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EVALUATION OF HYPOGLYCEMIC POTENTIAL OF CUMINUM CYMINUM AND ITS ROLE IN MODULATION OF COGNITIVE FUNCTION IN RATS WITH INDUCED DIABETES

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ABSTRACT

Background: This study investigated the effects of *Cuminum cyminum (C. cyminum)* on cognitive behaviour and acetylcholinesterase (AChE) levels in diabetic rats, comparing its efficacy with Glibenclamide, Sulbutiamine, and Resveratrol.

Methods: Wistar rats were randomized into 12 groups (n=10) half diabetic and half non-diabetic controls and administered *C. cyminum* 500 mg/kg and 1000 mg/kg, Glibenclamide (5 mg/kg), Sulbutiamine (50 mg/kg), and Resveratrol (25 mg/kg). Controls included diabetic and non-diabetic rats without treatment. Blood glucose, insulin, oxidative stress markers, and AChE levels were measured, along with behavioural parameters of learning and memory using the elevated plus maze, passive avoidance, and Morris water maze.

Results: Both doses of *C. cyminum* significantly reduced blood glucose levels (Dose I decreased blood glucose levels from 278.5 ± 3.66 mg/dl to 136.8 ± 4.91 mg/dl while dose II decreased the blood glucose levels to 138.8 ± 3.83 mg/dl) and improved learning and memory, as evidenced by faster transfer latency (TL) and better retention in the elevated plus maze and Morris water maze. The higher dose was particularly effective in reducing brain AChE levels and improving cognitive performance in passive avoidance tests.

Conclusion: Both doses of *C. cyminum* decreased the AChE activity induced by diabetes, improving learning and memory. The antioxidant and anti-hyperglycaemic potential may partially contribute to delaying cognitive impairment. Thus, the study suggests that *C. cyminum* may be beneficial in mitigating behavioural and biochemical changes associated with diabetes mellitus, offering potential as a complementary therapy to existing diabetes treatments. Elaborate studies in the future are essential to explore its antidiabetic and neuroprotective potential.

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INTRODUCTION

Diabetes is a severe, chronic condition marked by high blood glucose levels resulting from the effects of abnormal cell biology on insulin function [1,2]. Type 2 diabetes impacted 462 million people worldwide in 2017, accounting for 6.28% of the population (4.4% of those aged 15 to 49, 15% of people aged 50 to 69, and 22% over 70). This corresponds to a prevalence rate of 6059 cases per 100,000 people. By 2030, the global prevalence of type 2 diabetes is expected to reach 7079 cases per 100,000 people, demonstrating an ongoing rise in all geographical areas across the world [3]. India has the highest number of diabetes patients, which has earned it the reputation of being the '*Diabetes Capital of the World*'. According to projections, 77 million people in India had diabetes in 2019, and by 2045, the number is predicted to reach over 134 million unless the Government of India intervenes with proper and effective steps to control the disease [4]. Diabetes mellitus is characterized by gradual organ damage of the brain, blood vessels, kidneys, eyes as well as heart [5].

Impairments in cognitive function and memory, along with psychomotor decline and reduced mental capacity, have also been observed as a part of diabetes-induced neurobiological changes [6–10]. The American Diabetes Association has recognized the increasing incidence of cognitive impairment among older adults with diabetes. Their 2023 guidelines recommend routine screening for cognitive impairment in adults aged 65 and older with diabetes [11]. A recent systematic review and meta-analysis estimated that up to 45% of individuals with type 2 diabetes mellitus (T2DM) suffer from mild cognitive impairment [12]. Another meta-analysis encompassing 122 studies found that diabetes mellitus increases the risk of cognitive impairment and dementia by 1.25 to 1.91 times [13]. In the Indian subcontinent, a community-based study from Puducherry revealed that nearly one-third of older adults with diabetes are at risk of cognitive decline [14]. These studies highlight the urgent need for effective management strategies to address the increased risk of cognitive decline in diabetic patients. The exact mechanism of diabetes resulting in central nervous system damage is not completely clear; it's explained to be a multi-factorial causation involving a series of gradual cerebrovascular and metabolic disturbances resulting due to consistent blood glucose level fluctuations [15]. One potential mechanism contributing to cognitive dysfunction in T2DM is the development of insulin resistance in the brain [16]. Insulin resistance disrupts insulin signaling pathways that are essential for synaptic plasticity and cognitive function, leading to neuronal dysfunction and cognitive impairment [17].

Overnutrition and obesity, often precursors to T2DM, have been associated with disruption of the blood-brain barrier. This disruption leads to a state of neuroinflammation, which subsequently results in cognitive dysfunction. [18]. It is shown that hyperglycemia builds up oxidative stress in different brain areas, which plausibly causes cognitive deficit [19,20]. Diabetes often causes microvascular and macrovascular complications, leading to reduced cerebral blood flow and impaired oxygen delivery to the brain. This vascular damage can further contribute to cognitive deficits [21]. Numerous studies have demonstrated that alterations in the cholinergic system lead to increased AChE levels in the brain, which further potentiates cognitive impairments in diabetes mellitus [22,23]. Using ethnobotanicals and herbal medicines has a long traditional history in managing diabetes mellitus. *C. cyminum* (Family: Apiaceae), commonly known as jeera, is a popular food-based home ingredient used in indigenous systems of medicine as a remedy for various common ailments. Jeera is used as a stimulant and carminative. It is well known that *C. cyminum* reduces superficial inflammation and pain, it is also eulogized for its galactogog properties. Traditional medicine systems, including Ayurveda, have used cumin for managing diabetes, and it is believed to help regulate blood sugar levels. Studies have supported this use, showing that cumin extract can significantly lower blood glucose levels. It is also known as an effective blood sugar-reducing agent, depicted by its effects on glucosuria and reduction of hyperglycaemia [24,25]. There was also additional improvement in the effective body weights of diabetic animals put on a cumin diet. Dietary cumin also improved metabolic impairments, as demonstrated by decreased blood urea levels and reduced urea and creatinine excretion in diabetic animals [26, 27]. *C. cyminum* treatment has shown significant hypolipidemic effects in diabetic rats. Specifically, it has led to a notable reduction in plasma and tissue levels of cholesterol, phospholipids, free fatty acids, and triglycerides [28]. Given the hypoglycemic and antioxidant properties of *C. cyminum*, the study hypothesis was that *C. cyminum* will exhibit significant therapeutic effects in managing oxidative stress, hyperglycemia, and cognitive dysfunction in diabetic rats. The study also hypothesizes that *C. cyminum* will modulate AChE levels in the brains of diabetic rats. Glibenclamide is an

antidiabetic drug with well-established efficacy and mechanism of action. Its effectiveness and consistent results in clinical and preclinical settings make it a reliable standard for comparison. Research has shown that many herbal treatments, including *C. cyminum*, exhibit anti-diabetic properties through mechanisms that can complement or enhance the effects of conventional drugs like Glibenclamide. Sulbutiamine is chosen as a comparator in the current study because of its established cognitive enhancement capabilities and its multifaceted mechanism of action, which provides a robust standard for evaluating the cognitive benefits of *C. cyminum*. Resveratrol is a potent antioxidant used to compare the antioxidant capabilities of *C. cyminum*. These comparisons help to validate the efficacy of *C. cyminum* in potentially offering a natural alternative or complementary therapy for cognitive dysfunctions associated with diabetes. The overall objective of the research was to evaluate the potential therapeutic effects of *C. cyminum* on oxidative stress modulation, hyperglycemia, and cognitive function in diabetic rats and its comparative analyses with established agents such as the antioxidant Resveratrol, the antidiabetic drug Glibenclamide, and the cognition enhancer Sulbutiamine to determine the efficacy and potential of *C. cyminum* as a multi-faceted therapeutic agent.

MATERIALS AND METHODS

Animals

It was an open-label, prospective, randomized, controlled animal study. Wistar rats of both sexes with a weight range of 150-200g, aged 6-8 weeks, were randomly allocated into different groups of ten each and numbered. The rats were obtained from Central Animal House, University College of Medical Sciences, Delhi. The rats were maintained under standard laboratory conditions (natural light-dark cycle; temperature 22±1°C and relative humidity 50±2%) and with proper hygiene settings in polypropylene cages with paper bedding. The feeding of animals consisted of a standard pelleted diet, and water was given ad libitum. Prior acclimatization of rats to the general laboratory conditions was done. On the day of the experiment, animals were kept in an overnight fasting state to avoid any dietary influence on drug absorption; routine water intake was allowed. The study protocol was approved by the Institutional Animal Ethics Committee of the University College of Medical Sciences, Delhi (Approval No: 05/IAEC/UCMS/2010). Animals were taken care of as per the Committee for the Purpose of Control and Supervision of Experiments on Animals Guidelines.

Preparation of plant extract

The seeds of *C. cyminum* were procured commercially from a herbal company based in Noida, Delhi NCR, India. The extract preparation process was done in The Indian Council of Agricultural Research (ICAR), Pusa campus, New Delhi. Seeds were powdered in a grinder and extracted with methanol in a soxhlet assembly for 48 h. The methanolic extract was further air dried to obtain a semisolid mass of 10–12% w/w, stored at 4–8º C, and suspended in 0.5% w/v sodium CMC before use. The extract was authenticated in the Department of Pharmacognosy of the same institute (Authentication number ICAR/543/2010).

Drugs and treatment schedule

Methanolic extract of *C. cyminum* seeds was administered in two doses: Dose I at 500 mg/kg orally (p.o.) and Dose II at 1000 mg/kg p.o. Distilled water, used as the vehicle for *C. cyminum*, served as a control in non-diabetic rats. The chemicals were procured from Sigma Aldrich Chemicals Private Ltd, Delhi. Nicotinamide was administered at a dose of 230 mg/kg, streptozotocin (STZ) at 50 mg/kg, glibenclamide orally at 5 mg/kg, resveratrol orally at 25 mg/kg, and sulbutiamine orally at 50 mg/kg. All the chemicals used were of analytical grade.

Diabetes mellitus induction

Induction of diabetes was done in overnight fasting rats by administration of a single intraperitoneal (i.p.) injection of nicotinamide (230 mg/kg) followed by (15 minutes later) injection of STZ (50 mg/kg) dissolved in citrate buffer maintained at pH 4.5. Estimation of fasting blood glucose levels was done till stabilization of glucose levels (i.e., similar fasting blood glucose levels in three consecutive samples). Drug treatment was started from the next day (counted as day 1), and treatment continued till day 30. During the experiment, rats were allocated into 12 groups, with 10 rats per group (n=10 each) following simple randomization. Group 1 consisted of non-diabetic control rats administered distilled water (the vehicle for *C. cyminum*) orally (p.o.). Group 2 served as the diabetic control group, with diabetes induced by nicotinamide (230 mg/kg, i.p.) and STZ (50 mg/kg, i.p.). Group 3 included diabetic rats receiving dose I of *C. cyminum* (500 mg/kg, p.o.), while Group 4 comprised non-diabetic rats given the same doses of *C. cyminum* (500 mg/kg, p.o.). Group 5 consisted of diabetic rats administered dose II of *C. cyminum* (1000 mg/kg, p.o.), and Group 6 included non-diabetic rats receiving the same doses. In Group 7, diabetic rats were treated with glibenclamide (5 mg/kg,

p.o.), while non-diabetic rats in Group 8 received the same treatment. Group 9 included diabetic rats administered resveratrol (25 mg/kg, p.o.), and Group 10 consisted of non-diabetic rats receiving the same doses. Finally, Group 11 comprised diabetic rats treated with sulbutiamine (50 mg/kg, p.o.), while Group 12 included non-diabetic rats given sulbutiamine at the same doses. The diabetic and non-diabetic animals were placed in separate cages, and their serum glucose, body weight, insulin, cognition assessment, and AChE levels were measured at specified time points and compared.

Evaluation of anti-hyperglycaemic activity

Assessment of blood glucose levels

Blood samples were drawn from the retro-orbital plexus of rats kept fasting. Blood glucose estimation was done using the glucose oxidase method (Kit Q-line) on the Selectra Pro-XL Chemistry Analyzer Model. Rats exhibiting fasting blood glucose levels of 200 mg/dL or higher were categorized as diabetics.

Measurement of blood insulin levels

Blood samples were collected, and insulin levels were estimated using commercially available insulin ELISA kits (from DiaMetra). This is a direct solid-phase enzyme immunoassay performed on a BioRad ELISA reader.

Evaluation of Cognitive function

A group of diabetic rats was allocated to evaluate cognitive function. They were administered sulbutiamine (50 mg/kg, p.o.), a cognition enhancer. This group was then compared with groups treated with *C. cyminum*.

Behavioural paradigms to assess learning and memory

Elevated plus maze (EPM): Transfer latency (TL)

In animal models, TL in the elevated plus maze test is critical for assessing cognitive functions, particularly learning and memory. Comparing TL before and after drug administration helps to evaluate the drug's impact on learning and memory. In this study, TL was assessed in the elevated plus maze one day before diabetes induction and then on days 14 and 29. TL is the time taken by an animal to move from an open arm (2 in no., 50 × 10 cm) to a closed arm (2 in no., 50 × 10 × 40) of the maze [29]. If the animal did not enter a closed arm within the first 90 seconds, it was excluded from the experiment. Retention latency (RL) was assessed 24 hours after the first day of the trial (on days 1, 15, and 30).

Continuous avoidance apparatus: Step down latency (SDL)

SDL, assessed using the continuous avoidance apparatus, provides a reliable and quantifiable method for evaluating cognitive functions, particularly learning and memory, in animal models. The apparatus consists of an insulated platform at the center of a metal grid floor, serving as a shock-free zone. The rat was positioned in this shock-free zone, and when it stepped down, it received an electric shock of 20V through the grid floor. The time taken for the rat to step down was measured and referred to as SDL. A prolongation of SDL serves as a parameter for learning [30]. Retention was examined 24 hours after the first day of the trial (on days 1, 15, and 30).

Spatial navigation task in Morris water maze

The Morris water maze is a widely utilized behavioural test for evaluating spatial navigation and memory in animal models. It provides comprehensive insights into cognitive function and its modulation by various factors. In this study spatial navigation task was studied using a modified method developed by Morris to measure acquisition and retention parameters [31,32]. Training for swimming in rats was conducted to reach a visible stage in a circular pool (60 cm high; 180 cm in diameter) filled with water (28 ± 2˚C) to a depth of 40 cm. A circular platform (9 cm in diameter) mounted on a column was placed in the pool. Maze acquisition and maze RL were measured by positioning the platform 2 cm above and 2 cm below the water level. The pool was divided into four equal quadrants by marking the edges with directional points (E, W, N, and S), which served as starting points for the task. The water in the pool was rendered opaque by adding a non-toxic dye, and the circular platform was placed in the center of one of the quadrants.

Training for Maze acquisition

Rats were given a training session consisting of four trials, with a different starting position in each trial. At the beginning of each trial, the rat was released into the maze facing the pool wall. The latency to find the circular escape platform was recorded, with a maximum limit of 3 minutes. The time taken by the animal to reach the platform was noted as the initial acquisition latency (IAL). After each trial, the animals were returned to their cages, with a 5-minute interval between subsequent trials.

Maze retention phase

Following the maze acquisition phase, on days 15 and 30 after the IAL, animals were released from a random edge of the pool, facing the wall, to test retention. The time to find the hidden platform on days 15 and 30 of treatment with the study drugs was recorded as the first retention latency (1st RL) and the second retention latency (2nd RL), respectively. After that, the platform was removed from the water maze, and the total time spent by the rat in the "target quadrant" on days 15 and 30 of treatment was noted as the first quadrant time (QT-1) and the second quadrant time (QT-2), respectively. The evaluation of cognitive function in animals was conducted one day before diabetes induction and on days 15 and 30 after blood glucose levels had stabilized. If an animal did not exhibit any cognitive impairment even after 30 days, the experiment was extended to 45 days.

Measurement of Enzymatic activity

After completing all assessments on day 30, the animals were euthanized under halothane anesthesia. The brain was then removed, and biochemical parameters were assessed.

Sacrificing the animal and tissue preparation

At the end of the experiment, rats were euthanized under halothane anesthesia. A midline incision was made to remove the skin of the scalp, and the incision was also made on the dorsal neck to cut open the skull. The scalp was dissected, the skull opened, and the whole brain was gently scooped out of the cranial cavity using a steel spatula. The brain was washed immediately in ice-cold sodium phosphate buffer. It was then blotted dry, and weight was noted. The half brain tissue was dissected longitudinally and homogenized with 10 times (w/v) sodium phosphate buffer (7.4 pH, ice cold, mixture of KH2PO4 and Na_2HPO_4). The homogenate yield was centrifuged at 3000 rpm for 15 min with final supernatant AChE activity was estimated.

Acetylcholinesterase (AChE) level estimation

The estimation of brain AChE activity was performed photometrically using the method described by Ellman et al. (1961) [33]. In this method, thiocholine is formed from acetylthiocholine iodide in the presence of tissue cholinesterase. The rate of thiocholine formation was measured by reacting it with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB). Enzyme activity was assessed by tracking the increase in yellow color produced when thiocholine reacts with the dithiobisnitrobenzoate ion. The optical density of the resulting yellow compound was measured at 412 nm every minute for 3 minutes. Finally, AChE activity was calculated.

Estimation of malondialdehyde (MDA) levels

MDA estimation, a measure of lipid peroxidation, was conducted spectrophotometrically using the method described by Ohkawa et al. (1979) [34]. To 0.5 ml of the supernatant obtained previously, 1.5 ml of 20% acetic acid (pH 3.5), 0.2 ml of 8.1% sodium lauryl sulfate, and 0.8% thiobarbituric acid were added. The mixture was then heated at 1000°C for 1 hour in a boiling water bath, cooled under running tap water, and supplemented with 5 ml of butanol:pyridine (15:1, % v/v) and 1 ml of distilled water. After vigorous vortexing, the mixture was centrifuged at 4000 rpm for 10 minutes.

The organic layer was then withdrawn, and absorbance was measured at 532 nm using a spectrophotometer. MDA concentration was determined using a linear standard curve and expressed as nmol/g of wet brain tissue.

Assessment of reduced glutathione (GSH) levels

The determination of reduced GSH followed the method described by Ellman (1959) [35]. A 0.3 M phosphate buffer (K_2HPO_4, pH 8.4), 0.4% w/v 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) in 1% trisodium citrate, and tricarboxylic acid (TCA) were used. To 0.5 ml of the supernatant obtained above, 1 ml of 5% TCA was added, and the mixture was centrifuged to remove proteins. To 0.1 ml of this homogenate, 4 ml of 0.3 M phosphate buffer (pH 8.4), 0.5 ml of DTNB, and 0.4 ml of double-distilled water were added.

The mixture was vortexed, and absorbance was read at 412 nm within 15 minutes. Absorbance readings were plotted against the concentration of GSH to generate a standard curve. The reduced GSH concentration was determined using this linear standard curve and expressed as µg/g of wet brain tissue.

Statistical analysis

SPSS version 23 was used for statistical analysis. The continuous variables were presented as Mean ± Standard error of mean (SEM). Group comparisons were done through one-way analysis of variance (ANOVA) analysis. This was followed by a Tukey HSD post hoc test to determine the overall significance.

RESULTS

Effect of drug treatment on blood glucose levels and serum insulin levels (x30 days)

In non-diabetic rats, none of the studied agents significantly affected blood glucose and serum insulin levels on either day 0 or day 30 when compared to the non-diabetic control group (distilled water). In rats with diabetes, at day 30, *C. cyminum* dose I group (500 mg/kg), dose II group (1000 mg/kg), glibenclamide group (5 mg/kg) and resveratrol group (25 mg/kg) showed significant reduction ($p<0.001$) in blood glucose levels as compared to nicotinamide + STZ (diabetic control) group. However, unlike other groups sulbutiamine group (50 mg/kg) did not cause any significant difference in blood glucose measurements when compared to nicotinamide + STZ (diabetic control) group **(Table 1).** At day 30, *C. cyminum* dose I group (500 mg/kg), dose II group (1000 mg/kg) and glibenclamide group (5 mg/kg) showed significant reduction ($p<0.05$) in blood insulin levels as compared to nicotinamide + STZ (diabetic control) group.

Table 1: Effect of drug treatment (x30 days) on blood glucose levels in Nicotinamide + STZ induced-diabetic rats.

Groups	Dose and route (mg/kg, p.o)	Blood glucose (mg/dl) (Mean ± SEM)	
		Day 1	Day 30
Distilled water (non-diabetic control)	Vehicle of *C. cyminum*	80.0 ± 2.84	78.5 ± 2.49
Nicotinamide + STZ (diabetic control)	230 + 50, i.p.	273.6 ± 2.89	278.5 ± 3.66 [a]
C. cyminum Dose I+ STZ	500	288.8 ± 15.78	136.8 ± 4.91 [a, b]
C. cyminum Dose II + STZ	1000	284.3 ± 18.36	138.8 ± 3.83 [a, b]
Sulbutiamine + STZ	50	269.8 ± 5.63	267.6 ± 4.73 [a]
Resveratrol + STZ	25	274.5 ± 4.95	206.6 ± 9.66 [a, b]
Glibenclamide + STZ	5	273.3 ± 6.90	174.3 ± 5.20 [a, b]

Abbreviations: STZ: Streptozotocin; SEM: Standard error of mean;
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
[a] $p<0.001$ vs. non-diabetic control, [b] $p<0.001$ vs. Nicotinamide + STZ induced diabetic control

Table 2: Effect of drug treatment on Acquisition and Retention phase of TL in Nicotinamide + STZ induced-diabetic rats (x30 days)

Groups	Dose and route (mg/kg, p.o.)	Acquisition of TL (seconds) Mean ± SEM			Retention of TL (seconds) Mean ± SEM		
		Day 0	Day 14	Day 29	Day 1	Day 15	Day 30
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	68.2 ± 7.44	54.8 ± 8.14	25.2 ± 2.30	49.3 ± 11.07	28.2 ± 4.96	18.6 ± 2.50
Nicotinamide + STZ (Diabetic Control)	230 + 50, i.p.	85.0±3.77	73.0±9.53	67.6±7.31[a]	70.1 ± 7.35	58.8±10.29	54.2 ± 6.16 [a]
C. cyminum Dose I + STZ	500	76.1± 5.16	45.4± 5.28	37.1± 5.42 [b, c]	58.5 ± 6.59	34.8± 4.55	19.7± 4.01 [c]
C. cyminum Dose II + STZ	1000	74.2± 5.07	46.2± 4.32	41.7± 2.44 [a, c]	57.8± 5.57	43.2± 3.32	19.0± 4.45 [b]
Sulbutiamine + STZ	50	82.1±4.66	62.8± 9.44	39.6± 5.39 [a, c]	75.0± 4.35	46.0± 8.82	25.3 ± 5.11 [d]
Resveratrol + STZ	25	67.7± 8.47	60.8± 8.38	44.5± 6.14 [a, c]	64.8± 7.93	47.7± 7.21	31.2± 5.81
Glibenclamide + STZ	5	67.1± 6.73	56.8± 5.97	48.6± 6.35 [a, c]	51.8± 7.85	46.6± 4.52	32.9± 5.91

Abbreviations: STZ: Streptozotocin; TL: Transfer latency; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
For acquisition of TL: [a] $p<0.001$ vs. non-diabetic control, [b] $p<0.01$ vs. non- diabetic control, [c] $p<0.001$ vs. Nicotinamide + STZ diabetic control **For retention of TL:** [a] $p<0.001$ vs. non-diabetic control, [b] $p<0.001$ vs. Nicotinamide + STZ diabetic control, [c] $p<0.01$ vs. Nicotinamide + STZ diabetic control, [d] $p<0.05$ vs. Nicotinamide + STZ diabetic control

Effect of drug treatment on behavioural parameters of learning and cognition (x30 days)

Acquisition of TL in elevated plus-maze apparatus

In non-diabetic rats, none of the studied agents showed a significant change in the acquisition of TL time across all three periods (day 0, day 14, and day 29) compared to the non-diabetic control group (distilled water). In diabetic rats on day 29, the Nicotinamide + STZ group showed a significant increase in the acquisition of TL ($p<0.001$) compared to the non-diabetic control group (distilled water), suggesting diabetes-induced cognitive impairment. In comparison with the Nicotinamide + STZ (diabetic control) group, the groups that demonstrated significant reduction in acquisition of TL are C. cyminum dose I and dose II group, Sulbutiamine, Resveratrol, and Glibenclamide group, suggesting improved cognitive function. **(Table 2).**

Retention of TL in elevated plus-maze apparatus

In non-diabetic rats, none of the studied agents showed a significant change in the retention of TL time across all three periods (day 1, day 15, and day 30) when compared to the non-diabetic control group (distilled water). However, in diabetic rats, on day 30, there was a significant increase in the retention of TL in the Nicotinamide + STZ group ($p<0.001$) compared to the non-diabetic control group. This suggests that diabetes induces cognitive impairment, as evidenced by reduced memory retention in the elevated plus maze test. Among the diabetic groups, a significant reduction in the retention of TL was observed in both the *C. cyminum* (dose I and dose II) and Sulbutiamine groups compared to the Nicotinamide + STZ (diabetic control) group. This indicates that these treatments effectively mitigate the cognitive decline associated with diabetes, improving memory retention. However, the Resveratrol and Glibenclamide groups did not show any significant difference in the retention of TL compared to the Nicotinamide + STZ group, suggesting they may be less effective in this regard. **(Table 2).**

SDL using continuous avoidance apparatus: Acquisition phase

In non-diabetic rats, none of the agents studied demonstrated a significant change in the acquisition of SDL time across all three periods: day 0, day 14, and day 29, compared to the non-diabetic control group. On the 29th day, a significant reduction in the acquisition of SDL was observed in the Nicotinamide + STZ group ($p < 0.001$) compared to the non-diabetic control group. The significant reduction in SDL acquisition suggests impaired cognitive function in diabetic conditions induced by Nicotinamide + STZ. When compared with the Nicotinamide + STZ (diabetic control) group, the groups that showed a significant increase in SDL acquisition were the *C. cyminum* dose I and dose II groups, Sulbutiamine group, Resveratrol group, and Glibenclamide group **(Table 3).** These results indicate the potential cognitive benefits of these treatments. Improved SDL acquisition suggests enhanced learning and memory abilities, potentially mitigating the cognitive deficits associated with diabetes.

SDL using continuous avoidance apparatus: Retention phase

In non-diabetic rats, none of the studied agents exhibited a significant change in the retention of SDL time across all three periods, day 1, day 15, and day 30, compared to the non-diabetic control group treated with distilled water. Among the Nicotinamide + STZ-induced diabetic groups, no significant change was observed in any group on day 1 and day 15. This suggests that early stages of diabetes induction might not immediately affect cognitive function as measured by SDL retention. However, on day 30, a significant reduction in the retention of SDL was observed in the Nicotinamide + STZ group ($p < 0.001$) compared to the non-diabetic control group treated with distilled water, indicating impaired cognitive function after prolonged diabetic conditions. When compared with the Nicotinamide + STZ (diabetic control) group, the groups that showed a significant increase in SDL retention were the C. cyminum dose I and dose II groups, Sulbutiamine group, Resveratrol group, and Glibenclamide group **(Table 3).** Improved SDL retention indicates better cognitive function, possibly mitigating the cognitive deficits associated with diabetes.

Retention of Spatial navigation task in Morris Water Maze

In non-diabetic rats, none of the studied agents showed significant change in IAL and RL time on day '15' (RL-1) and day '30' (RL-2) as compared to the non-diabetic control (Distilled water) group, indicating that none of these agents affect spatial learning and memory in non-diabetic rats. On the 15th day, a significant increase in RL-1 was seen in the Nicotinamide + STZ group ($p<0.001$) compared to the non-diabetic control group (Distilled water). However, the *C. cyminum* dose I and II groups, Sulbutiamine group, Resveratrol

group, and Glibenclamide group showed a significant reduction in RL-1 compared to the Nicotinamide + STZ (diabetic control) group, indicating that these treatments can mitigate the cognitive impairments caused by diabetes, improving memory retention. On the 30th day, a significant increase in RL-2 was again observed in the Nicotinamide + STZ group ($p<0.001$) compared to the non-diabetic control group. All treatment groups demonstrated a significant reduction in RL-2 compared to the Nicotinamide + STZ group, further confirming the effectiveness of these treatments in improving memory retention in diabetic conditions. **(Table 4).**

Table 3: Effect of drug treatment on Acquisition and retention of SDL in Nicotinamide+STZ induced-diabetic rats (x30 days)

Groups	Dose and route (mg/kg, p.o.)	Acquisition of SDL (seconds) Mean ± SEM			Retention of SDL (seconds) Mean ± SEM		
		Day 0	Day 14	Day 29	Day 1	Day 15	Day 30
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	174.8±16.99	216.6±16.22	268.0±11.54	240.6±16.56	259.7±16.24	292.6±3.33
Nicotinamide + STZ (Diabetic Control)	230+50,i.p.	161.1±19.31	162.2±20.30	178.5±29.6[a]	167.5±13.23	171.0±18.9	184.8±12.09[a]
C. cyminum Dose I+ STZ	500	187.5±14.89	219.0±9.54	246.0±10.70[b]	213.5±11.98	248.8±8.35	267.4±12.03[b,c]
C. cyminum Dose II + STZ	1000	182.2±9.60	213.2±10.46	245.4±10.69[b]	192.0±9.55	248.5±9.77	267.7±12.35[b,c]
Sulbutiamine + STZ	50	183.1±15.94	234.3±17.26	248.5±17.26[b]	215.5±19.09	250.0±12.64	265.1±14.44[b,c]
Resveratrol + STZ	25	206.2±11.22	229.1±8.32	254.1±15.6[b]	241.14±11.60	244.5±10.60	249.8±11.50[a,c]
Glibenclamide + STZ	5	170.4±13.99	213.0±15.11	243.2±13.00[b]	204.4±15.26	235.7±11.98	269.7±8.18[c]

Abbreviations: STZ: Streptozotocin; SDL: Step-down latency; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
Acquisition of SDL: [a] $p<0.05$ vs. non-diabetic control, [b] $p<0.001$ vs. Nicotinamide + STZ diabetic control; **Retention of SDL:** [a] $p<0.001$ vs. non-diabetic control, [b] $p<0.05$ vs. non-diabetic control, [c] $p<0.001$ vs. Nicotinamide + STZ diabetic control

Table 4: Effect of drug treatment on retention of spatial navigation task in Nicotinamide+STZ induced-diabetic rats (x30 days)

Groups	Treatment and route	Latency (seconds) Mean ± SEM		
		Day 1; IAL	Day 15; RL-1	Day 30; RL-2
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	37.7 ± 8.01	39.0 ± 4.78	46.7 ± 5.07
Nicotinamide + STZ (Diabetic Control)	230 + 50, i.p.	50.6 ± 2.88	71.6 ± 3.00 [a]	95.8 ± 2.04 [a]
C. cyminum Dose I + STZ	500	55.4 ± 3.99	49.5 ± 3.74 [b]	46.7 ± 4.65 [b]
C. cyminum Dose II + STZ	1000	49.8 ± 3.19	44.4 ± 3.74 [b]	35.1 ± 3.85 [b]
Sulbutiamine + STZ	50	50.6 ± 4.33	51.8 ± 5.33 [d]	41.5 ± 5.15 [b]
Resveratrol + STZ	25	54.7 ± 3.68	46.1 ± 3.24 [b]	40.0 ± 2.98 [b]
Glibenclamide + STZ	5	51.5 ± 6.13	46.8 ± 5.01 [c]	40.1 ± 4.94 [b]

Abbreviations: STZ: Streptozotocin; RL: Retention Latency; IAL: Initial Acquisition Latency; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
[a] $p<0.001$ vs. non-diabetic control, [b] $p<0.001$ vs. Nicotinamide + STZ diabetic control, [c] $p<0.01$ vs. Nicotinamide + STZ diabetic control, [d] $p<0.05$ vs. Nicotinamide + STZ diabetic control

QT in spatial navigation task in Morris Water Maze

In non-diabetic rats, none of the studied agents showed significant changes in IAL or time spent in the target quadrant on day 15 (QT-1) and day 30 (QT-2) compared to the non-diabetic control group (Distilled water) suggesting that all the studied agents do not affect cognitive function in healthy, non-

diabetic rats. On the 15th day, a significant reduction in QT-1 was observed in the Nicotinamide + STZ group ($p<0.001$) compared to the non-diabetic control group. implying that diabetes causes early impairments in spatial memory, as evidenced by reduced time spent in the target quadrant. Similarly, on the 30th day, a significant reduction in QT-2 was observed in the Nicotinamide + STZ group ($p<0.001$) compared to the non-diabetic control group indicating a persistent and possibly worsening cognitive impairment over time due to diabetes. When compared to the diabetic control group, all other treatment groups showed a significant increase in QT-2 **(Table 5)** suggesting that treatments with *C. cyminum*, Sulbutiamine, Resveratrol, and Glibenclamide effectively improve spatial memory and cognitive function in diabetic rats.

Table 5: Effect of drug treatment on QT of Spatial navigation task in Nicotinamide + STZ induced-diabetic rats (x30 days)

Groups	Dose and route (mg/kg, p.o.)	Time (Seconds) Mean ± SEM		
		Day 1; IAL	Day15; QT-1	Day 30; QT-2
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	37.7 ± 8.01	65.7 ± 4.01	60.7 ± 4.39
Nicotinamide + STZ (Diabetic Control)	230 + 50, i.p.	50.6 ± 2.88	23.3 ± 2.56 [a]	13.3 ± 2.67 [a]
C. cyminum Dose I + STZ	500	55.4 ± 3.99	36.4 ± 2.69 [a]	45.5 ± 3.89 [c]
C. cyminum Dose II + STZ	1000	49.8 ± 3.19	32.0 ± 2.43 [a]	46.1 ± 3.82 [c]
Sulbutiamine + STZ	50	50.6 ± 4.33	36.5 ± 2.74 [a]	53.5 ± 3.74 [c]
Resveratrol + STZ	25	54.7 ± 3.68	34.2 ± 2.05 [a]	39.2 ± 1.68 [b, c]
Glibenclamide + STZ	5	51.5 ± 6.13	40.2 ± 5.12 [a]	47.0 ± 4.05 [c]

Abbreviations: STZ: Streptozotocin; QT: Quadrant Time; IAL: Initial Acquisition Time; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
[a] $p<0.001$ vs. non-diabetic control, [b] $p<0.01$ vs. non-diabetic control, [c] $p<0.05$ vs. Nicotinamide + STZ diabetic control

Table 6: Effect of drug treatment on brain levels of MDA and GSH in Nicotinamide + STZ induced Diabetic rats (x30 days)

Groups	Dose and route (mg/kg, p.o.)	MDA (nmol/g wet brain tissue) Mean ± SEM	GSH (µg/g wet brain tissue) Mean ± SEM
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	170.1 ± 8.79	383.1 ± 13.12
Nicotinamide + STZ (Diabetic Control)	230 + 50, i.p.	294.3 ± 16.16 [a]	221.1 ± 19.34 [a]
C. cyminum Dose I + STZ	500	254.4 ± 5.41 [a]	299.7 ± 14.89 [b, e]
C. cyminum Dose II + STZ	1000	226.7 ± 10.79 [e]	305.4 ± 9.61 [b, e]
Sulbutiamine + STZ	50	228.6 ± 14.57 [c, f]	289.8 ± 8.18 [a, f]
Resveratrol + STZ	25	223.1 ± 14.11 [e]	347.5 ± 11.05 [d]
Glibenclamide + STZ	5	241.0 ± 13.93 [b]	266.4 ± 11.02 [a]

Abbreviations: STZ: Streptozotocin; MDA: Malondialdehyde; GSH: Glutathione; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
[a] $p<0.001$ vs. non-diabetic control, [b] $p<0.01$ vs. non-diabetic control, [c] $p<0.05$ vs. non- diabetic control, [d] $p<0.001$ vs. Nicotinamide + STZ diabetic control, [e] $p<0.01$ vs. Nicotinamide + STZ diabetic control, [f] $p<0.05$ vs. Nicotinamide + STZ diabetic control

Effect of drug treatment on levels of MDA and GSH in the brain (x30 days)

MDA is a marker of lipid peroxidation, with elevated levels indicating increased oxidative damage. Among the nicotinamide + STZ-induced diabetic groups, a significant increase in brain MDA levels was observed in the nicotinamide + STZ group ($p < 0.001$) compared to the non-diabetic control group, indicating heightened oxidative stress in the brains of diabetic rats. Compared to the nicotinamide + STZ (diabetic control) group, the C. cyminum dose II, sulbutiamine, and resveratrol groups showed significant reductions in brain MDA levels. This reduction suggests that these treatments possess antioxidant properties capable of reducing oxidative stress **(Table 6).** A significant reduction in brain GSH levels was observed in the nicotinamide + STZ group ($p < 0.001$) compared to the non-diabetic control group, indicating increased oxidative stress in diabetic rats, as GSH is a key antioxidant responsible for neutralizing free radicals and protecting cells from oxidative

damage. Lower GSH levels suggest a diminished ability to combat oxidative stress. In contrast, the *C. cyminum* dose I and II groups, sulbutiamine group, and resveratrol group showed a significant increase in brain GSH levels compared to the nicotinamide + STZ (diabetic control) group. This increase in GSH levels suggests that these treatments enhance the brain's antioxidant capacity, thereby reducing oxidative stress and mitigating associated damage **(Table 6).**

Brain AChE levels

Among the Nicotinamide + STZ-induced diabetic groups, brain AChE levels were significantly elevated in the diabetic control group ($p<0.001$) compared to the non-diabetic control group. This increase reflects increased AChE activity in the brains of diabetic rats, which is commonly associated with impaired cholinergic function and potential cognitive decline. Elevated AChE activity can reduce acetylcholine levels, a neurotransmitter essential for memory and cognitive processes. In contrast, the *C. cyminum* dose II and Sulbutiamine groups significantly reduced brain AChE levels compared to the diabetic control group. This reduction indicates that these treatments may help normalize AChE activity, potentially improving cholinergic function and alleviating cognitive impairments associated with diabetes. By decreasing AChE levels, these treatments could help restore acetylcholine levels, potentially mitigating cognitive deficits and counteracting the cholinergic dysfunction caused by diabetes **(Table 7).**

Table 7: Effect of drug treatment on brain AChE levels in non-diabetic and Nicotinamide + STZ induced diabetic rats (x30 days)

Groups	Treatment and route	AChE activity (mol/min/g protein) Mean ± SEM	
		Non-diabetic	Diabetic
Distilled water (Non-diabetic Control)	Vehicle of *C. cyminum*	145.7 ± 9.29	----------
Nicotinamide + STZ (Diabetic Control)	230 + 50, i.p.	----------	233.0 ± 14.36 [a]
C. cyminum Dose I	500	145.5 ± 8.98	205.2 ± 9.12 [b]
C. cyminum Dose II	1000	146.2 ± 7.12	155.1 ± 12.44 [c]
Sulbutiamine	50	136.7 ± 9.37	159.1 ± 12.68 [c]
Resveratrol	25	147.2 ± 9.24	207.5 ± 13.04 [a]
Glibenclamide	5	156.8 ± 10.08	227.7 ± 14.13 [a]

Abbreviations: STZ: Streptozotocin; AChE: Acetylcholinesterase; SEM: Standard error of mean
Statistical test: One-way ANOVA followed by Tukey's post-hoc test
[a] $p<0.001$ vs. non-diabetic control, [b] $p<0.05$ vs. non-diabetic control, [c] $p<0.01$ vs. Nicotinamide + STZ diabetic control

DISCUSSION

Diabetes mellitus plays a significant role in the development of cognitive dysfunction through various mechanisms. Literature shows evidence of increased oxidative stress in uncontrolled hyperglycemia [36,37]. Probabilistic mechanisms for these changes include direct effects of insulin dysregulation resulting in fluctuating blood glucose levels, manifesting in the form of hypo/hyperglycaemia, and indirect effects on the cerebral vasculature [38].

C. cyminum is a popular spice used for centuries for its medicinal properties, especially its anti-diabetic potential. So, the current research evaluates the anti-diabetic potential of C. cyminum and compares its effects with **Glibenclamide, Sulbutiamine,** and **Resveratrol** in managing diabetes and its complications.

The current study measured fasting blood glucose levels as a biochemical indicator of diabetes. After 30 days of treatment with *C. cyminum*, Resveratrol, and Glibenclamide, a significant reduction in blood glucose levels was observed in diabetic rats. These findings suggest that *C. cyminum* effectively reduces hyperglycaemia induced by Nicotinamide + STZ, with an effect comparable to that of Glibenclamide. Rats in the diabetic control group exhibited a significant decrease in blood insulin levels. However, after 30 days of treatment with *C. cyminum* (500 and 1000 mg/kg) and Glibenclamide, blood insulin levels were significantly elevated in these rats. Similar results have been reported by Jagtap et al. (2010), where treatment of STZ induced diabetic rats with *C. cyminum* and Glibenclamide for 28 days caused a reduction in blood glucose and glycosylated

hemoglobin, and improved serum insulin when compared to diabetic control rats [39]. In a study conducted by Dhandapani S et al. (2002), oral administration of *C. cyminum* at a dose of 0.25 g/kg body weight for six weeks to diabetic rats resulted in a notable decrease in blood glucose levels and an increase in both total hemoglobin and glycosylated hemoglobin. Furthermore, the results indicated that *C. cyminum* was more effective than Glibenclamide in managing diabetes mellitus [28]. Mohamed et al. (2018), examined the antidiabetic effects of an ethanolic extract of cumin seeds in STZ-induced hyperglycemic rats. The rats were administered 200 mg/kg of the extract, which resulted in a 38.34% reduction in plasma glucose levels and a significant increase in insulin levels. The extract also improved the plasma lipid profile, reducing inflammation and oxidative damage [40]. Glibenclamide stimulates insulin secretion from pancreatic β-cells primarily by inhibiting ATP-sensitive K+ channels. Cuminaldehyde and cuminol have been identified as potent insulinotropic components of *C. cyminum*. The insulinotropic action of both components is glucose-dependent and occurs due to the closure of ATP-sensitive K+ channels and an increase in intracellular Ca2+ concentration [41]. It is hypothesized that the antihyperglycemic effect of *C. cyminum* may result from the protection of surviving pancreatic β-cells without causing hypoglycemia or β-cell burnout, as well as increased insulin secretion and glycogen storage [39,40].

In the current study, the behavioral parameters of learning and memory were assessed using an elevated plus maze (TL), passive avoidance apparatus (SDL), and Morris water maze (spatial navigation task). In these classical behavioral model tests, both acquisition and retention of TL in the elevated plus maze and components of TL and SDL increased in diabetic rats, suggesting learning deficits significantly. After 30 days of treatment with both doses of *C. cyminum*, sulbutiamine, resveratrol, and glibenclamide, a significant reduction in the acquisition component of TL was observed. Additionally, both doses of *C. cyminum* and sulbutiamine significantly reduced TL retention. These findings suggest that cognitive deficits in diabetic rats can be significantly reduced and/or reversed by *C. cyminum*, with effects comparable to sulbutiamine. In SDL, both acquisition and retention components were significantly reduced in diabetic rats, suggesting learning deficits. *C. cyminum*, sulbutiamine, and glibenclamide significantly increased the acquisition component of SDL, while *C. cyminum*, sulbutiamine, resveratrol, and glibenclamide significantly increased the retention component of SDL. These findings indicate that learning and memory impairments in diabetic rats can be significantly reduced and/or reversed by *C. cyminum*, with effects comparable to those of sulbutiamine and glibenclamide.

The Morris water maze was used to assess spatial navigation performance and evaluate learning and memory. Spatial navigation was assessed through two components: RL on day 15 (RL-1) and day 30 (RL-2), and time spent in the target quadrant on day 15 (QT-1) and day 30 (QT-2). Results demonstrated that diabetic rats significantly increased RL-1 and RL-2, while QT-1 and QT-2 were significantly reduced. This study demonstrated reversal of RL-1, RL-2, and QT-2 with all drugs used; however, none of the drug treatments reversed QT-1. These findings suggest that learning deficits in diabetic rats can be significantly reduced and/or reversed by *C. cyminum*, with effects comparable to those of sulbutiamine, resveratrol, and glibenclamide. The above results of behavioural parameters are consistent with results of Zakir M et al. (2023), Galicia U et al. (2020), and Wang X et al. (2020) [5,15,42]. Biochemical indicators of oxidative stress were assessed by measuring MDA and GSH levels in the brain. Diabetic rats demonstrated a significant increase in MDA levels and decreased GSH levels in the brain. Treatment with *C. cyminum*, sulbutiamine, and resveratrol resulted in a substantial reduction in brain MDA levels and a significant increase in brain GSH levels. AChE plays a key role in neural processes related to learning and memory. AChE activity was assessed as a marker of cholinergic dysfunction in the brains of diabetic rats. Zhao Q et al. (2020) and Gupta M et al. (2022) demonstrated a direct association between cognitive dysfunction and AChE activity in the brain [10, 20].

Diabetic rats showed a significant increase in AChE activity, while *C. cyminum* (1000 mg/kg) and sulbutiamine significantly reduced AChE activity. Increased AChE activity leads to rapid degradation of acetylcholine, resulting in the downregulation of acetylcholine receptors in the brain, negatively impacting learning and memory. The results of this study suggest that the increase in AChE due to diabetes leads to reduced acetylcholine levels in the synaptic cleft, resulting in impaired learning and memory loss. The behavioural tests used in the study revealed that diabetes led to significant cognitive impairments evident in the form of prolonged TL, increased maze retention latency, and shortened SDL. Treatment with *C. cyminum*, particularly at a higher dose (1000 mg/kg), significantly improved performance

across these behavioural tests, suggesting enhanced cognitive function. The biochemical analysis supported these findings, showing that *C. cyminum* reduced fasting blood glucose levels and improved insulin sensitivity, as indicated by lower insulin levels. Additionally, the extract decreased AChE activity, crucial for maintaining cholinergic function and cognitive processes. The positive correlation between improved behavioural outcomes and the modulation of blood glucose, insulin levels, and AChE activity suggests that *C. cyminum's* neuroprotective effects may be mediated through its ability to manage hyperglycemia, enhance insulin sensitivity, and preserve cholinergic function. These findings highlight the potential dual benefit of *C. cyminum* as a therapeutic agent both for managing diabetes and mitigating its impact on cognitive health. This suggests that incorporating *C. cyminum* into treatment regimens could be an effective approach for addressing both the metabolic and cognitive challenges associated with diabetes. Research on cognitive impairments in diabetes frequently emphasizes changes in neurotransmitter function, oxidative stress, and neuroinflammation. Traditional treatments often address these issues indirectly. However, the study's findings, which demonstrate improvements in AChE activity and cognitive performance, suggest that *C. cyminum* may directly influence neurotransmitter levels and mitigate oxidative stress. This direct action could provide a more comprehensive approach in managing cognitive decline associated with diabetes.

Study limitations and areas of future research

The study has a few limitations that should be considered. The drugs' effects were observed over a 30-day treatment period, which may not provide insight into the long-term effects or safety. The study did not explore the underlying molecular mechanisms, limiting our understanding of how the treatments work. Using a single diabetic rat model may not fully represent the complexity of diabetes in humans, and a broader range of behavioral assessments could have provided a more comprehensive evaluation of cognitive function. Future research should focus on long-term studies to assess the efficacy and safety of *C. cyminum* and its molecular mechanisms, which could provide deeper insights into its therapeutic potential. Additionally, diverse animal models and a battery of cognitive and behavioral tests would help validate these findings and offer a more comprehensive understanding of the neuroprotective effects of *C. cyminum*. The study indicates that *C. cyminum* has promising potential as a complementary therapy for diabetes, offering benefits in blood sugar management and cognitive protection. The ability of *C. cyminum* to lower blood glucose levels, boost insulin levels, and decrease oxidative stress suggests it could be useful in controlling hyperglycemia and addressing cognitive issues linked to diabetes. Its antioxidant effects and reduced brain AChE levels further imply potential support for cognitive function in diabetic patients. As a natural supplement, *C. cyminum* could complement traditional treatments like Glibenclamide, potentially enhancing overall therapeutic outcomes. However, further clinical research is needed to establish its effectiveness and safety in humans. In summary, the current study demonstrates that *C. cyminum* reverses and/or decreases excessive AChE activity (induced by diabetes), thereby improving learning and memory behaviors as shown by behavioral tests. The positive modulation of biochemical indicators of oxidative stress (MDA and GSH) through *C. cyminum* treatment suggests a protective effect against oxidative and neuronal damage. The neuro-modulatory and neuroprotective effects of *C. cyminum*, leading to improvements in learning and memory in diabetes, may be due to its anti-hyperglycemic, antioxidant, and memory-enhancing properties.

CONCLUSION

In the current study, *C. cyminum* reverses and/or decreases excessive AChE activity (induced by diabetes), thereby leading to improvements in learning and memory. This effect was demonstrated through various behavioral tests, including TL, SDL, and spatial navigation tasks. *C. cyminum* exhibited antioxidant and anti-hyperglycemic activity in experimental diabetes mellitus models, which may partially contribute to delaying cognitive impairment. As observed in this study, these effects were comparable, although varied, to those of Glibenclamide, Sulbutiamine, and Resveratrol. Further detailed studies are warranted to explore the antidiabetic and neuroprotective potential of *C. cyminum*.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Abhishek Kumar, Amit Shekhar, Umesh Suranagi, Mitali Dua, Ekta Arora, Indu Jangra contributed to the study conception and

design of the animal experiments; Abhishek Kumar performed animal experiments and collected data; Abhishek Kumar, Umesh Suranagi, Mitali Dua, Ekta Arora, Amit Shekhar discussed the interpretation of the results; Ekta Arora supervised and managed the study; Abhishek Kumar, Umesh Suranagi, Mitali Dua, Ekta Arora, Indu Jangra contributed to the draft manuscript & final approval of the version to be published

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