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Propofol protects rats against intra--cerebroventricular streptozotocin-induced cognitive dysfunction and neuronal damage

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Background: *Cognitive dysfunction is a severe issue of Alzheimer's disease. Thus, the present study was conducted to enumerate the protective effect of propofol (PPL) in rats against intra-cerebroventricular streptozotocin (STZ)-induced cognitive dysfunction and neuronal damage.*

Materials and methods: *The effect of PPL was investigated to evaluate behavioural changes in STZ-induced cognitive dysfunction in Wistar rats using Object Recognition Task (ORT) for nonspatial, Morris Water Maze (MWM) for spatial and locomotor activity. The effect of PPL was also investigated on acetylcholine (ACh) esterase (AChE) activity and oxidative stress markers, e.g., nitrite, malonaldehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH). The level of pro-inflammatory cytokines, e.g., tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, was also studied in the PPL-treated group. The effect of PPL on the level of neurotransmitters, e.g., dopamine (DA), serotonin (5-HT), and norepinephrine (NE) and their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) levels were also estimated in frozen hippocampal tissues by high-performance liquid chromatography. Histopathology analysis of neurons in the hippocampus of rats was performed using haematoxylin and eosin (H&E) staining.*

Results: *Propofol showed significant improvement in the spatial and nonspatial memory deficit of rats in the MWM test and ORT in rats. It also causes improvement in locomotor activity of rats by preserving ACh via inhibition of AChE. It also potentiates the expression of DA, 5-HT, and NE with a simultaneous reduction in the level of metabolites (DOPAC, HVA, and 5-HIAA). PPL showed a reduction of oxidative stress in rats by restoring the level of nitrite, SOD, MDA, and GSH near to normal. In the PPL-treated group, the level of TNF-α, IL-1β, and IL-6 was found reduced in a dose-dependent manner. In histopathology analysis of neurons in the hippocampus of the STZ rats, PPL causes dose-dependent reduction of pyknosis in the nucleus, which confirmed the protective effect of PPL.*

Conclusions: *The present study demonstrated that PPL could significantly attenuate cognitive dysfunction and neuronal damage in STZ-induced rats.* (Folia Morphol 2023; 82, 2: 248–255)

Key words: propofol, cognitive deficit, oxidative stress, inflammation

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INTRODUCTION

Current advances in therapeutics and diagnostics for cognitive dysfunction significantly impacted the lives of human well-being. It increases the mean life expectancy of individuals across the globe. It exposes the older people to many non-infectious diseases, such as cognitive dysfunction, osteoporosis, type 2 diabetes, cardiovascular diseases, cataracts, and cancer. Dementia is a cognitive disorder where the affected individual loses the ability to perform daily tasks due to reduced memory and disability [1, 8, 21].

Alzheimer's disease (AD) is a sub-type of dementia and is considered an irreversible, chronic progressive neurodegenerative brain disease due to the necrosis of brain cells. It mainly affects older people aged over 60 years and older. It is considered as both a structural and an inflammatory condition. The characteristic hallmark is the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs) in the brain, with abnormally folded amyloid-β42 (Aβ42) and tau proteins of AD. Studies have shown that cellular homeostasis and mitochondrial function are altered in AD patients due to oxidative stress induced by abnormal amyloid-β proteins, hence partially explaining the high prevalence of AD in the elderly [3, 10, 12]. In a study, institutionalized elderly patients showed a high level of oxidative stress and elevated concentration of pro-inflammatory cytokines, which is considered an underlying cause for their cognitive dysfunction. Thus, many current drugs target oxidative stress and inflammation to treat/control AD mainly [14, 16]. However, the current therapeutic option provides modest benefits against AD, necessitating discovering newer agents.

Propofol (PPL), which is commonly used as an anaesthetic agent, showed a protective effect against many ailments, such as ischaemic reperfusion injury of heart, liver, and kidney, ionising radiation-induced haematopoietic system damage mice, and lung injury via strong radical scavenging effect [17, 23, 24]. Considering the importance of free radicals in the pathogenesis of AD, and the strong radical scavenging effect of PPL, in the present manuscript, we intended to examine whether PPL has a protective effect against AD or not.

Experimental

Chemical

The chemicals used in the study were obtained from Sigma Aldrich, USA and used without further purification unless otherwise stated.

Animals

Male Wistar rats (220–260 g) were obtained from the institutional animal house and kept in strict hygienic conditions. The rats were supplied with food and water ad-libitum and accommodated in an alternate day and night cycles of 12 h. The study has been approved by Animal Ethical Board for Biomedical Experiments of Weifang People's Hospital (WPH/2020/00237).

Experimental induction of cognitive dysfunction

The anaesthesia was induced in the rats by intramuscular injection of ketamine/xylazine (90:10 mg/kg) and then fixed on the stable platform. The head of the rats was shaved to expose the skull for creating a sagittal midline incision. The streptozotocin (STZ) was diluted in freshly prepared citrate buffer (pH 4.4) before the injection and injected into the brain's exposed lateral cerebral ventricle. The animals were then further divided into five groups containing ten animals each.

— Group 1: control (received surgery with no treatment);
— Group 2: injected bilaterally with STZ (5 mg/kg) in a volume of 4 μL to each ventricle on day 1 and 3;

In the PPL-treated group, the PPL was administered to rats after 1 h of STZ administration (peroral) at the indicated dose for 21 days.

— Group 3: STZ + PPL (5 mg/kg, p.o.);
— Group 4: STZ + PPL (10 mg/kg, p.o.);
— Group 5: STZ + PPL (20 mg/kg, p.o.).

Behavioural assessment

Object Recognition Test

The Object Recognition Task (ORT) was performed using a wooden open box apparatus as per the previously reported procedure. The discrimination index to identify rats' ability between the novel and familiar item was estimated using D = N – F/N + F (F — familiar, N — novel).

Morris Water Maze test

The rats' spatial memory was estimated using the Morris Water Maze (MWM) test, per the reported procedure elsewhere. The apparatus consisted of a circular water tank with a depth of 50 cm to a depth, and skimmed milk powder was added to make the floor invisible. The time used up in the marked quadrant showed the extent of memory retention which had taken place after the acquisition trial.

Locomotor activity determination

Actophotometer was used to define the effect on the locomotor activity. Each animal was tested and observed over 10 min in a square closed arena (30 × 30 cm^2) equipped with infrared light-sensitive photocells using a digital actophotometer. The rats were examined for crossing light beam using infrared light-sensitive photocells.

Assessment of hippocampal catecholamines using HPLC

Catecholamines such as dopamine (DA), serotonin (5-HT) and norepinephrine (NE) and their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) levels were estimated by high-performance liquid chromatography (HPLC) using the electrochemical detector. Frozen hippocampal tissues were homogenized in 0.2 M perchloric acid, and samples were centrifuged at 12,000 g for 5 min. The supernatant was filtered through 0.22 mm nylon filters before injecting in the HPLC sample injector, and separation was carried out at a flow rate of 0.8 mL/min at 0.75 V. The concentration of neurotransmitters and their metabolites were calculated from the standard curve generated by using standard in the concentration range of 10–100 ng/mL.

Acetylcholine esterase activity

The acetylcholine (ACh) esterase (AChE) activity was determined using DTNB (Ellman reagent) as described by Ellman et al. [5] with minor modification [5, 25]. The assay mixture contained 0.05 mL of tissue supernatant, 0.10 mL of acetylthiocholine iodide, 3 mL of 0.01 M sodium phosphate buffer (pH 8), and 0.10 mL of DTNB (5,5'-dithiobis-(2-nitrobenzoic acid), Ellman's Reagent). The change in absorbance was measured spectrophotometrically immediately at zero and one minute at 412 nm.

Estimation of anti-oxidant biomarkers

The anti-oxidant biomarkers (malonaldehyde [MDA], superoxide dismutase [SOD], glutathione [GSH]) were studied using commercially available ELISA kits (Cayman Kits) as per the manufacturer's instructions. Briefly, after removing the brain, the rat hippocampal tissues were then homogenised with ice-cold 0.1 M phosphate buffer (pH 7.4) in a volume 10 times the weight of the tissue. The brain tissue homogenate pellets obtained after centrifugation at 10,000 g for 15 min (4°C) were suspended to the desired concentration with phosphate buffered saline (PBS) (pH 7.4) and plated at 30 μL/well in Immunol 2HB plates (Thermo Scientific Waltham, MA). Plates were incubated for 2 h at room temperature (RT). The liquid was gently removed from wells and plates were either allowed to air dry or fixed by adding 50 μL/well fixative (1% paraformaldehyde, 3% glutaraldehyde, or methanol). Plates were then blocked with PBS + 1% bovine serum albumin (BSA) (50 μL/well) for 1 h at RT. Primary antibodies were diluted with PBS + 1% BSA, added to the respective wells (50 μL/well), and plates were incubated for 2 h at RT. Unbound antibodies were removed by washing the plates 3 times with PBS. Secondary antibodies were diluted with PBS + 1% BSA (1:200) and added to each well (50 μL/well) for 1 h at RT. Plates were then washed with PBS were read on a SpectraMax M2 plate reader (Molecular Devices, Sunnyvale, CA) at 630 nm absorption.

Enzyme-linked immunosorbent assay (ELISA)

The determination of tumour necrosis factor alpha (TNF-α), interleukin 1beta (IL-1β), and interleukin 6 (IL-6) was performed using commercially available ELISA kits as per the manufacturer's instructions. Briefly, after removing the brain, the rat hippocampal tissues were then homogenized with ice-cold 0.1 M phosphate buffer (pH 7.4) in a volume 10 times the weight of the tissue. The brain tissue homogenate pellets obtained after centrifugation at 10,000 g for 15 min (4°C) were suspended to the desired concentration with PBS (pH 7.4) and plated at 30 μL/well in Immunol 2HB plates (Thermo Scientific Waltham, MA). Plates were incubated for 2 h at RT. The liquid was gently removed from wells, and plates were either allowed to air dry or fixed by adding 50 μL/well fixative (1% paraformaldehyde, 3% glutaraldehyde, or methanol). Plates were then blocked with PBS + 1% BSA (50 μL/well) for 1 h at RT. Primary antibodies were diluted with PBS + 1% BSA, added to the respective wells (50 μL/well), and plates were incubated for 2 h at RT. Unbound antibodies were removed by washing the plates 3 times with PBS. Secondary antibodies were diluted with PBS + 1% BSA (1:200) and added to each well (50 μL/well) for 1 h at RT. Plates were then washed with PBS were read on a SpectraMax M2 plate reader (Molecular Devices, Sunnyvale, CA) at 630 nm absorption.

Haematoxylin and eosin staining

The harvested brains were fixed in 4% paraformaldehyde for 2 days and paraffin-embedded after gra-

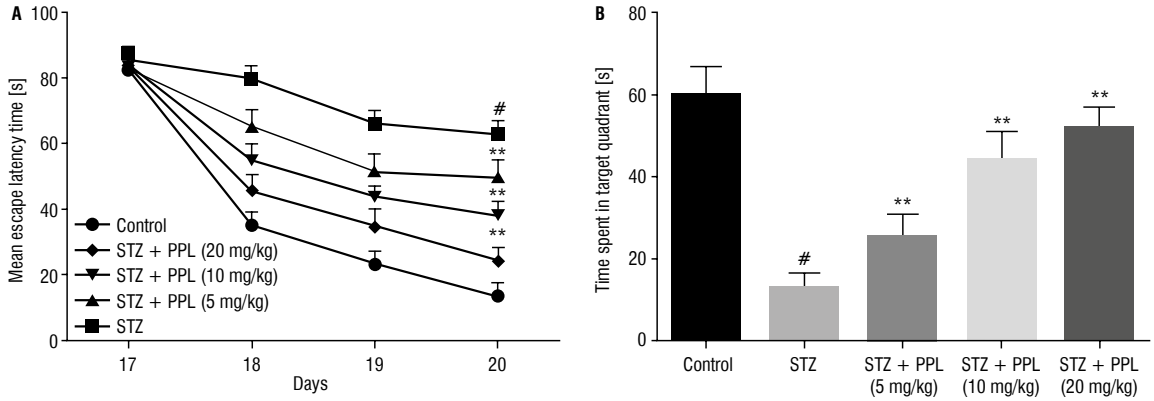

Figure 1. Effect of propofol (PPL) on the neuronal deficit; #P < 0.05 vs. control and **P < 0.01 vs. streptozotocin (STZ) group. Data are presented as means ± standard error of the mean.

Table 1. Effect of propofol (PPL) on the exploration and latency of streptozotocin (STZ) rats

Group	Total exploration time [s]		Total exploration time [s]		Discrimination Index (DI)
	FO1	FO2	Familial	Novel	
Control	10.66 ± 1.96	11.31 ± 2.32	4.76	15.26	0.52
STZ	9.73 ± 1.03#	8.8 ± 0.98#	3.97#	3.99#	0.0025#
STZ + PPL (5 mg/kg)	9.03 ± 1.23**	9.43 ± 1.12**	4.44**	7.76**	0.27**
STZ + PPL (10 mg/kg)	9.41 ± 1.34**	10.16 ± 1.63**	4.45**	10.28**	0.39**
STZ + PPL (20 mg/kg)	10.14 ± 1.04**	10.36 ± 1.20**	4.61**	12.9**	0.47**

#P < 0.05 vs. control and **P < 0.01 vs. STZ group. Data are presented as means ± standard error of the mean. The DI was calculated using D = N − F/N + F (F— familiar, N — novel).

dient alcohol dehydration. The wax blocks were sectioned (4-μm thick) on a paraffin slicer and stained with haematoxylin and eosin (H&E). Brain histopathological changes were observed under a light microscope.

Statistical analysis

The data were expressed as mean ± standard deviation (SD). Statistical analysis was executed using ANOVA pursued by Bonferroni *post hoc* multiple comparison test using GraphPad Prism 5.0 (California, USA). The p-value < 0.05 was measured as statistically significant.

RESULTS

Effect of PPL on the spatial memory deficit of rats

Initially, the effect of PPL was investigated on the memory deficit of rats. As shown in Figure 1, in the MWM test, the STZ rats showed a significant reduction in memory as they were not acquainted during acquisition and maintenance trials. The entire treated animals were guided for 5 days from the 17th day of STZ infusion in MWM. On the first training day, no significant variation was observed in mean latencies among the tested groups. The STZ rats showed significant memory deficits on the 2nd and 3rd day of the training compared to the control. Conversely, the PPL treated group considerably inhibited STZ-provoked memory deficit.

Effect of PPL on nonspatial memory deficit in rats

The effect of PPL was also investigated on the nonspatial memory deficit in rats, and results are presented in Table 1. After the 14th day of 1st STZ administration, the rats were exposed to ORT. In ORT, both items were alike. On the 15th day, the animals were open to both familiar and novel items. It has been observed that STZ-treated rats showed an inability to differentiate between the novel and familiar item compared to control. However, the PPL-treated rats showed dose-dependent improvement in differentiating between the novel and familiar items compared to STZ-rats.

Effect of STZ on the locomotor activity of rats

As shown in Table 1, no significant difference was observed among the treated and non-treated groups in spontaneous locomotor activity on the 16th day.

Effect of PPL on AChE activity in rats

The effect of PPL was investigated on the AChE level in brain homogenate of rats, and results are

Table 2. Effect of propofol (PPL) on the locomotor activity, acetylcholine esterase (AChE) activity, neurotransmitter level, and neurotransmitter metabolite level in the streptozotocin (STZ) rats

Group	Activity count/ /10 min	AChE activity (nmol/min/mg protein)	% Change in neurotransmitter level (ng/mg of tissue sample)			% Change in neurotransmitter metabolite level (ng/mg of tissue sample)		
			Dopamine	Norepinephrine	5-HT	DOPAC	HVA	5-HIAA
Control	250.34 ± 23.34	110.67 ± 32.26	98.02 ± 3.56	99.45 ± 5.23	99.32 ± 6.43	100.02 ± 4.56	99.45 ± 3.43	99.32 ± 3.26
STZ	226.02 ± 12.32#	423.12 ± 25.04#	26.54 ± 6.32#	44.63 ± 4.45#	30.45 ± 3.45#	233.50 ± 40.22#	274.51 ± 43.73#	265.52 ± 43.21#
STZ + PPL (5 mg/kg)	245.73 ± 9.03**	350.43 ± 21.42**	39.34 ± 3.27**	50.73 ± 3.42**	45.62 ± 4.53**	200.45 ± 37.27**	220.66 ± 36.54**	211.37 ± 34.62**
STZ + PPL (10 mg/kg)	248.05 ± 10.23**	267.22 ± 20.15**	47.62 ± 4.44**	66.21 ± 3.78**	55.45 ± 4.37**	175.28 ± 34.81**	175.59 ± 35.52**	168.23 ± 37.06**
STZ + PPL (20 mg/kg)	251.26 ± 8.45**	176.30 ± 22.25**	65.52 ± 4.51**	75.03 ± 5.34**	63.32 ± 3.83**	148.63 ± 22.37**	134.58 ± 25.43**	120.45 ± 26.57**

#P < 0.05 vs. control and **P < 0.01 vs. STZ group. Data are presented as means ± standard error of the mean; 5-HT — serotonin; DOPAC — 3,4-dihydroxyphenylacetic acid; 5-HIAA — 5-hydroxyindoleacetic acid; HVA — homovanillic acid

Table 3. Effect of propofol (PPL) on the oxidative and nitrosative activity in streptozotocin (STZ) rats

Group	Nitrite [μMol/mg prot.]	MDA [nMol/mg prot.]	SOD [μMol/mg prot.]	GSH [μMol/mg prot.]
Control	122.41 ± 20.48	2.41 ± 0.37	8.28 ± 1.26	9.63 ± 1.59
STZ	352.26 ± 35.40##	4.53 ± 0.58##	3.21 ± 0.45##	4.11 ± 0.73##
STZ + PPL (5 mg/kg)	303.17 ± 34.71**	4.02 ± 0.65**	4.07 ± 0.85**	5.89 ± 0.84**
STZ + PPL (10 mg/kg)	256.48 ± 28.36**	3.68 ± 0.61**	5.32 ± 0.97**	7.26 ± 1.43**
STZ + PPL (20 mg/kg)	188.27 ± 24.42**	3.03 ± 0.56**	7.18 ± 1.14**	8.06 ± 1.51**

##P < 0.05 vs. control and **P < 0.05 vs. STZ group. Data are presented as means ± standard error of the mean; MDA — malonaldehyde; SOD — superoxide dismutase; GSH — glutathione

presented in Table 2. The STZ-treated rats showed a significant increase in the level of AChE in the brain homogenate of rats compared with the control. On the contrary, the PPL-treated rats showed a dose-dependent reduction in the elevated level of AChE as compared to STZ-treated rats.

Effect of PPL on the level of neurotransmitters and metabolites

The effect of PPL was investigated on the level of numerous neurotransmitters and metabolites in the rat brain homogenate. As shown in Table 2, STZ-infusion significantly decreased DA, 5-HT, and NE compared to control. Moreover, the level of metabolites (DOPAC, HVA, and 5-HIAA) was significantly enhanced in the STZ treated group compared to the control. The PPL treated group significantly restored this tested neurotransmitter and metabolites near normal in a dose-dependent manner.

Effect of PPL on oxidative-nitrosative stress

The effect of PPL was investigated on the oxidative-nitrosative stress level in rats. As shown in Table 3, nitrite and MDA level was found to significantly increase, with a reduced level of SOD and GSH in STZ-treated rats compared to control ($p < 0.05$). However, PPL administration causes significant restoration of these biomarkers near to normal compared to STZ treated rats.

Effect of PPL on the pro-inflammatory cytokines

As shown in Table 4, the level of tested cytokines (TNF-α, IL-1β, and IL-6) was found significantly elevated after administration of STZ to the rats compared to control. However, PPL causes a dose-dependent reduction in the level of these cytokines near to normal compared to STZ-treated rats.

Effect of PPL on the histopathology of neurons in the hippocampus of rats

In the subsequent study, we examine the morphology of neurons in the hippocampus of rats following the administration of STZ and PPL. As shown in Figure 2, the rats in the STZ group showed a higher level of altered morphology with pyknosis in the nucleus with irregular arrangements than the control-treated

Table 4. Effect of propofol (PPL) on the inflammatory cytokines in streptozotocin (STZ) rats

Group	TNF-α [pg/mL]	IL-1β [pg/mL]	IL-6 [pg/mL]
Control	185.52 ± 76.20	15.35 ± 2.34	16.45 ± 2.05
STZ	502.28 ± 136.47##	233.82 ± 62.82##	178.92 ± 52.37##
STZ + PPL (5 mg/kg)	423.42 ± 112.28**	173.76 ± 56.38**	140.82 ± 30.72**
STZ + PPL (10 mg/kg)	336.72 ± 89.34**	103.51 ± 35.71**	110.34 ± 23.58**
STZ + PPL (20 mg/kg)	250.35 ± 67.06**	65.72 ± 23.37**	85.15 ± 19.42**

##P < 0.05 vs. control and **P < 0.05 vs. STZ group. Data are presented as means ± standard error of the mean; TNF-α — tumour necrosis factor alpha; IL-1β — interleukin 1beta; IL-6 — interleukin 6

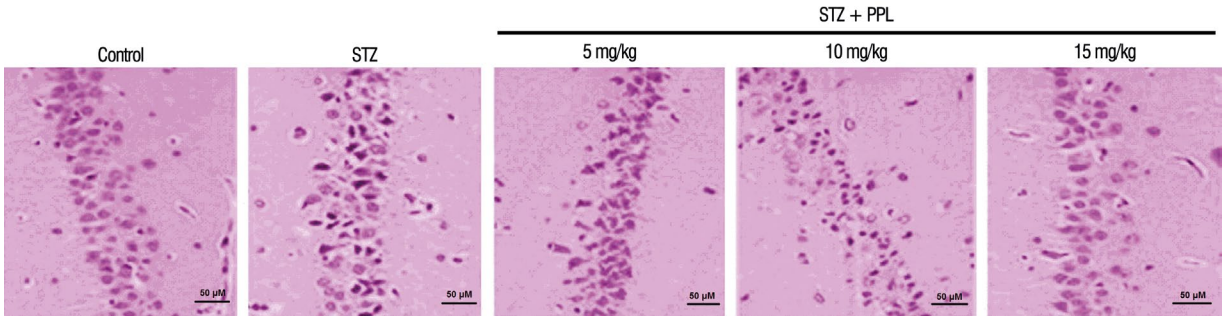

Figure 2. Effect of propofol (PPL) on the neurons in hippocampus of the streptozotocin (STZ) rats (×400).

group. In the PPL-treated group, these morphological features were improved and restored near to normal compared to STZ-treated rats. This result suggests the protective role of PPL against the neuronal damage in STZ-induced cognitive deficit in rats.

DISCUSSION

Cognitive impairment/dysfunction is a critical ailment for aged people and compromises their quality of life. The increased life expectancy has amplified the number of older people who experience mild to severe cognitive dysfunction after 60 years of age. It is considered a characteristic hallmark of AD, a type of degenerative brain disorder [6, 10]. According to a study, people with cognitive dysfunction have 3-fold more hospital stays than people hospitalised for any other causes. This has put significant demand for more in-home or institutional care and unpaid assistance by family and friends, causing a huge economic burden [15, 19]. Thus, an effective therapeutic agent is urgently needed to provide beneficial effects against cognitive dysfunction and associated neuronal damage. Anaesthetics agents are considered the main cause of cognitive dysfunction in elderly patients in the post-operative recovery phase; for instance, midazolam causes a serious cognitive deficit in patients after 1-week of operation [13]. In the present study, we have shown a strong protective effect of PPL against cognitive dysfunction in STZ-induced rats. The present study showed no mortality of rats during the duration of the study. The effect of PPL was investigated on the cognitive impairment in STZ infused rats by MWM and ORT to define spatial and nonspatial learning parameters. The MWM test is the most widely used behavioural procedure used in rodents to study drugs' psychological processes and effects. In this test, the distal cue is used to steer from the start spot in the boundary region of an open swimming ring to find a sunken escape platform. Spatial learning is calculated transversely frequent trials, and reference memory is assessed by an inclination for the platform area when the platform is missing. Reversal and shift trials increase the recognition of spatial impairments [11, 20]. On the other hand, the ORT tries to evaluate cognition, particularly recognition memory, in rodents. In this, the mouse is offered two similar items in the first session, and then one of the two items is restored by a new item during a second session. The total time to discover the new item affords an index of recognition memory. In this test, STZ treated rats showed significant spatial and nonspatial memory impairment, which is in line with previous studies. However, the PPL administration causes significant improvement in spatial and non-

spatial memory with improved ability to discriminate between different items and has increased latency. The results were found in agreement with a previous study where PPL showed the least impact on cognitive function of patients after 1 week of surgery [13]. The PPL-treated rats also showed no significant effect on the locomotor activity of the rats. Acetylcholine, a cholinergic neurotransmitter essential for processing memory and learning, is reduced in concentration and function in patients with AD. The over-activation of AChE is an important enzyme responsible for catalysing the degradation of ACh into acetic acid and choline. Thus, inhibition of AChE causes an increase in the total extracellular concentration of ACh and improves the cognitive dysfunction and other symptoms of AD [7, 18, 22]. In the present study, PPL-treated rats showed a reduction in AChE level compared to STZ--rats, which was highly elevated. Besides cholinergic neurotransmitters, monoaminergic and glutamatergic neurotransmitters also have a significant role in AD's pathogenesis. In AD patients, the level of these neurotransmitters was found significantly reduced, and studies have warranted the significance of restoring the deficit of these neurotransmitters in providing benefit against AD [9]. Thus, in the present study, we have determined the level of DA, NE, and 5-HT and their metabolite (DOPAC, HVA, and 5-HIAA) in rats. These neurotransmitters were found significantly reduced in STZ-treated rats with an increased level of metabolites and provoke cognitive decline, possibly by increased metabolic deactivation. However, the PPL-treated rats significantly reduced the generation of these metabolites, which restored the level of neurotransmitters near to normal. This modulation is suggested to be the probable mechanism behind the protective effect of PPL against cognitive dysfunction. Numerous studies have suggested the significance of oxidative stress and neuroinflammation in the pathogenesis of AD, which causes a reduction of neuronal viability. AD patients have a high level of oxidative stress, which arises due to the reduction of endogenous anti-oxidants, like GSH and SOD. It induces lipid peroxidation (MDA, a biomarker for lipid peroxidation). The flawed anti-oxidant system also leads to the production of peroxynitrite and nitrotyrosine, which causes cell injury and induces neuronal death [2, 4]. In the present study, STZ rats showed impaired anti-oxidant defence as evidenced by the low level of SOD and GSH, which results in a high concentration of MDA and nitrite. However, the PPL-treated rats showed improvement in anti-oxidant status by restoring the SOD and GSH, which caused a reduction in MDA and nitrite levels. The level of pro-inflammatory (TNF-α, IL-1β, and IL-6) cytokines was also found significantly reduced in PPL treated compared to control. The study's findings were consistent with previous results where PPL showed anti-oxidant activity and prevented the generation of pro-inflammatory cytokines. These observations suggest that PPL might abrogate cognitive dysfunction induced by STZ, possibly by strong anti-oxidant and anti-inflammatory effects. A similar trend was also observed in the histopathology of neurons in the hippocampus of rats. The STZ rats showed pyknotic nuclei and were found loosely and irregularly arranged. However, the PPL-treated rats showed an ameliorative effect on these morphological characteristics and improved nuclei morphology.

CONCLUSIONS

The present work demonstrated that PPL could significantly attenuate the cognitive dysfunction and neuronal damage in the STZ-induced rats, possibly by reducing oxidative stress and inflammation and restoring the level of vital neurotransmitters. It also prevented neuronal damage and provided significant benefits against the cognitive deficit in rats. This study has limitations, and future studies are warranted to explore the possible effect of PPL on microglial activation and Amygdala-dependent learning behaviour. However, the clinical applicability of PPL has been limited due to various disadvantages, such as emulsion instability, hyperlipidaemia, pain upon injection, microbial contamination, and PPL infusion syndrome. These disadvantages could be easily overcome by changing the dosage form, such as nano-formulation of PPL which improves anaesthetic, pharmacokinetic, hemocompatibility, safety, and permeation profile.

Conflict of interest: None declared

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