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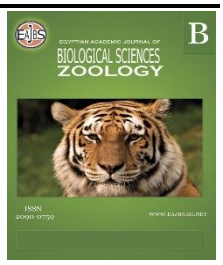

Study on Toxic Effects of Lead Acetate on Haematological Parameters of Adult Albino Rats and The Role of Mesenchymal Stem Cells and Flax Seeds Oil as Therapeutic Agents

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Lead acetate, mesenchymal stem cells, flax seeds oil, haematological parameters.

ABSTRACT

Background: Lead is a toxic heavy metal extensive in the environment. Lead induces oxidative stress. mesenchymal stem cells (MSCs) have multiplied great attention as an efficient tool in regenerative therapy. Flaxseed oil (FSO) natural source of antioxidant agents which reduced oxidative stress.**Aims:** The current study purposes to explore the effects of MSCs and FSO on the toxicity of lead acetate on haematological parameters. **Material and methods**: Forty rats were randomly divided into four groups and 10 rats per group. Group (1): healthy normal group, group (2): rats injected with lead acetate (100 mg/kg b.w.t./intraperitoneal injection) for seven days. group (3): rats were treated with a single dose of bone marrow mesenchymal stem cells (1×10^6 cells/rats) intravenously injected after lead intoxication. group (4): rats were given orally flax seeds oil (1ml/kg) for 30 days after lead intoxication. After the experiment, all rats were euthanized and collected blood for the examination of blood parameters. **Results:** Lead acetate induces a reduction in RBCs, Hb concentration and PCV. Also, lead increases WBCs count, lymphocytes, monocytes, neutrophils, eosinophils, MCV, MCH, MCHC and platelets. Although, MSCs and FSO improved all haematological blood. **Conclusions:** MSCs and FSO proved to have a powerful effect on the toxicity of lead acetate in the hematopoietic system.

INTRODUCTION

Lead is a heavy metal with widespread occupational and environmental effects in pollution and disease. The nervous, hematopoietic, and renal systems are just a few of the target organs that are more likely to experience harmful effects as a result of lead exposure (Abd El-Reheem and Zaahkcuk, 2007).

Lead has a direct effect on the hematological system because it decreases the life span of circulating red blood cells by making cell membranes more fragile. Lead has a dose-dependent effect on the heme production pathway by downregulating three critical enzymes involved in the synthesis of heme (Flora *et al*., 2012). Many physiological abnormalities were caused by lead, including protein biosynthesis disturbances, an inhibitory effect on hemoglobin synthesis, resulting in anemia, and an elevated level of

acid-aminolaevulinic (Pearce, 2007).

Moreover, the replacement of injured body parts and damaged organs with healthy new cells through stem cell transplantation is developing as a potentially ground-breaking new method of treating disease and injury. Several reports stated that (MSCs) can be used for tissue repair (Xi *et al*., 2013). Also, stem cells are different from other cells in the body by the capability of self-renewal and under certain conditions stimulated to differentiate into specific cells. In some organs (for example the bone marrow, or skin), stem cells divide to repair and replace worn-out tissues (Dubie *et al*., 2014).

Additionally, flax seeds oil has a benefit over other vegetable oils due to its high omega-3 content, particularly alpha-linolenic acid (ALA), of which it is the richest plant source. Lignans present in flaxseeds also exhibit antioxidant properties and additionally function as phytoestrogens (Pilar *et al*., 2017). The beneficial effect of flaxseed oil on the alleviation of oxidative stress accompanying various disease entities or intoxication and positively influence blood biomarkers (Sembratowicz *et al*., 2020).

Flax seeds oil has antioxidant and inflammatory factors against the bacterial wall including lipopolysaccharides. Flax seeds oil improved antioxidant enzymes in the blood and component of the blood in horses (Farrah *et al*., 2018). Flax seeds oil at various replacement levels resulted in significant improvement in lipids profile, liver and kidney functions and glucose levels in hypercholesterolemic rats (Aly-Aldin *et al*., 2015). Flaxseed oil included bioactive amino acids, including cyclolinopeptide A, which have strong immunosuppressive and antimalarial effects, preventing the human malarial parasite Plasmodium falciparum in culture (Bell *et al*., 2000).

Therefore, the aim of this study was to assess the effect of mesenchymal stem cells and flax seeds oil on the toxicity of lead acetate on haematological parameters of the blood.

MATERIALS AND METHODS

Experiments were carried out on 40 Wistar male albino rats at age (2-3 months) and weight about (250-280 g), which were obtained from the animal house of the Egyptian Organization for Biological Products and Vaccines (VACSERA), Helwan, Cairo, Egypt. The animals were housed in the animal house of the Faculty of Science, South Valley University, Qena, Egypt; rats were divided into nine groups (10 rats/group). Rats were housed in controlled suitable cages with the separate bottom and kept at room temperature(23±2^{o}C), and 12h light/dark period, and fed on a balanced stable commercial diet. For drinking tap water was provided *ad libitum*.

Experimental Design:

Group 1 (normal group): Rats were given dist.

Group 2 (lead intoxication group): Rats were injected with lead acetate (100 mg/kg b.w.t./intraperitoneal injection) for 7 days then left for 30 days.

Group 3 (treatment of mesenchymal stem cells group): Rats were injected with lead acetate (100 mg/kg b.w.t./intraperitoneal injection for 7 days) after 24 hours then it was treated with mesenchymal stem cells (1×10^6 cells/rats, intravenously injection) then left 30 days.

Group 4 (treatment of flax seed oil group): Rats were injected with lead acetate (100 mg/kg b.w.t./intraperitoneal injection for 7 days) then it was administered orally with flax seeds oil (1 mL/kg b.w.t.) for 30 days.

Ethics Statement: All of the rats' experiments were conducted in compliance with the National Institute of Health Council's guidelines for animal care and use. The ethical research committee of the faculty of veterinary medicine at the South Valley University

of Qena-Egypt reviewed the number (No. 39/12.062022). I confirm the experiment of the manuscript is stated in agreement with Animal Research Reporting of In Vivo Experiments guidelines. All rats were clinically examined before being used in the experiment.

Materials:

- Lead was purchased from El-Gomhouria Company for Chemicals and Laboratory Supplies as lead acetate in form of powder (Assiut-El-Gomhouria Company, Egypt) cas no. 6080-56-4.
- Flaxseed commercial oil was obtained from EL Captin Company (Al Obour City, Cairo, Egypt).
- Isolation and culture of rat bone marrow-MSCs from the femur of male rats (Huang *et al*., 2015). Identification and characterization of MSCs were done using flow cytometry. It was positive for Cd90, Cd31 and negative for Cd45 (Bayati ***et al.,*** 2013)**.**

Sampling Preparation:

At the end of the experiments, blood samples were collected from the eye medial canthus. Blood samples were collected on Disodium salt of ethylene diamine tetra-acetic acid (EDTA) for haematological analyses (CBC).

Haematological Examination:

The examination of the complete blood picture (platelets count, red blood cells count (RBCs), white blood cells count (WBCs)with differentiation, total haemoglobin, haematocrit assays blood indices) which was done by Automated Haematology Analyzer (Diff3) Mek-6410/MEK-6420.

RESULTS

Lead acetate-induced reduction in RBCs count, Hb and PCV but it increased in MCV, MCH and MCHC when compared with normal values. While MSCs and FSO improved all these parameters as referred by elevation in RBCs count, Hb, PCV and decline in MCV, MCH and MCHC when compared with the lead intoxication group (Table 1 and Figs. 1,2,3,4,5,6).

Rats intoxicated with lead acetate revealed an increase in total leukocytes count, neutrophils, lymphocytes, eosinophils, monocytes and platelets. Also, FSO enhanced all these parameters as indicated by a reduction in total leukocytes count, neutrophils, lymphocytes, eosinophils, monocytes and platelets (Tables 2,3 and Figs.7,8,9,10,11,12).

Table 1: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on RBCs count, Hb, PCV, MCV, MCH and MCHC in the blood of male Albino rats intoxicated with lead acetate.

Groups	RBCs count ($x\ 10^6$ / mm^3)	Hb (g/dL)	PCV (%)	MCV (fl)	MCH (pg)	MCHC (%)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Normal	9.09 ± 0.44	15.69 ± 0.53	42.66 ± 1.66	46.55 ± 1.38	16.83 ± 0.53	36.82 ± 1.62
Intoxicated with lead	4.60 $^{-a}$ ± 0.40	8.92 $^{-a}$ ± 0.67	22.87 $^{-a}$ ± 0.99	49.37 $^{+a}$ ± 2.33	19.62^{+a} ± 0.93	39.50 $^{+a}$ ± 1.64
Intoxicated with lead+stem cells	8.12 $^{-a+b}$ ±0.45	12.46 $^{-a+b}$ ± 0.48	34.36^{-a+b} ±0.93	46.56 $^{-b}$ ± 1.70	16.84 $^{-b}$ ± 0.58	36.91^{-b} ± 1.14
Intoxicated with lead+flax seeds oil	6.86 $^{-a+b}$ ±0.40	11.08 $^{-a+b}$±0.41	29.77 $^{-a+b}$ ±0.82	46.62 $^{-b}$ ± 1.44	16.88 $^{-b}$± 0.60	37.23 $^{-b}$ ± 1.33

Results are expressed as mean ± S.D. of 10 animals for each group.

-a = significant decreased compared with normal at $p<0.001$.

+a = significant increase compared with normal at $p<0.001$.

+b = significant increased compared with intoxicated with the lead group at $p<0.001$.

-b = significant decreased compared with intoxicated with the lead group at $p<0.001$.

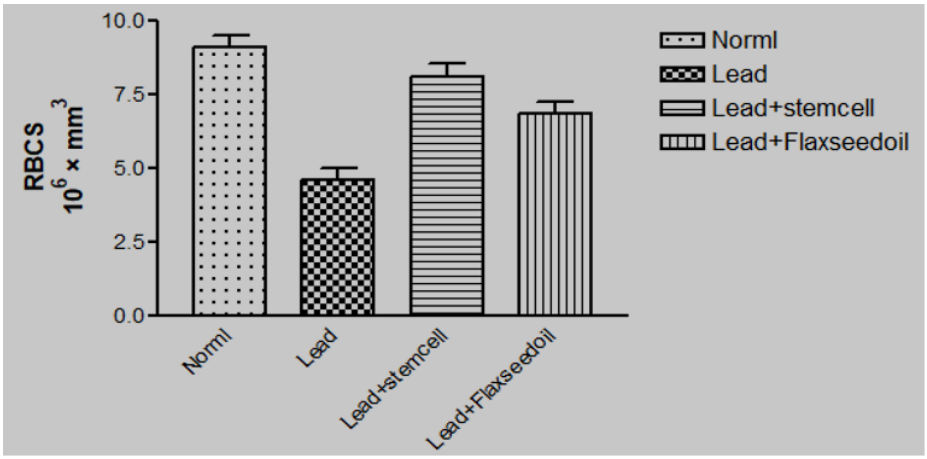

Fig. 1: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on RBCs count in blood of male Albino rats intoxicated with lead acetate.

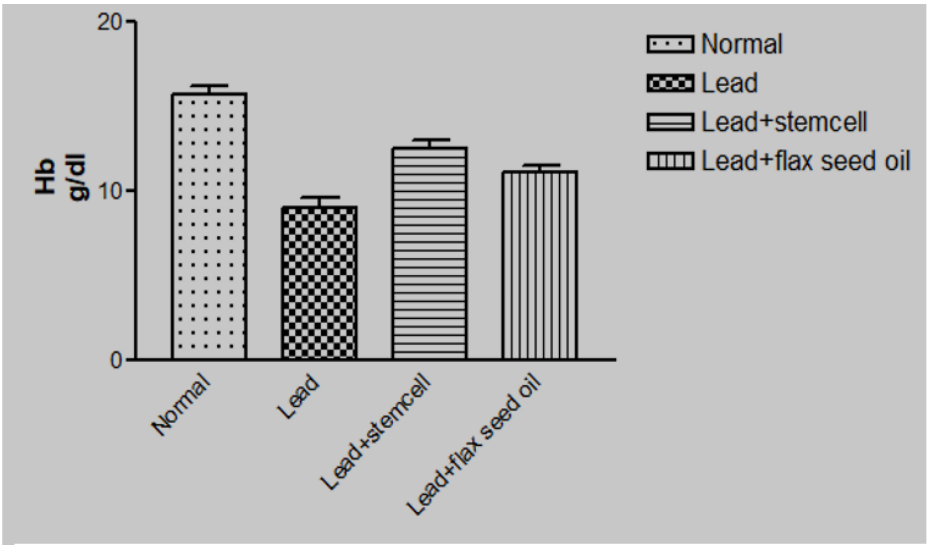

Fig. 2: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on Hb in the blood of male Albino rats intoxicated with lead acetate.

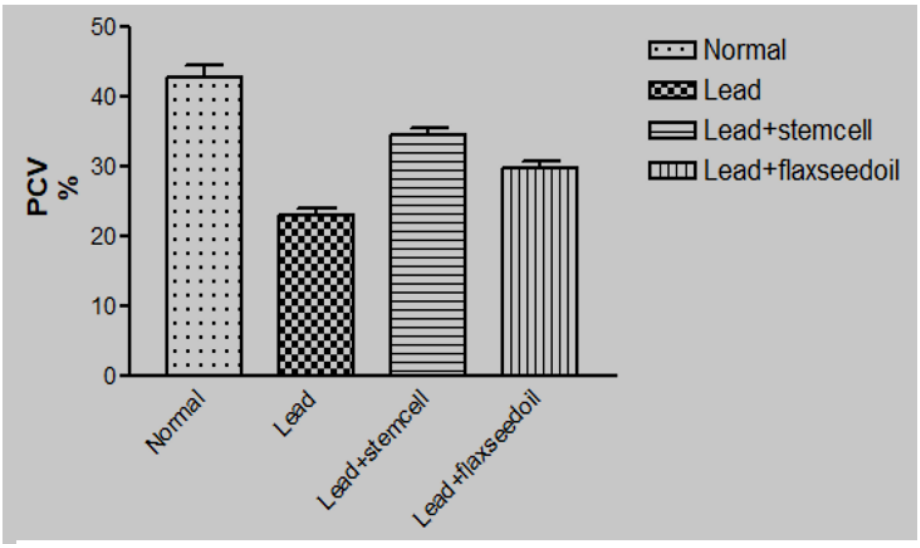

Fig. 3: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on PCV in the blood of male Albino rats intoxicated with lead acetate.

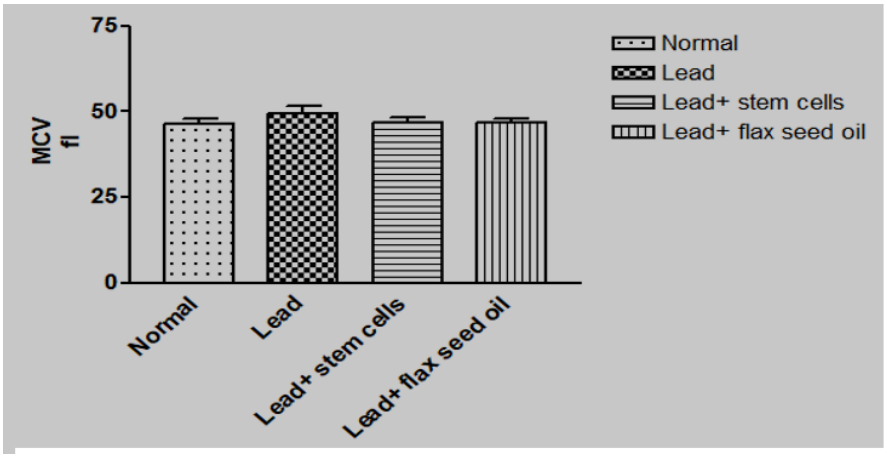

Fig. 4: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on MCV in the blood of male Albino rats intoxicated with lead acetate.

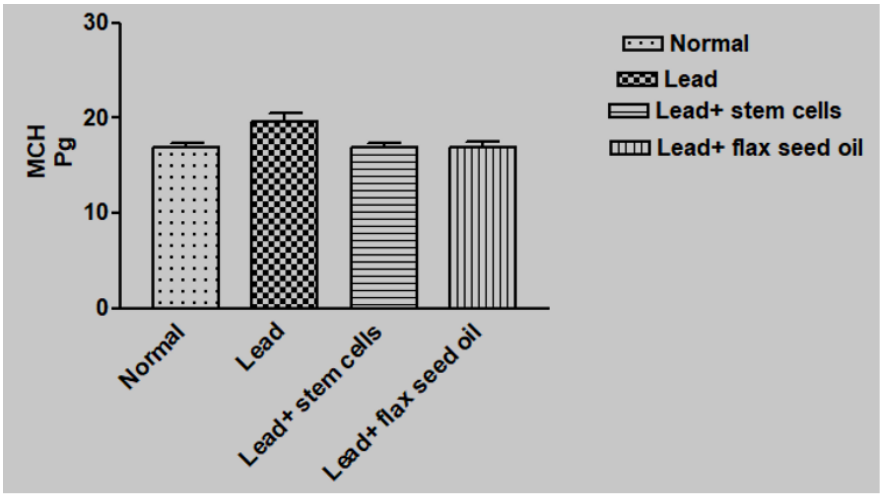

Fig. 5: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on MCH in the blood of male Albino rats intoxicated with lead acetate.

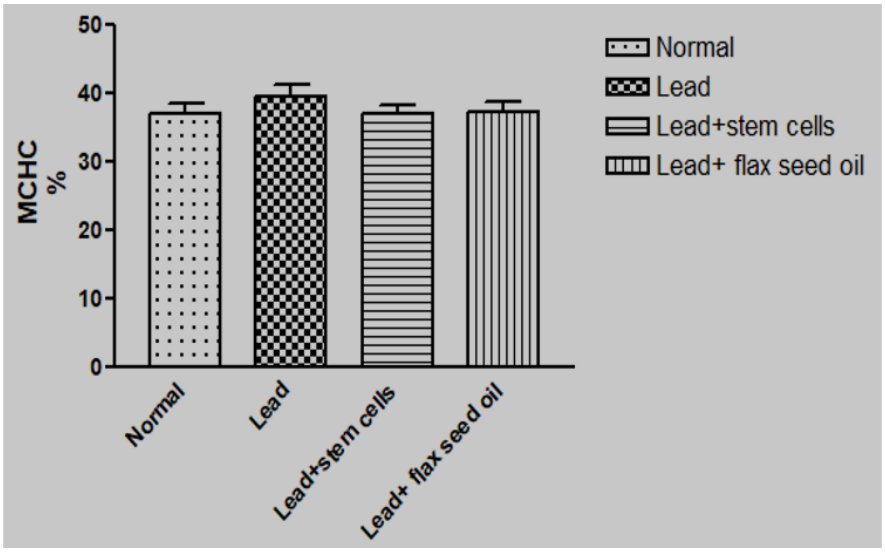

Fig. 6: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on MCHC in the blood of male Albino rats intoxicated with lead acetate.

Table 2: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on WBCs count, neutrophils, lymphocytes, eosinophils, monocytes and basophil in the blood of male Albino rats intoxicated with lead acetate.

Groups	WBCs count ($x 10^3$ / mm^3)	Neutrophils ($x 10^3$ / mm^3)	Lymphocytes ($x 10^3$ / mm^3)	Eosinophils ($x 10^3$ / mm^3)	Monocytes ($x 10^3$ / mm^3)	Basophil ($x 10^3$ / mm3)
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Normal	17.57 ± 0.96	2.84 ± 0.26	13.26 ± 1.07	0.21 ± 0.04	1.69 ± 0.14	00±00
Intoxicated with lead	41.86 $^{+a}$ ±1.92	9.94 $^{+a}$ ± 0.57	26.91 $^{+a}$ ± 1.13	1.99^{+a} ± 0.09	2.90^{+a} ± 0.11	00±00
Intoxicated with lead+stem cells	22.32$^{+a\ -b}$±1.06	4.22 $^{+a-b}$ ± 0.48	15.64$^{+a\ -b}$ ±0.87	0.80$^{+a\ -b}$ ± 0.09	1.88$^{+a\ -b}$ ± 0.10	00±00
Intoxicated with lead+flax seeds oil	28.25$^{+a\ -b}$±0.46	5.81 $^{+a\ -b}$ ±0.40	18.68$^{+a\ -b}$ ±0.17	0.90 $^{+a\ -b}$ ± 0.08	2.72$^{+a\ -b}$± 0.13	00±00

Results are expressed as mean ± S.D. of 10 animals for each group.
+a = significant increase compared with normal at $p<0.001$
-b = significant decreased compared with intoxicated with the lead group at $p<0.001$.

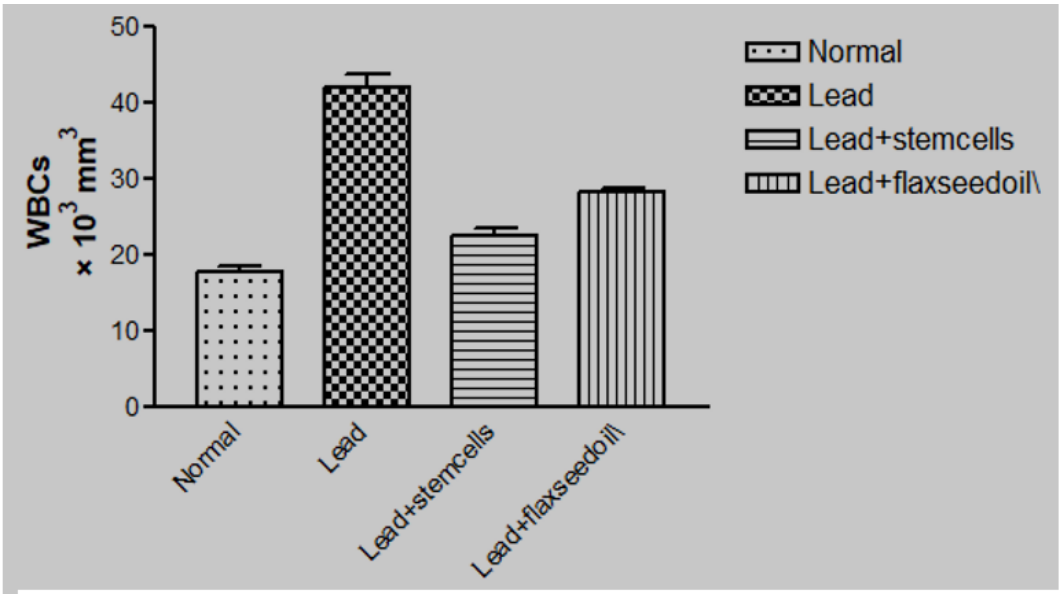

Fig. 7: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on WBCs count in the blood of male Albino rats intoxicated with lead acetate.

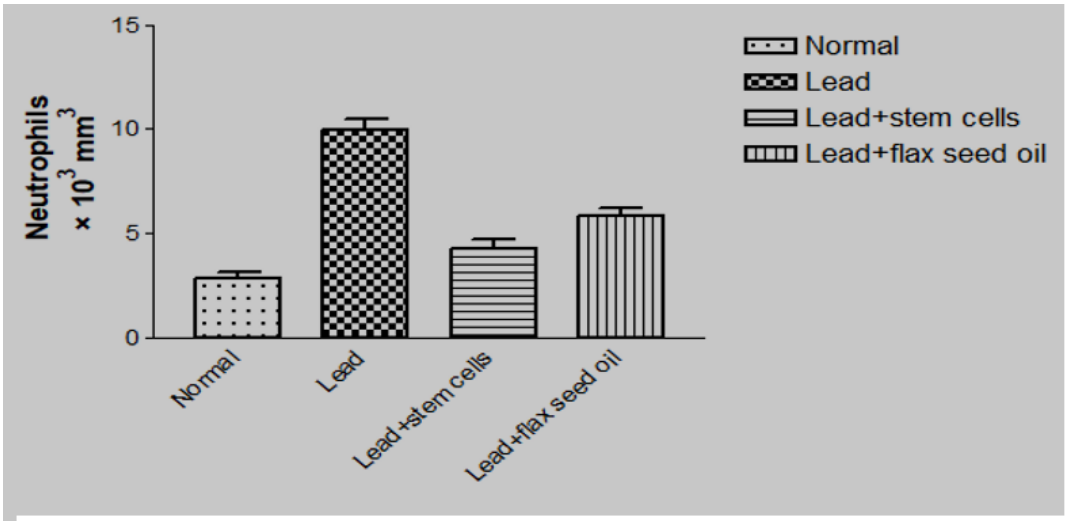

Fig. 8: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on a neutrophil count in the blood of male Albino rats intoxicated with lead acetate.

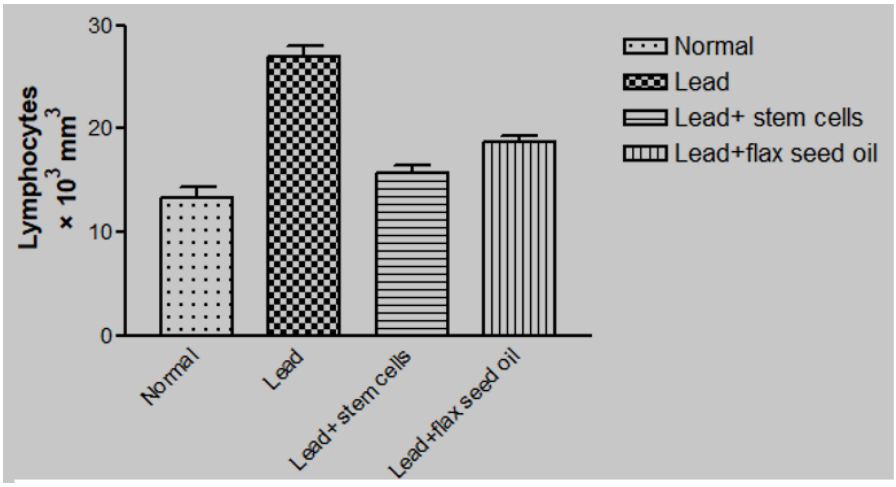

Fig. 9: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on lymphocytes count in the blood of male Albino rats intoxicated with lead acetate.

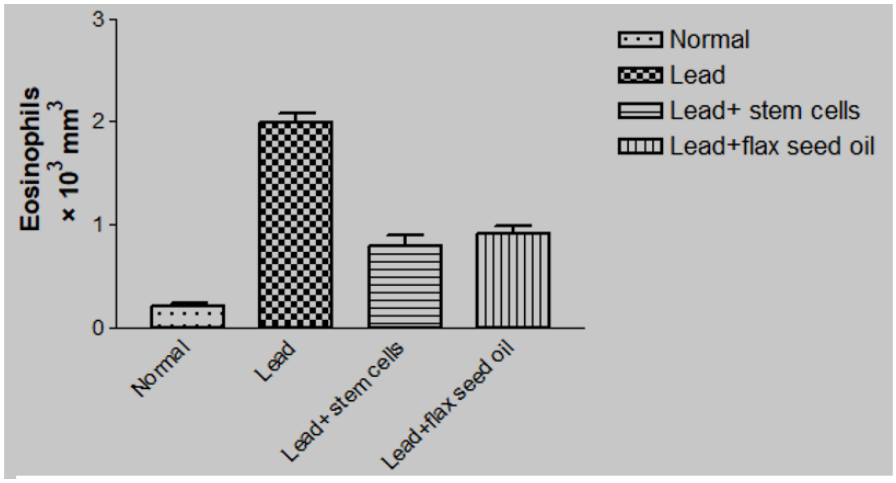

Fig. 10: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on an eosinophil count in the blood of male Albino rats intoxicated with lead acetate.

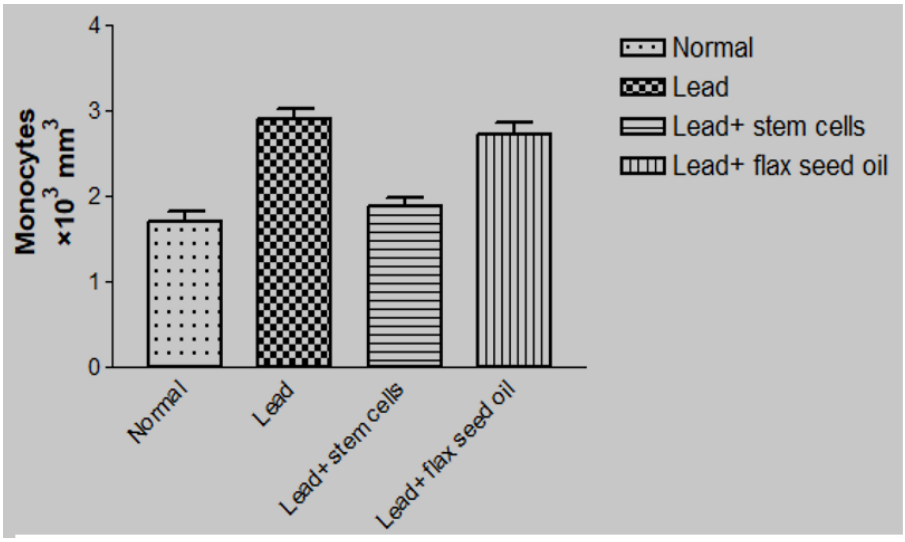

Fig. 11: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on a monocyte count in the blood of male Albino rats intoxicated with lead acetate.

Table 3: Effect of a single dose of mesenchymal stem cells and oral administration of flaxseed oil on platelets count in the blood of male Albino rats intoxicated with lead acetate.

Groups	Platelets ($10^3 \times mm^3$)
	Mean ± S.D.
Normal	373.6± 21.24
Intoxicated with lead	568.1^{+a} ± 14.68
Intoxicated with lead+stem cells	$439.0^{+a\ -b}$ ± 6.02
Intoxicated with lead+flax seeds oil	$477.7^{+a\ -b}$ ± 12.51

Results are expressed as mean ± S.D. of 10 animals for each group.
+a = significant increase compared with normal at p<0.001.
-b = significant decreased compared with intoxicated with the lead group at p<0.001.

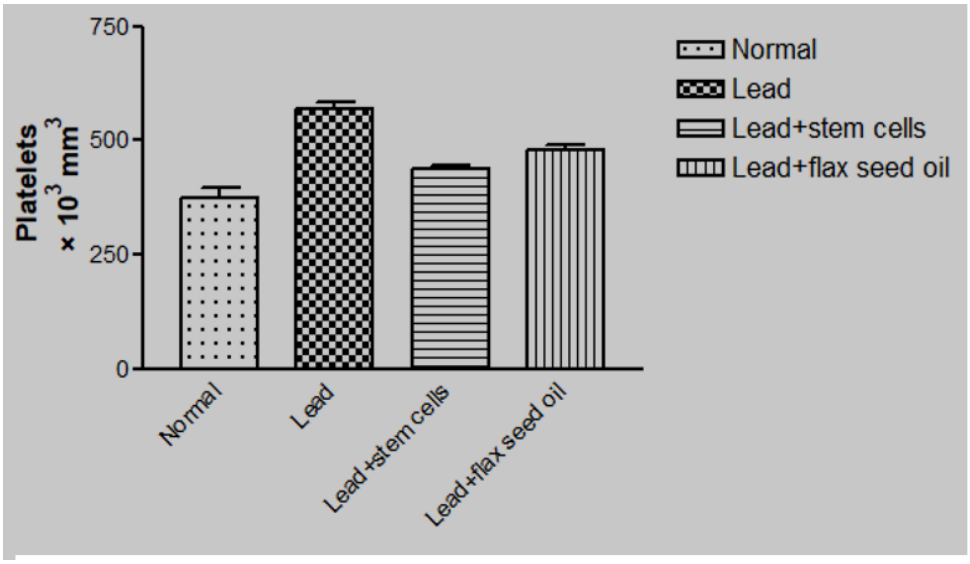

Fig. 12: Effect of a single dose of mesenchymal stem cells and oral administration of flax seeds oil on platelet count in the blood of male Albino rats intoxicated with lead acetate.

DISCUSSION

Previous studies suggested that lead was known to induce oxidative stress by increasing the production of reactive oxygen species (ROS) and reducing antioxidants which have an important role to ameliorate lead toxicity. Free radicals can lead to cell membrane damage, via lipid peroxidation, which in turn triggers the signaling cascades of the inflammatory process. Furthermore, inflammation is thought to act as a mediator of the adverse health effects caused by lead exposure (Sirivarasai *et al*., 2013).

Haematological indices are variables that help in assessing the health and physiological status of a man and are good indicators of many disease conditions (Adeyomoye *et al*., 2019).

The current study showed that RBCs, Hb and PCV a significant decrease in the blood of rats intoxicated with lead acetate, in contrast, MCV, MCH and MCHC a significant increase in the blood of rats intoxicated with lead acetate when compared with normal rats. Our results accordance with Andjelkovic *et al*., 2019 and Abdelhamid *et al*., 2020. Rat erythrocyte membranes may be damaged by lead, which would reduce their mobility. Lead may also cause oxidative damage in RBCs. Lead may inhibit the body's

ability to make hemoglobin by interfering with several enzymatic steps in the heme pathway. Specifically, lead decreases heme biosynthesis by inhibiting aminolaevulinic acid dehydratase and ferro chelatase activity (Abd EL Rahiem *et al*., 2007). Lead affects loss of Hb molecule stability and erythrocyte morphology and survival (Moussa and Bashandy, 2008). Interaction of lead with heme biosynthesis has been related to the inhibition of cytoplasmic and mitochondrial enzymes and a decrease in the activity of the main enzymes in heme biosynthesis due to defects in iron metabolism has also been reported (Mugahi *et al*., 2003).

This increase in MCV, MCH and MCHC is due to the effects of lead in cell metabolism, alteration of the enzyme activity, and interaction with reactions in which calcium is their secondary mediator (Mugahi *et al*., 2003).

Several studies have suggested a lead-induced reduction in RBCs, Hb and PCV (Mugahi *et al*., 2003; Suradkar *et al*., 2009; Karamala *et al*., 2011; Ibrahim *et al*., 2012; Gani *et al*., 2017 and Offor *et al*., 2017). The decreased life span of erythrocytes increased fragility of erythrocytes, Progressive destruction of RBCs due to binding of lead with RBCs and inhibitory effect of lead on erythrocyte enzymes (GA3PD & G6PD) (Suradkar *et al*., 2009). These reductions suggested that there is an etiology relationship between acute renal failure (ARF) and anemia through different suggested mechanisms such as bone marrow cell destruction and decrease or delay in mitosis (Sese-Owei *et al*., 2020).

On the other hand, our investigation showed improvement in RBCs count, Hb, PCV value, MCV, MCH and MCHC in rats treated with mesenchymal stem cells. This correction may be attributed to improving the rate of erythrocyte synthesis, and the ability of mesenchymal stem cells to lower lipid peroxidation level that causes hemolysis of erythrocytes. Mesenchymal stem cells were able to reverse the lytic effect of ROS and so reduced or rather completely prevent oxidative stress thereby giving room for the regeneration of erythropoietic cells, a process mediated by erythropoietin secretion from the bone marrow (Elzawahry *et al*., 2018).

Mesenchymal stem cells significantly improved RBC count, Hb, PCV value, MCV, MCH, and MCHC in diabetic rats, as stated by Mahmoud *et al*, 2020. This enchantment may be attributed to stem cells having anti-hematological disorders effects by reducing oxidative damage or stimulating differentiation and growth prevention in these disease models. MSCs exerted their influence by the secretion of massive amounts of growth factors such as vascular endothelial growth factor, transforming growth factor-beta.

In this work, we noticed that enhancement in RBCs count, Hb, PCV value, MCV, MCH and MCHC in rats treated with flaxseed oil. Hendawi *et al*., 2016 reported that amelioration in RBCs count, Hb, PCV value, MCV, MCH and MCHC of thiacloprid intoxication rats treated with flax seeds oil, these changes were ameliorated in response to flax seeds oil, which may be due to the antioxidant activities of the flax seeds oil and its properties in scavenging the free radical: protecting the erythrocyte membrane against the formed MDA and decreasing the toxic effects of thiacloprid.

Flaxseed oil improved hematological parameters of the blood (RBCs, Hb, PCV and blood indices) in horses, flaxseed oil exerts a beneficial effect by stimulating antioxidant defense mechanisms of horses and reducing the severity of oxidative stress (Sembratowicz *et al.*, 2020).

White blood cells (Leucocytes) are cells of the immune system that play a vital role in protecting the body against foreign invaders. They are produced by multipotent cells in the bone marrow and circulate in the blood and the lymphatic system (Adeyomoye *et al*., 2019).

Our study showed elevation in total leucocytes, lymphocytes and monocytes.

These results are in accordance with Mugahi *et al*., 2003 and Abdelhamid *et al*., 2020. Offor *et al*., 2017 reported that lead acetate induces an elevation in total white blood cells and lymphocytes.Karamala *et al*., 2011 and Andjelkovic *et al*., 2019 documented that lead caused increasing in WBCs and neutrophils. Increased values of WBCs might be due to lead induce inflammation in tissues. Increased Pb concentration in the blood induced an increase in leukogram including lymphocytes, neutrophils, eosinophils and monocytes (Abubakar *et al*., 2019).

Pb acetate-induced rats in this study showed an increase in total leucocytes, The results also are in harmony with the study of Gani *et al*., 2017. leukocytosis with lymphocytosis which indicates bone marrow toxicity and gives high implications for the development of a lymphoproliferative neoplasm (Aprioku and Obianime, 2014). There are related to the toxic effect of lead on leucopoiesis in lymphoid organs, which resulted in increased production from the germinal center of lymphoid organs (Alwaleedi, 2016). The impairment in the leukocyte function may be referred to as the metabolic changes that occurred in response to an increase of 5-aminolevulinic acid (ALA) which acts as an endogenous peroxidant. lead-induced oxidative stress could strongly alter neutrophil functions including bactericidal activity, phagocytosis, chemotaxis, and respiratory burst activity (Abdelhamid *et al*., 2020).

Furthermore, our study investigated the values of total leucocytes, lymphocytes, neutrophils, eosinophils and monocytes were significantly restored to near normal after being treated with mesenchymal stem cells (MSCs). this enhancement in leucogram and its differentiation may be due to mesenchymal stem cells having the ability to stimulate the production of white blood count and its related indices. MSCs have multipotent; they have angiogenic, anti-apoptotic, anti-inflammatory and immunomodulatory effects (Cao *et al*., 2015).

Improvement in total white blood cells and differentiation of leucocytes in diabetic rats treated with mesenchymal stem cells (Mahmoud *et al*., 2020). Numerous studies have shown that different stem cell types can enhance the pathological result of various tissues and reduce the disease's clinical symptoms (Agaev *et al*., 2014).

Our results showed that rats treated with flax seeds oil improved in total leucocytes, lymphocytes, neutrophils, eosinophils and monocytes. Hendawi *et al*., 2016 reported that rats treated with flax seeds oil amelioration total white cells and their differentiation, this improvement may be attributed to flax seeds oil’s protective effect through the high content of antioxidant agents such as beta-carotene and tocopherols.Flax seeds oil enhanced leucogram in horses, flax seeds oil exerts a beneficial effect by stimulating antioxidant defense mechanisms of horses and reducing the severity of oxidative stress (Sembratowicz *et al*., 2020). Basophils in all groups of this study exhibited zero. These findings are in harmony with Thanabhorn *et al*., 2005.

The platelet, a vital blood component, forms clots with other coagulation factors to stop bleeding after an injury (Adeyomoye *et al*., 2019). Platelets known as thrombocytes help to mediate blood clotting, which is a meshwork of fibrin fibers. The fibers adhere to any vascular opening and thus prevent bleeding. It plays a crucial role in reducing blood loss and repairing vascular injury (Periayah *et al*., 2017).

The present investigation showed lead acetate-induced elevation in platelets. This data is in agreement with Mugahi *et al*., 2003; Sese-Owei *et al*., 2020 and Andjelkovic *et al*., 2019.The increase in the platelet count in the exposed lead animals is due to the impairment of clotting function through endothelial tissue injury and nitric oxide synthesis caused by lead acetate (lead-induced thrombocythemia) (Adeyomoye *et al*., 2019).

The increase in platelet cell count in this study shows that lead influence on platelet parameters is exposure duration-dependent and that chronic lead exposure, unlike acute

exposure, may be associated with increased megakaryocytopoiesis and platelet turnover (Chwalba *et al*., 2018).

Additionally, the current results were a significant improvement in platelets after rats were treated with mesenchymal stem cells (MSCs). These results may be due to MSCs stimulating the biosynthesis of clotting factors. Also, MSCs have active compounds that might help to improve blood coagulation or clotting (Elzawahry *et al*., 2018). Rats treated with mesenchymal stem cells showed correction in platelets count, bone marrow-derived stem cells contribute to cell turnover and repair in various tissue types (Mahmoud *et al*., 2020).

In this study, there was a significant decrease in the platelet count of rats treated with flax seeds oil compared with rats intoxicated with lead acetate. This improvement may be due to flaxseed oil exhibiting mild antiplatelet properties by inhibiting thrombin and collagen-induced platelet aggregation. Flax seeds oil could be useful in the treatment of thrombotic disorders. Flax seeds oil exhibited antioxidant properties due to the presence of ω-3 fatty acid (α-linolenic acid) and lignans (Nandish *et al*., 2020).

Conclusion

This study supports the application of MSCs and FSO for combating hematological disorders induced by lead acetate reflected by improvement of hematological alterations as evidence of improved anemia and restoring WBCs and their relations and platelets to near normal, thereby preserving blood function. In addition, MSCs may be considered an effective therapeutic agent in the future against hematological defects induced by lead toxicity.

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Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this article.

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