Egypt. J. Chem. **Vol. 68,** SI: Z. M. Nofal, pp. 889 - 902 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Alzheimer's and Antipsychotics: Investigating Neuroprotective and Behavioural Outcomes in Rats

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Abstract

Alzheimer's disease (AD) remains the leading cause of dementia in the elderly, with no definitive cure. Recently, antipsychotic drugs (APDs) have shown effectiveness in managing neuropsychiatric symptoms liked those associated with AD. This study investigated the neurobiological effects of traditional APDs (chlorpromazine and haloperidol) and modern APDs (clozapine and olanzapine) on oxidative stress, neuroinflammation, neuronal injury, and cognitive-behavioral symptoms in an aluminum chloride ($AlCl_3$)-induced rat model of AD. Sixty adult male rats were divided into ten groups: a saline control, an $AlCl_3$-only group, and eight groups received $AlCl_3$ (10 mg/kg/day) for two months, alongside APDs at 1.5 or 3 mg/kg during the second month. At the end of the second month, behavioral responses were examined via the open field test, followed by immunohistopathological and biochemical assessments. A colorimetric spectrophotometer was used to determine the levels of malondialdehyde, nitric oxide, paraoxonase 1, and acetylcholinesterase. Meanwhile, the levels of reduced glutathione, monocyte chemoattractant protein-1, interleukin-1 beta, amyloid-beta peptide, and neuron-specific enolase were determined using an enzyme-linked immunosorbent assay. APDs mitigated $AlCl_3$-induced AD-like symptoms by improving behavioral deficits and reducing oxidative stress, neuroinflammation, neuronal injury, and acetylcholinesterase activity, with modern types enhancing cognition and behavior, while traditional ones exhibiting stronger antioxidant effects.

Keywords: Alzheimer's disease, aluminum chloride, clozapine, olanzapine, chlorpromazine, haloperidol.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, affecting approximately 11% of individuals over 65 and accounting for 60–70% of dementia cases **[1, 2]**. Currently, around 50 million people worldwide have AD, with projections indicating an increase to 152 million by 2050, in addition, dementia prevalence has increased considerably in the Middle East and North Africa **[3]**. AD typically begins with episodic memory deficits, progressing to cognitive impairments such as confusion and disorientation, leading to anxiety, agitation, and aggression. As the disease advances, semantic memory deteriorates, affecting language, recognition, and reasoning, which results in communication difficulties, social withdrawal, and impaired judgment. These memory deficits contribute to the hallmark cognitive symptoms and behavioural and psychological symptoms of dementia (BPSD), severely impacting independence and quality of life. BPSD are common, especially in later stages, affecting up to 50% of patients and manifesting as sleep disturbances, mood swings, delusions, and hallucinations **[4, 5]**. Depression is also a major concern, with AD patients facing a three- to tenfold higher suicide risk **[6, 7]**. AD is characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, and neuropil threads, as well as the loss of neurons, neuropil, and synapses, particularly in the hippocampus **[8]**. Additionally, neuroinflammation, oxidative stress, and cholinergic neuron damage contribute to neurodegeneration, exacerbating both cognitive symptoms and BPSD **[9, 10]**. Managing AD is acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists **[11]** which provide limited benefits, challenging and requires multifaceted approaches, including anti-amyloid and anti-tau interventions, neurotransmitter modulation and anti-neuroinflammatory strategies **[2]**. Currently, only two FDA-approved therapies are available: cholinesterase inhibitors mainly in early stages of AD, and do not prevent disease progression or effectively manage BPSD **[12]**. Research into AD treatments, particularly antipsychotic medications, highlights their potential benefits in symptom management and improving quality of life **[11]**. Notably, aluminium chloride ($AlCl_3$), associated with increased AD prevalence, is used to induce beta-amyloid

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Received date 08 April 2025; Revised date 15 June 2025; Accepted date 18 June 2025
DOI: 10.21608/ejchem.2025.373645.11559

plaque accumulation, along with tau hyperphosphorylation, neurofibrillary tangles, synaptic dysfunction, and neuroinflammation **[13, 14]**. Despite nearly two decades of effort and billions spent on drug development, international policies to prevent or manage AD have largely failed **[15]** as the disease's incidence continues to rise due to its strong link to aging and yet no effective therapies exist. Consequently, there is a growing shift toward repurposing existing medications, originally approved for other conditions, for potential use in AD treatment **[8]**, and given the urgent need for alternative therapeutic strategies. Thus, the current study specifically aimed to investigate the effects of traditional (e.g., chlorpromazine and haloperidol) and modern (e.g., clozapine and olanzapine) antipsychotic drugs on cognitive-behavioural changes, neuronal injury, oxidative stress, and neuroinflammation in aluminium chloride induced Alzheimer's disease in rat and to assess their potential neuroprotective mechanisms.

Materials and methods

Drugs and chemicals

Aluminium chloride ($AlCl_3$) was purchased from Sigma-Aldrich (St. Louis, USA). Antipsychotic drugs, which are Haloperidol (HP), Chlorpromazine (CPZ), Clozapine (CLZ) and Olanzapine (OLZ), were sourced from Sandoz Misr Pharmaceuticals and Multi Apex Pharma (Cairo, Egypt), while doses adjusted from human equivalents using the Paget and Barnes conversion table **[16]**.

Animals

Adult male Sprague-Dawley rats, weighing between 170-180 g, were used. Animals were sourced from the breeding colony at the animal facility of the National Research Centre (NRC) in Giza, Egypt. They were kept in standard laboratory conditions throughout the experiment, with a room temperature of 25±2°C, humidity ranging from 60-70%, and a 12-hour light/dark cycle. The rats were provided with standard laboratory chow (containing 20% protein, 5% fat, and 1% multivitamins) and had unrestricted access to tap water. All animals received human care and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (US National Institutes of Health publication No. 85-23, revised 2011) and were approved by Medical Research Ethics Committee (MREC) for Animal Experimentation at the National Research Centre (Permission Number 05211221).

Experimental design

Sixty rats were randomly allocated into 10 groups (6 rats each) and were interperitoneally injected daily for 2 months as follow: Group I (normal control) received 0.9% saline. Group II (untreated group) received $AlCl_3$ 1.5 mg/kg **[17]**. While, groups III–X (treated groups) received 1.5 mg/kg of $AlCl_3$ for the first month and continue the injection during second month along with $AlCl_3$ as follow: group III received $AlCl_3$ + CPZ (1.5mg/kg); group IV received $AlCl_3$ + CPZ (3mg/kg); group V received $AlCl_3$ + HP (1.5mg/kg); group VI received $AlCl_3$ + HP (3mg/kg); group VII received $AlCl_3$ + CLZ (1.5mg/kg); group VIII received $AlCl_3$ + (CLZ 3mg/kg); group IX received $AlCl_3$ + OLZ (1.5 mg/kg); group X received $AlCl_3$ + OLZ (3 mg/kg) (as illustrated table 1). Behaviour test was assessed using the open field test after the final injection and rats were sacrificed by cervical dislocation under anaesthesia **[18],** after which the rats' brains were removed and cleaned with cold saline (0.9%). Each group was then split into two smaller subgroups: one with three rats, where the brains were fixed in 10% formalin for histopathology and immunopathology; and the other with three rats, where the brains were quickly frozen on a cold glass plate and stored at -80°C until were homogenized in phosphate-buffer saline to prepare 10% homogenates using the Bradford method **[19]** for the biochemical investigation, including; malondialdehyde (MDA), nitric oxide (NO), glutathione (GSH) and paraoxonase-1 (PON1) which are indicators of oxidative stress, interleukin-1β (IL-1β) and monocyte chemoattractant protein-1 (MCP-1) which are markers for neuroinflammation, neuron specific enolase (NSE) and A-beta (Aβ) peptide which are neuronal injury markers, and acetylcholinesterase (AChE) that is a marker for cognitive impairment.

Table 1: Experimental design timetable

Group	Treatment (Daily, i.p.)	Duration	BehaviorTesting	Post-mortem Analysis
I	0.9% Saline (Normal control)	2 months	End of 2nd month	Brain dissection and analysis
II	$AlCl_3$ (1.5 mg/kg)	2 months		
III	$AlCl_3$ (1.5 mg/kg) + CPZ (1.5mg/kg)	$AlCl_3$:2 months, CPZ: 2nd month		
IV	$AlCl_3$ (1.5 mg/kg) + CPZ (3 mg/kg)	$AlCl_3$:2months, CPZ: 2nd month		
V	$AlCl_3$ (1.5 mg/kg) + HP (1.5 mg/kg)	$AlCl_3$:2months, HP: 2nd month		
VI	$AlCl_3$ (1.5 mg/kg) + HP (3 mg/kg)	$AlCl_3$:2months, HP: 2nd month		
VII	$AlCl_3$ (1.5 mg/kg) + CLZ (1.5mg/kg)	$AlCl_3$:2months, CLZ: 2nd month		

VIII	$AlCl_3$ (1.5 mg/kg) + CLZ (3 mg/kg)	$AlCl_3$:2months, CLZ: 2nd month		
IX	$AlCl_3$ (1.5 mg/kg) + OLZ (1.5 mg/kg)	$AlCl_3$:2months, OLZ: 2nd month		
X	$AlCl_3$ (1.5 mg/kg) + OLZ (3 mg/kg)	$AlCl_3$:2months, OLZ: 2nd month		

CPZ: chlorpromazine, HP: haloperidol, CLZ: clozapine, OLZ: olanzapine, each group had 6 rats, split after sacrifice into two subgroups:3 rats for histopathology and immunohistochemistry (fixed in 10% formalin) & 3 rats for biochemical assays (brains frozen at −80°C).

Behavioural parameter

Spontaneous locomotion in an open-field paradigm was used to assess the rats' motor activity. Each animal's time spent engaging in various behaviours such as grooming, freezing, and movement was recorded, ensuring at least one hour of rest between tests **[20]**.

Biochemical parameters

Calorimetrically using a spectrophotometer (Thermo Electron Corporation, England) and kits that were provided by Bio-diagnostic Company (Giza, Egypt), MDA was measured as described by the standard method of Ruiz-Larrea **[21]**, NO according to the protocol described by Miranda **[22]**, PON1 activity followed the method of Higashino **[23]**, and AChE was determined using a modified procedure based on Ellman **[24]** as described by Gorun **[25]**. While GSH, MCP-1, IL-1β, Aβ-peptide and NSE were determined by ELISA according to manufacturer's protocol and the kits were purchased from (Sunlong Biotech Co., LTD, Hangzhou, China).

Histopathological examinations and immunohistochemistry

Formalin-fixed rat brains were stained with haematoxylin and eosin (H&E) stain **[26]**, Congo red **[27]**, and Glial fibrillary acidic protein (GFAP) immunostaining **[28]**. Slides were examined and photographed using digital camera (Microscope Digital Camera DP70, Tokyo, Japan).

Statistical analysis

Data are presented as mean ± standard error (SE) in bar charts. Comparison between groups was performed using one-way analysis of variance (ANOVA), followed by post hoc test and Duncan's multiple comparison test, with significance set at $p < 0.05$. Statistical analysis was performed using Graph Pad Prism software version 7 (San Diego, CA, USA).

Results

Behavioural and cognitive parameters

Rats that received aluminium chloride ($AlCl_3$), demonstrated a marked increase in behavioural durations of both freezing and grooming and a significant reduction in movement duration compared to normal control group that received 0.9% saline. While, the administration of each chlorpromazine (CPZ), haloperidol (HP), clozapine (CLZ), and olanzapine (OLZ) had varied effects that resulted in a considerable improvement in the behavioural parameters, as depicted in table 2 and figure 1 (A, B & C). Regarding to cognitive parameter, $AlCl_3$ increased acetylcholinesterase (AChE) level however, CLZ and OLZ, especially at their high doses, significantly reduced the level of AChE. Moreover, CPZ and HP showed the highest decrease at their low doses, as illustrated in table 2 and figure 1D.

Table 2: Comparison of antipsychotic drug effects on behavioural and cognitive parameters

Parameter	AlCl3	CPZ (1.5mg)	CPZ (3mg)	HP (1.5mg)	HP (3mg)	CLZ (1.5mg)	CLZ (3mg)	OLZ (1.5mg)	OLZ (3mg)
Movement duration	↑0.55	↓35.7%	↓35.9%	↓28.1%	-			↑1.35	-
Freezing duration	↑1.58	-	↑1.31	↑1.04	-		↑1.3	-	↑1.25
Grooming duration	↑1.58	↓91%	↓96.5%	↓88.1%	↓89%	↓91.2%	↓89.9%	↓85.6%	↓88.6%
Acetylcholinesterase	↑1.36	-	↓25.4%	↓24.3%	↓33.6%	↓43.4%	↓37.8%	↓42.2%	↓36.9%

AlCl3: aluminium chloride
↑: fold increase; ↓: fold decrease
AlCl3 compared to saline while antipsychotic drugs compared to AlCl3
CPZ: chlorpromazine; HP: haloperidol; CLZ: clozapine; OLZ: olanzapine

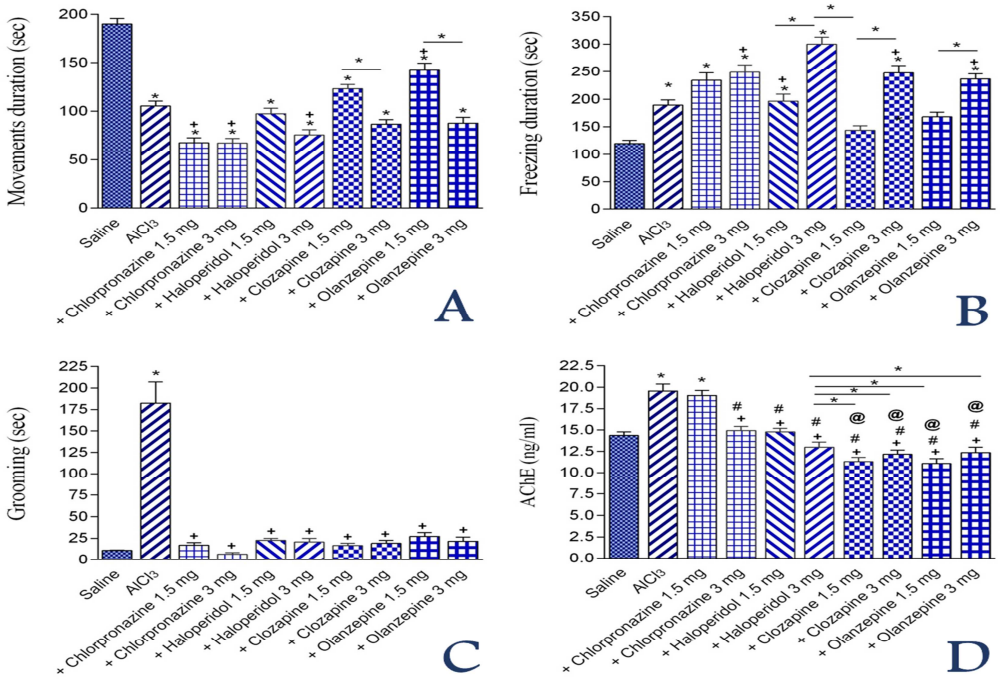

Figure 1: Effect of antipsychotic drugs on movement **(A)**, freezing **(B)**, grooming durations **(C)** and acetylcholinesterase activity **(D)** in aluminium chloride administrated rats**.**
$AlCl_3$: Aluminium chloride; AChE: acetylcholinesterase
*vs. normal control group (received 0.9% saline); @vs. Haloperidol 1.5 mg/kg; +vs. $AlCl_3$ untreated group (received 1.5 mg/kg $AlCl_3$); #vs. chlorpromazine 1.5 mg/kg. Data are presented as mean ± SEM.

Oxidative stress, inflammatory and neural cell injury parameters

The analyses of biochemical parameters revealed that rats received $AlCl_3$ exhibited a significant rise in brain malondialdehyde (MDA), nitric oxide (NO), interleukin-1beta (IL-1β), monocyte chemoattractant protein-1 (MCP-1), amyloid beta peptide (Aβ-peptide), and neuron-specific enolase (NSE) levels and a significant decrease in brain glutathione (GSH) and paraoxonase-1 (PON-1) levels compared to control group. Whereas, the treatment with all antipsychotic drugs led to a notable improvement in these biochemical parameters as follow. Regarding oxidative stress, HP and CLZ showed the most significant decrease in MDA and NO as shown in tables 3 and figure 2 (A, B, C&D). In terms of inflammatory results, all antipsychotic treatments showed significant decreases in IL-1β and MCP-1, with more pronounced reductions especially at their high doses, as represented in tables 4 and figure 3(A&B). With respect to neural cell injury results, low dose of OLZ showed a significant increase in Aβ-peptide compared to the high dose of CLZ or OLZ and a significant decrease in NSE compared to HP, as represented in tables 5&6 and figure 4 (A&B). Moreover, the comparisons of mentioned biochemical and neurophysiological effects amongst different antipsychotic drugs were illustrated in table 6.

Table 3: Comparison of antipsychotic drug effects on oxidative stress parameters

Parameter	$AlCl_3$	CPZ (1.5mg)	CPZ (3mg)	HP (1.5mg)	HP (3mg)	CLZ (1.5mg)	CLZ (3mg)	OLZ (1.5mg)	OLZ (3mg)
Lipid peroxidation	↑2.25	↓21.15%	↓28.78%	↓36.82%	↓61.34%	-	↓48.46%	-	↓44.60%
Nitric oxide	↑2.14	↓30.48%	↓44.67%	-	↓43.56%	↓32.19%	↓44.37%	↓12.68%	↓24.85%
Reduced glutathione	↓28.85%	-	↑1.33	↑1.20	↑1.22	↑1.18%	↑1.28%	-	↑1.24%
Paraoxonase-1	↓50.76%	-	↑1.69	↑1.82	↑1.66	-			

$AlCl_3$: aluminium chloride; CPZ: chlorpromazine; HP: haloperidol; CLZ: clozapine; OLZ: olanzapine
↑: fold increase; ↓: fold decrease; $AlCl_3$ compared to saline while antipsychotic drugs compared to $AlCl_3$

Table 4: Comparison of antipsychotic drug effects on inflammatory parameters

Parameters	$AlCl_3$	CPZ (1.5mg)	CPZ (3mg)	HP (1.5mg)	HP (3mg)	CLZ (1.5mg)	CLZ (3mg)	OLZ (1.5mg)	OLZ (3mg)
Interleukin-1β	↑3.06	↓30.77%	↓40.41%	↓37.33%	↓26.6%	↓31.49%	↓40.29%	↓28.96%	↓25.22%
Monocyte chemoattractant protein1	↑1.45	↓19.91%	↓38.01%	↓35.62%	↓38.7%	↓25.90%	↓33.78%	↓16.64%	↓36.54%

$AlCl_3$: aluminium chloride; CPZ: chlorpromazine; HP: haloperidol; CLZ: clozapine; OLZ: olanzapine
$AlCl_3$ compared to saline while antipsychotic drugs compared to $AlCl_3$ ↑: fold increase; ↓: decrease

Table 5: Comparison of antipsychotic drug effects on neural cell injury parameters

Parameter	$AlCl_3$	CPZ (1.5mg)	CPZ (3mg)	HP (1.5mg)	HP (3mg)	CLZ (1.5mg)	CLZ (3mg)	OLZ (1.5mg)	OLZ (3mg)
Amyloid beta peptide	↑1.3	↓21.46%	↓31.33%	↓24.37%	↓20.36%	↓32.42%	↓24.99%	↓19.5%↑	↓25.71%
Neuron-specific enolase	↑1.49	-	↓28.52%	-		↓44.70%	-	-	↓36.67%

$AlCl_3$: aluminium chloride; CPZ: chlorpromazine; HP: haloperidol; CLZ: clozapine; OLZ: olanzapine
$AlCl_3$ compared to saline while antipsychotic drugs compared to $AlCl_3$ ↓: fold decrease; ↑: increase

Table 6: Comparison of biochemical and neurophysiological effects among different antipsychotic drugs

Parameter	Drug and dosage (mg/kg)	Compared to	Effect observed
Oxidative Stress			
Lipid peroxidation	HP 3mg	CPZ 3mg	↓ 38.81%
	CLZ 3mg		↓ 18.42%
	OLZ 3mg	CPZ 1.5mg	↓ 29.75%
Nitric oxide	CPZ 1.5mg		↓ 20.39%
	CPZ 3mg		↓ 36.64%
	HP 3mg	OLZ 1.5mg	↓ 35.37%
	CLZ 1.5mg		↓ 36.29%
	CLZ 3mg		↓ 22.35%
	CPZ 3mg		↓ 26.37%
	HP 3mg	OLZ 3mg	↓ 24.89%
	CLZ 3mg		↓ 25.97%
Reduced glutathione	OLZ 1.5mg	CPZ 1.5mg	↓ 3.47%
Paraoxonase-1	CLZ 1.5mg		↓ 40.92%
	CLZ 3mg	HP 1.5mg	↓ 41.85%
	OLZ 1.5mg		↓ 58.84%
	OLZ 3mg		↓ 55.26%
Inflammation			
Monocyte chemoattractant protein-1	CPZ 1.5mg		↓ 25.63%
	HP 1.5mg	OLZ 1.5mg	↓ 22.77%
	HP 3mg		↓ 26.65%
	CLZ 3mg		↓ 20.55%
	OLZ 3mg		↓ 23.87%
Neural cell injury			
Amyloid beta peptide	OLZ 1.5mg	CLZ 1.5mg	↑ 1.19
Neuron-specific enolase	OLZ 3mg	HP 3mg	↓ 35.47%
Cognitive impairment			
Acetylcholinesterase	CPZ 3mg	CPZ 1.5mg	↓ 23.41%
	HP 1.5mg		↓22.31%

	HP 3mg	↓31.81%
	CLZ 1.5mg	↓40.68%
	CLZ 3mg	↓ 36.20%
	OLZ 1.5mg	↓41.84%
	OLZ 3mg	↓35.22%
	CLZ 1.5mg	↓23.65%
	CLZ 3mg	↓17.84%
	OLZ 1.5mg	↓25.14%
	OLZ 3mg	↓16.62%

CPZ: chlorpromazine; HP: haloperidol; CLZ: clozapine; OLZ: olanzapine; ↑: increase, ↓: decrease

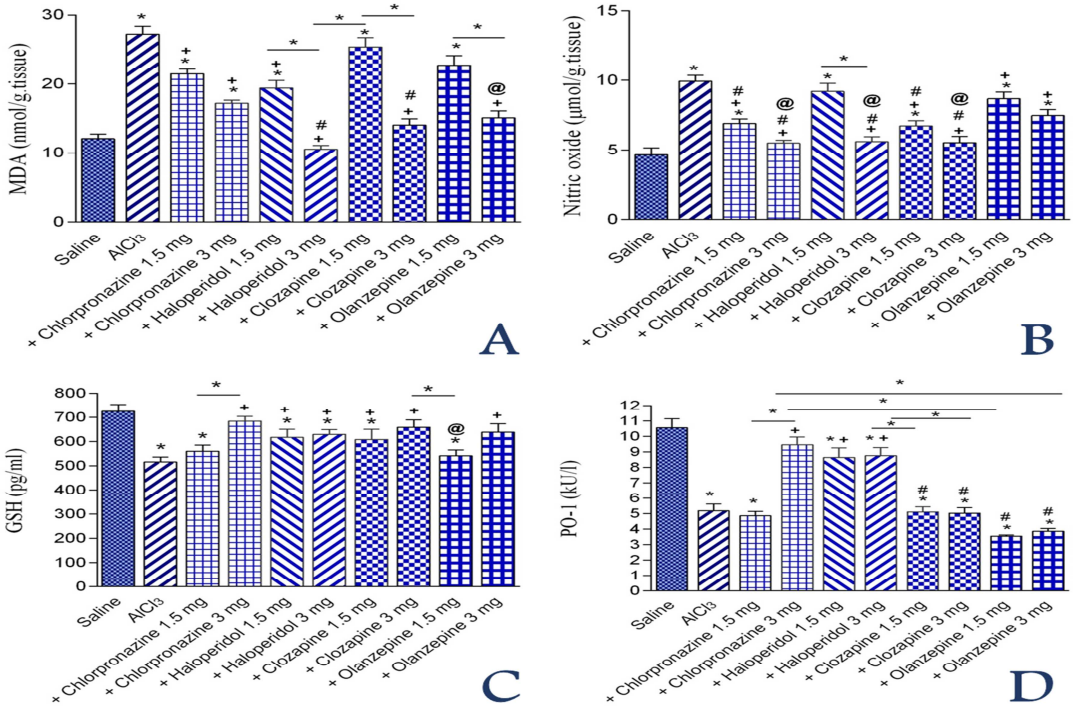

Figure 2: Effect of different antipsychotic drugs Chlorpromazine, Haloperidol, Clozapine and Olanzapine on brain malondialdehyde **(A)**, nitric oxide **(B)**, reduced glutathione **(C)** and paroxonase1 **(D)** levels in aluminium chloride administrated rats.

MDA: malondialdehyde
NO: nitric oxide
GSH: reduced glutathione
PON1: paroxonase1
AlCl3: aluminium chloride
*vs. normal control group
$^{+}$vs. $AlCl_3$ untreated group
*vs. olanzapine 1.5 mg/kg in MDA
$^{\#}$vs. chlorpromazine 3 mg/kg in MDA
$^{\#}$vs. olanzapine 1.5 mg/kg in NO
$^{\#}$vs. haloperidol 1.5 mg/kg in PON-1
$^{@}$vs. chlorpromazine 1.5 mg/kg in MDA&GSH
$^{@}$vs. olanzapine 3 mg/kg in NO
Data are presented as mean ± SEM

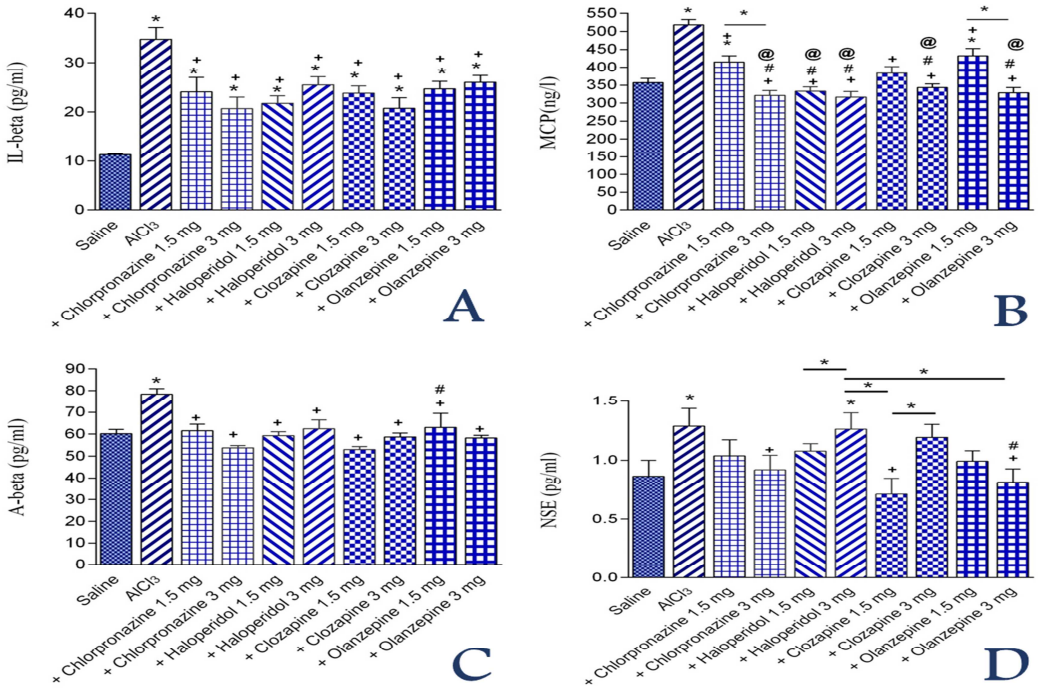

Figure 3: Effect of different antipsychotic drugs Chlorpromazine, Haloperidol, Clozapine and Olanzapine on brain interleukin 1beta **(A)**, monocyte chemoattractant protein **(B)**, amyloid-beta peptide **(C)** and neuron specific enolase **(D)** levels in aluminium chloride administrated rats.

IL-1beta: Interleukin 1beta
MCP: Monocyte chemoattractant protein
A-beta: Amyloid-beta peptide
NSE: Neuron specific enolase
$AlCl_3$: aluminium chloride
Data are presented as mean ± SEM

*vs. normal control group.
+vs. $AlCl_3$ untreated group.
#vs. chlorpromazine 1.5 mg/kg in IL-beta &MCP
#vs. clozapine 1.5 mg/kg in A-beta.
#vs. haloperidol 3mg/kg in NSE.
@vs. olanzapine 1.5 mg/kg.

Histopathological examination

The histopathological examination of brain tissues revealed distinct structural alterations across the different groups. In control group, normal cortical neurons were observed, characterized by a large vesicular nucleus, a prominent nucleolus, well-arranged hippocampal neurons, and flask-shaped Purkinje cells in the cerebellum, as represented in figure 4A. However, the untreated group that received $AlCl_3$ only exhibited significant structural damage, including dark cerebral cortical neurons with pyknotic nuclei, acidophilic cytoplasm, numerous neurofibrillary tangles, a disorganized hippocampal area, and smaller Purkinje cells in the cerebellum, in compared with the control group, as shown in figures 4A and 4B. Treatment with low doses (1.5 mg/kg) of CPZ, HP, CLZ, or OLZ caused mild neuronal degeneration and slight structural damage across most brain regions of treated groups as displayed in figures 4C, 4E, 4G, and 4I, respectively. CPZ slightly reduced neurofibrillary tangles, while HP exhibited dark neurons, no neurofibrillary tangles, and Purkinje cell depletion. Furthermore, CLZ showed neurofibrillary tangles and some hippocampal damage, whereas OLZ presented dilated capillaries, disorganized hippocampal neurons, and darkly stained Purkinje cells. On the other hand, treatment with high doses (3 mg/kg) of CPZ, HP, CLZ, or OLZ significantly reduced neuronal damage and improved brain histopathology, as shown in figures 4D, 4F, 4H, and 4J, respectively. CPZ notably decreased dark neurons, pyknotic nuclei, and neurofibrillary tangles, leaving only a few atrophied neurons. Similarly, HP preserved some normal cortical neurons and a healthy hippocampal structure, though Purkinje cells remained smaller. Additionally, CLZ minimized cortical damage, maintaining smaller yet normal hippocampal neurons and Purkinje cells. In contrast, OLZ exhibited mostly normal brain structures, but Purkinje cells were slightly smaller than usual. Overall, higher doses of these treatments contributed to a near-normal brain structure with reduced neuronal damage and notable histopathological improvements.

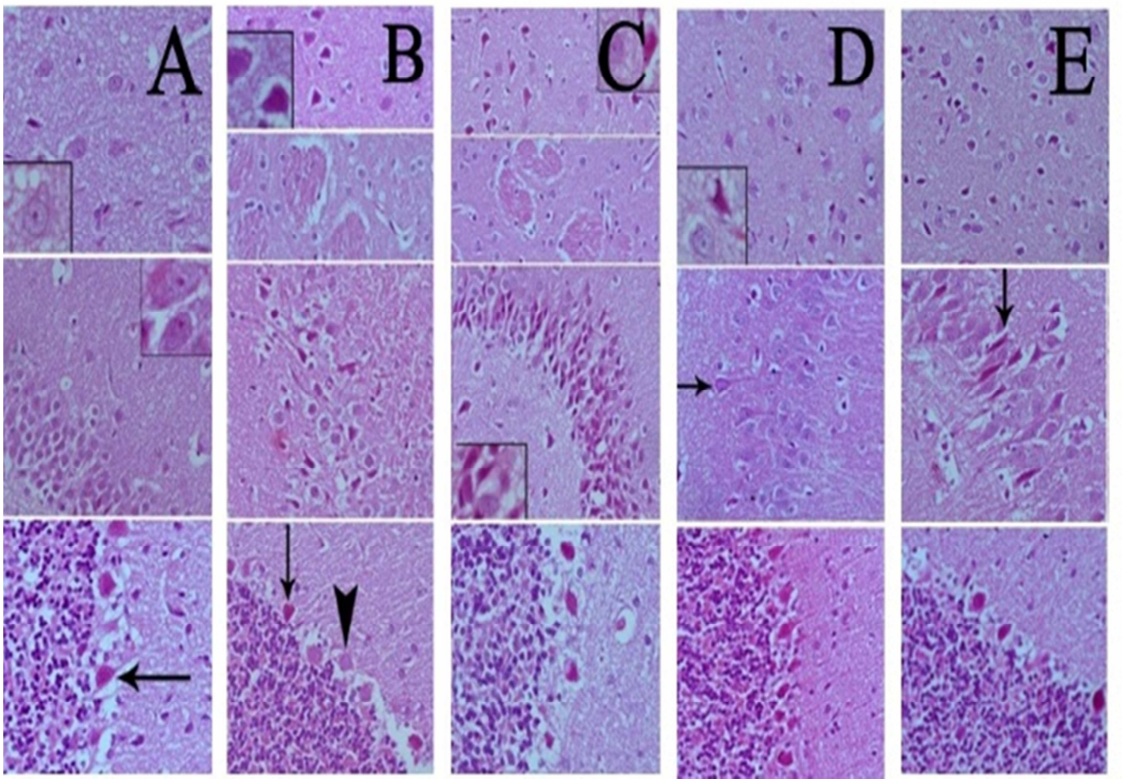

Figure 4(A-E): Representative haematoxylin and eosin stained brain tissue sections from rats received saline (A), **AlCl3** (B) **chlorpromazine 1.5mg** (C), **chlorpromazine 3mg** (D), **and haloperidol 1.5 mg** (E).

A) The lower right part is a higher magnification of a neuron with its large vesicular nucleus and prominent nucleolus of cerebral cortex., The upper left part shows highly magnified neurons of hippocampal area., Section of cerebellum region shows molecular area (M), granular area (G) and flask-shaped Purkinje cells in between (arrow).

B) The higher right part is a higher magnification damaged neuron with pyknotic nuclei and acidophilic cytoplasm in cerebral cortex with many neurofibrillary tangles., Section of hippocampal area shows disorganization of neurons., Many damaged neurons that appear dark in colour., Section of cerebellum region shows some Purkinje cells that appear smaller in size (arrow) or show karyolysis (arrowhead).

C) Section of cerebral cortex shows many damaged dark neurons are still detected with pyknotic nuclei and acidophilic cytoplasm and mild reduction of neurofibrillary tangles., The lower right part is a higher magnification of section of hippocampal area shows many damaged neurons that appear atrophied and dark in colour., Section of cerebellum region shows some Purkinje cells that appear smaller in size and darkly-stained although the neurons are normally oriented.

D) Section of cerebral cortex shows marked reduction of damaged dark neurons, the magnified lower right part shows damaged neuron with pyknotic nuclei and acidophilic cytoplasm and no neurofibrillary tangles are observed., Section of hippocampal area shows only a few neurons with dark cytoplasm (arrow)., Section of cerebellum region shows Purkinje cells that appear smaller in size than normal.

E) Section of cerebral cortex shows some damaged dark neurons but with no neurofibrillary tangles., Section of hippocampal area shows some elongated neurons with dark cytoplasm and pyknotic nuclei (arrow)., Section of cerebellum region shows depletion of Purkinje cells in some areas.

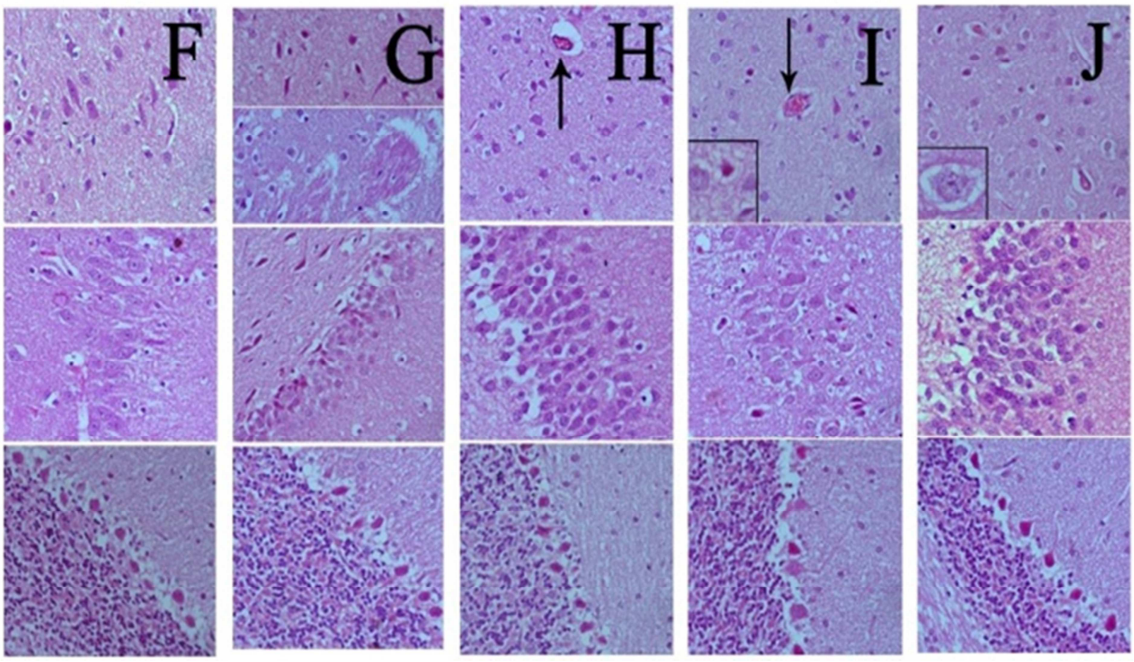

Figure 4 (F-J): Representative haematoxylin and eosin stained brain tissue sections from rats received haloperidol 3mg (F)**, clozapine 1.5 mg** (G)**, clozapine 3 mg** (H)**, olanzapine 1.5 mg** (I)**, and olanzapine 3mg** (J)**.**

F) Section of cerebral cortex shows some neurons with normally-shaped nuclei and acidophilic cytoplasm in between normal neurons., Section of hippocampal area shows some normal neurons, however, reduction of thickness in this area., Section of cerebellum region shows small sized Purkinje cells.
G) Section of cerebral cortex shows many damaged dark neurons with neurofibrillary tangles are still detected., Section of hippocampal area shows some damaged neurons in between normal neurons., Section of cerebellum region shows small sized Purkinje cells.
H) Section of cerebral cortex shows some damaged dark neurons and dilated capillaries (arrow)., Section of hippocampal area shows normal neurons although they are smaller in size than normal., Section of cerebellum region shows small sized Purkinje cells.
I) Section of cerebral cortex shows a few damaged dark neurons and dilated capillaries (arrow)., Section of hippocampal area shows normal neurons although they are disarranged., Section of cerebellum region shows small sized, darkly stained Purkinje cells.
J) Section of cerebral cortex shows most neurons are normally-appeared (lower right part)., Section of hippocampal area shows normal structure of this area., Section of cerebellum region shows normal Purkinje cells although they are smaller than normal.

Congo red staining

AlCl3 caused a marked amyloid plaque deposition as large red dots in brain tissues (figure 5B), in compared with control group that was with no red dots in the tissue section (figures 5A). Low doses of CPZ, HP, CLZ, or OLZ revealed fewer and medium-sized red dots indicating a mild marked reduction in red dots, as illustrated in figures 5C, 5E, 5G and 8I, respectively. While, elevated doses of CPZ, HP, CLZ, or OLZ exhibited a marked reduction with tiny-sized red dots, denoting a significant decrease in amyloid beta plaques, as presented in figures 5D, 5F, 5H and 5J, respectively.

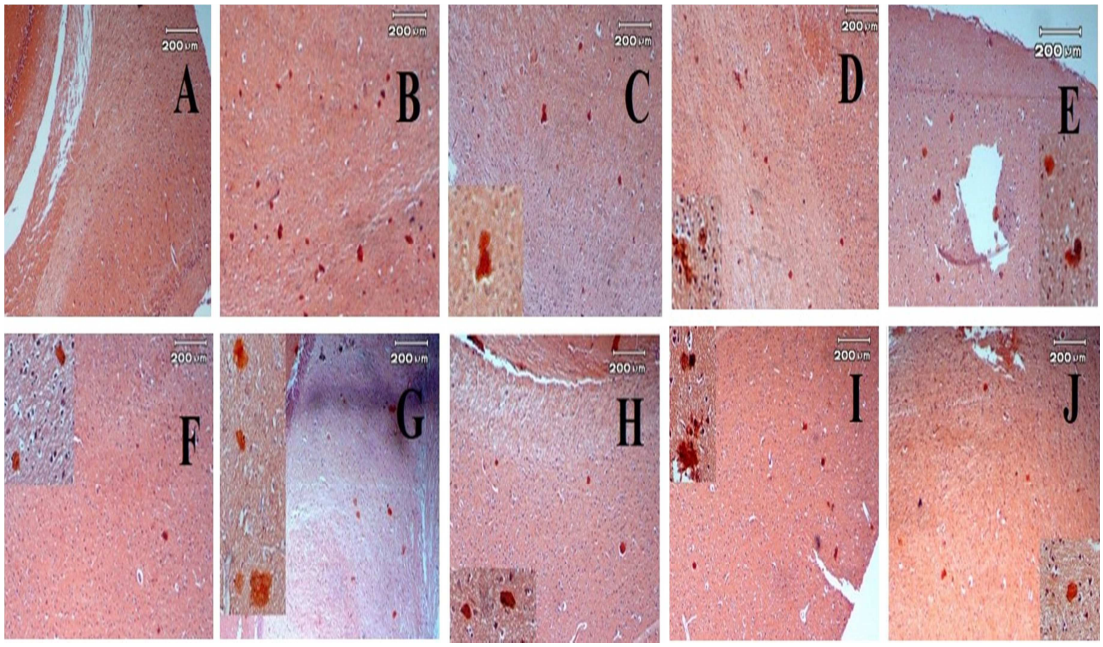

Figure 5: **Representative photomicrographs of cerebral cortex tissue sections stained by Congo red in rats that received saline** (A)**, AlCl3 (B), chlorpromazine 1.5 mg** (C)**, chlorpromazine 3 mg** (D)**, haloperidol 1.5 mg** (E)**, haloperidol 3 mg** (F)**, clozapine 1.5 mg** (G)**, clozapine 3 mg** (H)**, olanzapine 1.5 mg** (I)**, and olanzapine 3 mg** (J).

A) No red dots in the tissue section.
B) Many red dots of variable sizes scattered all over the tissue denoting the presence of amyloid beta plaques in tissue.
C) Many red dots are still observed and a higher magnification for this section shows some of these dots are large in size.
D) Some red dots are identified in tissue and a higher magnification for this section shows all the red dots are small in size.
E) A few red dots are seen in tissue and a higher magnification for this section shows same result.
F) Only a few red dots are observed and a higher magnification for this section shows all these dots are very small in size.
G) Marked reduction of the number of red dots and a higher magnification for this section shows all dots are small in size.
H) Decrease in number of red dots and the higher magnification for this section shows very small positive dots denoting a marked decrease of amyloid beta plaques.
I) Many red dots observed in tissue and a higher magnification for this section shows many of these dots are large in size.
J) Marked decrease in number of red dots and a higher magnification for this section shows medium sized positive dots.

Glial fibrillary acidic protein (GFAP) – immunoreactivity

Brains of rats that received $AlCl_3$ revealed a marked decrease in the number and size of astrocytes, with shortened processes, as represented in figure 6B, in comparing with rats of control group that showed positive staining of astrocytes with regularly shaped bodies and long processes, as shown in figure 6A. After administration of high doses of CPZ or HP, noticeable improvement in astrocyte cell number was demonstrated, but the cells' bodies are still smaller in size than normal with normal length processes, as displayed in figure 6C and 6D. Furthermore, after administration of high doses of CLZ or OLZ, noticeable increase in number of positive cells was demonstrated and many of them regain their normal body size with some amelioration in the processes as illustrated in figure 6E and 6F.

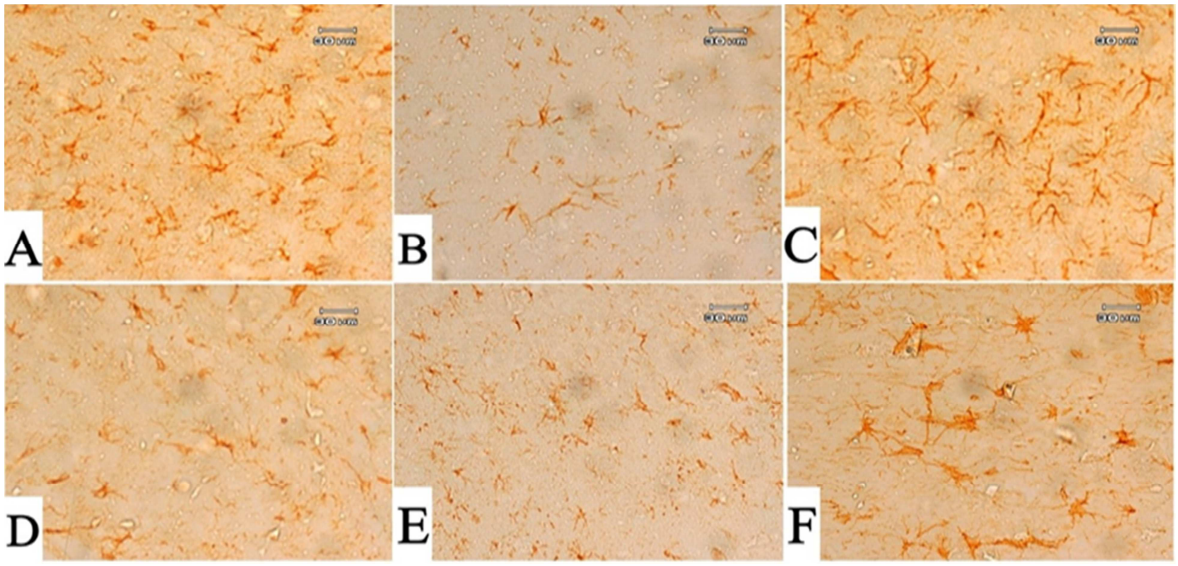

Figure 6: **Representative photomicrographs of cerebral cortex sections immunohistochemically stained by Glial fibrillary acidic protein (GFAP) for rats received saline** (A)**, $AlCl_3$** (B)**, chlorpromazine 3 mg** (C)**, haloperidol 3mg** (D)**, clozapine 3 mg** (E) **and olanzapine 3 mg** (F)**.**

A) Irregularly shaped body and the long processes of the astrocyte cells.
B) Marked decrease in number and body size of cells with shortness of processes.
C) Noticeable increase in number of cells. The cell bodies are smaller than normal and flattened in shape, although the processes are of normal length.
D) Mild amelioration of cell number, but the cells' bodies are still smaller in size than normal with short processes.
E) Increase in number of positive cells. Many of them regain their normal body size but with short processes.
F) Noticeable amelioration in cell body size and processes.

4. Discussion:

Alzheimer's disease (AD) is a progressive neurological disorder that affects memory and significantly impacts the quality of life for both patients and their families. Currently, traditional treatments are ineffective, as they focus only on providing temporary relief from cognitive symptoms without halting neurodegeneration or addressing behavioural and psychological symptoms of dementia (BPSD). Moreover, these treatments often come with undesirable side effects **[29]**. The antipsychotic medications have attracted attention due to their effectiveness in managing BPSD symptoms in elderly patients with schizophrenia, while having fewer side effects, as well as their antioxidant, anti-inflammatory, and neuroprotective properties**[30]**. Hence, the current study tried to explore the therapeutic capability of antipsychotic medications such as chlorpromazine (CPZ), haloperidol (HP), clozapine (CLZ) and olanzapine (OLZ) for the Alzheimer's disease through assessing their potential effects in alleviating aluminium chloride ($AlCl_3$)-induced AD-related behavioural, neuropathological, and neurochemical changes, which may pave the way for incorporating them into treatment strategies and developing more effective interventions for Alzheimer's disease management. $AlCl_3$ was used in this study, following previous researches, to induce AD in rats mimicking human AD progression **[31]**. Accordingly, current study found that $AlCl_3$ increased oxidative stress, inflammation, and brain injury, through elevating markers such as malondialdehyde (MDA), nitric oxide (NO), interleukin-1β (IL-1β), monocyte chemoattractant protein-1 (MCP-1), amyloid beta peptide (Aβ-peptide) and neuron-specific enolase (NSE), while reducing glutathione (GSH) and paraoxonase-1 (PON-1). Furthermore, behavioural, cognitive and histological analysis of $AlCl_3$-received rats showed neurotoxicity and hippocampal damage with increased acetylcholinesterase (AChE) level and glial fibrillary acidic protein (GFAP)-positive astrocytes. These results align with several previous studies, for instance, Abdel-Salam et al. reported AD-like biochemical changes, including higher AChE and lower GSH and PON-1, with $AlCl_3$ (10 mg/kg/day for 60 days) exposure **[32]**. Additionally, there are many evidences, consistent with findings of this study, supporting aluminium's role in accelerating brain aging via oxidative stress, neuroinflammation, Aβ-peptide aggregation, and cytotoxic agents (e.g., reactive oxygen species (ROS), NO, IL-1β, MCP-1) **[33, 34]**. Concerning oxidative stress, inflammation, and neural cell injury results in present study; all the studied antipsychotic drugs have demonstrated significant improvement across all parameters, with a more pronounced restoration of these markers at their higher doses. Notably, CPZ exhibited the strongest antioxidant effect, while both HP and CLZ caused the most significant reduction in MDA and NO levels. Moreover, low doses of HP and OLZ_proved more effective in

lowering IL-1β than their higher doses. In line with latest study's results demonstrated that traditional as, (HP and CPZ) and modern such as (OLZ and CLZ) antipsychotics enhance antioxidant defences by increasing GSH **[35, 36]**, reducing MDA **[37, 38]**and normalizing ROS metabolism in both psychiatric disorders and many other vivo studies**[39]**. As well**,** antipsychotic treatments have also been shown to lower IL-1β **[40]** and MCP1 levels which elevated during early psychosis episodes and contributed significantly to AD pathophysiology **[41, 42]**. Furthermore, in agreement with our results, modern antipsychotics, particularly CLZ and OLZ, suppress lipopolysaccharide (LPS) –induced NO release and microglial activation, providing their anti-inflammatory effects **[43]**. Besides that, present study supports the protective effect of antipsychotics against $AlCl_3$-induced brain injury by reducing Aβ peptide levels, reversing degenerative changes, and decreasing NSE activity, whereas high doses of CPZ and OLZ were more effective. Consistent with our findings, CLZ and OLZ mitigated Aβ-induced apoptosis and oxidative stress in AD as well as HP reduced damage of telomeres induced by oxidative stress in cultured leukocytes **[44, 45]**. OLZ further decreased Aβ-induced inflammation, preventing microglial activation and neurite damage and long-term of CLZ treatment improved memory deficit **[46]**. In contrast with our findings, HP lacked significant effects on amyloid precursor protein, while CPZ decreased NSE activity in schizophrenic models **[47]**. Moreover, contemporary study demonstrates that both CLZ and OLZ significantly reduced brain AChE activity, with a more pronounced effect at their higher doses. Among traditional antipsychotics, HP influenced AChE activity only at high doses but was less effective than CLZ and OLZ at low doses. Corroborating these findings, previous study suggested that modern antipsychotics, such as CLZ, counteract neuroinflammation by suppressing NO and cytokine production, thereby improving cognitive function through reducing microglial activation and oxidative damage **[48]** while, in contrast, traditional antipsychotics, such as CPZ, failed to return AChE to the same range as the control values after the 7-days from using the drug in a vivo study **[39]**. Likewise, past research indicates that CLZ (2.5–20 mg/kg) and OLZ (10 mg/kg) enhance cognitive function by improving cholinergic transmission, while HP does not. Notably, low-dose of OLZ was effective, aligning with our results on the cognitive benefits of modern antipsychotics **[49]**. Another aspect of measuring the effectiveness of antipsychotics is the neurobehavioral assessments used to evaluate sensory, motor, and cognitive functions during neurodegeneration **[50]**. Based on this, the open field test, commonly used as a tool for monitoring behaviour in comparative psychology, was selected in this study **[51]**. Furthermore, it is important to highlight that, consistent with this study's findings, $AlCl_3$ injection led to a reduction in spontaneous locomotor activity **[52]**. Coupled with this, according to current study, CLZ and OLZ at low doses improved behavioural deficits but did not fully reverse impairments. As well, grooming behaviour improved slightly with most antipsychotics, however high-dose of CPZ effectively restored it. In agreement with these findings, some supporting studies indicated that OLZ benefits AD patients by managing psychosis and behavioural disturbances while, CLZ, due to its strong anticholinergic effects, was also considered as the gold standard for treating psychosis in AD**[53, 54]**. Furthermore, additional research showed that CLZ reversed behavioural alterations induced by dysfunction of N-Methyl-D-Aspartate (NMDA) receptors, which play a crucial role in neurotransmission, learning, and memory **[55]**. Our results of histological evaluations using haematoxylin and eosin and Congo red stains along with glial fibrillary acidic protein (GFAP) immunostaining, a marker of astrocyte activation, supported the findings of the biological assessments in this study. These analyses demonstrated that high doses of CLZ and OLZ offer significant neuroprotection against $AlCl_3$-induced neurotoxicity by reducing astrocyte activation, preserving brain structure, and minimizing histological degeneration. In contrast, high doses of traditional antipsychotics, particularly HP, only moderately alleviated degenerative changes. These findings are consistent with previous studies suggesting that traditional antipsychotics contribute to restoring cellular morphology and enzymatic activity in brain regions affected by AD, likely mediated by growth factors. Likewise, high doses of CPZ, CLZ, and OLZ were found to mitigate changes in glial markers, whereas HP exhibited only limited effects in vitro studies **[55, 56]**.

Conclusion

Both traditional and modern antipsychotics have the potential to reduce oxidative stress and neuroinflammation, enhance cholinergic activity, and alleviate both behavioural and neuropathological deficits. Notably, modern antipsychotics, such as clozapine and olanzapine, offer greater cognitive and behavioural benefits, whereas traditional antipsychotics, like chlorpromazine and haloperidol, exhibit stronger antioxidant properties. By targeting mechanisms involved in the progression of Alzheimer's disease, these medications present promising therapeutic strategies to alleviate symptoms, delay the need for long-term care, and improve the quality of life for both patients and caregivers.

Conflicts of interest

The authors declare there are no conflicts of interest.

Acknowledgment

The authors gratefully acknowledge support from the National Research Centre (NRC).

Funding

Partially funded by the National Research Centre

Ethical considerations

The Medical Research Ethics Committee (MREC) at the NRC approved all animal studies (Permission Number 05211221), conducted according to National Institutes of Health (NIH) guidelines for laboratory animal care and use.

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