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Invivo Evaluation of Neuroprotective Effect of Inosine Against STZ (Streptozotocin) Induced Cognitive Dysfunction in Wistar Rats

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KEYWORDS

Inosine, Antioxidant, Anti-Inflammatory, Alzheimer Diseases, dementia

ABSTRACT:

Objective: To investigate the neuroprotective properties of *Inosine* against mild cognitive decline and cognitive dysfunction induced by Streptozotocin in experimental rats.

Methodology: Inosine (100, 200 & 300 mg/kg p.o.) was given once daily following the treatment of Streptozotocin (3 mg/kg i.c.v.) to male Wistar rats for 20 days. On the 1st, 10th, and 20th days, the walking track test, locomotor activity, and object recognition test were used as behavior characteristics to assess spatial and non-spatial memory.

Results: Treatment with *Inosine* significantly attenuated the STZ -induced alterations in body weight, motor coordination such as locomotion, stride length, object recognition, and oxidative defense parameters. *Inosine* at high doses had the most prominent therapeutic effects. $P<0.05$ and mean ± SD are used to compare mean values with normal control, disease control, and high doses of *Inosine*

Conclusion: Recently, oxidative stress has been proposed as a mechanism for streptozotocin-induced neurotoxicity. Treatment with *Inosine* substantially decreased oxidative stress and behavioral alterations in rats treated with streptozotocin. There is a possibility for net neuroprotective benefits from inosine, which might enhance memory and learning. The anti-inflammatory and antioxidant properties of *inosine* may be behind its neuroprotective action.

Introduction

Alzheimer's disease (AD) is a neurological disorder that progressively impairs a person's cognitive function and eventually results in death. It is the most common kind of dementia among the elderly [1]. As the fourth leading cause of death in the US, it comes in after cancer, heart disease, and stroke [2]. Neurofibrillary tangles (NFTs) and amyloid-β plaques (Aβ) are the two main neuropathological indicators of AD [3]. Amyloid-β peptides are clumped to form Aβ, whereas hyperphosphorylated tau proteins form NFTs, which are paired helical filaments (PHFs). The hyperphosphorylated state is known to promote tau aggregation in PHF, resulting in microtubule instability, membrane deterioration, and neuronal injury. Amyloid β peptide (Aβ) makes up the extracellular deposits and aggregates to create amyloid plaques, insoluble macromolecular structures with a unique structure [4].

There are several indications and symptoms that an Alzheimer's patient frequently shows. The effects of genetic and epigenetic factors, such as the ApoE4 status, the default mode network, and the evolutionary characteristics of human cognition are all revealed by AD memory loss. On the clinical level, the assessment of memory helps to define AD subtypes, grade the disease, and provide prognostications [5,6]. In 50 consecutive AD outpatients, the Neuropsychiatric Inventory assesses the incidence and seriousness of dementia's psychological and behavioral manifestations at different stages and levels of the illness. The most common symptoms reported by the carers ranged from 46 to 74% throughout the entire research population and included apathy, aberrant motor activity, dysphoria, and anxiety [7,8]. Hypothetical pathophysiological pathways and neurobiological connections between depression and Alzheimer's disease. The development and progression of depression and Alzheimer's disease are significantly impacted by dysfunction of the

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hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation, and dysfunction of neurotrophin signaling. These factors increase the levels of pro-inflammatory cytokines and glucocorticoids, while also lowering the levels of TGF-β1, BDNF, and brain-derived neurotrophic factor. These changes may render the hippocampus more susceptible to β-amyloid toxicity and shrinkage, which would facilitate the development of cognitive impairment and ultimately the transition from depression to Alzheimer's disease [9]. A growing body of research shows that moderate behavioral impairment (MBI), which includes psychosis, increases the likelihood of progression of AD and may even operate as a prodrome [10]. Numerous hypotheses have been proposed regarding the cause of AD. Instead of reading over each notion, the objective is to concentrate on the hypotheses that are anticipated to be implicated [11]. Therefore, the hypotheses can be categorized as follows: advancing age more rapidly; degeneration of anatomical pathways such as the cortico-cortical and cholinergic pathways; environmental factors such as exposure to heavy metal ions such as malnutrition; genetic factors such as amyloid precursor protein (APP) and mutations in the genes encoding presenilin (PSEN), a metabolic disorder that results from mitochondrial dysfunction, and allelic variation in apolipoprotein E (Apo E) [12].

Numerous neurotransmitter systems and pathophysiologic pathways make up part the convoluted pathophysiology of AD. The three primary attributes that define the pathophysiology of AD are amyloid-beta plaque (Aβ plaques), tangles of neurofibrillary fibers (NFTs), and neuronal cell death [13].

Amyloid precursor protein (APP) residue fragmentation promotes pathology and leads to Aβ plaque. "Diffuse" or "amyloid" plaques, amyloid fibrils, and plaques are much less dense and spherical deposits of Aβ seen in the majority of Alzheimer's brains [14].

In AD, the microtubule-associated protein tau experiences aberrant hyperphosphorylation and builds up as tangles of paired helical filaments in neurons that are degenerating.

[15]. Enzymes known as secretases have the ability to post-translationally digest APP by cleaving the protein into many smaller pieces. Proteases α-secretase and β-secretase have the ability to cleave APP initially. In addition, many proteins' regular functions depend on the activity of γ-secretase. In AD research, the amyloid hypothesis has become the dominant explanation due to the identification of causal mutations in the APP. The site of post-translational processing of the APP is assumed to be endosomes or the cell surface. Amyloidogenic pathway enzymes β-then γ-secretase or α-then γ-secretase (non-amyloidogenic) processes , resulting in the formation of amyloid beta (Aβ) [16].

During the process of tangle formation in AD, one of the initial neuronal changes is the buildup of improperly phosphorylated τ. During tangle maturation, an epitope found in the ubiquitin molecule's 50–65 amino acid residue area becomes more accessible and present. The failure of changed cytoskeletal proteins to be broken down by proteases might be indicated by the presence of ubiquitin in PHF [17].

Humans are exposed to streptozotocin (STZ) through food antacids, cooking utensils, and deodorants in addition to occupational exposure from things like defense-related companies, cars, and firearms, according to a report by the WHO. Several methods, including eating, intramuscular injection, and cutaneous absorption, can be used to deliver Al compounds into the systemic circulation. It is well known that streptozotocin (STZ) interacts with metabolic enzymes that are engaged in many pathways, making it a strong neurotoxic agent in both humans and animals. Lately, research on animals and humans has indicated that streptozotocin (STZ) has highly harmful effects on the central nervous system (CNS), primarily on cognitive processes. These effects may be attributed to modifications in the neuropathology caused by Al [18]. Heavy metal ions such as have been identified as the progenitor of neurodegenerative diseases [19]. Studies have shown a connection between occupational exposure to streptozotocin (STZ) and neurological disorders, as streptozotocin (STZ) is known to be neurotoxic [20]. A high concentration of Al in the brain is associated with several diseases and metabolic alterations that are also seen in AD, including amyloid beta aggregation, oxidative stress, neuroinflammation, and NFTs. In addition, quite a lot of research has been conducted on the causes and management approaches of AD using the Streptozotocin induced AD rat model [21].

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In recent years, researchers have been increasingly interested in using traditional herbal remedies to treat Alzheimer's disease [22]. The vast majority of the species in the plant kingdom have a variety of bioactive metabolites with various chemical scaffolds. The usage of plants that are significant for ethnomedicine and secure and efficient in human populations is particularly intriguing in terms of drug development [23]. *Inosine* is utilized as a bactericide [24], antifungal [25], and anti-inflammatory agent [26] in addition to treating skin conditions and pain [27]. Apart from their prospective therapeutic applications in clinical and experimental studies [35], they have also been shown to have antibacterial [28], anti-ulcer [29], anti-proliferative [30], antiparasitic [31], hypoglycemic [32], hypolipidemic [33], and wound healers [34] properties. The exact processes behind Calendula officinalis Linn.'s possible treatment against experimentally produced AD remain unclear, nevertheless. Additionally, there is no information on the potential therapeutic efficacy of Inosineagainst AD produced by STZ. Thus, the primary aim of the study was to investigate if euphoric properties of *Inosine* could alleviate oxidative stress and neuroinflammation in rats having AD after exposure to STZ

MATERIALS AND METHODS

Experimental Drugs and other Chemicals

Donepezil and Streptozotocin (STZ) were acquired from Sigma Aldrich Chemicals Pvt. Ltd. Bengaluru, Karnataka, and other chemicals utilized in this research were bought from excellent manufacturing companies.

Experimental Animal

The study is going to be carried out on male Wistar rats. Standard living conditions are provided for the animals, who are housed in polyacrylic cages with a 12-hour light/dark cycle, ambient temperature of 22±2ºC, and relative humidity of 60±5%. There is a perpetual amount of water and dry pellets for feeding. Each study needs to be completed in a 20-to 24-hour period. The research protocol was approved by IAEC with approval number **IAEC0624_14** the CCSEA's guidelines were followed when caring and handling for the experimental animals. The study was carried out at venus remedies, H.P. Animal House in Venus medicine research centre, Baddi, H.P.

Experimental Design

Table 1: Experimental Group

S.No.	Group name	Groups
1	I	Vehicle Control
2	II	STZ 3mg/kg (i.c.v) once (disease control)
3	III	STZ 3mg/kg (i.c.v) once + Inosine low dose 100mg/kg (p.o.)
4	IV	STZ 3mg/kg (i.c.v) once + Inosine high dose 200 mg/kg (p.o.)
5	V	STZ 3mg/kg (i.c.v) once + Inosine high dose 300 mg/kg (p.o.)
6	VI	STZ 3mg/kg (i.c.v) once +Donepezil 5 mg/kg (p.o.)

p.o. – oral route

The animals were split into six groups, with six animals in each: Rats in Group I get normal saline treatment and are maintained under constant surveillance. Group II rats get an oral dose of 100 mg/kg of STZ for a duration of 20 days in order to cause AD. Group IV animals received the same dose of 100 mg/kg Inosine for a duration of 20 days and they were also against the same STZ that was used in Group II. For a duration of 20 days, the animals in Group V were administered the same dosage of STZ as those in Group II, and they were also given oral 200 mg/kg Inosine for the same period. For a duration of 20 days, the animals in Group VI were administered the same dosage of STZ as those in Group II, and they were also given oral 300 mg/kg (high dose) Inosine for the same period. Animals in group III were given the same STZ challenge as those in group II for a duration of 20 days, along with a standard drug dose of 5 mg/kg of donepezil for the same duration of time.

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Experimental Timeline

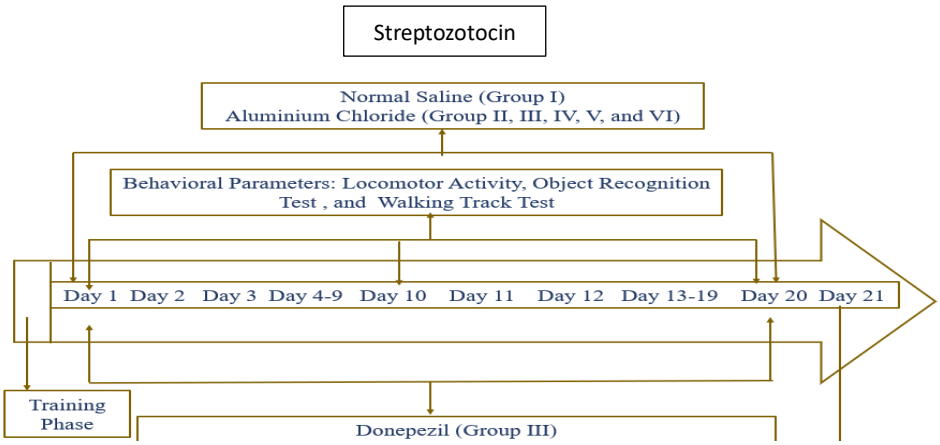

Fig: Timeline of Experimental Research

Body Weight

STZ models frequently show weight loss as a result of anxiety and depression symptoms. On the 1st, 10th, and 20th day days of the research, the animal's body weight was noted. The following formula was used for calculating the percentage change in body weight:

$$\%\text{Body weight} = \frac{\text{Weight on 1}^{st}\text{ day-Weight on 20}^{th}\text{ day}}{\text{Weight on 1}^{st}\text{ day}} \times 100$$

BEHAVIORAL STUDY

Object Recognition Test

The ORT was conducted in an open wooden box (70 x 70 x 25) filled with sets of comparable objects in different sizes and shapes that the animal failed to merely move [36]. This test for assessing a rodent's memory is the spontaneous object recognition test. An object that is both familiar and unfamiliar to the animal is assessed after it has been exposed to one or more similar samples, according to the prototype design [37]. The process doesn't need to be aversively motivated, does not entail restriction of food or water, and requires just a short amount of time for training and assessment, the behavioral neuroscience researchers believe the situation fascinating [38]. A very rapid and efficient way to assess different stages of learning and memory in rats is to administer the object recognition test (ORT), also called the novel object recognition test (NORT). For the test, a maximum of three sessions are needed: one for training, one for habituation, and one for the exam. While testing involves replacing a previously observed object with a new one, training involves just exploring two identical objects visually. A mouse that detects something familiar will spend more time investigating the new object since rodents are naturally drawn to novelty. The ORT utilizes rats' natural interest about novel surroundings, which gives it a major edge over other rat memory tests. As so, it is possible to encourage behavior without the need for several training sessions or any form of incentive, whether negative or positive. The ORT is therefore far less demanding and requires a significantly less time to complete than other commonly used memory tests [36].

Locomotor Activity

The locomotor activity, or ambulation, was measured with an actophotometer, which is a cage with a wire mesh at the bottom that is 30 cm lengthwise and 30 cm depth [39]. It is easy to quantify locomotor activity, also known as horizontal activity, using an actophotometer, which operates on photoelectric cells connected in a circuit with a counter[40]. On the 1st, 10th, and 20th days, each animal was examined for unrestricted locomotor activity. The animal spent some time undisturbed in the actophotometer ample space before being allocated a locomotor activity [41]. An animal crossing the light beam would cause the photoelectric

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cell to activate, cutting off the light rays falling on it. Six lights were set up to fall continuously on corresponding photoelectric cells. These cutoffs were tallied for 5 minutes and the result was used to calculate the animal's locomotor activity. Next, for five minutes, locomotor activity was recorded using an actophotometer. Every five minutes, the total number of photo beams was used to quantify and display ambulatory activity. The amount of lasers passed by the animal and the distance it went were precisely equal [39].

Walking Track Analysis

The assessment uses observations made during routine walking to evaluate motor coordination and synchronization. Nontoxic acrylic paint is used to tint the animal paws for this experiment. The absorbent paper that the rat must traverse. The walking tracks served as the source for the stride records [42].

BIOCHEMICAL ESTIMATION

Dissection and Homogenization

Animals were sacrificed on 21st day; tissue homogenate was prepared before animal sacrifice; rat brains were removed immediately; they were cleaned with ice-cold isotonic saline immediately after; they were then preserved in brain homogenate; biochemical tests were conducted on brain homogenate; the cortex and the hippocampus were separated and weighed; brain tissue samples were homogenized using very cold 0.1 molar phosphate buffers w/v (pH 7.4); aliquots of the homogenate's supernatant were separated for biochemical estimation following centrifugation at 12,000 g for 20 minutes.

Estimation of lipids peroxidation

Using the Placer technique, the final product of lipid peroxidation, malondialdehyde (MDA), was quantitatively quantified in brain homogenate [43]. 0.5 ml of Tris HCl (0.1 M, pH 7.4) was added to 0.1 ml of supernatant in this experiment, and it was then incubated for two hours. Centrifuge at 1000 g for 10 minutes after adding 1 milliliter of TCA (10% w/v) to this. After adding 1 ml (0.67% w/v) of thiobarbituric acid to 1 ml of supernatant, the mixture was heated to a boiling point and left for 10 minutes. Add one milliliter of distilled water once it has cooled. After MDA interacted with thiobarbituric acid, it was measured at 532 nm using a spectrophotometer.Using a standard curve, the amount of MDA present was calculated and represented as µM/mg protein.

Estimation of Nitrite

Greiss reagent was used to quantify the total quantity of nitrite that had accumulated in the supernatant [44]. Once equal parts of supernatant and Greiss reagent were combined and incubated for 10 minutes at room temperature in the dark, the absorbance at 540 nm was measured using a UV spectrophotometer. The sodium nitrite standard curve was utilized to determine the nitrite content in the supernatant, which was then expressed as µM/mg protein.

Estimation of Catalase

The catalase activity was measured using the UV spectrophotometer by the protocol described by Johansson (1988) [45]. In this process, 3 ml of H2O2-phosphate buffer solution was mixed with 0.05 ml of supernatant. The absorbance was recorded at 240 nm for two minutes at intervals of 30-60 seconds, and the catalase activity was expressed as a mole of H2O2 decomposed/min/mg pr.

Estimation of Superoxide Dismutase (SOD)

In this procedure, 0.1ml of homogenate was added after mixing 2ml of nitazo-bluetetrazolium (NBT) with 0.5ml of hydroxylamine hydroAfter that, for 2minutes, at intervals of 30-60 seconds, the absorbance at 560 nm was measured with a UV spectrophotometer. SOD unit/mg pr was used to measure SOD activity [46].

Estimation of reduced glutathione (GSH)

Glutathione (GSH) is an extremely prominent antioxidant in aerobic cells, with concentrations ranging from micromolar (M) in body fluids to millimolar (mM) in tissue [47]. 1 mL supernatant was mixed with 1 mL 4% sulfosalicylic acid and cold digested at 4 °C for 1 hour. A 1200 g centrifuge was used to spin the samples for 15 minutes at 4 °C. Phosphate buffer (0.1 mol/l, pH 8) and DTNB were each added to 1 ml of this supernatant. Using a UV spectrophotometer, the generated yellow hue was read at 412 nm right away. Calculating the glutathione level in the supernatant involved using a standard curve and representing the result as µM/mg protein.

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Estimation of Total Protein

The IFCC suggests using the biuret method as a reference method for estimating the total protein. such that the biuret method can accurately quantify the total protein [48]. To a test tube containing 2.9 ml of 0.9% NaCl, homogenate was added in an amount of 0.1 ml. After that, add 3 ml of active biuret reagent to the test tube mentioned above. Shake and combine the items thoroughly. Then, let them sit at room temperature for about 10 minutes. The sample should then be moved from the test tube to the cuvette so that BSA may be used as a standard to quantify the absorbance at 540 nm against a blank.

Estimation of Acetyl Cholinesterase (AchE)

Using the Ellman et al., 1961 technique, acetylcholinesterase (AchE) activity was determined[49]. The test combination consisted of 25 µl of tissue homogenate supernatant, 100 µl of DTNB, 100 µl of acetylthiocholine iodide, and 3 ml of 0.01 M phosphate buffer saline with pH 8.0. At a wavelength of 412 nm, absorbance was immediately recorded for two minutes. The results were given as µM of acetylthiocholine iodide hydrolyzed/min/mg protein, and Ellman et al. (1961) estimated the chromophore's molar extinction coefficient to be $1.36*10^4$ $M^{-1}cm^{-1}$ [50].

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism version 8. The mean ± SD was used to display the results. Results related to behavior were analyzed using a two-way repeated measure ANOVA and Tukey's post hoc test. Tukey's post hoc test was used after one-way ANOVA to assess the body weight and biochemical data, in contrast. In every test, values shown as statistically significant were those with a $P<0.05$.

RESULTS

Effect of *Inosine* on bodyweight in STZ induced experimental dementia in Rats

When compared to normal control rats, animals with experimental dementia caused by STZ had a significant decrease in body weight (Fig. 5.1.1). In contrast, the *Inosine* treatment significantly attenuates the decline in body weight. A similar trend was observed in standard donepezil treatment and the results of donepezil and *Inosine*s were compared and did not show any significant difference ($p<0.05$).

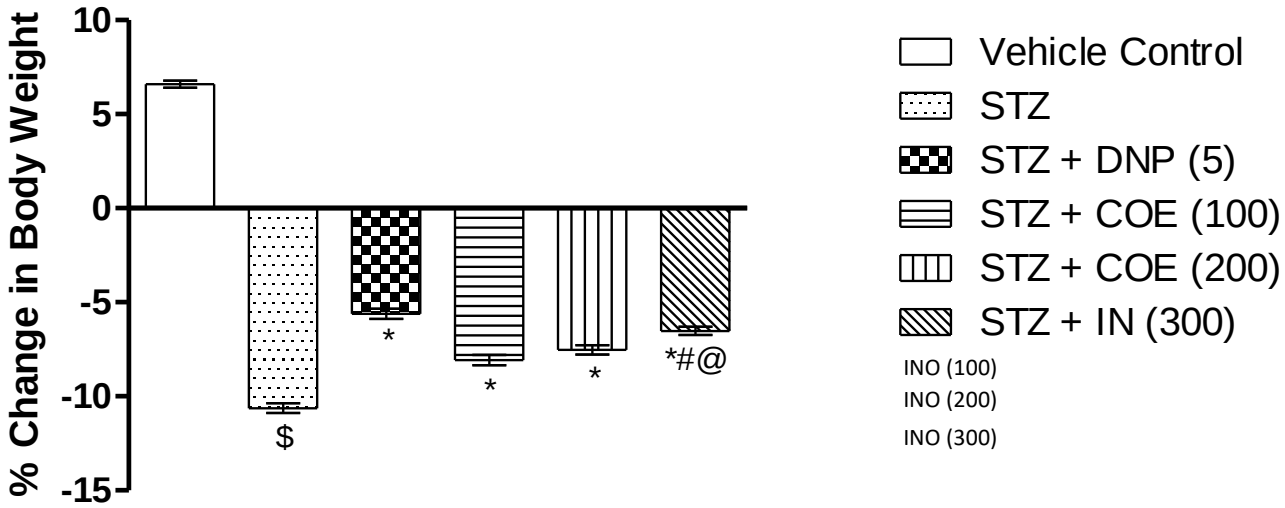

Fig. : Effect of *Inosine* on bodyweight in STZ -induced experimental dementia in rats. Data indicated as mean ± S.D. $^{\$}p<0.05$ vs. Normal control, $^{*}p<0.05$ vs. STZ control, $^{\#}p<0.05$ vs. inosine (100), $^{@}p<0.05$ vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

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Effect of *Inosine* on locomotor activity using Actophotometer in STZ induced experimental dementia in rats.

On day 1st day animals, the first trial of the locomotor activity was performed. An animal crossing the light beam would cause the photoelectric cell to activate, cutting off the light rays falling on it. Six lights were set up to fall continuously on corresponding photoelectric cells. These cutoffs were tallied for 5 minutes and the result was used to calculate the animal's locomotor activity. Whereas, on day 10th and 20th , when animals performed locomotor activity then they showed a significant difference ($p<0.05$) (Fig. 5.1.2). However, STZ induced experimental dementia in rats showed less locomotor counts, when compared to normal control group animals.

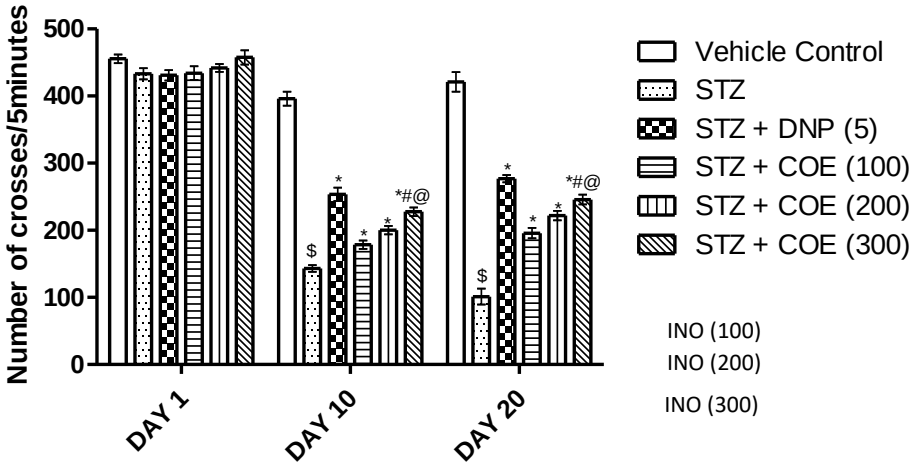

Fig : Effect of *Inosine* on locomotor activity using Actophotometer in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* in STZ induced experimental dementia in rats on non-spatial memory performance using Object Recognition Test (ORT)

The first trial (T1) of the ORT was carried out on the 10th day after STZ induction.In the initial trial, rats explored identical items for about the same amount of time on average, and there was no significant difference in the mean total exploration time across treatments ($p<0.05$) (Fig. a).In contrast, animals exposed to a fresh item (new object) in the trial phase (T2) on day 11 of the experiment had a significant difference ($p<0.05$) with a known object (previously exposed object T1) (Fig. b). Rats with -induced experimental dementia, however, were unable to distinguish between novel and familiar things.

On the other hand, STZ -induced rats' ability to distinguish between a known and unfamiliar item significantly improved when treated with *Inosine* Rats treated with combination demonstrated a reduced tendency to exhibit STZ-induced discriminating impairments ($p<0.05$) when comparing the unpaired T-test comparisons of exploration time, with the combination-treated rats spending more time examining the novel item (Fig. c). Without any notable variations, each group's exploration time of a known object was almost the same.

Effect of *Inosine* on total exploration time in STZ induced experimental dementia in rat

The amount of time the animals spent in the first trial exploring the family items is known as the total exploration time. On day ten, there was little difference in the amount of time spent investigating the objects and their approaches to them.The animals of each group spent almost the same time exploring both similar objects.

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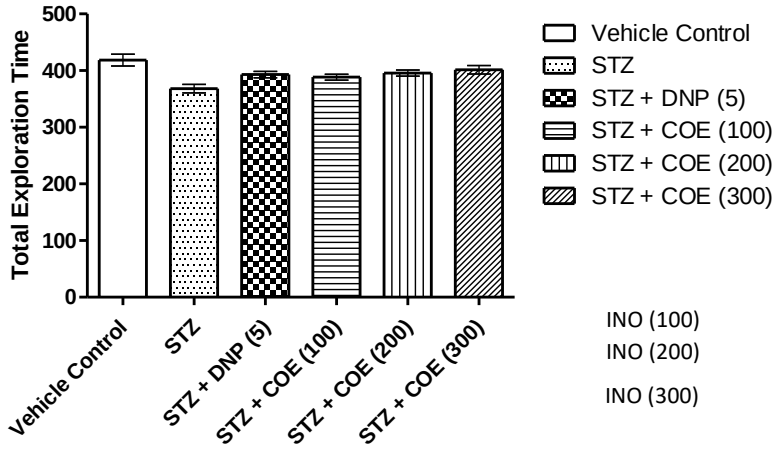

Fig. a: Effect of *Inosine* on total exploration time in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on time spent in exploring novel objects in STZ induced experimental dementia in rats

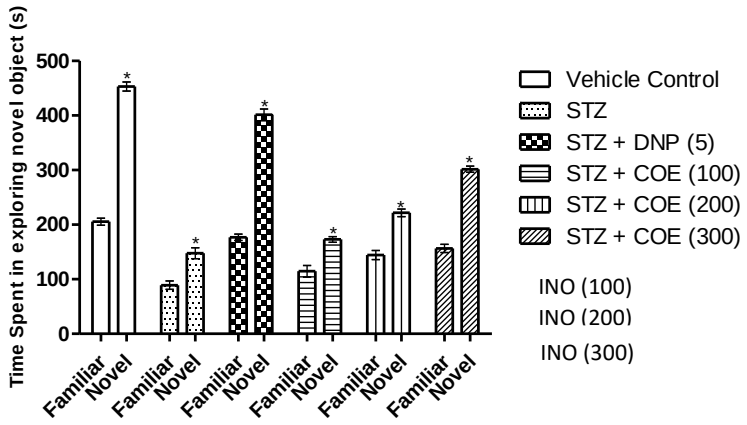

Fig. b : Effect of *Inosine* on time spent in exploring novel objects in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on total discrimination time in exploring novel objects in STZ induced experimental dementia in rats

Discrimination index is the important factor for determining distinguishing ability and spatial memory of experimental rats. The STZ control rats decreases the distinguishing ability and thus no significant difference in discrimination index as compared to normal control rats ($p<0.05$). However treatment groups *Inosine* when administered so, it produces significant synergistic net effect on discrimination ability as compared to individual Normal groups and STZ control rats. These results demonstrates the positive synergistic net effect of *Inosine* in improving the symptoms of spatial memory impairment in STZ induced experimental dementia in rats.

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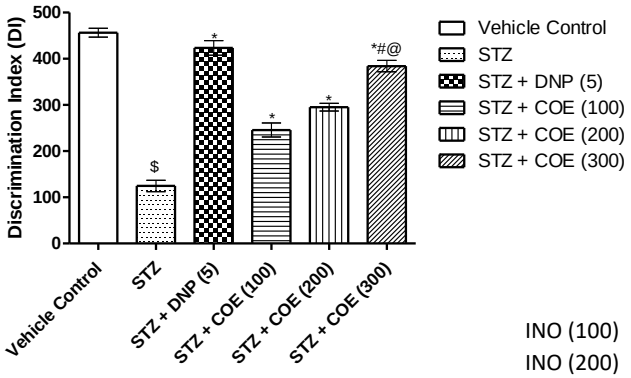

Fig. c: Effect of *Inosine* on total discrimination time in exploring no c induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* in STZ induced experimental dementia in rats on non-spatial memory performance using Walking track test

Through observation during routine walking, the assessment evaluates motor coordination and synchronization. In this experiment, nontoxic acrylic paint is applied to the animal paws on day 20. The absorbent paper that the rat must traverse. A substantial difference ($p<0.05$) was seen in the stride length data obtained from the walking track. But in contrast to the animals in the normal control group, the rats with - induced experimental dementia had shorter strides.

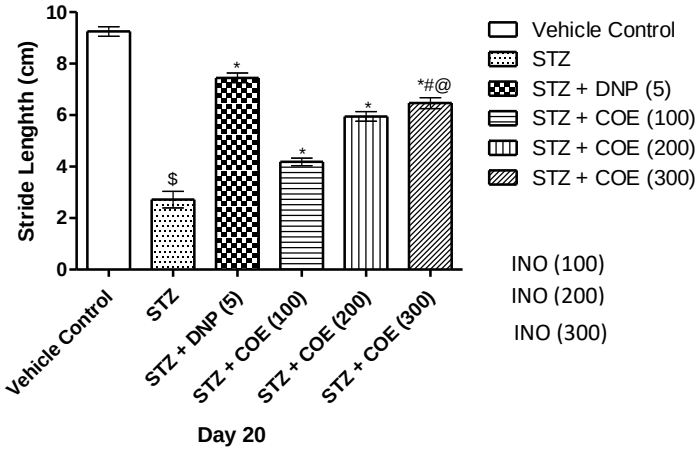

Fig: Effect of *Inosine* in STZ induced experimental dementia in rats on non-spatial memory performance using Walking track test. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on LPO in STZ induced experimental dementia in rats

After the probe trials were finished on day 21, the animals were sacrificed and their oxidative stress parameters were examined. STZ induced experimental dementia in rats produced elevation in lipid peroxidation as indicated by the significant rise in hippocampal and cortical MDA levels ($p<0.05$)

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indicating oxidative stress . Whereas the standard drug donepezil significantly decreases the levels of MDA ($p<0.05$). *Inosine* significantly attenuates the increased levels of MDA indicating its antioxidant potential ($p<0.05$).

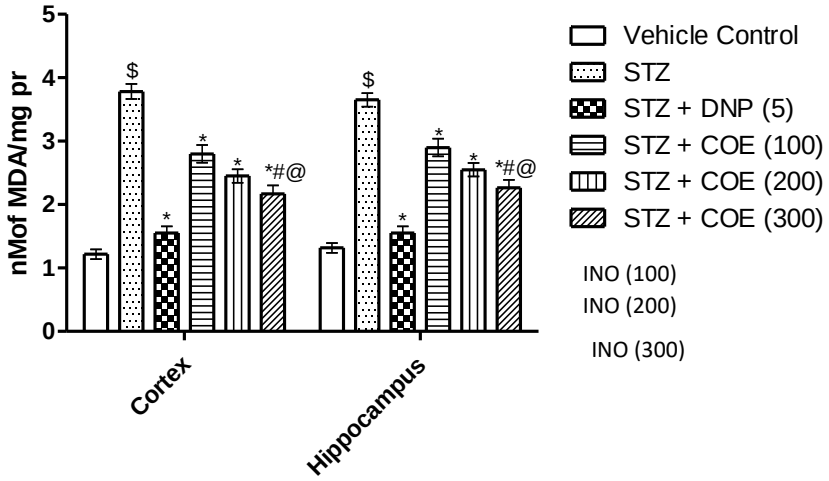

Fig.: Effect of *Inosine* on LPO in STZ lnduced experimental dementia in rats: Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on Nitrite in STZ induced experimental dementia in rats:

The plasma nitrite levels were estimated on day 21st in both cortical and hippocampal regions of the brain. There is a significant increase in the plasma nitrite levels of STZ induced experimental dementia in rats as compared to normal control rats ($p<0.05$). STZ rats, when treated with *Inosine*, significantly attenuate the elevated levels of plasma nitrite both in the hippocampus and cortex ($p<0.05$) .

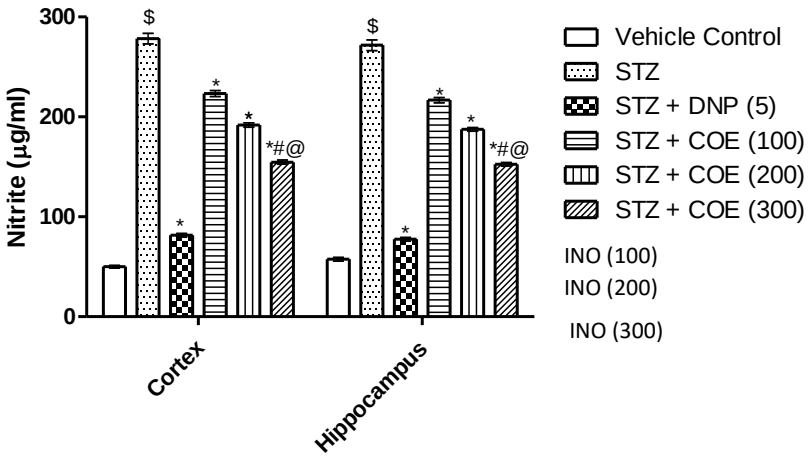

Fig: Effect of *Inosine* on Nitrite in STZ induced experimental dementia in rats: Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

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Effect of *Inosine* on glutathione in STZ induced experimental dementia in rats:

GSH is an endogenous antioxidant enzyme that showed a significant decline in the -induced experimental dementia in rats estimated on day 21st in both cortex and hippocampus regions of the brain ($p<0.05$). The treatment of STZ control rats with *Inosine* significantly attenuated the depleted levels of the GSH and is comparable to the standard drug donepezil.

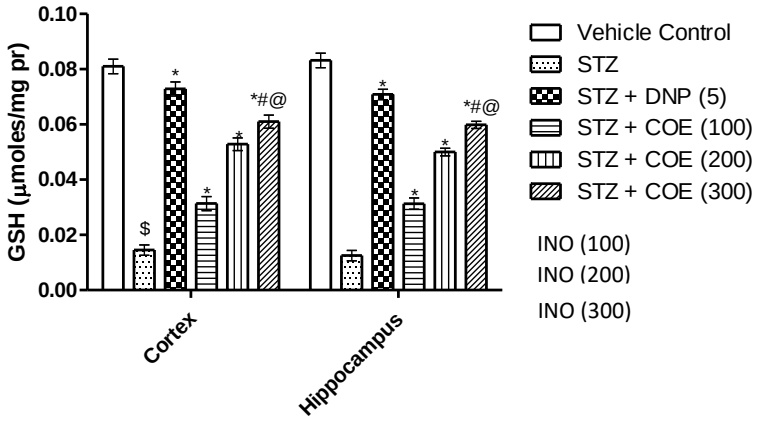

Fig.: Effect of *Inosine* on reduced glutathione in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on catalase activity in STZ induced experimental dementia in rats

The brain activity of catalase was significantly lower in animals treated with STZ than in normal control animals ($p<0.05$). In contrast to the rats treated with , the administration of c in this research considerably restored the lowered activity of catalase in the brain ($p<0.05$). In rats treated with , donepezil reverses the decreased catalase activity in the frontal cortex and hippocampal regions of the brain.

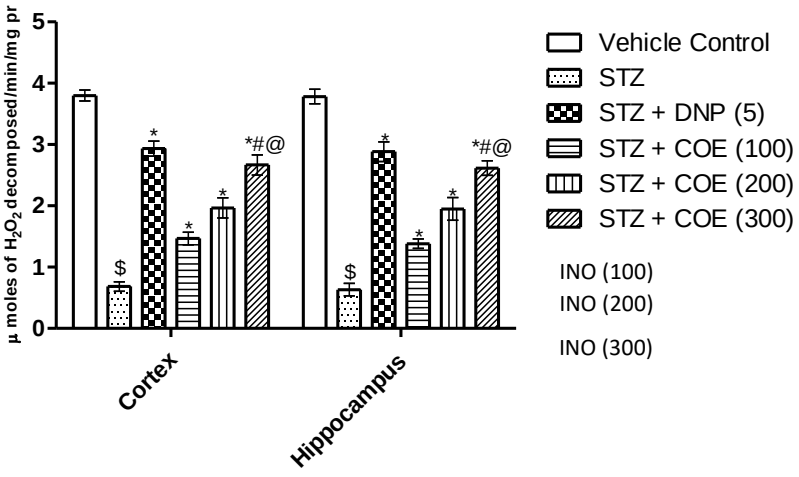

Fig.: Effect of *Inosine* on catalase activity in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

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Effect of *Inosine* on superoxide dismutase activity in STZ induced experimental dementia in rats

-treated animals showed a significant decrease in the activity of SOD in the brain as compared to the normal control group ($p<0.05$). In this study, the *Inosine* treatment significantly improves the SOD activity in the brains of STZ administered rats ($p<0.05$). Donepezil significantly increased the reduced SOD activity in both hippocampus and frontal cortical region of the brain in STZ treated rats.

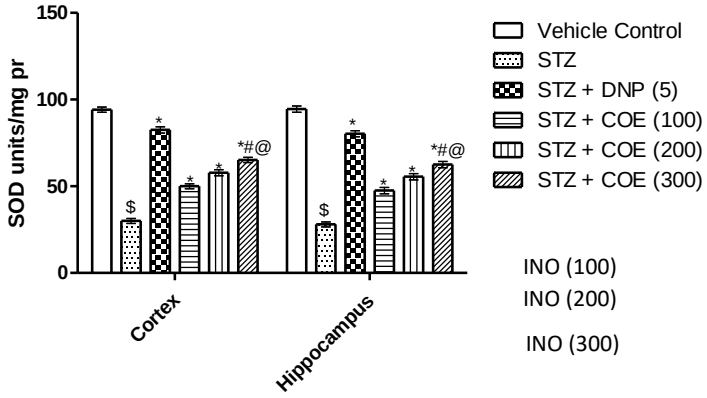

Fig.: Effect of *Inosine* on superoxidedismutase activity in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

Effect of *Inosine* on acetylcholinesterase activity in STZ induced experimental dementia in rats

AChE levels were determined on day 21st both in the hippocampus and cortical regions. The STZ control rats showed a significant rise in the AChE activity as compared with that of normal control rats. Whereas the standard drug donepezil significantly attenuates the increase in AChE as compared STZ rats ($p<0.05$). *Inosine* treated STZ induced experimental dementia in rats also showed a significant decrease in the increased levels of the AChE both in the cortex and hippocampus ($p<0.05$).

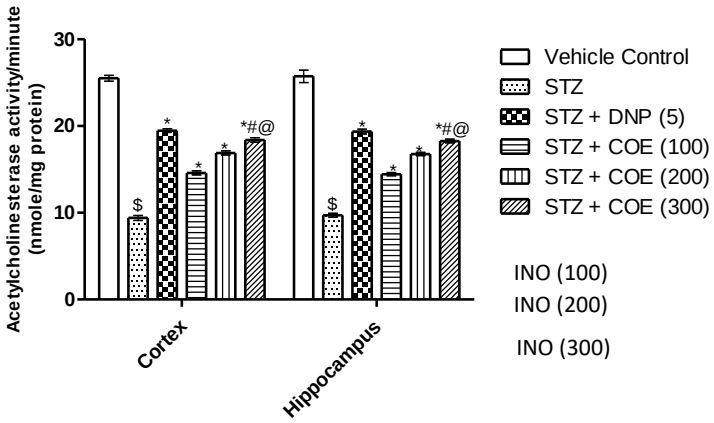

Fig: Effect of *Inosine* on acetylcholinesterase activity in STZ induced experimental dementia in rats. Data indicated as mean ± S.D. $p<0.05 vs. Normal control, *p<0.05 vs. STZ control, #p<0.05 vs. inosine (100), @p<0.05 vs. inosine (200). STZ, DNP: Donepezil, *Inosine*

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DISCUSSION

In the present investigation, we studied the neuroprotective potential of *Inosine*s against mild cognitive impairment and cognitive dysfunction caused by streptozotocin (STZ) in experimental rats. *Inosine* has synergistic neuroprotective properties that can help rats with cognitive and memory deficiencies brought on by and deficits in neurotransmitters and cholinergic function. For behavior parameters such as object recognition test (ORT) results, the rats treated with STZ had poor learning and memory consolidation, and they had trouble telling familiar items apart from unfamiliar ones. As part of the pathophysiology of AD and to evaluate potential therapy strategies, builds up as Aβ plaques and NFTs in the hippocampus. There have been reports of behavioral and biochemical changes following STZ treatment. Depending on the dosage and the passage of time, these changes progress. Therefore, it is regarded as a useful model system for researching anti-AD medications. According to the aforementioned data, the Locomotor activity, Walking track Test, and Object Recognition Test (ORT) results of the current study's rats showed that STZ significantly impaired their cognitive abilities. Integrated synaptic transmission in several brain areas, including the cortex and hippocampus, is what gives WFT its spatial memory. However, ORT depends on the natural behavior of the experimental rats to examine non-spatial memory. In STZ rats, both spatial and non-spatial memory were impaired, and the animals were unable to distinguish between family and unfamiliar items, particularly in ORT. However, there was an apparent improvement in cognitive abilities in the treatment groups and with *the Inosine* . However, co-treatment of *Inosine* was more efficient than that of their separate effects in reversing cognitive decline in STZ rats, demonstrating the potential for synergy. The environment is heavily populated with aluminum, a hazardous industrial pollutant. In addition, it may be found in many foods. It has been associated with skeletal, hematologic, and neurodegenerative diseases. accelerates both the formation of reactive oxygen species and the buildup of Fe, which causes neurodegeneration. exposure affects monoamine imbalance, especially in cholinergic and noradrenergic neurotransmission, and also causes the generation of free radical species as a result of abnormalities in glucose metabolism. The accumulation of iron and the creation of reactive oxygen species are two mechanisms through which has been shown to cause neurodegeneration brought on by oxidative stress. Superoxide dismutase activity in the cerebral cortex and hippocampus of the brain has been shown to be decreased by oxidative stress, and ROS affects the levels of antioxidant enzymes like catalase and superoxide dismutase.Due to their unique, high-affinity transferrin receptors, streptozotocin (STZ) may reach the brain. The effects of inflammation, long-term potentiation inhibition, aberrant synaptic structure, and the effects on rapid and slow axonal transports in the brain all contribute to severe memory loss. Several different experimental models have shown that *Inosine* is neuroprotective. Thus, the cognitive improvements seen in STZ rats may have been significantly influenced by their neuroprotective activities.

ACh is thought to be a key factor in learning and memory among these. ACh levels have been shown to significantly decrease and acetylcholinesterase (AChE) activity to significantly increase in both preclinical animal models of AD and clinically in AD patients. In the present research, STZ significantly increased the cortical and hippocampus AChE activity in rats, which may be related to ACh levels. ACh is transformed into acetate and choline by the enzyme AChE. On the other hand, STZ rats treated with *Inosine* had considerably lower levels of increased AChE activity, and there was a synergistic suppression of AChE activity in the group that received the AChE activity has been shown to be inhibited by *Inosine*.

Oxidative stress has been connected to the pathophysiology of AD and may have a major role in cognitive impairment. In preclinical and clinical AD models, the elevated oxidative-nitrosative stress triggers various pathogenetic pathways like as excitotoxicity, apoptosis, and neuroinflammation.

The development of age-related neurodegenerative conditions such as Alzheimer's disease and the acceleration of aging are believed to be significantly influenced by damage caused by free oxygen radicals to macromolecules (lipids, proteins, nucleic acids, etc.). The most prevalent non-protein thiol and buffer for free radicals in brain tissue is reduced glutathione, also known as gamma glutamyl-cysteinyl-glycine (GSH).

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Using glutathione peroxidase (GPxs), it removes H_2O_2 and organic peroxides. To create glutathione disulfide (GSSG), these oxygen radicals are reduced by GPx during detoxification at the expense of GSH. Through the process of redox recycling, glutathione reductase (GR), in conjunction with the consumption of one NADPH, converts GSSG into GSH. The production of OH, the moiety most harmful to the brain, and impaired H_2O_2 clearance might result from a loss in GSH, which would increase oxidative load and oxidative damage. Malondialdehyde (MDA), the byproduct of lipid peroxidation, is produced when polyunsaturated fatty acids are peroxidized as a result of an increase in H_2O_2. Reactive oxygen species (ROS) are produced by enhanced lipid peroxidation and STZ alkylating capabilities, which lead to oxidative stress and DNA damage. Increased ROS combine with free NO species to produce peroxynitrite and nitrotyrosine, which eventually impede normal cellular activity and cause the death of hippocampus neurons. Superoxide dismutase (SOD), an endogenous antioxidant enzyme, is usually able to sufficiently remove ROS and avert neuronal injury. It is known that abnormally high amounts of ROS, such as those found in pathological situations like AD, change the SOD's capacity to remove them, impairing synaptic function. The key findings of the current investigation revealed that STZ rats had defective endogenous antioxidant defense mechanisms, and elevated lipid peroxidation, and nitrite levels. The hippocampus and cortical areas of the brain of the STZ rats showed decreased levels of GSH, catalase, SOD. - induced impairment of cerebral energy metabolism has been proposed to be the cause of increased oxidative stress. Contrarily, the endogenous oxidant and anti-oxidant defense mechanisms are greatly restored by *Inosine*. In the cortex and hippocampus, the groups that received *Inosine* showed increased antioxidant enzyme activity as well as reduced levels of lipid peroxidation and nitrite. The synergistic neuroprotective potential of *Inosine* through its antioxidant action is demonstrated by the co-administration of *Inosine*.

Inosine was employed in an experimental model of neuropathic pain, the results of that study were in coincides with current research. The oxidative damage was dramatically decreased by and the depleted levels of endogenous antioxidant enzymes showed improvement in memory impairments.

Inosine works individually by preventing the production of neuroinflammatory signals by inactivating microglia. Increasing the availability of cysteine and glutamine by upregulating cysteine-glutamine anti-porter (xCT) expression is thought to boost glutathione peroxidase levels, causing the anti-oxidant effects of *Inosine*.

In addition to the aforementioned neuroprotective mechanisms, the synergistic impact of *Inosine* is presumably caused by the fact that it reduces the interaction of cytokines after repeated treatment. The anti-apoptotic, anti-oxidative, and anti-inflammatory properties of *Inosine* are indicated by its inhibition of the activities of several key enzymes involved in increased oxidative stress.

The combination of antibiotics also works to lessen neuronal damage, which enhances synaptic learning and memory processes, it may be worth mentioning in closing. Because of its antioxidant properties and capacity to regulate the levels of central neurotransmitters, *Inosine* has a net neuroprotective potential that can enhance cognitive and memory abilities. Even yet, further research is required to fully understand the molecular processes that underlie the extract of the *Inosine* synergistic effects on memory and cognition.

CONCLUSION

Inosine treatment significantly attenuated behavioral changes and oxidative stress in rats treated with STZ. Inosine have a net neuroprotective potential that can improve learning and memory. The observed neuroprotective activity of *Inosine* may be a result of its anti-inflammatory & antioxidant properties. Hence, the neuroprotective effect of *Inosine* against STZ mild cognitive impairment and cognitive dysfunction in experimental rats.

Ethics Approval & Consent to Participate

Human & Animal Rights

In accordance with ethical guidelines i.e. IAEC guidelines are followed and only 6 rats group were utilized in the experiment to ensure the validity of the results.

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Conflict of Interest

None

Declaration of Competing Interest

The authors declare that none of the work described in this research has been impacted by any discernible conflicting financial interests or relationships with others

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