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Potential Role of Silver Nanoparticles of Pterospermum acerifolium Plant Extract in Alzheimer disease

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Abstract

Stress is the key factor of the physiological change & deformity of the cell that leads to degeneration of the cell. Degeneration of the brain cells is the main cause of dementia this pathological condition also known as Alzheimer's disease (AD). The characteristics of AD are disorientation in thinking and liberation in individual daily activities in old age. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. *Pterospermum acerifolium,* basic plant in India, is viewed as carminative, stimulant, and emmenagogue. The improvement of control discharge conveyance systems could prompt huge preferences in the clinical employments of these medications to diminish the toxicities. The point of this study was to figure another conveyance framework for impacts of neurochemicals by the joining of concentrate of *P. acerifolium* into strong lipid nanoparticles (SLNs). Nanotechnology has given the likelihood of conveying medications to particular cells utilizing nanoparticles. Nano systems can convey the dynamic constituent at an adequate fixation amid the whole treatment time frame, guiding it to the fancied site of activity. Traditional medications do not meet these necessities. The fundamental motivation behind creating elective medication conveyance advancements is to expand effectiveness of medication conveyance and security during the time spent medication conveyance and give more accommodation to the patient, nano formulations were prepared by Ethanolic extract, silver nanoparticle were pictured by checking scanning electron microscopy. Particle size and size distribution were dictated by photon connection spectroscopy.
Results and Discussion: The change of molecule charge was contemplated by zeta potential estimations. Treatment with plant extract and nanoparticle was found to altogether diminish the serum levels of nitrite/ nitrates, Super oxide anions, GSH, TBARS and SOD . it also gives the beneficial effect on the learning memory, retention time and escaping time measured in the animal model of Morris water
Conclusion: The outcomes got from this study recommended that the memory-improving impact of nanoparticle with concentrate was interceded through directions of neurochemical and neuroendocrine frameworks.

1.0. Introduction

Alzheimer's disease (AD), the most common form of memory loss in old age person, it is a progressive loss of the memory with the time dementia, is increasingly prevalent and a worsening healthcare burden. The cognitive deterioration of AD has remained frustratingly recalcitrant to candidate disease-modifying therapeutics despite massive efforts over the last 35 years. Most research into therapeutics has been philosophically guided by the connection of the hallmark histopathology of AD, cortical amyloid plaques, and neurofibrillary tangles, with familial dementia-causing mutations associated with their most insoluble component proteins, the amyloid-β peptide (Aβ) and the microtubule-associated protein tau Both proteins are normal and soluble components of tissue that become denatured by events that are not simply related to overproduction. Alzheimer's disease is the root cause of dementia and is quickly becoming one of the most expensive, lethal, and burdening diseases of this century. important developments have taken place in the understanding of the underlying pathology, the recognition of multiple causative and protective genes, the identification of new blood-based and imaging biomarkers, and the first cautious signals of positive effects of disease-modifying treatments and lifestyle interventions.

2.0. Material & Methods

All the solvents used for extraction, qualitative tests and chromatographic studies were of analytical grade. All other chemicals and reagents used were of analytical grade and obtained from Loba Chemical, Mumbai.

Reagents:
Silver nitrate (AgNO3) and 1, 1-diphenyl-2- picrylhydrazyl (DPPH), were obtained from Sigma- Aldrich, St. Louis, USA while ascorbic acid, Carrageenan, and carboxymethyl cellulose (CMC) were procured from Hi-Media Laboratories Pvt. Ltd. Mumbai, India. All the glasswares were treated with aqua regia (HCl: HNO3 = 3:1) for 30 minutes, then thoroughly

washed with Milli-Q water (Milli-Q plus system, Millipore Co.) having high water resistivity (18.2 MΩ-cm) and finally dried in hot air oven for the period of 5 h prior to use.

2.1. Synthesis of Silver nanoparticle of extract of *Pterospermum acerifolium*

Synthesis of novel nanoparticle of extract of *Pterospermum acerifolium* carried out by adding 10 ml of PALE into 90ml AgNO3 (2mM) solution at 27°C with continuous stirring (120 rpm) for 2h. The change in color of the reaction mixture from colorless to yellowish brown indicated the formation of silver nanoparticle *P. acerifolium. After that* synthesized NP were washed (thrice) with Milli-Q water and centrifuged at 15,000 rpm for 10 minutes. The NPs were collected and redispersed in Milli-Q water for characterization.

2.2. Characterization of Placebo nanoparticles and Drug Loaded Nanoparticle

2.2.1. Zeta Potential and size

Zeta potential is the electric potential at the slipping plane of a particle in a liquid. It represents the charge on the surface of particles, influencing their stability in suspension. High positive or negative zeta potentials (e.g., > ±30 mV) generally indicate good colloidal stability, as particles repel each other, preventing aggregation. Low zeta potential (e.g., near 0 mV) can lead to particle aggregation due to reduced repulsive forces. Zeta potential depends on factors such as the pH, ionic strength, and nature of the solution.

2.2.2. Particle Size:

The size of particles (often in nanometres or micrometres) dispersed in a solution. It is typically determined through techniques like dynamic light scattering (DLS) or electron microscopy. Affects the physical, chemical, and biological behaviour of particles, such as solubility, stability, and cellular uptake. Smaller particles generally have higher surface area-to-volume ratios, leading to different reactivity compared to larger particles. Size distribution is crucial in assessing whether a sample is monodispersed (single size) or polydisperse (varied sizes).

3.0. Pharmacological studies

The present study employed adult male albino wistar rats weighing around 220−250 gm Animals were housed and taken care of, until the completion of the study in the animal house of the institution, with free access to standard laboratory's pellet chow diet. Animals had an exposure to 12 hours. light and dark cycle allowing proper acclimatization to the laboratory conditions for a span of 5 days prior to the behavioural study. The experiments conducted were as per the study protocol approved by Institutional Animal Ethics committee (IAEC) between 9:00 and 16:00 hour maintaining semi sound proof environment in laboratory, following the guidelines provided by CPCSEA, Ministry of Environment and Forests, Government of India (no. 1147/ab/07/CPCSEA).

3.1. Experimental Protocol

In the present study, total 8 groups have been employed with each group consisting of 6 male Wistar rats.

G**roup I** - Control group Animals were exposed to behavioural assessment from Day

Group II - Saline: Rats were administered saline (0.9% w/v; 10 ml/kg, i.p.; daily) for 26 days with exposure to behavioural assessment from 22nd day onwards.

Group III - PBS: Rats were administered PBS (10 ml/kg, p.o.; pH 7.4, daily) for 26 days with exposure to behavioural assessment from 22nd day onwards.

Group IV - Citrate buffer: Rats were administered a single dose of citrate buffer (0.1 M; 10 ml/kg, i.p.; pH 4.5) after which they were exposed to behavioral assessment from 52nd day of its administration.

Group V: Rats were administered a single dose of STZ (50 mg/kg, i.p.) after which they were exposed to behavioural assessment from 52nd day of its administration

Group VI - STZ + Ethanolic Extract of (100mg/kg)

Ethanolic Extract of (100mg/kg, p.o.) was administered to the STZ (50 mg/kg, i.p.) diabetic rats, starting from day 30th of the STZ treatment to day 56th, with exposure to behavioural assessment from 52nd day onwards.

Group VII - STZ + Drug loaded NP

Np formulation was administered for STZ (50 mg/kg, i.p.) diabetic rats, starting from day 30th of the STZ treatment to day 56th, with exposure.

Group VIII- STZ + Donepezil (0.5 mg/kg, i.p.) per se

Donepezil (0.5 mg/kg, i.p.) per se: Rats were administered donepezil (0.5 mg/kg, i.p., daily) for 26 days with exposure to behavioural assessment from 22nd day onwards. Donepezil serves as a positive control.

Assessment of Spatial learning and Memory by Morris Water Maze

Morris water maze apparatus is used to test memory. It consists of large circular pool equally divided into four quadrants. The water was filled and was made opaque using coloured dye. White painted platform was placed in the target quadrant, 1 cm below the water surface and the platform was left undisturbed aa through the training session.

4.0. Result and Discussion

4.1. Physical Characteristics The particles when assessed for physical characteristics showed following results in figure 1, 2 and 3

4.1.1. Size and zeta potential

the formulations were then studied for particle size and zeta potential. The results are shown in table 4.12. The average particle size for Pterospermum acerifolium nanoparticles made from Cremophor RH 40 was found to be 41nm to 74nm while particles made of Tanscutol P was 186nm, containing particles vary between 164nm to 720nm.

4.1.2. Surface Characteristics

The surface morphology was analysed by visual inspection of the images displayed on screen monitor. The sample images are shown in figure 4.8-4.25. The images revealed that the nanoparticles were spherical in shape, quite smooth and similar particles are seen throughout the slide. None of any perforations or imperfections was seen on the surface of Nanoparticles. It is good to have uniform smooth surface rather uneven and rough surface as it is helpful in proper dosing and release of drug from polymeric nanoparticle matrix. Polymeric nanoparticles were discarded because they were tacky and agglomerated on storage. Metallic nanoparticles prepared further up taken for in-depth studies. The composition of nanoparticles which was selected for further studies is shown as following: - (Table 4.18a & 4.18b) Based on physical characteristics, particle size Cremophor RH 40 & Tanscutol P were selected as polymer for preparation of nanoparticles. Nanoparticles NF2 and NF3, were further selected for in-depth studies. The results of various characteristics of drug loaded nanoparticles are shown in table 4.16 & 4.18.

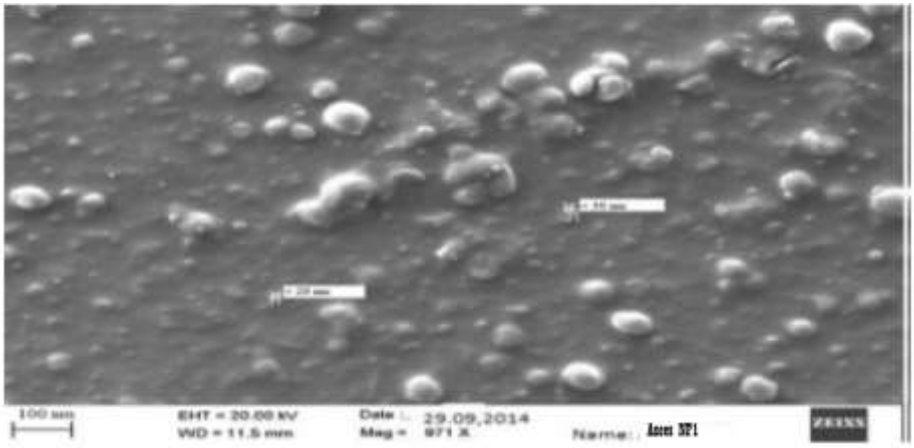


Figure 1: SEM image

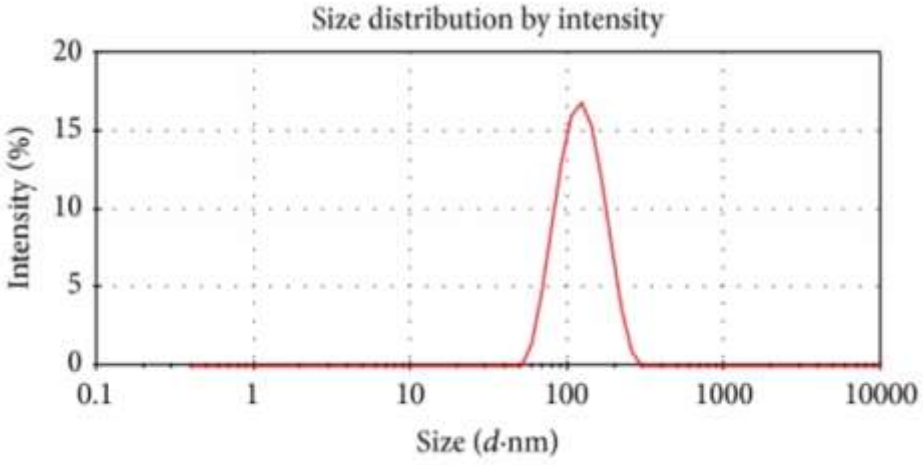
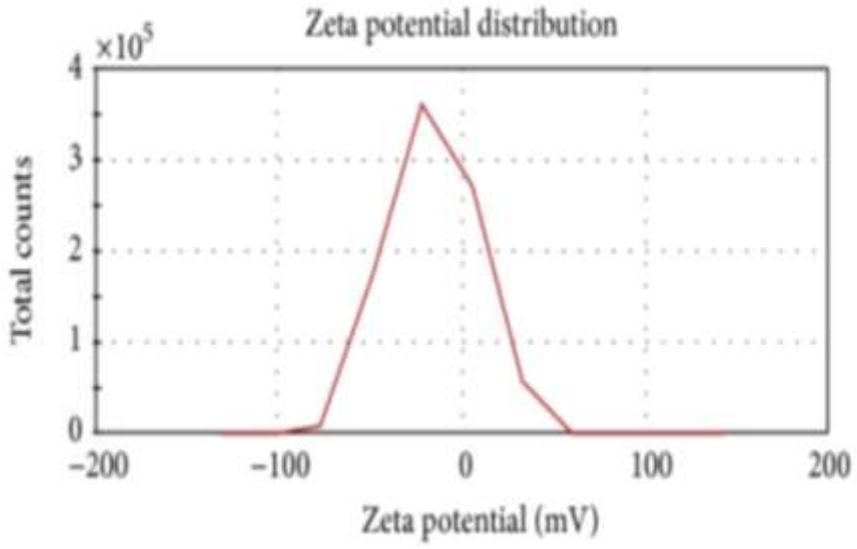


Figure 2: Size distribution Ethanolic extract of PASN (NF1)



Ethanolic extract of PASN (NF1)

Table 1 Depicting various characteristics of Pterospermum acerifolium Extract nanoparticles

Code	Physical Characteristics			Particle size (nm)	Zeta potential(mV)	Status of formulation
	colour	odour	texture			
NF1	Yellowish white	Lipidic odour	Tacky & greasy	500±36	5.9±6.7	Discarded
NF2	Yellowish white	no odour	Dry, shiny & gritty.	492±2	0.9±1.2	Further studied
NF3	yellow	no odour	gritty	427±22	1.7±1.2	Further studied
NF4	Off- white	no odour	Dry, shiny & gritty.	526±20	1.2±0.8	Discarded
NF5	Yellowish white	no odour	Dry, shiny & gritty.	172±12	23.6±2.0	Discarded

5.0. Pharmacological Investigation

5.1. Effect on body weight and serum glucose level

Table 2: Effect on body weight and serum glucose level

	Body weight		**Serum glucose level**	
Effect on body weight and serum glucose level	**Basal Value**	**Final Value**	**Basal Value**	**Final Value**
Group I - Control group	220	310	89	90
Group II - PBS	240	295	90	95
Group III - Citrate buffer	212	285	79	80
Group IV - Disease Control:	240	180	70	220
Group V - STZ + Ethanolic Extract of (100mg/kg)	210	190	80	180
Group VI - STZ + blank nanoparticle	215	200	88	260
Group VII - STZ + Drug loaded NP (100mg/kg)	230	200	84	140
Group VIII- STZ + Donepezil (0.5 mg/kg, i.p.) per se	215	220	86	220

5.2. Effect on Learning and Memory Using MWM

In MWM, control animals showed a significant decrease in day 4 ELT as compared to day 1 ELT, along with significant increase in day 5 TSTQ as compared to other quadrants, depicting effective learning and memory. STZ diabetic rats showed a significantly higher day 4 ELT whereas, a significantly lower day 5 TSTQ when compared to the control rats depicting reduced learning and memory. Treatment with and Ethanolic Extract of (100mg/kg) alone and nanoparticle formulation of Ethanolic Extract of (100mg/kg) and compare with the standard drug donepezil (0.5 mg/kg, i.p., daily)

decreased the day 4 ELT, (F [11, 84] = 113.474, p < 0.05) as well as increased the day 5 TSTQ, (F [11, 84] = 47.124, p < 0.05) when compared to STZ diabetic rats, signifying the attenuation of STZ diabetes induced reduction in learning and memory (Fig. 1A, B).

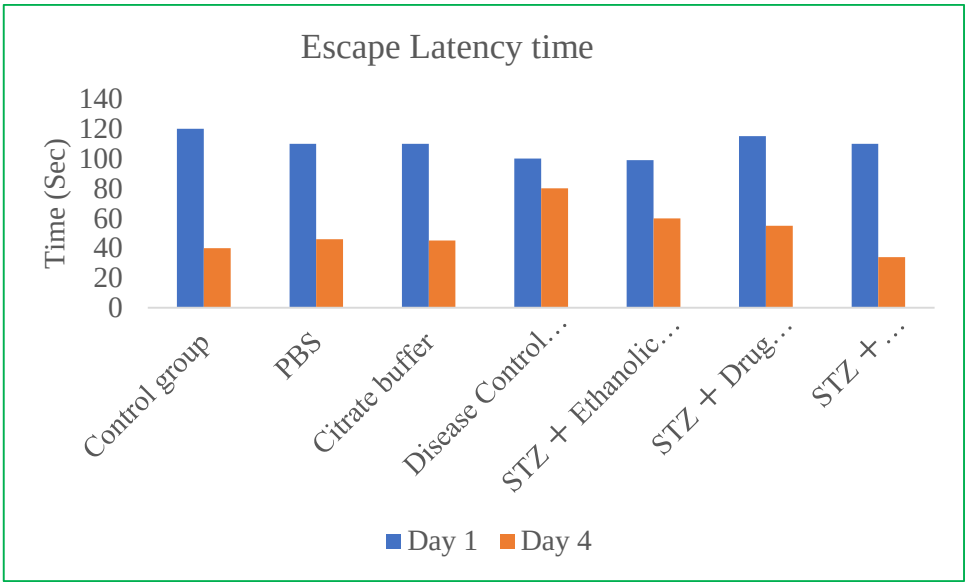


Figure 1 A Escape Latency time

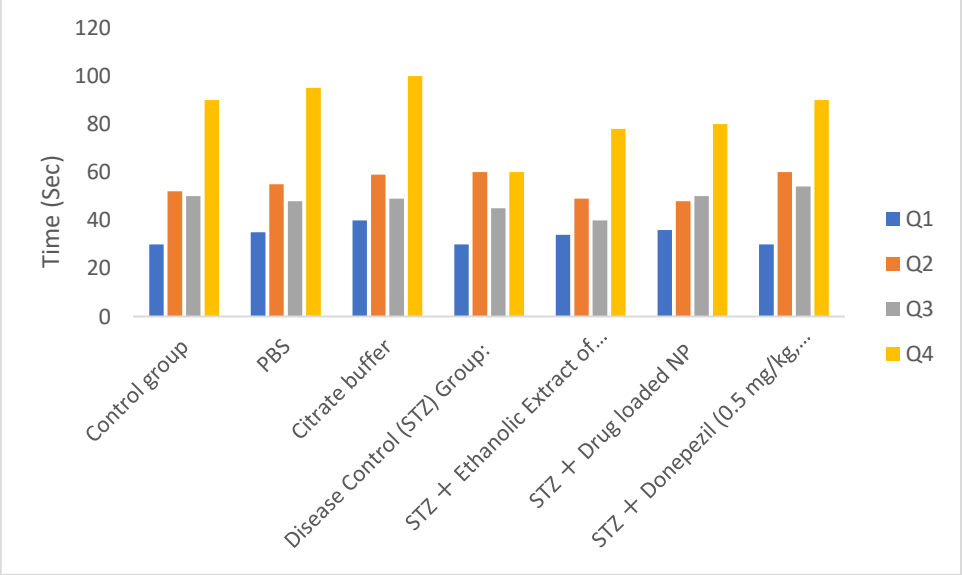


Fig B Mean time spend in the target quadrant

Fig. 4. Effect on learning and memory using MWM. Results are expressed as mean ± standard deviation (n = 8), and were statistically analysed using one-way ANOVA (sigma stat 12.5) followed by Bonferroni's post hoc test. (A) ELT= F (11, 84) = 113.474; ap < 0.05 vs. day 1 in respective group; bp < 0.05 vs. day 4 in control group. cp < 0.05 vs. day 4 in STZ group. (B) TSTQ = F (11, 84) = 47.124; ap < 0.05 vs. mean time spent in other quadrant in respective group; bp < 0.05 vs. mean time spend in target quadrant by control group; cp < 0.05 vs. mean time spend in target quadrant by STZ group. MWM, Morris's water maze; PBS, phosphate-buffered saline; STZ, streptozotocin.

5.2. Effect on Reversal Learning and Executive Functioning Using ASST

ASST can be used to detect such impairments by evaluating how long it takes for an individual to learn a new rule after the reversal, as well as how many errors they make during the process. ASST involves a series of tasks where the animal must discriminate between different stimuli (e.g., odor, texture) and then adjust when the rules change. In humans, a

computerized version of the ASST might involve visual or auditory stimuli, with participants needing to adjust their attention or response patterns when the rules governing the task change.

Figure 5: Platform of the Attentional Set-Shifting Task (ASST)

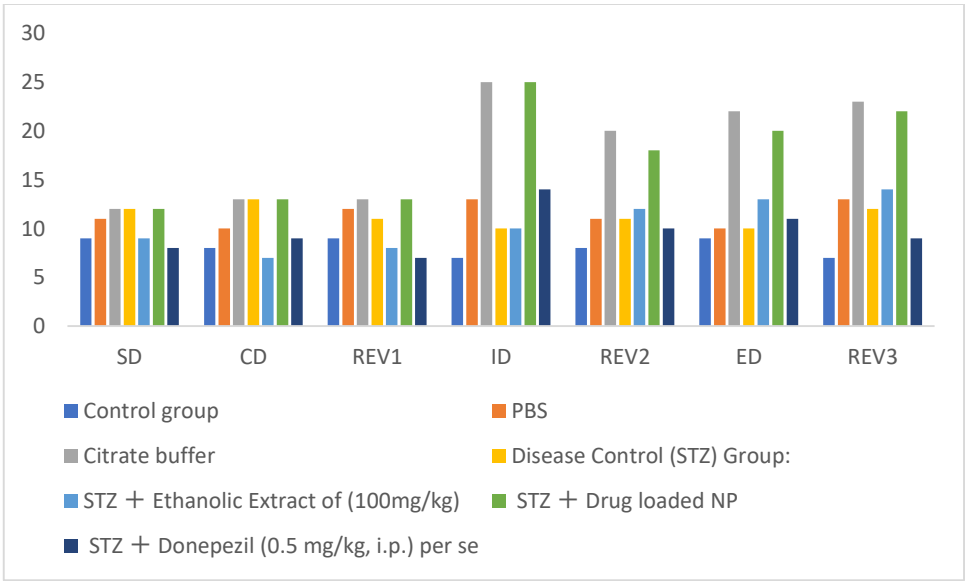


Figure 6: Effect on reversal learning and executive functioning using ASST. Results are expressed as mean ± standard deviation (n = 8), and were statistically analyzed using one-way ANOVA (sigma stat 12.5) followed by Bonferroni post hoc test. REV 1 = F (11, 84) = 385.836; ap $<$ 0.05 vs. control group; bp $<$ 0.05 vs. of STZ group. ED = F (11, 84) = 442.116; cp $<$ 0.05 vs. control group; dp $<$ 0.05 vs. STZ group. ASST, attentional set shifting tests; SAL, saline; PBS, phosphate-buffered saline; STZ, streptozotocin.

5.3. Estimation of serum nitrite/nitrate concentration and aortic production of super oxide anion

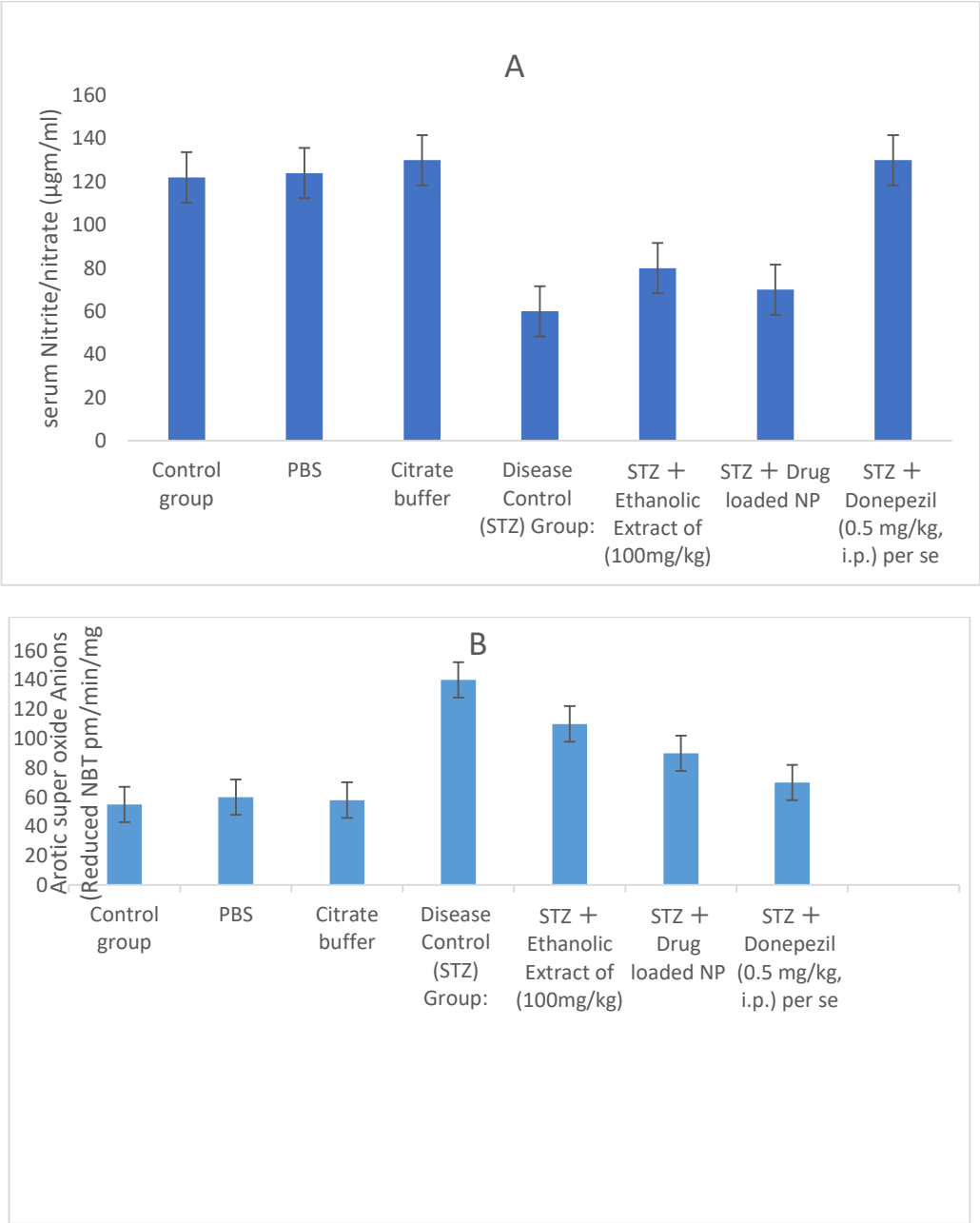


Figure 7: Effect on serum nitrite/ nitrate and aortic superoxide anion. Results are expressed as mean ± standard deviation (n = 6), one-way ANOVA (sigma stat 12.5) followed by Bonferroni's post hoc test. ap $<$ 0.05 vs. control group; bp $<$ 0.05 vs. STZ group. (A) Serum nitrite/nitrate = F (11, 84) =46.991. (B) Aortic superoxide anion = F (11, 84) = 220.936.SAL, saline; PBS, phosphate-buffered saline; CB, citrate buffer; UTI, ulinastatin; SUL, sulforaphane; DON, donepezil; STZ, streptozotocin

5.4. Assessment of brain glutathione (GSH) , TBARS and SOD levels

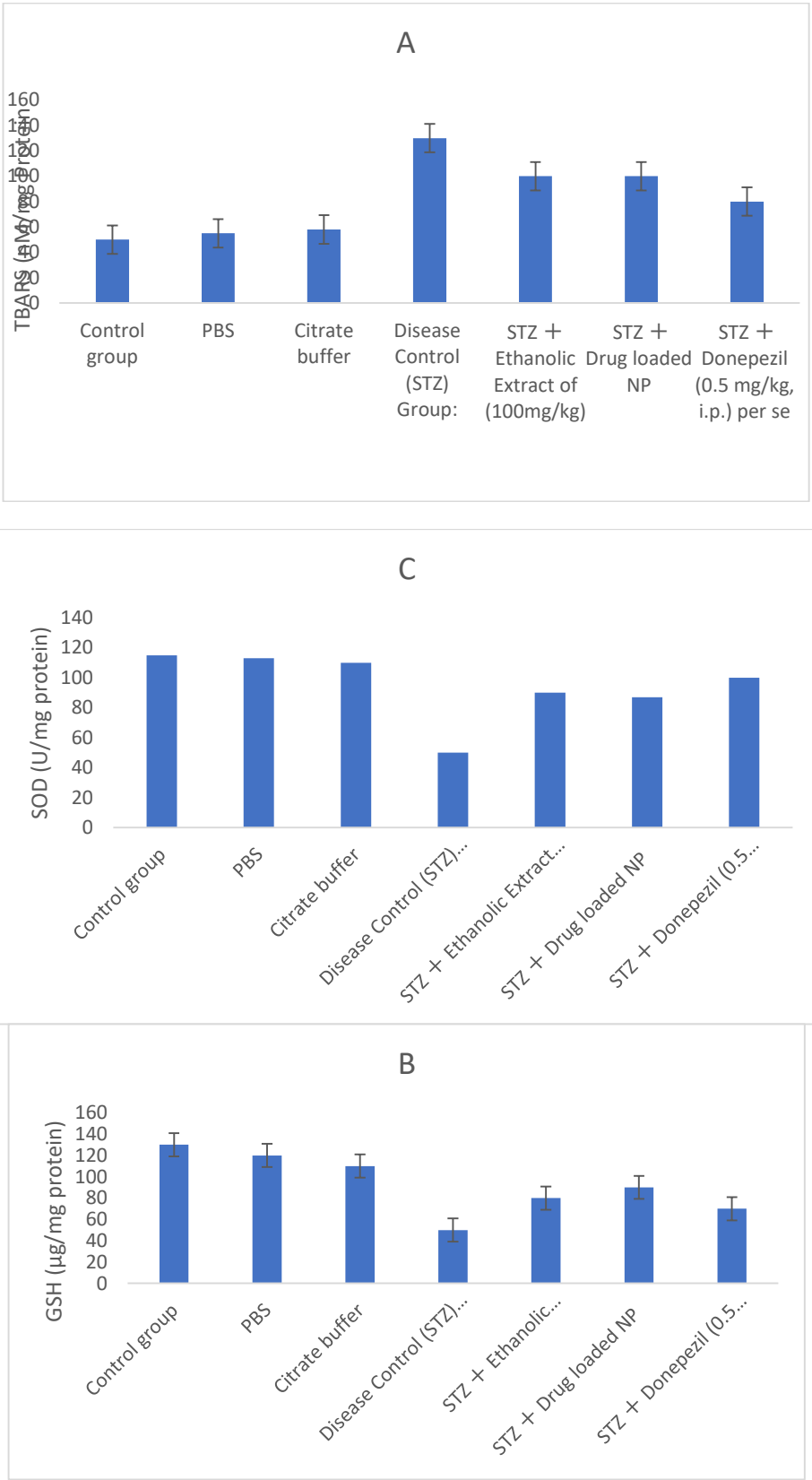


Figure 8, Effect on GSH, TBARS and SOD. Results are expressed as mean ± standard deviation (n = 6), one-way ANOVA(sigma stat 12.5) followed by Bonferroni's post hoc test. ap $<$ 0.05 vs. control group; bp $<$ 0.05 vs. STZ group. (A) GSH (µg/mg protein) = F (11, 84) =46.991. (B) TBARS = F (12, 86) (C) SOD = 220.936.SAL, saline; PBS, phosphate-buffered saline; CB, citrate buffer; UTI, ulinastatin; SUL, sulforaphane; DON, donepezil; STZ, streptozotocin

Discussion

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Dementia is the most prominent condition associated with the diabetes in old age it was resemble as the Alzheimer's disease The role of bioactive constituent of the *Pterospermum acerifolium*, traditionally used in Ayurvedic treatment it was helpful in the management of the Loss of memory in the Diabetic patient is the main concern of this research was to formulate the nanoparticle of the plant extract of *P. acerifolium.* It is rich in various bioactive compounds that contribute to its medicinal properties. Key phytochemicals include, flavonoids, alkaloids, saponins and tannins The extract of P. acerifolium can be used to reduce metal ions to form nanoparticles. This green synthesis method involves mixing the plant extract with a metal salt solution (such as silver nitrate for silver nanoparticles or gold chloride for gold nanoparticles). The phytochemicals in the extract act as reducing agents, converting the metal ions into nanoparticles and simultaneously stabilizing them. The physical character as shown in figure 1 with the SEM analysis the size present in the NP at the intensity 15±4.56 shown n figure 2 here we formulate the 5 formulation given the nomen cloture NF1, …NF5, After the evaluation of the Physical character shown in table 1 formulation code NF2 and NF3 were selected for the further investigation, In present investigation, STZ diabetes increased serum glucose levels (assessed every week), reduced body weight, learning, memory (MWM), reversal memory, executive functioning (ASST) and impaired endothelial function as well as BBB permeability in rats (assessed using thoracic aorta). STZ diabetic rats showed increased cerebral oxidative stress (↑TBARS, ↓GSH, ↓SOD, ↓CAT), inflammation (↑IL-6, ↑TNF-α, ↑MPO, ↓IL-10), AChE activity and histopathological changes. The results obtained are in accordance with the previously published result reports from ours as well as others' lab Further, treatment with plant extract (100mg/kg) and with the formulation NF2, attenuated the behavioural deficits, endothelial dysfunction, impaired biochemical parameters, and is to pathological changes in STZ diabetic rats. STZ diabetic rats shows loss in the body weight. This is probably due to their inability to metabolize carbohydrates which, shifts the reliance more towards fat metabolism for the energy purposes hence, results into wastage of fat resources [42]. Administration of STZ causes death of the insulin producing cells in the pancreas, which increases the serum glucose levels in rats [4]. In diabetic control animals it was found clearly that there was a marked increase in the levels of TBARS and decrease in the levels of antioxidant enzymes such as catalase, GSH, and SOD [24, 25]. Treatment with plant extract and NF2 (100mg/kg) reduces the TBARS levels and increases the levels of antioxidant enzymes compared to that of diabetic control and it clearly implies its role against oxidative stress. Histopathological studies showed that there was no regeneration of islet cells or no insulinogenic property and it reveals that the plant extract site of action may be extra pancreatic and not the regeneration of β-cells and the decrease in blood glucose may be attributed to the stimulation of glucose uptake by peripheral tissues and decrease in the gluconeogenesis. There are marked numbers of medicinal plants reported for antidiabetic activity without the stimulation of insulin secretion [23Thus, we have utilized STZ for induction of diabetes. Diabetes inhibits long term potentiation in hippocampal cells. This is responsible for mammalian learning and memory by decreasing nitric oxide (NO) , which itself is associated with memory deficits [9-11,34,35]. Our previous studies in diabetic rats have reported reduction in learning and memory due to endothelial dysfunction. Hence the above results evidenced strongly that the probable glucose lowering mechanism of action by increasing the glucose uptake in peripheral tissues and by inhibition of gluconeogenesis. Establishment of mechanism of action for antidiabetic property and identification bioactive molecules responsible for the glucose lowering effect were undertaken for the first time with flowers of *Pterospermum acerifolium*

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