Libyan Journal of Medical Research
www.ljmr.ly/
eISSN:2413-6096
DOI: https://doi.org/10.54361/LJMR.20.1.15

Original Article

Additive Effects of Streptozotocin and Aluminum Chloride on Cognitive Decline and Brain Damage in Rats: A Behavioral and Histopathological

Huda M Gargoum[1], Muftah M Muftah[2], Amira M Abelhamid[3], Kadija R Sharee[2]
[1] Pharmacology Department, Benghazi University
[2] Benghazi Medical Hospital
[3] Pharmacology Department, Zagazig University
Correspondence information: Huda M Gargoum.Email: huda.gargoum@uob.edu.ly

Abstract

Background: Streptozotocin (STZ) and Aluminum Chloride ($AlCl_3$) are recognized neurotoxins implicated in models of cognitive decline and neurodegeneration. This study investigated the comparative effects of STZ, $AlCl_3$, and their combination on cognitive performance and brain structural integrity. **Methods:** Cognitive function was assessed using the T-maze test, and structural damage was evaluated through histopathological examination of brain tissue across four groups: Control, STZ-treated, $AlCl_3$-treated, and Combination-treated. **Results:** All three treatment groups showed significant cognitive impairment and histopathological changes compared to the Control group. In the T-maze test, the Combination group exhibited the maximum degree of cognitive impairment, showing a significantly greater deficit than either the STZ or $AlCl_3$ groups alone. In contrast, histopathological assessment revealed that the magnitude of cellular and structural impairment was comparable across the STZ, $AlCl_3$, and Combination groups, though all were significantly different from the Control. **Conclusion:** Co-exposure to STZ and $AlCl_3$ leads to a marked synergistic or additive effect on behavioral neurotoxicity, resulting in maximal cognitive deficits. However, the histopathological evidence suggests that the individual agents (STZ or $AlCl_3$) may already induce a comparable level of maximal structural damage, indicating a dissociation between the severity of morphological and functional impairment under these experimental conditions.
Keywords: Steptozotocin, Aluminum chloride, cognitive impairment

Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by high blood sugar levels resulting from the body's ineffective use of insulin (insulin resistance) or insufficient insulin production by the pancreas [1]. The prevalence of T2D has reached epidemic proportions globally, posing a significant public health challenge [2]. The long-term consequences of T2D extend to its profound impact on brain health and cognitive function [3]. Alzheimer's disease (AD) is the most common cause of dementia [4]. It is characterized by the accumulation of abnormal protein deposits in the brain: amyloid plaques and neurofibrillary tangles. These pathological hallmarks lead to neuronal dysfunction and loss, brain atrophy, and a decline in cognitive abilities [5]. The exact cause of AD is not fully understood, but it is believed to involve a complex interplay of genetic, environmental, and lifestyle factors [6].

Recent epidemiological and scientific research has increasingly highlighted a significant and complex correlation between Type 2 Diabetes and Alzheimer's Disease, leading some researchers to even refer to AD as "Type 3 Diabetes" [7]. This designation underscores the growing understanding that metabolic dysregulation, particularly insulin resistance, plays a crucial role not only in the development of T2D but also in the pathogenesis of AD [8,9].

One of the primary links between T2D and AD is insulin resistance. Emerging evidence suggests that a similar phenomenon occurs in the brain, where neurons become insulin resistant, impairing their ability to utilize glucose for energy and disrupting vital cellular processes (9). This energy deficit can compromise neuronal function, synaptic plasticity, and overall brain health, contributing to cognitive decline. Elevated glucose levels can lead to the formation of advanced glycation end products (AGEs), which are harmful compounds that can accumulate in the brain, promoting oxidative stress, inflammation, and the formation of amyloid plaques and neurofibrillary tangles, the pathological hallmarks of AD [10]. Additionally, chronic inflammation, a common feature of both T2D and AD, acts as a bridge between the two conditions. Systemic inflammation associated with T2D can cross the blood-brain barrier, triggering neuroinflammation that exacerbates neuronal damage and contributes to the progression of AD [11]. The intricate relationship between T2D and AD highlights the importance of a holistic approach to health, emphasizing metabolic control not only for managing diabetes but also for preserving cognitive function and reducing the risk of neurodegenerative disorders.

Based on evidence that STZ disrupts central insulin signaling and induces cognitive impairment, and that $AlCl_3$ promotes neurotoxicity through oxidative stress, inflammation, and cholinergic dysfunction, the present

Received: 30-12-2025-*Accepted*: 05-02-2025 -*Published:* 09-02-2026

Libyan Journal of Medical Research
www.ljmr.ly/
eISSN:2413-6096
DOI: https://doi.org/10.54361/LJMR.20.1.15

study aims to investigate whether concurrent exposure to these compounds produces a greater detrimental effect on memory than either agent alone. Accordingly, we hypothesize that combined STZ and $AlCl_3$ use will result in additive cognitive impairment.

Materials and Methods

Animals and Experimental Design

Twenty-four male Wistar rats, weighing approximately 180-220 g, were obtained from the animal facility of Zagazig University. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature (22 ± 2°C), and humidity (50 ± 5%). All rats had free access to food and water, except during specific experimental procedures. The experimental protocol was approved by the Institutional Animal Ethics Committee of Benghazi University and conducted under the guidelines for the care and use of laboratory animals. After a one-week acclimatization period, rats were randomly divided into four groups (n=6 rats per group):

Control Group (**Control**): Received a normal chow diet and vehicle treatments.

Type 2 Diabetes Mellitus Group (**STZ**): Fed a high-fat diet and received low-dose streptozotocin by intraperitoneal (IP) injections (35 mg/kg).

Alzheimer's Disease Group (**AlCl3**): Received aluminum chloride by oral route (PO) (100 mg/kg).

Mixed Group (**STZ- AlCl3**): Fed a high-fat diet, received low-dose streptozotocin injections (35 mg/kg, IP), and aluminum chloride administration (100 mg/kg, PO).

Induction of Type 2 Diabetes Mellitus (T2DM)

Type 2 Diabetes Mellitus was induced in the DM and Mix groups using a combination of a high-fat diet (HFD) and low-dose streptozotocin (STZ) injections, a well-established method to mimic human T2DM [12,13]. Rats in these groups were fed a 60% HFD (60% kcal from fat, 20% from protein, 20% from carbohydrates) for a period of 2 weeks to induce insulin resistance. Following the HFD feeding period, a single low dose of STZ (35 mg/kg body weight) was administered intraperitoneally (i.p.) to overnight-fasted rats. Fasting blood glucose (FBG) levels were measured 1week post-STZ injection. Rats with FBG levels consistently above 126 mg/dL were considered diabetic and included in the study [14].

Induction of Alzheimer's Disease (AD)

Alzheimer's Disease was induced in the AlCl3 and Mix groups by oral administration of aluminum chloride (AlCl3). Rats in these groups received AlCl3 at a dose of 100 mg/kg body weight dissolved in distilled water daily for 28 days [15]. Control and DM groups received an equivalent volume of distilled water orally. The AlCl3 administration aims to induce neurotoxicity and AD-like pathology, including cognitive deficits and changes in brain biochemistry and histopathology.

Biochemical Analysis

Fasting blood glucose (FBG) levels were measured from tail vein blood after an overnight fast (12-16 hours) using a portable glucometer (e.g., Accu-Chek Performa, Roche Diagnostics, Germany). FBG measurements were performed at the end of the experiment for all groups

Behavioral Testing: T-Maze Test

Cognitive function was assessed using the T-maze spontaneous alternation test, which evaluates spatial working memory. The T-maze apparatus consists of a start arm and two goal arms (left and right) forming a 'T' shape. Rats were placed at the start arm and allowed to explore the maze for 5 minutes. Spontaneous alternation behavior was recorded, defined as entry into the arm opposite to the one entered on the previous trial. A higher percentage of spontaneous alternations indicates better spatial working memory. The test was performed at the end of the experiment for all groups [16].

Histopathology Study

At the end of the experimental period, rats were humanely euthanized, and their brains were rapidly excised. Brain tissues were immediately fixed in 10% neutral buffered formalin for at least 48 hours, followed by routine tissue processing and paraffin embedding. Coronal sections of the brain (5 µm thickness) were cut using a microtome and mounted on glass slides. Sections were then stained with Hematoxylin and Eosin (H&E) for general morphological examination and for amyloid plaques to assess neuropathological changes. Stained sections were observed under a light microscope by a blinded observer, and images were captured for further analysis [17]. Data were presented as mean +_ SE. Statistical analysis was performed using one-way ANOVA followed by Tukey post-hoc test using SPSS software version 25 (IBM Corp, USA).

Results

The effect on blood glucose

The blood glucose levels were significantly elevated following a single low dose of STZ. In the STZ group, glucose levels increased to 199.4 mg/dL. The $AlCl_3$ group also showed an increase, reaching 157.51 mg/dL. Notably, the STZ-$AlCl_3$ group, which received both $AlCl_3$ and STZ, exhibited the highest glucose levels at 214.69 mg/dL. One-way ANOVA revealed a significant difference in glucose levels among the studied groups ($F(3,20) = 259.1$, $P < 0.0001$). All three experimental groups exhibited significantly elevated glucose levels compared to the control group ($P < 0.0001$). While the $AlCl_3$ group demonstrated increased glucose levels, they were significantly lower than those observed in the STZ and STZ-$AlCl_3$ groups ($P = 0.0046$ and $P = 0.0003$, respectively). Although both the STZ and STZ -$AlCl_3$ groups showed markedly elevated glucose levels, the increase in the STZ -$AlCl_3$ group was only slightly higher compared to the STZ group, but was not statistically significant ($P = 0.36$), Figure 1.

The effect on the T-maze test

The investigation of the effect of STZ, AlCl3, and their combination on the spontaneous alteration demonstrates a significant difference in the number of right entries and

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

Libyan Journal of Medical Research
www.ljmr.ly/
eISSN:2413-6096
DOI: https://doi.org/10.54361/LJMR.20.1.15

latency among the STZ, AlCl3, and STZ-AlCl3 groups Figur 2 A and B (F (3,20)=12.73 (P = 0.0032) and F (3,20)=39.6 (P =0.0002)), respectively. The control group showed a large number of correct alternations, and the lowest time in deciding to enter the chosen alternation. As compared to the control group, the AlCl3 and STZ-AlCl3 groups showed a significant reduction in the number of right entries (P = 0.009, P = 0.0035, respectively), and the latencies were significantly prolonged (P = 0.002, P = 0.0003, respectively). While the $AlCl_3$ group demonstrated a decreased number of the right entry and prolongation in the time of deciding to enter the choice, they were significantly better than those observed in the STZ-$AlCl_3$ groups (P = 0.0093 Vs P = 0.0035, and P = 0.002 Vs P = 0.0003, respectively). Although the number of right entries decreased and the latency was minimally prolonged in the STZ group, these differences were not statistically significant compared to the control group (P = 0.165, P = 0.85, respectively). Interestingly, this group demonstrated a non-significant change in the corrected number of entries as compared to the AlCl3 and STZ-AlCl3 groups (P = 0.16, P = 0.37, respectively), while the changes in the time in deciding to enter the chosen alternation were significant (P = 0.010, P = 0.0014, respectively). This suggests a minimal defect.

Histopathological changes

Figure 3 (H&E, x100) shows the Dentate Gyrus (DG), Cornu Ammonis (CA), and cerebral cortex across all experimental groups. In the control group, the DG has 7–8 layers of granular cells with well-preserved morphology, featuring vesicular nuclei and a basal row of immature cells with darker nuclei. The average cell density is 170±1.4 cells/mm² (Panel A). The CA region displays 5–6 layers of healthy pyramidal neurons with vesicular nuclei, prominent nucleoli, and apical dendrites, without signs of degeneration, with a cell density of 63±2.7 cells/mm² (Panel B). The cerebral cortex contains upper-layer pyramidal cells and lower-layer granular cells with vesicular nuclei, a thin-walled blood vessel, and a cell density of 125±1.4 cells/mm² (Panel C).

In the STZ-AlCl3 group, the DG shows only 4–5 layers of granular cells, mostly with dark, irregular nuclei indicating degeneration, and the cell density is reduced to 78±2.5 cells/mm² (Panel D). The CA region has 2–3 layers of pyramidal neurons, characterized by many dark, irregular nuclei, a few intact cells, a congested blood vessel, and an amyloid plaque. Notably, cell density decreases to 15±0.9 cells/mm² (Panel E). The cerebral cortex displays thickened nerve fibers, amyloid plaques with reactive gliosis, and many degenerating cells with dark nuclei and halos, with the cell density dropping to 50±1.8 cells/mm² (Panel F).

In the STZ group, the DG shows 4–5 layers with a mix of intact granular cells (vesicular nuclei) and degenerated cells with dark, irregular nuclei and halos, with a cell density of 80±2.6 cells/mm² (Panel G). The CA region contains 3–4 layers of pyramidal cells, including healthy and degenerating ones, with a density of 18±1.4 cells/mm² (Panel H). The cerebral cortex exhibits some preserved granular cells along with multiple degenerating cells with dark nuclei and halos, plus congested, thick-walled vessels, with a cell density of 55±1.8 cells/mm² (Panel I).

In the AlCl3 group, the DG also has 4–5 layers of granular cells, with both healthy vesicular nuclei and degenerated cells with dark nuclei and halos, and a cell density of 79±0.9 cells/mm² (Panel J). The CA region features 3–4 layers of pyramidal neurons, some intact and others degenerating, with a density of 16±1.4 cells/mm² (Panel K). The cerebral cortex shows amyloid plaques with reactive gliosis, a few healthy granular cells, and many degenerating cells with halos, with a cell density of 51±0.9 cells/mm² (Panel L).

Statistical analysis of all groups reveals distinct effects of treatments on mean cell numbers in brain regions: DG, CA, and cortex (F (3,20)=20.16 (P <0.0001); F (3,20)=1092 (P <0.0001); F (3,20) =3420 (P <0.0001), respectively). As compared to the control group, the three treated groups exhibit a significant reduction in the cell count of all regions, with P <0.0001 in all groups Figure 4, Table 1

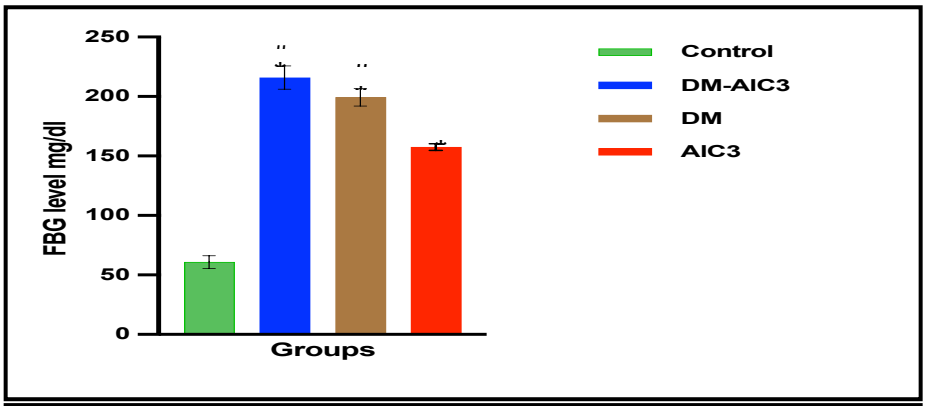

Figure 1: Effect of STZ, AlCl3, and their combination on the blood glucose levels Statistically
Two-star ** means highly significant change, P < 0.0001 (Compared to the control

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

Libyan Journal of Medical Research
www.ljmr.ly/
eISSN:2413-6096
DOI: https://doi.org/10.54361/LJMR.20.1.15

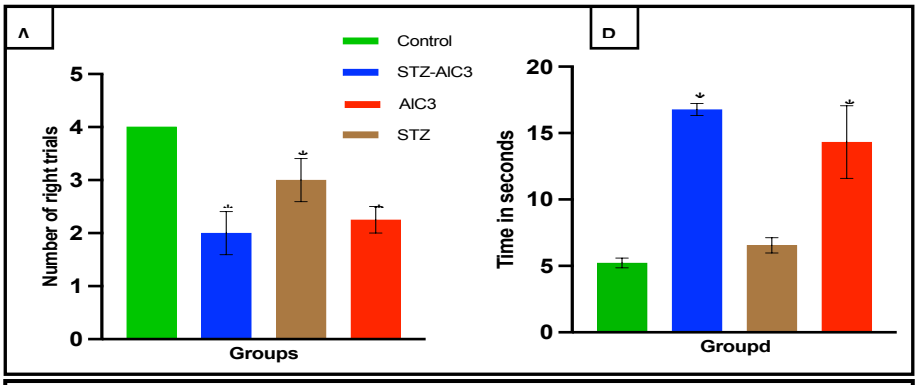

Figure 2: Effect of STZ, AlCl3, and their combination on the T-maze test
A: Duration of the right entry
B: Latency (time to make a decision)
Statistically

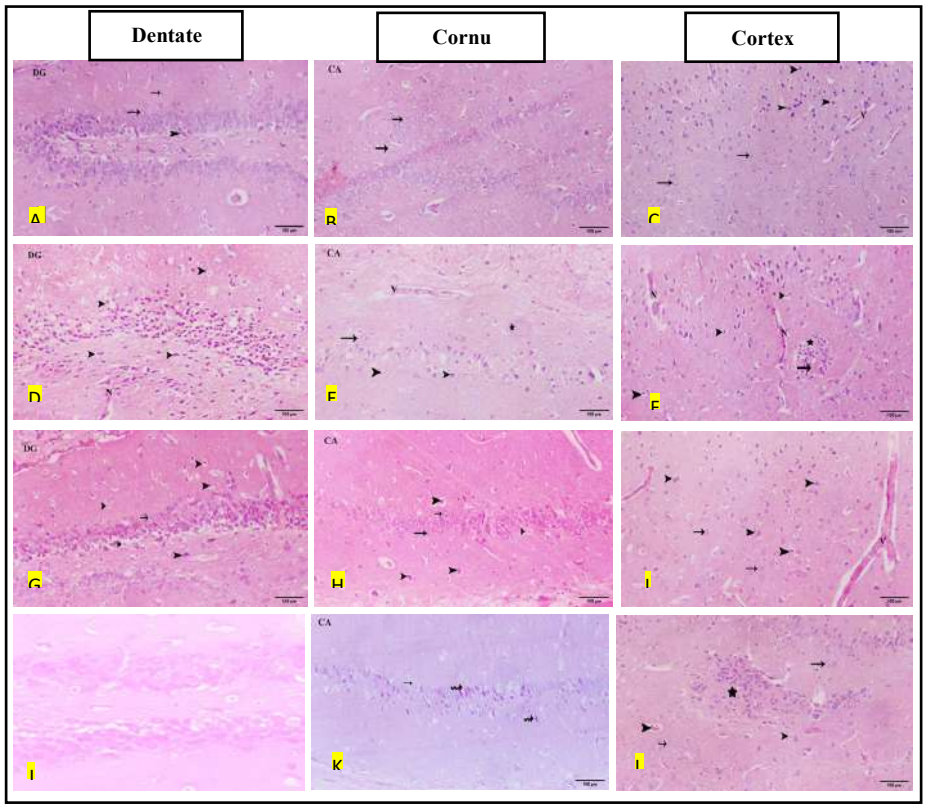

Figure 3 (H&E staining, x100) depicts histopathological changes in the Dentate Gyrus (DG), Cornu Ammonis (CA), and cerebral cortex across experimental groups. The **Control group**: **DG** (A) shows healthy granular cell layers (GC) with normal vesicular nuclei (VN). **CA** (B) shows a healthy pyramidal cell (PC) layer with VN. **Cortex** (C) shows healthy upper PC and lower GC with normal VN and a thin-walled blood vessel (V). The **STZ-AlCl₃: DG** (D) shows decreased GC layers with dark, irregular nuclei (DN) (arrow). **CA** (E) shows marked decreased PC with irregular DN (black arrows), a congested (V), and amyloid plaques (AP) (asterisk). **Cortex**: (F) shows thickened nerve fibers (N), AP (asterisks), with degenerating cells with DN (arrowheads). The **STZ and AlCl₃** groups: **DG** (G) &

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

Libyan Journal of Medical Research
www.ljmr.ly/
eISSN:2413-6096
DOI: https://doi.org/10.54361/LJMR.20.1.15

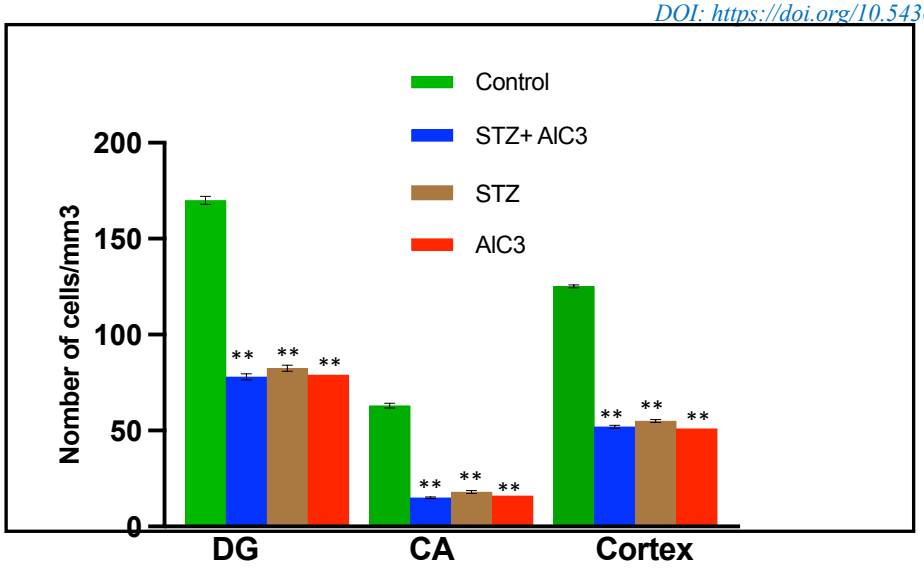

Figure (4): A representative graph of the effect on different parts of the brain.
Results are presented as Mean ± Std Error (n=6 rats).
Relative to control, values with superscript two-asterisks (**) are highly significant ($p<0.001$)

Tabel 1: Mean number of cells in different regions of the brain in the tested groups

control	control	STZ-AlCl3	STZ	AlCl3
DG	170	78	80	79
CA	63	15	18	16
Cortex	125	50	55	51

Discussion:

Streptozotocin (STZ) is well established for inducing hyperglycemia through selective pancreatic β-cell toxicity, resulting in insulin deficiency and elevated blood glucose levels. This is supported by studies showing significant increases in blood glucose and following STZ administration in rats, linked to β-cell apoptosis and disruption of glucose homeostasis[18,20]. Aluminum chloride (AlCl3) alone has been shown to produce a significant but less pronounced increase in blood glucose levels, which may be related to its oxidative damage effects on pancreatic tissue or interference with glucose metabolism. Dose-dependent elevations of blood glucose with AlCl3 have been reported, although the glucose rise is generally lower than that with STZ [21,22] . The combination of STZ and AlCl3, leading to the highest blood glucose levels, suggests a synergistic or additive effect, possibly due to AlCl3 exacerbating STZ-induced pancreatic damage or metabolic disruption. Some research indicates AlCl3 may affect insulin secretion and oxidative stress pathways, which could worsen STZ-induced hyperglycemia [22] .

The control group exhibited the highest number of correct trials and the shortest decision time on the T-maze test, indicating intact spatial working memory and rapid decision-making abilities. This performance aligns with the expected baseline cognitive function seen in healthy animals or subjects without induced impairments [23]. Studies consistently report that untreated control groups outperform experimental or disease model groups in such behavioral tests that assess learning and memory, as cognitive faculties remain unaltered, and exploratory behavior is efficient. In contrast, the STZ-alone group showed significantly reduced correct trials and increased decision time compared to the controls, which corresponds to previous findings that streptozotocin (STZ) causes cognitive deficits, presumably through the disruption of insulin and oxidative stress in brain areas involved in memory, such as the hippocampus. The moderate impairment seen in the STZ group aligns with its established role in models of sporadic Alzheimer's disease and diabetes-related cognitive decline [23,24] .

The group exposed to aluminum chloride (AlCl3) alone demonstrated a more pronounced cognitive impairment, with highly significant reductions in correct trials and longer decision times than both the control and STZ groups. This supports evidence that AlCl3 neurotoxicity

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

DOI: https://doi.org/10.54361/LJMR.20.1.15

results in marked learning and memory deficits, likely mediated by enhanced oxidative stress (25, 26), neuroinflammation, and neurotransmitter imbalances in cognition-related brain regions. The combined STZ + AlCl3 group exhibited the most severe cognitive deficits with the lowest number of correct trials and the longest decision time, significantly worse than either treatment alone. This synergistic or additive effect might be attributed to converging pathways of neurodegeneration involving metabolic dysfunction from STZ and neuroinflammatory and oxidative damage induced by AlCl3. Such combined treatment models simulate multifactorial forms of neurodegenerative diseases better, reflecting complex pathological processes that severely impair cognitive function as measured by tasks like the T-maze[27]. Overall, the pattern of results supports the progressive cognitive deterioration from control to single toxin exposure, and most drastically in their combination, consistent with current research.

The histopathological findings of this study align well with existing literature on the neurodegenerative effects induced by the combination of STZ (streptozotocin) and AlCl3 (aluminum chloride), which are often used to model Alzheimer's disease (AD) and related neurodegeneration. Consistent with this study, others report marked cell loss and degeneration in the dentate gyrus (DG) and Cornu Ammonis (CA) regions, characterized by reduced layers of granular and pyramidal cells with dark, irregular nuclei indicative of neurodegeneration. The sharply reduced cell densities in these hippocampal areas documented in the STZ-AlCl3 group align with previous findings where significant neuronal loss was noted, especially in the CA1 subregion, with accompanying signs of amyloid plaque deposition and reactive gliosis in the cortex[28,30]. The presence of amyloid plaques and reactive gliosis in the cortical samples supports prior reports linking AlCl3 exposure to neuroinflammation and oxidative stress, driving apoptosis and degeneration in cortical neurons [29,31]. Furthermore, the intermediate changes seen in the STZ or AlCl3 alone groups in the present study are consistent with other works showing that combined exposure exacerbates neurodegenerative changes more than either agent alone, emphasizing the synergistic impact in AD models with metabolic dysfunction[30,32,33].

However, some discrepancies arise when comparing the exact extent and pattern of pathology within different brain regions. For instance, while the STZ and AlCl3 alone groups showed mixed populations of healthy and degenerative cells in the DG and CA areas, some studies report more pronounced or earlier neuronal loss and amyloid deposition with AlCl3 alone, which may relate to differences in dosage, exposure duration, or animal strain [34,35]. Additionally, the observed reduction in vascular congestion in some groups contrasts slightly with findings that emphasize vascular changes as a hallmark of STZ-AlCl3 pathology, although these interpretations require detailed ultrastructural validation [28]. Overall, our data is well-supported by the literature as a valid in vitro correlate of hippocampal and cortical neurodegeneration due to combined STZ-AlCl3 insults, reflecting typical hallmarks such as neuronal loss, degeneration, amyloid pathology, and reactive gliosis, confirming the utility of this model for studying mechanisms and potential interventions in neurodegenerative disorders[28,30,33] .

conclusion

This study showed that streptozotocin (STZ) and aluminum chloride ($AlCl_3$) induce metabolic and neurodegenerative changes, with combined exposure producing the most severe hyperglycemia, cognitive impairment, and neuronal damage. The STZ + $AlCl_3$ group exhibited marked deficits in spatial working memory alongside pronounced hippocampal and cortical degeneration, indicating a synergistic interaction between metabolic dysfunction and aluminum-induced neurotoxicity. These findings validate the STZ–$AlCl_3$ model as an effective experimental tool for studying multifactorial neurodegeneration and related cognitive disorders.

This study is limited by the use of a single behavioral test and the absence of biochemical and molecular analyses to clarify underlying mechanisms. In addition, animal strain may affect the generalizability of the findings.

Funding statement

The study was conducted without external financial support.

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

Acknowledgements

The authors thank the technical staff of the departments of pathology and pharmacology, and of the animal housing

References

1. Hamed S. Brain Injury with Diabetes Mellitus: Evidence, Mechanisms and Treatment Implications.Expert Rev. Clin Pharmacol 2017;10:409–28.
2. IDF IDF. Facts & figures 2025 [Available from: https://idf.org/about-diabetes/diabetes-facts-figures/.
3. D Baglietto-Vargas, Shi J, Yaeger D, Ager R, LaFerla F. Diabetes and Alzheimer's Disease Crosstalk. Neurosci Biobehav Rev 2016;64:272–87.
4. Clinic M. Alzheimer's disease - Symptoms and causes 2024 [Available from: Retrieved from https://www.mayoclinic.org/diseases-

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

DOI: https://doi.org/10.54361/LJMR.20.1.15

conditions/alzheimers-disease/symptoms-causes/syc-20350447.
5. DeTure M, Dickson D. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019;14(1).
6. Weaver D. Thirty Risk Factors for Alzheimer's Disease Unified by a Common Neuroimmune–Neuroinflammation Mechanism. Brain Sciences. 2024;14(1).
7. Network MCN. Mayo Clinic Minute: Is Alzheimer's Type 3 diabetes? 2017 [Available from: Retrieved from https://newsnetwork.mayoclinic.org/discussion/mayo-clinic-minute-is-alzheimers-type-3-diabetes/.
8. Australia D. What is type 3 diabetes? 2019 [Available from: Retrieved from https://www.diabetesaustralia.com.au/blog/what-is-type-3-diabetes/.
9. Rad S, Arya A, Karimian H, Madhavan P, Rizwan F, Koshy S, et al. Mechanism involved in insulin resistance via accumulation of β-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease. Drug Design, Development and Therapy 2018;12:3999—4021.
10. Li J, Liu F, Li Y. Advanced Glycation End Products-Induced Alzheimer's Disease and Its Novel Therapeutic Approaches: A Comprehensive Review. Cureus. 2024;16(5).
11. Sim S, Kim S. Alzheimer's disease and type 2 diabetes via chronic inflammatory response. Journal of Diabetes Research. 2014;2014:1–10.
12. Srinivasan K, Ramarao P, Ghosh B. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat serves as an alternative animal model for type 2 diabetes. Journal of Pharmacological and Toxicological Methods. 2005;52(1): 105-11.
13. Islam M, Loots D. Experimental animal models of type 2 diabetes: An update. . Methods and Findings in Experimental and Clinical Pharmacology. 2009;31(4):249-57.
14. Gheibi S, Kashfi K, Ghasemi A. A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. Biomedicine & Pharmacotherapy. 2017;95:605-13.
15. Shunan D, Yu M, Guan H, Zhou Y. Neuroprotective effect of Betalain against AlCl3-induced Alzheimer's disease in Sprague Dawley Rats via putative modulation of oxidative stress and nuclear factor kappa B (NF-κB) signaling pathway. Biomedicine & Pharmacotherapy. 2021;137:111369.
16. d'Isa R, Comi G, Leocani L, . Apparatus design and behavioural testing protocol for the evaluation of spatial working memory in mice through the spontaneous alternation T-maze. Sci Rep. 2021;11:21177.
17. Bancroft J, Gamble M. Theory and practice of histological techniques 6ed: Churchill Livingstone Elsevier.; 2008.
18. Maaliah M, addadin M, Abdalla S. Hypolipidemic and Hypoglycemic Effects of Silybum marianum (L.) Gaertn. (Milk Thistle) Ethanol Seed Extract in Streptozotocin-induced Diabetes in Rats. 2024;20(3):841-52.
19. Qinna N, Badwan A. Impact of streptozotocin on altering normal glucose homeostasis during insulin testing in diabetic rats compared to normoglycemic rats. Drug Des Devel Ther. 2015(25):15-25
20. Rehman Hu, Ullah K, Rasool A, Manzoor R, Yuan Y, Tareen AM, et al. Comparative impact of streptozotocin on altering normal glucose homeostasis in diabetic rats compared to normoglycemic rats. Scientific Reports. 2023;13(1):7921.
21. Obermaier-Kusser B, Mühlbacher C, Mushack J, Rattenhuber E, Fehlmann M, Haring HU. Regulation of glucose carrier activity by AlCl3 and phospholipase C in fat-cells. Biochemical Journal. 1988;256(2):515-20.
22. Chary R, Eerike M, Konda V, Arunachalam R, Yeddula V, Meti V, et al. Effect of aluminum chloride on blood glucose level and lipid profile in normal, diabetic and treated diabetic rats. Indian J Pharmacol 2017;49(5).
23. Ma X, Song M, Ren YYG, Hou J, Qin G, Wang W, et al. Albiflorin alleviates cognitive dysfunction in STZ-induced rats. 2021;13:8287-18297
24. .
25. Li D, Huang Y, Cheng B, Su J, Zhou WX, Zhang YX. Streptozotocin Induces Mild Cognitive Impairment at Appropriate Doses in Mice as Determined by Long-Term Potentiation and the Morris Water Maze. J Alzheimers Dis. 2016;54(1):89-98.
26. Jadhav R, Kulkarni Y. Effects of baicalein with memantine on aluminium chloride-induced neurotoxicity in Wistar rats. Front Pharmacol. 2023;22(14).
27. Kaur K, Narang R, Singh S. AlCl3 induced learning and memory deficit in zebrafish. Neurotoxicology. 2022;92:67-76.
28. Hayat M, Khola N, Ahmed T. A Systematic Review of Preclinical Studies Investigating the Effects of Pharmacological Agents on Learning and Memory in Prolonged Aluminum-Exposure-Induced Neurotoxicity. Brain Sci 2025;15(6).
29. Mahdi O CS, Hidayat Baharuldin MT, Mohd Nor NH, Mat Taib CN, Jagadeesan S, Devi S, Mohd Moklas MA. . WIN55,212-2 Attenuates Cognitive Impairments in AlCl3 + d-Galactose-Induced Alzheimer's Disease Rats by Enhancing Neurogenesis and Reversing Oxidative Stress. Biomedicines. 2021;9(9).
30. Shata A, Elkashef W, Hamouda M, Eissa H. Effect of Artesunate vs Memantine in Aluminum Chloride Induced Model of Neurotoxicity in Rats
31. . Advances in Alzheimer's Disease. 2020;9(1):1-19
32. Akinola OB BS, Adediran RA, Adeniye KA, Abdulquadir FC. Characterization of prefrontal

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026

DOI: https://doi.org/10.54361/LJMR.20.1.15

cortex microstructure and antioxidant status in a rat model of neurodegeneration induced by aluminium chloride and multiple low-dose streptozotocin. Metab Brain Dis 2015;30(6):1531-6.
33. Jajin E, Esmaeili A, Rahgozar1 S, Noorbakhshnia M. Quercetin-Conjugated Superparamagnetic Iron Oxide Nanoparticles Protect AlCl3-Induced Neurotoxicity in a Rat Model of Alzheimer's Disease via Antioxidant Genes, APP Gene, and miRNA-101
34. Stanojevic JB ZM, Dragic M, Stojanovic IR, Ilic TV, Stevanovic ID, Ninkovic MB. Intermittent theta burst stimulation attenuates oxidative stress and reactive astrogliosis in the streptozotocin-induced model of Alzheimer's disease-like pathology. Front Aging Neurosci 2023;15.
35. Shaheen MA, Elshal LM, Mohamed GM, Reda S. Possible Effects of Empagliflozin on Hippocampal Structural Changes Associated with Alzheimer's Disease Induced by Aluminum Chloride in Adult Male Albino Rats (Histological and Immunohistochemical Study). Zagazig University Medical Journal. 2025;31(1):228-55.
36. Adelodun ST, Ishola OA, Abijo AZ, Olatunji SY, Owolabi JO, Olanrewaju JA, et al. Aluminium chloride-induced hippocampal damage: CA3 hippocampal subfield involvement and the neuroprotective role of Buchholzia coriacea ethanolic seed extract. Phytomedicine Plus. 2021;1(4):100104.
37. Kanan DD, Aydemir I, Alizade A, Ebrahimi S, Aksu F. Investigation of Behavioral Changes and Histopathological Changes in the Brain in Alzheimer's Modeled Mice with Aluminium Chloride (AlCl3). Cyprus J Med Sci. 2025;10:34-7.

Received: 30-12-2025-Accepted: 05-02-2025 -Published: 09-02-2026