Research Journal of Medicine and Pharmacy
(An Open access International peer reviewed journal)
ISSN: 2945-431X

Research Article

Lobeglitazone Attenuates Behavioral and Histopathological Alterations in 3-Nitropropionic Acid-Induced Huntington-Like Neurodegeneration

Pooja K. Dewani, Deepak S. Mohale, Nitin I. Kochar, Abhijit V. Shrirao, Anil V. Chandewar
Department of Pharmacology, P.Wadhwani college of pharmacy, Yavatmal, Maharashtra, India

Abstract
Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive impairment, psychiatric abnormalities, and neuronal degeneration. The present study was designed to evaluate the neuroprotective potential of Lobeglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, in a 3-nitropropionic acid (3-NP)-induced experimental model of Huntington's disease in rats. Healthy female Sprague–Dawley rats were divided into four groups: normal control, negative control, Lobeglitazone-treated group, and PPAR-γ antagonist-treated group. Huntington-like neurodegeneration was induced using 3-NP (20 mg/kg, i.p.), followed by treatment with Lobeglitazone (0.5 mg/kg, p.o.) for 14 days. Behavioral parameters were evaluated using Elevated Plus Maze (EPM), Morris Water Maze (MWM), and Rota-Rod apparatus. Histopathological examination of rat brain tissue was performed using hematoxylin and eosin staining.The results demonstrated that 3-NP administration produced significant behavioral impairments, reduced body weight, impaired spatial memory, and motor dysfunction associated with marked neuronal degeneration. Lobeglitazone treatment significantly improved body weight, reduced transfer latency in EPM, decreased escape latency, enhanced retention time in MWM, and improved motor coordination in the Rota-Rod test. Histopathological studies revealed restoration of neuronal architecture and reduction in neurodegenerative changes in Lobeglitazone-treated animals. However, co-administration with bisphenol A diglycidyl ether (BADGE), a PPAR-γ antagonist, attenuated the neuroprotective effects of Lobeglitazone, suggesting the involvement of PPAR-γ-mediated mechanisms.
Keywords: Huntington's disease, Lobeglitazone, 3-Nitropropionic acid, PPAR-γ, Neuroprotection, Morris Water Maze.

How to cite this article: Pooja K. Dewani, Deepak S. Mohale, Nitin I. Kochar, Abhijit V. Shrirao**,** Anil V. Chandewar. Lobeglitazone Attenuates Behavioral and Histopathological Alterations in 3-Nitropropionic Acid-Induced Huntington-Like Neurodegeneration. **Research Journal of Medicine and Pharmacy. 2026 May; 5(2): 43-57**
Source of support: Nil.
Conflict of interest: None
Doi.org/10.58924/rjmp.v5.iss2.p6

Received: 25-05-2026
Revised: 27-05-2026
Accepted 27-05-2026
Published: 27-05-2026

1. Introduction

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder caused by abnormal expansion of cytosine–adenine–guanine (CAG) trinucleotide repeats in the huntingtin (HTT) gene located on chromosome 4p16.3. The mutation results in the formation of abnormal huntingtin protein aggregates leading to progressive neuronal dysfunction and degeneration, particularly in the striatum and cerebral cortex [1].

Clinically, HD is characterized by choreiform movements, cognitive decline, psychiatric disturbances, and behavioral abnormalities. The disease usually manifests between 30 and 50 years of age, although juvenile forms may occur in cases with longer CAG repeat expansions [2].

The pathogenesis of Huntington's disease involves multiple interconnected mechanisms including mitochondrial dysfunction, oxidative stress, excitotoxicity, neuroinflammation,

and transcriptional dysregulation [3]. Experimental induction of Huntington-like neurodegeneration is commonly achieved using 3-nitropropionic acid (3-NP), an irreversible inhibitor of succinate dehydrogenase (complex II) of the mitochondrial electron transport chain. Inhibition of mitochondrial respiration leads to ATP depletion, excessive reactive oxygen species generation, neuronal damage, and behavioral abnormalities similar to those observed in HD patients [4].

Mitochondrial dysfunction is considered one of the earliest pathological events in Huntington's disease. Mutant huntingtin protein interferes with mitochondrial respiratory chain complexes, leading to impaired ATP synthesis, excessive reactive oxygen species (ROS) production, and activation of apoptotic signaling pathways [6]. Oxidative stress further enhances neuronal vulnerability by promoting lipid peroxidation, DNA damage, and protein oxidation, ultimately resulting in progressive neuronal loss within the striatum and cortex [7].

Neuroinflammation also plays an important role in the progression of Huntington's disease. Activated microglia and astrocytes release inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and nitric oxide, which contribute to neuronal injury and synaptic dysfunction [8]. Studies have demonstrated elevated inflammatory cytokine levels in both experimental models and patients with Huntington's disease, suggesting that suppression of neuroinflammation may provide therapeutic benefit [9].

Recent therapeutic approaches in Huntington's disease have focused on modulation of transcription factors and nuclear receptors involved in cellular survival pathways. Among these, PPAR-γ activation has emerged as a promising strategy due to its ability to regulate mitochondrial biogenesis, antioxidant defense mechanisms, and inflammatory signaling [10]. Activation of PPAR-γ has been shown to improve neuronal survival by enhancing expression of genes associated with energy metabolism and anti-apoptotic pathways [11].

Lobeglitazone, a novel thiazolidinedione derivative, exhibits strong binding affinity toward the PPAR-γ receptor because of its unique chemical structure containing a p-methoxyphenoxy group, which enhances hydrophobic interaction within the ligand-binding domain [12]. In addition to glycemic control, Lobeglitazone has demonstrated anti-inflammatory, anti-fibrotic, antioxidant, and cytoprotective activities in various experimental studies [13]. These pharmacological properties support its potential application in neurodegenerative disorders associated with mitochondrial dysfunction and oxidative stress.

Several investigators have reported neuroprotective effects of PPAR-γ agonists in models of neurodegeneration. Pioglitazone and rosiglitazone were shown to reduce neuronal loss, improve behavioral deficits, and suppress inflammatory cytokines in experimental Huntington's disease models [14]. Similar neuroprotective mechanisms may contribute to the beneficial effects of Lobeglitazone observed in the present investigation.

Recent research has highlighted the importance of peroxisome proliferator-activated receptor gamma (PPAR-γ) in neuroprotection and regulation of inflammatory responses. PPAR-γ is a ligand-activated transcription factor involved in glucose metabolism, lipid homeostasis, mitochondrial function, and anti-inflammatory signalling pathways [5].

Corresponding Author: poojakd.n99@gmail.com

2. Materials and methods

The chemicals and reagents (Table 1) used during the present investigation were of analytical grade and procured from standard commercial sources. Lobeglitazone was used as the test drug, while 3-Nitropropionic acid (3-NP) was employed for induction of Huntington-like neurodegeneration in experimental animals. Bisphenol A diglycidyl ether (BADGE) was utilized as a selective antagonist of the PPAR-γ receptor to evaluate receptor-mediated neuroprotective mechanisms of Lobeglitazone.

Table: 1. List of Chemicals and Reagents Used in the Study

Sr. No.	Chemicals	Company
1.	DMSO (Dimethyl Sulfoxide)	Pryoginalaboratries
2.	Ethanol	Thermosil fine chem Industries
3.	PEG 400	Thermosil fine chem Industries
4.	Carboxymethyl cellulose	Thermosil fine chem Industries
5.	Normal saline solution	Kaplife
6.	Diethyl ether	Thermosil fine chem Industries
7.	Bisphenol A diglycidyl ether	BLD pharmatech private limited

2.1 Experimental Animals and grouping

Healthy female Sprague–Dawley rats weighing between 220–280 g and aged approximately 8–12 weeks were selected for the study. The animals were maintained under standard laboratory conditions with controlled temperature, humidity, and 12-hour light/dark cycle. Standard pellet diet and water were provided ad libitum throughout the study period. All experimental procedures were conducted according to CPCSEA guidelines.The animals were randomly divided into four groups containing six animals in each group (n = 6).Group I NormalControl (Normalsaline), Group II Negative Control (3-NP induced HD model), Group III 3-NP + Lobeglitazone treated group, Group IV 3-NP + Lobeglitazone + BADGE treated group.

2.32 Induction of Huntington's Disease

Experimental Huntington-like neurodegeneration was induced using 3-Nitropropionic acid (3-NP) at a dose of 20 mg/kg administered intraperitoneally for four consecutive days. 3-NP is an irreversible inhibitor of succinate dehydrogenase of the mitochondrial electron transport chain.

2.3. Treatment Protocol

Following disease induction, Lobeglitazone treatment was initiated and continued for 14 consecutive days. Lobeglitazone was administered orally at a dose of 0.5 mg/kg . BADGE was administered intraperitoneally at a dose of 30 mg/kg for antagonist studies for 14 days (Table 2).

Corresponding Author: poojakd.n99@gmail.com

Table:2. Drug Administration Schedule

Sr. No	Experimental phase	Days	Procedure
1.	Training Period	Day 1–3 (Total Days = 3)	Animals were trained for behavioral assessment using experimental apparatus (Morris Water Maze, Elevated Plus Maze, Rota- Rod apparatus).
2.	Disease Induction Period	Day 4–7 (Total Days = 7)	Huntington's disease was induced by administration of 3-Nitropropionic acid (3-NP) for 4 consecutive days.
3.	Treatment Period 2	Day 8–21 (Total Days = 14)	HD induce rats treated with Lobeglitazone for 14 consecutive days
4.	Antagonist Treatment	Day 8–21 (Total Days = 14)	HD induce rats treated with Bisphenol A Diglycidyl Ether (BADGE) as a PPAR-γ antagonist along with lobeglitazone for 14 days.

2.4Behavioral Assessment

Behavioral parameters were assessed using Elevated Plus Maze (EPM), Morris Water Maze (MWM), and Rota-Rod apparatus before and after induction of Huntington's disease.

2.4.1 Elevated Plus Maze

The Elevated Plus Maze apparatus was used to evaluate anxiety-related behavior and learning performance in experimental animals. Transfer latency was recorded as an index of cognitive performance.

2.4.2 Morris Water Maze

The Morris Water Maze apparatus was employed for assessment of spatial learning and memory functions. Escape latency and retention time were recorded during training and probe trials.

2.543 Rota-Rod Apparatus

Motor coordination and muscular balance were evaluated using the Rota-Rod apparatus. Latency to fall was recorded as an index of motor coordination

2.5 Histopathological Examination

Brain tissues were isolated, fixed in formalin solution, processed for paraffin embedding, stained using hematoxylin and eosin stain, and examined under light microscope for neuronal degeneration and histopathological alterations.

2.6 Statistical Analysis

All data were expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-Way ANOVA followed by Dunnett's multiple comparison test. Values of $P < 0.01$ were considered statistically significant.

3. Results

3.1 Effect of Lobeglitazone on Body Weight

Body weight analysis was performed throughout the experimental period to evaluate the physiological impact of Huntington-like neurodegeneration and the protective effect of Lobeglitazone treatment. Reduction in body weight is a common characteristic of

Huntington's disease due to metabolic imbalance, mitochondrial dysfunction, and progressive neuronal degeneration.

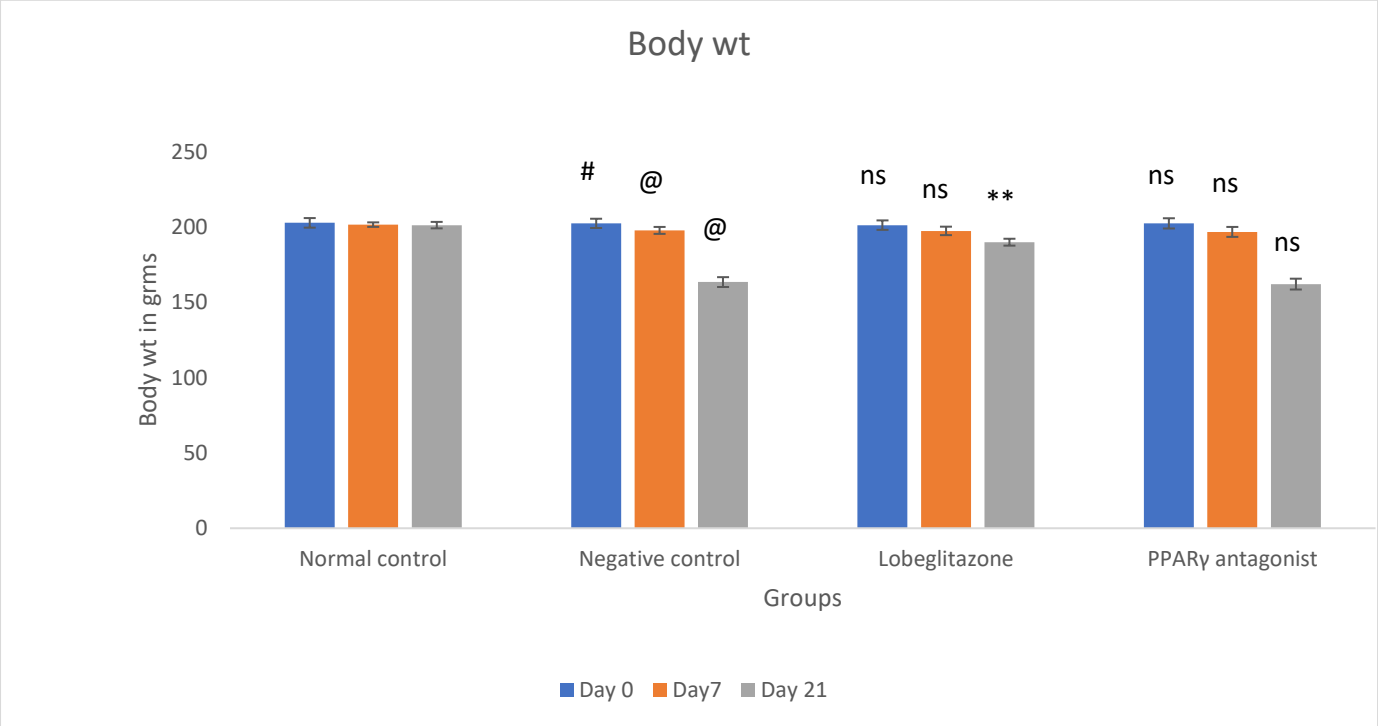

Figure 1. Body weight of animals

The results (Table 3) (Figure 1) indicate that administration of 3-Nitropropionic acid produced a marked reduction in body weight in the negative control group when compared with the normal control group. Lobeglitazone-treated animals demonstrated significant restoration of body weight by Day 21, suggesting improvement in metabolic activity and reduction of disease severity. BADGE-treated animals did not exhibit significant recovery, thereby confirming the involvement of PPAR-γ receptor-mediated mechanisms in the protective action of Lobeglitazone.

Table: 3 Effect of Lobeglitazone on Body Weight

Groups	Day 0	Day 7	Day 21
Normal Control	202.83 ± 3.18	201.67 ± 1.50	201.33 ± 2.16
Negative Control	202.50 ± 3.08	197.83 ± 2.31	163.50 ± 3.27
Lobeglitazone	201.33 ± 3.14	197.50 ± 2.81	190.00 ± 2.28
PPAR-γ antagonist	202.50 ± 3.39	196.83 ± 3.31	162.16 ± 3.60

3.2 Elevated Plus Maze Study

The Elevated Plus Maze apparatus was used to evaluate anxiety-related behavior and cognitive performance in experimental animals. Transfer latency was considered an important indicator of learning and memory functions.

Research Journal of Medicine and Pharmacy
(An Open access International peer reviewed journal)
ISSN: 2945-431X

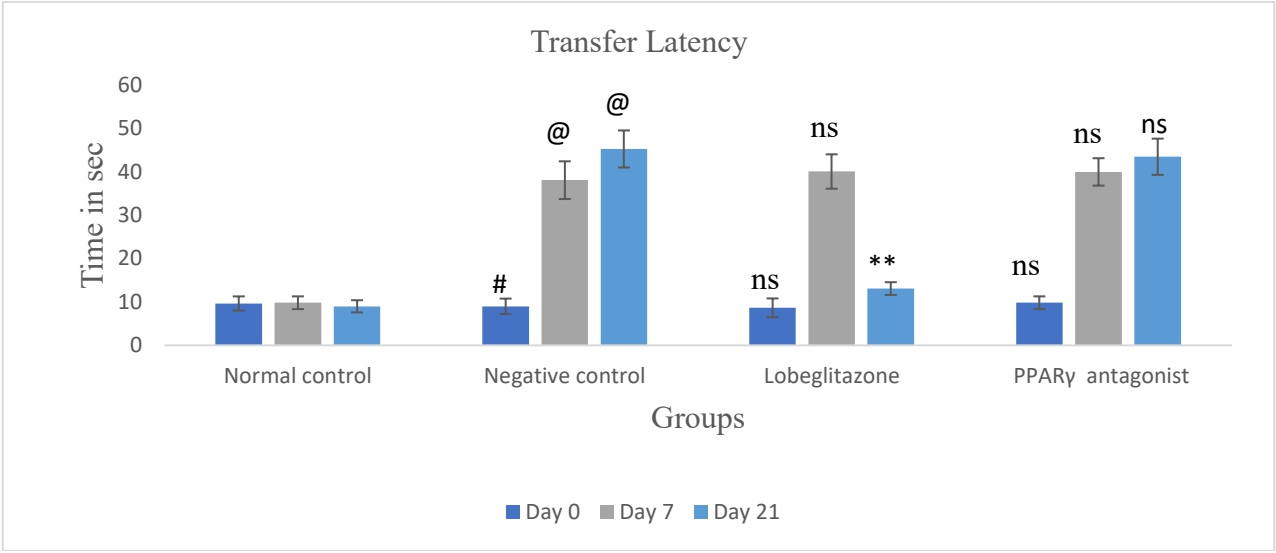

Figure: 2 Effect of Lobeglitazone on transfer latency of rats in EPM apparatus

The data (Table 4) (Figure 2) demonstrate that administration of 3-NP significantly increased transfer latency in the negative control group, indicating severe impairment in learning and memory functions. Lobeglitazone treatment significantly reduced transfer latency by Day 21, suggesting improvement in cognitive function and behavioral performance. The antagonist-treated group failed to show significant improvement, indicating attenuation of neuroprotective effects following blockade of PPAR-γ receptors.

Table:4 Elevated Plus Maze Study

Groups	Day 0	Day 7	Day 21
Normal Control	9.66 ± 1.63	9.83 ± 1.47	9.00 ± 1.41
Negative Control	9.00 ± 1.78	38.10 ± 4.35	45.30 ± 4.27
Lobeglitazone	8.66 ± 2.16	40.10 ± 3.97	13.10 ± 1.47
PPAR-γ antagonist	9.83 ± 1.47	40.00 ± 3.16	41.00 ± 3.16

3.3 Morris Water Maze Study

The Morris Water Maze apparatus was used to assess spatial learning and memory retention in experimental animals. Escape latency and retention time were recorded during training and probe trials.

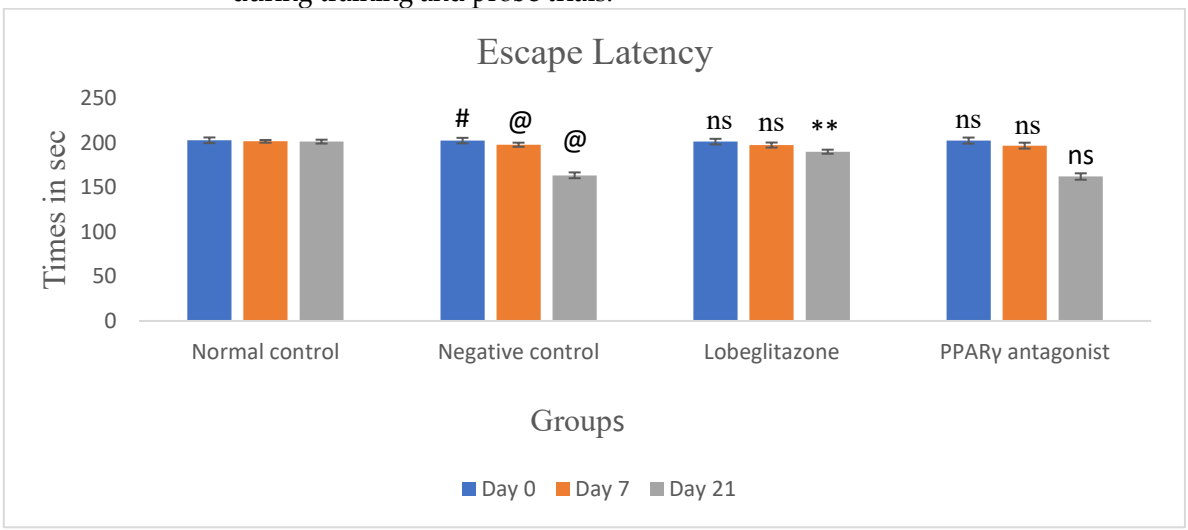

Figure : 3 Effect of Lobeglitazone on Escape latency of rats in MWM apparatus

Corresponding Author: poojakd.n99@gmail.com

Disease-induced animals exhibited significantly prolonged escape latency compared with normal control animals, indicating impairment of spatial learning and memory functions. Lobeglitazone-treated animals showed a marked reduction in escape latency on Day 21, suggesting improvement in cognitive function and spatial memory retention. The PPAR-γ antagonist-treated group exhibited persistent impairment in escape latency (Table 5) (Figure3).

Table:5 Escape Latency in Morris Water Maze

Groups	Day 0	Day 7	Day 21
Normal Control	10.80 ± 2.31	12.60 ± 1.50	14.30 ± 1.86
Negative Control	10.50 ± 1.87	51.30 ± 2.78	50.50 ± 2.42
Lobeglitazone	11.10 ± 2.04	52.50 ± 3.61	20.00 ± 1.41
PPAR-γ antagonist	50.60 ± 2.16	50.60 ± 2.16	47.50 ± 2.42

Disease-induced animals showed a marked reduction in retention time when compared with the normal control group, indicating severe memory impairment. Lobeglitazone treatment significantly increased retention time in the target quadrant, suggesting restoration of memory retention and improvement in hippocampal neuronal function. The antagonist-treated group exhibited poor retention time compared with Lobeglitazone-treated animals (Table 6) (Figure 4).

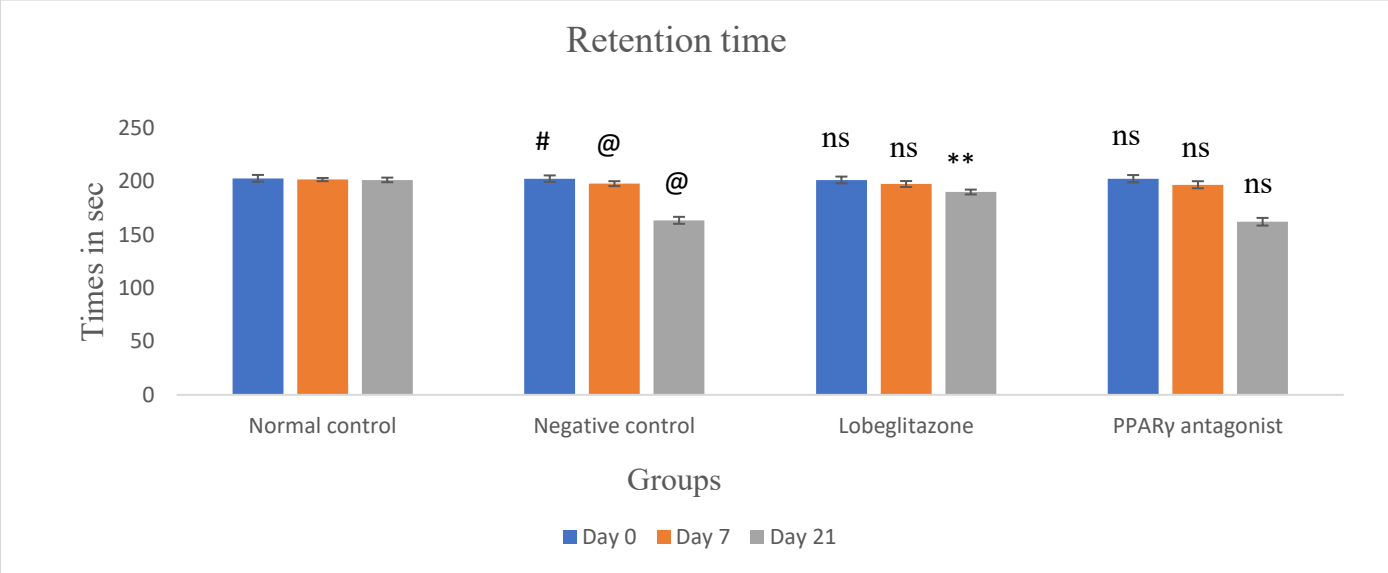

Figure: 4. Effect of Lobeglitazone on Retention time of rats in MWM apparatus

Table: 6 Retention Time in Morris Water Maze

Groups	Day 0	Day 7	Day 21
Normal Control	13.60 ± 1.86	20.50 ± 1.87	22.80 ± 1.47
Negative Control	15.00 ± 0.89	9.83 ± 0.75	6.00 ± 0.89
Lobeglitazone	14.50 ± 1.04	9.33 ± 1.21	23.00 ± 0.89
PPAR-γ antagonist	14.50 ± 1.04	9.16 ± 1.47	11.10 ± 1.47

3.5 Rota-Rod Test

The Rota-Rod apparatus was used to assess motor coordination, muscular strength, and balance in experimental animals.

Corresponding Author: poojakd.n99@gmail.com

Research Journal of Medicine and Pharmacy
(An Open access International peer reviewed journal)
ISSN: 2945-431X

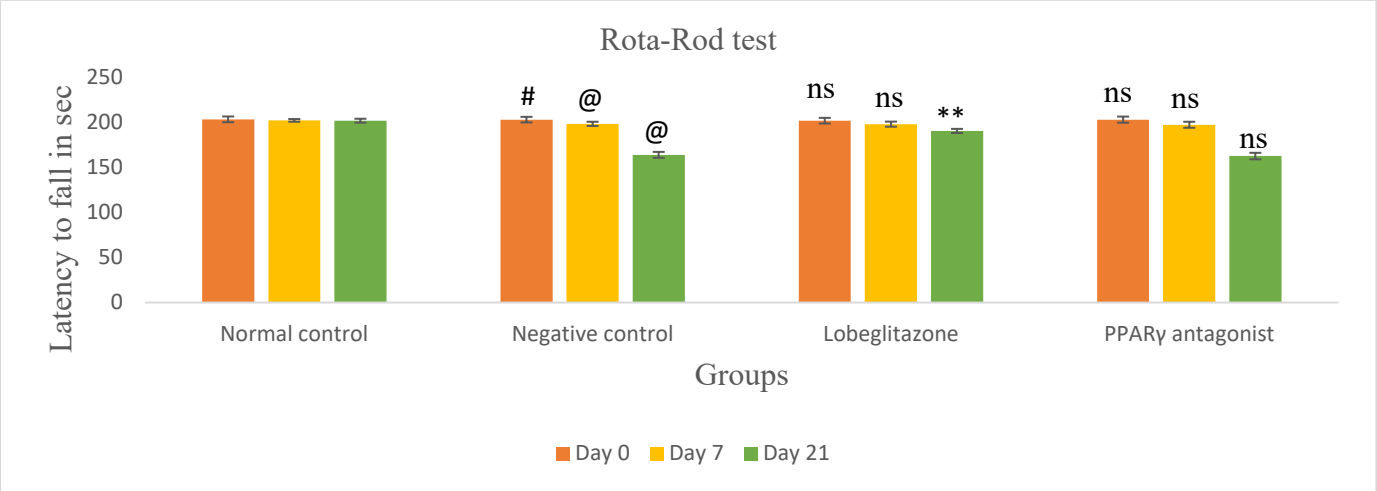

Figure: 5 Effect of Lobeglitazone on Latency to fall of rats in Rota – Rod test

The results obtained from the Rota-Rod test indicate that 3-NP administration significantly reduced latency to fall in the negative control group, indicating severe impairment in motor coordination and neuromuscular balance. Lobeglitazone treatment significantly improved latency to fall by Day 21, suggesting restoration of motor coordination and reduction in striatal neuronal degeneration. The antagonist-treated group exhibited persistent motor impairment (Figure 5) (Table 7).

Table: 7 Rota-Rod Test

Groups	Day 0	Day 7	Day 21
Normal Control	58.80 ± 3.31	59.00 ± 3.46	56.80 ± 2.31
Negative Control	57.50 ± 2.42	13.50 ± 2.16	11.50 ± 2.16
Lobeglitazone	57.10 ± 3.60	14.60 ± 1.75	21.60 ± 2.73
PPAR-γ antagonist	58.00 ± 2.09	15.50 ± 1.04	14.50 ± 2.16

3.6. Histopathological studies

Histopathological examination of rat brain sections stained with hematoxylin and eosin (H&E) revealed distinct morphological alterations among the experimental groups. The normal control group demonstrated intact neuronal architecture with well-organized cortical layers, normal neuronal morphology, and absence of degenerative changes. Neurons appeared healthy with prominent nuclei and normal distribution of neuroglial cells. No evidence of vacuolation, spongiosis, gliosis, or vascular congestion was observed, indicating normal histological organization of brain tissue.

In contrast, the negative control group exposed to 3-nitropropionic acid exhibited severe neurodegenerative changes characteristic of Huntington's disease pathology. Brain sections showed marked neuronal degeneration, extensive vacuolation, spongiform changes, gliosis, astrocytic proliferation, and vascular congestion, particularly in the striatum and cerebral cortex. Numerous neurons appeared shrunken with hyperchromatic nuclei and eosinophilic cytoplasm, indicating neuronal damage and neurotoxicity. These findings confirmed successful induction of Huntington-like neurodegeneration in untreated animals.

Treatment with Lobeglitazone markedly improved the histopathological alterations induced by 3-nitropropionic acid. The treated group demonstrated substantial restoration of normal brain architecture with preservation of neuronal integrity and reduced

Corresponding Author: poojakd.n99@gmail.com

neurodegenerative changes. Histological sections revealed decreased vacuolation, reduced spongiosis, and improved organization of neuronal cells in the cerebral cortex and striatal regions. Furthermore, reduction in huntingtin protein aggregates and attenuation of gliosis were observed, indicating significant neuroprotective and neurorestorative effects of Lobeglitazone treatment. The histological appearance of the treated group closely resembled that of the normal control group.

The BADGE + Lobeglitazone treated group exhibited moderate histopathological improvement compared to the negative control group. Brain sections showed partial restoration of neuronal morphology with moderate reduction in neuronal degeneration and gliosis. Although several neurons retained normal vesicular nuclei and improved cellular organization, some areas still exhibited residual neurodegenerative changes including shrunken hyperchromatic neurons and mild vacuolation. Neuroinflammatory changes were also reduced as evidenced by decreased astrocytic activation. However, the degree of histological recovery was less pronounced than that observed in the Lobeglitazone-treated group, suggesting partial attenuation of the neuroprotective effect in the presence of BADGE (Figure 6)

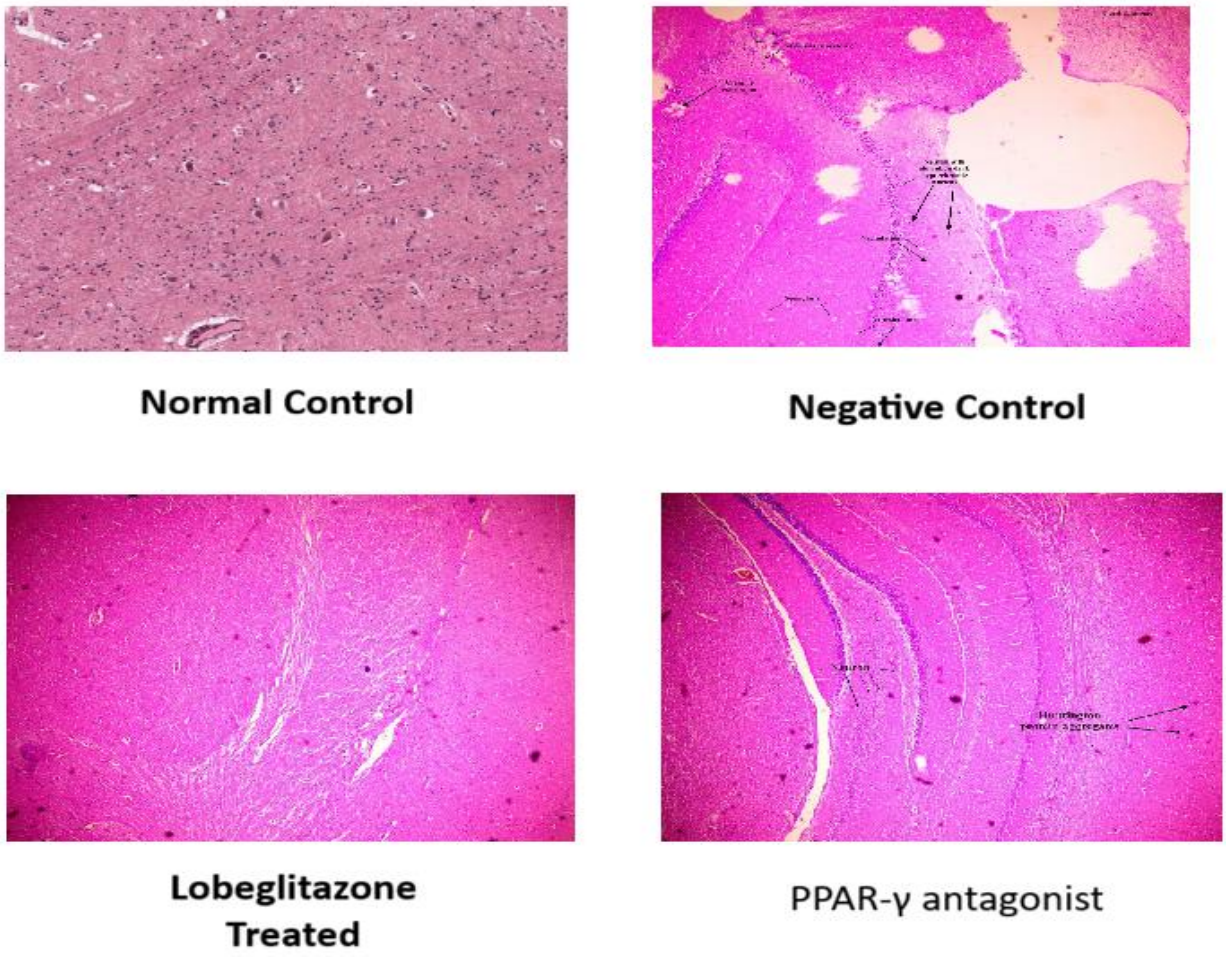

Figure 6: Histopatholgical results of isolated rat brain tissue from experimental animals

4. Discussion

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by selective neuronal degeneration, particularly within the striatum and cerebral cortex,

leading to cognitive dysfunction, psychiatric abnormalities, and motor impairment. The present investigation was undertaken to evaluate the neuroprotective potential of Lobeglitazone against 3-Nitropropionic acid (3-NP)-induced Huntington-like neurodegeneration in experimental animals. The findings obtained from behavioral, physiological, and histopathological studies demonstrated significant protective effects of Lobeglitazone against Huntington-like pathology.

3-Nitropropionic acid is a well-established mitochondrial neurotoxin commonly used for induction of Huntington-like neurodegeneration in experimental models. 3-NP irreversibly inhibits succinate dehydrogenase (Complex II) of the mitochondrial electron transport chain, resulting in impaired ATP synthesis, excessive generation of reactive oxygen species, oxidative stress, excitotoxicity, and neuronal degeneration [15,16]. The neuropathological alterations produced by 3-NP closely resemble those observed in Huntington's disease patients, particularly degeneration of GABAergic neurons within the striatum [17].

In the present study, administration of 3-NP produced significant behavioral impairments, cognitive dysfunction, reduction in body weight, and deterioration of motor coordination in experimental animals. These findings are consistent with previous investigations reporting severe mitochondrial dysfunction and neuronal damage following 3-NP administration [18].

The reduction in body weight observed in the negative control group may be attributed to impaired mitochondrial energy metabolism and progressive neurodegeneration. Weight loss is a characteristic feature of Huntington's disease and has been associated with hypermetabolism, oxidative stress, and hypothalamic dysfunction [19]. In the present investigation, Lobeglitazone-treated animals demonstrated significant restoration of body weight compared with disease-induced animals. The improvement in body weight suggests enhancement of metabolic activity and reduction in disease severity following Lobeglitazone treatment.

The beneficial effect of Lobeglitazone may be associated with activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear transcription factor involved in regulation of glucose metabolism, mitochondrial biogenesis, antioxidant defense, and inflammatory signaling pathways [20]. Activation of PPAR-γ has been shown to improve mitochondrial function and suppress oxidative stress-mediated neuronal injury [21].

Behavioral assessment using the Elevated Plus Maze revealed significant impairment in learning and memory functions in disease-induced animals, as evidenced by increased transfer latency. Cognitive dysfunction observed in Huntington's disease is primarily associated with degeneration of corticostriatal neuronal pathways and oxidative stress-induced neuronal damage within the hippocampus and cerebral cortex [22].

Treatment with Lobeglitazone significantly reduced transfer latency compared with the negative control group, indicating improvement in cognitive performance and learning behavior. These findings suggest that Lobeglitazone possesses significant neuroprotective activity capable of restoring neuronal function and reducing cognitive impairment.

The Morris Water Maze study further supported the cognitive protective effects of Lobeglitazone. Disease-induced animals demonstrated prolonged escape latency and significantly reduced retention time, indicating severe impairment in spatial learning and

memory retention. Similar observations have been reported previously in experimental Huntington's disease models induced by mitochondrial toxins [23].

Lobeglitazone treatment significantly reduced escape latency and increased retention time in experimental animals, indicating restoration of hippocampal function and improvement in memory retention. Improvement in spatial memory may be attributed to reduction in oxidative stress and suppression of inflammatory mediators following activation of PPAR-γ receptors.

Several studies have demonstrated that activation of PPAR-γ receptors improves neuronal survival by enhancing mitochondrial biogenesis and reducing inflammatory cytokine production [24]. PPAR-γ agonists also inhibit activation of microglial cells and suppress release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and nitric oxide, thereby reducing neuronal damage [25].

The Rota-Rod test demonstrated significant impairment in motor coordination and muscular balance in disease-induced animals. Huntington's disease is associated with progressive degeneration of medium spiny GABAergic neurons in the striatum, leading to severe motor dysfunction and loss of neuromuscular coordination [26].

Lobeglitazone treatment significantly improved latency to fall in the Rota-Rod test, indicating restoration of motor coordination and improvement in neuromuscular balance. The improvement observed following Lobeglitazone administration may be attributed to preservation of striatal neuronal integrity and reduction in oxidative stress-mediated neurotoxicity.

Histopathological examination further confirmed the neuroprotective effects of Lobeglitazone. Brain sections obtained from disease-induced animals demonstrated severe neuronal degeneration, vacuolation, gliosis, spongiosis, and vascular congestion, confirming successful induction of Huntington-like neurotoxicity. Similar histopathological alterations have been previously reported in 3-NP-induced experimental models of Huntington's disease [27].

In contrast, Lobeglitazone-treated animals demonstrated restoration of neuronal architecture with reduced vacuolation, gliosis, and inflammatory changes. These findings indicate that Lobeglitazone effectively protects neuronal tissue against mitochondrial dysfunction and oxidative damage.

The neuroprotective effect of Lobeglitazone may be attributed to multiple mechanisms including reduction of oxidative stress, suppression of neuroinflammation, enhancement of mitochondrial function, and activation of anti-apoptotic signaling pathways. Previous studies have demonstrated that PPAR-γ agonists enhance expression of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby protecting neurons against oxidative injury [28].

Furthermore, activation of PPAR-γ has been shown to inhibit nuclear factor-kappa B (NF-κB)-mediated inflammatory pathways, resulting in reduced production of pro-inflammatory cytokines and suppression of microglial activation [29]. These mechanisms collectively contribute to neuronal survival and improvement in behavioral performance.
The present investigation also included administration of Bisphenol A diglycidyl ether (BADGE), a selective PPAR-γ antagonist, to confirm receptor-mediated neuroprotective

mechanisms. Animals treated with BADGE along with Lobeglitazone failed to demonstrate significant improvement in behavioral and physiological parameters compared with Lobeglitazone-treated animals. The antagonist-treated group also exhibited persistent neuronal degeneration and motor impairment.

The attenuation of therapeutic effects following BADGE administration strongly supports involvement of PPAR-γ receptor-mediated mechanisms in the neuroprotective action of Lobeglitazone. Similar receptor-dependent protective effects have been reported previously with other thiazolidinedione derivatives including pioglitazone and rosiglitazone [30].

The findings obtained during the present investigation are consistent with previous reports demonstrating beneficial effects of PPAR-γ agonists in experimental neurodegenerative disorders. Pioglitazone and rosiglitazone have been shown to improve behavioral performance, reduce neuronal degeneration, and suppress oxidative stress in models of Huntington's disease, Parkinson's disease, and Alzheimer's disease [31,32].

Lobeglitazone possesses structural modifications that provide enhanced binding affinity toward PPAR-γ receptors when compared with conventional thiazolidinediones [33]. The superior receptor affinity and improved pharmacological profile of Lobeglitazone may contribute to its potent neuroprotective activity observed in the present investigation.

Although the present study demonstrated significant neuroprotective effects of Lobeglitazone, certain limitations should be acknowledged. The investigation primarily focused on behavioral and histopathological parameters, whereas biochemical estimation of oxidative stress markers and inflammatory cytokines was not performed. Evaluation of molecular biomarkers such as superoxide dismutase, catalase, malondialdehyde, glutathione, TNF-α, IL-1β, and BDNF could provide additional mechanistic insights into Lobeglitazone-mediated neuroprotection.

Future investigations involving molecular studies, immunohistochemistry, western blot analysis, and gene expression profiling may further elucidate the precise neuroprotective mechanisms of Lobeglitazone in Huntington's disease. Long-term studies and clinical investigations are also required to establish its therapeutic efficacy and safety in human subjects.

Overall, the findings of the present investigation strongly suggest that Lobeglitazone possesses significant neuroprotective activity against Huntington-like neurodegeneration and may represent a promising therapeutic strategy for management of Huntington's disease and other neurodegenerative disorders associated with mitochondrial dysfunction, oxidative stress, and neuroinflammation.

5. Conclusion

The present investigation successfully demonstrated the neuroprotective potential of Lobeglitazone against 3-Nitropropionic acid (3-NP)-induced Huntington-like neurodegeneration in experimental animals. Administration of 3-NP produced significant behavioral deficits, cognitive impairment, reduction in body weight, deterioration of motor coordination, and severe histopathological alterations, thereby confirming successful induction of Huntington's disease-like pathology.

Treatment with Lobeglitazone significantly improved behavioral performance, restored body weight, enhanced spatial learning and memory, and improved motor coordination in experimental animals. Behavioral studies performed using Elevated Plus Maze, Morris Water Maze, and Rota-Rod apparatus collectively demonstrated substantial recovery in cognitive and neuromuscular functions following Lobeglitazone administration.

Histopathological examination further confirmed the neuroprotective effects of Lobeglitazone by demonstrating restoration of neuronal architecture and reduction in neuronal degeneration, vacuolation, gliosis, and inflammatory changes in brain tissue sections.

The neuroprotective activity of Lobeglitazone may be attributed to activation of PPAR-γ receptors resulting in suppression of oxidative stress, reduction of neuroinflammation, improvement of mitochondrial function, and enhancement of neuronal survival pathways. The attenuation of therapeutic effects following administration of BADGE, a selective PPAR-γ antagonist, strongly confirmed the involvement of PPAR-γ-mediated mechanisms in the protective action of Lobeglitazone.

The findings obtained during the present study suggest that Lobeglitazone possesses significant therapeutic potential for management of Huntington's disease and other neurodegenerative disorders associated with mitochondrial dysfunction and oxidative stress.However, further investigations involving biochemical estimation of oxidative stress markers, inflammatory cytokines, molecular signaling pathways, and long-term safety studies are required to establish the precise mechanism of action and clinical applicability of Lobeglitazone in neurodegenerative disorders.

Overall, the present study provides substantial experimental evidence supporting the potential role of Lobeglitazone as a promising neuroprotective agent for Huntington's disease through PPAR-γ receptor-mediated neuroprotection.

References

1. Walker FO. Huntington's disease. Lancet. 2007;369(9557):218-228.
2. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 2011;10(1):83-98.
3. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, et al. Huntington disease. Nat Rev Dis Primers. 2015;1:15005.
4. Brouillet E, Conde F, Beal MF, Hantraye P. Replicating Huntington's disease phenotype in experimental animals. Prog Neurobiol. 1999;59(5):427-468.
5. Villapol S. Roles of peroxisome proliferator-activated receptor gamma on brain and peripheral inflammation. Cell Mol Neurobiol. 2018;38(1):121-132.
6. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther. 2012;342(3):619-630.
7. Browne SE, Beal MF. Oxidative damage in Huntington's disease pathogenesis. Antioxid Redox Signal. 2006;8(11-12):2061-2073.

8. Crotti A, Glass CK. The choreography of neuroinflammation in Huntington's disease. Trends Immunol. 2015;36(6):364-373.
9. Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, et al. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med. 2008;205(8):1869-1877.
10. Feher A, Juhasz A, Laszlo A, Kalman J Jr, Pakaski M, Kalman J. Association between PPAR-γ and neurodegenerative diseases. Curr Neuropharmacol. 2011;9(2):331-343.
11. Chiang MC, Chen HM, Lee YH, Chang HH, Wu YC, Soong BW, et al. Dysregulation of C/EBPα by mutant Huntingtin causes the impairment of PGC-1α expression in Huntington's disease. Hum Mol Genet. 2010;19(7):1435-1450.
12. Kim SG, Kim DM, Woo JT, Jang HC, Chung CH, Ko KS, et al. Lobeglitazone, a novel thiazolidinedione, improves insulin sensitivity and glycemic control in patients with type 2 diabetes mellitus. Diabetes Metab J. 2014;38(6):450-457.
13. Lim S, Kim JR, Moon JH, Lee HK. Anti-inflammatory and antioxidant effects of lobeglitazone in experimental models. Biomol Ther (Seoul). 2015;23(6):521-527.
14. Escribano L, Simón AM, Pérez-Mediavilla A, Salazar-Colocho P, Del Río J, Frechilla D. Rosiglitazone rescues memory impairment in Alzheimer's transgenic mice. Neuroscience. 2010;166(4):1119-1127.
15. Brouillet E, Conde F, Beal MF, Hantraye P. Replicating Huntington's disease phenotype in experimental animals. Prog Neurobiol. 1999;59(5):427-468.
16. Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, et al. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci. 1993;13(10):4181-4192.
17. Borlongan CV, Koutouzis TK, Freeman TB, Hauser RA, Cahill DW, Sanberg PR. Behavioral and histopathological effects of 3-nitropropionic acid in animal models of Huntington's disease. Brain Res Bull. 1997;43(1):1-16.
18. Tunez I, Tasset I, Perez-De La Cruz V, Santamaria A. 3-Nitropropionic acid as a tool to study the mechanisms involved in Huntington's disease: past, present and future. Molecules. 2010;15(12):878-916.
19. Aziz NA, van der Marck MA, Pijl H, Olde Rikkert MG, Bloem BR, Roos RA. Weight loss in neurodegenerative disorders. J Neurol. 2008;255(12):1872-1880.
20. Villapol S. Roles of peroxisome proliferator-activated receptor gamma on brain and peripheral inflammation. Cell Mol Neurobiol. 2018;38(1):121-132.
21. Johri A, Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. J Pharmacol Exp Ther. 2012;342(3):619-630.
22. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 2011;10(1):83-98.

Corresponding Author: poojakd.n99@gmail.com

23. Brouillet E, Jacquard C, Bizat N, Blum D. 3-Nitropropionic acid: a mitochondrial toxin to uncover physiopathological mechanisms underlying striatal degeneration in Huntington's disease. J Neurochem. 2005;95(6):1521-1540.
24. Feher A, Juhasz A, Laszlo A, Kalman J Jr, Pakaski M, Kalman J. Association between PPAR-γ and neurodegenerative diseases. Curr Neuropharmacol. 2011;9(2):331-343.
25. Crotti A, Glass CK. The choreography of neuroinflammation in Huntington's disease. Trends Immunol. 2015;36(6):364-373.
26. Walker FO. Huntington's disease. Lancet. 2007;369(9557):218-228.
27. Beal MF. Experimental models of Huntington's disease. Nat Rev Neurosci. 2001;2(5):325-334.
28. Browne SE, Beal MF. Oxidative damage in Huntington's disease pathogenesis. Antioxid Redox Signal. 2006;8(11-12):2061-2073.
29. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010;140(6):918-934.
30. Escribano L, Simón AM, Pérez-Mediavilla A, Salazar-Colocho P, Del Río J, Frechilla D. Rosiglitazone rescues memory impairment in Alzheimer's transgenic mice. Neuroscience. 2010;166(4):1119-1127.
31. Heneka MT, Landreth GE. PPARs in the brain. BiochimBiophys Acta. 2007;1771(8):1031-1045.
32. Carta AR, Pisanu A, Carboni E. Do PPAR-gamma agonists have a future in Parkinson's disease therapy? Parkinsonism RelatDisord. 2011;17(5):313-318.
33. Kim SG, Kim DM, Woo JT, Jang HC, Chung CH, Ko KS, et al. Lobeglitazone, a novel thiazolidinedione, improves insulin sensitivity and glycemic control in patients with type 2 diabetes mellitus. Diabetes Metab J. 2014;38(6):450-457.

***