; Romano et al., 2017). Thereupon, divergent environmental conditions and feeding habits may influence on fish blood parameters (Sehonova et al., 2018). This means that physicochemical differences in each environment may influence the haematological parameters, which makes them suitable for monitoring the effects of habitat changes on fish biology and fish culture practices (Fazio et al., 2012a, 2012b).

3. Haematological indices as biomarker of contaminated environments

Alterations in blood parameters associated to environmental pollutants have been received growing attention in assessing the health of fish (Zutshi et al., 2010; Corredor-Santamaría et al., 2016). The intensive use of pesticides in agriculture and the industrial and domestic sewage seem to increase the toxicity load to aquatic environment, causing haematological adverse effects on non-target organism like fish (Shankar Murthy et al., 2013; Fazio et al., 2014b; Sunanda et al., 2016a, 2016b; Fiorino et al., 2018; Biswas, 2018; Choudhury, 2018;). Exposure to different pollutants and toxicants, as heavy metals, pesticides, and industrial effluents can induce an increase or decrease in the various haematological components (Sancho et al., 2000; Oost et al., 2003; Choudhury, 2018). That is, the contaminants have a direct correlation with the fish blood anomalies and also the different environmental conditions of marine ecosystems can cause several changes in fish haematological parameters (Savari et al., 2011). Toxicology studies show that different insecticides can have disruptive action on erythropoietic tissues causing drop erythrocyte number and hemoglobin content. Meanwhile, organochlorines can alter haematological indices such as Ht, MCV, and MCHC (Banaee, 2013). These haematological variations are used to study the magnitude of stress in fish exposed to chemical agents (Sancho et al., 2000; Choudhury, 2018). Thus, changes in blood features may reflect the relative health of the aquatic ecosystem (Cazenave et al., 2005), as well as inferring the toxicity mode of potentially hazardous chemicals.

3.1. Effects of polluted environments on haematological parameters

In a report carried out by Corredor-Santamaría et al. (2016) it is emphasized that during the rain season, when industrial and domestic wastewater discharges increase, the two native species Twospot astyanax *Astyanax gr. bimaculatus* and Yellow acara *Aequidens metae* of a Colombian river presented alteration in the haematical parameters Hb, Hct, and RBC with a rise in WBC mainly thrombocytes and neutrophils. According to Cazenave et al. (2005), individual of neotropical freshwater fish peppered catfish *Corydoras paleatus* from polluted environments presented significantly higher values of RBC, Htc, Hb, MCV, MCH and MCHC compared with individual of same species present in pristine places. Additionally, these hematic parameters did not change according to maturation stages, sex or seasons. Instead, they established that Hb could be a key parameter to point out differences between populations exposed to different environmental conditions, because an increment in Hb concentration could be an especially reliable first indicator of an adaptive improvement in blood oxygen transporting capacity (Saint-Paul, 1984). Meanwhile, a study realized by Meraj et al. (2017) indicated that individuals of common carp *Cyprinus carpio* from Dal Lake, with intensive farming practiced in the surrounding area, presented significant decrements in the haematological parameters Hb, PCV and RBC compared with their counterparts of Mansbal Lake, with less anthropogenic alterations. The Hb reduction could be due to a possible inhibitory effect of pollutants on the enzyme system responsible for synthesis of hemoglobin, while reduction in RBC could be by a destructive action of pollutants released into the lake on erythrocytes and hemolysis (Ugokwe and Awobode, 2015). In another study, the freshwater fish roho labeo *Labeo rohita* showed haematological disruptions, erythrocyte destruction (hemolysis), and leukocytosis (leukopenia) due to a synergetic effect of various pollutants present in its habitat, affecting the immune system and making the fish vulnerable to diseases (Zutshi et al., 2010). Alteration on immune system was also observed in the native Nile tilapia from an area influenced by the discharge of runoff from agricultural and urban activities. A WBC analysis denoted a high percentage of eosinophils and monocytes and fewer thrombocytes, factors that indicate poor environmental quality (Corrêa et al., 2017). The high presence of eosinophil and monocyte cells can be associates with an inflammatory response (Clauss et al., 2008; Balla et al., 2010) due to either parasite infestation or chemical compounds present in effluents (Corrêa et al., 2017). While, a reduction in thrombocytes or thrombocytopenia may be associated with internal hemorrhagic foci, which can be detrimental to fish because these cells may be linked to inflammatory and phagocytic responses (Burrows et al., 2001; Mazon et al., 2002; Clauss et al., 2008). The red cells erythrocytes also seem to play a role in inflammation, where deformation of these cells caused by pathogen infection or xenobiotic exposure seem to alter the inflammation process (Straat et al., 2012; Pagano and Faggio, 2015; Santoso et al., 2015; Burgos-Aceves et al., 2018; Farag and Alagawany, 2018). Even more, erythrocytes can play a complementary role in immune responses in both fish and other vertebrates, since it has been found that RBC expresses immunity genes and responses (Shen et al., 2018). Hence, RBC can be used as a good indicator to evaluate the cytotoxicity of xenobiotics by membrane alteration and deformation (Pagano and Faggio, 2015; Farag and Alagawany, 2018) and could be associated to an important parameter in the study of any inflammatory response (Silva-Herdade et al., 2016).

3.2. Effects of heavy metals on haematological parameters

Pollution by heavy metal in aquatic environments has been an increasing ecological and global public health concern because of the risk of toxicity and bioaccumulation in the food chain (Adeyemo et al., 2010; Tchounwou et al., 2012; Fazio et al., 2014b; Gobi et al., 2018). In a study conducted by Gaber et al. (2013), individuals of African sharptooth catfish *Clarias gariepinus* presented higher values of RBC, Hb, Htc and WBC in water with elevated concentration of copper (Cu), iron (Fe), lead (Pb), cadmium (Cd), manganese (Mn) and zinc (Zn) due the great discharge of wastewater by agricultural, industrial and domestic activity compared with individual of same species from a water with less sewage discharge activity. Fish of common carp exposed to Pb, Cu, Cd and Zn also presented a rise in Htc without significant changes in RBC, and an initial increase in WBC but subsequently dropped remaining low (Witeska, 2005). The increment in Htc could be translated as alarm reaction and a subsequent dewdrop as an adaptation to stress (Vosyliene, 1996). Whereas the permanence of low levels of WBC may be due to the presence of cortisol secreted that shortens the life of lymphocytes, promoting the apoptosis and reducing their proliferation (Wyets et al., 1998; Verburg-van Kemenade et al., 1999; Espelid et al., 1996). The aluminum (Al) is one of the most abundant metal on earth releasing to the environment both natural or anthropogenic with no established biological functions (Sjögren et al., 2007). Due the acidification of surface waters, the Al becomes available to organisms that make it toxic to fish (Driscoll et al., 1980). In adult tropical freshwater fish redbelly tilapia *T. zillii* the haematological parameters RBC, Hct, Hb, MCHC, MCH and MCV increased significantly after Al exposure. These parameters increased progressively according to an increase in concentration of Al and time exposure, which can be a defensive mechanism against aluminum toxicity through stimulation of erythropoiesis (Alwan et al., 2009). The essential trace metal Mn is widely used in industry and its waste is dumped into water bodies becoming an indiscernible toxic metal in aquatic environment altering the physiological homeostasis of organisms. In the gold fish after an acute exposure of Mn, alterations in the blood cells were observed. A WBC differential account reveled a significant decrement of leucocytes thus compromising the immune system, while erythron profile revealed a significant increasing of cellular and nuclear alteration of red blood cells leading to eryptosis, compromising the blood oxygen carrying capacity and therefore the fish health status (Aliko et al., 2018). Meanwhile, decreasing trend in RBC, Hb and Hct followed by an exposure with Mn was reported in the sucker head *G. gotyla gotyla*. Such decline may due to Mn toxicity haemopoietic organs get affected and became unable to release normal RBCs in general circulation and thus can be held responsible for drastic decline in erythrocyte life span as well as slower erythropoiesis (Sharma and Langer, 2014). Mercury (Hg) is a mayor and common aquatic pollutant and can be converted into more toxic form by microbes (Schropre, 2001). It has been reported that Hg can penetrate the membrane of erythrocytes damaging the cells and causing hemorrhages as observed in the tench *Tinca tinca*, concomitant with elevated values of Hct, Hb, and RBC in acute lethal or chronic sub-lethal exposure. These increments could be due a splenic contraction (a common stress response), and subsequently releases of blood cells reserve or by simultaneous erythropoiesis in response to a transport demand for O_2-CO_2 (Shah and Altindag, 2004). Notwithstanding, at lower acute sub-lethal exposure does not appear have toxic effect both tench (Shah and Altindag, 2004), and Nile tilapia fish (Ishikawa et al., 2007). While in catfish *C. batrachus* exposure to Hg causes a reduction in RBC and Hb in a dose-dependent way. An increase in WBC mainly lymphocites was observed and this as a compensatory response of lymphoid tissues to the destruction of circulating lymphocytes (Maheswaran et al., 2008). The metals Cd and Pb are other two metals that both can have effects on haematological variables, reducing concentration of RBC, WBC and TC in the blood of flathead grey mullet (Fazio et al., 2014b). The reduction in concentration of RBC may be associated with internal bleeding from damage to the kidney caused by Cd and Pb, in addition to an impaired osmoregulation triggered by Cd, which may cause a haemodilution (Kori-Siakpere et al., 2006; Fazio et al., 2014b). While, reduction in WBC in blood of Striped Mullet seems to be associated to a bioaccumulation of Cd and Pb in kidney and liver (Kori-Siakpere et al., 2006), weakening the immune system and making the fish susceptible to diseases (Shah and Altindag, 2005). During the short-term exposure to Pb, individuals of common carp showed fluctuations in RCB, Hb, Hct, and MVC but accompanied by a persistent increase in the percentage of erythrocytes anomalies. In addition, a transient leukopenia was observed, thus compromising the immune system of the fish (Witeska et al., 2010). Similar accumulative effect of Cb in fish tissues was observed in Nile tilapia. Also, haematological parameters RBC, Hb, and Hct were reduced in fish exposed to Cd (Al-Asgah et al., 2015). According to Khadre (1988) reduction in these parameters might be due to destruction of mature RBCs and a reduction in haemosynthesis or an acute haemolytic crisis resulting in a severe anemia. Arsenic is cataloged as one of the most alarming chemicals given its high toxicity mainly in its salt form (ATSDR, 2007). Individuals of Indian catfish *C. batrachus* exposed to arsenic salt presented a progressive decrease in Hb, RBC, and packed cell volume (PVC) inducing anemia (Kumar and Banerjee, 2016). Several factors may be associated with the progress of anemia, either by reduction in the read cell rate production or an increasing loss of these cells (Shah and Altindag, 2004). An accelerated destruction of hemoglobin or reduction in its rate synthesis (Reddy and Bashamohideen, 1989), a depression/exhaustion of hemopoitic potential of fish (Sawhney and Johal, 2000), or may be a suppression of hematopoietic activity of the kidney in addition to the increased removal of dysfunctional RBCs what decrease the PVC value following arsenic exposure (Kumar and Banerjee, 2016). According to Gill and Epple (1993) the reasons for anemia might be impaired erythropoisis caused by the direct effect of metal on kidney or spleen, accelerated erythroclasia due to altered membrane permeability and/or increased mechanical fragility, and defective iron metabolism or impaired intestinal uptake of iron due to mucosal lesions. Nikel (Ni^{+2}) is greatly utilized in industry and is a common aquatic pollutant that when interacting with other organic and inorganic compounds, can produce adverse effects (Eisler, 1998). In gold fish *C. auratus* the exposure to Ni^{+2} may cause changes in haematoly with significant reduction in WBC, Ht, and Hb accompanied by increases in RBC and MCH (Moosavi and Shamushaki, 2015). According to Svoboda (2001) the decrease in WBC may be due to the release of epinephrine during stress, which is capable of causing the contraction of spleen. While, decrease in Ht and Hb is an indication of severe anemia caused by exposure to Ni^{+2} in the water (Vinodhini and Narayanan, 2009). On the other hand, the RBC elevation to blood cell reserve blood integrated with cellular contraction as a result of osmotic alterations of blood by the action of the metal (Annune et al., 1994; Moosavi and Shamushaki, 2015).

3.3. Effects of nanoparticles on haematological parameters

Up to date, the increased use of nanoparticles (NPs) in the manufacture of industrial, biomedical and domestic products, and their impact on the environment and living organisms have attracted considerable attention in recent years (Hasan, 2015; Khan et al., 2017; Guzzetti et al., 2018). Silver nanoparticles (AgNPs) are novel silver agents increasingly used in global markets for their antibacterial properties (Wijnhoven et al., 2009). AgNP-induced toxic on fish has been documented (Yeo and Kang, 2008; Bilberg et al., 2010; Choi et al., 2010). Recently, Thummabancha et al. (2016) reported haematological alterations and immunosuppression in Nile tilapia exposed to AgNPs. The amount of RBC, Hct and WBC decreased significantly after exposure time. Similar effect was reported for *roho labeo* exposed to AgNPs, might be a result of stressful conditions that affect the metabolism and normal functioning of fish physiology (Rajkumar et al., 2016). The Copper oxide nanoparticles (CuO-NPs) also have been shown to have adverse effects on fish. In the roach *Rutilus rutilus*, haematological parameters RBC, Hb and Hct decrease significantly in concomitant with an increment in WBC, MCH, MCHC and MCV (Jahanbakhshi et al., 2015). While in the rainbow trout *Oncorhynchus mykiss*, CuO-NPs can affect WBC, Hct, MCH, MCHC and MCV but not Hb (Khabbazi et al., 2015). The toxixity CuO-NPs was also observed on the Mozambique tilapia *T. mossambica* (=*Oroechromis mossambicus*), where all the haematological parameters WBC, RBC, Hb, Hct, PLT, MCH, MCHC and MCV can be significantly dropped (Siddiqui and Noorjahan, 2018). This may be the result to transient changes in haematology and depletion of plasma Na + which occurs after treatment with CuO-NPs that affects in branchial Na+/K + -ATPase activity in cells and leads to depletion of plasma and ion concentrations suggest that copper nanoparticle are an ion regulatory toxicant (Shaw et al., 2012; Remya et al., 2015). While in the freshwater fish streaked prochilod *Prochilodus scrofa* exposed to Cu cause an increase in RBC and Hb, suggesting compensatory response to respiratory surface reduction of gills in order to maintain oxygen transference from water to the tissues (Mazon et al., 2002). Potential toxicity action of Zinc oxide Nanoparticles (ZnO-NPs) on blood parameters was evidenced in Nile tilapia. The erythrogram revealed a significant decrement in RBC, PCV, Hb, and Hct with no changes in MCV, MCH and MCHC. Resulting in anemia due to decrease of the life span of RBCs or suppression of the bone marrow stem cell activity (Alkaladi et al., 2015). Likewise the Zinc Oxide nanoparticles (ZO-NPs) can also affect the haematology of the common carp by significantly reducing the value of RBC and Hb, and as a result there was a reduced O2 carrying capacity in exposed fishes (Channappa et al., 2018).

3.4. Effects of pesticides on haematological parameters

The use of pesticides is a worldwide practice used for control and eradication of pest in intensive agricultural production and fish farms (Oruç, 2010; Saravanan et al., 2011). Phenol and its chemical derivatives are essential for production of nylon, detergents, herbicides, and pharmaceutical drugs and can be present in aquatic environment from domestic and industrial wastewater (Michalowicz and Duda, 2007). Haematological alterations by phenol have been reported in fish (Roche and Bogé, 2000). Individuals of channel catfish *Ictalurus punctatus* exposed to phenol did not present variations in the blood parameters Ht, Hb and RBC during the exposure time. However, a significant rise in RBC followed by reduction in MCV and MCH were reported after a recovery period (De Moraes et al., 2015). These haematological alterations suggest an increased erythropoiesis and a presence of circulating young erythrocytes (Clauss et al., 2008). While an exposure of phenol in pacu *Piaractus mesopotamicus* resulted in significant rise of Hct, Hb and RBC. This increase could be due to spleen contraction or erythropoiesis, and to the excessive mucus observed during the toxic test (De Moraes et al., 2015). The 4-tert-octylphenol (OP) is one of the worldwide surfactants used as a food additive and can pollute the aquatic environment (Ying et al., 2002). The OP can cause hemodynamic stress in acará *Cichlasoma dimerus* with decrement in RBC, Hb, and RCV values, which can be reflected in an anemia (Rey Vázquez and Lo Nostro, 2014). Conversely, individuals of Mozambique tilapia exposed to phenolic compounds showed significant increase in the haematological parameters RBC, PCV and Hct (Varadarajan et al., 2013). Maybe due to an erythropoietic activity or a release of a large number of mature red blood cells in the general circulation as a compensatory reflex for poor oxygen uptake in prevailing hypoxic conditions (Wepener et al., 1992). The phenoxy acid herbicide (MCPA) is widely used in agriculture, forestry and horticulture (Kudsk and Streibig, 2003) and has been reported present in aquatic environments, however, little is known about its effects on fish. Lutnicka et al. (2018) evaluated the effects of this herbicide on common carp juveniles presented that a chronic exposure of MCAP induces only minor and transient alterations in red blood parameters but not in leukocytes. A differential WBC count showed a significant and persistent depletion of mature neutrophils, and monocytes, indicating a possible inflammatory process and immunosuppression caused by this herbicide (Lutnicka et al., 2018). While unlike the MCAP the synthetic pyrethroid pesticide Cypermethrin (25% EC) causes a significant decrease in RBC, Hb and PCV with variant tendency of WBC on juveniles of common carp and white carp (Neelima et al., 2015, 2016). Another synthetic pesticide extensively used for controlling pests in agriculture is the Quinalphos 25EC (QP), a highly toxic organophosphate classified as a yellow label pesticide, which has become a matter of concern (Das and Mukherjee, 2000). A chronic exposure to this pesticide caused a reduction on blood parameters RBC, Htc, MCV, MCH, and MCHC in the silver barb *Barbonymus gonionotus* in a dose-dependent way (Mostakim et al., 2015). The QP like others chemicals has the faculty to induce histological alterations in liver and kidney but the extent of damage varies depending upon the dose of toxicants, duration of exposure, toxicity of chemical, and susceptibility of the fish (Magar and Shaikh, 2013; Shanta et al., 2013; Mostakim et al., 2015). The Chlorpyrifos (CPS), a worldwide organophosphate pesticide used to control insects in agricultural, residential and commercial settings, has also been shown to be very toxic to fish (Deb and Das, 2013; Sunanda et al., 2016a, 2016b; Biswas, 2018). An exposure to CPS can significantly decrease erythrocyte, Hb, Ht and leucocyte as concentrations and exposure periods increased causing physiological problems like leukemia and immune system abnormalities in the freshwater fish spotted snakehead *Channa punctatus* (Malla et al., 2009; Ali and Kumar, 2012). The agricultural herbicide Clomazone can also alter the haematological parameters in a dose-dependent way as observed in juveniles of streaked prochilod *Prochilodus lineatus*. Calmozone concentrations higher than 5 mg L^{-1} seem to cause a significant decrease in the parameters Hct, Hb, HCM and MCHC, indicating an anemic condition. But at low concentrations an increase in RBC was observed, which could be due the release of new red blood cells into the bloodstream in response to splenic contraction, as an adaptive response to the stressor agent (Pereira et al., 2013).

In a previous study with common carp, Qureshi et al. (2016) pointed out that a sub-acute exposure with the pesticide fipronil and the insecticide buprofezin can induce biochemical, haematological, histopathological and genotoxic damage. At hematic level, both pesticide and insecticide (in combination or along) caused significant reduction in RBC, TC, Htc and Hb but an increment in WBC. The fungicide Cruzate also seems to be able to induce a progressive significant reduction in RBC, Hb, RVC, and MCHC in parallel to the increasing concentration of the fungicide, but an increase in WBC, MCV and MCH in the Mozambique tilapia (Desai and Parikh, 2012). Similarly, the two pesticides Chlorpyrifos and DDforce induce a significant reduction in the blood parameters RBC, PVC and Hb with an increment in WBC and MCHC in the African sharptooth catfish (Adewumi et al., 2018). Then, reduction in RBC may leads to development of hypoxic condition, which in turn may leads to increase in destruction of RBC or decrease in rate of formation of RBC due to non-availability of Hb content in cellular medium (Chen et al., 2004). The WBC enhance may indicate that the fish can develop a defensive mechanism to overcome the toxic stress during exposure period of curzate (Desai and Parikh, 2012). On the other hand, juvenile of African sharptooth catfish exposed to glyphosate herbicides showed significant elevations in RBC, HCV, MCH, PLT and WBC counts compared to control (Alohan et al., 2014). This may be as result of activation of protective mechanisms (Cazenave et al., 2005). Saravanan et al. (2011) also reported a similar effect of lindane (gamma-hexachlorocyclohexane) on haematological parameters in the same species as well as Ramesh et al. (2015) for exposure to Furadan; a carbamate pesticide is widely used in paddy fields. The levels of Hb, Hct, RBC, MCV, MCH and MCHC were decreased, whereas WBC increased in the treated fish. Such decrement in haematological parameters indicated an anemia probably due to hemosynthesis, and osmoregulatory dysfunction, erythrocyte destruction along with the damage in the gill tissues causing a reduction in oxygen carrying capacity of blood and inefficient exchange of gases (Jenkins et al., 2003; Seth and Saxena, 2003; El-Murr et al., 2015). While, the morari *Aspidoparia morar* exhibited to lindane presented a marked decline in RBC, Hb, Hct and WBC with fluctuating values for MCV, MCH and MCHC (Sachar and Raina, 2014). Which can be translated as a fish in anemia stage and a suppressed immune system. The phenolic compound Bisphenol A (BPA), classified as potent endocrine disruptors, detected in water environments by sewage discharges (Kamaraj et al., 2013), has been shown to have toxic effects in fish physiology (Liu et al., 2011; Faheem and Lone, 2013; Gentilcore et al., 2013; Liu et al., 2014). Recently, in a work done by Krishnapriya et al. (2017), the BPA caused a significant drop in the haematological parameters Hb, Hct, MCV, and MCH with a significant increment in WBC value in *roho labeo*. The RCB value, on the contrary, presented an initial increase with a subsequent decrement. The observed reduction in haematological values may be due to a reduction in the rate of formation of erythrocytes, destruction of them and/or an anemic condition of the fish due BPA toxicity (Jenkins et al., 2003; Seth and Saxena, 2003; El-Murr et al., 2015). The increase in WBC count indicates an immunostimulation against the toxicity of BPA as also observed in yellow perch *Perca flavescens* (Rogers and Mirza, 2013). Similar effect was reported in spotted snakehead by effect of Nonylphenol (NP) exposure, a worldwide used non-ionic surfactant and found in aquatic environment. The NP significantly decreases the value of RBC, Hb, PCV, MCH, MCV, and MCHC with a WBC increased. Causing an anemic state in fish, while the leukocytosis observed probably reflects increased demand for WBC for removal of cellular debris at a faster rate (Madhu and Pooja, 2015). Otherwise for Nile tilapia where the NP is apparently associated with a significant increase in RBC and PVC and an insignificant increase in Hb, and leukopenia (Ismail and Mahboub, 2016). Such RBC, PVC and Hb rises may be due to compensatory erythropoiesis due to elevated demands for O_2 or CO_2 transportation as a result of destruction of gill membranes which a common consequence of exposure to NP causing faulty gaseous exchange with asphyxiation (Zaki et al., 2010). Cuesta et al. (2008) also reported a non-negative effect on the gilthead seabream head-kidney leucocytes viability with an up-regulation of some immune-related genes after exposure to the organochlorines 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p′-DDE) and lindane, exhibiting mostly a genetic effect. By contrast, it seems that in early life-history stages the Dichlorodiphenyltrichloroethane (DDT) metabolite o,p-DDE can compromise the viability of lymphocytes triggering long-term humoral immunosuppression in the Chinook salmon *Oncoryhnchus tshawytscha* (Milston et al., 2003). Same reduction in lymphocyte-granulocyte viability associated to an increasing apoptotic cells was observed in both spleen and head-kidney of Chinook salmon (Misumi et al., 2005). Notwithstanding, any information exists regarding the direct effect of DDT and/or its metabolites on fish haematology.

Despite the clear evidence of the effects of pollutants on fish haematology, it is limited to data focusing on the effects of the residual pesticides/metals on the blood system of fish, especially on the correlations between different parameters and influencing the extent of environmental factors such as pollutant concentrations or/and exposure time in each parameter (Li et al., 2011a, 2011b).

4. Haematological indices as biomarkers in fish farm aquaculture

The study of haematological characteristics in cultured fish species is an important tool in the development of aquaculture system (O'Neal and Weirich, 2001; Percin and Konyalioglu, 2008; Mauri et al., 2011). It is necessary to know the basic environmental factors that influence on fish health (Bosisio et al., 2017), which they are traditionally been based on the conditions found in its natural habitat (Deacon and Hecht, 1996). In addition to the variation of the physical and chemical properties of water, availability and food type may even influence erythropoiesis in caged fish (Řehulka and Adamec, 2004).

4.1. Effects of controlled temperature on haematological parameters in captive fish

Temperature has consistently been identified as the primary abiotic factor controlling key physiological, biochemical and life-history processes in fish (Beitinger and Fitzpatrick, 1979). Therefore, knowledge of fish-thermal interaction is of fundamental importance to aquaculturist (Deacon and Hecht, 1996). How fish respond to changes in temperature can be evaluated through haematological parameters since cell number, maturation grade, etc. are factors that restrict the hematic cell responses (Houston et al., 1996). The rainbow trout during warm periods haematological parameters Hb, Hct, and RBC are slightly lower than in cold season, which can be linked to an elevate O_2-carrying capacity, and O_2 demand. These responses appear to be anti-adaptive or, at best, neutral (Tun and Houston, 1986; Houston et al., 1996). Meanwhile, leucocyte population increased significantly during the warm period, and decreased for cold period as was also observed in common carp (Engelsma et al., 2003) and in the channel catfish (Martins et al., 2011). This would indicate that temperature could have an effect on the haematology of fish modifying the kinetic of hematic cells (Martins et al., 2011; Engelsma et al., 2003). Fish can adapt to the increased temperature of their habitat but when a particular temperature exceeds thermal stress occurs. Individuals of Danube barbel *Barbus balcanicus* subjected to thermal stress by raising the water temperature showed an increase in MCV and PCV (Radoslav et al., 2013). Swelling of erythrocytes under adrenergic influence probably caused rise in MCV (Jensen, 2004), which is typical for the alarm phase of stress reaction (Wendelaar Bonga, 1997). While, the increase in PCV can be associated with an increase in oxygen demand (Radoslav et al., 2013).

4.2. Effects of controlled photoperiod on haematological parameters in captive fish

Photoperiod is a key factor for maintaining the physiological balance of fish, since several organs participate in receiving external light signals (Li et al., 2016). Consequently, photoperiod manipulation is another common technique employed in fish aquaculture in order to optimize the production of a species (Boeuf and Le Bail, 1999; Bromage et al., 2001; Guerrero-Tortolero et al., 2010; Stuart and Drawbridge, 2011; Gunnarsson et al., 2012; Aragón-Flores et al., 2017). Effects of stress induced by photoperiod manipulation on haematology in captive fish have been assessed (Solomon and Okomoda, 2012a, 2012b). However, few studies have been carried out with variable haematological responses (Srivastava and Choudhary, 2010). In the African catfish haematological parameters PCV, MCHC, MCH, WBC, RBC, Hb, Hct, and PLT presented variations according to photoperiod exposed (Solomon and Okomoda, 2012a). Fish submitted in a photoperiod of 24 h of light (24 L:00D) presented the lowest value of WBC, Hb, Hct, RBC, and PCV compared to fish submitted to a photoperiod of 24 h dark (24D:00 L) or 12 h light (12 L:12D). According to Solomon and Okomoda (2012a), the low level of PCV, Hct and Hb appears to be linked to a reduction in RBC, which seems to be associated to a depletion of ATP (Emelike et al., 2008), inability to transport excess sodium out of the cell membrane and a consequent haemolysis (Guyton and Hall, 2005). Whereas, individuals of Indian catfish exposed to artificial photoperiod of 24 L:00D and 00 L:24D, the haematological parameters RCB and WBC did not presented differences in both artificial photoperiod regimes. Nevertheless, a differential leukocyte count showed a lymphopenia and neutrophilia in fish submitted to 24 L:00D (Srivastava and Choudhary, 2010), which seems to be a characteristic of fish under stress as a direct cytolytic effect of cortisol on lymphocytes or as a distribution of immunological cells in lymphoid tissues (Espelid et al., 1996; Grzelak et al., 2017). In the great sturgeon *Huso huso*, changes in haematological parameters was observed due to the stress caused by photoperiod manipulation. An increment in Hct accompanied by a reduction in Hb and erythrocytes was found in fish under extreme 24 L:00D and 00 L:24D light regimes, what denotes the development of a possible anemia (Bani et al., 2009).

4.3. Effects of controlled salinity on haematological parameters in captive fish

Salinity is also extensively studied because it is considered a determining growth and survival factor in fish farming (Lisboa et al., 2015; Baliarsingh et al., 2018). There is also a relationship between salinity stresses associated with haematological alterations, which can have a physiological impact on the immune system (Choi et al., 2013). In Nile tilapia, the haematological parameter Hct and Hb presented a decreasing tendency accompanied by a drop in RBC, probably as a consequence of changes in the water content in the blood due to exposure to an increasing hyperosmotic environments (Bosisio et al., 2017; Elarabany et al., 2017). Meanwhile, WBC does not present significant differences in increasing salinity environments (Bosisio et al., 2017), but not so for environments with declining salinity, where a lymphopenia, neutrophilia and monocytosis can be observed leading to immune dysregulation (Choi et al., 2013). Whereas, the euryhaline species flathead grey mullet submitted to salinity of 25 and 45‰ reported also lowest levels of RBC, Hb, Hct compared to fish at salinity of 35‰, while WBC level was highest in fish at 25‰ and lower at 45‰ (Fazio et al., 2013c). The reduction in RCB, Hb, and Hct parameters may be attributed to salinity-induced osmoregulatory dysfunction (Girling et al., 2003), and decrement in WBC indicates an immunosuppressive effect some hemorrhagic injury caused by variation in salinity (Anyanwu et al., 2007). For the freshwater fish *Notopterus notopterus*, the haematological parameters Hb, Hct, RBC, WBC along with other blood index were raised after exposure to an increasing saline medium, this as response of fish trying to cope up with the changing salinity condition of the water (Kavya et al., 2016). Through induction of splenetic contractions and the subsequent mobilization of stored erythrocytes, in addition to an increase in muscle activity and the concomitant movement of water from plasma to muscle (Kavya et al., 2016). Then, understanding how seasonal variations can influence haemotological parameters can help to optimize husbandry practices (Faggio et al., 2014a).

4.4. Effects of farming system on haematological parameters in captive fish

The characteristics of farming system also seem to influence the haematological characteristics of cultured fish species. According to a study conduced by Fazio et al. (2013b) in the gilthead sea bream, the fish rearing with different aquaculture system have different baseline haematological value. Fish in onshore farming system tend to present lower value of RBC, Hct and WBC and higher value of MCV, MCH, MCHC, and Hb than fish in offshore farming system. The increase in MCV and Hb reported in onshore system could be due to compensatory mechanism to balance the low value of RBC; likewise the low value of WBC indicates a weakened defense in fish due to a much lower present water quality than in an offshore system (Fazio et al., 2013a). However, fish in recirculating systems tend to present lower levels of haematological variables than fish in tidal systems probably to relatively high physical and metabolic activity in fish, which are known to elicit a higher erythrocyte to plasma ratio in response to tidal shifts (Akinrotimi et al., 2010, 2011). Then, water quality in aquaculture is an important factor to consider since it directly influences the evaluation of haematological parameters as well as fish health (Küçük, 2010; Fazio et al., 2013b; Gorjipour, 2014). Seriani et al. (2011) indicated a strong association between the water quality and haematological changes in Nile tilapia. Fish in ponds with poor water quality exhibited increased immature erythrocytes and decreased of lymphocytes, total leukocytes and neutrophyls and thrombocytes (Seriani et al., 2011). Additionally, acclimation to captivity, a procedure commonly used in aquaculture, is a stressing factor able to alter the physiology of fish that in extreme cases results in mortality (Akinrotimi et al., 2007, 2009). Acclimation procedure (method and period) appears to exert an effect on fish haematology (Gabriel et al., 2004, 2011; Ezeri et al., 2004; Akinrotimi et al., 2007, 2010). In most of these studies a significant decline in the blood parameters RBC, Hct, and Hb is observed after a period of acclimation as reported for African catfish (Gabriel et al., 2011), blackchin tilapia *Sarotherodon melanotheron* (Akinrotimi et al., 2007), Guinean tilapia *Tilapia guineensis* (Akinrotimi et al., 2010), Nile Tilapia (Gabriel et al., 2011), and flathead grey mullet (Faggio et al., 2014b). The significant reduction on these parameters can be an indicator of severe anemia caused by acclimation stress effect (Akinrotimi et al., 2010; Faggio et al., 2014b). Notwithstanding, fish may be able to recover from an anemia caused by various adverse environmental and/or aquaculture factors as demonstrated in flathead grey mullet (Fazio et al., 2015). After a reduction in RBC, Hct, Hb, and WBC due to a bleeding period, fish prepare themselves for the persistence of stress, reorganizing the hematopoietic response in the kidney to contrast the injury from anemia (Kondera, 2011; Fazio et al., 2015). Instead, an increase in WBC is reported in most cases, which may be as result of recruitment of more cells to combat the effect of acclimation in an attempt to maintain external homeostasis (Gabriel et al., 2011). Hence, acclimation-induced stress causes alterations in blood, which react in response to disturbances in both metabolic and haem activities of fish exposed to acclimation to captivity (Akinrotimi et al., 2010; Faggio et al., 2014b, 2014c). Handling and transportation of fish are factors normally employed into aquaculture that may also lead to metabolic disturbance; enzymatic dysfunction, haematological variations, and several other malfunction in fish (Kurosvskaya and Osadchaya, 1993). According to a study carried out by Adeyemo et al. (2009) in the African catfish, handling and transportation stress can cause changes (non-significant) in haematological parameters Hct, Hb, and RBC compared to a non-stressed fish group, but a significant decrease in WBC, which can make the fish susceptible to disease, parasite infection and even death (Wiik et al., 1989). Thus, changes in the composition of circulating WBC can be more reliable indicators of chronic crowding stress (Pottinger and Pickering, 1987) as reported also in the pejerrey *Odontesthes bonariensis* with a described lymphopenia and neutrophilia (Zebral et al., 2015). Presumably glicocorticoid hormones can modulate the lymphocytes redistribution from blood to another tissues, and stimulate the release of neutrophils from leucopoetic organs into the blood (Dhabhar et al., 1996; Espelid et al., 1996; Grzelak et al., 2017).

4.5. Effects of dietary supplements on haematological parameters in captive fish

On the other hand, the use of specific substances as immunostimulant is being introduced into fish farming routine procedures in order to improve the fish health with significant effect on haematological and biochemical parameters (Kumari and Sahoo, 2006; Yonar et al., 2012; Carbone and Faggio, 2016; Hoseinifar et al., 2018; Rashidian et al., 2018). In the European carp *C. carpio carpio*, propolis has a stimulating effect on the immune system, and a protective action on the haematogical parameters RBC, Ht, Hb counteracting the pesticide-induced toxicity such as CPF or Malathion (Yonar et al., 2012; Yonar et al., 2014). Both CPF and Malathion are broad-spectrum organophosphate pesticides for agriculture, domestic and public health purposes (Ali et al., 2009; Moore et al., 2011). Exposure to these pesticides can affect growth, swimming ability, and depletion of anti-oxidant system, biochemical and haematological parameters among other, even at a low concentration (Brewer et al., 2001; Girón-Pérez et al., 2006; Sweilum, 2006; Venkataramana et al., 2006; Huculeci et al., 2009; Tripathi and Shasmal, 2010; Yonar et al., 2014; Yonar et al., 2012; Yonar, 2018; Ural, 2013; Narra et al., 2015; Zahran et al., 2018). Another substance with immunostimulatory, anti-inflammatory, and anti-oxidant effects is the Gum Arabic (GA) (Cuesta et al., 2005). According to Faggio et al. (2015), fish of flathead grey mullet fed with 12% GA-pellets presented an increment only in TC values with no adverse effects on RBC, Hct, Hgb, WBC, MCV, MCH, MCHC values. Then, a positive effect on TC value suggests an immunostimulatory action by GA on fish (Passantino et al., 2005). Recently, the use of homeopathic medicine is proving to have an equally stimulating effect in fish leucocyte cells but without negative side effects like conventional vaccines (Ortiz-Cornejo et al., 2017). A work done by Mazón-Suástegui et al. (2018) showed that the use of ultra-diluted substances derived from phosphorus, silica and pathogenic *Vibrio* potentially stimulate leukocyte cells, mainly macrophages, as reported in juveniles of longfin yellowtail *Seriola rivoliana*.

The inclusion of phytoestrogens in fish feed has been used in monosex culture and sexual reversal in aquaculture (Gabriel et al., 2015; Nwangwu et al., 2016). A wide range of consequences on various physiological processes in fishes has been reported (Citarasu, 2010; Chakraborty and Hancz, 2011; Chakraborty et al., 2012). In blood, the use of pawpaw (*Carica papaya*) seed meal (PSM) can cause reduction in parameters such as PCV, Hb, MCH and MCV without significantly altering values in RBC and WBC as reported for freshly hatched fry of Nile tilapia. However, any significant reduction or change in these parameters was indicative of anemia or stress (Solomon et al., 2017). Otherwise, in adults of the same species, PSM can cause a significant reduction in RBC, WBC, Hb, MCV and MCH, triggering hemorrhage and other physiological alterations to death as concentration and time of exposure to PSM increases (Ayotunde and Ofem, 2008; Ayotunde et al., 2010, 2011).

Finally, haematology is an important tool that can be used as an effective and sensitive index to monitor physiological and pathological changes in fishes (Kori-Siakpere et al., 2005) by the variants commonly used in aquaculture (Valenzuela et al., 2007; Corrêa et al., 2017).

4.6. Haematological parameters in transgenic fish

Induction to triploidy has been widely diffused of fish growth enhancement in the modern aquaculture industry (Maclean and Laight, 2000; Hulata, 2001). In addition a broad range of pleiotropic effects on morphology, physiology, metabolism, immunology and behavior have been shown (Kerby et al., 2002; Guan et al., 2008). Haematological indices can provide baseline data and evaluate the feasibility of intensive hybrid production and culture (Akhan et al., 2011). According to Benfey (1999) triploid fish present larger erythrocytes with increased hemoglobin content but reduced in number than diploid erythrocyte. Estructural modifications that could have a negative impact on the quantity of bound and transported oxygen and carbon dioxide. Cogswell et al. (2002) have been speculated that alterations in transgenic fish erythrocyte morphology are likely an adaptive mechanism to meet increased metabolic requirements of such fish. Based on results obtained in triploid species, it has been postulated that it does not produce the appearance, under optimal conditions, of disadvantageous physiological pathology (Peruzzi et al., 2005). However, triploid individuals have increased susceptibility to stress, oxygen deficiency, and pathogens. Specimens of Siberian sturgeon, *Acipenser baerii*, subjected to triploidization exhibited lower RBC, increased Hb, MCH and MCHC. In addition, reduction in WBC mainly lymphocytes was also observed, reported. In spite of this, the changes in erythrocyte volume did not seem to have negative effect, suggesting that triploid Siberian sturgeon can be more resistant to stress and more sensitive to oxygen deficit and disease factors, which can lead to increased mortality (Rożyński et al., 2015). Triploidization in Caspian salmon *S. trutta caspius* a remarkable decrease in RBC, Hb, Ht and WBC was also reported but without significant difference in MCV, MCH, and MCHC among diploid and triploid fishes (Jamalzadeh et al., 2008). In most comparative haematological studies, the total blood volume (%) of triploids is similar as in diploids, reason why some authors suggest that there is no significative difference in Hb, Ht or other haematical parameters between diploids and triploids fish (Cogswell et al., 2002; Cal et al., 2005; Peruzzi et al., 2005; Akhan et al., 2011; Li et al., 2011a, 2011b; Fukushima et al., 2012).

5. Mitochondria as a tool in haematological analyzes

In fish, erythrocytes have been demonstrated to possess complete cellular machinery with functional ribosomes (Lane and Tharp, 1980), and mitochondria (Ferguson and Boutilier, 1989; Pica et al., 2001; Moyes et al., 2002; Rey Vázquez and Guerrero, 2007). Allowing protein synthesis and full cellular activity (Currie et al., 1999). The red blood cells are long-living cells with a relatively high level of respiratory activity. This determines the importance of the studies on the evaluation of the energy potential of mitochondria in the erythrocytes (Silkin et al., 2017). Moreover, due to their sensitivity to xenobiotics, fish erythrocytes are often used to evaluate xenobiotic-induced damage to different cellular compartment (Tiano et al., 2003; Witeska, 2013). Mitochondria are employed to investigate in great detail the mechanism of toxicity of xenobiotics, because of the key role of these organelles in the mechanism of cell death (Zamzami et al., 1995; Petit et al., 1995). This may be due to mitochondria being both the source and the final target of free radicals effects. It seems that mitochondrial susceptibility to xenobiotics is associated to some factors. One of this is the presence of cytochrome P450s in mitochondria, which can activate chemicals that are relatively nonreactive prior to metabolism, such as PAHs and mycotoxins (Dong et al., 2009). On the other hand, the high lipid content of mitochondrial membranes facilitates accumulation of lipophilic compounds such as polycyclic aromatic hydrocarbons (PAHs) (Backer and Weinstein, 1982), some alkylating agents (Wunderlich et al., 1972), and certain organic chemicals, particularly amphiphilic xenobiotics such as ethidium bromide, paraquat, 1-methyl-4-phenylpyridinium (MPP+), and others (Cohen, 2010). Cationic metals, such as Pb, Cd, HG, and Mn, have also been shown to accumulate in mitochondria preferentially (Atchison and Hare, 1994; Bucio et al., 1999; Castellino and Aloj, 1969; Gavin et al., 1992; Sokolova et al., 2005; Gomes et al., 2015). A study done by Tiano et al. (2003) evidenced the toxic effect of tributyltin chloride (TBTC) on erythrocytes and leukocytes in fish of rainbow trout. The TBTC is able to display a consistent drop in mitochondrial membrane potential both in erythrocytes and leukocytes, and release of proapoptotic proteins (cytochrome *c*, caspase-3), and consequently mitochondrial pathways are able to trigger apoptosis in these cell type. Effects that can be reversed through an increase in antioxidant and detoxifying enzyme activities by supply diets with low-fat content (Lionetti et al., 2012).

Finally, mitochondria are essential organelles for ATP production, cell life-and-death process (Lee and Wei, 2012), and primary source of reactive oxygen species (ROS), which can be both cytotoxic and regulatory (Dröge, 2002). Then, the ability of cells to produce heat due to hydrolysis that produces ATP heat over a long period of time indicates the importance of the study of the mitochondrial bioenergetic complex in erythrocytes (Silkin et al., 2017). Then, mitochondria seem to be a convenient material to study the bioenergetics activities, biogenesis and disappearance of mitochondria in these cells as well as in red blood cells in general.

6. Conclusions

The present review shows that a great variety of exogenous and endogenos factor participate in the modulation of haematological parameters in fish; stress effects of environmental factors, biological peculiarities of species, size and the way of their breeding. So, the alteration of one or several of these factors can induce stress and alter the haematological parameters leading to physiological dysfunctions. It summarizes some of the most common haematological abnormalities documented in fish and an idea of factors that cause haematological variations and alterations that justify further investigation and documentation. For example, Hct or PCV is essential in clinical haematology to determine alterations in RBC leading to heamolytic crisis that results in severe anemia in fish exposed to heavy metals and herbicide respectively. Although the robust interpretation of fish eritrogram and leukogram is often hampered by the lack of reference values, this knowledge deficit represents an opportunity for expansion in studies of clinical pathology and adaptability among fish.

7. Perspectives

Unfortunately, the accumulation of various types of xenobiotics in water bodies is increasing as the amount and types of wastewater generated by a snowballing human activity. Therefore, it is necessary to carry out more basic studies for all new pollutants on the fish haematology that allows having a starting point before any environmental alteration. It is also necessary to consider that wild fish from natural environments may exhibit different physiological behaviors related to their survival strategies. In addition, another important point to consider when making an environmental or aquaculture assessment is to take into account additional sources such as dietary exposure (Putti et al., 2015; Meador et al., 2017; Lepretti et al., 2018). A more multidisciplinary framework in field studies is also essential for better understanding wildlife disease outbreaks and multi-trophic impacts on ecosystems. Therefore, a complementary bioenergetics and dynamic mitochondrial study would give greater strength to a haematological analysis both in environmental and aquaculture evaluations. Since there is no standardized method to determine the health of the fish or the environment, it is the combination of indicators of impairment that will give us the best diagnostic picture (Todgham and Stillman, 2013). Haematology is still an opaque science for wildlife but promoting its standardization of pre-analytical procedures plus some suggestions for a more systematic examination of blood smears to increase the diagnostic value of blood data. Establishing various hematologic changes that occur in fish is crucial in assessing their health and also provides the opportunity to expand the use of some fish as models for human disease.

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Declaration of interest

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