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Effect of Pregabalin Against Aluminium Chloride Induced Neurotoxicity in Male Albino Wistar Rats

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ABSTRACT

Pregabalin ((S)-(amino methyl)-5-methylhexanoic acid) or (S-(+)-3- isobutylgaba), is a chiral branched-chain neutral amino acid. It was first synthesized as a racemate in 1989. Pregabalin (PGB) a gabapentin derivative had a wide variety of pharmacological activities such as anti-epileptic activity, it is beneficial in the partial onset seizures, painful diabetic neuropathy, and post hepatic neuralgia pain and in many non-epileptic conditions, including bipolar disorder, anxiety, alcohol, benzodiazepine dependence, hot flashes, neuropathic purities, central post-stroke pain, and chronic pain in adult patients and trigeminal neuralgia, migraine, reflex sympathetic dystrophy, and prophylaxis of chronic daily headache with analgesic overuse. The aim of the present study is to evaluate the effect of Pregabalin on aluminium chloride induced oxidative stress and neurotoxicity in rats. In this study aluminium chloride treated animals had shown anxiety like behavior. AlCl3 increased the overall time spent in closed arm and animals took more time to cross the closed arm to open arms in elevated plus maze. Therefore, pregabalin had shown anxiolytic activity against the AlCl3 induced anxiety like behaviour in rats. These contemporary results were collaborated with the former reports of pregabalin as an anxiolytic agent. Pregabalin accomplished as neuroprotective agent by attenuating the neuronal loss in DG, CA1, CA3 and cortex regions of rat brain caused by AlCl3 and had shown more potent anti-oxidant, antiacetylcholinesterase, neuroprotective agent against AlCl3 neurotoxicity.

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INTRODUCTION

Pregabalin ((S)-(amino methyl)-5-methylhexanoic acid) or (S-(+)-3- isobutylgaba), is a chiral branched-chain neutral amino acid. It was first synthesized as a racemate in 1989 [1]. Pregabalin (PGB) a gabapentin derivative had a wide variety of pharmacological activities such as anti-epileptic activity, it is beneficial in the partial onset seizures, painful diabetic neuropathy, and post hepatic neuralgia pain and in many non-epileptic conditions, including bipolar disorder, anxiety, alcohol, ben-

zodiazepine dependence, hot flashes, neuropathic purities, central post-stroke pain, and chronic pain in adult patients and trigeminal neuralgia, migraine, reflex sympathetic dystrophy, and prophylaxis of chronic daily headache with analgesic overuse [2].

Pregabalin is a potent drug used in 110 countries worldwide for the treatment of neuropathic pain [3]. According to WHO in UK- 1 %, Denmark-9.6 %, Sweden, 8.5% of people use Pregabalin prescribed by physicians with more than 600mg/day. In experimental studies, PGB showed an antinociceptive effect in inflammatory pain via inhibiting the release of neuropeptides on sensory neurons. Numerous studies have proved that Pregabalin has anti-apoptotic, neuroprotective activity, antioxidant activity and anti-inflammatory activity [4].

The word neurotoxicity refers to damage to the nervous system of humans and animals after exposure to natural or synthetic chemical compounds [5]. At present, development of facilities for investigation of neurotoxicity is growing importance because chemicals cause major public health issues [6]. Aluminum has been associated with epidemiologically and etiologically to numerous neurological conditions.

Aluminum targets brain tissue by crossing the blood brain barrier causes oxidative damage to lipids, proteins and nucleic acids further it enervates the antioxidant system. Neurodegenerative diseases are being continuously to oxidative damage [7]. In Alcl3 induced rats glutamate levels were noted to be significantly increase [8]. Oxidative stress is a biochemical process it involves the formation of reactive oxygen species (ROS) in the electron transport chain. Aluminum can raise ROS production by iron (Fe) and copper. pro-oxidant metals (Fe and Cu) which are present in most cell compartments. Aluminum potentiates the capability of these transition metals to produce oxidative stress [9]. The present study was undertaken to investigate the effect of Pregabalin in Alcl3-induced neurotoxicity in rats.

Aim

To evaluate the effect of Pregabalin on aluminium chloride induced oxidative stress and neurotoxicity in rats.

Objectives

To study the effect of Pregabalin on aluminium chloride induced oxidative stress and neurotoxicity in rats by evaluating following parameters:

1. Body weight measurement
2. Motor co-ordination assessments
   - Actophotometer
   - Hanging wire test
3. Behavioral assessments
   - Y-maze test
   - Elevated plus maze
4. Biochemical estimations in hippocampus and cortex
   - Lipid peroxidation
   - Reduced Glutathione
   - Catalase (CAT)
   - Superoxide Dismutase (SOD)
5. Enzyme activity estimation in hippocampus and cortex
   - Acetyl Cholinesterase Activity (AChE)
6. Estimation of Neurotransmitters level
   - Glutamate
   - Gamma Amino Butyric Acid (GABA)
7. Histopathology
   - Hippocampus
   - Cortex

MATERIALS AND METHODS

Animals

Experimental Protocol

Animals were divided into three groups, 10 rats in each and treated as follows: Group I received normal saline; Group II: received AlCl3 34mg/kg and Group III received 25 mg/kg Pregabalin, 30 min prior to AlCl3 injection. The treatment schedule followed for 7 days period, 3 hrs after the last treatments all the group animals were subjected to behavioural assessment and 24 hrs of the last treatment schedule all the animals were sacrificed by cervical decapitation method under deep ether anaesthesia and the brains were isolated to carry out biochemical estimations and histopathological studies.

Statistical Analysis

All values were expressed as mean $\pm$ SEM. Statistical analysis was performed with one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test (Graph pad prism 5 v). Values, *P< 0.05, **P< 0.01 and ***P< 0.001 were considered as statistically significant.

RESULTS

Effect of Pregabalin on Percent change in Body Weights of AlCl3 Induced Oxidative Stress in Rats

Body weights were measured as the % change of weight by comparing the final (7^{th}) day with the initial day. There was a significant diminution (***P<0.001) in the body weight of Aluminium chloride (AlCl3 34 mg/kg) administered group when compared with the control group. Pregabalin treated group (25 mg/kg) vetoed the drop of body weight and showed its significant change (***P<0.001) against the AlCl3 group. Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3 (Figure 1).

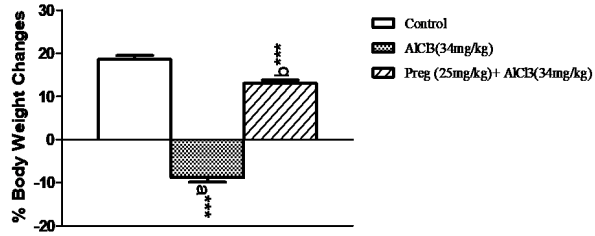

Figure 1: Effect of Pregabalin on Percent Change in Body Weights of AlCl3 Induced Oxidative Stress in Rats

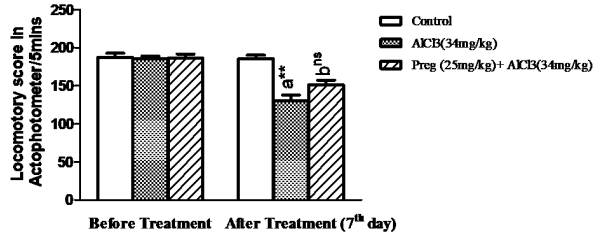

Figure 2: Effect of Pregabalin on Locomotor Activity of AlCl3 Induced Oxidative Stress in Rats

Effect of Pregabalin on Locomotor Activity of AlCl3 Induced Oxidative Stress in Rats

Treatment with AlCl3 (34 mg/kg) decreased the locomotor count significantly (***P<0.001) when compared with control group. There was no significant increase in Pregabalin administrated group in the locomotor count when compared with the AlCl3 induced animals (Figure 2). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

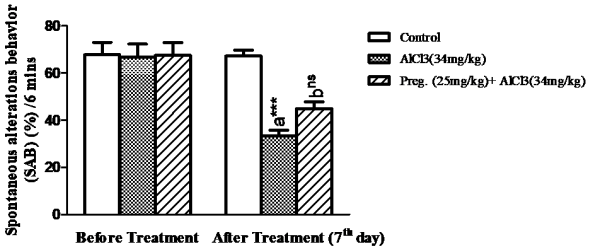

Figure 3: Effect of Pregabalin on % Spontaneous Alterations in Y-maze/ 6 Minutes of AlCl3 Induced Oxidative Stress in Rats

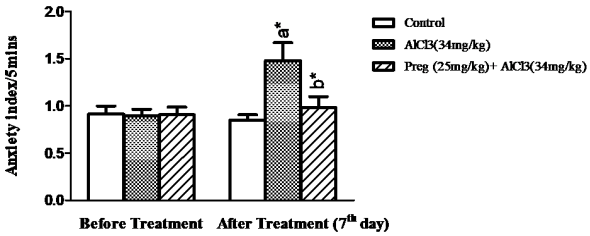

Figure 4: Effectof Pregabalin on Anxiety like Behavior of Rats in Elevated Plus Maze of AlCl3 Induced Oxidative Stress

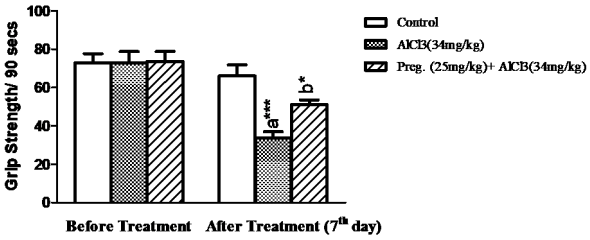

Figure 5: Effect of Pregabalin on Grip Strength in Hanging Wire Test/90 Seconds of AlCl3 Induced Oxidative Stress in Rats

Effect of Pregabalin on % Spontaneous Alterations in Y-maze/6mins of AlCl3 Induced Oxidative Stress in Rats

Y-maze paradigm is generally used to assess the Short-term spatial memory. The administration of pregabalin was not significantly increased the % Spontaneous Alterations Behavior (SAB), when compared with the AlCl3 alone treated group animals. Concurrently, AlCl3 treatment group showed hampered % SAB significantly (***P<0.001) in comparison with control group (Figure 3). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical differ-

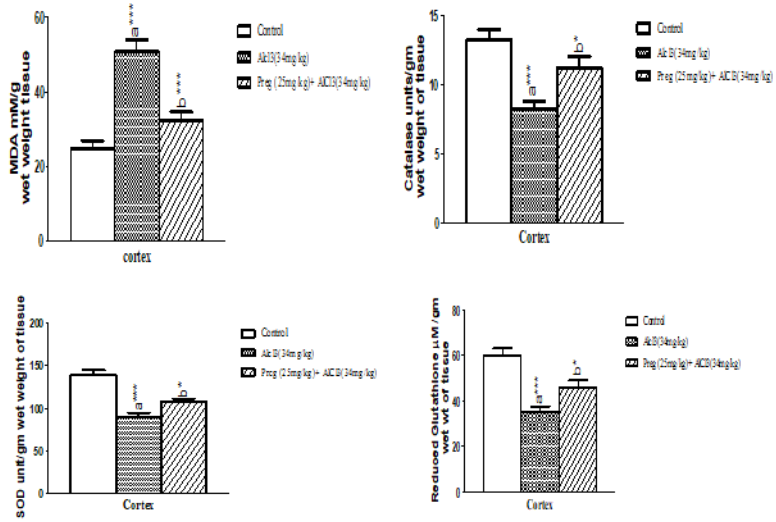

Figure 6: Effect of Pregabalin on Various Oxidative Stress Parameters and Anti-Oxidant Defense System: MDA Levels, Catalase, Super Oxide Dismutase (SOD) Activity and Reduced Glutathione (RG) Levels in Cortex Region of Rats

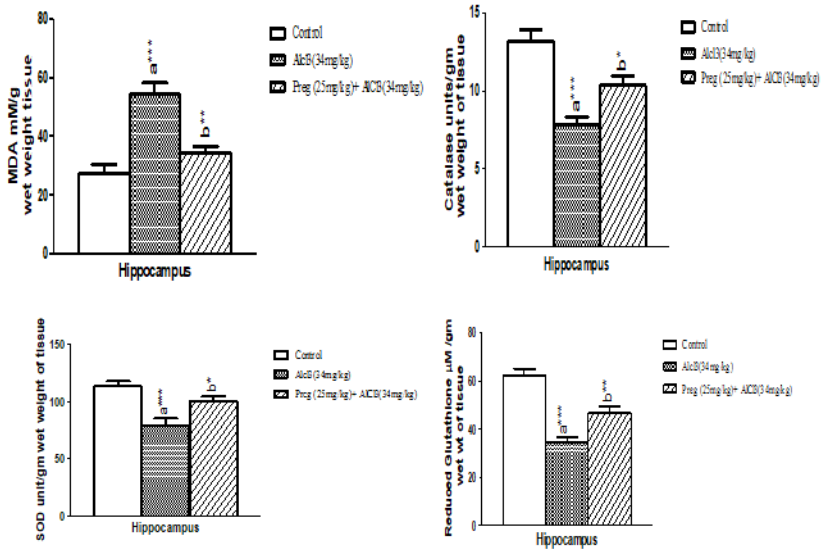

Figure 7: Effect of Pregabalin on Various Oxidative Stress Parameters and Anti-Oxidant Defense System: MDA Levels, Catalase, Super Oxide Dismutase (SOD) Activity and Reduced Glutathione (RG) Levels in Hippocampus Region of Rats

ence is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Anxiety like Behavior of Rats in Elevated Plus Maze of AlCl3 Induced Oxidative Stress

Anxiety like behavior can be expressed by means of anxiety indices. The anxiety index can be determined by assessing number of open arm and closed arm entries in plus maze. Pregabalin treated

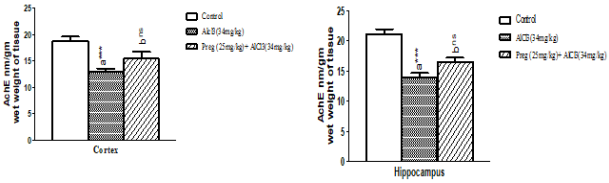

Figure 8: Effect of Pregabalin in Acetylcholinesterase (AChE) of Cortex and Hippocampus of Aluminium Chloride Induced Oxidative Stress in Rats

group significantly reduced (*P<0.05) the anxiety like behavior produced by AlCl3. Animals adminis-

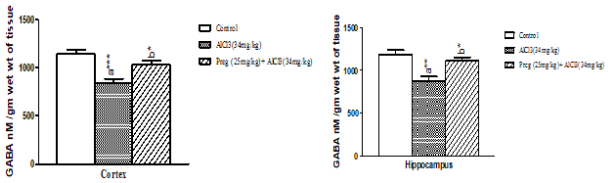

Figure 9: Effect of Pregabalin in GABA Levels of Cortex and Hippocampus of Aluminium Chloride Induced Oxidative Stress in Rats

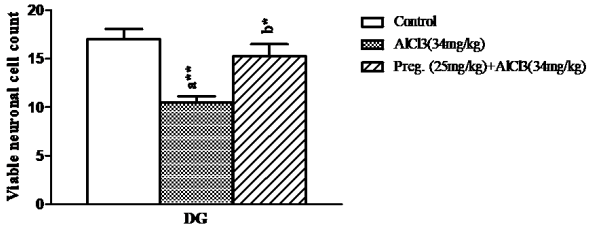

Figure 10: Effect of Pregabalin in Viable Neuronal Cell Count of Aluminium Chloride Induced Oxidative Stress in DG Region of Rat Brain

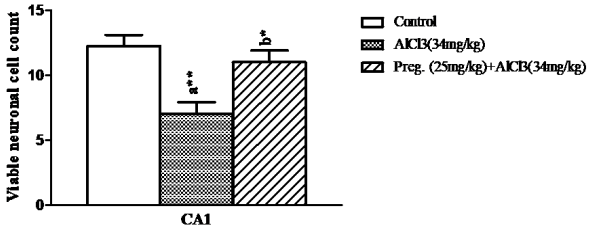

Figure 11: Effect of Pregabalin in Viable Neuronal Cell Count of Aluminium Chloride Induced Oxidative Stress in CA1 Region of Rat Brain

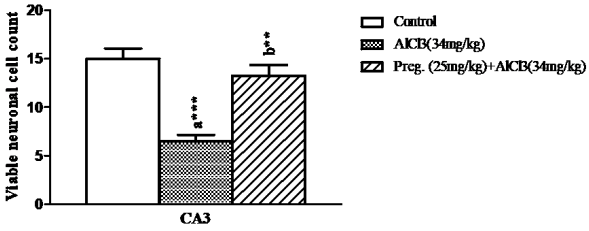

Figure 12: Effect of Pregabalin in Viable Neuronal Cell Count of Aluminium Chloride Induced Oxidative Stress in CA3 Region of Rat Brain

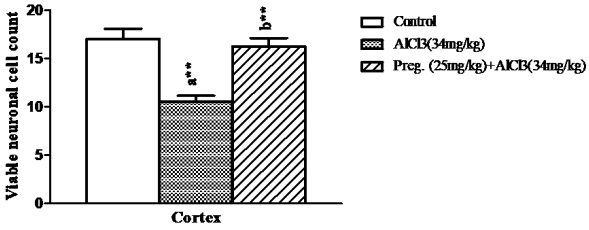

Figure 13: Effect of Pregabalin in Viable Neuronal Cell Count of Aluminium Chloride Induced Oxidative Stress in Cortex Region of Rat Brain

tered with Aluminium chloride 34 mg/kg expressed significantly more (*P<0.05) Anxiogenic behavior when compared to control group animals (Figure 4). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Grip Strength in Hanging Wire Test / 90 Seconds of AlCl3 Induced Oxidative Stress in Rats

Administration of AlCl3 significantly (***P<0.001) reduced the time to fall by impeding the grip strength when compared to the control group animals. The Pregabalin treatment group significantly (*P<0.05) increased the time to fall when compared to the AlCl3 administered group of animals (Figure 5). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Various Oxidative Stress Parameters and Anti-Oxidant Defense System

MDA Levels, Catalase, Super Oxide Dismutase (SOD) Activity and Reduced Glutathione (RG) Levels in Cortex and Hippocampus of Rats

Aluminium Chloride intoxication significantly winched Malondialdehyde (MDA) levels (***P<0.001) in the Hippocampal and cortical regions of AlCl3 (34mg/kg) treated group in comparison with vehicle group. A significant decrease in MDA levels were observed in cortex and hippocampus in pregabalin treated groups (***P<0.001 and ***P<0.05) in concurrence with AlCl3 administered rats. Significant reduced levels (***P<0.001) of

anti-oxidant enzymes catalase, SOD and Reduced Glutathione in hippocampal and cortical regions of AlCl3 treated rats as compared with the vehicle group. Pregabalin significantly mitigated the AlCl3 consequences on anti-oxidant enzymatic levels of catalase (*P<0.05), SOD (*P<0.05) and Reduced Glutathione (**P<0.01) (Figure 6 and Figure 7). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Various Oxidative Stress Parameters and Anti-Oxidant Defense System

MDA Levels, Catalase, Super Oxide Dismutase (SOD) Activity and Reduced Glutathione (RG) Levels in Hippocampus of Rats

Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin in Acetyl Cholinesterase (AChE) of Cortex and Hippocampus of Aluminium Chloride Induced Oxidative Stress in Rats

AchE was meandering appraise of acetylcholine activity. Significant (***P<0.001) increased cortical and hippocampal levels of AChE were observed with the administration AlCl3 when compared to the control group animals. There was no significant change in treatment with Pregabalin regarding levels of AChE in hippocampus and cortex, when compared with the AlCl3 alone treatment group (Figure 8). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Neurochemical Estimations (GABA and Glutamate) of Cortex and Hippocampus of AlCL3 Induced Oxidative Stress in Rats

The alterations produced in hippocampal and cortex GABA and Glutamate by Aluminium Chloride (34mg/kg, I.P) administration was significantly ameliorated (*P<0.05) in pregabalin treated group.

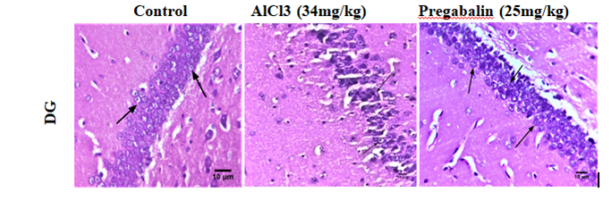

Figure 14: Photomicrographs of DG (Hematoxylin & Eosin, 400×) (Arrows Represents Neuronal Cells)

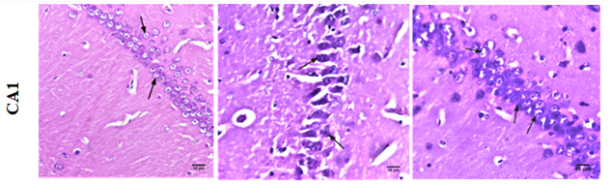

Figure 15: Photomicrographs of CA1 (Hematoxylin & Eosin, 400×) (Arrows Represents Neuronal Cells)

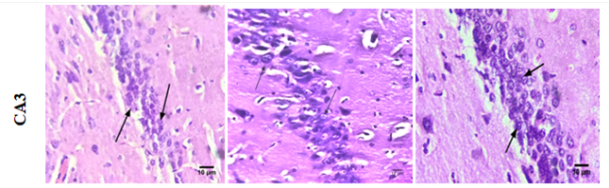

Figure 16: Photomicrographs of CA3 (Hematoxylin & Eosin, 400×) (Arrows Represents Neuronal Cells)

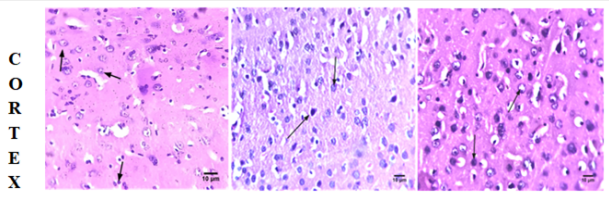

Figure 17: Photomicrographs of Cortex (Hematoxylin & Eosin, 400×) (Arrows Represents Neuronal Cells)

Whereas, AlCl3 administered rats depicted significant decrease of GABA and increase in glutamate levels of rats as compared to vehicle-treated group (***P < 0.001) (Figure 9). Values are expressed as Mean ± SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

Effect of Pregabalin on Histopathological Changes of Cortex and Hippocampus of AlCL3 Induced Oxidative Stress in Rats

The cortex and hippocampus CA1, CA3 and DG

region of the brain were observed for the viable neuronal cell count. The AlCl3 intoxicated group significantly decreased (**P<0.01 and ***P<0.001) the viable cell count in comparison with the control group animals. Concomitantly, the Pregabalin treatment group significantly (*P<0.05 and **P<0.01) attenuated AlCl3 induced histological alterations in cortex and hippocampus CA1, CA2 and DG region of the brain (Figure 10, Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16 and Figure 17). Values are expressed as Mean $\pm$ SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3. Values are expressed as Mean $\pm$ SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3. Values are expressed as Mean $\pm$ SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3. Values are expressed as Mean $\pm$ SEM (n = 6) One-way ANOVA followed by Tukey's post hoc test. Statistical difference is represented as (***P<0.001, **P<0.01 and *P<0.05). a= significantly different from control group, b=significantly different from AlCl3 treated group and ns=no significance when compare to AlCl3.

DISCUSSION

Pregabalin is a well notorious GABA analog. It was proven as a potent therapeutic agent in the treatment of post-herpetic neuralgia, diabetic neuropathy, generalized anxiety and social anxiety disorders, fibromyalgia, spinal cord damage etc., apart from convulsions [10]. Pregabalin shows anti apoptotic activity, anti inflammatory activity, neuroprotective activity and antioxidant activity [11] (11).

Systemic administration of Aluminium Chloride (AlCl3) (34mg/kg) for seven days had shown behavioral alterations by decreasing locomotor activity by actophotometer, decreasing muscle strength by hanging wire test, enhanced anxiety by elevated plus maze. In the biochemical alterations, elevated lipid peroxidation in terms of malandialdehyde levels and decreased level of anti-oxidant enzymes like superoxide dismutase, catalase and Reduced Glutathione.

In this study aluminium chloride treated animals had shown the anxiety like behavior. AlCl3 increased the overall time spent in closed arm and animals took more time to cross the closed arm to open arms in elevated plus maze. Pregabalin attenuated the alterations occurred due to aluminium chloride in anxiety like behavior of animals and it was observed by increased time spent in open arms. Therefore, pregabalin had shown anxiolytic activity against the AlCl3 induced anxiety like behaviour in rats. These contemporary results were collaborated with the former reports of pregabalin as an anxiolytic agent [12].

Aluminium exposure leads to oxidative stress by multiple mechanisms. Aluminum potentiates the pro-oxidant properties of iron by providing the colloidal surface for sequestration of iron that leads to Fenton reaction. In addition, aluminum was a superoxide dismutase (SOD) and catalase enzyme repressor. As a repercussion, hydrogen peroxide (H_2O_2) formed from superoxide anion by activated SOD enzyme. The conversion of H_2O_2 into water and oxygen does not be occur because of deactivated catalase that further leads to generation of hydroxyl radical ion. Neurodegeneration occur due to oxidative stress, is contributed by these components [13].

Lipid peroxidation plays an imperative role in assessment of neuron toxicity induced in AlCl3. Aluminium chloride challenged animals had shown increased level of Malondialdehyde due to increased lipid peroxidation levels in both cortex and hippocampus. It is an inebriation mechanism of aluminium chloride to the nervous system. Pregabalin significantly reduced the levels of lipid peroxidation and our results are correlated with preceding results [14].

Catalase, SOD, and reduced glutathione levels were hindered in AlCl3-treated group. Whereas, Pregabalin significantly attenuated these alterations by increasing antioxidant enzyme levels, these results are in line with earlier studies [15].

Pregabalin at presynaptic nerve endings diminishes the calcium (Ca^{2+}) influx and release of excitotoxic neurotransmitters (glutamate) by binding to the $\alpha 2$-δ subunit of voltage gated calcium channels. Aluminium impede with the metabolism of acetyl Co-A will leads to reduced formation of Acetylcholine. In the present scientific work, there was an increased acetylcholinesterase activity (AChE activity) after Aluminium exposure to brain, which was an indirect measure of Acetylcholine. Pregabalin does not effectively ameliorate the AChE activity produced by AlCl3. The obtained results in this study were in

accordance with the previous reports.

Numerous studies said that AlCl3 administration showed behavioral alterations, biochemical alterations and change in GABA (Gamma- Amino Butyric acid) and glutamate levels. Decreased GABA and increased Glutamate level in the hippocampus and cortex of rat brain were observed in AlCl3 treatment and Pregabalin ameliorated these alterations in neurochemicals by increasing GABA levels and diminishing glutamate levels and these results were in collaboration with former reports.

The morphological changes in the cortex and hippocampus (CA1, CA3 and DG) were observed by histopathological examination. Optimally sized undamaged neuronal cells with a clearly observable cell nucleus and continues cell membrane was observed in control treated group brain sections. The AlCl3 treatment group showed marked fibrillar inclusions with the H&E stain which indicates neurofibrillary degeneration and cell shrinkage in the regions of cortex and hippocampus (CA1, CA3 and DG). The protective potential of pregabalin was further appraised by histopathological observations of both the cortex and hippocampus (CA1, CA3 and DG) regions. It was apparent that our results were furnished the earlier affirmed reports.

CONCLUSION

The aim of the present study was to evaluate the effect of Pregabalin against Aluminium Chloride induced neurotoxicity in male albino wistar rats. The present study is to estimate the behavioral parameters, biochemical parameters, neurochemical alterations and histopathological studies. Aluminium Chloride (AlCl3) 34mg/kg/7 days has shown alterations in weight loss, motor function, cognitive dysfunction, anxiety like behavior, neurochemical alterations, and elevated levels in acetylcholinesterase. Systemic administration of Pregabalin had ameliorated AlCl3 alterations in weight loss, motor function, cognitive dysfunction, anxiety like behavior, neurochemical alterations. Aluminium Chloride (AlCl3) 34mg/kg manifested neuronal loss with the Hemotoxylin and eosin (H&E) stain which designates neurotoxic effect in DG, CA1, CA3 and cortex regions of rat brain. Pregabalin accomplished as neuroprotective agent by attenuating the neuronal loss in DG, CA1, CA3 and cortex regions of rat brain caused by AlCl3 and had shown more potent anti-oxidant, antiacetylcholinesterase, neuroprotective agent against AlCl3 neurotoxicity.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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