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ORIGINAL RESEARCH

Neuroprotective effect of Donepezil in type 2 diabetes mellitus induced cognitive impairment in male wistar rats

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with cognitive impairment and neurodegeneration. **Objective:** To investigate the neuroprotective effects of donepezil on cognitive impairment in a T2DM rat model. **Materials and Methods:** Twenty four male Wistar rats were divided into three groups: normal control, diabetic control and treatment groups receiving donepezil (4 mg/kg). Cognitive function was assessed using the elevated plus maze novel object recognition test and Morris water maze. **Results:** Donepezil treatment significantly improved spatial and non-spatial memory, reduced anxiety-like behavior and enhanced cognitive function in T2DM rats. However, donepezil had no effect on blood glucose levels or body weight. **Conclusion:** This study suggests that donepezil may be a potential therapeutic agent for ameliorating cognitive deficits associated with T2DM, without affecting glucose metabolism or weight management.

Keywords: Type 2 diabetes mellitus, cognitive impairment, donepezil, neuroprotection, rat model.

INTRODUCTION

Diabetes, or diabetes mellitus (DM), is a chronic and complex metabolic disorder that affects the homeostasis of blood glucose level in the body. In diabetes there is a continued elevated blood glucose level, called hyperglycemia. Hyperglycemia results mainly due to inadequate insulin secretion or inability of body to utilize the insulin when it is secreted (insulin resistance) or both. This leads to carbohydrate, fat, and protein metabolic dysfunctions.[1,2]Globally, a staggering 240 million people are estimated to be living with undiagnosed diabetes. This translates to nearly half of all adults with diabetes being unaware of their condition.[3]

Diabetes mellitus (DM) constitutes a significant risk factor for the development of both vascular dementia and mixed dementia subtypes.The pathological mechanisms underlying this association are multifaceted. DM's deleterious effects on the vascular system, including microvascular and macrovascular complications, contribute substantially to the increased risk. Consequently, individuals with type 2 DM exhibit a heightened propensity for developing vascular dementia due to the synergistic impact of these vascular disturbances on cerebral blood flow and neuronal integrity.[4,5]

Donepezil, primarily known for its cholinesterase inhibitory properties in Alzheimer's disease (AD), exhibits additional neuroprotective actions. Beyond enhancing cholinergic transmission, donepezil safeguards neurons from oxidative stress, amyloid-beta toxicity, glutamate excitotoxicity, and neuroinflammation.[6] It modulates key intracellular signaling pathways, including PI3K-Akt and GSK-3, and interacts with receptors like α7 nAChRs and σ1 receptors. These mechanisms contribute to its effects on tau pathology and vascular health. While preclinical data is promising, clinical studies suggest donepezil can modestly improve cognition and daily function in AD patients, potentially delaying disease progression and the need for long-term care.[7]

Donepezil treatment in patients with AD showed preservation of brain glucose metabolism compared to placebo, suggesting it might maintain functional brain activity.[8]

Studies suggest early donepezil treatment in mild cognitive impairment (MCI) and AD patients might slow cognitive decline compared to delayed treatment.[9,10]

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Donepezil treatment in patients with mild to moderate AD may preserve regional cerebral blood flow in areas crucial for memory, planning, and motivation.[11]Increased cerebral blood flow in the cingulate cortex after donepezil treatment correlates with improved cognitive function in AD patients.[12]Donepezil treatment appears to slow the progression of hippocampal atrophy compared to placebo in patients with AD and suspected prodromal AD.[13]

Donepezil treatment reduces the rate of hippocampal volume decline compared to controls in AD patients.[14]Donepezil-treated AD patients show higher cognitive function, larger hippocampal volumes, and higher N-acetylaspartate levels (indicating preserved neuronal function) compared to placebo.[15]

Donepezil's neuroprotective potential extends beyond its well-established role in managing Alzheimer's disease symptoms.By influencing multiple cellular pathways implicated in cognitive impairment, donepezil demonstrates promise in slowing disease progression and preserving cognitive function. Further investigation into the underlying mechanisms of donepezil's neuroprotective effects is warranted to fully elucidate its therapeutic potential for neurodegenerative disorders. Hence, the present study was undertaken.

MATERIALS AND METHOD

High fat diet (HFD) and normal pellet diet (NPD) both were purchased from National Institute of Nutrition (NIN) Hyderabad, India. Extra pure 98% Streptozotocin (STZ) was purchased from Sisco Research Laboratories (SRL) Pvt Ltd (Maharashtra, India. Donepezil from Alkem laboratories LTD (India). Glucose was purchased from Zydus Lifesciences. One touch glucometer (ACCU-CHEK® Active) with glucose oxidase-peroxidase reactive strips was purchased from Roche Diabetes Care (Mannheim, Germany). Bedding material corn cob was purchased Top Feed Delhi and 26 Gauge needle was used to puncture tail vein.

Twenty four male Wistar rats, aged 2-3 months and weighing 150-200 g, were procured from the National Institute of Nutrition (NIN), Hyderabad, India. Animals were housed in standard polypropylene cages under controlled conditions (temperature: 22 ± 2°C, humidity: 55 ± 5%, 12:12-hour light-dark cycle) at the animal house of Ravishankar College of Pharmacy, Bhopal, Madhya Pradesh, India. All rats had ad libitum access to standard rat feed and tap water.

This study was conducted after obtaining approval from the Research Advisory Committee (RAC), Institutional Animal Ethics Committee (IAEC) and other relevant authorities of PMCRC (People's University) as well as Ravishankar College of Pharmacy, Bhopal, Madhya Pradesh, India, in compliance with the guidelines of the Committee for Control and Supervision of Experiments on Animals (CCSEA).

All the rats were allowed to acclimatize to the experimental environment for 1 week prior to the experiment.

Induction of type 2 diabetes mellitus[16]

Type 2 diabetes mellitus (T2DM) was induced in male Wistar rats using a high-fat diet (HFD) and low-dose streptozotocin (STZ) protocol adapted from Srinivasan et al. (2005) with minor modifications.

Initially, rats were randomly divided into two groups: a normal pellet diet (NPD) group (n=8) and an HFD group (n=16). The HFD group was fed ad libitum with a high-fat diet (4.58 Kcal/gram) for eight weeks. Subsequently, all rats were fasted for 16 hours, followed by intraperitoneal injection of STZ 25 mg/kg to the HFD group and an equal volume, 1 ml/kg body weight of 0.1 mol/L ice-cold citrate buffer (pH 4.4) as a vehicle control to NPD group. A 5% glucose solution was administered overnight to counteract STZ-induced hypoglycemia.

Forty-eight hours post-injection, fasting blood glucose levels were determined via tail vein blood samples. In HFD group, animals exhibiting blood glucose levels ≥ 200 mg/dl were considered diabetic and divided into two groups for subsequent experiments. Following diabetes induction, the HFD group was transitioned to a normal pellet diet. The High Fat Diet was comprised of several key ingredients. Casein made up 342.0 grams of the diet, while L-Cystine contributed 3.0 grams. Starch and sucrose were both present in equal amounts, at 172.0 grams each. Additionally, the diet included 50.0 grams of cellulose, 25.0 grams of groundnut oil, and 190.0 grams of lard. Rounding out the composition were 35.0 grams of AIN salt mix and 10.0 grams of AIN vitamin mix. In total, the High Fat Diet weighed 999.0 grams.

All the animals were divided into 3 groups, having 8 each (n=8).

Experimental design and distribution of rats in different groups

Group	Treatment	Dose	Route	Duration
1	Normal Control (NC)	2 ml/kg distilled water	Oral	28 days
2	Diabetic Control (DC)	2 ml/kg distilled water	Oral	28 days
3	Donepezil (Don)	4 mg/kg	Oral	28 days

Drug administration was performed daily via oral gavage between 2:00 PM and 3:00 PM for 28 consecutive days. Following a 12-hour fasting period, blood samples were collected for fasting blood glucose assessment, and oral glucose tolerance tests were conducted. Subsequently, animals underwent behavioral evaluations, including the elevated plus maze, novel object recognition test (at 2 and 24

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hours), and Morris water maze to assess memory and learning functions.

General assessments

Body weights of all animals were monitored weekly throughout the experimental period.

Monitoring and Behavioral Tests

Weekly Monitoring

Body weights and fasting blood glucose levels were monitored weekly throughout the 28-day treatment period.

Fasting Blood Glucose Measurement[17]

Fasting blood glucose levels were measured using an Accu-Chek Active glucometer after a 12-hour fast.

Oral Glucose Tolerance Test (OGTT)

Rats underwent an OGTT on the 29th day of treatment, involving a 12-hour fast, an oral glucose load, and blood glucose measurements at 0, 15, 30, 60, and 120 minutes.[17] Glucose tolerance was assessed by calculating the area under the curve (AUC_{0-120}).[18]

Cognitive Function Assessment

Behavioral tests were conducted between 9:00 am and 6:00 pm.

Elevated Plus Maze (EPM)[19]

The EPM test assessed spatial memory, involving a familiarization phase and a retention phase where transfer latency was recorded. Behavioral testing was conducted in a dimly lit, quiet room to minimize external disturbances. The experiment comprised two phases: familiarization and retention. On day one (familiarization), rats were placed individually at the end of an open arm for 90 seconds to acclimate to the EPM environment. Animals unable to enter an enclosed arm within this period were gently guided. The maze was cleaned with 70% ethanol between trials to prevent olfactory cues.

Novel Object Recognition Test (NORt)[20,21]

The NORt assessed short- and long-term memory, utilizing a wooden box, plastic objects, and an overhead camera to record behavior.

The novel object recognition test (NOR) was conducted to assess both short-term (T1) and long-term (T2) memory. The test comprised three phases: habituation, training, and testing. Habituation Rats were acclimated to an empty arena on Day 1. On Day 2, they explored two identical objects (A and B) for 3 minutes, followed by a 2-hour interval. One object (B) was then replaced with a novel object (C), and exploration time was recorded. On Day 3, object A was replaced with a novel object (D) to assess long-term memory. Exploration time was recorded, and a discrimination index was calculated to evaluate memory retention.[19]

Discrimination ratio (DI) = (Time spent with novel object - Time spent with familiar object) / (Time spent with novel object + Time spent with familiar object)

Discrimination index (%) = (Time spent with novel object / (Time spent with novel object + Time spent with familiar object)) x 100

The Morris Water Maze (MWM) test[22] was used to assess spatial learning and memory in rats. The test involved a circular pool of water with a hidden escape platform, and rats were trained for four consecutive days with four trials per day. On the fifth day, a probe trial was conducted without the escape platform to evaluate memory. Following the MWM test, rats were euthanized according to guidelines, and their brains, pancreas, and other vital organs were quickly dissected and preserved for further study.[21]

Data were entered into the excel sheet. Data were analysed using SPSS (Statistical Package for Social Sciences) 25.0 version, IBM, Chicago. Data were analysed for probability distribution using Kolmogorov- Smirnov test and was found to be normally distributed. Descriptive statistics were performed. Inter group comparison was done using One- way ANOVA followed by post hoc tukey test (if required). Intragroup comparison was done using Paired t-test and Repeated measures ANOVA followed by Bonferroni post hoc test (if needed). p value <.05 was considered statically significant.

RESULTS

A one-way ANOVA analysis revealed no significant difference in weight (table 1) between groups at 1 week, but significant differences were observed at 8, 9, 10, 11, and 12 weeks. Post-hoc analysis showed that Group 1 had significantly lower weight than other groups at 8 and 9 weeks. Post-hoc analysis showed significant increases in weight at each subsequent time interval in Group 1, while Groups 2 and 3 showed significant increases at 8 weeks followed by significant reductions at subsequent time intervals.

Table 1: Inter-group and intra-group comparison of body weight.$^{\Omega}$One-way ANOVA for inter-group comparison. $^{\infty}$Repeated measures ANOVA for intra-group comparison. *p-value<.05 was considered statistically significant.

Time interval	Mean ± Standard deviation (grams)			F-value	p-value$^{\Omega}$
	Group 1	Group 2	Group 3		
At 1 week	176.00 ± 7.329	178.25 ± 12.498	175.37 ± 11.636	.346	.882
At 8 weeks	243.75 ± 20.310	372.50 ± 19.272	380.00 ± 10.690	89.309	<.001*
At 9 weeks	250.62 ± 19.899	343.75 ± 15.294	348.12 ± 5.938	67.122	<.001*
At 10 weeks	258.12 ± 20.863	300.00 ± 14.142	306.87 ± 7.039	35.197	<.001*

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At 11 weeks	265.00 ± 21.547	256.87 ± 14.376	270.62 ± 6.232	29.844	<.001*
At 12 weeks	272.50 ± 22.677	221.25 ± 14.820	236.87 ± 10.329	36.926	<.001*
f-value	157.604	524.701	842.852		
p-value$^{\infty}$	<.001*	<.001*	<.001*		

A significant increase in the glucose AUC during the OGTT (table 2) confirmed severe glucose intolerance in the diabetic group 2 and donepezil treated group 3 (p-value <.05) whereas group 1 showed least AUC

Table 2: AUC Glycemic Index

Time interval	Mean ± Standard deviation	Standard Error	95% Confidence Interval for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
Group 1	242.06 ± 9.274	3.27897	234.30	249.81	226.75	256.50
Group 2	938.31 ± 25.463	9.00270	917.02	959.60	903.25	969.00
Group 3	921.37 ± 55.258	19.53694	875.17	967.57	843.50	1000.50

Transfer latency (TL) was measured to evaluate spatial memory in rats. Among all the groups, diabetic control group 2 had maximum TL whereas normal control group 1 had minimum TL (p-value <.05).Compare to the diabetic group, doenepezil treated group 3 had minimum TL. (p-value <.05).
The mean, standard deviation, standard error 95% confidence interval, and range for different variables have been presented in the tables below.

Table 3: Elevated Plus Maze (EPM)

Time interval	Mean ± Standard deviation	Standard Error	95% Confidence Interval for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
Group 1	9.37 ± 1.597	0.56497	8.0390	10.7110	7.0	12.0
Group 2	25.50 ± 2.777	0.98198	23.1780	27.8220	22.0	30.0
Group 3	14.87 ± 1.807	0.63913	13.3637	16.3863	13.0	18.0

Table 4: Inter-group and intra-group comparison of discrimination index. $^{\Omega}$One-way ANOVA for inter-group comparison. $^{\infty}$Paired t-test for intra-group comparison. *p-value<.05 was considered statistically significant.

Time interval	Mean ± Standard deviation			F-value	p-value$^{\Omega}$
	Group 1	Group 2	Group 3		
At 2 hours	67.53 ± 3.210	44.48 ± 4.788	63.39 ± 2.480	52.540	<.001*
At 24 hours	68.83 ± 3.097	43.65 ± 4.727	63.68 ± 3.690	53.825	<.001*
T-value	-.621	.304	-.174	-	
p-value$^{\infty}$	.554	.770	.867	-	-

Table 5: Post hoc analysis (intergroup, discrimination index). *p-value <.05 was considered statistically significant.

Groups	At 2 hours		At 24 hours	
	Difference in mean	p-value	Difference in mean	p-value
Group 1 vs. Group 2	23.04	<.001*	25.18	<.001*
Group 1 vs. Group 3	4.13	.144	5.15	.052
Group 2 vs. Group 3	-18.90	<.001*	-20.02	<.001*

MWM test was performed to evaluate spatial memory and learning in diabetes induced cognitive impaired rats.
The mean, standard deviation, standard error 95% confidence interval, and range for different variables have been presented in the tables below.

Table 6.1. Description of findings of Morris Water Maze in group 1.

GROUP 1						
Variable	Mean ± Standard deviation	Standard Error	95% Confidence Interval for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
Morris escape latency (sec)	4.87 ± 0.834	0.29505	4.17	5.57	4.0	6.0
Time spent in the target quadrant (Sec)	45.50 ± 3.207	1.13389	42.81	48.18	40.0	51.0

No of times crossing platform	6.25 ± 1.035	0.36596	5.38	7.11	5.0	8.0

Table 6.2. Description of findings of Morris Water Maze in group 2.

GROUP 2						
Variable	**Mean ± Standard deviation**	**Standard Error**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
			Lower Bound	**Upper Bound**		
Morris escape latency (sec)	29.12 ± 2.587	0.91491	26.96	31.28	26.0	33.0
Time spent in the target quadrant (Sec)	11.87 ± 1.959	0.69276	10.23	13.51	10.0	15.0
No of times crossing platform	1.62 ± 0.744	0.26305	1.00	2.24	1.0	3.0

Table 6.3 Description of findings of Morris Water Maze in group 3

GROUP 3						
Variable	**Mean ± Standard deviation**	**Standard Error**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**
			Lower Bound	**Upper Bound**		
Morris escape latency (sec)	11.37 ± 1.302	0.46049	10.28	12.46	9.0	13.0
Time spent in the target quadrant (Sec)	24.62 ± 3.335	1.17925	21.83	27.41	20.0	30.0
No of times crossing platform	4.00 ± 0.755	0.26726	3.36	4.63	3.0	5.0

Escape latency was observed highest in group 2 and lowest in group 1((p-value <.05).).
The escape latency in decreasing order was seen in:Group 2 > Group 3 > Group 1. One-way ANOVA revealed a significant difference between the groups (p-value <.05). On post hoc analysis, it was found that Escape latency in Group 2 was significantly greater than that in other groups (p-value <.05).

Table 7: Inter-group comparison of escape latency. $^{\Omega}$One-way ANOVA for inter-group comparison. *p-value<.05 was considered statistically significant.

Variable	**Mean ± Standard deviation (seconds)**			**F-value**	**p-value$^{\Omega}$**
	Group 1	**Group 2**	**Group 3**		
Escape latency	4.87 ± 0.834	29.12 ± 2.587	11.37 ± 1.302	195.891	<.001*

Table 8: Post hoc analysis (intergroup, escape latency).*p-value <.05 was considered statistically significant.

Groups	**Escape latency**	
	Difference in mean	**p-value**
Group 1 vs. Group 2	-24.25	<.001*
Group 1 vs. Group 3	-6.50	<.001*
Group 2 vs. Group 3	17.75	<.001*

Time spent in the target quadrant
The time spent in the target quadrant in decreasing order was seen in:
Group 1 > Group 3 > Group 2
One-way ANOVA revealed a significant difference between the groups (p-value <.05). On post hoc analysis, it was found that time spent in the target quadrant in Group 1 was significantly greater than that in other groups (p-value <.05).Time spent in the target quadrant in Group 3 was significantly greater than that in Group 2 (p-value <.05).

Table 9: Inter-group comparison oftime spent in the target quadrant.$^{\Omega}$One-way ANOVA for inter-group comparison. *p-value<.05 was considered statistically significant.

Variable	**Mean ± Standard deviation (seconds)**				
	Group 1	**Group 2**	**Group 3**	**F-value**	**p-value$^{\Omega}$**
Time spent in target quadrant	45.50 ± 3.207	11.87 ± 1.959	24.62 ± 3.335	108.805	<.001*

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Table 10: Post hoc analysis (inter group, time spent in the target quadrant).*p-value <.05 was considered statistically significant.

Groups	Time spent in the target quadrant (seconds)	
	Difference in mean	p-value
Group 1 vs. Group 2	33.62	<.001*
Group 1 vs. Group 3	20.87	<.001*
Group 2 vs. Group 3	-12.75	<.001*

Number of times crossing platform

The mean number of times crossing platform in decreasing order was seen in:

Group 1 > Group 3 > Group 2

One-way ANOVA revealed a significant difference between the groups (p-value <.05). On post hoc analysis, it was found that the number of times crossing platform in Group 1 was significantly greater than that in other groups (p-value <.05).The number of times crossing platform in Group 3 was significantly greater than that in Group 2 (p-value <.05).

Table 11: Inter-group comparison of the number of times crossing platform.$^{\Omega}$One-way ANOVA for inter-group comparison.*p-value<.05 was considered statistically significant.

Variable	Mean ± Standard deviation (seconds)			F-value	p-value$^{\Omega}$
	Group 1	Group 2	Group 3		
Number of times crossing platform	6.25 ± 1.035	1.62 ± 0.744	4.00 ± 0.755	27.440	<.001*

Table 12: Post hoc analysis (intergroup, number of times crossing platform).*p-value <.05 was considered statistically significant.

Groups	Number of times crossing platform	
	Difference in mean	p-value
Group 1 vs. Group 2	4.62	<.001*
Group 1 vs. Group 3	2.25	<.001*
Group 2 vs. Group 3	-2.37	<.001*

DISCUSSION

Type 2 diabetes mellitus (T2DM) has emerged as a significant global health challenge, characterized by a complex interplay of genetic, environmental, and lifestyle factors. Obesity, a prevalent component of this metabolic disorder, contributes to insulin resistance and the subsequent decline of beta cell function. These pathological changes underlie the development of numerous micro- and macrovascular complications, among which neurodegeneration and cognitive impairment have garnered considerable attention.

To effectively investigate the mechanisms underlying diabetes-induced cognitive impairment, an appropriate animal model is essential. The high-fat diet (HFD)-low-dose streptozotocin (STZ) rat model has been widely adopted to mimic the pathophysiological features of human T2DM, including obesity, insulin resistance, and partial beta cell loss. This model offers a valuable platform to explore the cognitive deficits associated with diabetes and to evaluate potential therapeutic interventions.

Previous studies have consistently demonstrated that a high-fat diet regimen of 2-8 weeks induces insulin resistance in rats. Subsequent administration of low-dose STZ (15-35 mg/kg) to these insulin-resistant rats results in the development of hyperglycemia, characterized by blood glucose levels exceeding 200 mg/dl, mimicking the metabolic profile of type 2 diabetes. Our findings align with these previous reports, as rats subjected to both 8 weeks high-fat feeding and low-dose (25 mg/kg) STZ injection exhibited hyperglycemia consistent with the established T2DM phenotype.[16]

Our study demonstrated that donepezil had no significant impact on body weight. Both donepezil-treated and diabetic control groups experienced comparable weight loss, suggesting that donepezil does not influence weight management in the context of type 2 diabetes.

Consistent with the findings of Gomaa et al. (2021),[23] our study demonstrated that donepezil (4 mg/kg) exerted no significant influence on blood glucose levels in a type 2 diabetes mellitus (T2DM) rat model. Furthermore, oral glucose tolerance tests (OGTT) revealed no improvement in glucose tolerance in donepezil-treated rats compared to the diabetic control group, as evidenced by comparable area under the curve (AUC) values. These results collectively indicate that donepezil, at the administered dose, lack a discernible impact on glucose metabolism and do not possess glucose-lowering properties in the context of T2DM.

In alignment with the findings of Ojha et al. (2022),[24] who reported reduced transfer latencies to enclosed arms of the elevated plus maze in an AlCl3-induced Alzheimer's disease rat model,our study demonstrated a similar improvement in anxiety-like behavior in donepezil-treated T2DM rats. This observed decrease in transfer latency suggests that donepezil treatment

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may alleviate anxiety-related components of cognitive impairment associated with T2DM, thereby contributing to enhanced spatial memory.

Similar to the findings of Ojha et al. (2022)[24] who reported improved object recognition in an AlCl3-induced Alzheimer's disease (AD) rat model following donepezil (3 mg/kg) treatment, our study demonstrated enhanced non-spatial memory in a T2DM rat model treated with donepezil (4 mg/kg). Both studies observed increased exploration time for novel objects and improved discrimination indices compared to untreated disease controls. These findings suggest that donepezil may possess a comparable efficacy in ameliorating cognitive deficits associated with both AD and T2DM, although further research is warranted to directly compare the two disease models.

Consistent with the findings of Gomaa et al. (2021),[23] our study demonstrated impaired spatial memory in T2DM rats,as evidenced by increased escape latency and decreased time spent in the target quadrant during the Morris water maze task. Similar to their observations, donepezil treatment (4 mg/kg) significantly ameliorated these cognitive deficits, reducing escape latency and increasing time spent in the target quadrant. Furthermore, our study extended these findings by incorporating platform crossing as an additional measure of spatial memory. We observed a significant increase in the number of platform crossings in the donepezil-treated group compared to diabetic controls, further supporting the cognitive enhancing effects of donepezil in this model.

Similar to the findings of Ojha et al. (2022),[24] our study demonstrated the efficacy of donepezil (4 mg/kg) in ameliorating spatial memory deficits in a T2DM rat model. Similar to their observations in an AlCl3-induced AD model, donepezil significantly reduced escape latency in the Morris water maze task, indicating improved spatial learning and memory.

Our findings demonstrated that donepazil effectively ameliorated cognitive deficits, as evidenced by improvements in spatial and non-spatial memory but having no improvement on blood glucose level and body weight.

CONCLUSION

This study investigated the neuroprotective effects of donepezil on cognitive impairment in a type 2 diabetes mellitus (T2DM) rat model. The results showed that donepezil significantly improved spatial and non-spatial memory, reducing anxiety-like behavior and enhancing cognitive function. However, donepezil had no effect on blood glucose levels or body weight. These findings suggest that donepezil may be a potential therapeutic agent for ameliorating cognitive deficits associated with T2DM, without affecting glucose metabolism or weight management.

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