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Original research

Protective Role of Curcumin against Aluminum Induced Cerebral Cortical Toxicity in Rats

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Abstract:

Aluminum (Al) is one of the most poisonous metallic elements commonly used. Aluminum is the third most common element and the most common metal on the earth's surface, after oxygen and silicon. Aluminum is one of the most neurotoxic metals which cause oxidative damage. Medicinal plants have been used to treat various pathologies, and bioactive substances are now extracted from plants in therapeutic science. Curcumin (Cur) is a beneficial antioxidant and neuroprotective agent. The goal of this study was to see if curcumin could protect the brain against aluminium toxicity. Seventy adult male albino rats were used in the present study and divided into two main groups 20 days and 40 days each main group subdivided into 5 groups includes: control, vehicle (DMSO), Cur, Al and Al+Cur group. Administration lasted for 20 and 40 days. Nitric oxide (NO) level was estimated and specimens from brain cortex were taken for histopathological studies. The results showed that Aluminum administration exhibited a marked increase in nitric oxide levels and histopathological alterations. Overall, curcumin attenuated the elevation in NO levels and the morphological disturbances caused by aluminum.

Keywords: Curcumin, Aluminum, Cerebral Cortex, Nitric oxide

1- Introduction

Aluminum is widely utilized in daily life, making it easier for humans to be exposed to it, resulting in a variety of negative physiological effects, including neuropathological alterations **(Bhalla et al., 2010).** Aluminum is used to purify drinking water and is found in many processed foods **(Shi et al., 2004).** Cooking tools made of aluminium (pans, pots, kettles, and trays) are said to account for approximately 20% of daily aluminium consumption **(Kawanishi et al., 2002).**

Aluminum is the most common neurotoxicant. Research has shown that Al has had major toxic manifestations in the central nervous system **(Ghribi et al., 2001a).** The brain is the most sensitive organ to all toxicity. Aluminum can easily penetrate the blood-brain barrier (BBB) in the brain through its conclusive high affinity for transferrin receptors **(Liaguat et al., 2019; Tietz et al., 2019)**.

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Many studies have shown that Al- toxicity causes neuropathological, neurobehavioral, neurophysical and neurochemical shifts **(Colomina et al., 2002; Walton et al., 2013)**. Treatment with Al+3 has also been demonstrated to play a role in neuronal degeneration processes linked to antioxidant enzyme suppression, lipid peroxidation, and protein denaturation **(Walton, 2007).** Nitric oxide is a diffuse, short-lived molecule that recombines quickly to create stable nitrate and nitrite metabolites. It is considered a pro-inflammatory mediator because of its ability to react with superoxide anion to the formation of nitrite, a deleterious anion, leading to various pathological conditions **(Abolaji et al., 2018).** Abnormal nitric oxide synthase (NOS) activation during aluminium administration causes an increase in NO levels, as well as the destruction of intracellular signalling systems **(Stevanovic et al., 2009).**

Medicinal plants have been used to treat various pathologies, and bioactive substances are now extracted from plants in therapeutic science. Antioxidant-marked plants have gained interest in oxidative stress-related neurodegenerative disorders **(Kar et al., 2019).** Curcumin (Cur), an active yellow pigment found in the rhizome of the curcuma longa (turmeric) plant, has been demonstrated to have a variety of pharmacological effects, including anti-inflammatory, anti-carcinogenic, anti-ischemic, and hypotensive properties (**Chakravarty and Yasmin 2008; Aggarwal and Sung, 2009)**. Several studies have shown that Cur has protective effects against oxidative damage and has antioxidant properties that exert powerful scavenging effects of oxygen free radicals and increased concentration of intracellular glutathione, thus shielding lipid peroxidation **(Kuhad et al., 2007; Ciftci et al., 2012).** Curcumin-treated rats had lower levels of brain NO, which was linked to peroxynitrite scavenging by inhibiting xanthin oxidase and inducible NOS in ischemia rats **(Thiyagarajan and Sharma, 2004).**

In the light of this literature, the present study was carried out to investigate the protective effect of curcumin as a neuroprotector against aluminum induced cerebral alterations in the experimental animal's model of neurotoxicity.

2-Materials and methods:

2.1-Chemicals

Aluminum chloride ($AlCl_3$) was purchased from Acmatic Co. Egypt. Curcumin extract was purchased from (Sigma Aldrish Co, USA). All other chemicals were of the highest purity commercially available.

2.2-Animal Selection

In the present experiment, seventy adult male albino rats (weighing 140 ± 20 g) were obtained from the Serum and Vaccine Laboratory- Helwan Farm. Animals were housed in a well-ventilated clean cage maintained under a 12-h of light-dark cycle at 25 ± 2º C with a relative humidity of 50 ± 5 % at Zoology department, Aswan University, Aswan, Egypt. Rats were held for approximately one week before the beginning of the experiment for acclimatization to laboratory conditions. The rats were fed on pellet diet and water.

2.3-Experimental design and treatments

Rats were randomly divided into two main groups according to period (20 and 40 days). Each group was subdivided into five groups, each with seven animals:

- Gr I (Control): received one oral dose of saline solution only.
- Gr II (Vehicle): received a daily oral dose of 33% DMSO.
- Gr III (Curcumin): received a daily oral dose of 100 mg/kg b. wt. of Cur.

- Gr IV (Aluminum): received a daily oral dose of 20 mg/kg b. wt. of $AlCl_3$.
- Gr V (Al + Cur): received a daily oral dose of 100 mg/ kg b. wt. Cur then after one hour were given 20 mg/kg b. wt. $AlCl_3$.

2.4- Estimation of nitric oxide levels

Determination of nitric oxide levels were carried out in the homogenate of the brain cortex according to the method of **Montgomery and Dymock (1961).**

2.5- Histological studies

Brains were collected from all groups and washed in sterile saline and kept in 10% neutral phosphate-buffered formalin (PH7.0). For microscopic preparations, specimens were dehydrated in gradual ethyl alcohol (50-99%), cleared in methyl benzoate and embedded in molten paraffin wax at 58-62˚C, tissue sections, 5µm in thickness were prepared and stained with hematoxylin and eosin **(Gabe, 1976)** for microscopic investigation. The stained sections were examined and photographed by using light microscopy to study the histological changes in cerebral cortex.

2.6- Statistical analysis:

Data of nitric oxide levels were expressed as means ± S.E. Differences between means were tested by one-way analysis of variance ANOVA followed by the Student-Newman-Keuls T-test using Minitab 19 software so that the data obtained can be compared and statistically evaluated. Statistical significance was considered when $p < 0.05$.

3-Results and discussion

3.1- Nitric oxide (NO) levels

From the present data, Al-administration increased NO level in the cortical homogenate versus those of control rats (Table 1). The increase or stimulation in NO was 104.35% and 146.39% at 20 and 40 days respectively. Statistically, this stimulation was significant ($p<0.01$). Similarly, **Kar et al. (2019)** reported that NO levels increased in $AlCl_3$-induction. Previous study of **Prakash et al. (2013)** stated that $AlCl_3$-induced proinflammatory cytokines (IL-1β and TNF-α) release can trigger activation of inducible nitric oxide synthase (iNOS). Consequently, activated iNOS leads to production of large amount of nitric oxide (NO) which in turn, reacts with ROS to form more reactive and toxic nitrogen species i.e. peroxynitrite. Also, **Kaizer et al. (2005)** reported that aluminum exposure led to oxidative damage by increasing NO levels in different mouse brain regions.

The same table (Table 1) when curcumin was given to Al-administered rats, it inhibited the increase of NO level at 20 and 40 days by 25.19% and 52.97% , respectively. The statistical analysis of this data showed that the inhibition of curcumin to the NO level was significant ($p<0.01$). Further supporting evidence in favor of our findings published by **Kar et al. (2019)** who showed that NO levels in aluminum-induced synaptosomes were normalized by curcumin treatment. Consistently, curcumin can play a crucial role in down-regulation of NOS expression and specifically scavenge RNS in rats after aluminum exposure **(Kumar et al., 2009).** Furthermore, **Edrees et al. (2018)** indicated that curcumin treatment may be a strategy to reduce the nitric oxide concentration of brain tissues, perhaps via inhibition of NO synthase. Similarly, **Jung et al. (2006)** and **Song et al. (2011)** reported that curcumin decreased NO production and iNOS gene expression in Lipopolysaccharides (LPS)-stimulated microglial cells and in a mouse ascites tumor model which agree with the present findings.

Table 1: The effect of curcumin on nitric oxide (NO) levels in homogenates of brain cortex of control and different treated rats.

Measurements / Groups	Nitric oxide levels (nmole/mg tissue)	
	20 days	40 days
Control	18.158±0.29	18.158±0.29
Vehicle	18.084±0.246*	17.60±0.23*
Curcumin	17.55±0.188*	16.976±0.411*
Aluminum % of control	37.106±2.95# 104.35%	44.74±0.159# 146.39%
Al + cur % of Aluminum	27.758±0.453## 25.19%	21.038±0.695## 52.97%

Values are means ± S.E. of 6 animals in each group.
* Non-significant compared with control group ($p>0.05$).
# Highly significant compared with control group ($p<0.01$).
Highly significant compared with aluminum group ($p<0.01$).

3.2-Histopathological findings

H&E staining and microscopic examination showed six layers of cerebral cortex of control group; molecular layer, outer granular layer, outer pyramidal layer, inner granular layer, inner pyramidal layer and polymorphic layer. Also, Pia mater was appeared (Figure 1). Higher magnification of external granular layer of control group revealed numerous granular neurons and pyramidal cells. Also, the intercellular area is occupied by numerous neuroglia of various types and blood capillaries (Figure 2).

Also, DMSO- treated group for 20 days revealed a normal histological structure of cerebral cortex that was similar to control group presenting more or less normal appearance of granular and pyramidal cells as well as glial cells and blood capillaries (Figure 3). After 40 days, external granular layer of DMSO-treated group displayed almost normal appearance of granular and pyramidal cells. Neuroglia with nearly normal size and blood capillaries were also viewed (Figure 4).

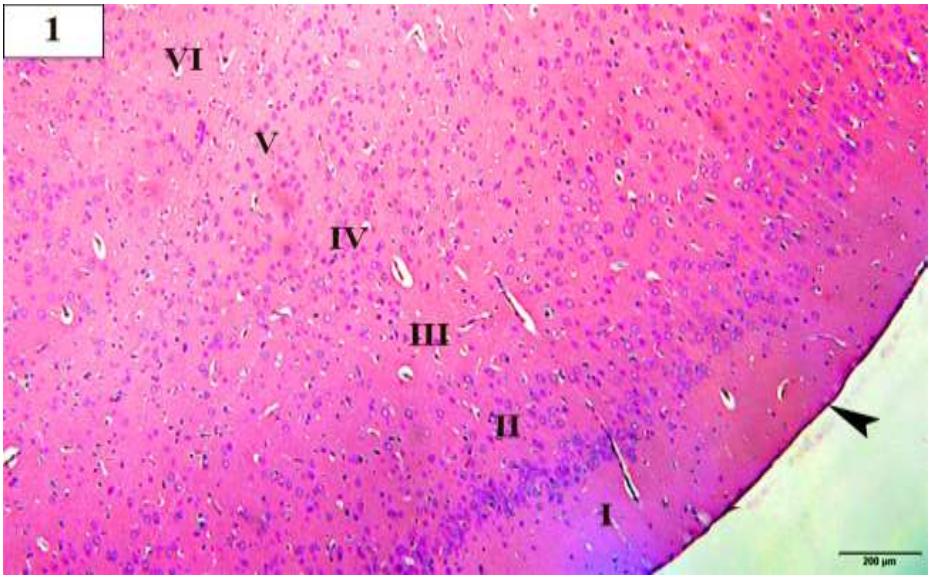

Fig. 1: Light micrograph displaying of cerebral cortex of control group. Molecular layer (I), outer granular layer (II), outer pyramidal layer (III), inner granular layer (IV), inner pyramidal layer (V), polymorphic layer (VI) and Pia mater (arrow head). **(H&E, scale bar: 200µm)**

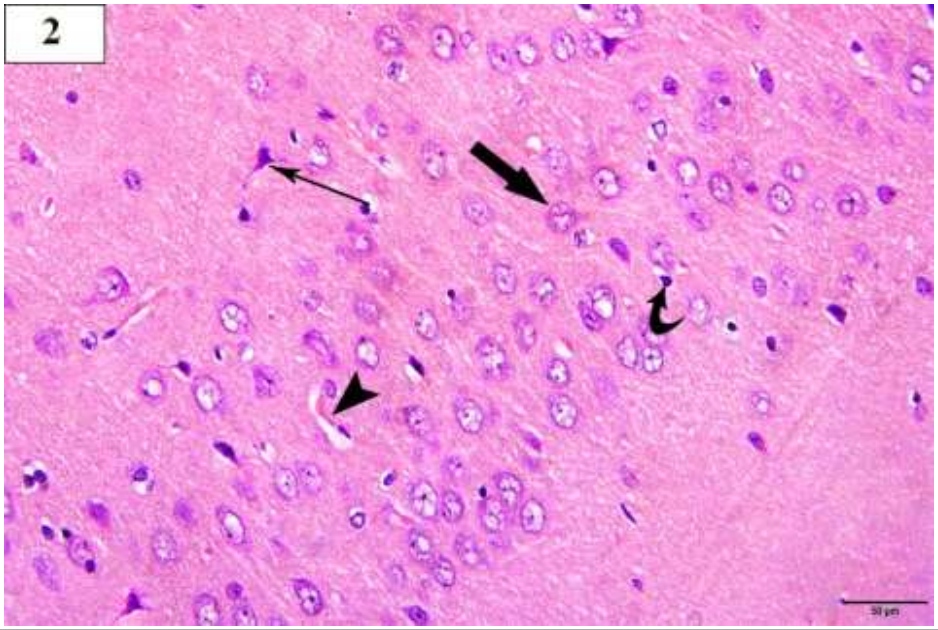

Fig. 2: Higher magnification of external granular layer of control group. Granular neurons (thick arrow), pyramidal cells (thin arrow), neuroglia (↷) and blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

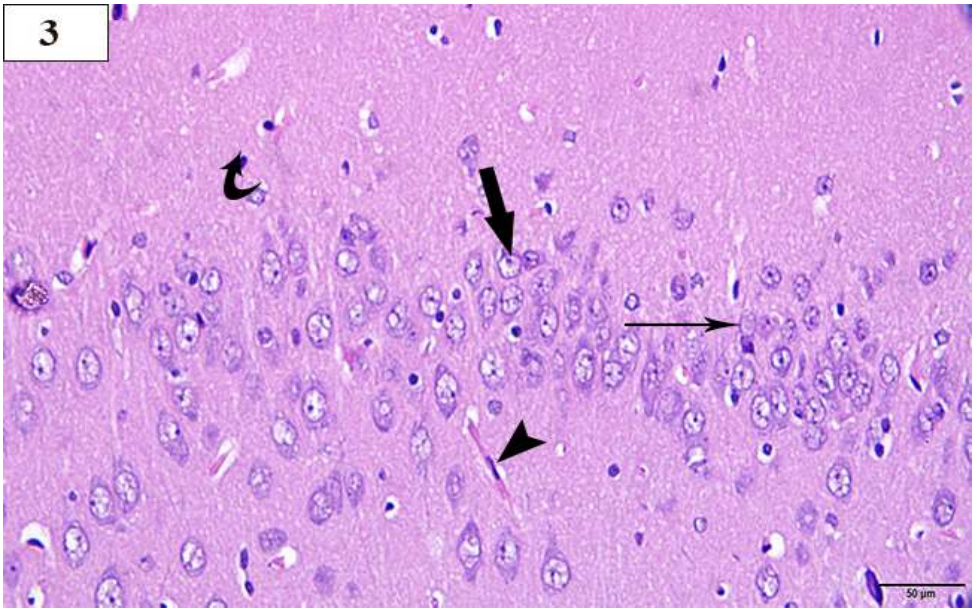

Fig. 3: Higher magnification of external granular layer of DMSO-treated group at 20 days. Granular cells (thick arrow), pyramidal cells (thin arrow), glial cells (↶) and blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

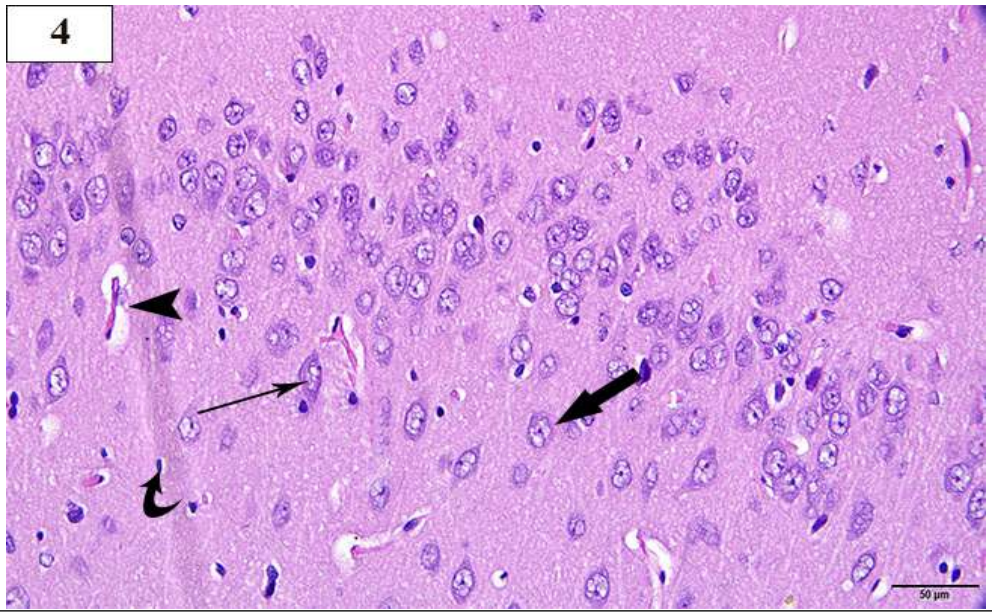

Fig. 4: Higher magnification of external granular layer of DMSO-treated group at 40 days. Granular cells (thick arrow), pyramidal cells (thin arrow), neuroglia (↶) and blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

Sections of Cur-group treated for 20 days showed a healthy structure of cerebral cortex like those of control group. The external granular layer appeared with normal appearance of granular cells, pyramidal cells, glial cells and blood capillaries (Figure 5). After 40 days, Cur administration -group displayed structural integrity of granular cells, pyramidal cells, glial cells and blood capillaries of external granular layer of cerebral cortex (Figure 6).

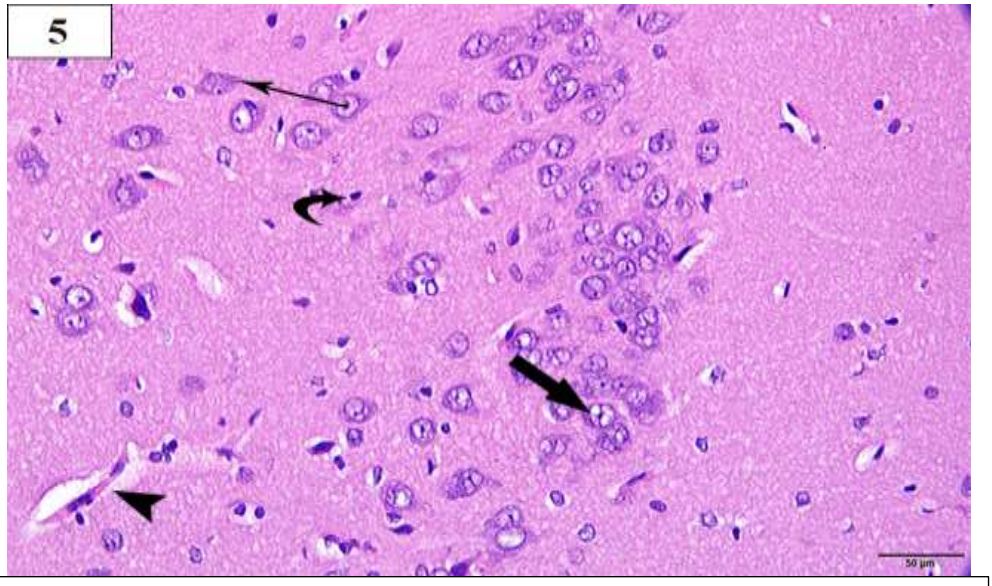

Fig. 5: Higher magnification of external granular layer of curcumin treated group at 20 days. Granular cells (thick arrow), pyramidal cells (thin arrow), glial cells (↷) and blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

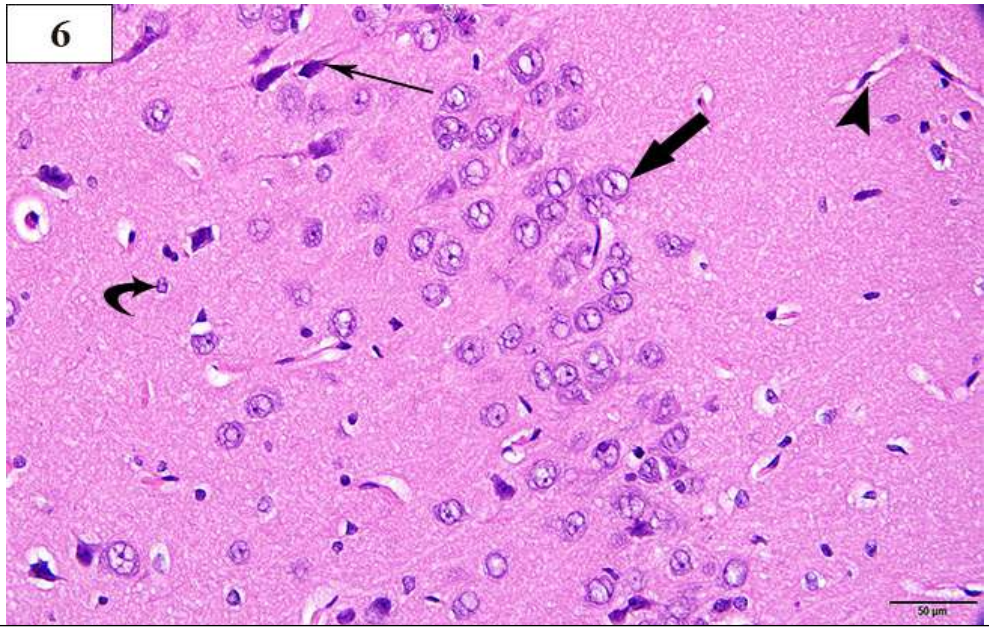

Fig. 6: Higher magnification of external granular layer of Cur-treated group at 40 days. Granular cells (thick arrow), pyramidal cells (thin arrow), glial cells (↷) and blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

Aluminum-administration group for 20 days showed several alterations in the external granular layer of cerebral cortex when compared with control group. These alterations included pyramidal neurons with pyknotic nuclei and shrinkage of cell bodies, granular cells with small nuclei as well as glial cells appeared with large perinuclear halo and congestion of dilated blood

capillaries (Figure 7). After 40 days of Al- administration, external granular layer of cerebral cortex showed neuronal degeneration with neuronal loss. Necrosis and degenerative change of pyramidal cells, granular cells with chromatolysis of nuclear chromatin, abnormal shape of glia cells and congestion and dilatation of blood capillaries were also inspected (Figure 8).

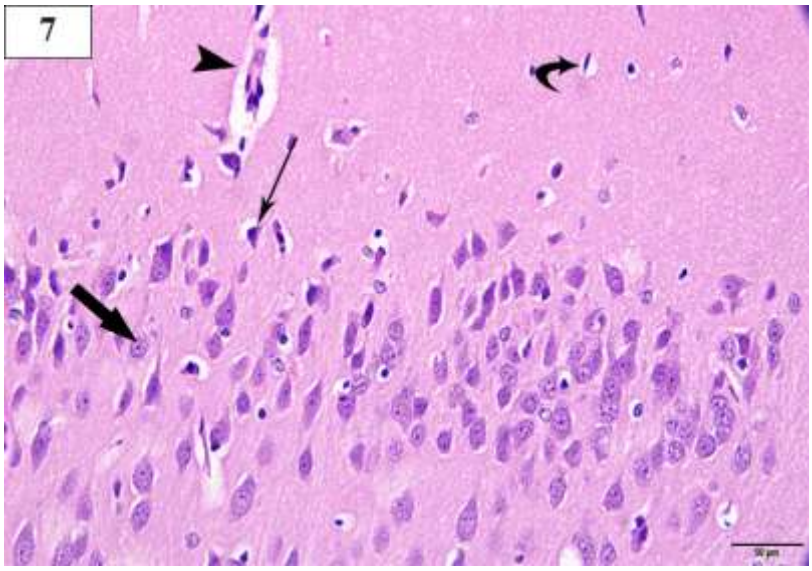

Fig. 7: External granular layer of cerebral cortex of Al- administrered group at 20 days. Congestion of dilated blood capillaries (arrow head), pyramidal neurons (thin arrow) with pyknotic nuclei and shrinkage of cell bodies, granular cells (thick arrow) with small nuclei, glial cells appeared with large perinuclear halo (↷). **(H&E, scale bar: 50µm)**

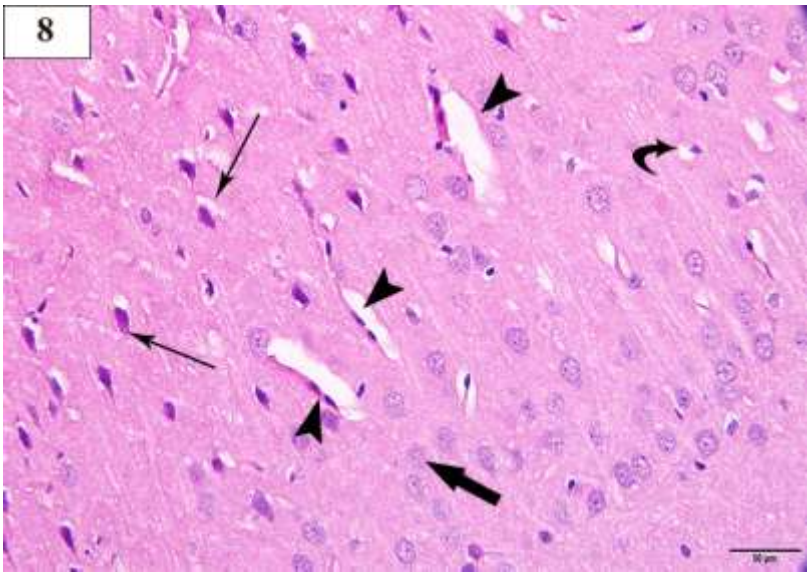

Fig. 8: External granular layer of cerebral cortex of Al- administrered group at 40 days. Necrosis of pyramidal cells (thin arrow), granular cells (thick arrow) with chromatolysis of nuclear chromatin, abnormal shape of glia cells (↷) and congestion and dilatation of blood capillaries (arrow head). **(H&E, scale bar: 50µm)**

Aluminum is the most common neurotoxicant **(Belyaeva et al., 2012; Mahboob et al., 2016).** In recent years, mounting evidence has indicated that aluminum has a significant toxic manifestation in the central nervous system **(Ghribi et al., 2001b)**. Chronic aluminum exposure not only induces neurological symptoms that resemble progressive neurodegeneration, but also aluminum accumulates in the brain mainly in parts of the spinal cord, hippocampus, brain stem and cerebral cortex **(Bharathi et al., 2006; Cheng et al., 2019).** The findings of this study are consistent with those of **Lahouel et al. (2020),** who found that aluminium exposure causes gradual changes in the rat brain. This is manifested by a decrease in the number of cellular units, fibrosis and vacuolation of neuronal cells in the cerebral cortex. Also, Al causes structural abnormalities in the cerebral cortex due to the loss of neurons, ghost cells, and gliosis, according to **Lakshmi et al. (2014).**

Other studies also demonstrated a neuropathological finding, **Abdel-Moneim (2012)** and **Lakshmi et al. (2015)** showed degenerated neurons with vacuolation as well as necrotic and apoptotic neurons in different regions of rat brain. Also, **Abdel-Salam et al. (2015)** stated that, the brain tissue of rats administered with $AlCl_3$ showed a reduced size of pyramidal cells, shrinkage of cytoplasm and gliosis in the cortex. In addition, **Kaddour et al. (2016)** reported that Al can cause marked histopathological abnormalities in brain tissues including neuronal vacuolization, spongiosis, gliosis and cellular rarefaction in cerebral cortex. These results are correlated to those claimed by many authors **(Matyja, 2000; Bihaqi et al., 2009; Bhadauria, 2012; Sumathi et al., 2013)** who reported the same modifications induced by Al on cerebral cortex histoarchitecture.

These pathological changes confirm that Al is involved in the development of a number of clinical conditions. Increased lipofuscin accumulation in Al poisoning could explain the observed pathogenic alterations **(Jyoti and Sharma, 2006).** Another study linked the accumulation of Al in the brains of mice (hippocampus and cortex) to the harmful effects of Al **(Rebai and Djebli, 2008).**

Microscopic examination of Al+Cur-treated group sections at 20 days showed that external granular layer of cerebral cortex appeared more or less normal structure. Most granular cells appeared with central large vesicular nuclei and prominent nucleoli, nearly normal pyramidal cells, neuroglia with normal outlines and blood capillaries with normal size (Figure 9).

Co-treatment with curcumin for 40 days showed improvements in cerebral cortex of brain sections. These improvements represented by normal histoarchitecture in a clear picture. Most of the granular cells with open face nuclei and prominent nucleoli, normal shape of pyramidal cells, glial cells with round dark nuclei and a slight perinuclear halo and normal shape of blood capillaries (Figure 10).

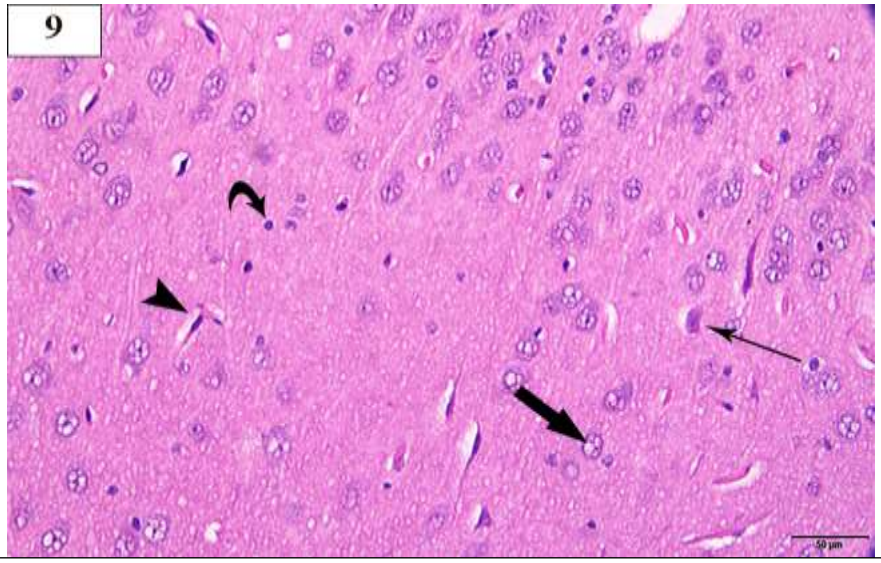

Fig. 9: External granular layer of cerebral cortex of Al+ cur- treated group at 20 days. Granular cells (thick arrow), pyramidal cells (thin arrow), neuroglia (↶) and blood capillaries (arrow head). **(H&E, 400X)**

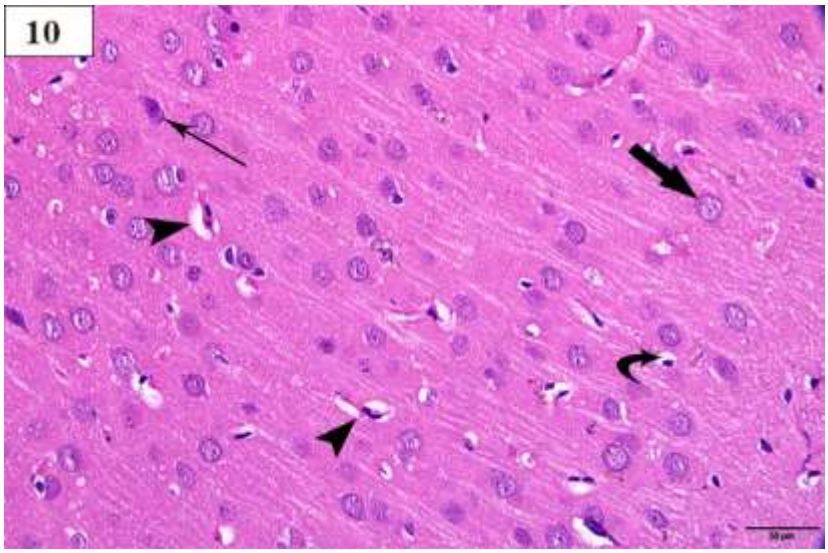

Fig. 10: External granular layer of cerebral cortex of Al+ cur- treated group at 40 days. Granular cells (thick arrow), pyramidal cells (thin arrow), glial cells (↶) and blood capillaries (arrow head). **(H&E, 400X)**

On the other hand, pre-treatment with curcumin showed that it protected neuronal cell through neuroprotector properties. Cerebral cortex retained its normal structure compared to Al-exposure group. These results are in agreement with **Edrees et al. (2018)** who demonstrated that the amelioration of the oxidant/antioxidant status of brain tissues by curcumin could be attributed to a direct reduction of ROS generation and release **(Joe and Lokesh, 1994),** scavenging of free radicals and subsequent inhibition of oxygenation reactions, as curcumin has been reported to be

a good antioxidant and free radical scavenger which inhibits lipid peroxidation **(Ak and Gülçin, 2008).** Together, these mechanisms might explain, at least in part, the cytoprotective effects of curcumin which confirmed by the improvement of brain structure.

Conclusion

The present study confirmed that chronic exposure to aluminum leads to elevation in NO levels and severe changes in the cerebral cortex structure. However, pre-treatment with curcumin ameliorated the neurotoxic effect of aluminum. These data, along with the previous accumulating evidences suggests that curcumin may be a precious neuroprotector and non-toxic agent for the treatment of associated neurological conditions caused by aluminum.

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