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Original Article

Neuroprotective Effect of Ginger in Ameliorating ATPases Activities in Streptozotocin: Induced Diabetic Rats

Kondeti Ramudu Shanmugam[1,*], Meesala Guru Sekhar[2], Chilakala Ramakrishana[3], Kesireddy Sathyavelu Reddy[4]

[1]Department of Zoology, PRR and VS Government Degree College, Vidavalur, SPSR Nellore, Andhra Pradesh, INDIA.
[2]Department of Zoology, Government Degree College, Cumbum, Prakasam, Andhra Pradesh, INDIA.
[3]Department of Marine Bio-Food Sciences, College of Fisheries and Ocean Sciences, Chonnam National University, Yeosu, SOUTH KOREA.
[4]Department of Zoology, Division of Molecular Biology and Ethanopharmacology, Sri Venkateswara University, Tirupati, Andhra Pradesh, INDIA.

ABSTRACT

Background: Diabetes affects each and every part of the human body and is a chronic health condition. About 422 million people worldwide have diabetes and 1.5 million deaths are directly attributed to diabetes each year. **Objectives:** The aim of this study was to investigate the effect of ginger on ATPases (Na+/K+, Mg^{2+} and Ca^{2+}) activities and Malondialdehyde (MDA) levels in the mitochondrial fractions of Hypothalamus (HT), Cerebral Cortex (CC), Hippocampus (HC) and Cerebellum (CB) of diabetic rats. **Materials and Methods:** 30 wistar strain albino rats are divided into five groups Normal Control (NC), ginger treatment (Gt), diabetic control (DC), Diabetic+Ginger (D+Gt) and Diabetic+Glibenclimide (D+Gli). Na+/K+, $Mg^{2+}Ca^{2+}$ MDA levels and liver markers estimated in all the groups. **Results:** Diabetic rats showed depletion in Na+/K+, $Mg^{2+}Ca^{2+}$ activities, body weights, plasma insulin and elevation in MDA levels in brain structures. Whereas blood glucose levels increased and liver markers Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatise (ALP) are elevated in diabetic rats. Our results suggest that ginger treatment prevent the diabetes induced depletion of brain ATPases, body weights, insulin and MDA, thus enabling to preserve brain function in regulation of intracellular homeostasis of Na+ /K+, $Mg^{2+,}$ Ca^{2+} ions. Blood glucose, plasma insulin, body weights and liver markers are also normalized with ginger supplementation in diabetic rats. **Conclusion:** Our findings may suggest that ginger treatment may decrease the diabetes associated neuronal dysfunction. Further our histopathological study also proves that ginger protected brain cells from diabetic induced oxidative stress. Our study indicates that ginger treatment may reduce neuronal complications during diabetes condition.

Keywords: Diabetes, Ginger, ATPases, MDA, Brain regions, Rats.

Correspondence:
Dr. K. R. Shanmugam
Assistant Professor, Department of Zoology, PRR and VS Government Degree College, Vidavalur, SPSR Nellore, Andhra Pradesh, INDIA.
Email: krshanmugamphd@gmail.com

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INTRODUCTION

Diabetes is a metabolic disease which effects heart, liver, brain and kidney. Diabetes alters brain ATPases and neuroendocrine functions and neurotransmitters.[1] Streptozotocin (STZ) induces diabetes in many experimental animals and it causes production of free radicals which cause oxidative stress.[2] Oxidative stress can cause stroke and brain haemorrhage in diabetic subjects.[3] The reason for this is due to consumption of more oxygen by the brain and it also have less amounts of antioxidants and high levels of fatty acids and catecholamines that make the brain more susceptible to oxidative tissue damage than other organs in the body.[4]

Sodium and potassium (Na+/K+ ATPase) was responsible for the preservation of intracellular sodium and potassium ion concentrations in brain. The function of Na+/K+ ATPase is to transport sodium in to the cell and potassium out of the cellular environment. Calcium (Ca^{2+}-ATPase) is liable for calcium protein transport and maintenance of normal intracellular calcium levels in many cells. It has been postulated that free radicals suppress Na+/K+, Ca^{2+}, Mg^{2+} ATPases activities.[5] It is believed that an impairment in Na+/K+, Mg^{2+}, Ca^{2+} ATPases may play important role for the complications of diabetes like nephropathy, neuropathy and retinopathy.[6]

Medicinal plants are the major source of isolation of drugs and have been used in Indian traditional system of Medicine and other parts of the globe. Medicinal plants have large number of bioactive compounds, which helps in protecting the body against the oxidative stress from neurotoxicity. Many medicinal plants like ocimum, tinospora, phyllanthus, curcumin and ginger

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possess neutoprotective properties. Ginger have many medicinal properties like anti-tumor, antioxidant and anti-diabetic.[7] The bioactive compounds of ginger are zingerone, gingerols, shogaols, phenols exhibit potent antioxidant and antilipidemic effects. But there were no reports on the ATPases with reference to diabetes and ginger.

The aim of our study was to investigate the neuroprotective effect of ginger on Na+/K+, Mg^{2+}, Ca^{2+} Ca2+ ATPases activities in mitochondrial fraction of cerebral cortex and hippocampus and liver markers in serum of diabetic rats.

MATERIALS AND METHODS

Animals

Male wistar strain albino rats, body weight of 180±20 g are purchased from Indian Institute of Science (IISc), Bangalore. They are kept in an air-conditioned room (24±2°C) with a 12 hr light and 12 hr dark. Rats are given feed and water with *ad libitum*.

Chemicals

All the chemicals used in this study are of analytical grade and are purchased from HiMedia, Merck, qualigens pharma. Streptozotocin was bought from Sigma-Aldrich, St. Louis, USA. UMB (purity, >98%).

Experimental induction of diabetes

The rats are given a single intraperitoneal injection of STZ (50 mg/kg) for the induction of diabetes. All the STZ-induced rats are given 20% glucose solution for 24 hr to prevent hypoglycemic deaths. Accucheck glucometer (Roche-Germany) was used to check the blood glucose levels. After 3 days of STZ injection, the rats with the blood glucose levels higher than 250 mg/dL are used for the study.

Preparation of Ginger ethanolic extract

Ginger rhizome was purchased in Tirupati, Andhra Pradesh, India. 4 Kg of ginger powdered mechanically and add 95% ethanol and store for 24 hr. The ethanolic extract was filtered, again to the residue add ethanol, this process was continued for three times. Later all these extracts are mixed together and air dried. The resulting ethanolic extract was 100 g of dark brown, gelatinous and pungent in smell. The resulting ethanolic extract was used in the present experiments.

Grouping of Animals

The rats are divided into 5 groups, each group containing six rats.

Group l: Normal Control (NC): Rats received vehicle solution (2% of tween 80) for 30 days.

Group 2: Ginger treatment (Gt): Ginger ethanloic extract (200 mg/kg body weight) was given orally to rats for 30 days.

Group 3: Diabetic control (STZ 50 mg/kg body weight), (DC): For the induction of diabetes streptozotocin was given to rats.

Group 4: Diabetic plus Ginger treatment, (D+Gt): Ginger was given to diabetic rats for 30 days.

Group 5: Diabetic+Glibenclamide treatment (D+Gli): Glibenclamide (600 µg/kg body weight orally) was administered to diabetic rats for 30 days.

30 days treatment was given to rats. Later rats are sacrificed by cervical dislocation and brain regions Hippocampus (HP), Cerebral Cortex (CC), Hypothalamus (HT) and Cerebellum (CB) are isolated and washed with ice cold saline. The brain tissues are stored at -80°C for estimation of ATPases and serum was used for estimation of liver markers enzymes.

Isolation of Mitochondria

All the ATPases are estimated in the mitochondrial fraction of brain regions by the method of Kaushal *et al.*[8]

Biochemical analysis

Estimation of blood glucose, body weights and plasma insulin in diabetic rats

Blood glucose levels, body weights and plasma insulin levels are analysed by standard protocols.

Estimation of ATPase activities in diabetic rats

Na+/K+, Ca^{2+}ATPase and Mg^{2+}ATPase activities are estimated by the method of Fritz and Hamrick[9] as reported by Desaiah and Ho[10] with slight modifications.

Estimation of MDA levels in diabetic rats

MDA levels are estimated in brain mitochondrial fraction by the method of Ohkawa *et al.*[11]

Estimation of Liver markers in serum of diabetic rats

ALT, AST and ALP are estimated in serum of all groups by standard protocol.

Histopathology of the Brain tissue

The brain tissue was fixed in formalin (10%) solution and dehydrated in alcohol, later it was embedded in paraffin wax. The brain tissue blocks are cut to 5 µm and hematoxylin and eosin are used as stain for histopathological observation. These slides are examined at a magnification of 10X in microscope for pathological changes.

Statistical analysis of the data

The data of the present study expressed as mean±SD. The statistical analysis was done by using SPSS software. Dunnett's multiple comparison tests and one-way Analysis of Variance

(ANOVA) have been used to test the differences. p values <0.001 was considered as statistically significant.

RESULTS

Impact of ginger on blood glucose, body weight and insulin levels in diabetic rats

In this study, we observed increased levels of blood glucose and decreased body weights and plasma insulin in diabetic condition. Whereas with ginger administration in diabetic rats, blood glucose levels are depleted and body weights, plasma insulin levels are elevated (Table 1).

Effect of ginger on ATPases and MDA levels in diabetic rats

Figure 1 depicts Na+/K+, Mg^{2+}, Ca^{2+} ATPases and MDA levels in all the groups. Na+/K+, ATPase activity was depleted in diabetic rats. Whereas with ginger supplementation in diabetic subjects, activity of Na+/K+ ATPase was elevated significantly (p<0.00I). Mg^{2+} ATPase activity was significantly decreased in diabetic rats than that of control group. Ginger administration increased Mg^{2+} ATPase activity in diabetic group.

Ca^{2+}ATPase activity was also inhibited in diabetic rats. Whereas with ginger administration Ca^{2+}ATPase activity was increased in diabetic rats. From this study, we observed that all the ATPases depleted in diabetic condition, but with ginger supplementation these ATPases are reverted back to normal levels (Figure 1).

MDA levels are up regulated in diabetic condition. Whereas with ginger administration in diabetic rats, MDA levels are down regulated. Our study proved that ginger have hypolipidemic activity in diabetic condition (Figure 1).

Impact of ginger on liver markers in diabetic rats

Liver markers AST, ALT and ALP activities are elevated in diabetic subjects. But with ginger treatment in diabetic rats' liver marker enzymes are depleted. This shows that ginger hepatoprotective activity (Table 2).

Effect of ginger on brain tissue in diabetic rats

In our study, the pictograph of normal control and ginger treated rats showed normal neuronal cells, glial cells and myelin in brain. Whereas in diabetic rats, degeneration of neuronal cells, degeneration of glial cells and demyelination are observed in the brain. These pathological changes in diabetic rats are due to oxidative stress. But with ginger supplementation in diabetic rats, we observed regeneration of neuronal cells, glial cells and remyelination was observed (Figure 2).

DISCUSSION

Diabetes is one of the world's fastest growing disease. As per the available information China, India and Pakistan are the leading diabetic patients in the world. India is the diabetic capital of the world and in India every sixth person is with diabetes. For the past three decades diabetes increased 150% in the number in India.

During diabetic condition, there was alterations in glucose metabolism, lipid metabolism and protein metabolism, which in turn causes elevation in blood glucose levels. The increased blood glucose levels in diabetic rats are due to oxidative stress caused by STZ. STZ induces diabetes, which is characterized by loss of body weight, it might be due to unavailability of carbohydrates.[12] In our study, we reported that blood glucose levels are elevated, plasma insulin levels and body weights are depleted in diabetic rats. Our present investigation reported that ginger treatment depleted the blood glucose levels and increased the body weight and plasma insulin in the diabetic animals. Ginger supplementation resulted in a significant decrease in blood glucose levels, increment in body weights and plasma insulin levels. These changes are due to pharmacological compounds and antioxidant compounds in ginger, these compounds may responsible for hypoglycemic effect. AI-Qattan *et al.*[13] observed that blood glucose levels are decreased in diabetic rats, which received ginger. AI-Amin *et al.*[14] also reported that ginger depleted the blood glucose levels in diabetic rats. Many investigators reported that bioactive compounds gingerols, shogaols and paradols, quercetin and zingerone of ginger possess hypoglycemic effect.[15]

Table 1: Effect of ginger and glibenclamide on blood glucose level, body weight change and plasma insulin in diabetic rats.

Blood Glucose (mg/dL)	Body Weight (g) (µIU/mL)						Plasma Insulin
Groups	1st Day	15th day	30th day	1st Day	15th day	30th day	
NC	81±1.41	88±1.32	94±2.8	195±9.6	197±2.72	195±14.28	16.4±1.6
Gt	82±1.62	82±1.46	81±2.6	192±8.4	196±4.6	205±12.6	14.2±1.4*
Dc	253±3.54	277±7.22*	269±15.6*	187±2.78	170± 4.47	150±6.84	8.4±1.2*
D+Gt	259±4.6	177± 6.48*	138±5.84*	185±6.32	186± 3.7	186±4.28	12.8±1.4*
D+Gli	260±1.74	143± 8.6*	94±3.72*	190±3.12	186± 7.35	185±6.4	14.6±2.8

All the values are mean±SD of six individual observations, values in the parenthesis denote percent change over normal control.*Significant at p<0.001.

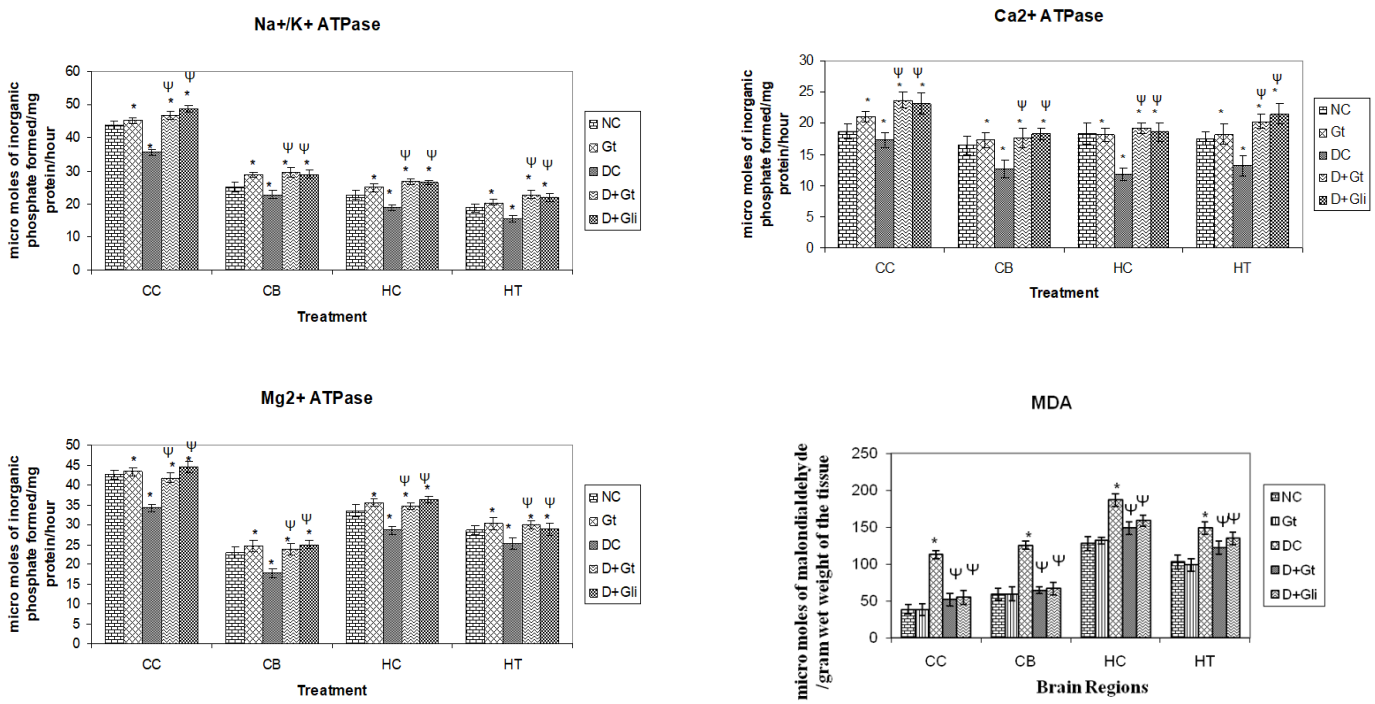

Figure 1: Impact of ginger on Na+/K+ ATPase, Mg^{2+}ATPase, Ca^{2+}ATPase activities and MDA levels in the brain regions of normal and diabetic rats. Data are expressed as means±SD (*n*=6). *The values are significant compared to *Normal Control (NC) and (ψ) Diabetic Control (DC). (Dunnett's multiple comparison tests).

Hence, ginger administration modulated the blood glucose, plasma insulin levels in diabetic subjects (Table 1).

Na+/K.+ATPase is a responsible for the active transport of sodium and potassium ions in the central nervous system. Na+ / K+ ATPase plays a vital role in the functional activity of nervous cells. Our current study reported that decreased Na+ /K+ ATPase activity in cerebral cortex, hypothalamus, cerebrum and cerebellum of diabetic rats in agreement with the earlier reported data.[16] The depletion in Na+/K+ATPase in diabetic tissue may be due to the membrane peroxidative damage. The oxidative damage of lipids and proteins might responsible for amelioration of Na+/K+ATPase. Na+ /K+ATPase is rich in thiol groups and oxidation of thiol groups has been reported to reduce enzyme activity.[17] However with ginger supplementation in diabetic rats Na+/K+ activity was increased. Ginger treatment prevents oxidative stress during diabetic condition that results in depletion in Na+ /K+ ATPase activity.[18] Hence, ginger supplementation protects the brain tissue from neuronal injury during diabetes (Figure 1).

Mg^{2+} ATPase plays a main role in Mg^{2+} homeostasis in the brain. In our study, brain Mg^{2+}ATPase activity is found to be remarkably depleted in hypothalamus, cerebral cortex, cerebellum and hippocampus of diabetic rats. Depletion in Mg^{2+}ATPase activity may be due to protective effect against oxidative stress. Makar *et al.*[19] reported that Mg^{2+}ATPase activity was decreased in diabetic condition. Ramesh and Pugalendi[20] reports that cardiac, hepatic and kidney Mg^{2+}ATPase activity was decreased in diabetic rats. On administering ginger to diabetic rats, the activity of Mg^{2+}ATPase was significantly increased in cerebral cortex, hypothalamus, cerebellum and hippocampus of diabetic rats. This shows the neuroprotective effect of ginger in diabetic rats (Figure 1).

Ca^{2+}ATPase is responsible for fine-tuning of intracellular calcium levels.[21] In our study, Ca^{2+}ATPase activity was decreased in cerebral cortex, hippocampus, cerebellum and hypothalamus of diabetic rats. This could be due to insulin deficiency in diabetic condition. The supplementation of ginger may prevent the diabetes-induced decrease in Ca^{2+}ATPase enzyme activity. Ginger treatment increased the Ca^{2+}activity in diabetic rats. This may be due to the inhibition of lipid peroxidation during diabetic condition. Kowluru *et al.* [22] reported that with antioxidant diet Ca^{2+}ATPase activity was increased in diabetic rats. So, in this study Ca^{2+}ATPase activity was increased in diabetic rats which received ginger (Figure 1).

MDA is oxidative stress biomarker. In diabetic rats, MDA levels are upregulated, this may be due to more production of free radicals which cause the lipid peroxidation of polyunsaturated fatty acids. In this study, we also observed the same result i.e. higher levels of MDA in diabetic rats. Whereas with ginger supplementation MDA levels are down regulated in diabetic rats. Ginger have shogaols, gingerols and many pharmacological compounds, these compounds may suppress the production of

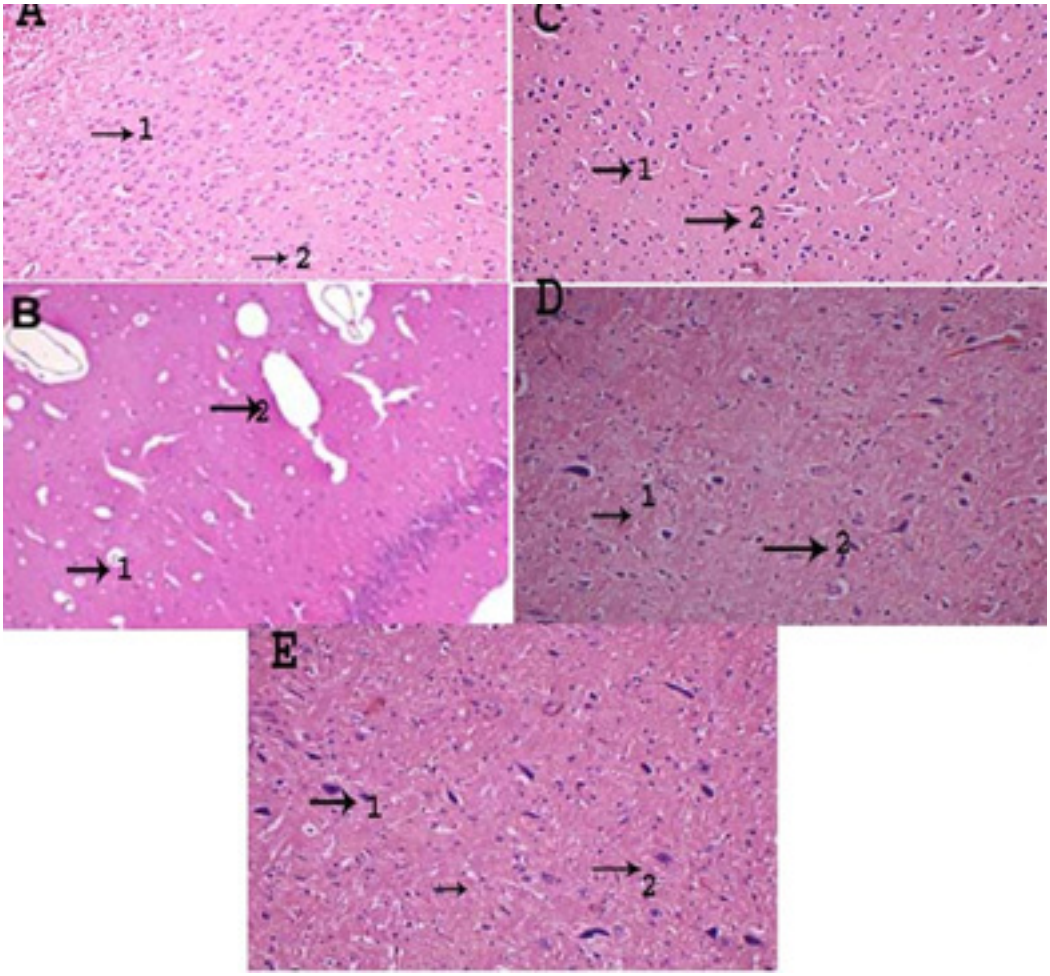

Figure 2: Effect of ginger on Brain tissue in diabetic rats. A: Normal Control-1. Normal neurons, 2. Normal glial cells, B. Diabetic control-1. Degenerated neurons, 2. Vacuoles, C: Ginger treated-1. Normal neurons, 2. glial cells, D: Ginger+ Diabetic Regenerated neurons, 2. Regenerated glial cells, E. Diabetic+ glibenclimide -1. Regenerated neurons, 2. Regenerated glial cells.

Table 2: Effect of Ginger on ALT, AST and ALP in diabetic rats.

Groups	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
NC	40.42±8.2	38.46±4.2	134.2±10.4
Gt	42.6±21.46	36.8±5.6*	128.4±32.6
DC	288.2±36.4	186.84±30.2*	312.7±40.2
DC+Gt	56.8±24.2	31.24±34.6	154.6±42.64
DC+Gli	61±6.4*	49±2.8*	146.8±8.2

All the values are means±SD of six individual observations.*Significant at $p<0.001$ with respect to normal control.

free radicals, which ultimately results in depletion of MDA. Our study shows that ginger possess anti-lipidemic effect in diabetic subjects (Figure 1).

Liver markers are important for diagnosis of liver related diseases. Serum ALP, ALT and AST activities are elevated in diabetic rats. This may be due to oxidative stress during diabetic condition, hence liver markers are increased in diabetic rats.[23] But with ginger supplementation all the liver marker enzymes are decreased in diabetic rats. Ginger have many bioactive compounds, pharmacological compounds like gingerols, shogaols and paradols, these compounds may inhibit the free radical production in alcohol intoxicated rats. Hence, ginger may protect the liver tissue from diabetic associated oxidative stress in rats. So in diabetic rats AST, ALT and ALP activities are decreased. Our study reports that ginger have hepatoprotective effect. (Table 2).

In this study, we can observe normal neuronal cells, normal glial cells in normal control and ginger treated rats. But in diabetic rats, we observed degenerated neurons, demyelination and scattered glial cells. But treatment with ginger in diabetic rats, remyelination, neuroglial cells and neuronal cells are observed. Our investigation reported that neuro protective effect of ginger in diabetic rats. This may be due to bioactive compounds gingerols, shogaols and paradols of ginger. These bioactive compounds protected that brain tissue from oxidative stress in diabetic rats. Further our study reported that ginger have neuroprotective effect in diabetic rats (Figure 2).

Na+/K+, Mg^{2+}ATPases and Ca^{2+}ATPase activities are depleted and MDA levels are elevated in diabetic condition. Whereas with ginger supplementation in diabetic rats Na+/K+, Mg^{2+}ATPases and Ca^{2+}ATPase are increased and MDA levels are decreased in hippocampus, cerebral cortex, hypothalamus and cerebellum of brain. The present findings are in agreement with the observations of Yazdi *et al.*[24] and Siddiqui *et al.*[25] who demonstrated that trigonella reversed the effects of free radicals in diabetic rats in order to protect brain tissue against STZ-induced diabetes and ATPase inhibition. Liver markers like AST, ALT and ALP activities are also elevated in diabetic rats. But in diabetic rats, ginger treatment reversed back all the liver markers to normal levels. Further studies are needed to know the impact of ginger bioactive compounds (gingerols, shogals) on all ATPases in diabetic rats.

CONCLUSION

From our studies, we reported that brain ATPases are depleted in diabetic rats. Blood glucose levels are increased and plasma insulin levels and body weights are decreased in diabetic rats. But with ginger treatment ATPases are elevated, blood glucose levels are down regulated and plasma insulin levels and body weights are up regulated in diabetic rats. Further, histopathological studies also prove that ginger administration protected the brain tissue from oxidative damage in diabetic rats used to treat neurological disorders.

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ETHICS APPROVAL

Studies are conducted as per the principles, guidelines and protocols approved by the Institutional animal ethics committee (Resolution No: 09(i)/a/CPCSEA/IAEC/SVU/ZOOL/KSR/Dt. 08-07-2012), Sri Venkateswara University, Andhra Pradesh, India.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MDA: Malondialdehyde; **HT:** Hypothalamus; **CC:** Cerebral Cortex; **HC:** Hippocampus; **CB:** Cerebellum; **NC:** Normal Control; **Gt:** Ginger treatment; **DC:** Diabetic control**; D+Gt:** diabetic+ginger; **D+Gli:** diabetic+glibenclamide; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **ALP:** Alkaline phosphatase; **STZ:** Streptozotocin; **Na+/K+ ATPase:** Sodium and potassium; **Ca^{2+}-ATPase:** Calcium; **IISc:** Indian Institute of Science; **ANOVA:** Analysis of variance.

SUMMARY

Ginger posses' hypoglycemic activity in diabetic rats. Our results prove that in diabetic rat's ginger showed anti-diabetic activity. Ginger also reported the neuroprotective effect in diabetic subjects.

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