MALAYSIAN JOURNAL OF SCIENCE
MJS
ISSN 1394 - 3065

MAHSA International Medical Sciences and Technology Conference (Mi-MED) 2024

Special issue

Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

https://mjs.um.edu.my

# Therapeutic Potential of Cannabidiol in Alleviating Cognitive Decline and Hippocampal Damage in a Rat Model of Alzheimer's Disease

Sreenivasulu Sura[1a,d], Saravanan Jagadeesan[2b], Thirupathirao Vishnumukkala[3c], Siti Saleha Binti Masrudin[4a], Mohamad Aris Mohd Moklas[5a], Mohd Amir Kamaruzzaman[6a,e], Krishna Chaitanya Reddy Dandala[7d], Ravindranadh Gandrakota[8d] and Nurul Huda Mohd Nor[9a]*

**Abstract:** Alzheimer's disease (AD) is a common neurodegenerative disorder marked by progressive cognitive decline. Due to its effects on cognitive functioning and hippocampal integrity, the combined treatment of D-galactose (D-gal) and Aluminium chloride (AlCl3) in rats is a widely used model for producing AD-like symptoms. Previous studies demonstrated that Cannabidiol (CBD) exhibits neurotherapeutic effects. This study examines the efficacy of CBD in reducing cognitive deficits and brain ultrastructural damage induced by D-gal and AlCl3. Male Wistar rats were treated with D-gal (60 mg/kg body weight/day) and AlCl3 (200 mg/kg body weight/day) for 10 weeks to induce AD-like symptoms, followed by CBD administration at doses of 20, 40, and 80 mg/kg/day. Donepezil (1 mg/kg body weight/day) served as a positive control. Cognitive performance was evaluated using the modified elevated plus maze and T-maze spontaneous alternation tests. Ultrastructural changes in the hippocampus were examined using transmission electron microscopy. Rats exposed to D-gal and AlCl3 exhibited significant cognitive impairments, including deficits in spatial learning and memory, as well as hippocampal ultrastructural damage. The results indicated that D-gal and AlCl3 exposure produced notable cognitive deficits and structural alterations in the hippocampus. Administration of CBD at all doses significantly enhanced cognitive function and reduced pathological changes, providing protective effects comparable to donepezil. These findings support CBD's potential as a neurotherapeutic compound for mitigating cognitive decline and hippocampal damage associated with AD.

*Keywords: Alzheimer's disease, Cannabidiol, Cognitive deficits, Hippocampus, Neurotherapeutic effects.*

## 1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that primarily affects the elderly, characterized by progressive memory impairment (Safiri et al., 2024). As life expectancy increases and populations age, AD has become a major global healthcare challenge (Zhang et al., 2021). AD is marked by neurofibrillary tangles (NFTs) formed from hyperphosphorylated tau protein and senile plaques (SP) composed of beta-amyloid protein (Ju & Tam, 2022). The progression of AD and other neurodegenerative diseases is believed to be strongly influenced by oxidative stress and reactive oxygen species (ROS) (Buccellato et al., 2021). Studies suggest oxidative stress may contribute to the onset and progression of AD. An imbalance in the production and removal of ROS can accelerate the initiation and advancement of AD by causing widespread and persistent damage to the central nervous system (CNS) (Ganguly et al., 2021; Olufunmilayo et al., 2023; Plascencia-Villa & Perry, 2023).

Chronic treatment with D-galactose (D-gal) is widely accepted to accelerate aging processes by causing modest neuronal damage and cognitive deficits, which are typical of the early stages of AD (Flores-Cuadra et al., 2021). As a result, animals treated with D-gal are frequently used as models to study the molecular causes of aging, including memory impairments and neurodegeneration, as well as to test potential anti-AD treatments (Xu et al., 2023). Aluminium (Al) is a toxic metal that is widely dispersed and primarily affects the brain, bones, liver, and spleen. Al accumulation in the brain can cause dementia by increasing malondialdehyde (MDA) levels, acetylcholinesterase (AChE) activity, and producing oxidative stress (Pankaj Bhargava et al., 2021). Consequently, rats exposed to Al over long periods serve as useful models for evaluating anti-AD therapies (Xia et al., 2023). Given that both D-gal and Al are established neurotoxins, researchers have investigated their combined effects (Luo et al.,

**Authors information:**
[a]Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, MALAYSIA. E-mail: sreenivasulu.sura@gmail.com[1]; ct_saleha@upm.edu.my[4]; aris@upm.edu.my[5]; mohdamir2183@gmail.com[6]; hudamohdnor@upm.edu.my[9]
[b]School of Medicine, Taylors University, Lakeside Campus, Bandar Sunway, Selangor, MALAYSIA.
E-mail: saravanan.jagadeesan@taylors.edu.my[2]
[c]Department of Human Biology, IMU, Kuala Lumpur, Malaysia
Email: thirupathirao@imu.edu.my [3]
[d]Department of Anatomy, Faculty of Medicine, MAHSA University, Jenjarom, Selangor, MALAYSIA. Email: sreenivasulu.sura@gmail.com[1]; krishnachaitanya@mahsa.edu.my[7]; ravindranadh@mahsa.edu.my [8]
[e]Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia, Bandar Tun Razak, Cheras, Kuala Lumpur, MALAYSIA Email: mohdamir2183@gmail.com[6]

*Corresponding Author: hudamohdnor@upm.edu.my

**Received:** May 11, 2025
**Accepted:** July 17, 2025
**Published:** December 12, 2025



DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

2024). In mice, it was observed that the combination of D-gal and aluminium chloride (AlCl3) causes cognitive impairment, increased amyloidogenic proteins, cholinergic system impairments, and the formation of neurofibrillary tangles (NFTs) and senile plaques (SP) (Mahdi et al., 2021). Thus, treating rats with D-gal and $AlCl_3$ has been shown to be a viable and cost-effective approach for developing AD models to evaluate potential anti-AD therapies (Xu et al., 2023).

Cannabis is a plant recognized for its psychoactive and therapeutic properties, which are primarily due to the presence of a wide variety of chemical components such as cannabinoids, terpenes, and flavonoids (Fordjour et al., 2023). Cannabinoids such as tetrahydrocannabinol (THC) induce the well-known "high" and alter mood and pain perception, while cannabidiol (CBD) provides therapeutic benefits without psychoactivity (Pagano et al., 2022; Prenderville et al., 2015; Valeri & Mazzon, 2021). Research conducted to investigate the effect of CBD on hyperphosphorylation of tau and amyloid pathways in AD models of rodents induced by AlCl3 and injecting beta amyloid demonstrated neuroprotective and anti-inflammatory effects (Bhunia et al., 2022; Tambe et al., 2023). CBD may help reduce some AD symptoms by lowering oxidative stress, inflammation, and neurodegeneration, all of which contribute to the disease's progression (Hickey et al., 2024). CBD has been shown in studies to improve cognitive function and reduce behavioural symptoms in AD models (Trojan et al., 2023). Its capacity to interact with the endocannabinoid system may also support neurotransmitter regulation and brain cell protection (Kamaruzzaman et al., 2023).

Despite the pharmacological benefits attributed to CBD, it is uncertain if CBD can potentially reduce neurotoxicity caused by D-gal and $AlCl_3$, and effectively prevent cognitive decline and neurodegeneration in rats. This study aims to investigate the potential therapeutic effects of CBD against D-gal and $AlCl_3$-induced cognitive impairments and structural brain alterations. The study also compared CBD's effects to those of donepezil, an FDA-approved medication for cognitive deficits associated with AD. However, the limitations of donepezil include only symptomatic relief, no impact on disease progression, and usefulness only in mild cases. Other side effects include gastrointestinal distress, muscle weakness, and bradycardia.

## 2. Materials and methodology

*2.1 Animals*

The study included 36 male albino Wistar rats (180-250g, 2-3 months old) purchased from Takrif Bistari Enterprise, Seri Kembangan, Malaysia. The rats were housed in climate-controlled cages with free access to food and water during a 12-hour light/dark cycle. The Institutional Animal Ethics Committee (UPM/IACUC/AUP-R017/2023) approved the study procedure, and it was conducted according to their authorized parameters.

*2.2 Chemicals*

CBD was obtained from Aktin Chemicals (China), and D-gal, AlCl3, and donepezil from Sigma-Aldrich (USA). All chemicals were of analytical grade. For intraperitoneal (i.p.) administration, D-gal was dissolved in distilled water (Chiroma et al., 2018); CBD was dissolved in Tween 80 (Feng et al., 2021). For oral dosing, AlCl3 and donepezil were dissolved in distilled water (Jagadeesan et al., 2019).

*2.3 Design of the experiment*

After seven days of acclimatization, the rats were randomly divided into six groups (n=6), as shown in Figure 1.

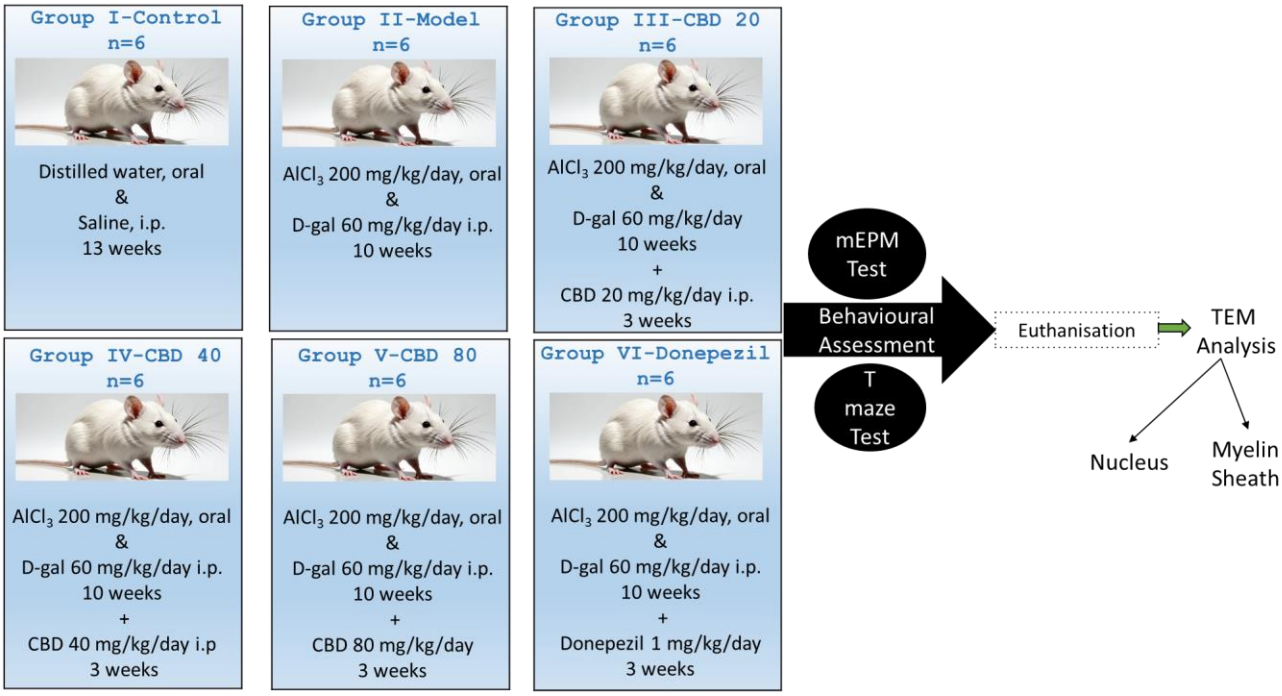


**Figure 1.** Experimental design; mEPM-Modified elevated plus maze.


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

The dosages of D-gal, AlCl3, and CBD used in this study were selected based on previous research and published literature (Chiroma et al., 2019; Khan et al., 2024). After a 91-day treatment period, the rats underwent behavioural testing, which included the modified Elevated Plus Maze Test and the T Maze Spontaneous Alternation. At the end of 13 weeks, the rats were sacrificed, and their hippocampal tissue was collected for TEM analysis to examine the nucleus and myelin sheath.

*2.4 Apparatus*

The experimental apparatus used in this study, consisting of a modified elevated plus maze and a T-maze, was constructed in the workshop of the Department of Human Anatomy, Faculty of Medicine and Health Sciences (FMHS), Universiti Putra Malaysia (UPM).

*2.5 Modified elevated plus maze Test (mEPM):*

The apparatus used in the experiment was a plus-shaped piece of dark plexiglas with two open arms (50 cm long, 10 cm wide) and two enclosed arms (50 cm long, 10 cm wide, 40 cm high) positioned opposite each other (Nabeshima & Kameyama, 1990). It was elevated 50 cm off the ground with a central square platform (10 × 10 cm) connecting the arms. The room was dimly illuminated by a 60 lx red halogen bulb. On the first day of the acquisition phase, each rat was placed at the end of an open arm, facing away from the centre, and allowed 90 seconds to explore and enter one of the enclosed arms. The time taken to enter was recorded as the Initial Transfer Latency (ITL). Once inside, rats remained for 20 seconds (Mutlu et al., 2011). If a rat did not enter an enclosed arm within 90 seconds, it was gently guided in. A rat was considered to have entered when all four paws crossed the entrance line. Retention sessions were conducted 24 hours (TL1) and 7 days (TL2) after the initial trial. If the rat did not enter within 90 seconds, TL1 or TL2 was recorded as 90 seconds, marking the test's end. Longer latencies suggested possible memory impairment, while shorter latencies indicated better memory (Raghavendra & Kulkarni, 2001). The apparatus was cleaned with 70% alcohol between tests to eliminate scent cues. Data were recorded using ANY-maze software.

*2.6 T maze Test for spontaneous alternation:*

The T-maze apparatus was constructed from dark Plexiglas, comprising a start arm (50 cm long, 16 cm wide) and two goal arms (50 cm long, 10 cm wide), extending perpendicularly. Each arm was enclosed by 30 cm high walls, and the maze featured an open top. Three guillotine doors were placed at the junctions of the arms. A central barrier extended 15 cm into the start arm, compelling rats to choose between the left or right goal arm (d'Isa et al., 2021). During testing, rats were placed at the start arm and permitted to choose a goal arm. After 30 seconds, the chosen arm was closed with a guillotine door, the middle barrier removed, and the rat gently returned to the start. The rat then faced away from the arms and was provided another choice. A correct choice occurred if the rat alternated arms, and only choices where all four paws entered the goal arm were recorded. Each rat performed the test 11 times, with 30-second intervals, resulting in ten spontaneous alternations (Deacon & Rawlins, 2006). Data were recorded using ANY-maze software.

*2.7 Transmission Electron Microscopy:*

Transmission electron microscopy (TEM) was employed to investigate the neuronal ultrastructure following neurodegeneration induced by a combination of D-gal and AlCl3, as well as to assess the neurotherapeutic effects of CBD. Hippocampal tissue was promptly extracted from the brains of decapitated rats using a cold plate (Lam et al., 2021). A 1 × 1 mm segment of the hippocampus was dissected and preserved in a 5% glutaraldehyde solution at 4 °C for 12 hours for conventional electron microscopy (Abdelmeguid et al., 2021). The hippocampal tissues were prepared and examined following the methods described by Ojo and Barsoum (Peng et al., 2013). The tissue samples were analysed using a TEM LEO LIBRA-120. Images of the hippocampus were captured from at least twelve random fields per rat group.

*2.8 Statistical analysis:*

The data were analysed using one-way ANOVA in GraphPad Prism version 6 software (ISI, USA). Tukey's post hoc test was performed after ANOVA to determine statistical significance among groups. A significance level of $p < 0.05$ was chosen. The results were presented as mean values with their corresponding standard deviation (mean ± SD), representing the central tendency and variability in the data. This comprehensive methodology ensured that the experimental results were rigorously assessed and that statistical interpretations were accurate.

## 3. Results

*3.1 CBD Mitigates Spatial Learning Deficits Induced by D-gal and $AlCl_3$:*

The therapeutic effects of CBD on spatial learning and memory impairment induced by D-gal and AlCl3 were first assessed using the mEPM. No significant differences in initial transfer latency (ITL) were observed among the various rat groups [$F = 0.6052$, $p = 0.6964$] (Fig. 2A). However, one-way ANOVA revealed significant differences in first transfer latency (TL1) values [$F (5, 30) = 6.396$, $p = 0.0004$] (Fig. 2B). Tukey's post hoc test showed a significant reduction in TL1 for the control group and CBD-treated groups (CBD 20: $p = 0.0056$; CBD 40: $p = 0.0087$; CBD 80: $p = 0.0013$) and donepezil group ($p = 0.0040$) compared with the model group of rats ($p = 0.0003$). Similarly, significant differences were observed in second transfer latency (TL2) values [$F (5, 30) = 6.018$, $p = 0.0006$] (Fig. 2C). Tukey's post hoc test indicated significant reductions in TL2 for the control, CBD groups (CBD 20: $p = 0.0150$; CBD 40: $p = 0.0064$; CBD 80: $p = 0.0009$) and donepezil group ($p = 0.0055$) compared to the model group ($p = 0.0009$).

*3.2 CBD attenuates hippocampal dysfunction induced by D-gal and $AlCl_3$ in the T-Maze spontaneous alternation test:*

Rats with hippocampal lesions generally scored less than 60% across several trials. Control groups generally achieved more than 80% accurate alternations in the T-maze when the right strains of rats were used, and the right conditions were met. The control group in this trial obtained 83.33% correct alternations, followed


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

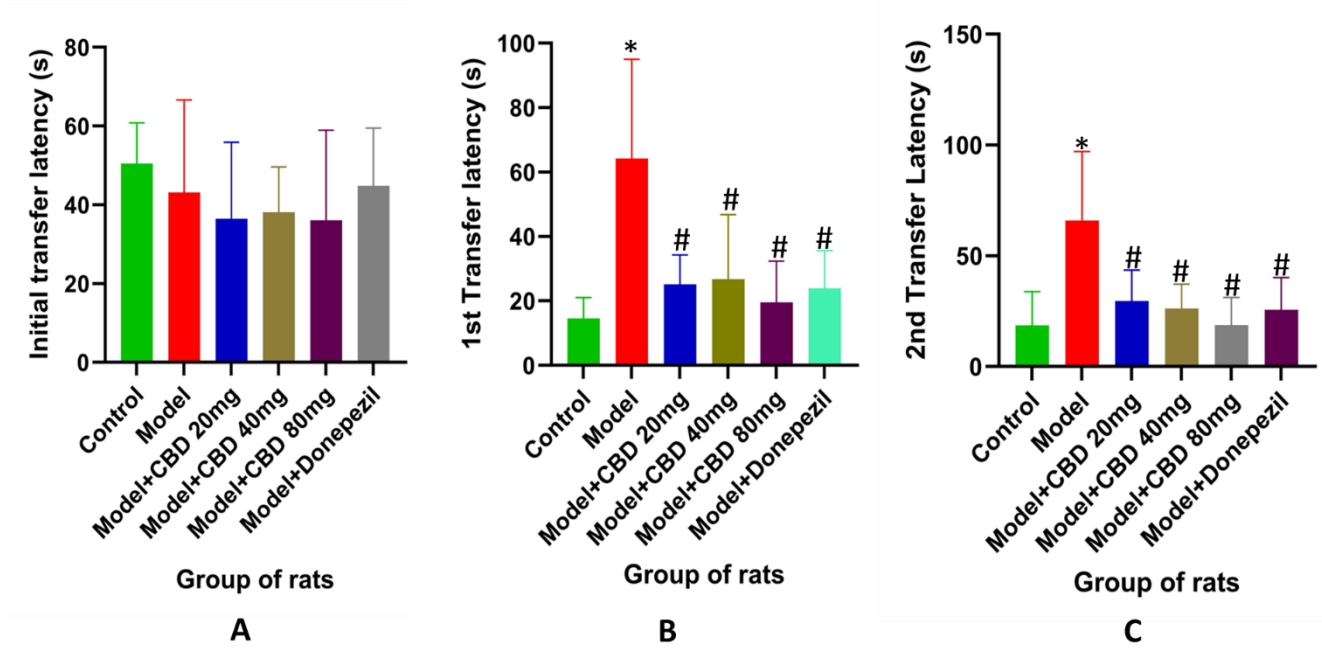


**Figure 2:** Modified Elevated Plus Maze. Effects of *CBD* on spatial learning and memory in rats induced with D-galactose and aluminium chloride. Panel A shows the initial transfer latency recorded on the first day of testing. Panel B displays the first transfer latency measured 24 hours after the initial trial, while Panel C illustrates the second transfer latency assessed 7 days post-initial trial. Data are presented (n = 6). Significant differences are indicated by *p < 0.05 compared to the Model group.

by the model group at 43.33%, the donepezil group at 70%, the CBD 20 group at 63.33%, the CBD 40 group at 73.33%, and the CBD 80 group at 80%. According to Tukey's post hoc test, significant variations in alternation rates were found using a one-way ANOVA test ($F(5, 26) = 22.76$, $p < 0.0001$) (Fig. 3).

In comparison to the model group (43.33 ± 4.30, $p < 0.0001$), the control group (83.33 ± 3.0), CBD 20 group (63.33 ± 2.65, $p = 0.0057$), CBD 40 group (73.33 ± 4.47, $p = 0.0002$), CBD 80 group (80.0 ± 3.79, $p < 0.0001$), and donepezil group (73.33 ± 3.79, $p < 0.0002$) all showed significantly higher accurate alternations, according to Tukey's post hoc test.

*3.3 CBD Alleviates Ultrastructural Morphological Alterations in the Hippocampus Induced by D-gal and $AlCl_3$:*

TEM investigations were conducted to confirm the impact of CBD on neuronal ultrastructure following rats' hippocampal D-gal and AlCl3-induced neurodegeneration.

*3.4 Nucleus:*

Electron photomicrographs of the hippocampus nucleus from each group of rats are presented in Figure 4. The nucleus in the control group (Fig. 4A) showed normal features, including double-layered nuclear membranes, intact nucleoli, and evenly distributed chromatin. Conversely, pyknosis, crescent formation, degraded chromatin, damaged nucleoli, and deformed nuclear membranes were among the morphological changes observed after treatment with D-gal and AlCl3 in the nucleus of pyramidal neurons (Fig. 4B). Some of these nuclear abnormalities were attenuated by treatment with CBD or donepezil (Fig. 4C–F).

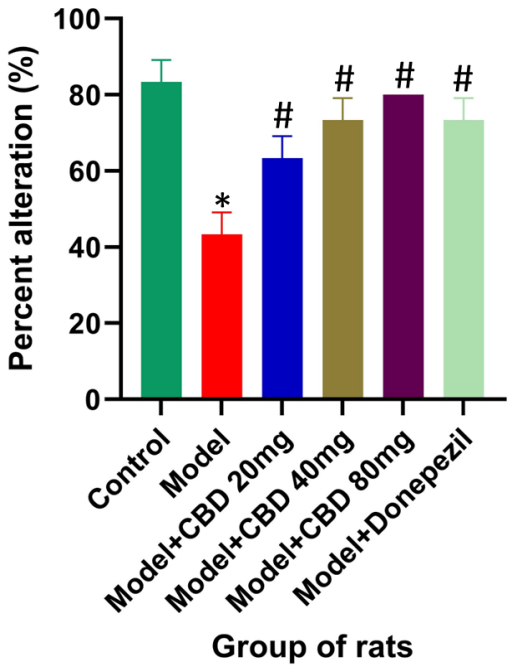


**Figure 3:** T Maze Spontaneous Alternation. Effects of *CBD* on hippocampal dysfunction caused by D-galactose and aluminium chloride in rats. Data are presented as mean ± SEM (n=6). # indicates *p < 0.05 for comparisons between Control, CBD 20, CBD 40, CBD 80 and Donepezil groups versus Model group.


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

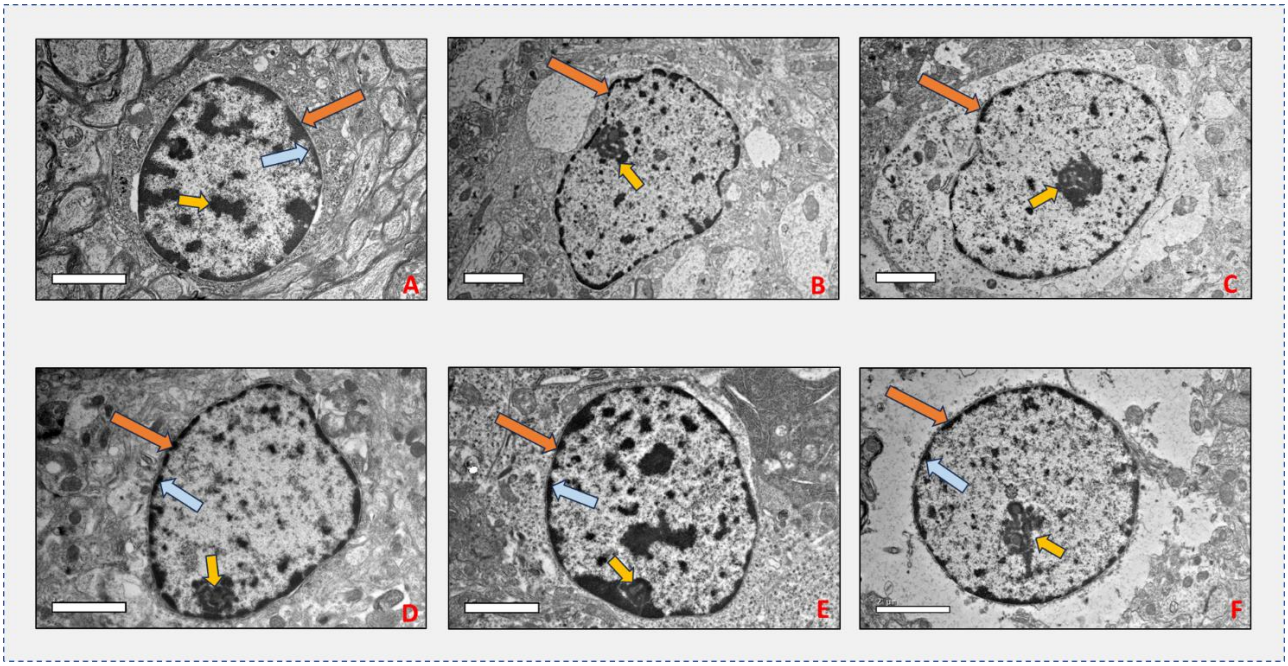


**Figure 4:** TEM photomicrographs of the rat's hippocampus showing the nucleus and its components. A) Control group of rats showing nucleolus (yellow arrow), evenly distributed chromatin and double nuclear membrane (orange and blue arrows), B) Model group of rats showing pyknotic nucleus and crescent formation and distorted nuclear membrane, C-E) CBD 20, 40 & 80 group of rats showing normal nucleus with double nuclear membrane F) Donepezil group of rats showing nucleus with normal nuclear membrane and nucleolus

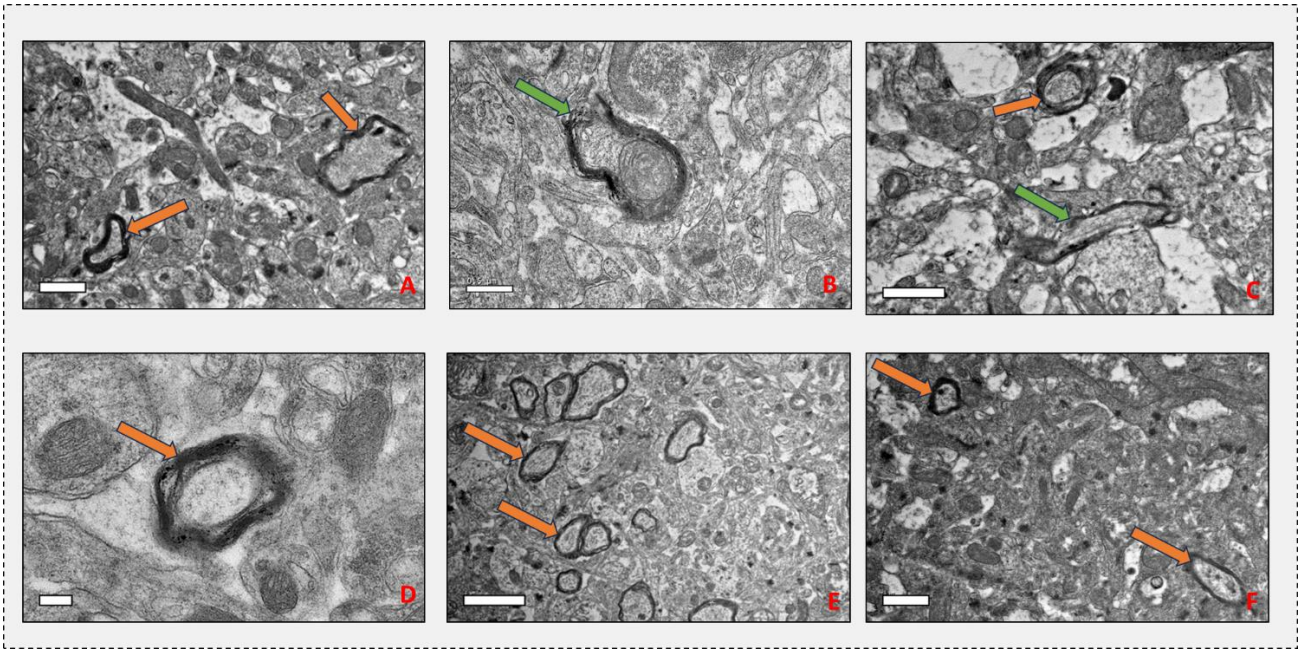


**Figure 5:** TEM photomicrographs of rat hippocampus showing myelin sheath, A) The control group of rats showed normal myelin sheaths that appeared dense, thick, and tightly wrapped around their axons (orange arrows). B) The model group of rats showing discontinuous myelin (green arrow). C-E) CBD 20 group shows both normal myelin (Orange arrow) and slightly disrupted myelin sheath (green arrow), D-F) CBD 40, 80, and donepezil group of rats showing normal myelin sheath tightly wrapped around an axon.


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

The therapeutic effects of CBD against neurotoxicity caused by D-gal and AlCl3 were assessed by analysing the ultrastructure of the myelin sheath. The myelin sheaths in the control rats were continuous, thick, highly electron-dense, and firmly wrapped around the axonal membranes (Fig. 5A). In contrast, animals given D-gal and AlCl3 treatments exhibited various myelin abnormalities. Among the prominent myelin defects observed were myelin sheath disintegration (Fig. 5B); CBD and donepezil administration helped in reducing these defects (Fig. 5C-5F).

## 4. Discussion

Chronic administration of D-gal or AlCl3 in rats induces aging-like changes, including cholinergic dysfunction, cognitive impairments, oxidative stress, and advanced glycation end product accumulation (Chiroma et al., 2018; Stanciu et al., 2020; Di Benedetto et al., 2022). This combination causes cognitive deficits and hippocampal pyramidal neuron degeneration (Khan et al., 2024). In this study, rats treated with D-gal and AlCl3 exhibited hippocampal ultrastructural alterations and learning and memory impairments, making this rat model valuable for studying Alzheimer's disease (AD)-related conditions. Additionally, the co-administration of CBD significantly reduced cognitive deficits and ameliorated the morphological abnormalities caused by D-gal and AlCl3.

To further assess cognitive function, the mEPM test was employed to evaluate anxiety, spatial learning, and memory in rats (Walf & Frye, 2007). Previous studies have demonstrated that D-gal and AlCl3 impair spatial learning and memory in rats (Chiroma et al., 2018). The mEPM results in this study corroborated these findings, showing that CBD significantly improved spatial memory and learning in rats, comparable to the effects of donepezil. These results indicate CBD's potential in enhancing cognitive performance.

The T-maze test was also utilized to evaluate cognitive function, particularly to identify hippocampal dysfunction in spontaneous and rewarded alternation tasks (Deacon & Rawlins, 2006; d'Isa et al., 2021). Rats treated with D-gal and AlCl3 performed poorly on the T-maze spontaneous alternation task, with less than 60% correct alternations. However, the CBD and donepezil groups achieved scores higher than 60%, with the 80 mg/kg CBD group demonstrating results comparable to donepezil (Tournier et al., 2021). These findings align with previous studies indicating that CBD enhances learning and memory retention (Peres et al., 2016; Singh et al., 2023; Watt, 2020).

Electron microscopy (TEM) analysis provided clear evidence of the neurotoxic effects of D-gal and AlCl3 treatment and the neurotherapeutic potential of CBD. The control group's hippocampal nuclei displayed normal characteristics, including intact nucleoli and evenly distributed chromatin. In contrast, the D-gal and AlCl3-treated group exhibited severe nuclear abnormalities, including pyknosis, crescent formation, and disrupted nuclear membranes, consistent with previous research on the neurotoxic effects of these substances (Chiroma et al., 2019). However, CBD and donepezil administration mitigated these nuclear abnormalities, suggesting their potential therapeutic roles in maintaining cellular health and nuclear integrity.

The therapeutic effects of CBD were further corroborated by the analysis of myelin sheath integrity. Rats treated with D-gal and AlCl3 showed significant myelin abnormalities, including swelling, disintegration, and detachment from axons. In contrast, the control group's myelin remained intact. Treatment with donepezil and CBD decreased these myelin abnormalities, with the 80 mg/kg CBD group showing the most favorable results. This aligns with prior studies indicating that CBD possesses myelin-protective properties, potentially reducing damage caused by neurotoxic substances like D-gal and AlCl3 (Navarrete et al., 2021). These findings emphasize the neurotherapeutic potential of CBD in preventing neurodegeneration and maintaining myelin integrity.

Together, these results suggest that CBD provides significant neuroprotective benefits by improving cognitive function, preserving neuronal integrity, and mitigating the neurotoxic effects of D-gal and AlCl3. The combination of CBD with established treatments such as donepezil may offer a promising strategy to alleviate the effects of Alzheimer's disease and related neurodegenerative disorders.

## 5. Conclusion

This study shows that continuous administration of D-galactose and aluminium chloride to rats causes severe cognitive deficits as well as histological and ultrastructural abnormalities in the hippocampus. The results indicate that Cannabidiol (CBD) effectively reduces these cognitive deficits, as demonstrated by improved performance in the modified Elevated Plus Maze test and greater alterations in the T-maze spontaneous alternation test. Furthermore, CBD treatment diminished the histopathological hippocampal abnormalities detected and confirmed by transmission electron microscopy. The findings of this study suggest CBD has potential as an alternative treatment for AD. Further research is needed to investigate the other pathways involved in the pathogenesis of AD.

## 6. Acknowledgements

The authors would like to express their gratitude to Universiti Putra Malaysia for their financial support of this research project (Grant number GP-IPM/2021/ 9700000).

## 7. References

Abdelmeguid, N. E., Khalil, M. I. M., Elhabet, R., Sultan, A. S., & Salam, S. A. (2021). Combination of docosahexaenoic acid and Ginko biloba extract improves cognitive function and hippocampal tissue damages in a mouse model of Alzheimer's disease. *Journal of Chemical Neuroanatomy, 116*, 101995. https://doi.org/10.1016/j.jchemneu.2021.101995

Bhunia, S., Kolishetti, N., Arias, A. Y., Vashist, A., & Nair, M. (2022). Cannabidiol for neurodegenerative disorders: A comprehensive review. *Frontiers in Pharmacology, 13*, 989717. https://doi.org/10.3389/fphar.2022.989717


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

Buccellato, F. R., D'anca, M., Fenoglio, C., Scarpini, E., Galimberti, D., & Barone, E. (2021). Role of oxidative damage in Alzheimer's disease and neurodegeneration: From pathogenic mechanisms to biomarker discovery. *Antioxidants, 10*(9). https://doi.org/10.3390/antiox1009

Chiroma, S. M., Hidayat Baharuldin, M. T., Mat Taib, C. N., Amom, Z., Jagadeesan, S., Adenan, M. I., & Mohd Moklas, M. A. (2019). Protective effect of Centella asiatica against D-galactose and aluminium chloride induced rats: Behavioral and ultrastructural approaches. *Biomedicine and Pharmacotherapy, 109*, 853–864. https://doi.org/10.1016/j.biopha.2018.10.111

Chiroma, S. M., Mohd Moklas, M. A., Mat Taib, C. N., Baharuldin, M. T. H., & Amon, Z. (2018). d-Galactose and aluminium chloride induced rat model with cognitive impairments. *Biomedicine & Pharmacotherapy, 103*, 1602–1608. https://doi.org/10.1016/j.biopha.2018.04.152

Deacon, R. M. J., & Rawlins, J. N. P. (2006). T-maze alternation in the rodent. *Nature Protocols, 1*(1), 7–12. https://doi.org/10.1038/nprot.2006.2

Di Benedetto, G., Burgaletto, C., Bellanca, C. M., Munafò, A., Bernardini, R., & Cantarella, G. (2022). Role of microglia and astrocytes in Alzheimer's disease: From neuroinflammation to Ca2+ homeostasis dysregulation. *Cells, 11*(17). https://doi.org/10.3390/cells11172728

d'Isa, R., Comi, G., & Leocani, L. (2021). Apparatus design and behavioural testing protocol for the evaluation of spatial working memory in mice through the spontaneous alternation T-maze. *Scientific Reports, 11*(1). https://doi.org/10.1038/s41598-021-00402-7

Feng, W., Qin, C., Cipolla, E., Lee, J. B., Zgair, A., Chu, Y., Ortori, C. A., Stocks, M. J., Constantinescu, C. S., Barrett, D. A., Fischer, P. M., & Gershkovich, P. (2021). Inclusion of medium-chain triglyceride in lipid-based formulation of cannabidiol facilitates micellar solubilization in vitro, but in vivo performance remains superior with pure sesame oil vehicle. *Pharmaceutics, 13*(9). https://doi.org/10.3390/pharmaceutics13091349

Flores-Cuadra, J. A., Madrid, A., Fernández, P. L., Pérez-Lao, A. R., Oviedo, D. C., Britton, G. B., & Carreira, M. B. (2021). Critical review of the Alzheimer's disease non-transgenic models: Can they contribute to disease treatment? *Journal of Alzheimer's Disease, 82*(s1), S227–S250. https://doi.org/10.3233/JAD-200870

Fordjour, E., Manful, C. F., Sey, A. A., Javed, R., Pham, T. H., Thomas, R., & Cheema, M. (2023). Cannabis: A multifaceted plant with endless potentials. *Frontiers in Pharmacology, 14*. https://doi.org/10.3389/fphar.2023.1200269

Ganguly, U., Kaur, U., Chakrabarti, S. S., Sharma, P., Agrawal, B. K., Saso, L., & Chakrabarti, S. (2021). Oxidative stress, neuroinflammation, and NADPH oxidase: Implications in the pathogenesis and treatment of Alzheimer's disease. *Oxidative Medicine and Cellular Longevity, 2021*. https://doi.org/10.1155/2021/7086512

Hickey, J. P., Collins, A. E., Nelson, M. L., Chen, H., & Kalisch, B. E. (2024). Modulation of oxidative stress and neuroinflammation by cannabidiol (CBD): Promising targets for the treatment of Alzheimer's disease. *Current Issues in Molecular Biology, 46*(5), 4379–4402. https://doi.org/10.3390/cimb46050266

Jagadeesan, S., Chiroma, S. M., Mohd Moklas, M. A., Hidayat Baharuldin, M. T., Mat Taib, C. N., Amom, Z., Vishnumukkala, T., Thomas, W., & Mahdi, O. (2022). Centella asiatica L. Urban protects against morphological aberrations induced by chronic unpredictable mild stress in rat's hippocampus via attenuation of oxidative stress. *Egyptian Journal of Basic and Applied Sciences, 9*(1), 324–339. https://doi.org/10.1080/2314808X.2022.2091265

Jagadeesan, S., Gopalakrishna, P. K., Sura, S., Karikalan, B., Dandala, K. C. R., Ravindranadh, G., Moklas, M. A. M., & Vishnumukkala, T. (2024). Prevention of neuronal damage in brains of chronic stress induced male Wistar rats administering Centella asiatica (L) Urban. *Journal of the Anatomical Society of India, 73*(3), 204–213. https://doi.org/10.4103/jasi.jasi_80_24

Jagadeesan, S., Musa Chiroma, S., Baharuldin, M. T. H., Taib, C. N. M., Amom, Z., Adenan, M. I., & Moklas, M. A. M. (2019). Centella asiatica prevents chronic unpredictable mild stress-induced behavioral changes in rats. *Biomedical Research and Therapy, 6*(6), 3233–3243. https://doi.org/10.15419/bmrat.v6i6.550

Ju, Y., & Tam, K. (2022). Pathological mechanisms and therapeutic strategies for Alzheimer's disease. *Neural Regeneration Research, 17*(3), 543–549. https://doi.org/10.4103/1673-5374.320970

Kamaruzzaman, M. A., Romli, M. H., Abas, R., Vidyadaran, S., Hidayat Baharuldin, M. T., Nasaruddin, M. L., Thirupathirao, V., Sura, S., Warsito, K., Mohd Nor, N. H., Azwaruddin, M. A., Alshawsh, M. A., & Mohd Moklas, M. A. (2023). Regulatory role of the endocannabinoid system on glial cells toward cognitive function in Alzheimer's disease: A systematic review and meta-analysis of animal studies. *Frontiers in Pharmacology, 14*. https://doi.org/10.3389/fphar.2023.1053680

Khan, K., Emad, N. A., & Sultana, Y. (2024). Inducing agents for Alzheimer's disease in animal models. *Journal of Exploratory Research in Pharmacology, 000*(000), 000–000. https://doi.org/10.14218/jerp.2023.00028

Lam, J., Katti, P., Biete, M., Mungai, M., Ashshareef, S., Neikirk, K., Lopez, E. G., Vue, Z., Christensen, T. A., Beasley, H. K., Rodman, T. A., Murray, S. A., Salisbury, J. L., Glancy, B., Shao, J., Pereira, R. O., Abel, E. D., & Hintonjr., A. (2021). A universal approach to analyzing transmission electron microscopy with imagej. *Cells, 10*(9). https://doi.org/10.3390/cells10092177


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)

Luo, L., Yan, T., Yang, L., & Zhao, M. (2024). Aluminum chloride and D-galactose induced a zebrafish model of Alzheimer's disease with cognitive deficits and aging. *Computational and Structural Biotechnology Journal, 23*, 2230–2239. https://doi.org/10.1016/j.csbj.2024.05.036

Mahdi, O., Chiroma, S. M., Baharuldin, M. T. H., Nor, N. H. M., Taib, C. N. M., Jagadeesan, S., Devi, S., & Moklas, M. A. M. (2021). Win55,212-2 attenuates cognitive impairments in $AlCl_3$ + D-galactose-induced Alzheimer's disease rats by enhancing neurogenesis and reversing oxidative stress. *Biomedicines, 9*(9), 1270. https://doi.org/10.3390/biomedicines9091270

Mutlu, O., Ulak, G., Celikyurt, I. K., Tanyeri, P., Akar, F. Y., & Erden, F. (2011). Effects of olanzapine and clozapine on memory acquisition, consolidation, and retrieval in mice using the elevated plus maze test. *Neuroscience Letters, 501*(3), 143–147. https://doi.org/10.1016/j.neulet.2011.07.004

Nabeshima, T., & Kameyama, T. (1990). Utility for the effects of Jiro Itoh 3, of an elevated plus-maze evaluation of memory in mice: Of nootropics, scopolamine, and electroconvulsive shock. *Psychopharmacology, 101*, Springer-Verlag.

Nascimento, A. B., Rodrigues, A. L. S., & Santos, A. R. S. (2020). The role of cannabinoids in the regulation of cognitive processes: A comprehensive review. *Pharmacology & Therapeutics, 208*, 107478. https://doi.org/10.1016/j.pharmthera.2019.107478

Schmitt, J. M., de Souza, L. P., & Silva, M. L. (2022). Neuroinflammation in Alzheimer's disease and potential therapeutic approaches. *Neurochemistry International, 153*, 104254. https://doi.org/10.1016/j.neuint.2021.104254

Sheppard, H. S., Perry, C. M., & Mitchell, S. J. (2023). The effects of cannabidiol on cognitive function and neurodegeneration: A systematic review and meta-analysis. *Journal of Neurochemistry, 165*(1), 1-18. https://doi.org/10.1111/jnc.15529

Solis, E., Zhang, J., & Reiner, D. J. (2021). Long-term memory improvement in Alzheimer's disease models: Cannabidiol and the potential for neurogenesis. *Journal of Alzheimer's Disease, 79*(2), 305–319. https://doi.org/10.3233/JAD-200966

Wang, Y., & Liu, X. (2021). Cannabis-derived compounds in Alzheimer's disease therapy: Mechanisms, evidence, and challenges. *Frontiers in Neuroscience, 15*, 668544. https://doi.org/10.3389/fnins.2021.668544

Zhang, R., & Wang, Y. (2023). Recent advances in the molecular mechanisms of neurodegeneration in Alzheimer's disease and their therapeutic implications. *Neuropharmacology, 189*, 108460. https://doi.org/10.1016/j.neuropharm.2021.108460

Zhang, J., Shao, J., & Yang, M. (2022). Targeting the endocannabinoid system in neurodegenerative diseases: A critical review of current findings. *Frontiers in Pharmacology, 13*, 904500. https://doi.org/10.3389/fphar.2022.904500

Zhuang, X., & Du, W. (2023). Alzheimer's disease and neuroinflammation: The role of cannabinoids and future therapeutic perspectives. *Neuroscience Bulletin, 39*(2), 215–226. https://doi.org/10.1007/s12264-023-00887-9


DOI: https://doi.org/10.22452/mjs.vol44sp1.14
Malaysian Journal of Science 44 (Special Issue 1): 89-96 (December 2025)