Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008425

Effect of Eugenol on Brain Neurotrace Elements and Cytoarchitecture of the Cerebral Cortex of Wistar Rats Following Aluminium Induced Neurotoxicity

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ARTICLE INFO

Received: October 09, 2023

Published: November 06, 2023

Citation: Samuel Bolaji Mesole, Omachonu Alfred Okpanachi, Uthman A Yusuf, Elvis Tams Godam and Abel Nosereme Agbon. Effect of Eugenol on Brain Neurotrace Elements and Cytoarchitecture of the Cerebral Cortex of Wistar Rats Following Aluminium Induced Neurotoxicity. Biomed J Sci & Tech Res 53(4)-2023. BJSTR. MS.ID.008425.

ABSTRACT

The present study was carried out to study the effects of Eugenol on Brain neurotrace elements (Iron Fe; Manganese Mn: Magnesium Mg) following administration of Aluminium chloride on Wistar rats. Materials and Methods. Thirty (30) adult Wistar rats were randomly divided into six (6) groups namely:

- Group I: Rats receiving 300 mg/kg Eugenol for 21 days,
- Group II: Rats receiving 150 mg/kg eugenol for 21 days,
- Group III: Rats receiving 300 mg/kg Eugenol and 100 mg/kg Aluminium chloride for 21 days,
- Group IV: Rats receiving 150 mg/kg Eugenol and 100 mg/kg Aluminium chloride for 21 days,
- Group V: Rats receiving 100 mg/kg aluminium chloride for 21 days and
- Group VI: Rats receiving 2ml of distil water as placebo for 21 days respectively. The rats were sacrificed 24 hours after administration of the last dose by 0.8ml ketamine as an anesthetic agent.

Results: Aluminium chloride treatment of rats resulted in significant ($p<0.05$) elevation of manganese and Aluminium levels in the brain of rats when Group V is compared to eugenol treated groups (Group I, II, III, and IV). This is accompanied by a significant decrease ($p<0.05$) in brain levels of Iron (Fe) and Magnesium when group V is compared to eugenol treated groups (Group I, II, III and IV). Histological examination of the cerebral cortex Layer III and V using haematoxylin and Eosin revealed pyknosis perineuronal vacuolations of pyramidal cells of group-administered 100 mg/kg of aluminium chloride. However, treatment with Eugenol revealed an almost normal cytoarchitecture of the pyramidal cells of the cerebrum of the Wistar rats. Conclusions: Eugenol has the ability to protect rat brain from the deleterious effect of aluminium chloride on brain neurotrace elements and preserve cytoarchitecture of the brain of rats.

Keywords: Eugenol; Prineuronal Vacoulations; Neurotrace Elements; Pyramidal Cells

Introduction

It is of interest to note that humans live in what is referred to as "the Aluminium Age". Objects made with aluminium are strong, durable, light and corrosion-resistant [1]. With regards to bioavailability, aluminium can be found in drinking water and this is due to its property as a flocculant, it is a common additive to various processed foods, also added to cosmetics of various types, and increasingly shows up in pharmaceutical products [2]. Aluminium mimics metals such as magnesium, calcium, and iron in their biological functions in the human body hence resulting in biochemical alterations within the normal functioning of the body system [2,3]. Aluminium can induce neurodegeneration, by increasing the accumulation of iron and generation of reactive oxygen species (ROS) production [3]. The physical and chemical properties of aluminium allow it to effectively mimic the above-mentioned metals in their respective biological functions and trigger a series of biochemical abnormalities. Aluminium has been proven to replace Mg and bind to phosphate groups on the cell membrane [4]. Eugenol (4-allyl-2-methoxyphenol), with a molecular formula of $C_{10}H_{12}O_2$ and a molecular weight of 164.21, mainly exists in clove oil, camphorated oil, cinnamon leaf oil, and nutmeg oil. At normal temperatures, eugenol is a pale yellow viscous oily liquid with a strong clove flavor and a special hot taste or brown powder in the dried form [5]. Eugenol, which is an active compound (nutraceuticals) in many spice plants such as clove, Ocimum sanctum and Ocimum gratissimum is a well-established antioxidant [6]. This present study was undertaken to investigate the protective effect of eugenol on brain neurotrace elements (Iron, Magnesium and Manganese) and the cytoarchitecture of the cerebral cortex (Layer III and V) following aluminium induced neurotoxicity in rats.

Materials and Methods

Chemicals

Eugenol used for this study was purchased from Wuhan JCJ Logis, china and manufactured by Yueyang Jiazhiyuan Biological Co Ltd china. While aluminium chloride which was used as a neurotoxic agent was obtained from Guandong Guanghua Sci-Tech Co. Ltd china.

Animals

A total of thirty (30) apparently healthy adult Wistar rats of both sex (140 to 160g) were obtained from the Animal House of the Department of Human Anatomy, Faculty of Basic Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State Nigeria and housed in wired cages in the Animal House of the Department of Human Anatomy, Ahmadu Bello University, Zaria and they were acclimatized for two weeks prior to the commencement of the experiments. Ethical approval was obtained from Ahmadu Bello University research and ethics committee. All rats were given food (rat chow – vital feeds) and water *ad libitum*. Treatment groups were administered Eugenol/Aluminium Chloride in addition to water and rat chow.

Treatment

All groups consisted of 5 rats each and all route of administration was via the oral route. Eugenol and aluminium were administered simultaneously. Group, I included rats that received 300 mg/kg of eugenol (10% L D_{50}), Group II included 150 mg/kg (5% LD_{50}) of eugenol, Group III included rats that received 300 mg/kg of eugenol and 100 mg/kg of aluminium chloride, Group IV included rats that received 150 mg/kg of eugenol and 100mg/kg of aluminium, Group V included rats that received 100 mg/kg of aluminium chloride [7], Group VI included rats that was administered 2ml of distilled water as placebo. Duration of the entire treatment was for 21 days. Rats were humanely sacrificed 24 hours after the last administration with 0.8ml of ketamine as anesthesia (Table 1).

Table 1: Shows Wistar rat groups and corresponding dosage.

Groups	Dose
Group I	300 mg/kg eugenol
Group II	150 mg/kg eugenol
Group III	300 mg/kg eugenol + 100 mg/kg aluminium chloride
Group IV	150 mg/kg eugenol + 100 mg/kg aluminium chloride
Group V	100 mg/kg of aluminium chloride
Group VI	2 ml distil water

Preparation of Sample

The brains were dissected out from the rats carefully and cleared of the adhering tissues, weighed and 0.25g of homogenized sample i.e. 1g in 4ml of phosphate buffer. The analytical method for metal analysis in biological tissues was determined by the method of monitoring method index [8].

Preparation of Tissue for Microscopy

The brain a removed and fixed in formol saline and processed for microscopy. Tissues were processed to obtain 5 µm thick paraffin wax, stained with haematoxylin and eosin according to the methods of Dury, et al. [9].

Statistical Analysis

Results obtained were analysed using statistical software, statistical package for social sciences (IBM SPSS version 21.0, SPSS Inc., 233 South Wacker Derive, 11th floor, Chicago, IL 60606-641, USA) and Microsoft Office Excel 2007 for charts. Results were reported as mean ± Standard error of mean (S.E.[M0]), and one way analysis of variance (ANOVA) with least squares was used to identify whether there were any significant differences between the group means. For significance, use the significant difference (LSD) post hoc test. Paired sample t-test was employed for comparison of means as appropriate. Values were considered significant when $p \leq 0.05$.

Results

Figure 1 shows the effect of Eugenol treatment on brain neurotrace element (Iron) following aluminium chloride-induced neurotoxicity. This outcome demonstrates a noteworthy (p 0.01) reduction in brain iron levels as shown in rats in Group V (100mg/kg of AlCl3) when compared to Group VI (CONTROL). Treatment with Eugenol, however, was able to raise the level of brain iron in Group III and IV. This elevation was found to be significant ($p<0.001$) when compared to Group V. But when the comparison is made with Group VI, the reduced levels of Iron (Fe) in the brain which can be observed in Group III and IV. These reductions could be as a result of the treatment with aluminium chloride. This reduction was found not to be significant when compared to Group VI (control). The Increase observed in Groups I and II were found to be not significant ($p>0.05$) when compared to Group VI. This could be as a result of eugenol administration. Figure 2 Shows the effect of Eugenol treatment on brain neurotrace element (Magnesium) following aluminium chloride-induced neurotoxicity. This result shows a significant ($p<0.01$) reduction in brain levels of magnesium in Group V when compared to Group VI. Treatment with eugenol, however, revealed a significant ($p<0.05$) increase in the level of brain magnesium as observed in Groups III and IV when compared to V. However Groups I and II levels of brain magnesium shows no significant ($p>0.05$) difference when compared to Group VI.

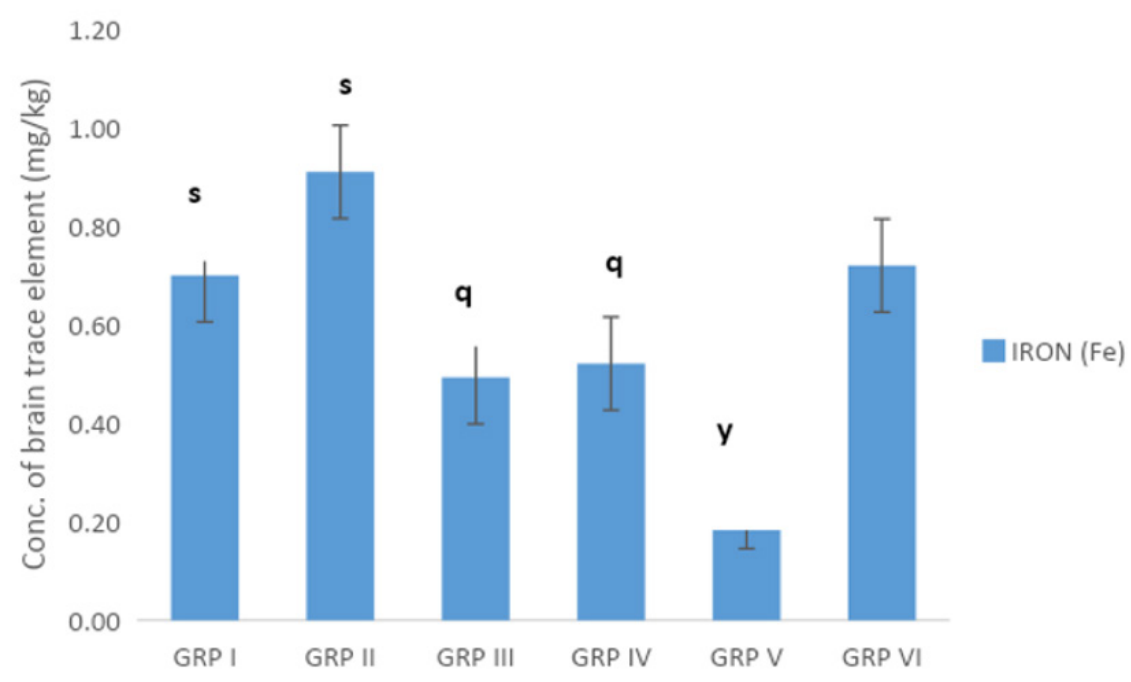

Figure 1: Effect of Eugenol on Neurotrace Brain element (Iron Fe) following administration of aluminium chloride on Wistar rats.

Note: n = 5; mean ± SEM One way ANOVA LSD post hoc test: q, s, y, = $p<0.05$; $p<0.01$ when compared with aluminium chloride. Group I and II (Eugenol 300mg/kg; 150mg/kg), Group V = AC (Aluminium chloride 100mg/kg), Group VI = CTRL (Control 2.0ml/kg)

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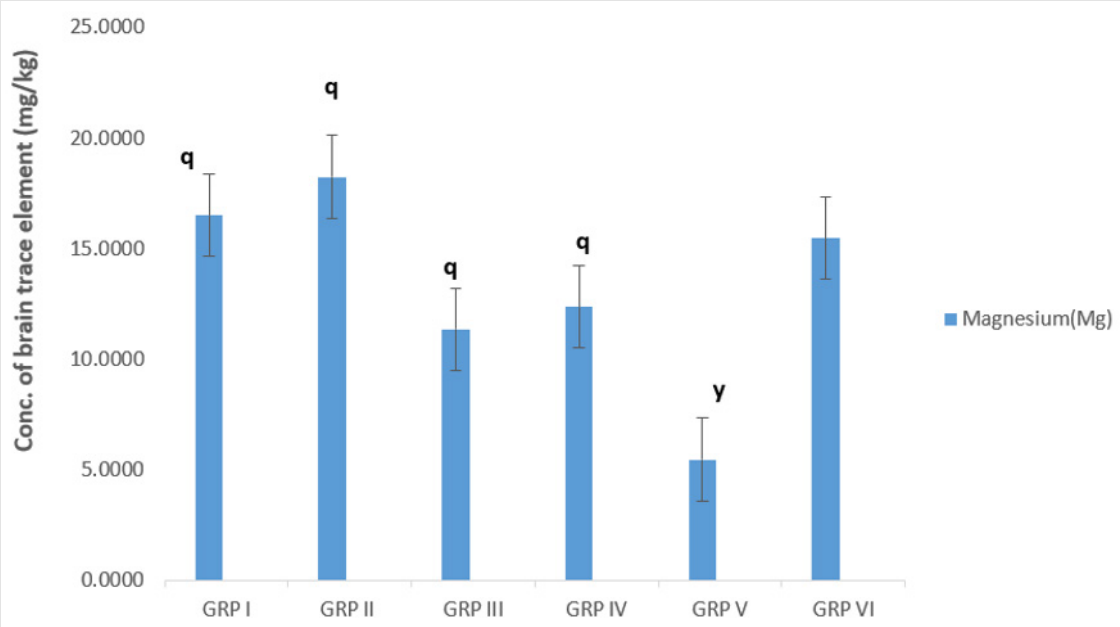

Figure 2: Effect of Eugenol on Neurotrace Brain element (Magnesium Mg) following administration of aluminium chloride on Wistar rats.

Note: n = 5; mean ± SEM One way ANOVA LSD post hoc test: q, y = $p<0.05$; $p<0.01$; when compared with aluminium chloride group control group respectively. Groups I and II (Eugenol 300mg/kg; 150mg/kg), Group V (Aluminium chloride 100mg/kg), Group VI (Control 2.0ml/kg)

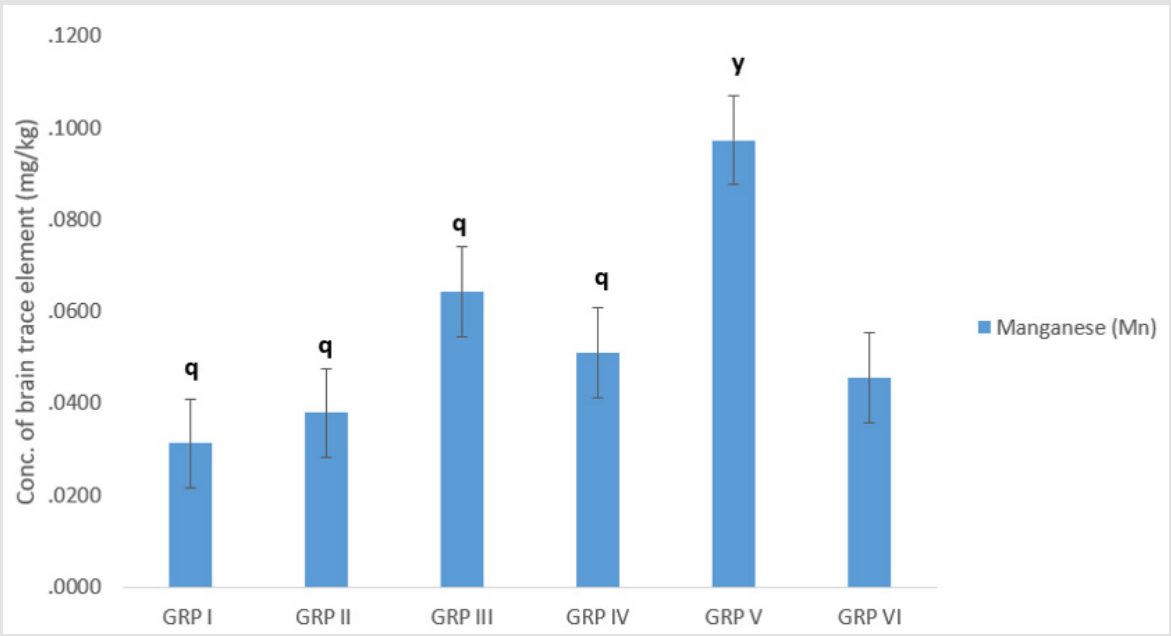

Figure 3: Effect of Eugenol on Neurotrace Brain element (Manganese Mn) following administration of aluminium chloride on Wistar rats.

Note: n = 5; mean ± SEM One way ANOVA LSD post hoc test: q, y = $p<0.05$; 0.01 when compared with aluminium treated group; $p<0.05$ when Group V is compared to Group VI. Groups I and II (Eugenol 300mg/kg; 150mg/kg), Group V (Aluminium chloride 100mg/kg), Group VI (Control 2.0ml/kg).

Figure 3 shows the effect of Eugenol treatment on brain neurotrace element Manganese (Mn) following aluminium chloride-induced neurotoxicity. This result shows a significant ($p<0.01$) elevated level of brain Manganese in Group V when compared to Group VI. Treatment with Eugenol however significantly ($p<0.05$) reduced the manganese level in Groups III and IV when compared to Group V. When Groups I and II is compared to Group VI there is a non-statistical significance ($p>0.05$) between the brain levels of manganese. Figure 4 shows the level of aluminium in the brain following oral administration of aluminium chloride. The result shows a significant ($p<0.001$) elevation in brain Al levels when Group V is compared to Group VI. It will be observed that the administration of Eugenol significantly reduced ($p<0.045$) the level of aluminium as observed in Groups III and IV when compared to Group V. Figure 5 shows Histological image of the section of the cerebral cortex (Layer III and V). A and B shows the histological features of the cerebral cortex of the control rat. C and D shows cerebral cortex (layer III and V) of Group V that was administered 100mg/kg aluminium chloride with perineuronal vacoulations (PV). E and F shows cerebral cortex (Layer III and V) of rats administered 300 mg/kg of eugenol and 100mg/kg aluminium chloride showing mild perineuronal vacoulations.

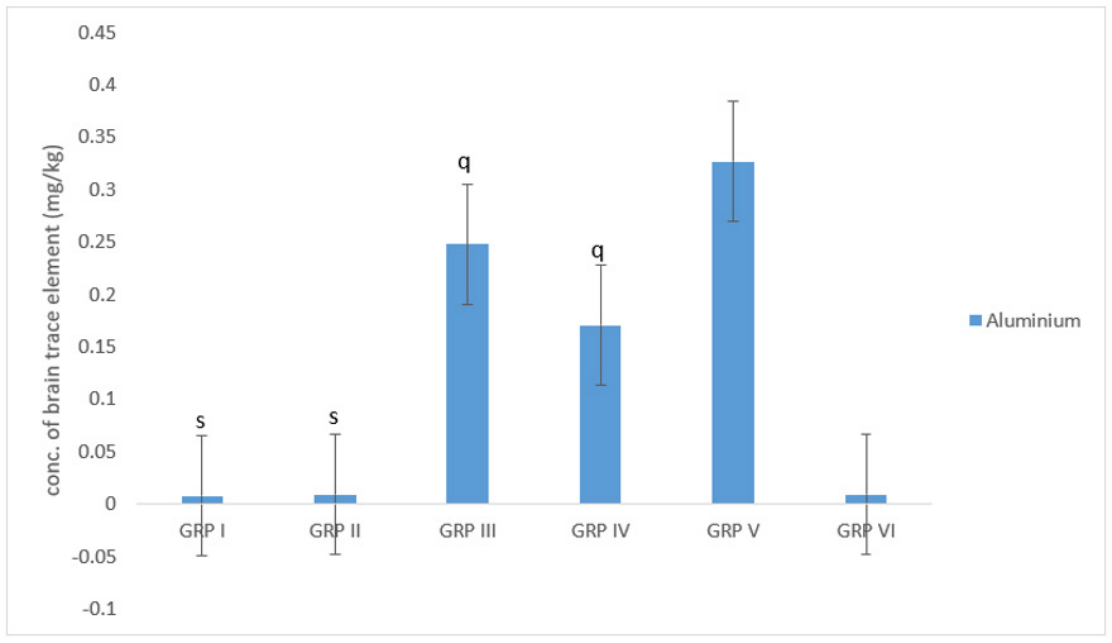

Figure 4: Effect of Eugenol on Aluminium Brain element following administration of aluminium chloride on Wistar rats.

Note: n = 5; mean ± SEM One way ANOVA LSD post hoc test: q = $p<0.05$ s = $p<0.001$ when compared with the aluminium chloride group respectively. Groups I and II (Eugenol 300mg/kg; 150mg/kg), Group V (Aluminium chloride 100mg/kg), Group VI (Control 2.0ml/kg)

G and H shows the cerebral cortex of rats (Layer III and V) administered 150mg/kg eugenol and 100mg/kg aluminium chloride showing very mild perineuronal vacoulations when compared to the group administered 100mg/kg of aluminium chloride only, I and J shows the cerebral cortex of rats (Layer III and V) administered 300mg/kg of eugenol showing normal histology of the cortex when compared to the control group, L and M shows the cerebral cortex of rats (Layer III and V) administered 150mg/kg eugenol showing a normal histology of the cerebral cortex when compared to the control (Pyramidal cell P, Glial cell G, Oligodendrocyte, O, Perineuronal vacoulations PV).

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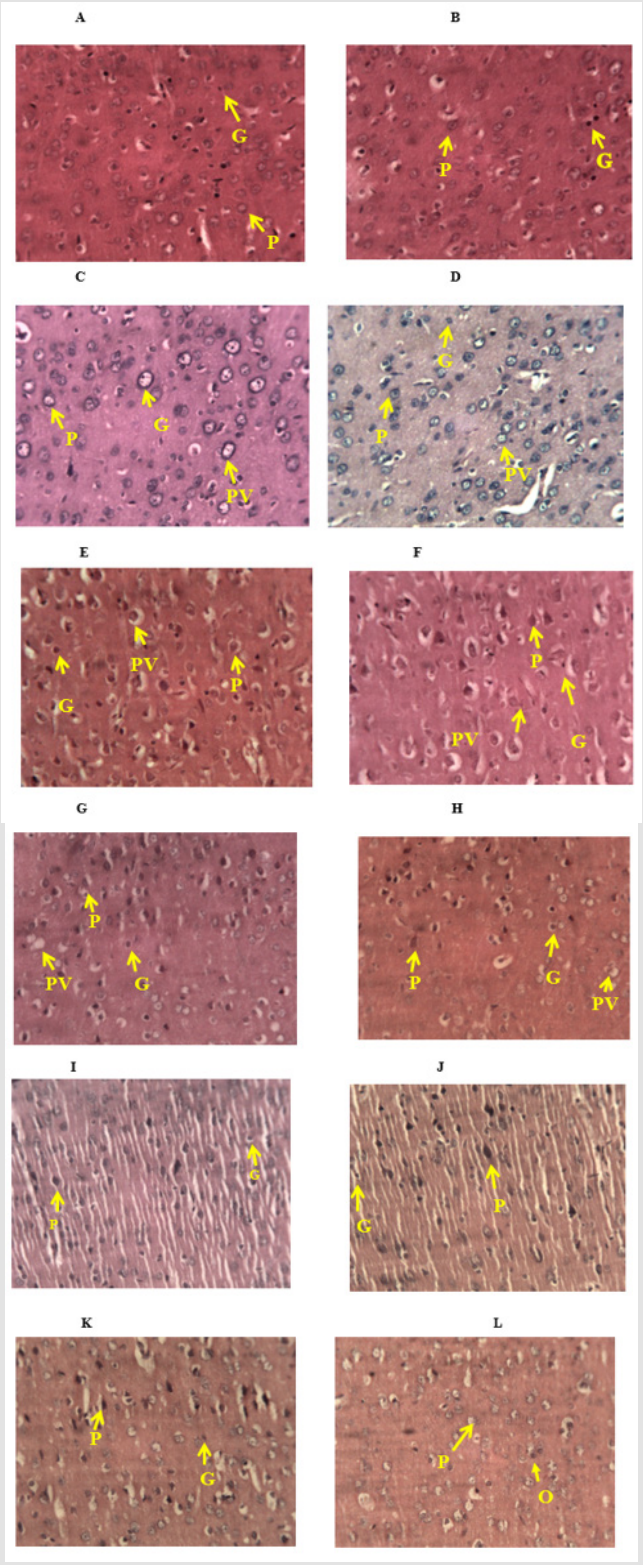

Figure 5.

Discussion

Oral administration of aluminium chloride has been reported to induce cerebellar cellular neuronal degeneration [10]. These degenerative changes could occur in the following ways such as suppression of neuronal energy production (especially mitochondrial energy production) and greatly enhances excitotoxic sensitivity of neurons [11-13]. Aluminium is also known to inhibit or suppress cellular energy-producing enzymes, including mitochondrial electron transport enzymes [14]. Because mitochondrial energy suppression is closely linked to neurodegenerative disorders like Alzheimer's dementia and Parkinson's disease as an early event, the therapeutic significance of aluminum-induced neuronal energy suppression stems from this. [15-17]. Hence neuronal energy suppression is one of the bases for cellular degeneration within the central nervous system. The main mechanism of aluminium toxicity involves the disruption of the homeostasis of metals, such as magnesium (Mg), calcium (Ca), and iron (Fe) manganese. The physical and chemical properties of aluminium allow it to effectively mimic these metals in their respective biological functions and trigger biochemical anomalies. Aluminium has been shown to replace Mg and bind to phosphate groups on the cell membrane [18].

Oral exposure to aluminium results in accumulation within the cerebral cortex, cerebellum and hippocampus of the brain and thus affect some essential elements (Fe, Zn, Cu, Mn, and Mg) contents at varying levels [19].

Previous studies have correlated neurological disorders to the accumulation of aluminium chloride in the brain of Wistar rats [20,21]. Manganese is an essential mineral for maintaining brain function, manganese toxicity in humans is associated with Parkinsonian-like symptoms such as ataxia and altered balance may develop [22]. Exposure to aluminium has been shown to induce changes in the cerebral, cerebellar and hippocampal levels of neurotrace elements [23]. In this study exposure to aluminium resulted in increased levels of manganese and this increase was higher than the control group. Increase in the levels of manganese within the brain also act as a prooxidant and hence a toxicant to the brain (elevated amounts) which is deleterious to neurons within the brain. However, administration of eugenol was able to lower brain manganese levels close to normal as observed in Group III and IV. Magnesium (Mg) is known to play an important role in supporting brain plasticity, this primes the brain for maximal learning, memory and cognitive function. Increasing brain magnesium levels have been shown to restore critical brain Plasticity and thus improves cognition [24]. In this study, decreased Mg brain levels as observed in aluminium treated group. This is in tandem with the study of Slutsky, et al. [22]. Eugenol was able to reverse the reduction in the Mg levels that were induced by aluminium resulting in an increase in Mg levels when compared to the control group. The groups administered eugenol only (Groups I and II) showed elevated brain Mg levels when compared to the control (Group VI).

Eugenol's ability to increase brain Mg levels might be responsible for its cognitive improving properties. In a Eugenol the salvaged groups (Group III and IV) was able to elevate magnesium close to Group VI. Iron deficiency is not perceived as a life-threatening disorder. But lowered levels of Iron (Fe) has resulted in impaired behaviors including learning [23]. Results from this study revealed reduced brain iron levels in Group V when compared to Group VI. Also, groups treated with eugenol (III and IV) showed an increase in Fe levels when compared to the aluminium treated group. Rats that received eugenol showed increased levels of Fe When compared to the control group. Reduced Fe levels in rat brains (Group V) might be responsible for cognitive deficits elicited by rats which might result in a defective dopaminergic interaction with the opiate system and cholinergic neurotransmission. Elevated levels of aluminium in the brain have been associated with neurological diseases such as Alzheimer's or Parkinsonism [25], which has been attributed to the accumulation of such metals in the brain of affected individuals [26]. Oral exposure to aluminium results in accumulation within the hippocampus of the brain and thus affect essential trace elements (Fe, Zn, Cu, Mn, and Mg) contents in the hippocampus at varying levels [27]. Previous studies have correlated neurological disorders to the accumulation of aluminium chloride in the brain of Wistar rats [28]. Aluminium has been revealed to affect the homeostasis of brain neurotrace elements which are essential for brain function.

Histological Studies

In this study, light microscopic examination of histological (Haematoxylin and Eosin H&E) sections routinely stained histological sections of the Cerebral cortex –layer III and V were conducted as shown in Figure 5. Neurodegeneration is a process involved in both neuropathological conditions and brain ageing [29]. Histoarchitectural distortion of neural tissue manifesting as neuronal degenerative changes are indicative of neurotoxicity in the central nervous system [30,31]. Degenerative changes are observed as cortical neuronal shrinkage, perineuronal vacuolations, loss of pyramidal neurone process in sections of the brain studied regions of aluminium-treated rat compared to the control, indicates treatment (aluminium) related neurotoxicity.

Conclusion

The present study concludes that Eugenol has the ability to protect and enhance brain function by restoring brain neurotrace elements (Iron, Magnesium and Manganese) and preserving histoarchitecture of the cerebral cortex from histoarchitectural changes induced by aluminium chloride.

Data Availability

Authors can confirm that all relevant data are included in the article and / or provided as supplementary files.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

Funding Statement

Authors declare that this study was self-funded and no external funding.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008425

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