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Original Research Article

Haemotoxicity in Rats Exposed to Cadmium and Iron Polluted African Catfish from a Southern Nigeria River

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Abstract: This study evaluated the effects of consuming contaminated *Clarias gariepinus* fish on the haematological parameters of Wistar albino rats. Twenty- four adult male rats were randomly assigned to four groups I, II, III, IV (n = 6 per group). These rats were fed ad libitum for 90 days with a diet composed of wild *Clarias gariepinus* fish from the two different river bodies admixed with commercial rat pellet. Group I served as controls, while Group II rats ingested *Clarias gariepinus* fish from the polluted Nun river. Group III consumed fish from Otamiri river, while Group IV was fed 100g of polluted fish from Nun river along with 1mg of Vitamin C per 100g of body weight dissolved in drinking water. Results showed that group II rats exhibited a significant reduction in haemoglobin concentration (8.70 ± 0.26 g/dl) compared to Groups I, III, and IV rats (10.32 ± 0.41 g/dl, 10.28 ± 0.14 g/dl, and 12.96 ± 1.3 g/dl) respectively at $P < 0.05$. Haematocrit value was significantly reduced in Group II rats (43.17 ± 0.90 %) compared to groups I, III and IV (45.55 ± 0.37, 48.21 ± 2.3, 49.5 ± 1.9) % respectively at $P < 0.05$. Erythrocyte count significantly reduced in Group II rats (2.63 ± 0.70 × 10^6/µL) compared to groups I, III and IV (3.30 ± 0.20, 3.59 ± 0.36, and 5.75 ± 0.6 × 10^6/µL) respectively at $P < 0.05$. White Blood Count was markedly increased in group II rats (4.46 ± 0.15) compared to I, III and IV (3.54 ± 0.18, 3.90 ± 0.02, and 3.65 ± 0.03) respectively at $P < 0.05$. The lymphocyte and eosinophil counts in group II were significantly elevated (7.49 x 10 cells/mm^3 and 1.5 x 0.24 x 10 cells/mm^3) compared to groups I (3.35 x 10 cells/mm^3 and 0.5 x 10 cells/mm^3), group III (3.6 x 10 cells/mm^3 and 0.6 x 10 cells/mm^3) and group IV (4.23 x 10 cells/mm^3 and 0.3 x 10 cells/mm^3) at $P < 0.05$. there were no significant differences in neutrophil, basophil and monocyte counts. Mean corpuscular volume and mean corpuscular hemoglobin values were also significantly increased in groups II, III and IV rats (88.7 ±0.15 and 29.8 ±0.41, 62.5 ±0.42 and 25.5 ±0.31, and 57.2 ±0.31 and 28.5 ±0.40) mm^3 to group I rats (41.3 ±0.28 and 21.1 ±0.60) mm^3 at $P < 0.05$. However, there was a significant rise in the mean corpuscular volume of group II rats compared to groups III and IV at $P < 0.05$. Conversely, the mean cell hemoglobin concentration was elevated in group I rats (26.4 ±1.2 mm^3) compared to experimental groups II, III and IV respectively (21.4 ± 0.87, 22.9 ± 0.94 and 23.7 ± 0.70) mm^3. This study probably indicates that some haematological parameters are adversely affected among rats exposed to cadmium and iron polluted African catfish from a Southern Nigeria River.

Keywords: *Clarias gariepinus*, heavy metals, haematological parameters, albino wistar rats.

INTRODUCTION

Nigeria is home to numerous important river systems. Nearly two-thirds of the nation is located within the watershed of the River Niger and other significant river systems, such as the Benue, Cross, Anambra, Imo, Qua Iboe, Ogun, and Oshun rivers, as well as their byproducts. It's interesting to note that artisanal fisherman rely on these rivers for their living, and these rivers also support other local economies. The ecosystem of deteriorated of several river bodies have significantly deteriorated due to pollution (Olapade *et al.*, 2015).

Freshwater systems are impacted by a range of pollutants, including oil and gas residues, organic and inorganic contaminants, and microbial pathogens. Heavy metals are among the most hazardous inorganic contaminants in aquatic ecosystems (Sahiti *et al.,* 2018). Several studies have documented the adverse effects of heavy metal toxicity on haematological parameters (Ahmed *et al.,* 2022; Capitag *et al.*, 2022; Sani *et al.*, 2023).

Additionally, blood is frequently employed in environmental monitoring and toxicological research as a promising indicator of pathological and physiological changes brought on by toxic stress in organisms (Saravanan *et al.*, 2021).

Studies in fishes have also shown that poor water quality due to pollution increases blood parameters in fishes (Singh and Tandon, 2009). These water pollutants accumulate in the blood stream of the fishes, distort the osmolarity of the blood cells, increase the fragility of blood cells leading to haemolysis of red cells, destruction of leucocytes in the tissues and blood stream, damage the organs and kill these fishes. Fishes exposed to Cd, have reduced red blood cells (RBC), haemoglobin (Hb) and haematocrit (Hct) (Al-Asgah *et al.*, 2015). The consumption of contaminated fish poses significant ecological and public health risks. The consumption of fish contaminated with harmful metals or toxins including dioxins, pesticides, methylmercury, polychlorinated biphenyls (PCBs), and plastic debris is raising the rates of sickness and mortality worldwide. When ingested in excess, these pollutants can have detrimental health consequences on humans, particularly in pregnant, lactating, and young children. They also build up in fish tissues (Montana *et al.*, 2022; Chen and Dong, 2022).

In the present study, Albino Wistar rats were given African catfish (Clarias gariepinus) from the Nun and Otamiri rivers in Bayelsa State (Southern Nigeria) and Imo State (Eastern Nigeria) for ninety days. The following haematological parameters were assessed: mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. These metrics included the number of red blood cells, leucocytes, platelets, hemoglobin, packed cell volume, mean hemoglobin concentration in cells, and differential white blood cell count.

MATERIALS AND METHODS

Twenty-four healthy adult male Wistar rats (180 – 200g; 3-4 months old) were procured from the animal house of the Department of Pharmacology, Niger Delta University, Bayelsa state, Nigeria. Animals showing signs of ill-health were excluded.

Body weights were recorded weekly using a weighing balance throughout the 90- day feeding period.

This research was endorsed by the University of Port Harcourt Research Ethics Committee. The rats were indiscriminately allocated to 4 groups with 6 rats per group, after being allowed to acclimatize to laboratory conditions in well ventilated cages for two weeks. Compounded feed were given *ad libitum* to the rats subsequent to a mean daily feed consumption which had been determined during the period of adaptation. Distilled water was provided *ad libitum*. The control group and experimental groups II, III and IV rats were fed for 90 days.

Group I rats: The control rats were fed with rat pellet (Pfizer Livestock Plc, Lagos, Nigeria) daily. Group II rats were fed with 100g of polluted fish from the Nun river added to rat chow.

Group III rats were fed with 100g of Polluted fish from Otamiri river added to rat chow, whereas.

Group IV rats were fed with 100g of Polluted fish from Nun river + Vitamin C Supplementation of 1mg/100g body weight dissolved in water and mixed with rat chow.

On day 90, the rats were sacrificed under Chloroform anaesthesia. 5ml of blood was achieved via cardiac-puncture for haematological examination.

Data from the animal experimentation were analysed for the calculation of Standard Error of Mean. One-way ANOVA was employed for testing the hypothesis. Data were analysed to calculate the standard error of mean (SEM). A P value of <0.05 level was considered significant.

RESULTS

In the present study, exposure of Wistar rats to a polluted fish diet for 90 days resulted in a number of haematological alterations. Group II rats (fed with fish from River Nun) showed a significant reduction in haemoglobin concentration (8.70 ± 0.26 g/dl) compared to Groups I (10.32 ± 0.41 g/dl), III (10.28 ± 0.14 g/dl), and IV (12.96 ± 1.3 g/dl ($P < 0.05$).

Haematocrit (PCV) was significantly reduced in Group II rats (43.17 ± 0.90 (%)), compared to groups I, III and IV respectively (45.55 ± 0.37, 48.21 ± 2.3, 49.5 ± 1.9 (%)). for Groups I, III and IV respectively ($P < 0.05$).

Erythrocyte (RBC) count too was significantly decreased in Group II rats (2.63 ± 0.70 × 10^6/µL) compared to Groups I (3.30 ± 0.20 ×10^6/µL), Group III (3.59 ± 0.36 ×10^6/µL), and Group IV (5.75 ± 0.6 × 10^6/µL) (($P < 0.05$).

Conversely there was a marked increase in total White Blood/Leucocyte Count (WBC) in all the groups with the greatest increase found in group II rats (4.46 ± 0.15) compared to groups I, III and IV respectively (3.54 ± 0.18, 3.90 ± 0.02, 3.65 ± 0.03) ($P < 0.05$).

The lymphocyte and eosinophil counts in group II were significantly elevated (7.49 x 10 cells/mm^3 and 1.5 x 0.24 x 10 cells/mm^3) compared to groups I (3.35 x 10 cells/mm^3 and 0.5 x 10 cells/mm^3), group III (3.6 x 10 cells/mm^3 and 0.6 x 10 cells/mm^3) and group IV (4.23 x 10 cells/mm^3 and 0.3 x 10 cells/mm^3) ($P < 0.05$). However, there were no significant differences in neutrophil, monocyte and basophil levels of group II rats (6.12 x 10 cells/mm^3, 0.10 x 10 cells/mm^3 and 0.11 x 10 cells/mm^3) compared with groups I (6.41 x 10 cells/mm^3, 0.10 x 10 cells/mm^3 and 0.30 x 10 cells/mm^3), group III (5.96 x 10 cells/mm^3, 0.11 x 10 cells/mm^3 and 0.18 x 10 cells/mm^3) and group IV (6.54 x10 cells/mm^3, 0.30 x 10 cells/mm^3 and 0.24 x 10 cells/mm^3.

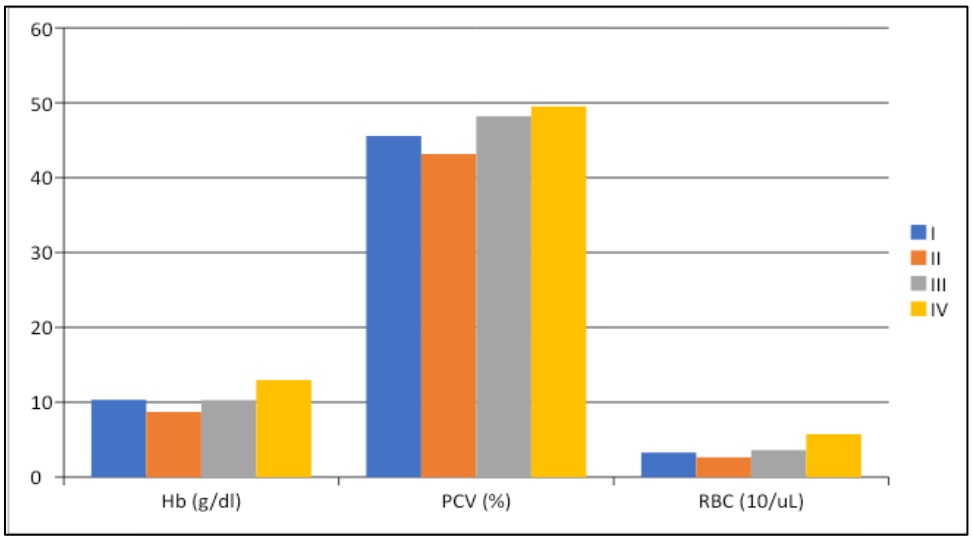

Figure 1: Effects of polluted fish packed cell volume (%) and red blood cell (RBC) count on control group I, II, III and IV rats at $P < 0.05$diets on hemoglobin (Hb)

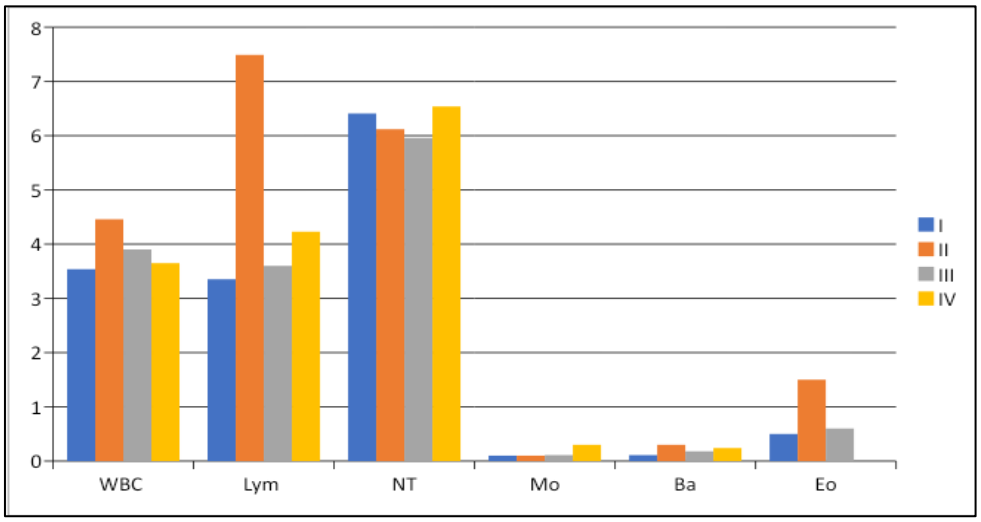

Figure 2: Effects of polluted fish diets on total white blood cell count (WBC), lymphocyte count (Lym), neutrophil count (NT), monocyte count (Mo), basophil count (Ba) and eosinophil count (Eo) (10 x cell/mm^3) in group I, II III and IV rats at $P < 0.05$

The results in figure 3 showed significant elevation in the MCV and MCH values of group II, III and IV (88.7 ±0.15 mm^3 and 29.8 ± 0.41 mm^3, 62.5 ± 0.12 mm^3 and 25.5 ± 0.31 mm^3, 57.2 ± 0.31 mm^3 and 28.5 ± 0.40 mm^3) compared to control group I (41.3 ± 0.28 mm^3 and 21.1 ± 0.60 mm^3) at $P < 0.05$. Meanwhile, the MCV was significantly elevated in group II compared to groups III and IV. MCHC was significantly elevated in the control group I (26.4 ± 1.2 mm^3) compared to group II, III and IV (21.4 ± 0.87 mm^3, 22.9 ± 0.94 mm^3 and 23.7 ± 0.7 mm^3).

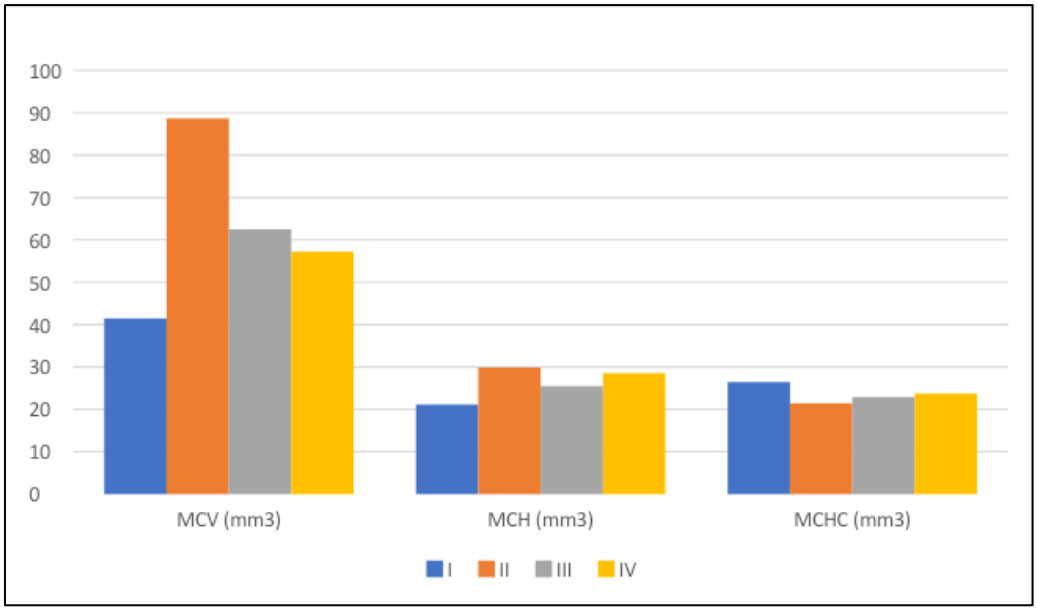

Figure 3: Effects of polluted fish diets on MCV, MCH and MCHC in control group I, II, III and IV rats at $P < 0.05$

DISCUSSION

The erythrocyte count, PCV, and Hb content all significantly decreased in Group II rats that were fed River Nun contaminated fish. The decline may be related to the presence of heavy metals in the Nun River. Previous studies have shown that heavy metals associated with crude oil spills significantly alter the physicochemical, microbiological, and hydrobiological characteristic of the Nun river which serves as the main supply of drinking water, aquatic food, and recreational opportunities for the populations along its banks and estuaries and are impacted by heavy metals linked to crude oil spills (Ezekwe, *et al.*, 2014; Ifelebuegu *et al.*, 2017). More so, results from surface water studies of Nun river indicated a significant deterioration of river water quality due to petroleum related activities characterized by high concentration of heavy metals such as cadmium, chromium, copper, lead, nickel and zinc as well as noticeable changes in phytoplankton, zooplankton and microbial diversities (Osuji and Onojake, 2004; Ifelebuegu *et al.*, 2017; Aghoghovwa *et al.*, 2018; Gijo and Allagoa, 2022).

The elevated concentrations of cadmium and iron metals in the Nun River likely contributed to the significant reduction in red blood cell count observed in Group II rats fed with contaminated fish. Anaemia and heavy metal pollution have been linked in a number of studies. Exposure to blood cadmium and lead was strongly correlated with hemolysis and abnormal erythropoietic function.

(Peters *et al.*, 2021), whereas, nickel generates cytotoxic reactive oxygen species (ROS) in human red cells which cause oxidative damage that can decrease the oxygen carrying capacity of blood and also leads to anaemia in pregnant women (Pieczyaska *et al.*, 2021). Cadmium (Cd) has been demonstrated to be a major cause of anemia through hemolysis, iron deficiency and insufficient erythropoietin production (Horiguchi *et al.*, 2011). Furthermore, rats on a high-zinc diet had a marked decrease in hemoglobin, hematocrit, MCV, MCH, and MCHC values, indicating a microcytic, hypochromic anemia, according to Yanagisawa *et al.*, (2009). When compared to rats fed a regular diet, the rats fed the high zinc diet also showed a significant drop in serum iron levels. Curiously, in spite of this finding, the two groups' erythrocyte counts were comparable, even though iron deficiency anemia often results in a lower erythrocyte count. Despite being "essential" micronutrients for the homeostatic regulation of biological processes, zinc, copper, nickel, cobalt, manganese, chromium, and even iron become toxic at high tissue concentrations.

While there will be an initial erythrocytosis, prolonged consumption of cadmium and iron-polluted *clarias* fish will eventually result in anemia because cadmium interferes with iron metabolism, and the elevated iron itself will cause a defective erythropoiesis due to oxidative stress damage and altered hemoglobin synthesis (Adebayo *et al.*, 2007; Moneim, 2015; Jabeen and Chaudhry, 2010; Abdel-warith *et al.*, 2011).

Between 1976 and 2014, approximately 3.1 million barrels of crude oil enriched with manganese, iron, copper, zinc, lead, and nickel leaked into the Niger Delta's waterways (Chinedu and Chukwuemeka, 2018). It is reasonable to assume that the Nun River is contaminated with accumulated heavy metals that resulted in a decrease in the red cell count, PCV, and Hb concentration in group II rats. This is because these heavy metals are linked to crude oil spills (Osuji and Onojake, 2004), and sediments taken from the river revealed high levels of lead, zinc, nickel, cadmium, and manganese (Gijo and Allagoa, 2022).

Meanwhile, there were significant elevations in the red cell count, PCV and Hb concentration in Groups I, III and IV. The Otamiri river is a source of drinking water for many households in Owerri with no significant presence of waste plastic dumps, oil drilling or spillage thus no heavy accumulation of heavy metals in the river. Therefore, Group III is expected to have red cell count, PCV and Hb concentrations near normal (control, Group I versus Group III). In the Group IV, the effect of heavy metal on red cell was attenuated by vitamin C supplementation. Johnston *et al.*, (1993) indicated that vitamin C supplementation (500 mg/day) maintains reduced glutathione concentration in the blood and improves overall antioxidant protection capacity of blood and maintains redox properties of human red cells (Eigenschink *et al.*, 2021). Vitamin C has been shown to play an important role in the kinetics of iron metabolism and utilization of iron for red cell formation (Finkelstein *et al.*, 2012) and improves absorption of dietary iron in the intestine (Fidler *et al.*, 2003), therefore it is plausible to suggest that Vitamin C contributed to the overall improvement of red cell components in the group IV rats fed with polluted fish from river Nun plus vitamin C supplementation in contrast to group II fed with polluted fish from river Nun without vitamin C supplementation. Fox *et al.*, (1971) also showed that Vitamin C pre-treatment simultaneously with a heavy metal blocks the detrimental effects of the metal on haematological parameters of rats compared to controls.

However, the WBC, lymphocyte, and eosinophil counts in group II rats significantly increased. Given the significant degree of open defecation in the river nun, the high concentration of lymphocytes and eosinophils is not surprising. According to a study by Silas-Olu and Alagoa (2022), the majority of coliform bacteria were ascribed to open defecation by humans, when the number of coliform bacteria surpassed the international allowed limit. Furthermore, it has been demonstrated that Bayelsa State contributes significantly to the total number of open defecators (Sample *et al.*, 2016).

Remarkably, the ability of bacteria to elicit an immune response depends critically on their immunogenicity (Steimle *et al.*, 2019). It's possible that the contaminated fish from the Nun River caused an invasion of enteric bacteria, particularly coliform bacteria. Although coliform bacteria, which are gram-negative bacteria found in aquatic environments, do not cause serious illness, their presence suggests the presence of other faecal pathogenic organisms, which include bacteria, viruses, protozoa, and numerous multicellular parasites that cause disease (Li and Liu, 2019). It is expected that the numbers of B and T lymphocytes will rise due to the presence of disease-causing bacteria and viruses, as shown by the increasing lymphocyte count in figure II. Research has demonstrated that eosinophils can destroy parasite larvae. (Capron *et al.*, 1979; Buys *et al.*, 1981), nematode larvae (Yasuda and Kuroda, 2019). The ingestion of polluted fish from the river Nun triggered lymphopoiesis and eosionophilia leading to an elevated lymphocyte and eosinophil counts.

The calculated blood indices which are usually derived from primary haematology tests include MCV, MCH and MCHC. These indices are particularly important in diagnosing mammalian anaemia (Coles, 1986). Changes in these haematological parameters may result from a homeostatic response to counteract the toxicity of a pollutant or toxin by stimulating erythropoeisis or alternatively, it could be linked to a reduction in red blood cells, haemoglobin and haematocrit due to increased disruptions in metabolic and haematopoeitic functions in mammals exposed to sublethal levels of pollutants.

MCH – Mean Corpuscular Haemoglobin is a value that denotes the average amount of haemoglobin in each erythrocyte and is derived by dividing the total haemoglobin by the number of red blood cells. Mean Corpuscular Haemoglobin Concentration meanwhile is a measure of the concentration of haemoglobin in a given volume of erythrocytes reflecting the average amount haemoglobin relative to the size of the erythrocytes. Thus, MCH and MCHC both describe the average haemoglobin content of erythrocytes, but in different ways. Wherein MCH indicates content of haemoglobin per erythrocyte, MCHC reflects the amount of haemoglobin per unit volume of erythrocytes.

Apart from diagnosing anemia's, MCHC is relevant in characterizing types of anaemia i.e. Hypochromic or Hyperchromic anaemia. MCV provides insights into different anaemia types i.e. Microcytic, Normocytic, and Macrocytic. A decrease in MCV values signifies that the erythrocytes have shrunk, either due to anaemia, stress, impaired water balance, or by a large concentration of immature erythrocytes that have been released from the reduced haemoglobin in tissues (reticulocytosis) (Kumar *et al.*, 1999).

Even at very low levels, prolonged consumption of cadmium and iron-polluted fish by rats causes biological effects that can be additive, potentiating, or synergistic. A notable decrease in MCHC has been noted in this scenario, indicating a disruption in the processes involved in the biosynthesis of hemoglobin (Lee and Kim, 2019).

This study differs from others that found that rats given individual and combined doses of hazardous metals showed blood pictures of normocytic, normochromic anemia with no alterations in MCH and MCHC following acute therapy (El-Boshy *et al*., 2014; El-Boshy *et al*., 2017; Cobinna *et al*., 2015).

Almost a quarter century ago, Shakoori *et al*., (1990) noted a reduction in MCHC when rabbits ingested the newly developed pyrethroid insecticide bifenthrin (talstar) orally for a month. Reduction in MCHC suggests that there was a decrease in haemoglobin synthesis leading to an associated decrease in oxygen carrying capacity in the experimental animals. Chronic co-exposure of Cd and Fe polluted fish in rats even in very low levels may result in a number of biological actions which may be synergistic, potentiation or additive. Thus rats ingesting a combination of Cadmium and Iron polluted fish had a significant reduction of MCHC suggesting an interference with the biosynthesis of haemoglobin (Lee and Kim, 2019).

In mammals, increases in MCV greater than 100 femtoliters (fL) are indicative of Macrocytosis. In situations where there is an associated decrease in MCHC, the blood picture is that of a macrocytic, hypochromic anemia. This condition may result from an enhancement or augmentation of the activity of the mammalian bone marrow. Lack of haemopoeitic factors e.g. Vit B12 and Folate are other causes of the condition (Barger, 2003).

El-Boshy *et al*., (2017) investigated the protective effects of *Cynara scolymus* (artichoke) against Cadmium toxicity induced oxidative stress and haematological disorder in wistar rats found a significant decrease in platelet and erythrocyte counts. There was also a decrease in hemoglobin, haematocrit, and lymphocyte count while neutrophil counts were significantly raised. In their study, other haematological indices i.e. WBCs, MCV, MCH, MCHC, the granulocytes eosinophils and basophils were non-significantly changed in contrast to the controls.

Likewise, Isiyaku and Mohammed (2021) reported increases in the calculated values of MCV, MCH, and MCHC in *Oreochromis Niloticus* fish after a 96-hour exposure study to Cadmium chloride. They attributed these haematological peturbations to direct or feedback responses to anatomical impairment of the erythrocyte membranes leading to destruction of the erythrocyte and deficiency in erythropoiesis and the liberation of erythrocytes from the spleen as well as tissue hypoxia.

Contrarily, Elgharib *et al*., (2023) noted no changes in MCV, MCH and MCHC in their study on the ameliorative effects of ascorbic acid against haematological, biochemical, oxidative and immunosuppressive effect of cadmium chloride in rats. Elgharib *et al*.,s findings were in agreement with those of El-Boshy *et al*., (2015) who revealed that treatment of cadmium exposed experimental rats with selenium, attenuated the haematological effects of cadmium highlighting the presumable protective effects of selenium.

Regarding platelets, there was marked thrombocytopenia found in the Group II rats, correlating with the findings of Beddard *et al*., (2000) who decades earlier reported a significant decrease in platelet count in their research on the effects of Copper Sulphate (CuSO4) in Long Evans Cinnamon rats given different doses of this inorganic agent.

Al-Akel and Shamsi (1996) have argued that a stressful condition in fish is not invariably accompanied by significant increase in thrombocytes count and that the glucocorticoid cortisol may affect fish thrombocytes in a similar manner as white blood cells do, eventually reducing their numbers.

More recently, Owunari *et al*., (2015) found that Disulfiram, Copper gluconate and Disulfiram/Copper gluconate combination for 90 days caused a significant decrease in platelet count of experimental rats at low, medium and high doses in comparison with control tending to suggest a synergistic dose-dependent toxicity of the blood cells.

The consensus amongst these different researchers is that secondary thrombocytopenia occurs as a result of heavy metal poisoning interfering with clotting and the hemorrhagic process.

Despite all of the above, there are still conflicting reports as regards the levels of platelets following exposure to metal pollutants. Studies by Cobbina *et al*.,*(* 2015); Yildrim *et al*., (2018) reported unchanged platelet values following acute and subacute exposures to toxic metals while Hounkpatin *et al*., (2013) observed an elevation. On the other hand, Mladenovic *et al*., (2014) and El-boshy *et al*., (2015) observed low doses of platelets in Cd induced changes in blood indices and oxidative damage in rats.

Some of the responses can be ascribed to a non-monotonic dose – response (NMDR) which describes the complex relationship between a given dose of a substance and the response or effect it elicits, whereby this response does not increase or decrease consistently with the dose. This inconsistency can result in a U-shaped curve or an inverted U-shaped curve. O'Doherty *et al*., (2019) having shown that a number of heavy metals exhibit this phenomenon at different doses.

Blood toxicants can cause increases or decreases in platelet count with the process of blood clotting being activated by metal induced stress. Blood clotting is thus speeded up arising from conditions of thrombocytosis a homoeostatic defense mechanism.

CONCLUSION

The information gathered from this study shows that a combination of large iron load and cadmium, in particular, are significant stressors. Significant alterations in haematological variables demonstrated that metals, particularly iron and cadmium, when present in combination are poisons of the rat hematopoietic system, and that long-term ingestion of metal-polluted *clarias* fish may have negative health implications on humans. Additionally, the study demonstrates that rat blood may be utilized as a tool for detecting the potential for hemotoxicity of toxic metals or other pollutants, particularly in settings with limited resources where access to sophisticated analytical techniques may be limited.

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