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Research Article

Lead induced mitochondrial oxidative stress in brain regions of maternal and female offspring rats: Protective effects of α-tocopherol acetate

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ABSTRACT
The objective of this research is to assess the effects of lead (Pb) on behavioural and antioxidant enzymes and the protective effects of α-tocopherol acetate in various brain regions of maternal and female offspring rats. Rats were separated into three groups: control, 0.2% Pb-exposure, and 0.2% Pb+α-tocopherol acetate (100 mg/kg body weight) supplemented. Following Pb-exposure, the animals were allowed to recover for a month to observe the recovery levels in the behavioural mechanisms and antioxidant enzyme activity levels. During this recuperation time, the animals were evaluated twice, on the 7th and 30th day, for behavioural and biochemical changes in the cerebral cortex, cerebellum, and hippocampus. A decrease in superoxide dismutase (SOD), catalase activity (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) activity, and an increase in l ipid peroxidation (LPO) content levels were seen in three brain regions when Pb exposure was compared to control rats. The Pb-induced alterations of these antioxidants were more pronounced in female offspring than maternal rats. This study establishes the role of α-tocopherol in the brain development of rats against lead exposed.

Keywords: rat brain, lead acetate, antioxidant enzymes, α-tocopherol acetate (Vitamin-E).

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Introduction

Lead (Pb) has the potential to induce health-related harmful effects in multiple environmental conditions. Exposure to Pb can take place during various periods of the developmental process, influences the central nervous system, and results in encephalopathy, cognitive, learning impairments, and degenerative disorders [1]. Lead exposure can result in neurobehavioral problems in children [2].

According to Singh et al., nervous system is extremely subtle to the Pb. Many studies have proven the mechanisms of Pb neurotoxicity [3]. It can affect the nervous system in different ways, among which oxidative stress (OS) and cell death are commonly recognized mechanisms [4-6].

Lead has the potential to pass through the placenta. It may enter the conceptus and easily breach the blood-brain barrier in the event of maternal exposure, owing to the growing organism's incapacity to do so [7]. Numerous reports on the effects of Pb exposure on pregnancy and/or lactation behaviour reported inconsistent findings [8]. Pb exposure during pregnancy resulted in cognitive impairment, as demonstrated in Open field and Shuttle-Box studies [9].

OS in the brain can lead to impaired cognitive function in living organisms [10]. Lead impairs neuronal function in a variety of ways, the most prevalent and pervasive being oxidative stress and cell death [4,6].

Additionally, lead inhibits superoxide dismutase activity, thus causing an increase in malondialdehyde and catalase activity and a reduction in glutathione (GSH) levels. Inhibiting or activating some of these enzymes contributes to the maintenance of metal-induced lipid peroxidation [10]. Different levels of Pb exposure in epidemiological and animal studies respond differently to oxidative stress at different target sites such as lungs, blood vessels, testes, sperm, liver, and brain [11]. Utilizing the appropriate medications to combat oxidative stress has become critical for avoiding Pb-induced neurotoxicity. Studies of animals exposed to lead have shown that vitamin E has a synergistic effect with DMSA by lowering GSH levels and preventing damage from free radicals [4].

Vitamin E has several proven benefits, like antioxidant, neuroprotective, and anti-inflammatory advantages [12]. It acts as a generic term for all tocopherols and its derivatives [13]. Evidence suggests that OS has a consequence on learning and memory skills in pre-clinical studies [14]. In rat models, vitamin E has proved beneficial in preventing oxidative damage and cognitive deficits [15]. It has the ability to prevent the injurious effects of OS in the brains of aging rats [16]. Recently, supplements of vitamin E have emerged as popular antioxidants [17].

The aim of this current study is to examine whether vitamin E supplements can avert lead induced antioxidants, peroxidation of lipids and cognitive impairment. To test this possibility, exposed lead and vitamin E and then studied in terms of restraint-induced oxidation status in the brain regions of maternal and female offspring rats.

Materials & Methods

Selection of Chemicals

We used lead acetate and α -tocopherol as our test compounds in this investigation. In St. Louis, Missouri, USA, they were purchased from the Sigma Chemical Co., while the rest of the chemicals were procured from reliable Indian sources. The doses of lead acetate and α -tocopherol acetate was determined using previously published data [18, 19]. A stock solution of 1% lead acetate in de-ionized water was dissolved and diluted to the desired concentrations. Vitamin-E was dissolved in soyabean oil (1g/10ml) and before experimentation; 1ml (100 mg/Kg body weight) of the above stock was used to get a desired concentration, calculated according to the body weight of the animal.

Procurement and maintenance of animals

For the present study, both maternal and female offspring rats were selected. The rats were obtained from IISc Bangalore and maintained in rat polypropylene cages lined with paddy husk as bedding material under well controlled laboratory conditions (Temperature: 28 ± 2º C; Relative humidity: 60 ± 10%; Light/dark cycle: 12/12 cycle). Water was freely available to the rats, who were given normal rat pellets from Bangalore (Sai Durga feeds). Indian government's Committee for Purpose of Animal Experimentation Control (CPCSEA) and S.V. University, Tirupati's Ethical Committee for Animal Experimentation performed the experiments.

Experimental design

Animal Exposure

Lead acetate's biochemical and behavioural effects on female offspring rats weighing 170± 10gm were studied in this investigation (4 months old). Three sets of 12 mother rats and female offspring rats were randomly selected from a total of 12. Rats in groups 1 and 2 were fed a standard rat diet and had free access to tap water to serve as a control. Rats in group 2 of maternal and female offspring rats were fed lead ad libitum for 42 days (Gestational day 1 to postnatal day 21 in the case of pregnant rats), while rats in group 3 of maternal and female offspring rats were fed α-tocopherol by gavage at a level of 100 mg per kilogramme of body weight per day during the last 21 days of the experiment.

After the end of the test, the animals were sacrificed by cervical dislocation to measure Pb concentrations and neurochemical changes in the brain on days 7 and 30 of the experiment (after post vitamin-E treatment). On day 7, six rats from each group of both maternal and female rats (control and experimental rats) were used to examine brain function related parameters and on day 30, remaining six rats from control and experimental rats were used to examine the selected brain related parameters.

Isolation of tissues

After completion of the behavioural experiments, the rats in all groups were sacrificed and the brain was immediately isolated, weighed to its nearest milligram by using Shimadzu electronic

balance. It was quickly possible to extract and preserve different brain regions such cerebral cortex, the hippocampus and cerebellum for subsequent biochemical analyses.

Behavioural Studies

Locomotor Activity

The Opto-Varimex small was used to measure the locomotor activity of the rat (Columbus Instruments, USA). The locomotor activity was recorded for every 5 minutes interval in 30 minutes duration and the data was expressed in seconds.

Open Field Test

One of the most used methods for measuring emotional reactivity is the open-field test. Horizontal activity may be seen in the number of line crossings, whereas vertical activity can be seen in the frequency of raising. Three- and one-month old rats were tested in an open field with a 90cm high x90cm wide x30cm deep wooden cages. Using black lines, the arena floor has been partitioned into 36 equal squares. Upon being put in the middle of an open field, a rat's every movement was instantaneously was scored. Each square that is traversed with all paws (crossing), and each square that is raised (raising), and each square that is raised with forelimbs placed against the arena wall (standing) (wall rearing). Sniffing and grooming are tallied in every session, as are any sniffing, wiping, licking or combing scratching of any area of the animal's body. The session's mean total behaviour was calculated by combining all of the activities. Pb and vitamin-E treated mice underwent five days of testing in five-minute intervals. The frequency with which crossings occurred indicated locomotor activity [20,21].

Isolation of mitochondrial fractions

Ficoll-sucrose gradients were employed to recover mitochondrial fractions from cortical, hippocampus, cerebellum, and medulla brain homogenates [22].

The cerebral cortex, Cerebellum hippocampus and medulla were isolated from the remainder of the brain, which was kept at a cool temperature. After the tissues were weighed and homogenised, the volume was increased to 25 ml using an ice-cold homogenising buffer. The homogenates were separated by centrifugation at 750 g for 10 minutes. For 20 minutes, the supernatants were centrifuged at 17,000g. Pellets were suspended in 10 ml of 0.32 M sucrose for 45 minutes before being placed on a two-step discontinuous Ficoll-sucrose gradient containing 13 and 7 percent Ficoll solution. A milky layer developed at the 13 percent and 7.5 percent Ficoll contact. Removed and suspended in a homogenising buffer, the centrifuge tube pellet was dissolved. After being diluted with nine volumes of 0.32 M sucrose, the milky layer fraction was re-centrifuged at 17,000g for 30 minutes at room temperature. After the supernatant was discarded, the pellet (synaptosomal fraction) was dissolved in 0.32 M sucrose and used as the substrate for the enzyme assay after it had been dissolved in 0.32 M sucrose.

Lipid peroxidation

The lipid peroxides were determined using Ohkawa and Yagik's TBA method (1979). The tissues were homogenised in a solution of 1.5% KCl (20% W/V). 2.5ml of 20% TCA was added to 1ml of tissue homogenate, it was necessary to dissolve the precipitate in 2.5ml of 0.05M sulphuric acid before centrifuging it for 10 minutes at 3,500g. Thirty minutes were spent in a hot water bath with three millilitres of thiobarbituric acid added to each sample (TBA). In a spectrophotometer, the 530nm wavelength of malonaldehyde (MDA) was compared to a blank reagent after the samples had been cooled. It was decided to utilise TMP (trimethyl pentane) as an external reference standard. Per gm of moist tissue, the values are in moles of malonaldehyde produced.

Superoxide dismutase activity (EC 1.151.1)

According to Beachamp and Fridovich, the activity of superoxide dismutase was assessed as the suppression of photoreduction of nitro blue tetrazolium (NBT) by the enzyme (1971). In order to homogenise the tissues (20% weight by volume), polyvinyl pyrolidone was added to a potassium phosphate buffer pH (7.5) and centrifuged at 16000g for 15 minutes at room temperature. Further, the reaction mixture included 1.5ml of phosphate buffer pH (7.5), 0.03 mg/ml of NBT, 0.03 mg/ml of methionine, 0.03 mg/ml of NBT, 0.03 mg/ml of NBT, and 0.01 mg/ml of enzyme source. The addition of riboflavin was necessary to start the reaction, and samples were then exposed to fluorescent light (fluorescence) for 30 minutes before the 560 nm absorbance of the end product was compared to a reagent blank that had been maintained in perfect darkness for the entire experiment. According to the literature, the enzyme's activity was measured in terms of moles of superoxide removed per mg of protein per minute.

Catalase activity (EC 1.11.1.6)

The Beers and Sizer's technique was used to measure catalase activity in the samples (1952). Centrifuged at 16,000 g for 45 minutes, the tissues were homogenised (10% W/V) in 50 mM phosphate buffer (pH 7.0) and centrifuged. Centrifuged at 105,000g for one hour, the supernatant was then employed as a source of enzyme. Hydrogen peroxide (H2O2) in buffer, 1.0 ml, 0.059 M, and 1.9 ml reagent grade water made up the reaction mixture. An incubation period of around 4-5 minutes was necessary to accomplish temperature equilibration and establish any possible blank rates. After adding 0.1ml of dilution enzyme, the absorbance decreased at 240nm for 2 to 3 minutes. It was possible to derive A240 / min from the linear component of the curve that began after 45 seconds. It was possible to measure the enzyme activity in moles of H2O2 degraded per milligram of protein each minute.

Glutathione reductase

Staal et al (1969) measured the activity of glutathione reductase in the mitochondria of rat kidneys. It was necessary to add the following materials to get a final volume of 3.0 ml: A total of 1.0 ml of sodium phosphate buffer pH-6.8 0.3 M, 0.25ml of 250 mM EDTA, 0.25 ml of 12.5% GSSG, 0.7ml of distilled water, 0.2ml of 30 mM NADPH, and 0.1ml of enzyme extract were used in this experiment. The variations in absorbance at 340 nm were detected with the use of a spectrophotometer. Measuring enzyme activity in moles of NADPH oxidised per milligramme of protein per minute [23].

Glutathione peroxidise activity

This study used the method established by Rotruck and colleagues to measure the activity of GPX in the mitochondrial fraction of rat kidney (1973). Glutathione reduced, H_2O_2, 0.02 millilitres of sodium azide, 0.02 millilitres of sodium pyrophosphate buffer (pH-7.0), and 0.01 millilitres of enzyme source were all included in the reaction mixture. When it had been heated to 37oC for 10 minutes, the reaction mixture was arrested. After then, 0.5 percent 10% TCA was added to the reaction to bring it to a halt. After that, the mixture was centrifuged for 10 minutes at 2000 rpm. Following the extraction of the supernatant, the DTNB and 0.3M DHP were added, and the reaction was monitored at 412 nm using a fluorometer to determine the rate of reaction. Each micromole of NADPH oxidised per minute of protein was used to determine the enzyme activity.

Estimation of protein content

Lowery and colleagues' approach, which is discussed in further detail below, was used to determine the protein composition of the tissues. Homogenates of the tissues were generated at a concentration of 1% (W/V) in a 0.25M ice-cold sucrose solution. After mixing 0.5 ml of homogenate with 1 ml of a 10% TCA solution, the mixture was centrifuged at 1000g for 15 minutes at room temperature. After removing the supernatant, 1ml of 1N sodium hydroxide (NaOH) was used to dissolve the remaining residues. Following this, 4ml of alkaline copper reagent and 0.4ml of folin-phenol reagent were added to the mixture (1:1folin: H2O). A UV/VIS spectrophotometer at 600 nm was used to compare the sample's colour to a white reference (Hitachi model U-2000). A typical protein graph was used to assess the tissues' protein composition (BSA).

Statistical analysis

Statistics were performed on the data (ANOVA and t-test, if appropriate) using normal statistical techniques to arrive at a conclusion.

Results

The findings of the current study revealed the importance of the treatment period and dosage for both lead and vitamin E. Vitamin E has the effect of minimizing memory defects in lead-treated rats, and thus vitamin supplementation could be a modest and cheap way to overcome the effects of harmful agents. The current study discovered that the Pb caused a significant reduction in the behavioural activity like locomotor, open-filed behaviour (Fig.1.1 to 2.2) and in the brain enzyme activities of SOD, CAT,GR,GPx (Fig.3.1 to Fig.6.2) and increase of TBARS levels (LPO)(Fig.7.1 to Fig.7.2) in cerebral cortex and followed by cerebellum and hippocampus as compared to controls of both female and maternal rat groups. Vitamin E (Oral) resulted in a significant alteration in the behavioural mechanisms and these brain enzyme levels towards their maternal and female offspring rats in the both groups. Vitamin E supplemented female offspring rats show more reversal effect against Pb induced rats than the maternal rats at two time points (7^{th}& 30^{th} day).

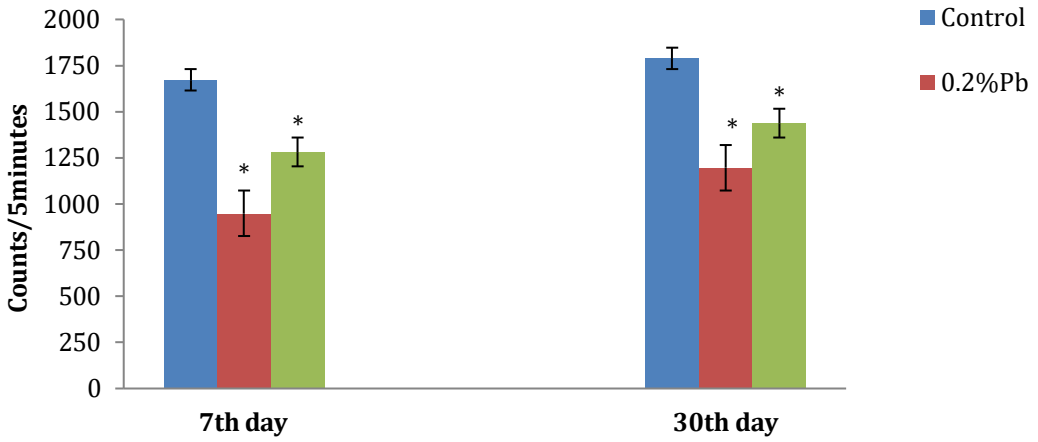
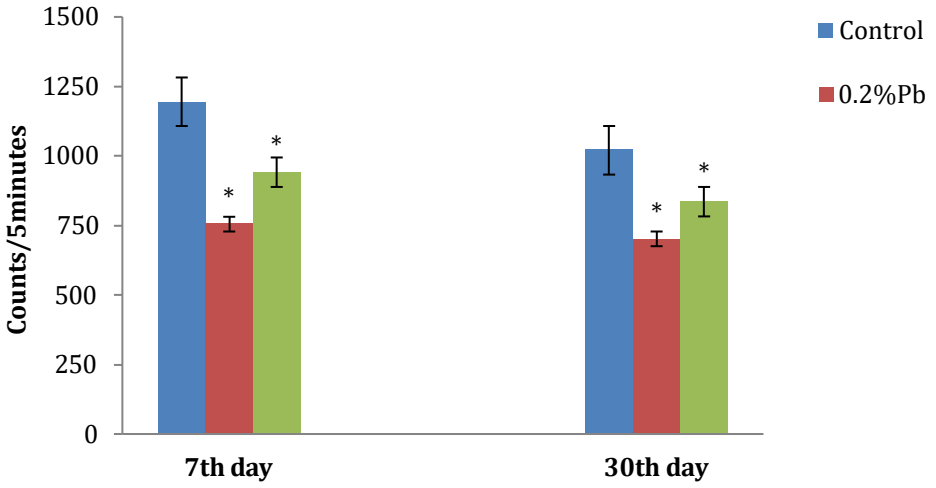


Fig. 1.1: Alterations in locomotor activity of female offspring rats (4 months old) exposed to 0.2% lead and α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally)



* All the values are significant at P<0.001

Fig. 1.2: Alterations in locomotor activity of maternal rats (4 months old) exposed to 0.2% lead and α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally)

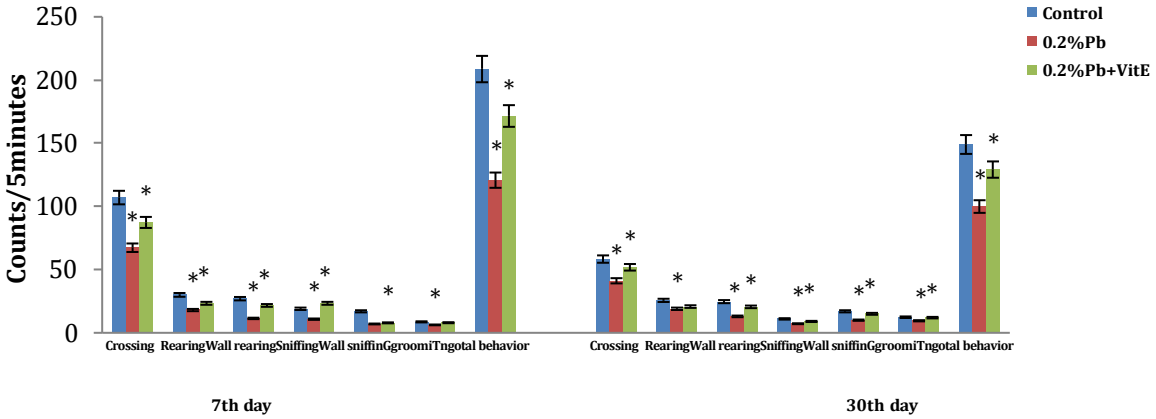
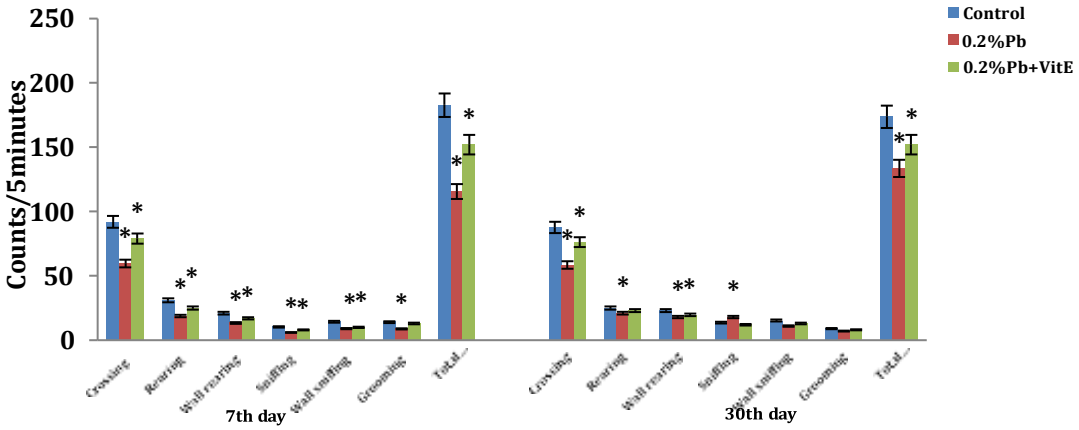


Fig. 2.1: Alterations in Open-field behavior of female offspring rats (4 months old) exposed to 0.2% lead and α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) at 7th & 30thday of post vitamin E treatment period



*All the values are significant at P<0.001

Non-significant values are at P>0.05

Fig. 2.2: Alterations in Open-field behavior of maternal rats (4 months old) exposed to 0.2% lead and α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) at 7th & 30th day of post vitamin E treatment period

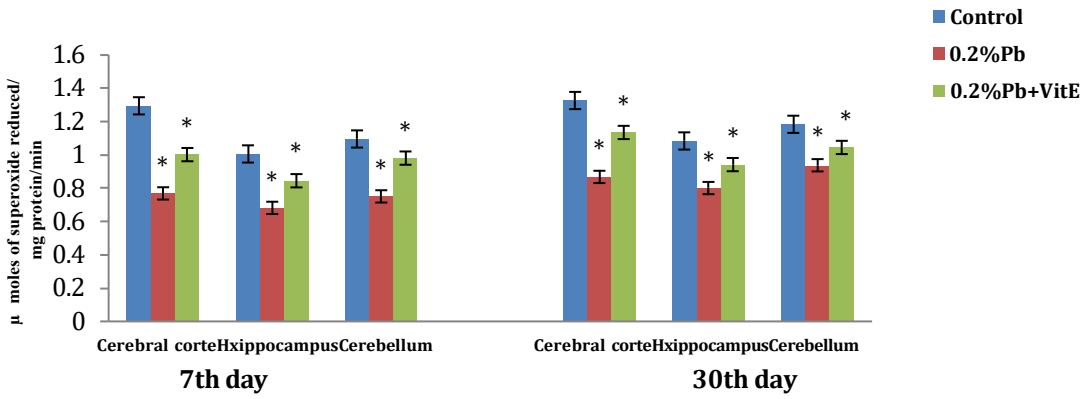
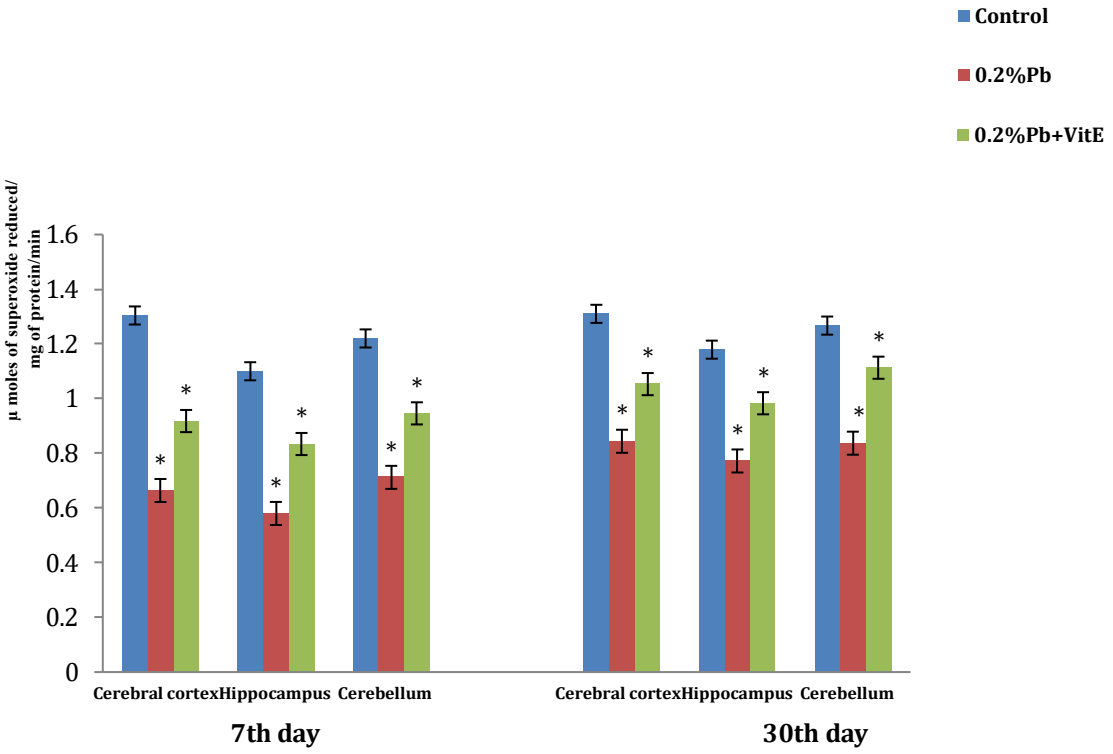


Fig. 3.1: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in SOD activity (μ moles of superoxide reduced/mg protein/min) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of female offspring rats (4 months old)



*All the values are significant at P<0.001

Fig.3.2: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in SOD activity (μ moles of superoxide reduced/mg protein/min)) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of maternal rats (4months old)

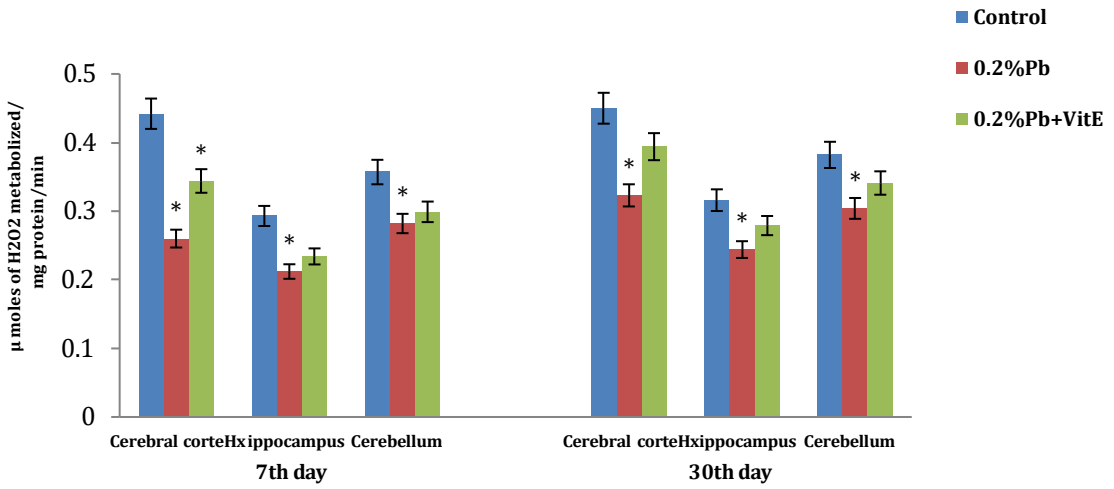
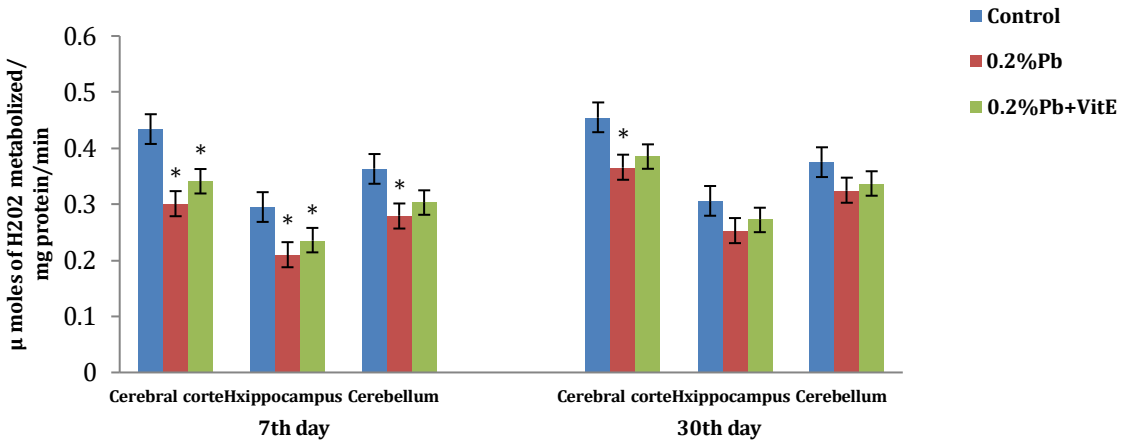


Fig. 4.1: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in CAT activity (µ moles of H_2O_2 decomposed/mg protein/hr) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of female offspring rats (4 months old)



*All the values are significant at P<0.001-0.05
Non-significant values are at P >0.05

Fig. 4.2: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in CAT activity (µ moles of H_2O_2 decomposed/mg protein/hr) in brain mitochondrial fractions of cerebral cortex, hippocampus, and cerebellum of maternal rats (4 months old)

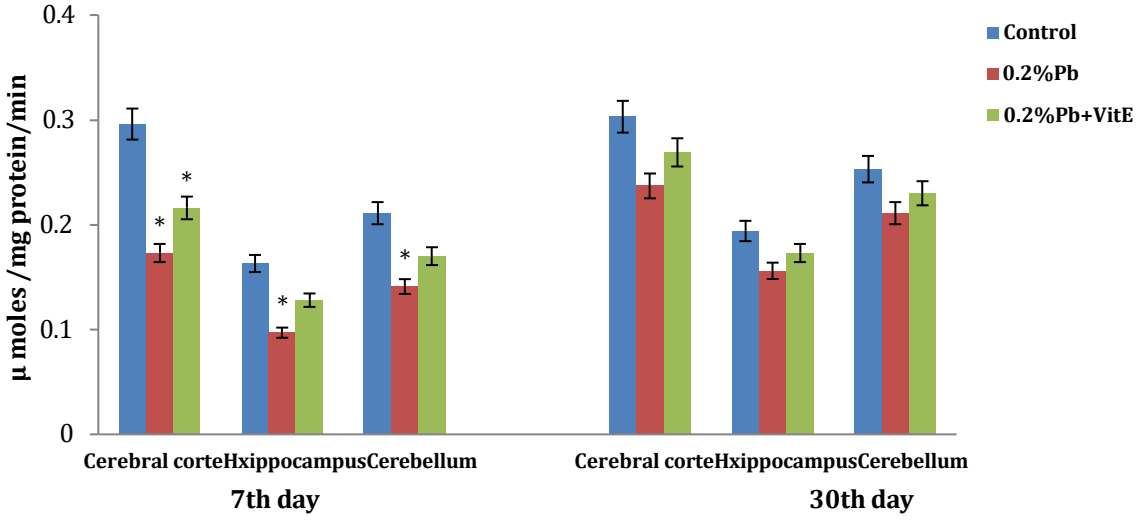
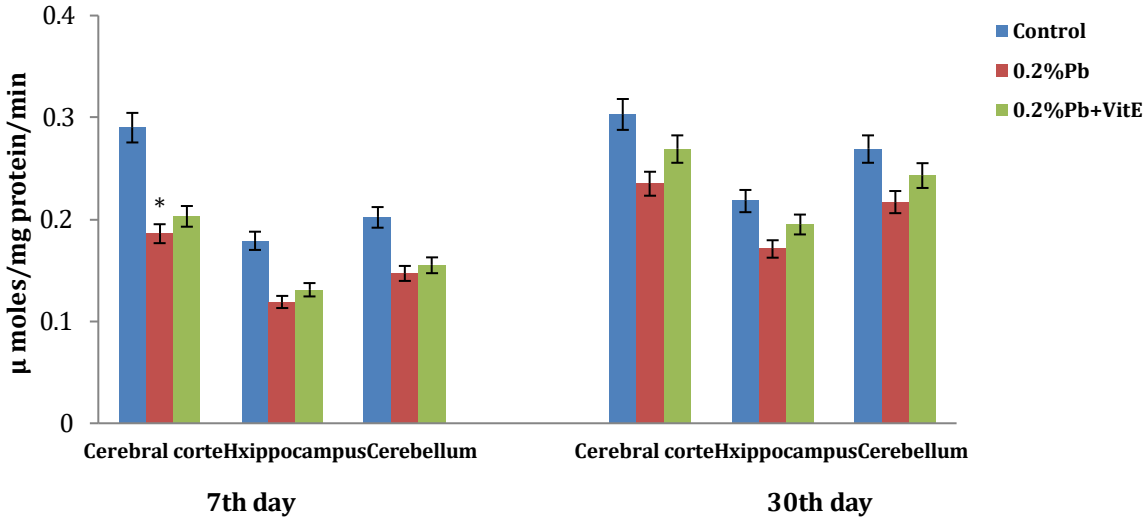


Fig. 5.1: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in GPx activity (µmoles of NADPH oxidized/mg protein/min) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of female offspring rats (4months old)



*All the values are significant at P<0.001-0.05
Non-significant values are at P> 0.05

Fig. 5.2: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in GPx activity (µmoles of NADPH oxidized/mg protein/min) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of maternal rats (4 months old)

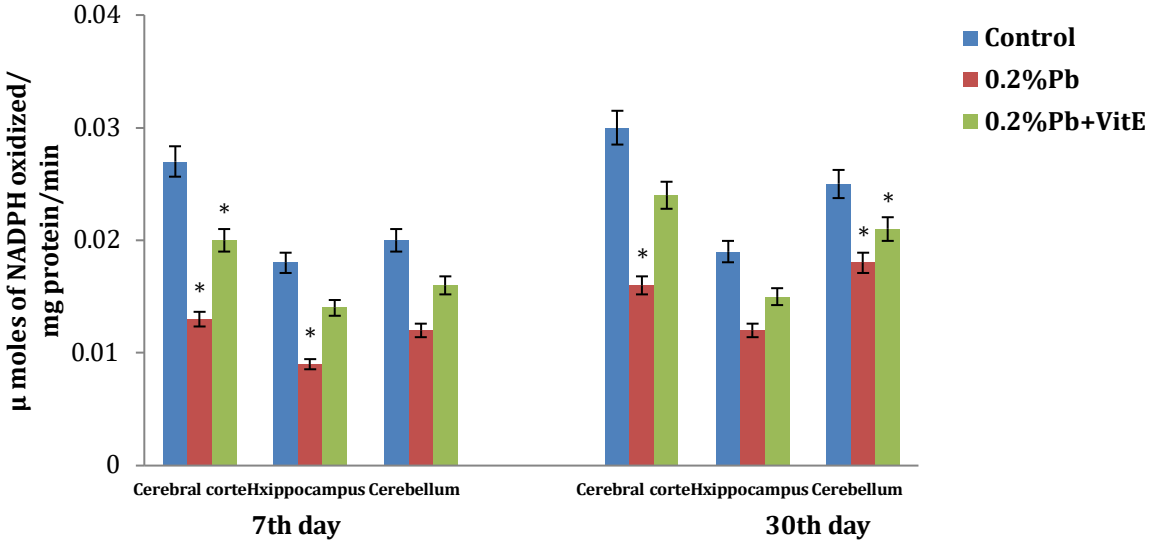
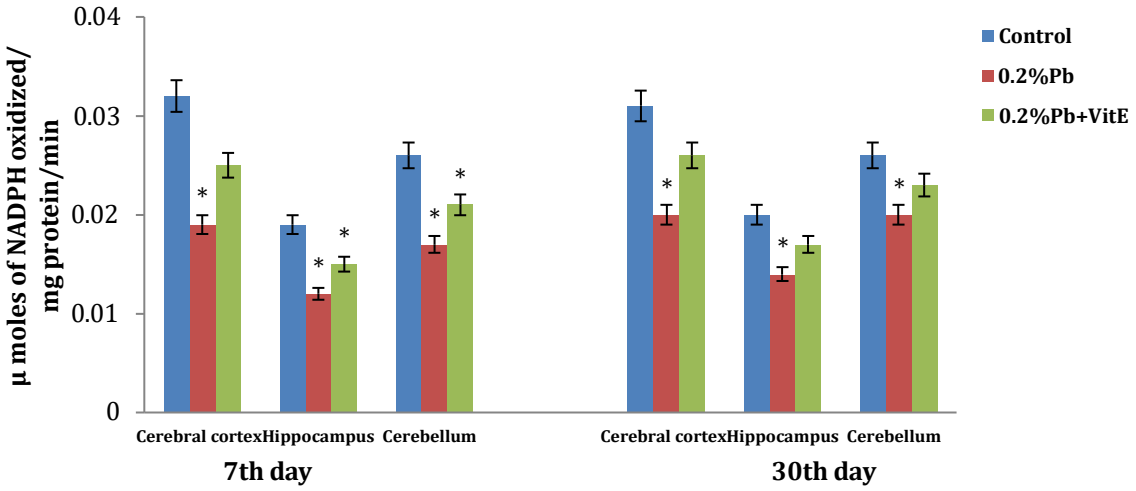


Fig. 6.1: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in GR activity (µ moles of NADPH oxidized/mg protein/min) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of female offspring rats (4months old)



*All the values are significant at P<0.001-0.05
Non-significant values are at P>0.05

Fig. 6.2: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in GR activity (µ moles of NADPH oxidized/mg protein/min) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of maternal rats (4 months old)

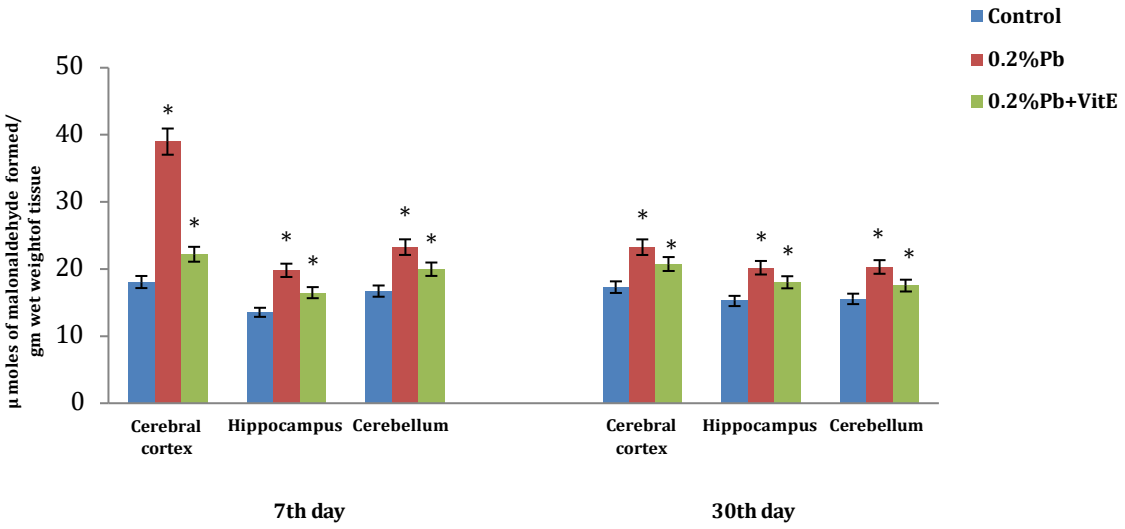
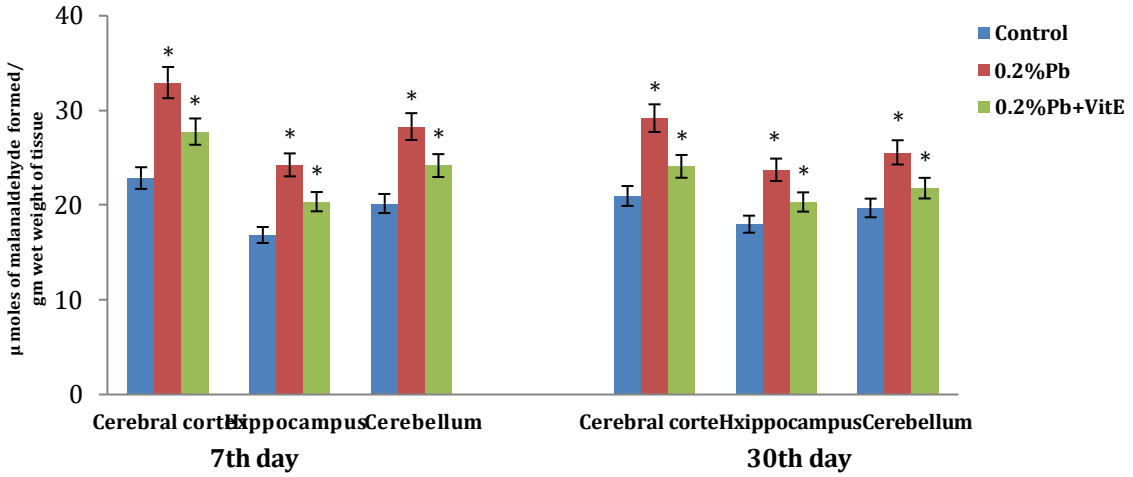


Fig. 7.1: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in malonaldehyde content (µ moles of malonaldehyde /gm wet wt. of tissue) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of female offspring rats (4 months old)



All the values are significant at P<0.001

Fig. 7.2: Effect of α-tocopherol acetate (Vitamin-E) (100 mg/kg body wt/orally) on 0.2% lead induced alterations in malonaldehyde content (µ moles of malonaldehyde/gm wet wt. of tissue) in brain mitochondrial fractions of cerebral cortex, hippocampus and cerebellum of maternal rats (4 months old)

4. Discussion

The results of the current research suggest that vitamin E has a beneficial influence on antioxidant activities when exposed to lead. Many studies have demonstrated that vitamin supplements have the ability to decrease the toxic effects of lead [24,25].

In the current work, we observed that lead acetate exposure resulted in impairments in learning and memory. Rats that are exposed to 0.2% doses of lead acetate have notable changes in comparison to their maternal and female offspring. Reports from previous animal studies have proven that lead acetate exposure results in deficits in learning and memory [7,26].

It is observed that lead exposure impairs both behaviour and the recovery from mitochondrial oxidative stress in the current research. Female offspring rats revealed substantial variations in vitamin E supplementation when compared to maternal. Early studies have shown that lead exposure causes damage in multiple brain regions and in particular in learning and memory [7,26].

Lead has the greatest impact on the brain, making it the most vulnerable organ [27]. Exposure to lead caused in a reduction in performance on tests such as open-field and water maze. Rats exposed to Pb during open-field testing sessions showed lower locomotor activity, indicating that they were having difficulty

moving about. Salinas and Huff also reported reduced performance latencies in a Pb-exposed adult rat open-field motivated place learning task [28].

Exposure to lead during lactation results in cognitive impairment in female and maternal rats, as evidenced by habituation rejection to field tasks. Only the control group's mating, rearing, and sniffing reactions had the memory of addiction, according to the results of the study. Researchers [29, 30] have shown that the hippocampus is involved in the processing of open-field habituation memories. In this study, control mice performed well in the field and exhibited higher overall behavior than lead-treated mice in both maternal and female offspring's rats.

OS play a significant role in both human and rat brain injury [31]. Brain lead concentrations, antioxidant status, and adverse effects of α-tocopherol acetate in three brain regions in lead-exposed female and maternal brain regions. The hypothalamus, quedrigemina, and striatum's antioxidant functions were affected differently by Pbexosure, in accordance with a Sandhirs report [32].

The antioxidant parameters GPx, CAT, SOD, GST, and GSH are substantially diminished by exposure to Pb, while the oxidative parameters MDA and H_2O_2 are increased [33]. According to Omobowale *et al.,* Pb resulted in an increase of MDA and H_2O_2 concentrations and the expression of the cyclooxygenase-2 enzyme (COX-2) [34]. It has a high affinity for GSH's reactive -SH group and can reduce GSH levels. The antioxidant functions of metalloproteins like GPx, CAT, and SOD are affected by Pb exposure. Pb has a direct effect on lipid peroxidation and minimises the antioxidant parameters, resulting in lead-induced oxidative damage in various body organs [35,36].

Several studies have shown that various vitamin supplements can reduce lead toxicity [24,25]. This study was examined the behavioural perturbations and oxidative stress in Pb-induced maternal and female offspring rats against α-tocopherol.

Lipid peroxidation and SOD and CAT activity were inhibited by vitamin E to protect against lead-induced hepatitis in rats [37]. Neuro protective as well as antioxidant effects of vitamin E have been shown to ameliorate cognitive decline with age [15]. High dosages of vitamin E in the elderly have been proven to enhance cognitive performance [38] over time. The cholinergic system and vitamin E have been linked in studies on memory consolidation [39]. Vitamin E and DMSA were shown to function together synergistically to reduce oxidised glutathione levels and prevent free radical damage in research on lead-exposed rats. Vitamin E's ability to protect against lead poisoning may be enhanced by its interaction with other antioxidants. Lead-induced lipid peroxide levels in rats' livers and brains have been reduced by vitamin E alone or in conjunction with the common chelating agent CaNa2EDTA [40].

The remedy of rats each previous to or after pressure with the nutrients E ended in a boom within side the sports of SOD, GST, catalase and ranges of decreased glutathione with a lower in lipid peroxidation. Post-diet remedies have been determined greater powerful in preventing pressure brought on pr-oxidant modifications than pre-diet remedy. Vitamin A, E and C are pronounced to behave as a powerful antioxidant of primary significance for safety towards sicknesses and degenerative strategies as a result of oxidative pressure [25,26].

Conclusion

In conclusion, the current study established that vitamin E has a significant effect on reversing or limiting stress-induced oxidative derangements in the rat brain. Pb induced free radical enhancement and its toxicity on both maternal and female offspring rats brain regions was assessed by estimating the behavioural and levels lipid peroxidation, depletion of antioxidant enzymes activity status and the influence of vitamin E was examined at interval time periods (7^{th}&30^{th} day).

Author contributions

All authors contributed equally towards the preparation of the manuscript.

Ethics approval

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