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AMELIORATIVE EFFECT OF THE AQUEOUS LEAF EXTRACT OF FICUS SYCOMORUS ON THE PREFRONTAL CORTEX OF MALE WISTAR RATS WITH LEAD ACETATE INDUCED OXIDATIVE STRESS

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ABSTRACT

Background: This study investigated the ameliorative effect of the aqueous leaf extract of *Ficus Sycomorus* on the prefrontal cortex of male wistar rats with lead acetate induced oxidative stress.**Methodology:** Thirty adult male wistar rats (185 – 222g) were divided into six groups of experimental protocols, n=5: Group I received Normal saline, Group II received Lead (Pb^{2+}) only, Group III received 200mg/kg *Ficus Sycomorus* (F.S) only, Group IV received (Pb^{2+} + 100mg/kg F.S), Group V received (Pb^{2+} + 200mg/kg F.S), Group VI received (Pb^{2+} + 5mg/kg Vitamin E). Oxidative stress was induced by oral administration of 120mg/kg of Pb^{2+} daily, for 7 days, and treated with *Ficus Sycomorus* for 14 days. After the experimental period, the animals were sacrificed via cervical dislocation, and blood samples were collected for oxidative stress assays. Perfusion was made, and the brains were harvested, rinsed in normal saline, fixed in 10% formal saline, and subjected to histological studies. **Results:** There is a statistically significant increase ($p < 0.05$) in the serum level of MDA with decreased SOD and Catalase in the Pb^{2+} treated animals without *Ficus Sycomorus* intervention when compared with post-treatment with Ficus Sycomorus and Vitamin E after inducing oxidative stress with Pb^{2+}. Post-treatment with *Ficus Sycomorus* significantly ($p < 0.05$) decreased the serum level of MDA, but significantly increased ($p < 0.05$) SOD and Catalase in the *Ficus Sycomorus* treated rats. This biochemical fact is supported by the histological results. **Conclusion:** There were comparable degrees of abatement as evidenced by the oxidative balance, normal appearance of the prefrontal cortex cytoarchitecture, with conspicuous neuroglial cells, and no signs of degeneration in the tissue. Therefore, *Ficus Sycomorus* has suggested in this study that well-restored prefrontal cortex may be the indication of its antioxidative properties. Meanwhile, it is worthwhile to consider this aspect at a deeper level of investigation using different animal models and methods.

Keywords: Ameliorative, Ficus Sycomorus, Prefrontal cortex, Wistar Rats, Oxidative stress

1.0 INTRODUCTION

1.1 Background of the study

The use of medicinal plants for health reason is as old as humanity (El-Sayyad et al., 2015). In many developing countries, herbal medicines are of vital importance in primary health care (Ezugwu et al., 2021). The extensive use of natural plants as primary health remedies is because their pharmacological properties is quite common (Al-matani et al., 2015). Natural products are preferred for biological screening based on ethno-medical use of plants because many infectious diseases are known to have been treated with herbal remedies throughout the history of humanity (Al-matani et al., 2015). The investigation of efficacy of plant-based drugs has been paid great attention because of the few or no side effects, and affordability (Ezugwu et al., 2021). Medicinal plants represent a rich source from which antimicrobial agents is obtained (Al-matani et al., 2015). Nearly 70% of human population is reported to be dependent on plant-based medicines (Dawod et al., 2021). Infections due to pathogenic bacteria and fungi represent a critical problem to human health and are one of the main causes of morbidity and mortality worldwide (Igbokwe et al., 2010). *Ficus Sycomorus* (FS) is a traditionally used medicinal plant that has been cultivated globally since the ancient times (Saleh and Mariri 2017; Slatnar et al., 2011). It is originated from Africa, but currently distributed in almost all tropical countries. The plant belongs to the Moraceae family (Konai et al., 2017), and has about forty genera. The selected family has more than 800 species. The plant species also have several sub-species. The name Ficus is the Latin word for fig, which originates from the Persian 'fica'. The species, sycomorus, originates from the Greek name sykamorea (i.e, sycamore). Its flowering and fruiting occurs all the time, but mostly between July and December (Dawod et al., 2021). *Ficus sycomorus* have been reported in some literature to contain bioactive substances in its leaves, roots, fruits and flowers, and are used in combination with other plants for the treatment of diseases like diarrhea, mental illness, epilepsy, dysentery, convulsive disorder and vomiting (Slatnar et al., 2011; Abba, 2018). *Ficus sycomorus* have been reported to possess antifungal and anti-diarrhoea activities (Konai et al., 2017). The sedative and anticonvulsant properties of this plant have also been reported (Foyet et al., 2017). The extracts of *Ficus Sycomorus* have been reported to inhibit gastro-intestinal motility (Hassan et al., 2007). It has been reported to possess analgesic, anti-inflammatory and anti-contraceptive activities (Al-matani et al., 2015).

Lead (Pb^{2+}) is a very heavy metal that occurs in nature as oxide or salts, (Ahmed

et al., 2013). It is one of the most hazardous and cumulative environmental pollutant (Flora et al., 2012). It is used in making medicine, paint, pipes, ammunition, and in more recent times in alloys for welding storage materials for chemicals reagents (Flora et al., 2012). Lead toxicity is probably one of the common causes of oxidative stress and neuroinflammation (Ezugwu et al., 2022; Teleanu et al., 2022; Zhang et al., 2017). It is well documented as one of the most dangerous and insidious poisons (Barkur and Badiry, 2015). Its continuous environmental and occupational exposure may contribute to renal, nervous, hepatic, hematological and reproductive disorders in man and animals (Ezugwu et al., 2022; Flora et al., 2012). Lead in the body is distributed to the brain, the liver, kidney, and bones (Ezugwu et al., 2022). It is stored for long time in the teeth and in the bone (Flora et al., 2012; Liu et al., 2021).

2.0 MATERIALS AND METHOD

2.1 Experimental Animals

Thirty (30) adult male wistar rats (185-222g) were procured from the animal house of the Department of Veterinary Medicine, University of Nigeria, Nsukka. The rats were handled according to the guideline of the committee for the purpose of control and supervision of experiments on animals.

2.2 Chemicals and drugs

Lead acetate was procured from Dani Chemicals^{R}, Enugu, Nigeria. Vitamin E capsule (Batch number 14354) was supplied by Care Root Pharmaceuticals Enugu, Nigeria.

2.3 Preparation of extract

Mature and healthy *Ficus Sycorum* leaves were gotten from bush in Nsukka, Enugu state, Nigeria. A taxonomist in the Department of Plant Science and Technology, University of Nigeria Nsukka identified the plant, and a voucher specimen (Ref No: 2171) was deposited in the herbarium for reference. The leaves were dried in the room temperature for seven days, which its aqueous extract was prepared under standard laboratory conditions.

2.5 Experimental Design

Group I received normal saline, Group II received 120mg/kg Pb^{2+} only, Group III received 200mg/kg Ficus Sycomorus (F.S) only, Group IV received (120mg/kg Pb^{2+} + 100mg/kg F.S), Group V received (120mg/kg Pb^{2+} + 200mg/kg F.S), Group VI received (120mg/kg Pb^{2+} + 5mg/kg Vitamin E).

Table 2.1: Administration Schedule

Treatment	Dosage	Duration
Group I: Food only	Normal saline	14 days
Group II: Lead acetate daily for 7 days	120mg/kg Pb^{2+}	7 days
Group III: *Ficus Sycomorous* (F.S) daily for 14 days	200mg/kg Ficus Sycomorus (F.S)	14 days
Group IV: Lead acetate daily for 7 days + low	120mg of Pb^{2+} + 100mg/kg	21days

dose extract from 8th day to 21st day	F.S
Group V: Lead acetate daily for 7 days + high dose extract from 8th day to 21st day	120mg of Pb^{2+} + 200mg/kg F.S 21days
Group VI: Lead acetate daily for 7 days + 5mg/kg of Vitamin E from 8th day to 21st day	120mg of Pb^{2+} + 5mg/kg Vitamin E 21 days

2.6: SACRIFICE OF EXPERIMENTAL ANIMALS

After twenty-four hours of the last administration for various groups, the rats were sacrificed via cervical dislocation. Blood samples were collected with capillary tube via orbital puncture into plain specimen bottle, and taken to a laboratory for test on the oxidative and anti-oxidative stress activities. Perfusion was done, and the 'whole' brain tissues were removed from the skull, and fixed in 10% formal saline for histological studies on the prefrontal cortex.

2.7: HISTOLOGICAL ANALYSIS

Procedures:

The standard tissue processing protocols involves the following procedures below;

Fixation: The tissues were received in a container with formaladehyde to prevent autolysis; improve staining quality and aid optical differentiation of cell.

Dehydration: The tissues were dehydrated to remove water that is not miscible with xylene and wax using different grades of alcohol ranging from 50%-absolute alcohol for 30minutes each.

Clearing/Dealcoholization: The dehydrated tissue was cleared by removing the alcohol from the tissue by immersing it through 3 changes of xylene for 30minutes each.

Wax impregnation/infiltration: The cleared tissue was impregnated and infiltrated to remove the clearing agent (xylene) in the hot oven temperatureof 60°C by passing it through three changes of molten paraffin wax in a hot air oven for 30minutes.

Embedding: The infiltrated tissue was attached with molten paraffin wax in an embedded mold and allowed to solidify.

Mounting on wooding block: The paraffin block of tissue was attached to a wooding block with the aid of a hot spatula held in between wood block and paraffin wax, the spatula melts the wax which solidifies when spatula was removed.

Microtomy: The block of tissues was sectioned using rotary microtome; it was trimmed to obtain the cutting surface of the tissue at 15 micron and was sectioned at 5micron, and dry in hot plate for staining.

2.7.1: Haematoxylin and Eosin (H&E) staining Procedure:

The methods of H and E staining were carried out according (Bancroft and Gamble, 2008). Sections of the tissues were viewed under a light microscope, and

photomicrographs were made using a microscope camera.

2.8 OXIDATIVE STRESS BIOMARKERS

Superoxide dismutase (SOD) and Catalase (CAT) was estimated by (Fridovich, 1989) method, also Malondialdehyde (MDA) was estimated by Thiobarbituric acid reaction method.

Determination of superoxide dismutase activity

Superoxide Dismutase (SOD) activity was determined by Colorimetry a method described by (Fridovich, 1989).

Determination of catalase activity

Catalase activity was determined using the method described by (Sinha, 1972). In this procedure, 5% Potassium heptaoxochromate (VI) K2Cr2O7 was mixed with glacial acetic acid in the ratio 1:3, and stored in brown bottle at room temperature, after which 0.9 ml of distilled water was added to 0.1 ml of sera and mixed thoroughly.

Determination of Malondialdehyde (MDA) activity

Malondialdehyde (MDA) is one of the final products of polyunsaturated fatty acid peroxidation in cells and is commonly known as a biomarker of oxidative stress.

2.9 Data Analysis

Data obtained were expressed as mean ± SEM (standard error of mean). One-way analysis of variance (ANOVA) was used to compare the mean differences. Tukey's post hoc test was done where the result was significant. P-value less than to 0.05 was considered statistically significant. All results were analyzed using the Statistical Package for Social Sciences (SPSS version 22).

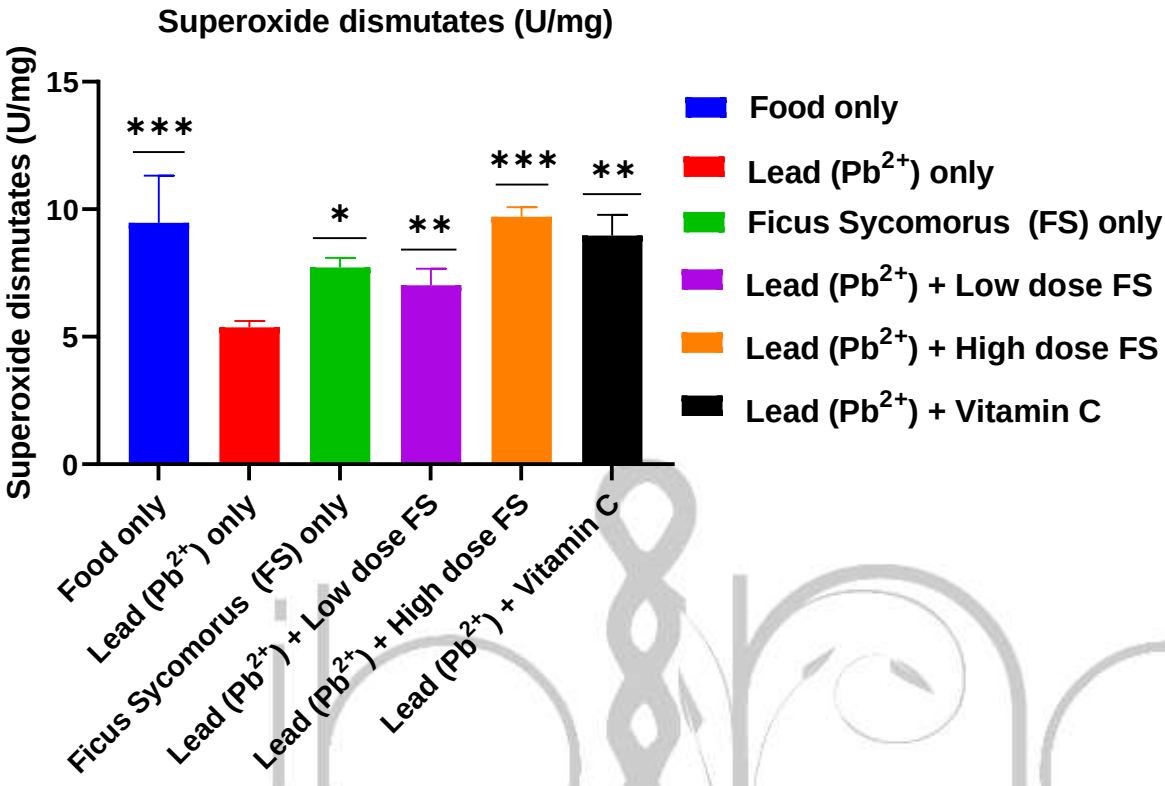
3.0 RESULTS

3.1 BIOCHEMICAL RESULTS

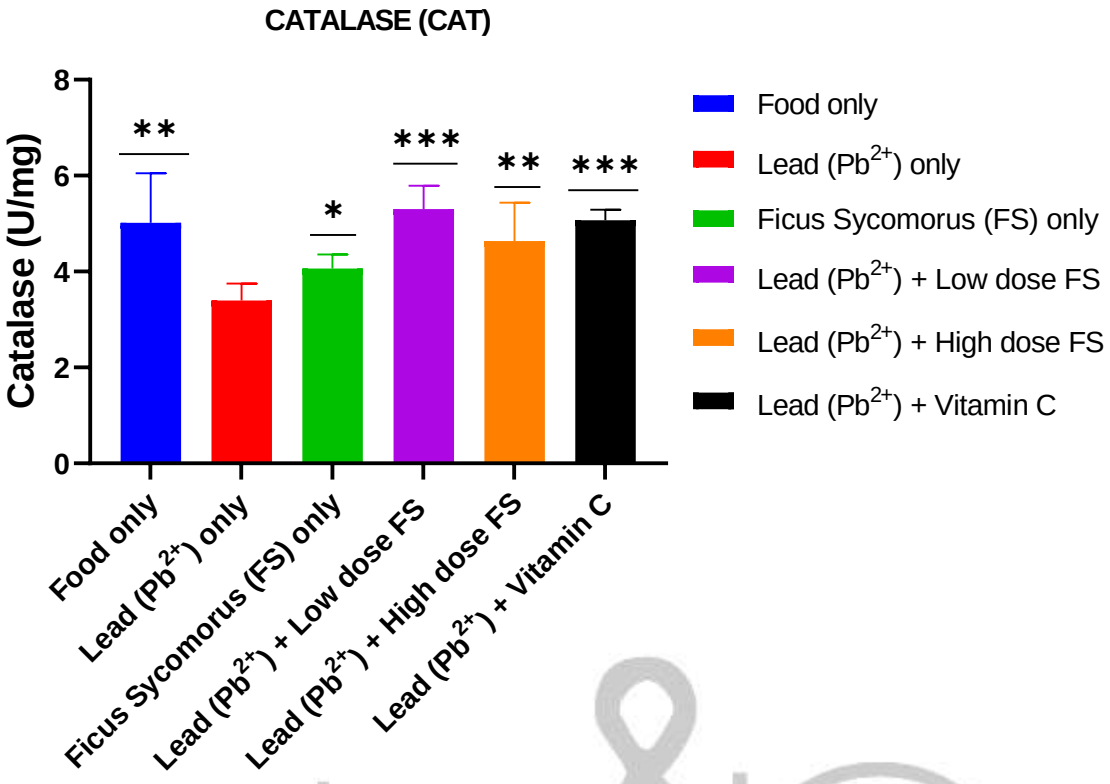
Table 3.1: Oxidative stress activities of Superoxide dismutase, Catalase, and Malondialdehyde

Administration and Treatment	SOD (µ/mg)	CAT (µ/mg)	MDA (mg/dl)
Group 1: Food and water for 14 days	9.475±1.846***	5.020±1.032**	19.130±0.1909*
Group 2: Lead acetate daily for 7 days	5.370±0.247	3.3950±0.3536	23.230±0.834
Group3: Ficussycomorous aqueous extract daily for 14 days	7.715±0.375*	4.065±0.289*	18.990±2.249**
Group 4: Lead acetate daily for 7 days + low dose extract from 8th day to 14 days	7.020±0.651*	5.305±0.488***	18.330±0.679**
Group 5: Lead acetate daily for 7 days + high dose extract from 8 day to 14 days	9.710±0.368***	4.635±0.799**	16.960±1.499***
Group 6: Lead acetate daily for 7 days + mg/kg of Vitamin E from 8 day to 14 days	8.966±0.813**	5.070±0.217***	17.760±0.169***

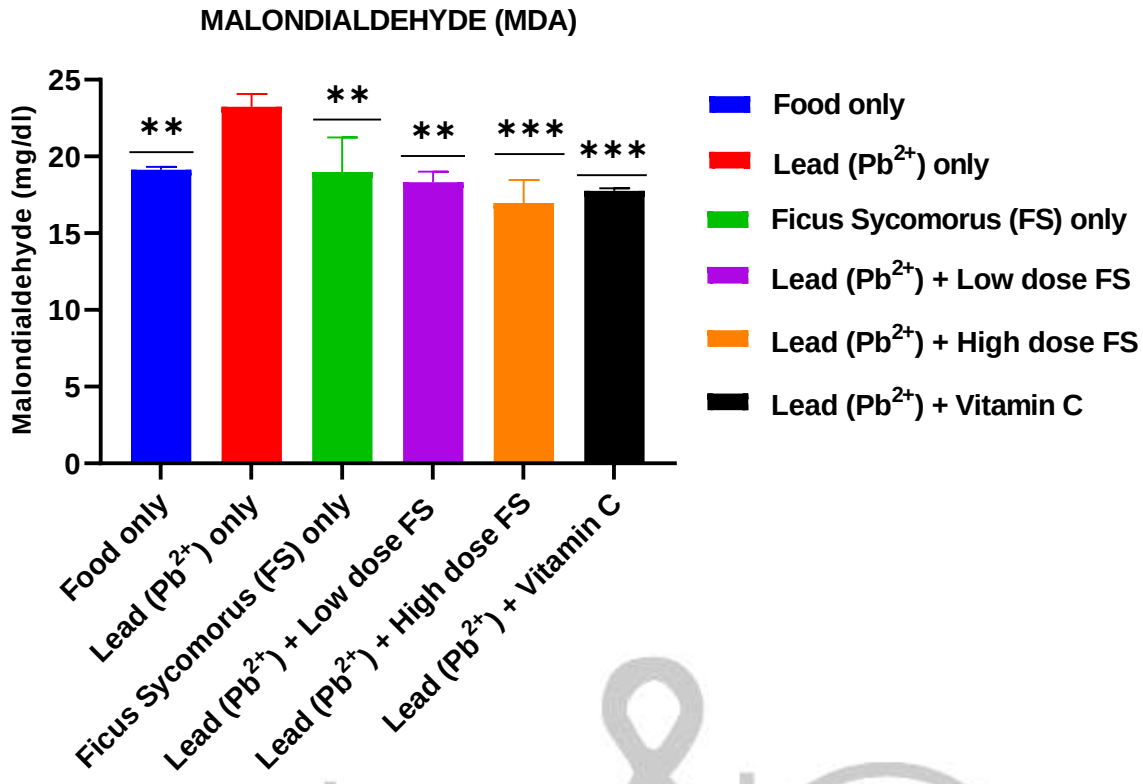
Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant.
* Significant when compared to the control at P < 0.05
** Significant when compared to the control at P < 0.01
*** Significant when compared to the control at P < 0.001



Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant.
* Significant when compared to the control at P < 0.05
** Significant when compared to the control at P < 0.01
*** Significant when compared to the control at P < 0.001
Figure 3.1 :Component bar graph showing oxidative stress level for Superoxide dismutase SOD

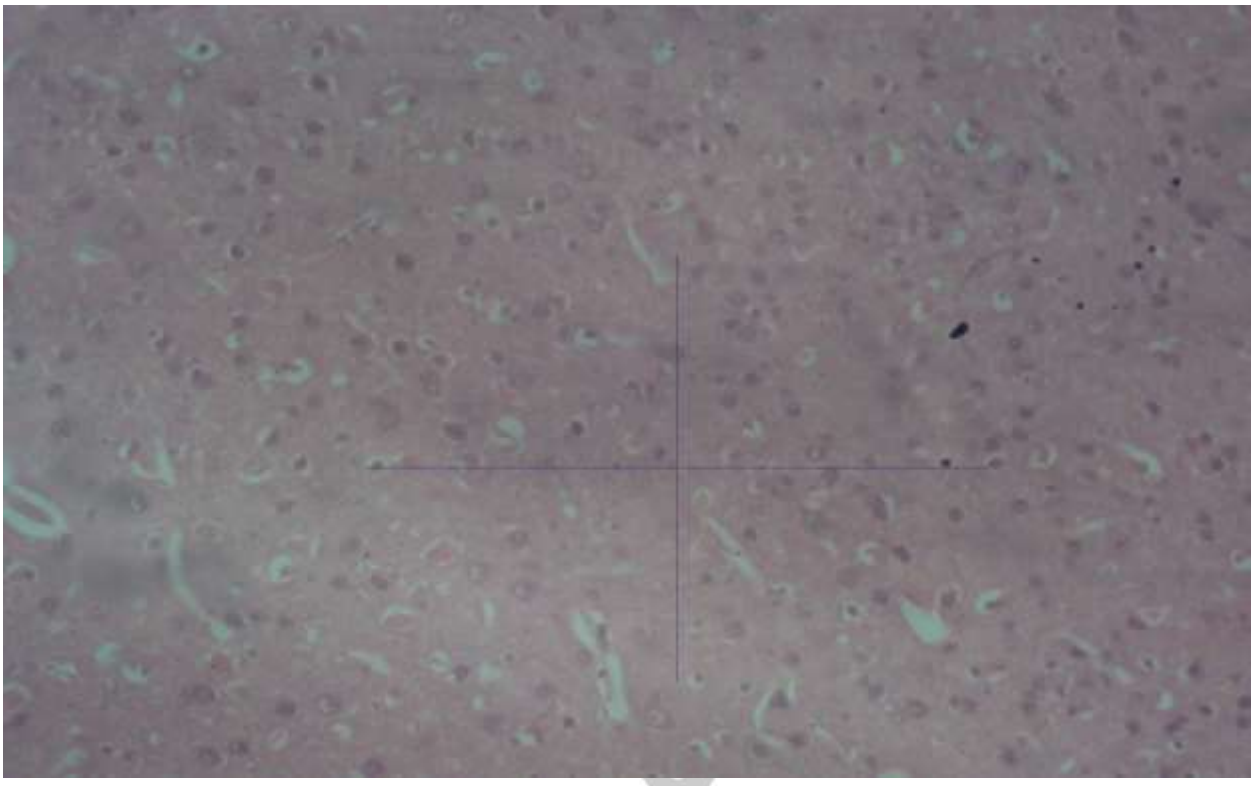


Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant.
* Significant when compared to the control at P < 0.05
** Significant when compared to the control at P < 0.01
*** Significant when compared to the control at P < 0.001
Figure 3.2 :Component bar graph showing oxidative stress level for Catalase (CAT)

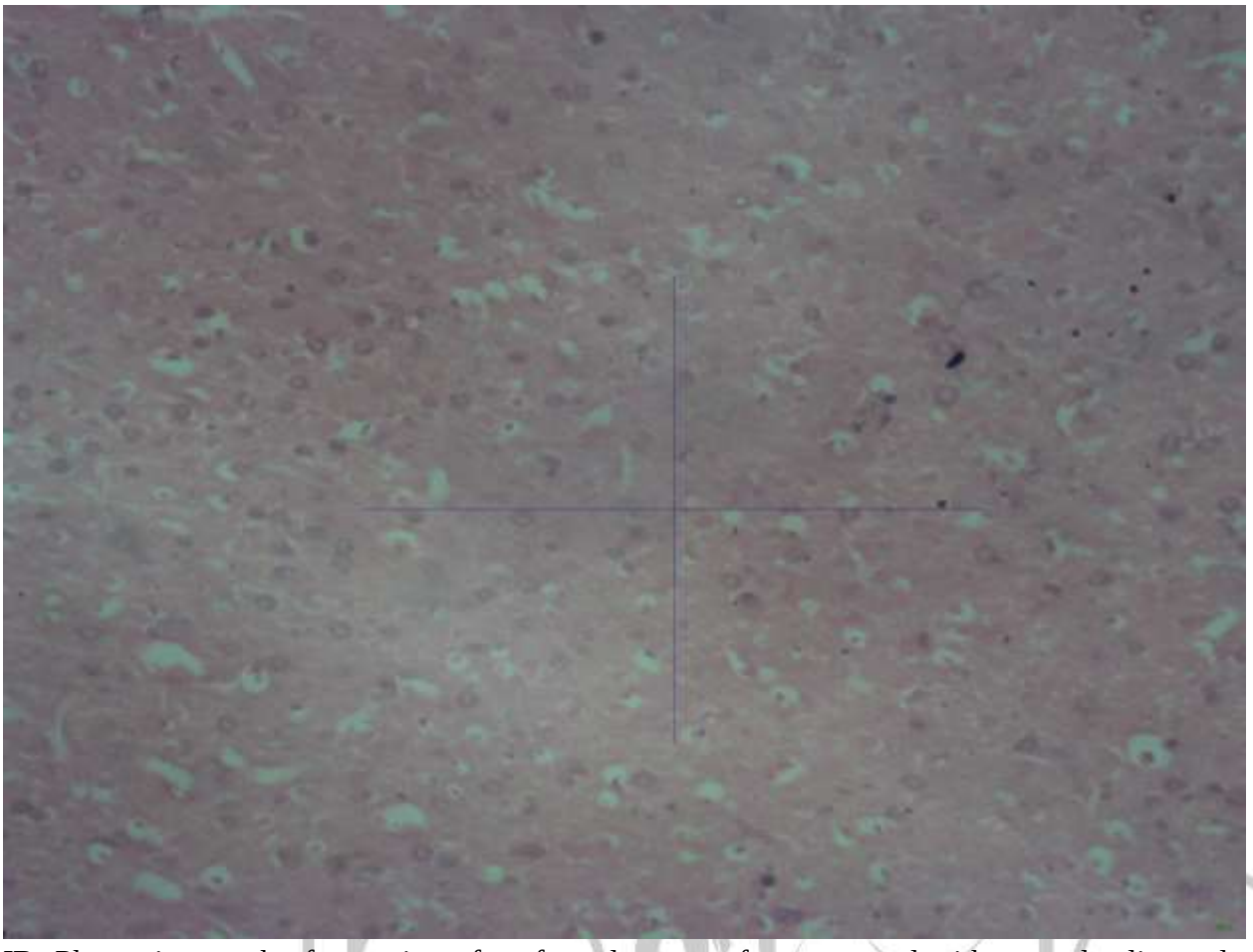


Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant.
* Significant when compared to the control at P < 0.05
** Significant when compared to the control at P < 0.01
*** Significant when compared to the control at P < 0.001
Figure 3.2: Component bar graph showing oxidative stress level for Malondialdehyde (MDA)

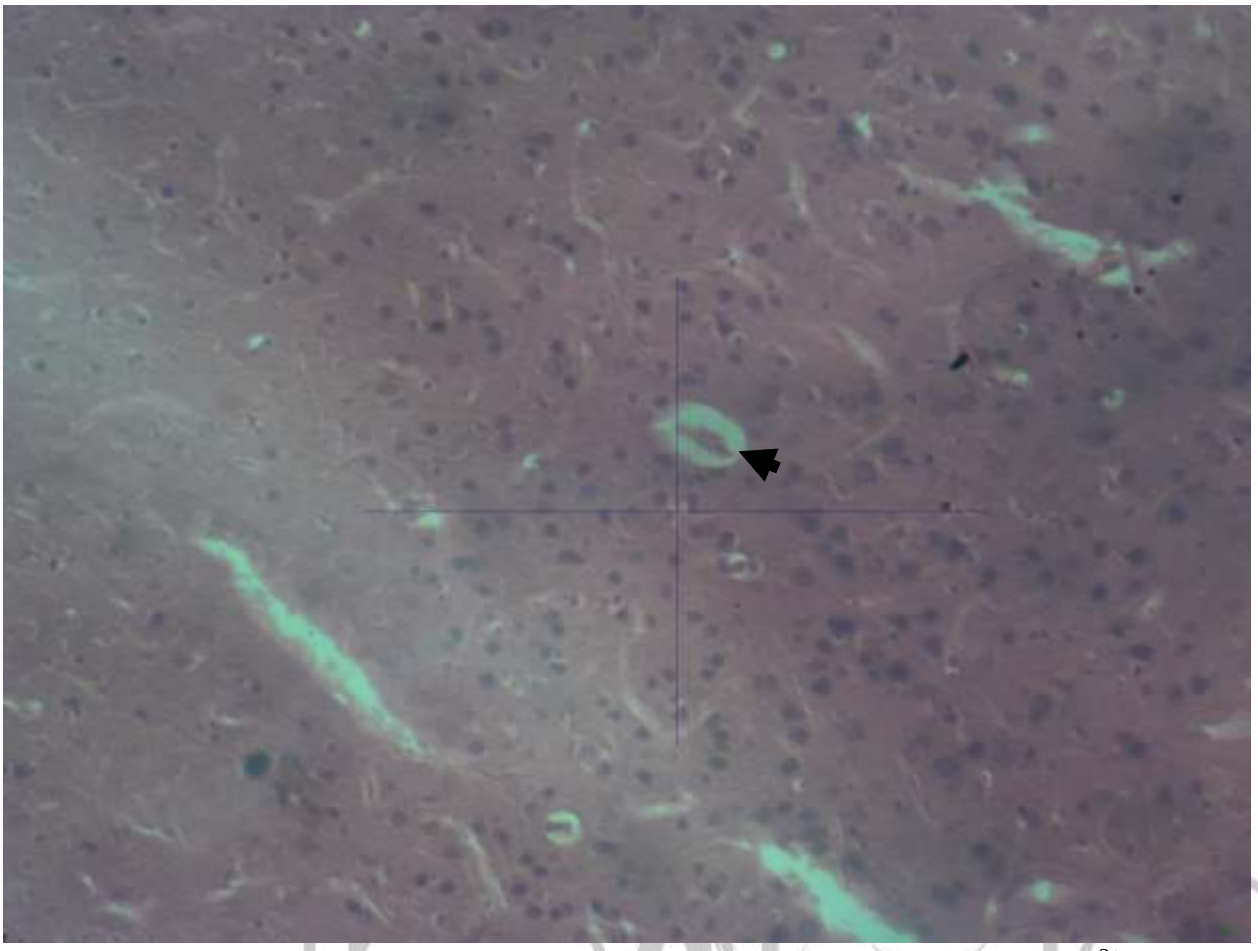
3.2 HISTOLOGICAL RESULT



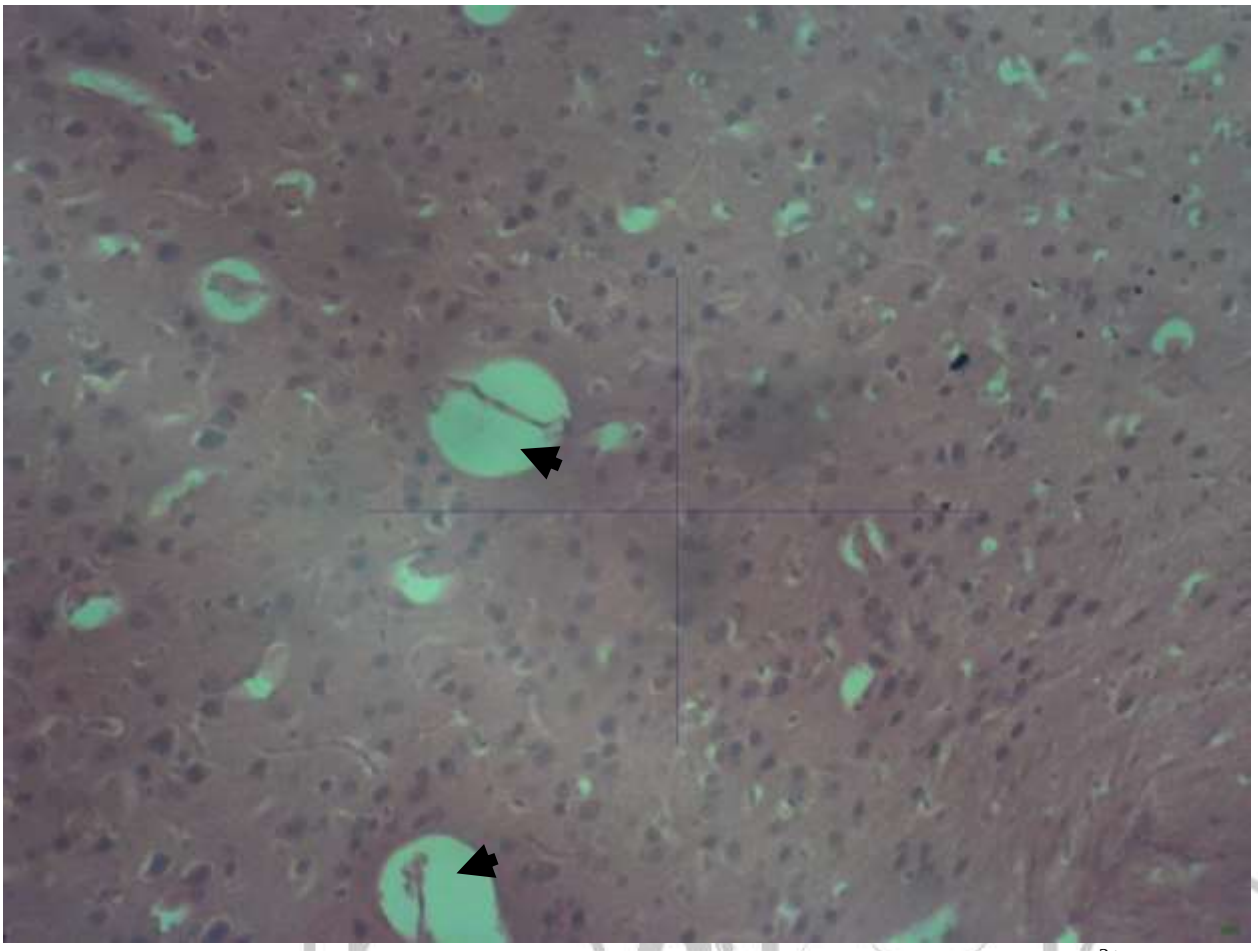
IA: Photomicrograph of a section of the prefrontal cortex of a rat treated with normal saline only shows normal cortical neurons of different categories, numerous glia cells and a normal condensed neurofibrillary network.H&E.X100.



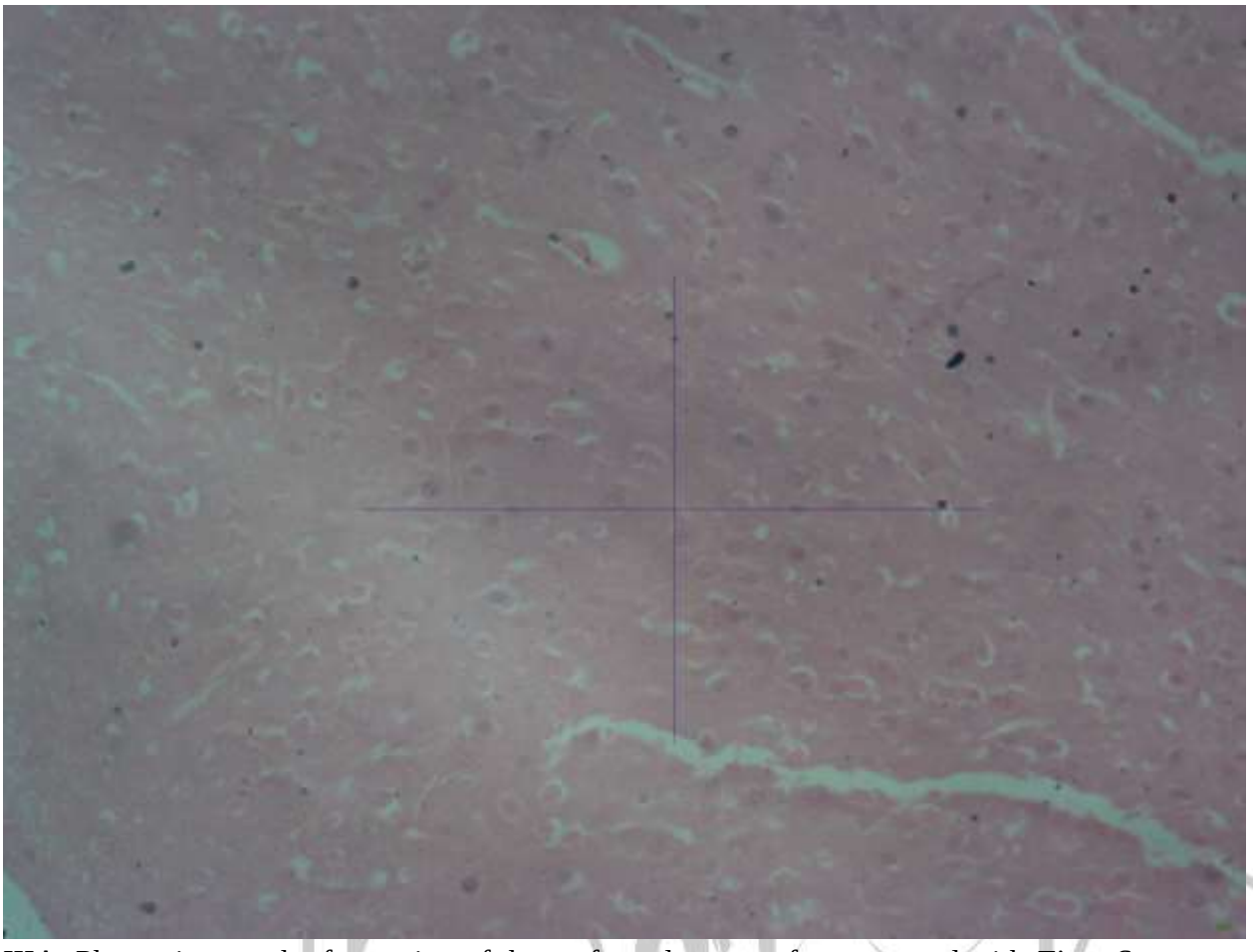
IB: Photomicrograph of a section of prefrontal cortex of a rat treated with normal saline only shows normal neurons of different categories, numerous glia cells and a normal condensed neurofibrillarynetwork.Blood vessels (Arrow) H&E.X100.



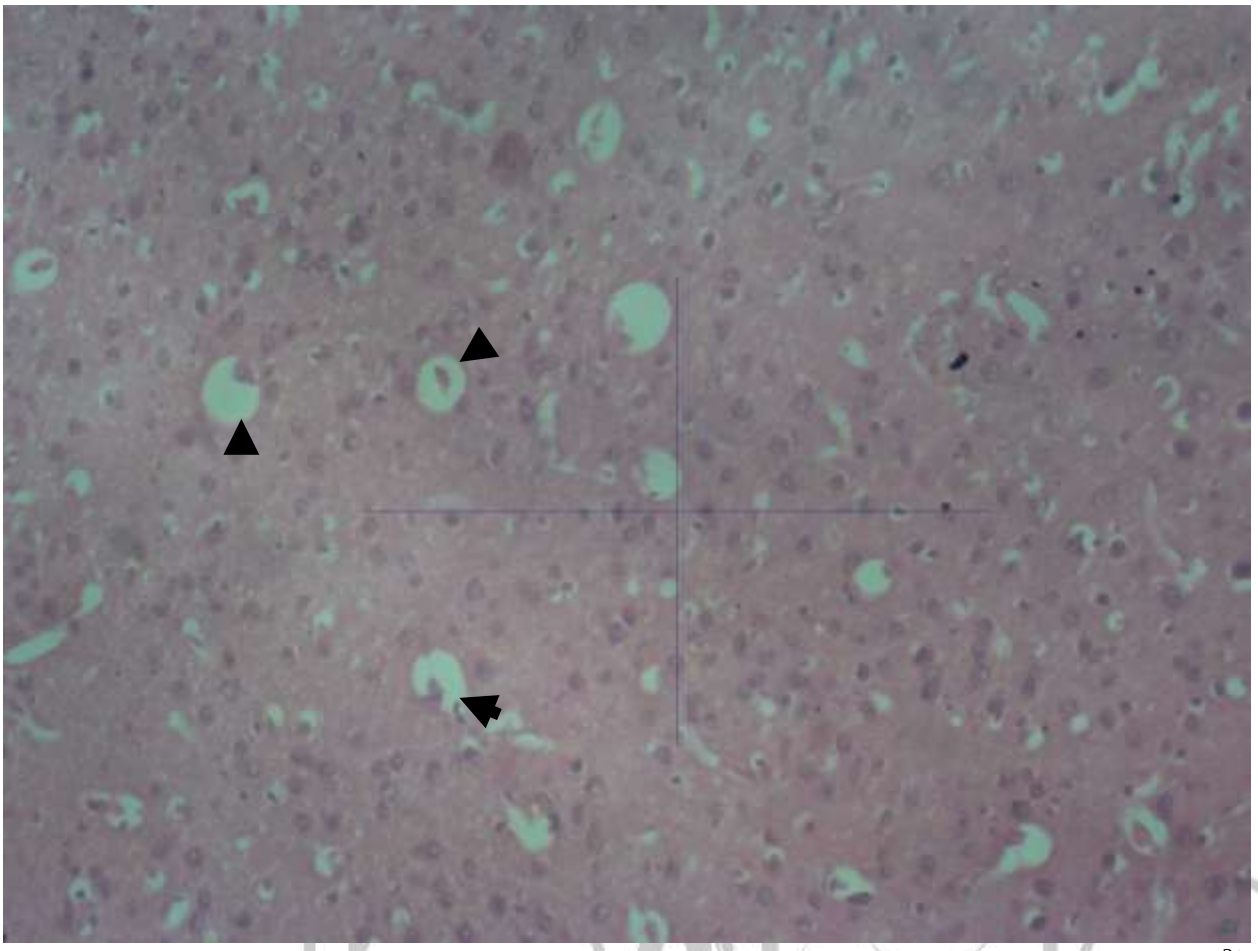
IIA: Photomicrograph of a section of the prefrontal cortex of a rat treated with Pb^{2+} only showing abnormal cortical neurons of different categories and a normal condensed neurofibrillary network. However, a few neurons with well-developed vacuolated cytoplasm were noticed (Arrow heads). H&E.X100.



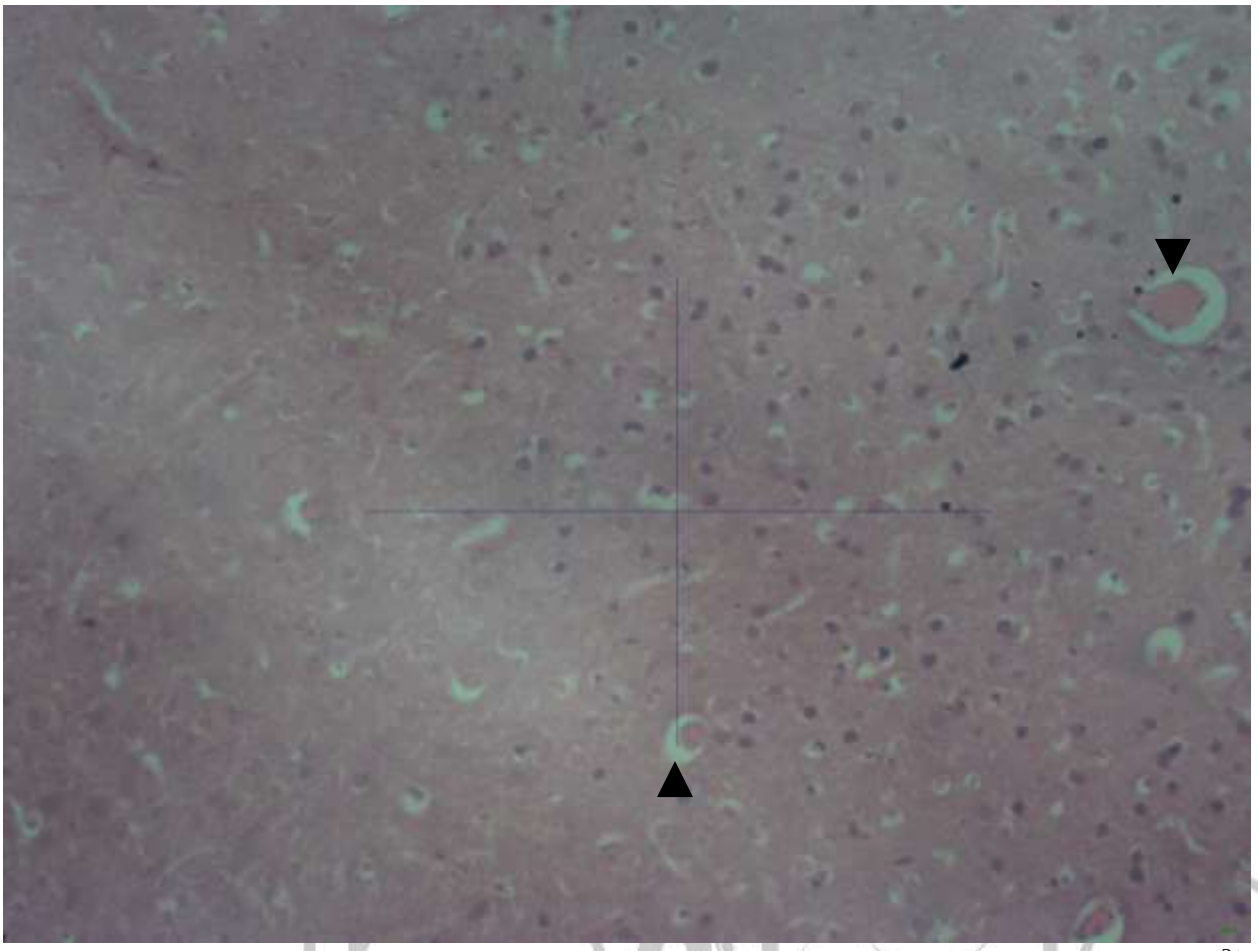
IIB: Photomicrograph of a section of the prefrontal cortex of a rat treated with Pb^{2+} only showing abnormal cortical neurons with mild vacuolated cytoplasm and blood vessels with dilated perivascular spaces (Arrow heads). H & E. X100.



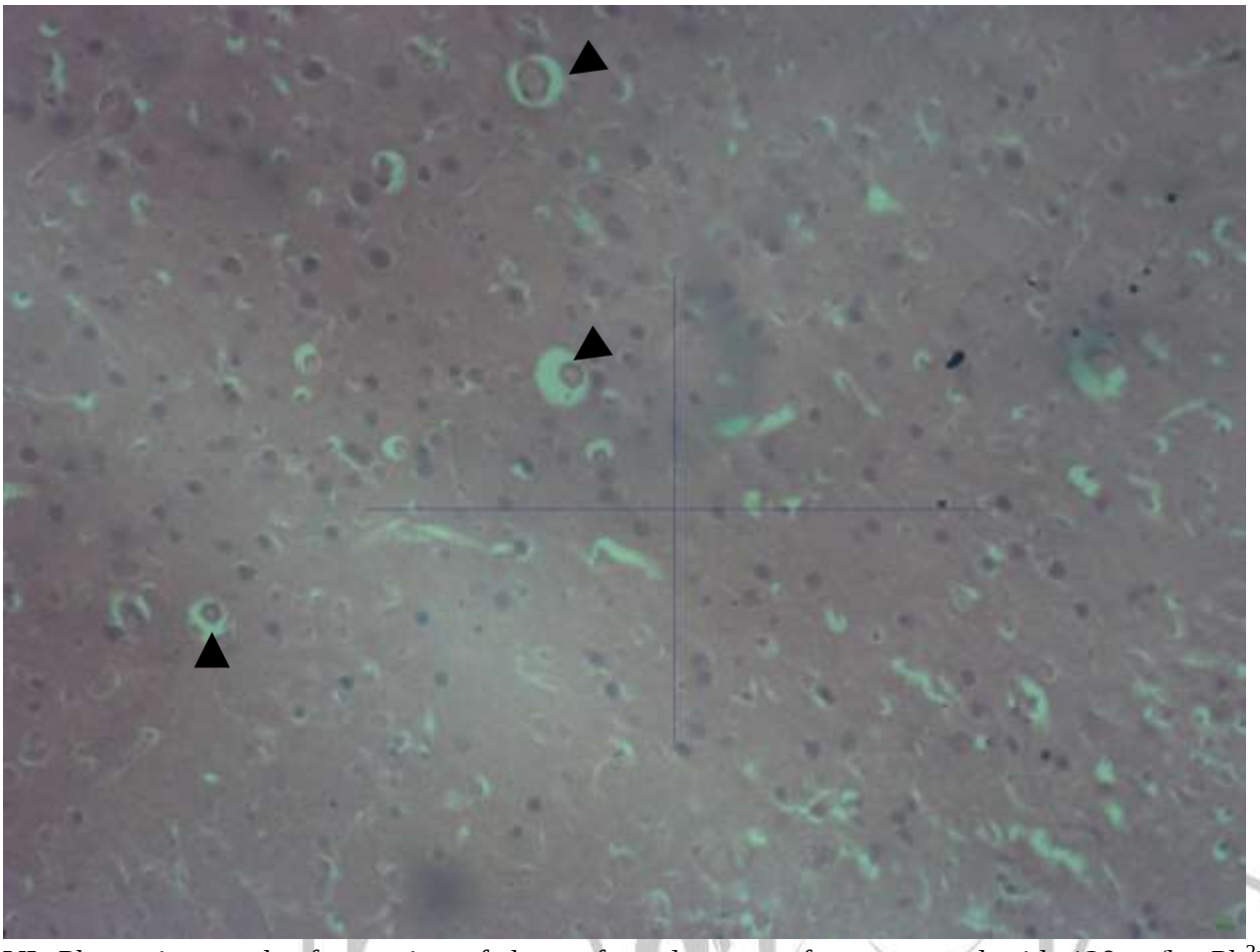
IIIA: Photomicrograph of a section of the prefrontal cortex of a rat treated with *Ficus Sycomorus* only showing normal cortical neurons of different categories and a normal condensed neurofibrilary network.H&E.X100.



IV: Photomicrograph of a section of the prefrontal cortex of a rat treated with 120mg/kg Pb^{2+} and 100mg/kg *Ficus Sycomorus* showing mild degeneration of the cortical neurons with well-developed vacuolated cytoplasm (Arrow heads).H&E.X100.



V: Photomicrograph of a section of the prefrontal cortex of a rat treated with 120mg/kg Pb^{2+} and 200mg/kg *Ficus Sycomorus* showing normal cortical neurons and a normal condensed neurofibrillary network. However, a few blood vessels with dilated perivascular spaces were noticed (Arrow heads). H&E.X100.



VI: Photomicrograph of a section of the prefrontal cortex of a rat treated with 120mg/kg Pb^{2+} and 5mg/kg Vitamin E showing normal cortical neurons and a normal condensed neurofibrillary network. However, a few blood vessels with dilated perivascular spaces were noticed (Arrow heads). H&E.X100.

4.0 DISCUSSIONS AND CONCLUSION

The study investigated ameliorative effect aqueous leaf extract of *Ficus Sycomorus* on the prefrontal cortex of adult wistar rats with lead acetate induced oxidative stress. In the present study, lead acetate was administered at a dose of 120mg/kg for 7 days to adult wistar rat and at the end of the induction, there was a decrease in the body and brain weight of the rat, but was not significant. During the treatment with *Ficus Sycomorus* extract, with an increasing dose and vitamin E, the rat started gaining weight when compared with normal control. In the SOD (Superoxide dismutase) activity, there is significantly ($p < 0.05$) decreased level in the rats induced oxidative stress without treatment (5.370 ± 0.247), it is the lowest, followed by lead acetate and low dose extract, (Group IV), (7.020 ± 0.651), then the high dose (Group V), (9.710 ± 0.368), but there is no significant ($p < 0.05$) decrease when compared to the normal control (Group I), (9.475 ± 1.846). In the CAT (Catalase) activity, there was a significant ($p < 0.05$) decrease in the positive control (Pb^{2+}) (3.395 ± 0.3536) when compared with the *Ficus Sycomorus* treated groups, it is the lowest followed by lead acetate and low

dose extract, (Group IV), (5.305 ± 0.488). There is no significant ($p < 0.05$) difference in the Vitamin E treated rats (Group VI), (5.070±0.217), when compared to normal control (Group I), (5.020±1.032). In the MDA (Malondialdehyde) activity there was a increase in the positive control (23.230 ± 0.834), it is the lowest followed by lead acetate and high dose (Group V), (16.960 ± 1.499), then the low dose extract, (Group IV), (18.330 ± 0.679), but it was not significant when compared to normal control (Group I), (19.130 ± 0.1909). This suggest that *Ficus Sycorum* may have ameliorated the injury caused by lead (Pb^{2+}) due to its antioxidant potential (Panahi et al., 201).

The histopathological examination carried out on the prefrontal frontal cortex of various groups show: Plate I (normal control group) shows normal cortical neurons of different categories, numerous glia cells and a normal condensed neurofibrillary network. However, photomicrograph of plate II (positive control group) showed a few cortical neurons with mild vacuolated cytoplasm and blood vessels with dilated perivascular spaces (Arrow heads), This neurotoxicity observed is suggested to be continuous intake of lead acetate. The ameliorative groups (IV and V), treated with different doses of aqueous leaf extract of *Ficus Sycomorus* after lead acetate induced oxidative stress is showing high therapeutic effect. Photomicrograph of plate III (low dose group) does not show signs of neurotoxicity. There is normal cortical neurons of different categories, and a normal condensed neurofibrillary network. This indicates that healing process may be already taken place as a result of the intake of *Ficus Sycomorus*. Plate IV (high dose group) shows a normal prefrontal cortex, normal cortical neurons and a normal condensed neurofibrillary network. However, a few blood vessels with dilated perivascular spaces were noticed (Arrow heads), when compared with normal control. This also indicates that the *Ficus Sycomorus* may have therapeutic effect at the high dose level when compared to the normal control and group three. According to Ezugwu et al., 2022, disorganization of cells in the successive layers of cerebral cortex was seen in the lead-treated animal model. Cells appeared to be larger in size and large vascular spaces were seen around them. Similarly, in case of cerebellum, although all three layers were visible, the granular layer was separated out from the molecular layer. Purkinje's cell layers of the cerebrum were disorganized and disrupted. At high visibility, complete dislocation of the Purkinje cell layer from the granular cell layer was seen. Using quantitative histological methods, Kumawat et al., 2014, reported a number of alterations in lead-exposed cerebellum, including a decrease in molecular layer width, granular cell density.

Several factors seem to account for the neurotoxic manifestations due to lead, (Kumawat et al., 2014). These include the integrity of blood brain barrier, clearance from the brain, role of lead-binding proteins, and the presence of large number of cellular scavengers, such as catalase, malondialdehyde and superoxide dismutase, as well as

interactions with other micronutrients, (Adekomi et al., 2017).

Neurotoxicity involves cognitive, affective, and physiological changes caused by toxic exposure, (Ezugwu et al., 2022). Some of the most common toxic agents include acute and chronic exposure to heavy metal like lead (Pb^{2+}) can induce significant neuro physiological and neuropsychological deficits, depending on the level of exposure. Consistent neuropsychological research over the years has revealed that lead exposure can result in declines in intelligence, memory, processing speed, comprehension and reading, visuospatial skills, motor skills and to a probable lesser extent, executive skills. Among the cognitive deficits induced by Pb^{2+} toxicity, visuospatial deficits appear to be notably prominent. Anxiety, depression, and phobia can also occur, while outcome, intervention, and rehabilitation results are largely dependent on the level of toxic exposure, (Ezugwu et al., 2021). There is also a growing evidence of anti-social behavior linked to early lead exposure. Early detection, accurate assessment, and treatment are important, especially since earlier intervention may aid in reversal of certain post toxicity sequelae. Deficits due to chronic exposure pose less favorable outcomes, making early detection and intervention that much more important (Flora et al., 2012). Similar observations have been reported by different authors like Ezugwu et al., 2022.

5.0 CONCLUSION

In conclusion this study shows that the aqueous extract of *Ficus Sycomorus* may have ameliorative effect in the biochemical parameters as it significantly normalized the superoxide dismutase, (SOD) catalase (CAT) and Malondialdehyde (MDA) concentration in the treated rats. Meanwhile the high dose group of *Ficus Sycomorus* showed a better intervention in the prefrontal cortex histology when compared to the low dose group as seen in the ameliorating effect on the damages (oxidative stress) that could be caused as a result of lead acetate intoxication. Therefore, *Ficus Sycomorus* has suggested in this study that well-restored prefrontal cortex may be the indication of its antioxidative properties. Meanwhile, it is worthwhile to consider this aspect at a deeper level of investigation using different animal models and methods.

5.5 CONTRIBUTION TO KNOWLEDGE

This study has added more knowledge to the existing literatures on the use of aqueous extract of *Ficus Sycomorus* as a possible ameliorating agent for lead acetate induced neurotoxicity.

5.6 RECOMMENDATION FOR FUTURE STUDIES

1) We recommend that further studies should be carried out to back up the claims made by ameliorative effect of this aqueous extract of *Ficus Sycomorus* on the frontal cortex of lead acetate induced neurotoxicity of adult male wistar rat.
2) We also recommend that more, studies should be carried out to access the actual phytochemical constituents of this plant

that was responsible for its ameliorative effect.

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