

Evaluation of Sinapic Acid on STZ-induced Depression in Diabetic Wistar Rats

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ABSTRACT

Objectives: Presently, diabetes is a major chronic metabolic abnormality characterized by sustained hyperglycemia. Diabetic neuropathy, encephalopathy, diabetes induced anxiety, depression is common life-threatening complications in which hyperglycemia mediated oxidative stress plays major role in pathogenesis. Sinapic acid is a phenolic acid, reported with anti-inflammatory, antioxidant, anti-bacterial, anti-tumor, anxiolytic activity and also it is proven to be neuroprotective in diabetic neuropathy. **Materials and Methods:** This study was designed to evaluate anti-depressant activity of Sinapic acid on STZ induced diabetic Wistar rats. Animals were divided into six groups ($n=6$). Diabetes was induced by single dose of STZ injection 55 mg/kg i.p. and sinapic acid was administered orally (5, 10, 20 mg/kg) after confirmation of hyperglycemia for next 4 weeks. Behavioural parameters like tail suspension test and forced swim test, antioxidant enzymes (SOD, GSH), oxidative stress (NO, MDA), total protein level were estimated and morphology of brain was examined histopathologically. **Results:** The results suggested that sinapic acid have decreased duration and percent of immobility, oxidative stress and increased antioxidant enzymes and total protein level. Morphological damage and neuronal degeneration in brain tissue was normalised by Sinapic acid. **Conclusion:** Thus, Sinapic acid shows antidepressant activity in diabetes induced depression.

Keywords: Sinapic acid, STZ, Diabetes, Depression.

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic syndrome characterized by hyperglycaemia resulting from absolute or relative impairment in insulin secretion or its action. DM is chronic metabolic disorder of low blood insulin level. STZ is anticancer antibiotic having diabetogenic activity.¹ The compound with cell specific ligand is cytotoxic to pancreatic beta cells. STZ induces the type 1 DM, which is also called as Insulin Dependent Diabetes Mellitus (IDDM) with severe hyperglycemia.² Hyperglycaemia can enhance oxidative stress in body and this is the major contributor for various diabetic complications like nephrotoxicity, cardiopathy, retinopathy, cornealpathy and neuropathy.¹

Prolonged diabetes can also induce anxiety and depression. Diabetes, if not controlled, results in structural and functional changes in various tissues. Diabetes induced reduction of serotonin and non-epinephrine level or receptor expressions can lead to manifestation of depression.³ The increased oxidative

stress leads to decrease in monoamine level, alteration in the function of HPA axis and impaired synaptic plasticity. Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HAP) axis in patients with hyper cortisolemia has been reported to be physiologically associated with diabetes and depression. Also, the dopamine level in hippocampus decreased in STZ Control group compared to the normal group. Corticosterone level was significantly decreased by imipramine and Sinapic acid.³ Oxidative stress not only related to bundle of oxidants caused by over production of Reactive Oxygen Species (ROS) but also the impaired antioxidant mechanism through non enzymatic glycation of the scavenging enzymes. This oxidative stress may cause apoptosis in nervous system. The inhibitory activity of phenolic acids can reverse sorbitol accumulation, so that phenolic acids can be used therapeutically in diabetic complications.⁴

Sinapic acid is a hydroxycinnamic acid derivative with 3,5-dimethoxyl and 4-hydroxyl substitutes in the phenyl group of cinnamic acid. Sinapic acid extensively found in species, citrus, berry fruit, vegetable, cereals, oilseeds, different plant foods like pea, hazelnut, cabbage, wheat, rye, and brown rice and known to have antioxidant, Anti-inflammatory, Anti-cancer, anti-mutagenic, neuroprotective, anti-bacterial activities. Phenolic acids are capable to donate their phenoxy hydrogen for



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free radical neutralization which contributes for its antioxidant activity. The previous study suggested that the Sinapic acid is effective in avoidance of memory loss and decline of oxidative stress, so can be recommended in treatment of Alzheimer disease. Reactive oxygen species are constantly created and used in normal pathophysiology activities.⁵ Previous scientific studies have displayed that Sinapic acid has anti-inflammatory, antioxidant, anti-bacterial, anti-hyperglycemic, anxiolytic, neuroprotective, anti-apoptotic, anti-tumor effects. From the different literature survey, doses of Sinapic acid were finalized as 5, 10, 20 mg/kg/p.o.⁶ Since there were no evidences regarding treatment of Sinapic acid on depression, we hypothesized that it may have protective effect on STZ induced depression in diabetic Wistar rats.

MATERIALS AND METHODS

Drugs and chemicals

Streptozotocin (STZ) as an inducing agent (Sigma-Aldrich), Sinapic acid as test drug, Imipramine as standard antidepressant agent, EDTA, DTNB, TBA-TCA-HCl, Epinephrine, Griss reagent, Triss buffer etc.

Animal Housing

The research proposal was approved by the Institutional Animal Committee (MGV/PC/CPCSEA/XXXVIII/01/2021-22/01) and the experiment was carried out according to the guidelines of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Experimental design

All the rats were randomly divided into six groups ($n=6$) for experimental treatment. Single dose of STZ solution (i.p.) administration induces diabetes mellitus. After 72 hr. of STZ injection, hyperglycemia was confirmed and then animals were selected for further study.

- Group 1 (Normal): Non-diabetics rats received a normal diet and served as control.
- Group 2 (Diabetic control): Diabetic control rats received STZ 55 mg/kg, i.p. once.
- Group 3 (STZ+SP1): Received STZ+Sinapic acid 5 mg/kg, p.o.
- Group 4 (STZ+SP 2): Received STZ+Sinapic acid 10 mg/kg, p.o.
- Group 5 (STZ+SP 3): Received STZ+Sinapic acid 20 mg/kg, p.o.
- Group 6 (STZ+Standard): Received STZ+Imipramine 10 mg/kg, p.o.

The animals were fasted overnight and injected with STZ (55 mg/kg, i.p.) dissolved in 0.1 M Sodium Citrate buffer to induce

hyperglycaemia. Fasting Blood Sugar Level (BSL) of rats was checked after 72 hr of STZ administration. For this blood taken withdrawn tail vein under light anaesthesia and by measured by glucometer (Dr. Morepain). The animals with glucose level >250 mg/dL were considered as diabetic and selected for further study. Sinapic acid (5,10, 20mg/kg, p.o.) dissolved in distilled water⁷ and treatment started after confirmation of hyperglycemia. On the zero and 4th week of treatment, behavioural parameters for depression were studied by Forced Swim Test (FST) and Tail Suspension Test (TST). At the end of treatment schedule, animals were sacrificed by euthanasia and brain was isolated for biochemical and histopathological examination. Tissue was excised, washed with saline solution and immediately stored in triss buffer for tissue homogenate (for oxidative, antioxidant, biochemical) analysis and formalin for histopathological examination.

Behavioural parameters

Forced Swim Test (FST)

This test was conducted in two sessions, first trial test and next main test. Rats were separately placed in vertical plexiglass cylinder (18 cm diameter; 40 cm height containing 25 cm deep water, water maintained 25°C) for 5 min. After training, rats were taken out from cylinder, allowed to dry and placed in home cage. After 24 hr, animals were again placed in cylinder for 5 min. test session in which onset and duration of immobility measured. Then animal was taken out, allowed to dry and returned to home cage.³

Tail Suspension Test (TST)

In this test also training session was conducted for animals before main test. Adhesive tape was wrapped around the animal tail from the 2 cm away from tip of the tail. Rat was suspended to the edge of shelf, 50-60 cm above from the surface. After suspending the rats, the onset and duration of immobility was recorded.³

Biochemical Analysis

Total protein level was estimated by using biochemical kit (Auto Span Kit). Blood was withdrawn from retro orbital plexus by using fine capillary and by cardiac puncture.⁸

Antioxidant and oxidative Study

The excised brain tissue sample was homogenized by five volumes (w/v) of Triss buffer solution. Assay for Superoxide Dismutase (SOD), reduced Glutathione (GSH), Nitric Oxide (NO) and Lipid Peroxidation (MDA) was performed using previously reported methods.

Superoxide Dismutase (SOD)

To 0.05 mL of homogenate, 2.0 mL of carbonate buffer and 0.5 mL of EDTA solution were added. The reaction was initiated

after adding 0.5 mL epinephrine. This epinephrine starts auto-oxidation of adrenaline to adrenochrome at pH 10.2. Change in the optical density, every minute was measured for 5 min at 480 nm against blank.⁹

Reduced Glutathione (GSH)

To 1.0 mL of homogenate, 1 mL of 10% TCA was added and then centrifuged at 10,000 × g for 5.1 mL of supernatant was added with 0.5 mL of DTNB and phosphate buffer of pH 8.0 (Ellmans reagent). Changed colour absorbance was measured at 412nm.⁹

Nitric Oxide (NO)

NO level was measured with Griss reagent method. This is simplest method of NO level determination in which tissue homogenate and griss reagent was added in (1:1 ratio). Incubate it for 15 min at 37°C and cooled it at room temperature. Then the absorbance was measured at 546 nm.¹⁰

Lipid Peroxidation (MDA)

MDA is by-product of lipid peroxidation. It was determined by method of Ohkawa *et al.* 0.1 mL homogenate was reacted with 2 mL of TBA-TCA-HCl reagent (1:1:1 ratio) and placed into water bath for 15 min (37°C). After cooling, it was centrifuged at room temperature for 10 min 1000 rpm. Then absorbance was measured at 535 nm of clear supernatant against blank.^{10,11}

Histopathological Examination

The excised brain tissue specimens were stored for histopathological study in 10% formalin solution and sent to laboratory for histopathological examination. Slides were observed in the light microscope under 10X and 40X magnification power.⁴

Statistical analysis

All presented data were measured as mean±SEM and evaluated by one-way ANOVA followed by Dunnett's test using Graph Pad Prism version 9.3.

RESULTS

Behavioural parameters

FST and TST are utilised to evaluate behavioural changes in experimental animals. Due to depression, animals become immobile and reduction in immobility indicates antidepressant effect. Onset, duration and % of immobility measured by FST (Table 1) and by TST (Table 2) are represented here. Significant changes by sinapic acid in % immobility are indicated in Figure 1.

Biochemical Analysis

Assay of various oxidative and antioxidant parameter and total protein was performed using standard methods. Total protein level was decreased in diabetic control group and found to be

Table 1: Onset, duration and percent of immobility in forced swim test.

Treatment	Onset of immobility 4 th week	Duration of immobility 4 th week	% of immobility 4 th week
Normal	10±1.141	82±10.940	26.332±3.647
Control	12.6±2.561 [#]	115.6±9.729 [#]	38.53±3.243 [#]
STZ+SP1	17.8±1.685 [*]	110.3±10.690 [*]	36.764±3.562
STZ+SP2	10.2±1.2 [*]	87.2±5.228 [*]	29.066±1.743 [*]
STZ+SP3	19.6±7.658 [*]	71.8±12.626 ^{**}	23.93±4.209 [*]
STZ+Std	29±5.932 [*]	77±9.654 ^{**}	25.664±3.219 [*]

Table 2: Onset, duration and percent of immobility in tail suspension test.

Treatment	Onset of immobility 4 th week	Duration of immobility 4 th week	% of immobility 4 th week
Normal	6±0.707	62±6.480	20.662±2.159
Control	11.8±2.267 [#]	141.9±6.972 [#]	47.298 2±.324 [#]
STZ+SP1	17.6±5.714 [*]	134.4±10.403 [*]	44.93±3.336
STZ+SP2	10.4±2.249 [*]	89.52±13.281 [*]	29.83±4.426 ^{**}
STZ+SP3	18±5.549 [*]	71.7±9.104 ^{**}	23.896±3.034 ^{***}
STZ+Std	27.8±2.492 [*]	30.8±2.4928 ^{**}	10.264±0.832 ^{***}

Data is represented as mean±SEM, analysed by one way ANOVA followed by Dunnet test in Graph Pad Prism. # indicates significant change compared to normal and **p*<0.05, ***p*<0.001, ****p*<0.0001 are significant compared to control group.

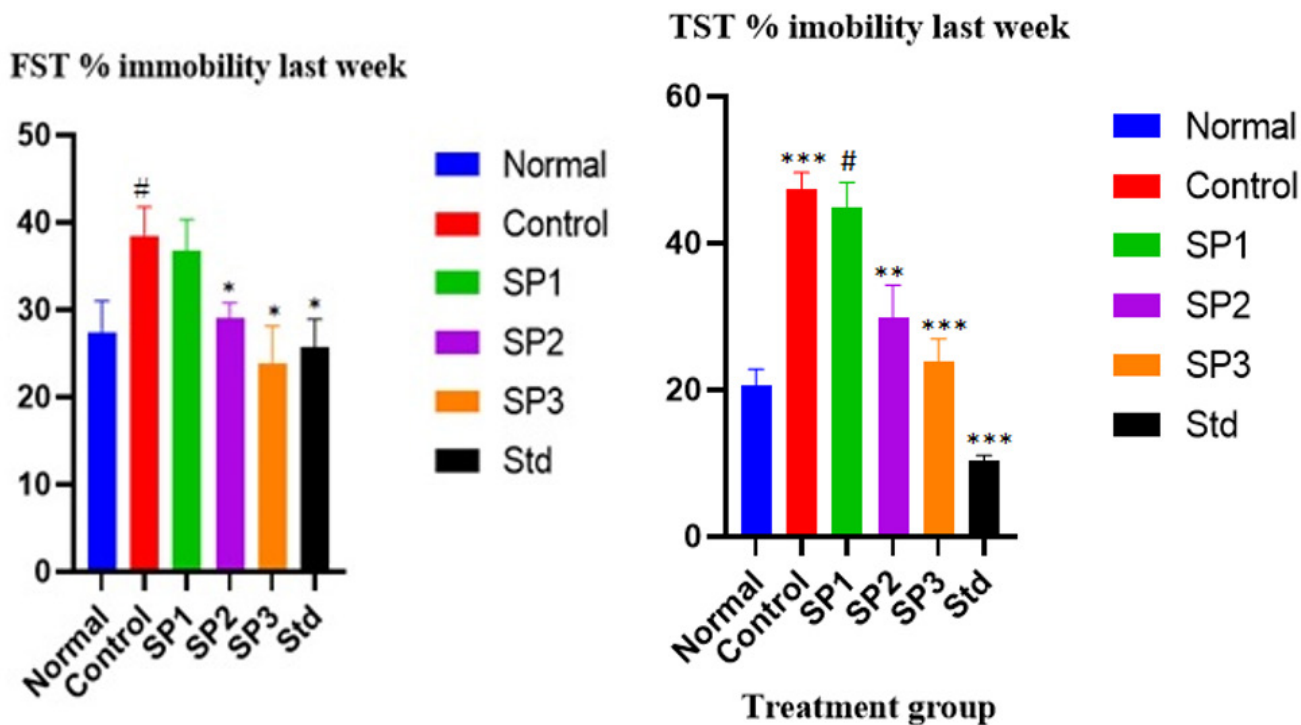


Figure 1: Percent immobility on 4th week in forced swim and tail suspension test. # indicates significant change compared to normal and **p*<0.05, ***p*<0.001, ****p*<0.0001 are significant compared to control group.

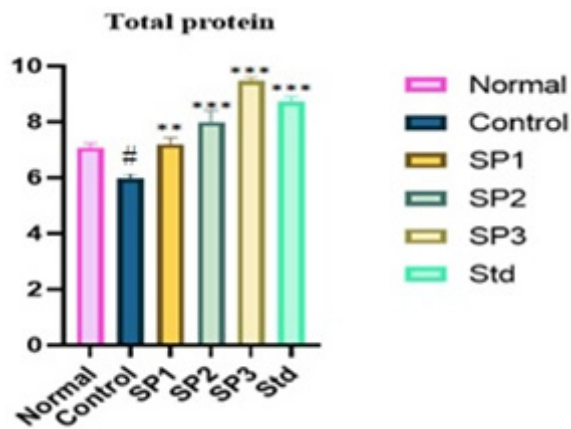


Figure 2: Total protein level in normal, control and treated groups. # indicates significant change compared to normal and **p*<0.05, ***p*<0.001, ****p*<0.0001 are significant compared to control group.

Table 3: Effect of Sinapic acid on total protein.

Treatment	Total protein level
Normal	7.075±0.154
Control	5.982±0.166 [#]
STZ+SP1	7.206±0.225 ^{**}
STZ+SP2	7.997±0.415 ^{***}
STZ+SP3	9.458±0.136 ^{***}
STZ+Std	8.726±0.181 ^{***}

improved with Sinapic acid treatment (Table 3). Significant changes observed in total protein compared to control (Figure 2).

Antioxidant and Oxidative stress parameters

The SOD, GSH, NO, MDA level of enzyme activities in the brain tissue are presented in the chart and graphically represented. The level of NO and MDA in diabetic control group is increased that indicated oxidative stress in the brain tissue treatment with sinapic acid have decreased this. The level of antioxidant enzymes SOD, GSH was decreased in control group and in treatment group

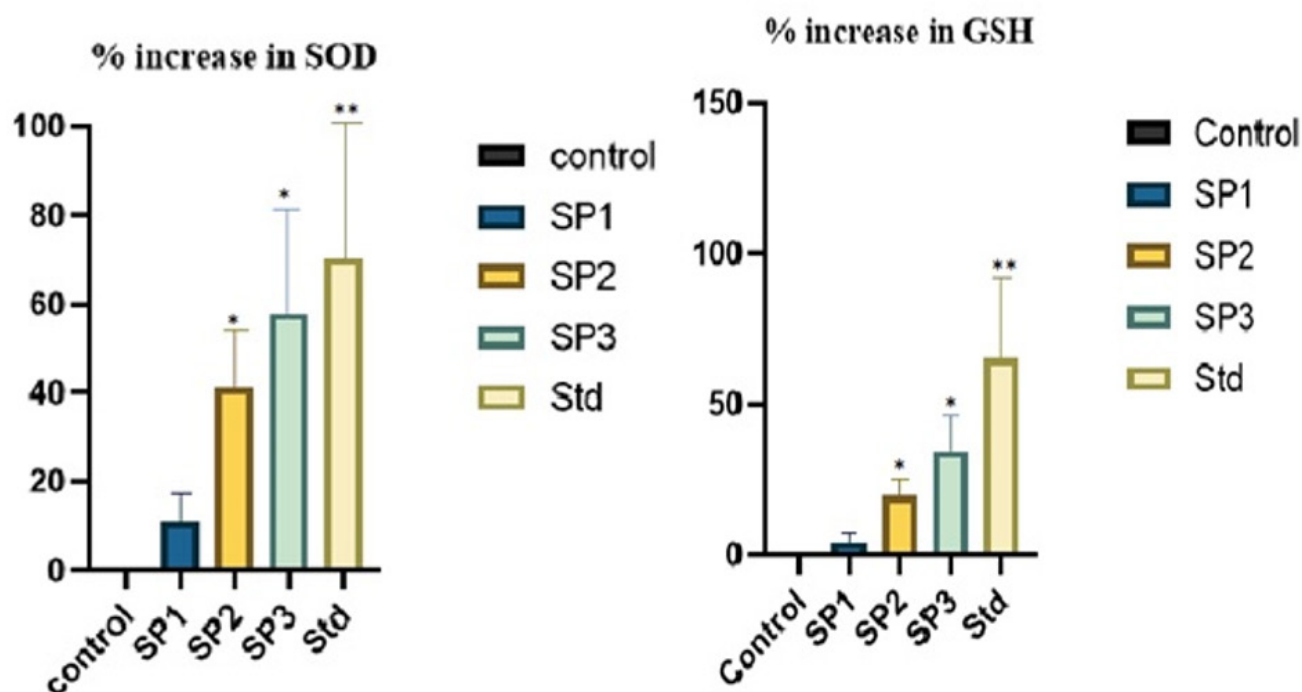
change was normalised. The MDA and NO absorbance of control group was considered as 100% (i.e., 0% inhibition of MDA/NO) and comparatively % inhibition calculated for test and standard groups. Absorbance is comparatively decreased and % inhibition is increased significantly by sinapic acid. % increase in GSH and SOD level is calculated by considering 100% GSH/SOD level of normal and 0% in control group (Table 4). Significant changes are observed after sinapic acid treatment in antioxidant enzymes (Figure 3) and biomarkers of oxidative stress (Figure 4).

Histopathology

The characterized changes in brain tissue in control and treated groups were examined under light microscope under 40x. Histopathological examination of brain with light microscopy is given in Figure 5. In STZ control group, brain tissue showed the degenerated nerve cells with nuclei, inflammatory cell infiltration

Table 4: Effect of Sinapic acid on % inhibition in MDA, NO (Oxidative stress markers) and % increase in SOD, GSH (antioxidant enzymes).

Treatment	% increase in SOD	% increase in GSH	% inhibition in NO	% inhibition in MDA
Control	0	0	0	0
STZ+SP1	11.159±4.990	4.285±1.916	38.677±17.296	26.386±11.800
STZ+SP2	40.955±18.315*	19.448±8.697*	46.984±21.012*	41.601±18.604*
STZ+SP3	57.788±25.843*	34.289±15.334*	52.821±23.622*	66.420±29.704**
STZ+Std	70.117±31.357**	65.339±29.220**	67.919±30.374**	76.458±34.193**

**Figure 3:** Effect of Sinapic acid on % increase in SOD, GSH (antioxidant enzymes). * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ are significant compared to control group.

in cerebral cortex and several apoptotic changes. These abnormal changes are normalised by sinapic acid treatment.

DISCUSSION

The present study was undertaken to evaluate effect of sinapic acid in STZ induced depression. As hyperglycemia induced oxidative stress in major contributor for diabetic complication, antioxidants can be used in its treatment. Sinapic acid has the ability to reduce the oxidative damage in diabetes. Sinapic acid is a phenolic acid with potent antioxidant and neuroprotective role.⁵

Hyperglycemia in diabetes is further associated with anxiety and depression like behaviour.¹² Current treatment of diabetes and depression is with high cost so there is a need to explore new effective therapeutic alternatives.

Depression is prevalent 3 times more in type 1 and 2 times more in type 2 diabetes in comparison to general population. So, it is

a great need to develop antidepressants with anti-diabetic action and this would be novel strategy in process of drug discovery.¹³

The Forced Swim Test (FST), also known as the 'behavioral despair' test, was developed in 1978 by Porsolt *et al.* as a rodent model for predicting the clinical efficacy of antidepressant drugs.¹⁴ In experimental animals, depression like behaviour can be assessed by various valid test like FST and TST which are helpful in strong prediction. In these tests, immobile behaviour is considered to be associated with depression as a tendency to give up in stressful situation.³ At the beginning of the FST, the rat swims vigorously in attempt to get exit. Later, the animal becomes almost immobile by maintaining its head above the water's surface. Many antidepressant drugs reverse this observation of immobility. Effective antidepressant drugs support the assumption that immobility reflects despair. In this present study, latency to immobility was measured. It was the time between immersing the animal in the water to when it becomes completely immobile for the first time.¹⁵

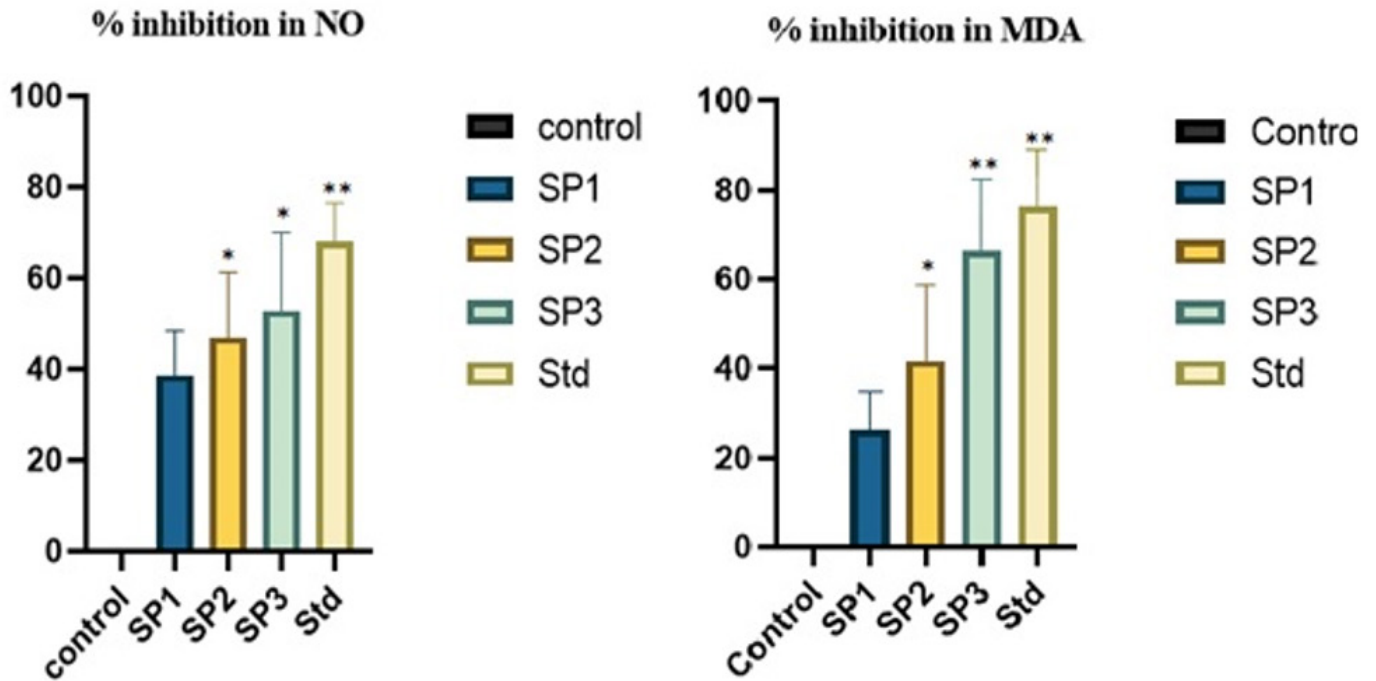


Figure 4: Effect of Sinapic acid on % inhibition in NO and MDA (Oxidative stress markers) * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ are significant compared to control group.

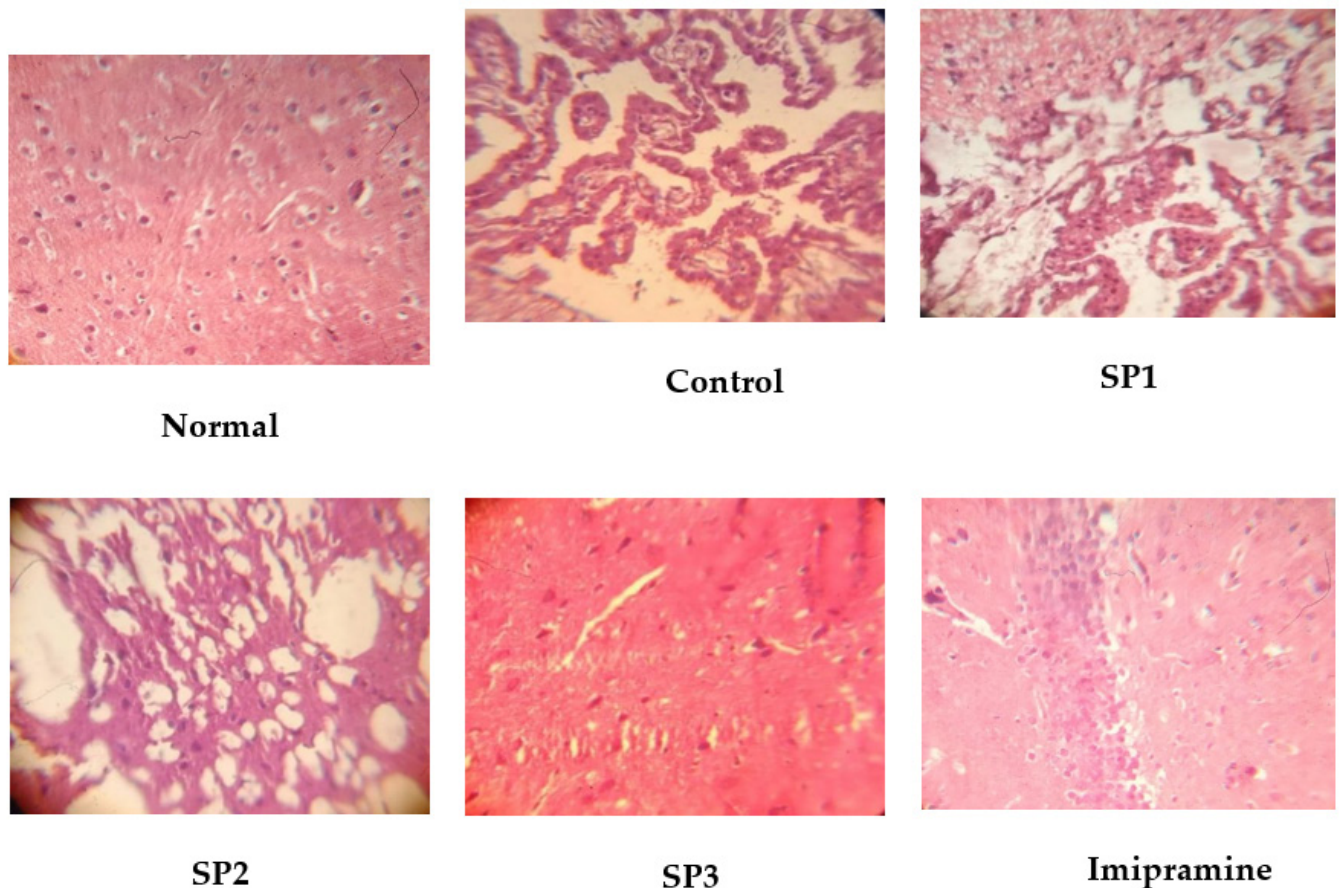


Figure 5: Brain tissue section of normal, control and treated animals.

In STZ control group, decreased immobility latency was found compared to normal. Total duration of immobility and percent of immobility in 5 min. Time duration was calculated. Treatment with sinapic acid increased the immobility latency significantly ($p < 0.05$) in both FST and TST tests.

Depression is more correlated with reduced level of serotonin and norepinephrine in brain. Previous preclinical research has shown that in STZ control animals, monoamine neurotransmitter level in hypothalamus and brain stem was reduced. Also, hyperactivity of Hypothalamic–Pituitary–Adrenal (HPA) axis with hypercortisolaemia has been reported to be associated with diabetes and depression.³

Hyperglycemia induced oxidative stress and protein glycation may play crucial roles in the pathogenesis of emotional disorder in diabetic rats. Previous research has found a remarkable elevation in oxidative stress in the amygdala and hippocampus of diabetic rats denoted by increased markers of lipid peroxidation i.e., MDA and decreased antioxidant enzyme reduced GSH.¹⁶ Diabetes and associated mental disorders are affecting 10% of population worldwide. Depression associated with diabetes is major challenge in the field of therapeutics. It reduces patient compliance and affects quality of patient's life.¹⁷

Excess Reactive Oxygen Species (ROS) levels caused by increased ROS production or decreased antioxidant defence can result in oxidative stress, which further damage proteins, phospholipids and mitochondrial DNA leading to cell death. Antioxidants have the ability to delay or prevent the oxidation of a substrate. Trauma, neuronal excitotoxicity and excess oxidative stress may trigger the neuronal degenerative process leading to certain neuronal disorders, such as Alzheimer's Disease (AD), Parkinson's Disease (PD) and epilepsy. Because of its high oxygen consumption, the brain is especially vulnerable to oxidative stress; additionally, it contains unsaturated fatty acids that are targets of Lipid Peroxidation (MDA). GSH is widely recognized as one of the most important physiological antioxidants against free radicals, preventing subsequent lipid peroxidation. The most common effect of oxidative stress is lipid peroxidation, which is a normal phenomenon that occurs at low levels in everyone. Malondialdehyde (MDA) is the final product of lipid peroxidation and is toxic to cells and cell membranes. Antioxidants may give some level of protection against the neurotoxicity. Decreased oxidative stress indicated by a significant decrease and increase in brain MDA and GSH level, respectively.¹⁸ In the present study, MDA level in brain homogenate was significantly increased in control group and sinapic acid treatment has decreased it in dose dependant manner. SP1 have decreased MDA but statistically non-significant manner. SP1 and SP2 ($p < 0.05$) and SP3 and standard ($p < 0.01$) significantly reduced the oxidative stress by decreasing lipid peroxidation. In control group of STZ, antioxidant enzyme level of brain was found to be significantly decreased and sinapic acid treatment has increased it in dose

dependant manner. SP1 have increased GSH and SOD but statistically non-significant manner. SP1, SP2 and SP3 ($p < 0.05$) and standard ($p < 0.01$) significantly increased the availability of these antioxidant enzymes.

Additionally biological system comprises of large molecules like proteins viz. albumin, globulin as an endogenous antioxidant. In our study total protein level was found to be decreased in STZ control group and sinapic acid treatment has increased total protein level significantly by SP1 ($p < 0.01$) and SP2, SP3 and standard ($p < 0.001$).

Histopathological studies have revealed that neuronal degeneration and inflammatory cell infiltration have reduced by sinapic acid treatment. These findings supported the hypothesis that sinapic acid has antioxidant, anti-inflammatory, anti-apoptotic and neuroprotective capacity, which may be help to reduce depression like behaviour induced by STZ.

Histopathology

The characterized changes in brain tissue in control and treated groups were examined under light microscope under 40x. Histopathological examination of brain with light microscopy is given in Figure 5. In STZ control group, brain tissue showed the degenerated nerve cells with nuclei, inflammatory cell infiltration in cerebral cortex and several apoptotic changes. These abnormal changes are normalised by sinapic acid treatment.

CONCLUSION

In conclusion, oral administration of Sinapic acid at 5, 10, 20 mg/kg exerts antioxidant, neuroprotective and anti-depressant like effect. The results of present study propose that Sinapic acid show antidepressant effect in STZ induced diabetic rats. It is now upcoming approach to treat diabetic associated neurologic complication. Sinapic acid can be used in the therapeutically in treatment of depression as an adjuvant with other pharmacological approaches. Clinical trials are required to confirm its individual therapeutic effect.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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