Ind. J. Pharm. Edu. Res., 2023; 57(4):1053-1060.
https://www.ijper.org

Original Article

Citrollenol Abrogates Neuroinflammatory Pathway Regulated via Induction of NF-kB in $AlCl_3$ Induced Alzheimer's Disease – Molecular Approach

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ABSTRACT

Background: Alzheimer's Disease (AD), a neurodegenerative disorder characterized by dementia, is linked to ROS-induced stress, neuroinflammation, and gut microbiota imbalance. **Objectives:** The antioxidant and anti-inflammatory properties of citrollenol have already been reported. The current research was aimed at discovering the salutary properties of citrollenol against Aluminum Chloride ($AlCl_3$)-induced AD in rats. **Materials and Methods:** The $AlCl_3$ was used to induce the AD in rats and then treated with citrollenol (25 and 50 mg/kg/bw). The behavioral tests were conducted on both control and treated rats. The levels of antioxidants and acetylcholine esterase were assessed using kits. The histopathological and immunohistochemical analyses were performed on the brain tissues. **Results:** The findings revealed that the $AlCl_3$-induced group had a loss of memory capability as well as an increase in the production of proinflammatory and neurodegenerative disorder-related AD proteins; otherwise, these characteristics were contrasted in the citrollenol-treated groups. Citrollenol-induced rats showed higher production of antioxidant enzyme levels and lower MDA status. Additionally, citrollenol abrogates proinflammatory mediator expression by suppressing NF-κB signaling and regulating microglial activation. **Conclusion:** Citrollenol can drawnback the AD brain tissue appearance of pathology study by leaking dysfunction in memory, learning capability, production of higher antioxidant enzymes levels, changing immunomodulatory cytokines levels in $AlCl_3$ induced rats, exhibiting that AD pathogenesis may be represented by treatment with citrollenol via the neurodegenerative disorder causes from AD.

Keywords: Alzheimer's, $AlCl_3$, NF-kB, Malonaldehyde, Citrollenol, Neuroinflammation.

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Received: 31-01-2023;
Revised: 23-03-2023;
Accepted: 01-05-2023.

INTRODUCTION

Alzheimer's Disease (AD), a neurodegenerative disease that causes memory loss, is the most common cause of dementia. Important characteristics of AD are progressive cognitive dysfunction and memory loss. Globally, 44 million people were affected by Alzheimer's disease in 2015; while this figure is higher than expected, more than 115 million patients are expected by 2050.[1] Every year, nearly 4.6 million new people are born and spread around the world wide.[2] In the classification of AD in accordance with the exhibition of cerebral atrophy, the temporal lobes, and the hippocampus. The association of histacampus, which aids in the stimulation of neuronal dysfunction and free radical causes, can be used to aid in the development of AD. The causes of Alzheimer's disease are unknown, but several studies suggest that $AlCl_3$ is a major factor.[3] Globally, aluminum is a lower-grade metal; it is easily accessed by the human body through additives, tools, and antacids. Aluminum is a bound form of a heavier metal in the living system, and its poisonous action on various functional organs such as the neuronal, hepatic, and cardiac systems.[4]

Neuroinflammation is the main mechanism in cancer, and it is an important factor in infections through balanced diseases. The important function of various stages of brain injury caused by neuronal causes is the induction of microglia, which finally leads to thinking, learning, and memory in the hippocampus-dependent brain.[5,6] On the other hand, the abbreviated inductions of bauxite mines usage contributed expression the aluminum higher amount elevation by insoluble minerals which releasing the risks of $AlCl_3$ interactions.[7,8] According to the previous findings, further aluminum is important to exhibit the actual mechanism

DOI: 10.5530/ijper.57.4.127

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by which aluminum salts stimulate toxicity in neurons. Numerous reports of preceding preclinical model animal evaluations proved that the extended interaction with aluminum by $AlCl_3$ caused malformation in a neuronal region that ultimately affects the loss of memory and learning capacity of AD.[9,10]

Naturally derived plant products from food have a broad range of numerous pharmacological effects, such as antioxidant, anti-mutagenic, anti-tumor, and anti-aging properties. The importance of pharmacotherapy in suppressing the causes of AD was highlighted in laboratory, epidemiological, and clinical findings explaining the interaction between nutrition and cognition.[11,12] The lower toxicity capacity of dietary food compounds and the simultaneous application of human, eatable phytochemicals are good agents in pharmaceutical application in Alzheimer's disease. The actual well-auctioned, secured, and very safe plant-derived preventive therapies for suppressing dementia and their interventions.[13] Important medicinal plants containing oils are rich in secondary metabolites that function as plant defense mechanisms. Citronellol is a secondary metabolite that contains isoprene units and produces a part found in plants. Citronellol has a variety of biological effects, including anti-hyperalgesic activity, anti-inflammatory properties, and antioxidant properties. Terpenes are promising agents due to their ease of incorporation into drug actions, which leads to lower expanses and the potential for novel agents.[14]

Citronellol, a monoterpene alcohol found in plants that produce oils from the genus Cymbopogon, has a wide range of biological properties with highly medicinally valuable actions such as anticonvulsant, antihyperalgesic, and orofacial antinociceptive.[15] Thetherapeutic importance of the citrollenol against several neurological disorders were already been reported.[16,17] However, its importance in treating AD was not studied yet. Therefore, in the present study, we aimed at discovering the salutary properties of citrollenol against Aluminum Chloride ($AlCl_3$)-induced AD in rats.

MATERIALS AND METHODS

Animals and Treatment

Twenty four male Wistar rats (6–7 weeks) were treated *ad libitum* carried out to food and water, and maintained under similar light/dark cycle of 12 hr, humidity of 15% laboratory conditions with 22°C at end of the terminal period. Wistar rats were serially parted into 4 groups (n = 6 per group). $AlCl_3$ were treated as per to previously reported literature article dose that gives the toxic effect of neuron for 90 days. Citronellol dose was administered as per earlier reports mentioned dose that auctioned the secure neuron for sixty days. The vehicle untreated control rats parted as Group 1 - vehicle control. Group 2 - $AlCl_3$ 100 mg/kg/bw administered with 12 hr interval. Group 3 - treated orally by $AlCl_3$ at 100 mg/kg/bw + Citronellol (25mg/kg/bw). Group 4 - orally administered $AlCl_3$ at 100 mg/kg/bw + Citronellol (50mg/kg/bw).

Tissue sample preparation

The experimental rats dissected after that brain tissues sample and/or hippocampus were released out. Select the animal used in test of behavioral test were carried out using Congo red stain in subsequent study.

Morris water maze

Behavioral test were carried out using Morris Water Maze (MWM) test. The MWM was a 160 cm diameter circular pool with 30 cm deep water. The MWM test carried in two ways one an trial, other one a probe trial. A circular pool have a transparent round platform with filed water northeast quadrant in the acquisition trial. Totally 6 rats for each group were first kept over the place minimum 30 sec, kept at an initial point. May reached the rats at 60 sec they were entered when to remain for 30 sec in the place. Likewise the testing animals were practiced more than 5 days at every interval time period 10 min. Even, probe trial practice in the place out was translocated, further the animals keep over at the initial point of southwest quadrant and entered the swim individually for 90 sec. We entered the repeated times of duration and their location at particular time utilized were analyzed swimming in target quadrant.

Estimation of Acetylcholinesterase (AChE)

Using hippocampus tissues the AChE activity and ON levels in (n = 6/group) were identified kits as per the to the manufacturer's instructions. Absorbance range were calculated suddenly by using the spectrophotometer at 412 nm.

Estimation of malonaldehyde and antioxidant markers

The levels of Malonaldehyde (MDA), Catalase (CAT), Glutathione (GSH) and Superoxide Dismutase (SOD) in brain tissues (n = 6/group) calculated. The analysis of GSH was according to DTNB and GSH to created a spectrophotometrically measured end product and further absorbance were read at 405 nm. The activity of SOD levels were measured on its potent to suppresses lowered valued of Nitrazobluetetrazolium (NBT) and then read out using absorbance at 450 nm.

Histopathological investigation

Using Hematoxylin and Eosin (H&E) the formalized brain tissues were repeatedly stained and detected histological modifications was quantified as per the tissues affected part to their incidence. As per the method Le *et al.*, 2018,[18] tissue of brain were sliced and stained using Bielschowsky silver stain, the neurofibrillary tangles and plaques were observed. Number of amyloid plaques appearance, tangles of cells was noted over hippocampus. Slides containing tissue was identified using light microscope with Olympus using digital camera.

Immunohistochemistry Analysis

The immunohistochemical identification of Brain tissue sections, and then make paraffin blocks, further rehydrated then processed the heat induced antigen retrieval. After that the subjected to protein interaction with the endogenous peroxidases blocking steps. Then Association of Primary mouse monoclonal anti-NF-kB with sliced tissues (at a dilution of 1:100) at 4°C for 24hr. HRP-labelled secondary antibody were kept and allowed to the (HRP-Goat anti-mouse at a dilution of 1:200), for 1hr at 37°C after PBS wash. Then, visualize the DAB-substrate chromogen reaction. Untreated vehicle tissues were procured through primary antibody removal steps. Area % of Positive expressions were quantified as using fluorescence microscope (Olympus Software).

Statistical analysis

The present data are expressed as mean±SD. The data were analyzed by SPSS 22.0 software; SPSS Inc., Chicago, IL, USA. We considered $p < 0.05$ as significant and $p < 0.01$ as markedly significant.

RESULTS

Citrollenol potentially reversed the dysfunction of spatial and working memory in AD rats. Figure 1 depicts the behavioral changes detected by the MWM test in the control and treated rats. The changes in working memory retention and special memory in the $AlCl_3$ induced AD rats were determined. The period utilized in spatial memory by animals to reach the place was examined. When compared to untreated rats, rats in the $AlCl_3$-induced group used the identified leakage period to reach their destination. Citrollenol (25 and 50 mg/kg/bw) administration to the $AlCl_3$-induced rats significantly improved their behavior, indicating that Citrollenol administration could improve spatial memory in the AD-induced rats (Figure 1). Data were notified in working memory, including the location of the platforms and the total number of entries into the quadrant, and then the untreated control was hypothesized. Here, $AlCl_3$-stimulated rats showed a particularly reduced number of entries into the intended quadrant when compared to the untreated control. In contrast, the citrollenol (25 and 50 mg/kg/bw) administered to $AlCl_3$-simulated rats appreciably abrogates the effect noted in the quadrant. In the elevated plus maze test, $AlCl_3$ performs well in AD, and leakage was observed in the retention transfer latency. Further, citrollenol (25 and 50 mg/kg/bw)-treated rats exhibited a lower retention transfer latency when compared to $AlCl_3$ alone administered to AD rats. On the other hand, untreated control rats did not show any changes in retention latency when compared to the untreated normal rats. So this data confirmed that there were changes in the escape latency of $AlCl_3$-stimulated rats compared to the untreated control; these changes were initiated on the second day of the training period of the Morris water maze test.

Effect of Citrollenol on $AlCl_3$-induced MDA and antioxidant status in rats

We analyzed the status of MDA content, and antioxidant status of GSH, SOD, CAT, and GSH were diminished significantly in the hippocampus of $AlCl_3$ administered AD animals than the untreated normal rats (Figure 2). The citrollenol (25mg/kg/bw)

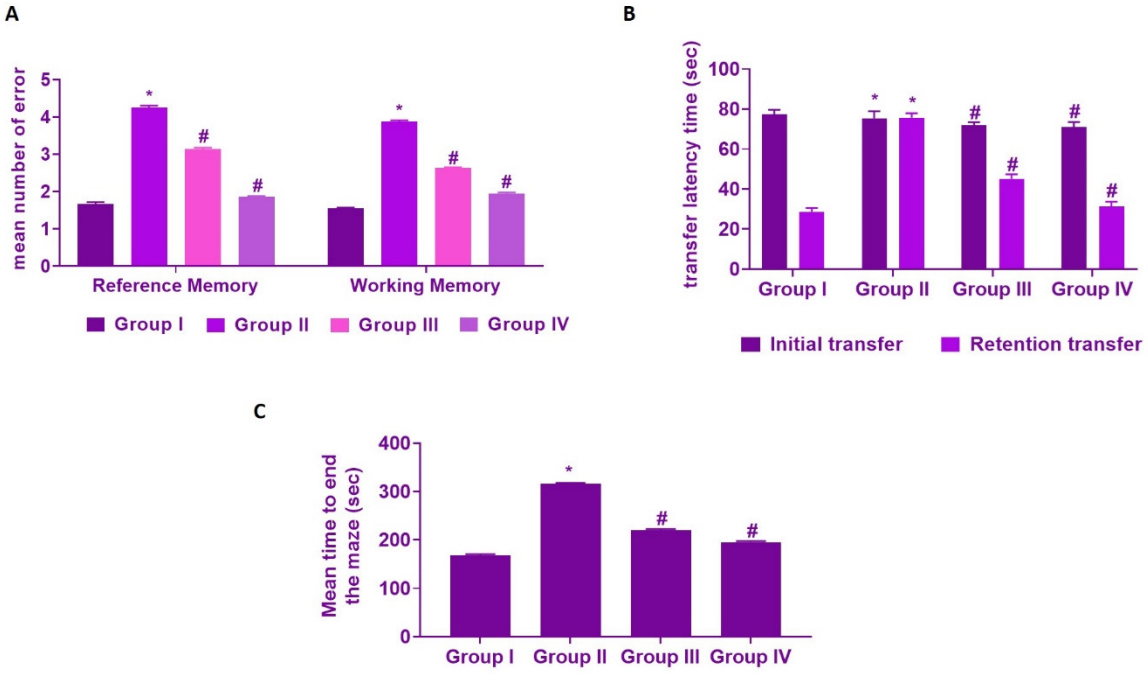

Figure 1: Effect of citrollenol on behavioral status in experimental rats.

administrated rats with AD caused has significantly reduced the levels of MDA then leaked the GSH, further antioxidant enzymatic reactions of SOD, CAT, and GSH over neurodegenerative disease caused of AD rats compared to the $AlCl_3$ induced AD rats. There were no more changes were observed in between untreated control rats. The citrollenol treated with $AlCl_3$ induced AD rats has surprisingly lowered the amount of malonaldehyde and the freely leaked the GSH and also the higher production of SOD and CAT in hippocampus of AD rats than $AlCl_3$ induced AD caused rats. No more changes were identified in untreated control rats.

Effect of citrollenol on LDH and NO levels in the AD rats

Figure 3 reveals that $AlCl_3$ administered AD rats appeared the higher amount of LDH and NO levels in the hippocampus when compared with the untreated normal rats. The 25 and 50 mg/kg of citrollenol administration showed the significant lower in the LDH and NO levels on the hippocampus of $AlCl_3$-induced AD rats. But no more modifications were observed in the untreated normal rats.

Effect of citrollenol on the AChE and Na+K+ATPase in the AD rats

Figure 4 demonstrates the therapeutic action of citrollenol on the neurotransmitter AChE and Na+K+ATPase levels in the hippocampus of untreated control rats and experimental rats. The levels of AChE and Na+K+ATPase leakage were higher in the hippocampus of $AlCl_3$-induced AD rats. Remarkably, the administration of citrollenol to the $AlCl_3$ induced AD rats has significantly lowered the levels of AChE and Na+K+ATPase in the hippocampus. The present data identified the beneficial effects of citrollenol in regulating the neurotreansmitters in the AD rats.

Effect of citrollenol on the expression of the inflammatory markers

Figure 5 demonstrates the citrollenol actions on the status of inflammatory mediators like TNF-α, IL-1 and IL-6 in the brain tissues of untreated rats and $AlCl_3$-stimulated AD rats. The induction of microglia and astrocytes exhibits the additional accumulation of pro-inflammatory changers and toxic materials. Significantly inflammatory protein expressions of TNF-α, IL-1, and IL-6 were identified by using ELISA method. Finally we found that the citrollenol repressed the levels of pro-inflammatory cytokines in the $AlCl_3$ induced rats, when treated with citrollenol administered creates the changes the levels due to their anti-inflammatory potential.

Effect of Citrollenol on histopathology of hippocampus in the AD rats

Histopathological modifications of the hippocampus of the untreated rats and experimental rats were identified, and results were showed in Figure 6. The untreated rats showed the regular pattern arrangement of neuronal cells with vesicular nuclei exhibition. But in the $AlCl_3$ induced AD rats in hippocampus appeared the neuron cells congestion along with enlargement of nuclei and Space between the vacuoles with the others surrounding place of neurons. The treatment with citrollenol (25 and 50 mg/kg bw) with administered $AlCl_3$ protects the congestion of neuron cells leads vacuoles production loss around the neuronal region and appeared in the large vesicular nuclei

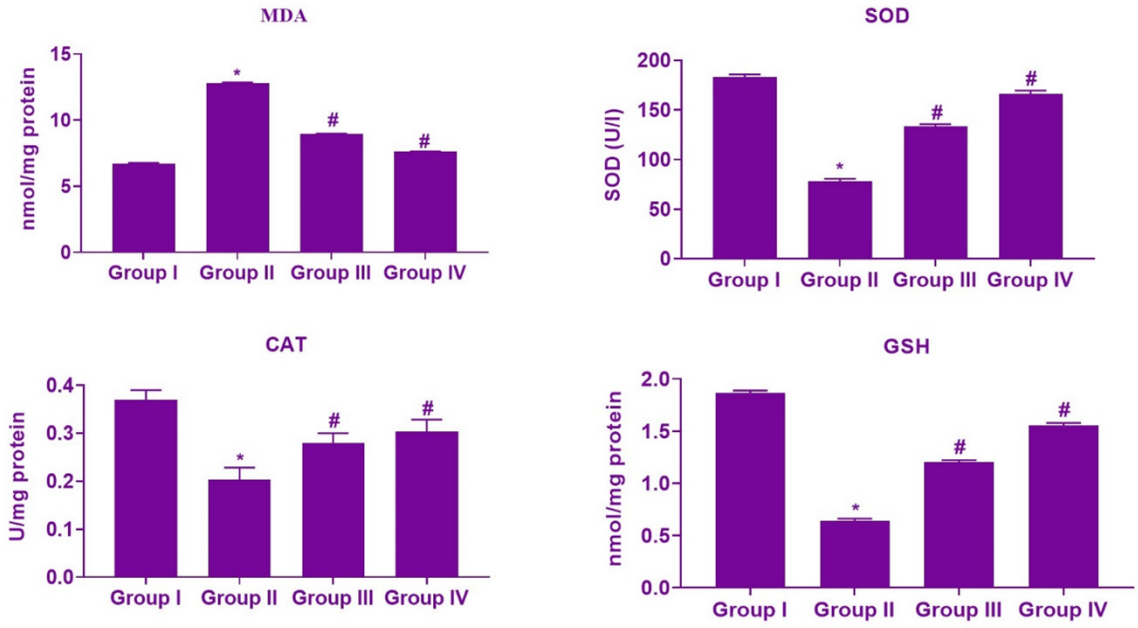

Figure 2: The hippocampus Malondialdehyde and antioxidant levels were assessed in control and experimental animals.

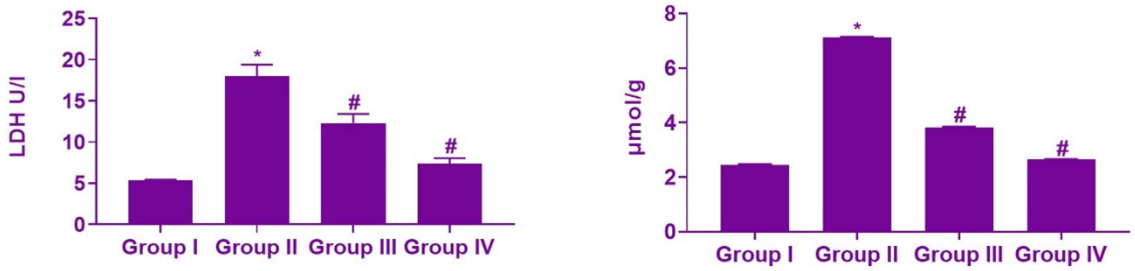

Figure 3: The hippocampus Lactatodehydrogenase activity and Nitric Oxide level were measured in control and experimental animals.

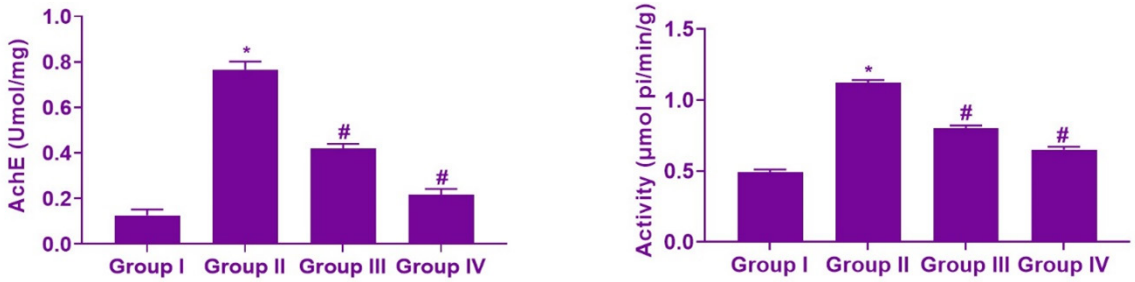

Figure 4: The hippocampus Acetylcholinesterase activity and Na + K+ ATPase activity were assessed in control and experimental animals.

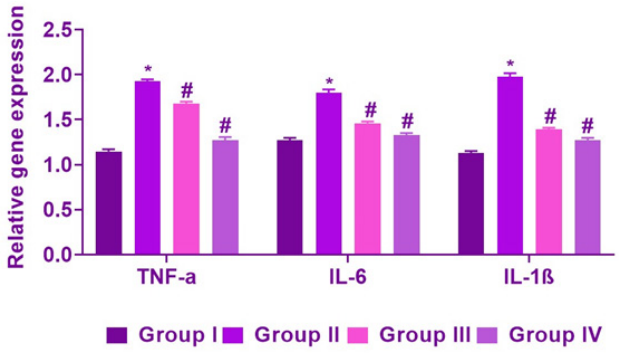

Figure 5: The hippocampus TNF-α, IL-6and IL-1β gene expression were assessed in control and experimental animals.

formation with identified nucleoli creation and amphophilic cytoplasm arrangement.

Citrollenol modify the NF-kB expressions in Immunohistochemical pattern in AD rats

In brain tissues, we analyzed the expression pattern of inflammatory mediator of NF-kB in untreated control rats and experimental rats using immunohistochemistry. In Figure 7, neuronal NF-kB expression were significantly lowered in all treated groups compared to $AlCl_3$ group. There was no significant difference were observed in untreated control. But $AlCl_3$ treated group showed over expression of NF-kB, and in moderate expression were identified in citrollenol (25 and 50mg/kg/bw) with $AlCl_3$ administered AD group.

DISCUSSION

In the present investigation, it was hypothesized that the neuroprotective potential of citrollenol on $AlCl_3$ induced AD in the experimental rats via the suppressive action of an inflammatory signaling pathway. The cognitive dysfunctions were important clinical signs of neurogenerative health-relevant causes in $AlCl_3$-induced AD.[3,19,20] $AlCl_3$-induced behavioral, biochemical, and brain impairments were associated with the cognitive dysfunctions that affect major outcomes simultaneously identified in AD incidences.[21-23] The current findings show that oral administration of citrollenol (25 and 50 mg/kg/bw) significantly altered behavioral, neuronal, and biochemical abnormalities in $AlCl_3$-induced AD rats, indicating potential preventive and therapeutic effects of citrollenol on the $AlCl_3$-induced neurogenerative disease.

ROS production in the hippocampus tissues could change communication link between the synaptic and non-synaptic neuronal cells that gives the neuroinflammation and apoptosis that significantly represent in AD rats neuronal cell damage and loss of memory.[24] On the other hand, Zhao and Zhao, 2013.,[25] has been reported that inflammation are simultaneously helps to neurological changes including neural apoptosis, neurofibrillary tangles, amyloid deposits and mitochondrial damage which were induced pathological progression of AD. In the current study showed that, citrollenol (25 and 50 mg/kg/bw) administered rats showed that caused the $AlCl_3$ induced pathological modifications were decreased the inflammatory responses via leakage of higher

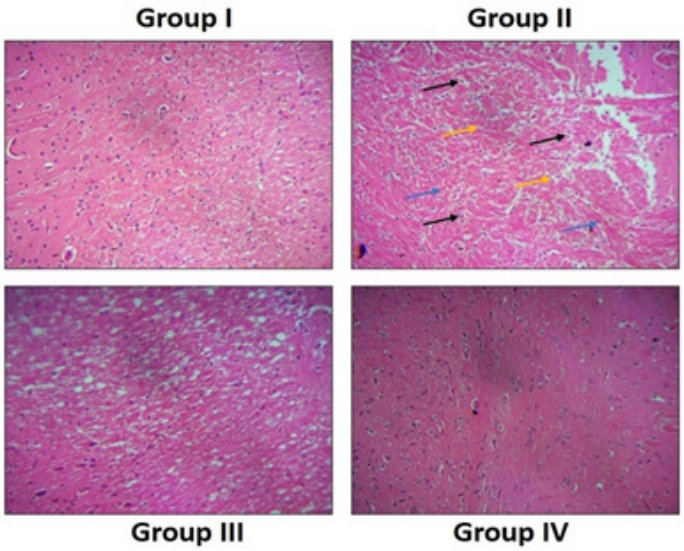

Figure 6: Photomicrograph of sections of cerebral cortex of rats.

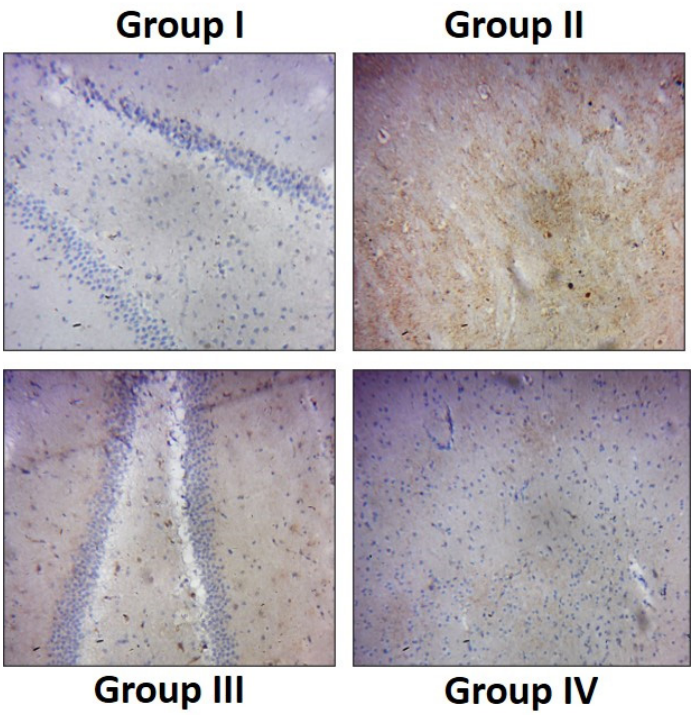

Figure 7: Representative photomicrograph showing IHC staining patterns of NF-kB protein in vehicle control and experimental rats.

amount of levels of SOD, CAT and GSH status, which developing the levels that the Citrollenol (25 and 50 mg/kg/bw) abreacted the $AlCl_3$ stimulated oxidative stress in the hippocampus.

AD progression has been prolonged effect in Hippocampus were observed.[26] Hippocampus is normally higher content of glutamatergic and cholinergic contents were created mechanism of these neurotransmitters signaling are simultaneously derived, which is mostly associated with the AD.[27-30] In this present finding were examined, citrollenol (25 and 50mg/kg/bw) administered $AlCl_3$ AD rats were showed that stimulated a higher amount AChE leakage status. The leakage of AChE induces catalysis of acetylcholine that contribute suppression of neurotransmission by inhibition cholinergic, AChE most association form with AD disease.[31] In the current study was revealed that citrollenol (25 and 50mg/kg/bw) administered elevated the cognitive potential in the $AlCl_3$ induced rats model, that was one of the recovered mechanism of preventive and therapeutic efficacy against neurodegenerative disorder. The previous reports were described that the association between the oxidative stress and inflammation. The proves noted that the reactive oxygen production functioned as in the chronic inflammatory uses via inflammation.

Neuroinflammation and oxidative stress, are earliest incidence of neurodegenerative disorder of AD, it exhibits the many functional capabilities for the initial function of their pathological machineries of AD. In this present finding showed that citrollenol administered significantly decreased the NF-kB induced pro-inflammatory cytokines like TNF-α, IL-6 and IL-1β levels development in the hippocampus of $AlCl_3$ induced rats. In central nervous system showed that the proinflammatory cells are the Microglial cells. Normally dormant but it accepts the induced accretes the NF-kB induced pro-inflammatory cytokines of TNF-α, IL-6 and IL-1β were supported as broad range of investigation of inflammatory markers in the neuron and impact in the pathological development of AD.[32] The present reports showed that this hypothesis were confirmed that the citrollenol (25 and 50 mg/kg/bw) administered was revealed that the decreased the protein levels of NF-kB regulated proinflammatory mediatory cytokines like TNF-α, IL-6 and IL-1β levels in the hippocampus in the $AlCl_3$ stimulated AD rats, which was finally reported that prevent the neuronal disease.

CONCLUSION

In the summary we found that citrollenol evidenced that the therapeutic actions of against the $AlCl_3$ induced neuroinflammatory responses in rat model of AD. Citrollenol (50 mg/kg/bw) showed the remarkable neuroprotection by restore antioxidant SOD, CAT and GSH production, elevation of MDA, NO, AChE and LDH and further in their study showed the anti-inflammatory action via suppression of TNF-α, IL-6 and IL-1β levels synthesis of neuronal tissues via behavioral changes. But in confirmed the assessed $AlCl_3$ induced neuro-inflammation through its suppressive potential of inflammatory responsive mechanism. So that it could be a good therapeutic and preventive drug to cure the AD. Even though, the future studies still required to evaluate exact mechanism of action through furthermore signaling action.

ACKNOWLEDGEMENT

This work was supported by the Department of Neurology, Hanzhong Traditional Chinese Medicine Hospital, Hanzhong, 723000, China. This project was supported by Researchers Supporting Project number (RSP2023R283), King Saud University, Riyadh, Saudi Arabia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NO: Nitric oxide; **MDA:** Malondialdehyde; **AD:** Alzheimer's disease; **MWM:** Morris water maze; **AChE:** Acetylcholinesterase; **CAT:** Catalase; **GSH:** Glutathione; **SOD:** Superoxide dismutase.

SUMMARY

Citrollenol showed remarkable neuroprotection by restoring antioxidant SOD, CAT, and GSH production and decreasing MDA, NO, AChE, and LDH.

Citrollenol significantly reduced the levels of NF-kB-induced pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 in the hippocampus of $AlCl_3$-induced rats.

(A) The reference memory and working memory was evaluated in control and experimental animals. (B) The arm radial maze task completion was evaluated in control and experimental animals. (C) The elevated plus maze (initial and retention) transfer latencies were evaluated in control and experimental animals. # $p \leq 0.05$ and * $p \leq 0.01$ are statistically significant.

The normal level of antioxidants were noted in the control animals (Group-I) and the significantly reduced antioxidants level was noted in the Alzheimer's disease induced animals (Group-II). The low and high dose of citrollenol treated animals (Group I and II, respectively) showed the significantly increased antioxidants level. Each bar represents as a mean ± SD of triplicate values. #$p \leq 0.05$ and * $p \leq 0.01$ are statistically significant.

The normal level of LDH and NO was observed in the control (Group-I), however, the significantly increased levels of LDH and NO was noted in the Alzheimer's disease induced animals (Group-II). The low and high dose of citrollenol treated animals (Group I and II, respectively) showed the noticeably reduction in the LDH and NO level. Each bar represents the mean ± SD of triplicate measurements. # $p \leq 0.05$ and * $p \leq 0.01$ are statistically significant.

The acetylcholine esterase and ATPase level found normal in the control animals (Group-I) and the significant elevation was noted in the disease induced animals (Group-II). The low and high dose of citrollenol treated animals (Group I and II, respectively) showed the significant reduction. Each bar represents as a mean ± SD of triplicate values. # $p \leq 0.05$ and * $p \leq 0.01$ are statistically significant.

The control animals revealed regular and healthy neuronal cells with normal vesicular nuclei (Group I). The disease induced rats displayed the brain cells shrinkages and spacing of vacuole around the neurons (Group II). The pre supplementation of citrollenol (25 and 50 mg/kg) recovered the neuron cells shrinkage and diminished the vacuoles around the neurons (Group III and IV, respectively).

H&E reveals well organized structure with neurons having rounded pale nuclei and basophilic cytoplasm in Control. Disturbed structure (yellow arrows), shrunk neurons with condensed pyknotic nuclei (black arrows), and areas of hyaline degeneration (blue arrows) noted in group II. Sections of AD treated with Citrollenol + AD reveals restoration of the well-organized structure of the cortex and the neurons.

Magnification (20x and 40x). Depicted immunoexpression of NF-kB showed in Control group.

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Cite this article: Zhou X, Almoallim HS, Ravindran B, Qin R. Citrollenol Abrogates Neuroinflammatory Pathway Regulated via Induction of NF-kB in $AlCl_3$ Induced Alzheimer's Disease – Molecular Approach. Indian J of Pharmaceutical Education and Research. 2023;57(4):1053-60.