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Neuroprotective Effects of Indomethacin Through PPAR-γ Modulation in an Experimental Model of Alzheimer's Disease

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Abstract: ***Background****: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, and behavioral dysfunction. Despite extensive research, current therapeutic options remain largely symptomatic. Streptozotocin (STZ)-induced intracerebroventricular (ICV) administration is a well-established experimental model that mimics sporadic AD-like pathology, including cognitive deficits and metabolic dysfunction. Modulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) has emerged as a potential neuroprotective strategy. Bisphenol A diglycidyl ether (BADGE), a PPAR-γ modulator, was investigated for its possible role in attenuating AD-like changes.*

Objective: *To evaluate the neuroprotective potential of BADGE alone and in combination with indomethacin in STZ-induced Alzheimer's disease in rats using behavioral and cognitive assessments.*

Material and Methods: *AD was induced in male Sprague Dawley rats via intracerebroventricular administration of streptozotocin (3 mg/kg). Animals were divided into normal control, negative control, indomethacin-treated, and BADGE + indomethacin groups. Behavioral evaluations were performed using the Morris Water Maze (escape latency, retention time) and Elevated Plus Maze (transfer latency). Data were analyzed using one-way ANOVA followed by Dunnett's test.*

Results: *STZ administration caused significant impairment in learning and memory, evidenced by increased escape latency and transfer latency and decreased retention time compared to the normal control group ($p < 0.01$). Indomethacin treatment significantly improved cognitive performance by reducing escape and transfer latency and increasing retention time ($p < 0.01$). However, BADGE co-administration with indomethacin showed attenuated or non-significant improvements in behavioral parameters compared to the STZ group ($p > 0.05$), indicating reduced neuroprotective efficacy.*

In this study when BADGE given along with indomethacin in AD animal changes their non-significant related all behavioural parameters compared to negative control group. This shows the involvement of PPAR-γ receptor and proves indomethacin shows anti-AD through its action on PPAR-γ receptor

Keywords: Alzheimer's disease; Streptozotocin; Indomethacin; BADGE; PPAR-γ; Morris Water Maze; Elevated Plus Maze; Cognitive impairment; Neuroinflammation; Rats.

I. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia worldwide. It is characterized by progressive impairment of memory, cognition, learning ability, and behavioural functions, ultimately affecting an individual's capacity to perform daily activities. The prevalence of AD is increasing rapidly with the aging population, making it a major global health concern. Despite extensive research, currently available therapies provide only symptomatic relief and do not effectively halt disease progression (Lane et al., 2018).

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The pathological hallmarks of AD include extracellular deposition of amyloid-beta (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles. These abnormalities contribute to synaptic dysfunction, neuronal loss, neuroinflammation, oxidative stress, and cognitive decline. In addition to the amyloid and tau hypotheses, growing evidence suggests that chronic inflammation and metabolic dysfunction play crucial roles in AD pathogenesis (Knopman et al., 2021; Sharma et al., 2024).

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-activated nuclear receptor involved in regulating glucose metabolism, lipid homeostasis, oxidative stress, and inflammatory responses. Activation of PPAR-γ has been shown to suppress neuroinflammation, reduce amyloid burden, improve mitochondrial function, and enhance neuronal survival. Therefore, PPAR-γ has emerged as a promising therapeutic target for the management of neurodegenerative disorders, particularly Alzheimer's disease (Abeysinghe et al., 2020).

Bisphenol A diglycidyl ether (BADGE) is a synthetic compound widely recognized as a modulator of PPAR-γ signaling. Recent computational and experimental studies have indicated that compounds interacting with PPAR-γ may exert neuroprotective effects through modulation of inflammatory pathways and reduction of oxidative stress. However, the therapeutic potential of BADGE in Alzheimer's disease remains insufficiently explored and warrants further investigation. (Lindkvist, T., et.al., (2020), (Wright, H. M., et.al., (2000)

Animal models play a vital role in evaluating novel therapeutic strategies for AD. Intracerebroventricular administration of streptozotocin (ICV-STZ) is a well-established experimental model that reproduces several pathological and behavioural features of sporadic Alzheimer's disease, including impaired glucose metabolism, oxidative stress, neuroinflammation, cholinergic dysfunction, and memory deficits. This model is therefore widely used for preclinical assessment of potential anti-Alzheimer agents (Moreira-Silva et al., 2019). The present study was designed to investigate the neuroprotective potential of Bisphenol A diglycidyl ether (BADGE) in an ICV-STZ-induced rat model of Alzheimer's disease. Molecular docking studies were performed to evaluate the interaction of BADGE with the PPAR-γ receptor, followed by behavioural, biochemical, and histopathological assessments to determine its effects on cognitive impairment and neurodegeneration. The findings of this study may provide insights into the therapeutic relevance of PPAR-γ modulation as a novel approach for the treatment of Alzheimer's disease.

II. MATERIALS AND METHODS

2.2 In Vivo Study

2.2.1 Animals

8 weeks old healthy male Sprague-Dawley rats (weighing 170-220 gm) were used for this study. Rats were housed in polypropylene cages with wire mesh top and husk bedding and maintain under control condition of light (12h – light, 12h - dark), temperature (25 ± 2 ˚C), and humidity (60 ± 5 %) and fed with a standard pellet diet and water. The experiments were performed during day (8.00 – 16.00 hrs.). The rats were housed and treated according to the rules and regulations of CCSEA and IAEC. The protocol for all the animal study was approved by Institutional Animal Ethics Committee (IAEC) with research project number 650/Po/Re/S-2002/2026/CCSEA/05.

2.2.2 Experimental Design

A total of 24 rats were randomly divided into four groups, with six animals in each group.

Table: -1 Experimental protocol

Sr. No.	Group	Treatment	Doses	No. of Rats	Route of Administration	References
	Normal Control	Saline treated 0.9 %	1 ml/kg	6	ICV	Oria et.al., (2023)
	Negative Control	Streptozotocin	1-3mg/kg	6	ICV	More, S. A., et.al (2026)

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	Indomethacin	Streptozotocin +Indomethacin	3mg/kg+ 4mg/kg	6	STZ-ICV Indomethacin-IP	Ho, N., et.al (2015), Kumar, A., et.al (2018)
	Indomethacin+	Streptozotocin +Bisphenol A Diglycidyl ether +Indomethacin	3mg/kg +30mg/kg 4mg/kg+	6	STZ-ICV BADGE-IP Indomethacin-IP	Wang, Y., et.al (2019), Churi, S. B., et.al (2008)

An experimental model of Alzheimer's disease was established in adult male Sprague Dawley rats through intracerebroventricular (ICV) administration of streptozotocin (STZ). The animals were anesthetized using ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and positioned in a stereotaxic frame. STZ was freshly dissolved in sterile normal saline immediately before use to ensure stability. Using stereotaxic coordinates corresponding to the lateral ventricles, STZ (3 mg/kg) was delivered bilaterally at a controlled rate of 1 µL/min, with a total volume of 2 µL injected into each ventricle. Following administration, the injection needle was maintained in position for approximately 2 min to minimize solution reflux before gradual withdrawal. The surgical wound was closed with sterile sutures, and animals were carefully observed during the postoperative period until complete recovery. This protocol is widely employed to reproduce cognitive deficits and neurodegenerative alterations resembling sporadic Alzheimer's disease in rodents (Moreira-Silva et al., 2019; Akhtar et al., 2020).

2.2.3 Behavioral Assessments

a) Morris Water Maze (MWM): Spatial learning and memory performance were assessed using the Morris water maze paradigm, which consists of a circular pool containing a concealed platform beneath the water surface. Memory retention and learning ability were determined by measuring the time required to locate the platform (escape latency) and the duration spent in the target quadrant during the probe trial (Morris, 1984; Vorhees & Williams, 200)

b) Elevated Plus Maze (EPM): The Elevated Plus Maze test was employed to investigate anxiety-like behaviour and learning ability in rats. The apparatus consisted of elevated open and closed arms arranged in a plus-shaped configuration. Transfer latency from the open arm to the closed arm was measured on Days 0 and 14 and analysed using Image EP software as an indicator of memory and anxiety levels (Pellow et al., 1985; Walf & Frye, 2007).

2.2.6 Statistical Analysis

All data were expressed as the mean ± standard deviation. For statistical Analysis of the rats, group mean was compared by one-way (ANOVA) followed by Dunnett's test, $p<0.01$ was considered as significant value.

III. RESULTS

3.2 In Vivo Behavioral Results

3.2.1 Morris Water Maze (MWM)

Table 2: - Effect of Indomethacin on escape latency (EL) of rats in MWM apparatus

Group	Escape Latency Day 0 (s)	Escape Latency Day 14 (s)	Escape Latency Day 21 (s)
Normal Control	15 ± 1.78	14.16 ±1.94	14±1.41
Negative Control	15.33± 1.36^{NS}	21.33 ± 1.21$^{@}$	37.33±5.22$^{@}$

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(Stz-3mg/kg)			
Indomethacin (4mg/kg)	14.16 ± 2.13 ^{NS}	16.16 ± 2.13**	15.16±2.13**
BADGE+INDOMETHACIN (30mg/kg)	14.5 ± 2.34 ^{NS}	19.83 ± 0.75^{NS}	34.33±4.80^{NS}

A] Escape Latency: -

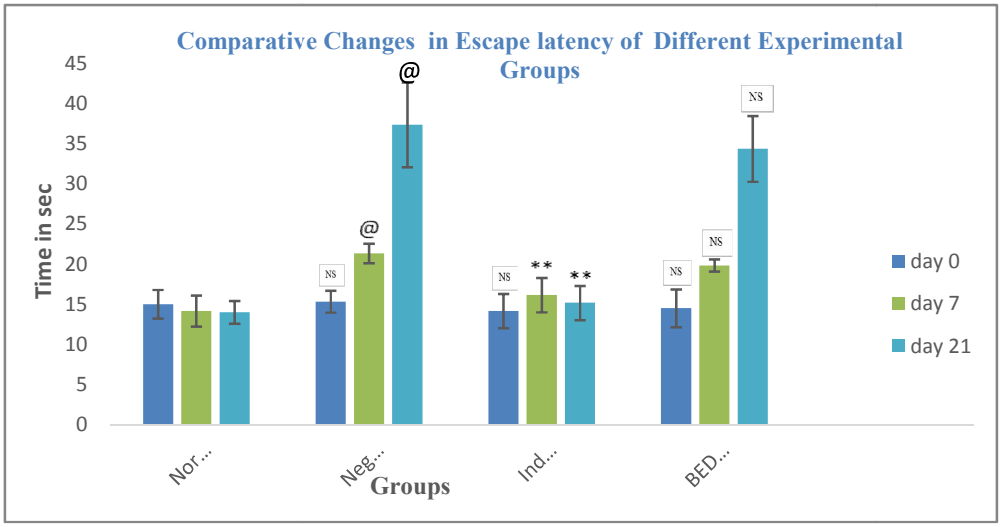

Figure 1: - Effect of Indomethacin on escape latency of rats in EPM apparatus

All values are expressed as Mean ± SD $^{@}p<0.01$ Highly Significant increase transfer latency was observed compared to normal control group. $^{**}p<0.01$ Significant decrease in transfer latency as compared to Negative control group. ^{NS} $p>0.05$ non-significant difference in transfer latency as compared to negative control group.

Escape latency values were expressed as Mean ± SD (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test, with $p < 0.05$ considered statistically significant. No significant differences in escape latency were observed among the groups on Day 0, indicating comparable baseline performance before disease induction and treatment administration. During the experimental period, the negative control group exhibited a highly significant increase in escape latency on Days 7 and 21 compared with the normal control group (@$p < 0.01$), indicating impaired spatial learning and memory. Treatment with indomethacin significantly reduced escape latency relative to the negative control group (** $p < 0.01$), with a progressive improvement observed from Day 7 to Day 21. Co-administration of BADGE (Bisphenol A Diglycidyl Ether) with indomethacin resulted in a non-significant increase in escape latency compared with the negative control group (NS, $p > 0.05$), suggesting attenuation of the cognitive benefits produced by indomethacin. The normal control group showed no significant changes in escape latency throughout the study period (NS, $p > 0.05$).3.2.2 Elevated Plus Maze (EPM)

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B] Retention Time

Table 3: - Effect of indomethacin on retention time (RT) of rats in MWM apparatus

Group	Retention Time Day 0 (s)	Retention Time Day 14 (s)	Retention Time Day 1 (s)
Normal Control	33.83 ± 3.430	35.22± 2.082	36.02±1.317
Negative Control (Stz 3 mg/Kg)	34.66± 3.011 NS	29.33 ± 3.077*	24.66 ±3.011@
Indomethacin (4mg /kg)	35.16 ± 4.021 NS	29.5 ± 3.728**	60.66 ± 2.160**
BADGE + Indomethacin (30 mg/kg/4mg/kg)	35.83 ± 3.869 NS	31.66 ± 3.559NS	26 ± 2.828 NS

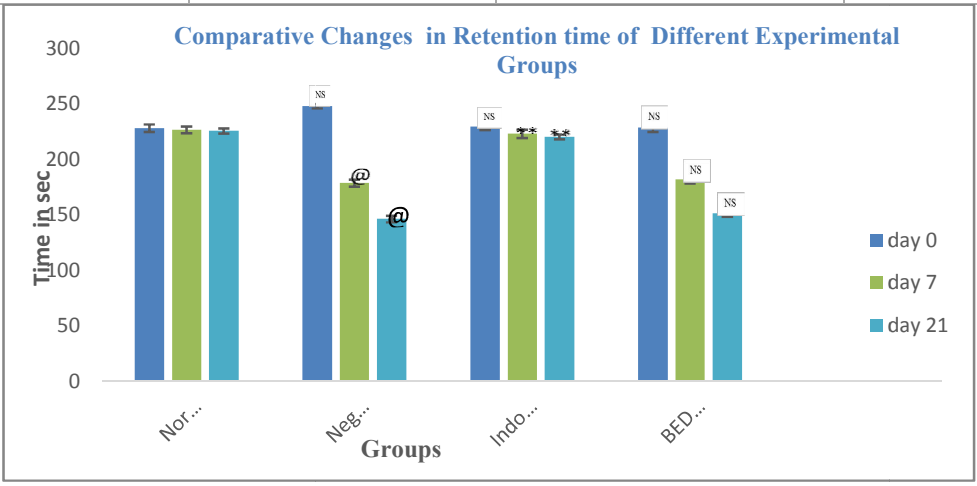

Figure 2: - Effect of indomethacin on retention time of rats in MWM apparatus

All values are expressed as Mean ± SD $^{@}p<0.01$ Significant decrease in retention time was observed compared to normal control group. $^{**}p<0.01$ Significant increase in in retention time as compared to Negative control group. ^{NS} $p>0.05$ non-significant increase in in retention time as compared to negative control group.

Retention time data were expressed as Mean ± SD (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test, with $p < 0.05$ considered statistically significant. No significant differences in retention time were observed among the experimental groups on Day 0 (NS, $p > 0.05$), indicating comparable baseline cognitive performance prior to disease induction and treatment administration. During the study period, the negative control group exhibited a significant reduction in retention time on Days 7 and 21 compared with the normal control group (@$p < 0.01$), reflecting impaired memory retention. In contrast, treatment with indomethacin significantly increased retention time relative to the negative control group (** $p < 0.01$), indicating improvement in memory function. Co-administration of BADGE (Bisphenol A Diglycidyl Ether) with indomethacin produced only a non-significant increase in retention time compared with the negative control group (NS, $p > 0.05$). The normal control group showed no significant changes in retention time throughout the experimental period (NS, $p > 0.05$), demonstrating stable memory performance.

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C] Transfer Latency

Table 4: - Effect of indomethacin on retention time (RT) of rats in MWM apparatus

Group	Transfer Latency Day 0 (s)	Transfer Latency Day 14 (s)	Transfer Latency Day 21 (s)
Normal Control	13.5 ± 1.472	13.33 ± 1.36	14±1.67
Negative Control (Stz 3 mg/Kg)	14.66± 1.75 NS	23 ± 2.53@	27.66±1.50@
Indomethacin (4mg /kg)	15.5 ± 1.38 NS	13.16 ± 2.48**	11.16±1.16**
BADGE + Indomethacin (30 mg/kg/4mg/kg)	15 ± 2.19 NS	20.33 ± 2.251NS	23.83±1.722 NS

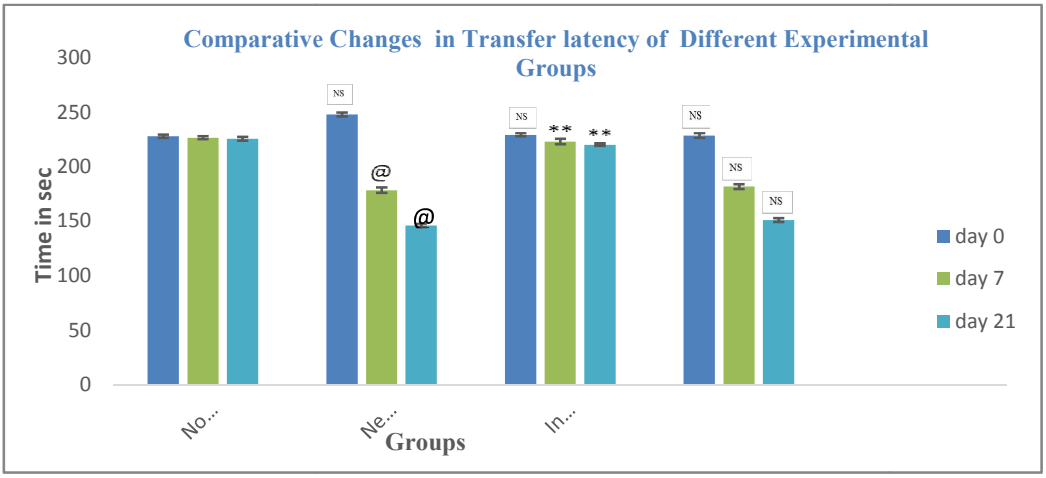

Figure 3: - Effect of Indomethacin on transfer latency of rats in EPM apparatus

All values are expressed as Mean ± SD $^{@}p<0.01$ Highly Significant increase transfer latency was observed compared to normal control group. $^{**}p<0.01$ Significant decrease in transfer latency as compared to Negative control group. ^{NS} $p>0.05$ non-significant increase in transfer latency as compared to negative control group.

Transfer latency data were expressed as Mean ± SD (n = 6). Statistical analysis was carried out using one-way ANOVA followed by Dunnett's multiple comparison test, with $p < 0.05$ considered statistically significant. No significant differences in transfer latency were observed among the experimental groups on Day 0, indicating comparable baseline cognitive performance before disease induction and treatment. The negative control group exhibited a significant increase in transfer latency on Days 7 and 21 compared with the normal control group (*$p < 0.01$), suggesting impaired learning and memory. Treatment with indomethacin significantly reduced transfer latency relative to the negative control group (*$p < 0.01$), with a progressive improvement observed from Day 7 to Day 21. In contrast, co-administration of BADGE with indomethacin attenuated this effect and resulted in a non-significant increase in transfer latency compared with the indomethacin-treated group (NS, $p > 0.05$). The normal control group showed no significant changes in transfer latency throughout the experimental period (NS, $p > 0.05$).

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V. DISCUSSION

The present study evaluated the neuroprotective effect of Indomethacin in an intracerebroventricular streptozotocin (ICV-STZ)-induced rat model of sporadic Alzheimer's disease and investigated the involvement of the PPAR-γ signaling pathway using BADGE, a selective PPAR-γ antagonist. ICV-STZ administration produced significant body weight loss and cognitive impairment, as evidenced by altered performance in the Elevated Plus Maze (EPM) and Morris Water Maze (MWM) tests. These findings are consistent with previous reports showing that ICV-STZ induces cerebral insulin resistance, oxidative stress, neuroinflammation, and memory deficits resembling sporadic Alzheimer's disease (Agrawal et al., 2011; Moreira-Silva et al., 2019).

Treatment with Indomethacin significantly improved body weight and cognitive performance by decreasing transfer latency and escape latency while increasing retention time. These results suggest that Indomethacin effectively attenuates neurodegeneration and enhances learning and memory functions. The observed effects may be attributed to its anti-inflammatory properties and its ability to activate PPAR-γ, thereby reducing neuroinflammation, oxidative stress, and neuronal damage (Combs et al., 2000; Heneka et al., 2007). Importantly, co-administration of BADGE markedly reduced the beneficial effects of Indomethacin on both physiological and behavioural parameters. This reversal indicates that activation of the PPAR-γ pathway plays a significant role in mediating the neuroprotective and cognitive-enhancing actions of Indomethacin. Similar findings have been reported for PPAR-γ agonists, which improve neuronal survival and cognitive function in experimental models of Alzheimer's disease (Mishra & Mishra, 2024).

Overall, the findings suggest that Indomethacin possesses significant neuroprotective potential against STZ-induced Alzheimer's-like pathology, and that its therapeutic effects are mediated, at least in part, through activation of the PPAR-γ signaling pathway. These results support the potential of PPAR-γ-targeted therapies for the management of sporadic Alzheimer's disease.

VI. CONCLUSION

The present study demonstrated that Indomethacin significantly improved cognitive performance in an ICV-STZ-induced rat model of Alzheimer's disease. Treatment reduced memory impairment and enhanced learning and retention abilities, indicating its neuroprotective potential. In this study when BADGE given along with indomethacin in AD animal changes their non-significant related all behavioural parameters compared to negative control group. This shows the involvement of PPAR-γ receptor and proves indomethacin shows anti-AD through its action on PPAR-γ receptor. Overall, the findings indicate that Indomethacin may be a promising candidate for the management of sAlzheimer's disease through its anti-inflammatory and PPAR-γ-mediated neuroprotective effects.

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