

**Original Research Article****Neuroprotective Effect of *Cinnamomum zeylanicum* in streptozotocin induced diabetes in Mice**

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Background: Diabetes is recognized as one of the leading causes of morbidity and mortality & representing as an emerging global epidemic worldwide. Diabetes and stroke both are the conditions which share various common threats. A patient with Diabetes has higher risk of stroke as compared to non Diabetics. Diabetes and stroke both affects the blood vessels. There are several biochemical pathways which are responsible for the developments of vascular complications due to hyperglycemia. Thus prevention and treatment of diabetes and stroke can reduce the risk of various vascular diseases. *Cinnamomum zeylanicum* has been used for the treatment of diabetes since long time. *Cinnamomum zeylanicum* rich in phenolic contents (antioxidants) have been identified as a major active component exhibiting antioxidant, and neuroprotective effects. The present study evaluate the neuroprotective effect of *Cinnamomum zeylanicum* in streptozotocin induced diabetes in mice and experimentally induced global cerebral ischemia/reperfusion injury in mice. **Materials and methods:** Swiss albino mice (male) weighing 20-30 g were randomized into eight groups. Diabetes was induced by administering streptozotocin (65 mg/kg, i.p). Starting from seven days after streptozotocin injection, insulin and *Cinnamomum zeylanicum* were administered for 3 weeks. Serum glucose level and body weight were measured weekly. Neuroprotective activity was carried out by global cerebral ischemia on swiss albino mice by carotid artery occlusion for 10 min followed by 24 hr. reperfusion. Measurement of Triglycerides, Malondialdehyde, cerebral infarct size and glutathione level was carried out at the end of the study. **Results:** After 21 days of treatment with *Cinnamomum zeylanicum* (75 mg/kg, 150 mg/kg and 300 mg/kg, p.o) significant increase in body weight and glutathione level and a significant reduction in serum glucose level, triglycerides, MDA levels and cerebral infarct size was observed as compared to diabetic control and diabetic+ stroke group. **Conclusion:** The present study concludes that Polyphenolic fraction of *Cinnamomum zeylanicum* not only attenuates the diabetes but also reverse the cerebral infarction in mice through its neuroprotective actions and thus *Cinnamomum zeylanicum* may serves as a new therapeutic alternative for management of brain damage associated with type-1 diabetes.

Introduction

Diabetes is recognized as one of the leading causes of morbidity and mortality & representing as an emerging global epidemic worldwide.[1] It is a disorder characterized by resistance to the action of insulin, insufficient insulin secretion, or both. The clinical manifestation of these disorders is hyperglycemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.[2] Hyperglycemia is a key determinant of vascular complications of diabetes and there is extensive evidence showing that both acute and chronic hyperglycemia has a deleterious effect. Hyperglycemia contributes to the development of vascular complications

through several mechanisms: activation of the polyol and hexosamine pathways, activation of protein kinase C, increased oxidative stress, increased production of advanced glycation end-products, increased synthesis of growth factors, cytokines and angiotensin II.[3] These factors can, in turn, induce a diffuse endothelial dysfunction and contribute to the progressive development of micro- and macrovascular complications.[4] Stroke is a long term complication of diabetes. Diabetes and stroke both are the conditions which share various common threats. A patient with Diabetes has higher risk of stroke as compared to non Diabetics.[5] Diabetes and stroke both affects the blood vessels and both are associated with other risk factors such as hypertension and dyslipidemia. High blood pressure increases the risk of stroke.[6] Oxidative stress plays a key role in brain damage after cerebral ischemia. When an imbalance occur either by

increasing free radicals or decreased antioxidant defence, the accumulation of free radicals is known as the state of oxidative stress.[7] After ischemia, an excess of cytosolic free Ca^{++} due to excitotoxicity may overload the mitochondrial proton circuit, which leads to failure in oxidation together with increased ROS production.[8] Overproduction of ROS by mitochondria causes the impairment of the ETC, which leads to decreased ATP production, increased formation of free radicals. In this study we investigated the antidiabetic as well as neuroprotective effect of *Cinnamomum zeylanicum* in diabetic mice. Many synthetic drugs protect against oxidative damage, but they have side effects. An alternative solution to the problem is to consume natural antioxidants from food supplements and traditional medicines. Hence tremendous input is made worldwide, in search of the antioxidant rich herbal plants to combat diseases. In this study cinnamon bark extract was used as a test drug in mice. As per the previous reports it can be concluded that the extracts of Cinnamon barks exhibited higher antioxidant activity than other parts of cinnamon and ethanol is the best solvent to obtain the main antioxidant constituents. All these findings indicate that Cinnamon extracts possess antioxidant activity.[9] Antioxidant activity of cinnamon is due to phenolic compound such as hydroxycinnamaldehyde, hydroxycinnamic acid present in the cinnamon extract act as a scavenger of peroxide radical and prevents oxidative damage. A proanthocyanidine found in *Cinnamomum zeylanicum* i.e cinnamatannin B1 exhibit antioxidant activity. It is an active compound which inhibit lipid peroxidation and also an active scavenger of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals.[10] Antidiabetic and antioxidant activity of cinnamon was investigated by the induction of diabetes mellitus and global cerebral ischemia reperfusion injury in mice.

Material and methods

Procurement of Plant

Cinnamomum zeylanicum plant was procured from patanjali haridwar from the month of april. Bark of the plant was collected from the local market of dehradun. Plant sample was authenticated from Forest Research Institute (FRI) Dehradun.

Procurement of drug and chemicals

Insulin was procured from Shri mehent indires hospital, Dehradun.

Procurement of Animals

Swiss albino mice (male) weighing 20-30 g was procured in the animal house facility of Shri Guru Ram Rai Institute of Technology and Sciences, Patel Nagar, Dehradun. Animals will be acclimatized in the animal house facility of department and housed in polypropylene cages with husk bedding (renewed every 48 h), under 12:12 h light dark cycle at $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$. and will be fed with standard Commercial pellet and water *ad libitum*. The Experimental protocol was approved by

Institutional Animal Ethical Committee (M.PH/IAEC/01/2014/ECC-12) and care of animals was as per guidelines of Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Extraction of Polyphenolic fraction of *Cinnamomum zeylanicum* Bark

500 g of dried bark powder was extracted for 56 hrs with (1000ml) ethanol by hot continuous percolation method in Soxhlet apparatus. After the effective extraction, solvent were concentrated using rotary flash evaporator and water was removed by evaporated to dryness on a hot water bath to yield a soxhlet crude extract.

The presence of polyphenol was confirmed by ferric chloride test for tannins. Addition of ferric chloride solution to *C. zeylanicum* extract gave bluish-black colour, conforming the presence of polyphenol (tannins) in the extract.

Induction of Type-I Diabetes Mellitus with STZ

A single dose of streptozotocin (65 mg/kg) prepared in citrate buffer (pH 4.5, 0.1 M) was administered intraperitoneally to overnight fasted mice to induce diabetes in all the group except control group. All the mice were allowed free access to water, pellet diet and maintained at room temperature in polypropylene cages. STZ treated mice were also fed with glucose solution (10%) for 12 hr to avoid hypoglycemia. Rats having serum glucose more than 250 mg/dl after 72 hrs of induction were considered diabetic and selected for further study.

Experimental Protocol

Control and Diabetic mice were randomly selected and divided into nine groups and each group comprises 6 animals.

Group I (Normal Control group) : Normal saline (10 ml/kg, i.p.) was administered in mice.

Group II (Sham control) : Only surgical procedure was performed.

Group III (Diabetic control group) : Mice were treated with streptozotocin (65mg/kg, i.p.) for the development of type-1 diabetes.

Group IV (diabetes + stroke induced group) : 10 min global ischemia was induced in diabetic mice followed by 24 hr. reperfusion.

Group V (Standard drug treated group (diabetes+stroke induced) : insulin (2 I.U/kg body weight, s.c) was administered daily for 15 days before the global ischemia in diabetic mice.

Group VI (Test group) : *Cinnamomum zeylanicum* (75 mg/kg body wt.p.o.) was administered daily for 15 days before the global ischemia in diabetic mice.

Group VII (Test group) : *Cinnamomum zeylanicum* (150 mg/kg body wt.) was administered daily for 15 days before the global ischemia in diabetic mice.

Group VIII (Test group) : *Cinnamomum zeylanicum* (300 mg/kg body wt.) was administered daily for 15 days before the global ischemia in diabetic mice.

Insulin (standard) and *Cinnamomum zeylanicum* (test drug) were administered for next 15 days starting from 2nd week of STZ injection, before the global ischemia in diabetic mice.

Induction of Global cerebral ischemia:

Mice were anaesthetized using chloral hydrate (400 mg/kg, ip). A midline ventral incision was made in the neck to expose the right and left common carotid arteries, which were isolated from surrounding tissue and vagus nerve. A cotton thread was passed below both the carotid arteries. Global cerebral ischemia was induced by occluding the carotid arteries. After 17 min of global cerebral ischemia, reperfusion was allowed for 24 h. The incision was sutured back in layers. The sutured area was cleaned with 70% ethanol and was sprayed with antiseptic dusting powder. The animals were shifted individually to their home cage and were allowed to recover overnight. During surgery, the animals were kept on a heating pad in order to maintain the body temperature, so as to avoid the effect of temperature variations on the final results.[11]

Preparation of post-mitochondrial supernatant (PMS).

Following decapitation, the brain was removed and washed in cooled 0.9% saline, was kept on ice and subsequently blotted on filter paper, then weighed and homogenized in cold phosphate buffer (0.1 M, pH 7.4) using a homogenizer. Homogenization procedure was performed as quickly as possible under completely standardized conditions. The homogenates were centrifuged at 10,000rpm for 20 min at 4°C and post-mitochondrial supernatant was kept on ice until assayed.[12]

Analysis of biochemical parameters

Glucose level: Blood glucose level was estimated using commercially available kit based on glucose oxidase-peroxidase method.[13]

TBAR estimation: TBAR was estimated by the method of Slater and Sawyer (1971).[14]

Reduced glutathione: Reduced glutathione was estimated by Ellman G. method (1959).[15]

Estimation of serum triglyceride level: Triglyceride level was estimated by using commercially available triglycerides enzymatic assay kit.[16]

Estimation of total protein:

Protein values were estimated to express the biochemical parameters in terms of per mg protein. The quantitative measurement of the total protein was determined by Lowry's method.[17]

Assessment of cerebral infarct size: At the end of 24 hr. of reperfusion after global ischemia brain samples were sliced and slices were incubated in TTC at 37°C. TTC is converted to red form zone pigment by NAD and lactate dehydrogenase and thus stained the viable cells deep red. Infarcted cells lost the enzyme and remain unstained dull yellow.[18]

Statistical analysis: All the data were expressed as mean $\pm$ standard error mean (SEM). All the data were analyzed by one way ANOVA followed by Tukey's test for significance, except body weight and glucose level. Data of body weight and glucose level was analyzed by two way ANOVA followed by Bonferroni's multiple comparison test using Graph Pad Prism version 5.3 software.

Results

Effect of *Cinnamomum zeylanicum* on body weight (g):

Administration of streptozotocin 7 days prior to *Cinnamomum zeylanicum* treatment produced a significant decrease in body weight in mice as compared to normal control. Administration of *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o.) in diabetic mice did not have any significant effect on body wt. till 7 days of treatment. After 14 days and 21 days treatment of *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o.) showed significant ($P < 0.001$, $P < 0.01$) improvement in body weight in comparison with diabetic control. (Fig. 1.1, 1.2)

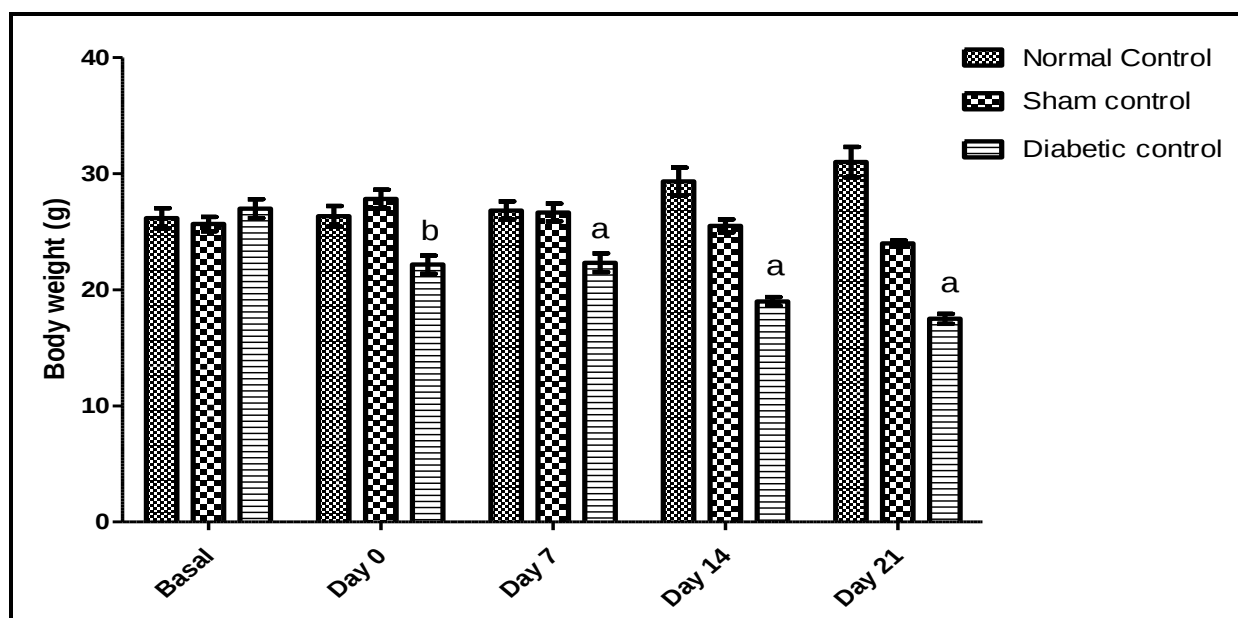


Fig.1.1: Effect of streptozotocin on Body weight of mice

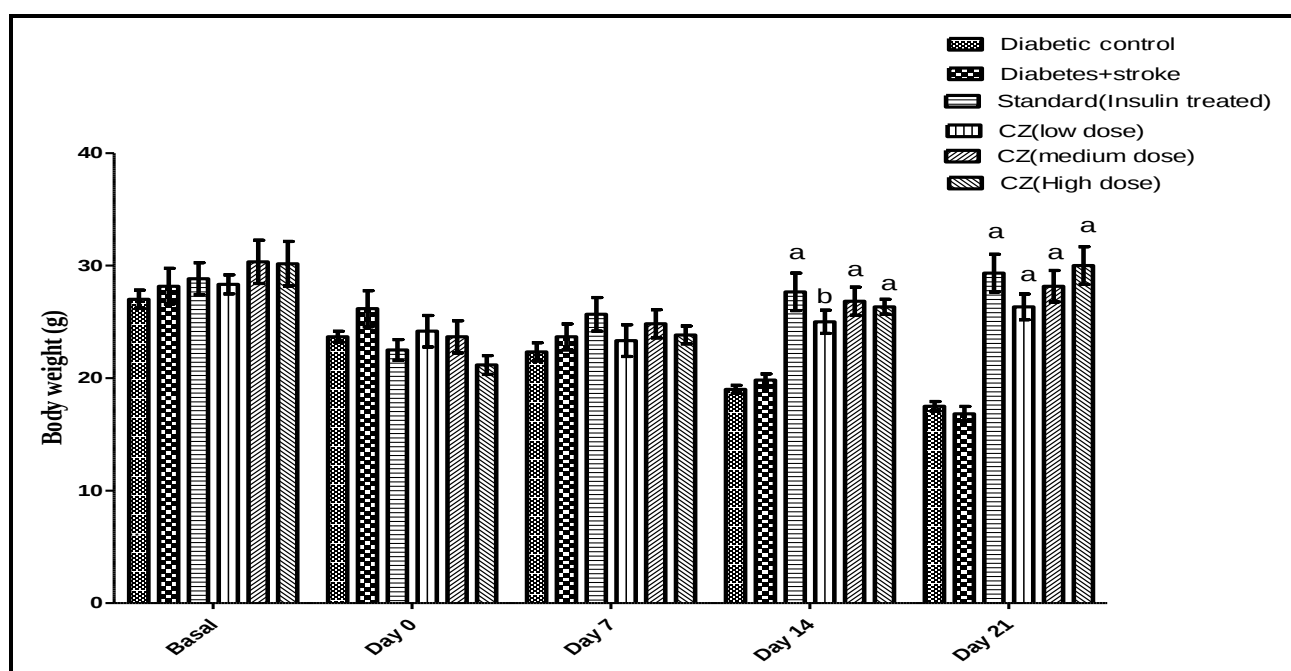


Fig.1.2: Effect of *Cinnamomum zeylanicum* on Body weight of Diabetic mice

Values are expressed as mean $\pm$ SEM, (n=6). a represents $P < 0.001$: As compared to normal control group. b represents $P < 0.01$: As compared to normal control.

Effect of *Cinnamomum zeylanicum* on serum glucose level (mg/dl)

Administration of streptozotocin 7 days prior to *cinnamomum zeylanicum* treatment produced a significant increase in fasting serum glucose level in mice as compared to normal control.

Administration of *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o) in diabetic mice did not have any effect on serum glucose level on day 0. Administration of *Cinnamomum zeylanicum* showed a significant ($P < 0.001$, $P < 0.001$) lowering of serum glucose level after 7, 14, 21 days in comparison with diabetic control.(Fig. 2.1, 2.2)

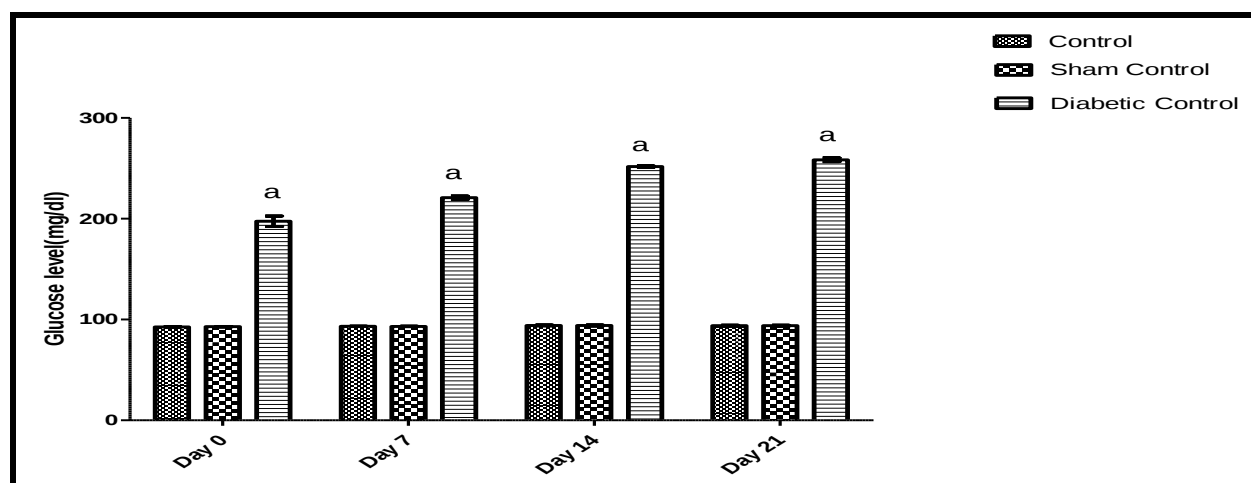


Fig.2.1. Effect of streptozotocin on serum Glucose level in Diabetic mice

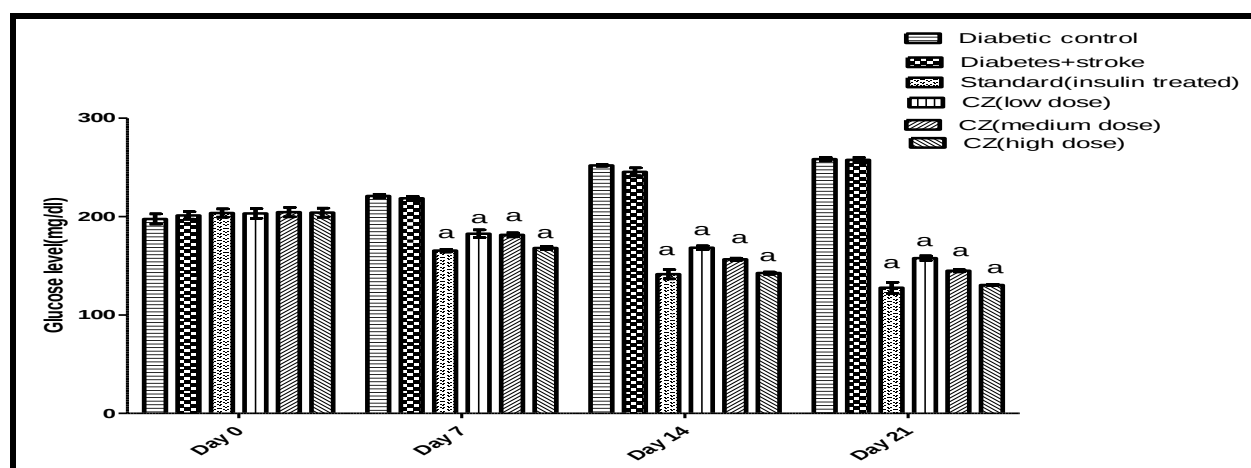


Fig.2.2. Effect of *Cinnamomum zeylanicum* on Serum Glucose level in Diabetic mice

Values are expressed as mean $\pm$ SEM, (n=6). a represents $P < 0.001$: As compared to normal control group.

Effect of *Cinnamomum zeylanicum* on serum triglycerides level(mg/dl)

Administration of streptozotocin 7 days prior to *cinnamomum zeylanicum* treatment produced a significant increase in serum triglycerides level in mice as compared to normal control.

Administration of *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o) in diabetic mice showed a significant ($P < 0.001$) lowering of serum triglycerides level after 21 days in comparison with diabetic control.(Fig.3)

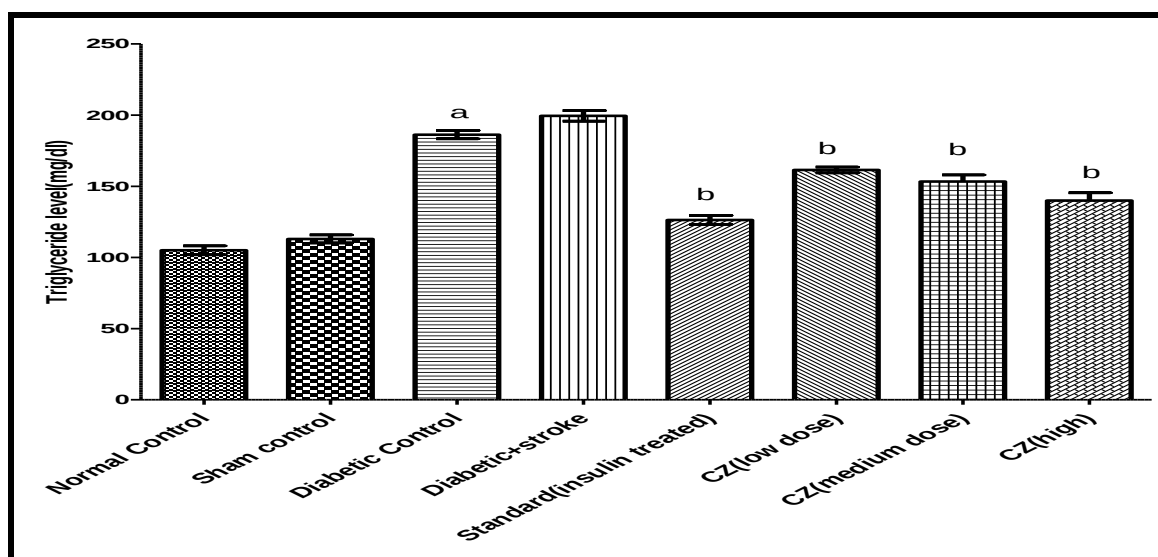


Fig.3. Effect of *Cinnamomum zeylanicum* on triglycerides level in diabetic mice

Values are expressed as mean $\pm$ SEM (n=6). a represents $P < 0.001$:As compared to Normal control group. b represents $P < 0.001$: As compared to diabetic control group.

Effect of *Cinnamomum zeylanicum* on cerebral infarct size

Global cerebral ischemia of 10 min followed by 24 hr. reperfusion produced a significant increase in the cerebral infarct size in diabetes+stroke group as compared to normal control and diabetic control group. when we compared control and sham control group there is no significant difference when

measured by both volume and weight methods. Administration of *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o) significantly ($P < 0.001$, $P < 0.01$) decrease the diabetes and I/R induced increase in the cerebral infarct size that was measured by volume and by weight methods.(Fig.4.1, 4.2)

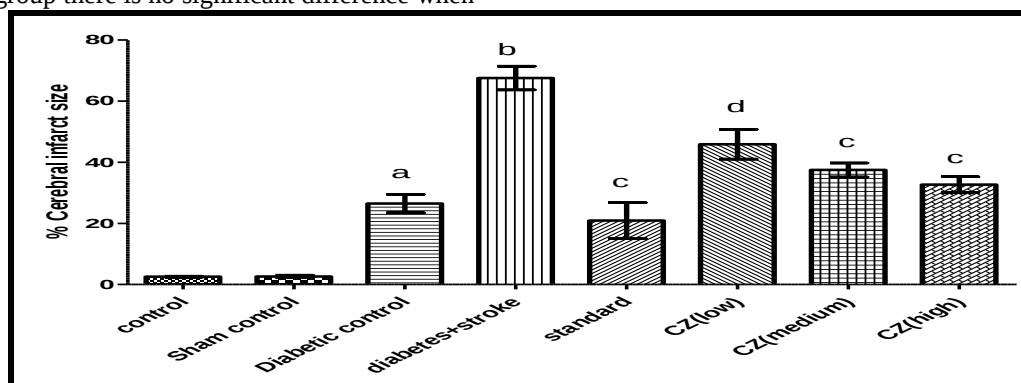


Fig.4.1. Effect of *Cinnamomum zeylanicum* on global cerebral ischemia I/R injury induced cerebral infarct size in mice by weight method.

Values are expressed as mean $\pm$ SEM, (n=6). a represents $P < 0.01$: As compared to Normal control group. b represents $P < 0.001$: As compared to Diabetic control group. c represents $P < 0.001$: As compared to Diabetes+ stroke group. d $P < 0.01$: As compared to diabetes + stroke group.

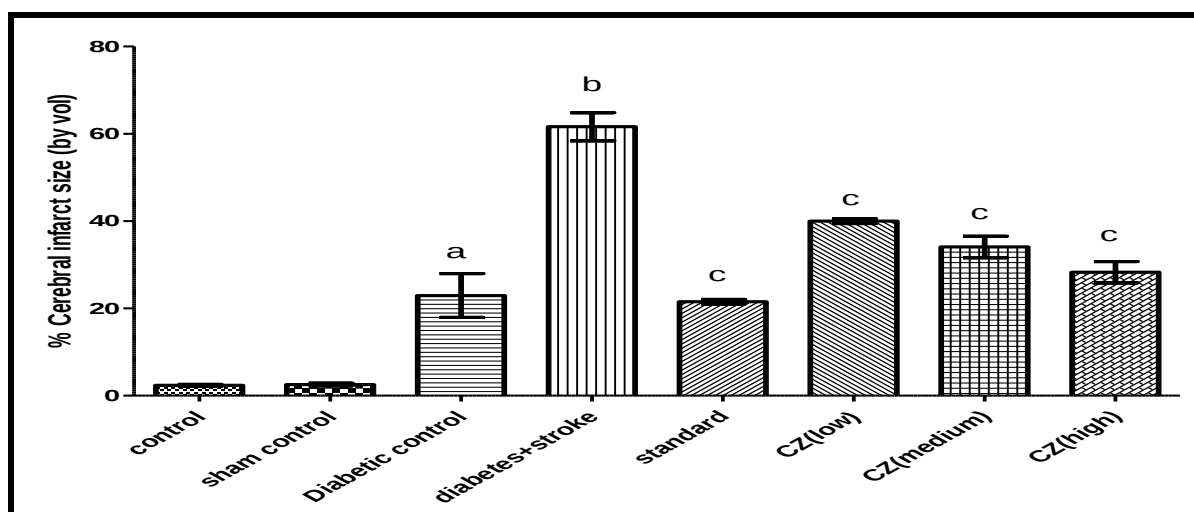


Fig 4.2 Effect of *Cinnamomum zeylanicum* on global cerebral ischemia I/R injury induced cerebral infarct size in mice by volume method.

Values are expressed as mean $\pm$ SEM (n=6). a represents $P < 0.001$: As compared to Normal control group. b represents $P < 0.001$: As compared to Diabetic control group. c represents $P < 0.001$: As compared to Diabetes+ stroke group.

Effect of *Cinnamomum zeylanicum* on Glutathione level(nM/mgprotein)

Global cerebral ischemia of 10 min followed by 24 hr. reperfusion and diabetes produced a significant decrease in the

glutathione level in diabetic and diabetes+ stroke group as compared to normal control group. Treatment with *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o) significantly($P < 0.01, P < 0.001$) increase the glutathione level as compared to diabetes+stroke group.(Fig.5)

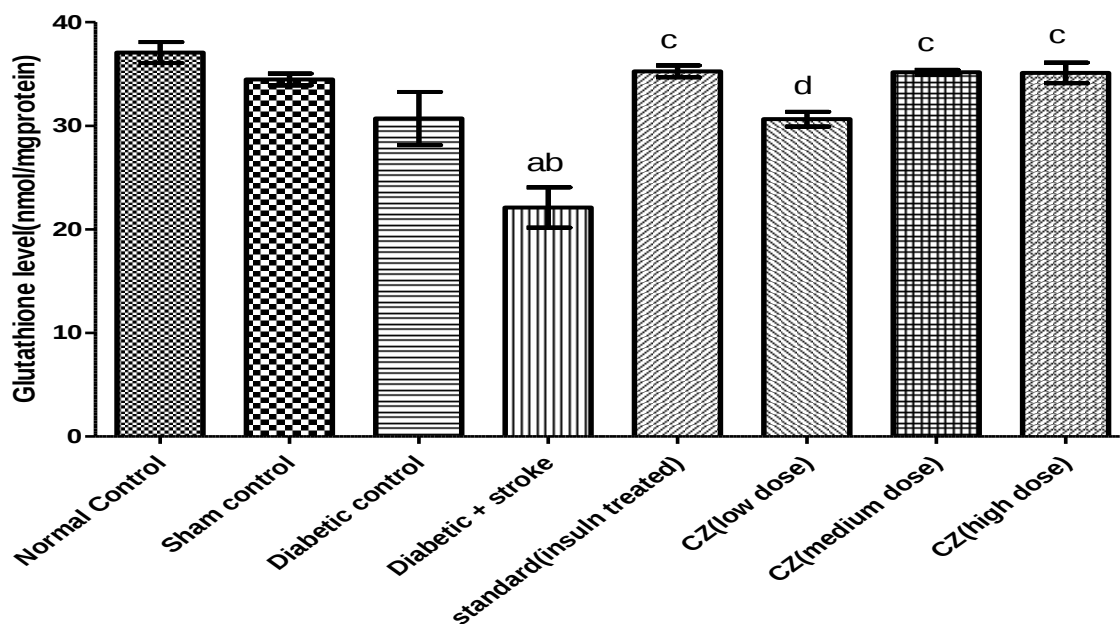


Fig.5. Effect of *Cinnamomum zeylanicum* on glutathione level in Diabetic mice.

Values are expressed as mean $\pm$ SEM (n=6). a represents $P < 0.001$: As compared to Normal control group. b represents $P < 0.001$: As compared to Diabetic control group. c represents $P < 0.001$: As compared to Diabetes+ stroke group. d represents $P < 0.01$: As compared to diabetes + stroke group.

Effect of *Cinnamomum zeylanicum* on Thiobarbituric acid reactive substances TBAR level (nM/mgprotein)

Global cerebral ischemia of 10 min followed by 24 hr. reperfusion and diabetes produced a significant increase in the TBARS level in diabetic and diabetes+ stroke group as

compared to normal control group. when we compared control and sham control group there is no significant difference in TBARS level. Treatment with *Cinnamomum zeylanicum* (75, 150, 300 mg/kg p.o) significantly ($P<0.01, P<0.001$) decrease the TBARS level as compared to diabetes+stroke group.(Fig.6)

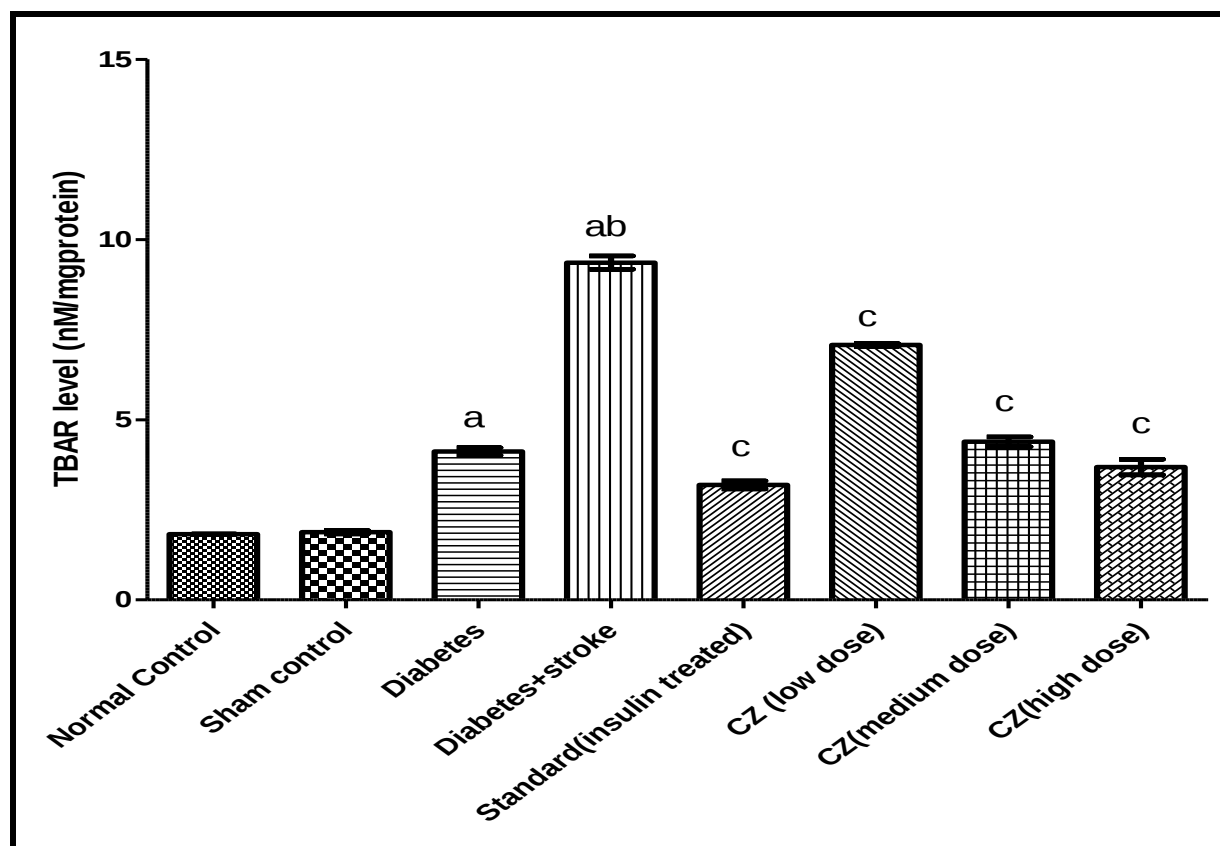
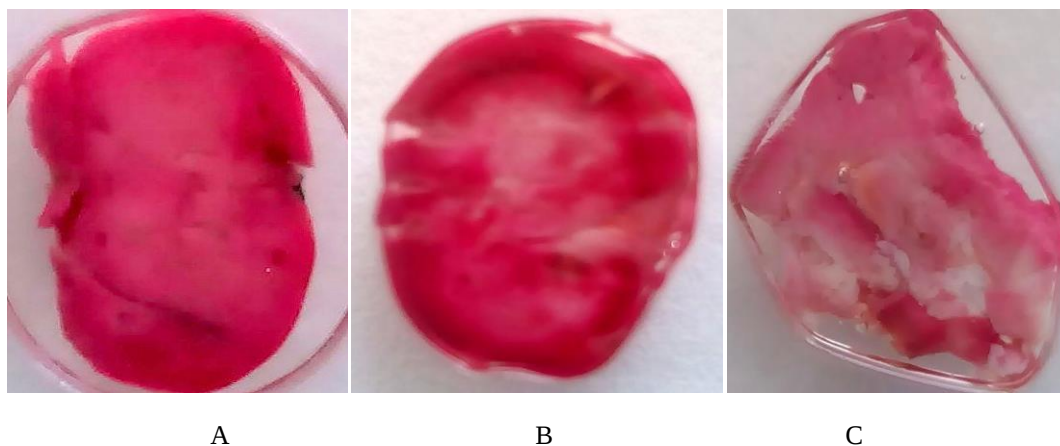


Fig.6: Effect of *Cinnamomum zeylanicum* on TBAR level in Diabetic mice.

Values are expressed as mean $\pm$ SEM, (n=6). 'a' represents $P<0.001$: As compared to Normal control group. 'b' represents $P<0.001$: As compared to Diabetic control group. 'c' $P<0.001$: As compared to Diabetes+ stroke group.



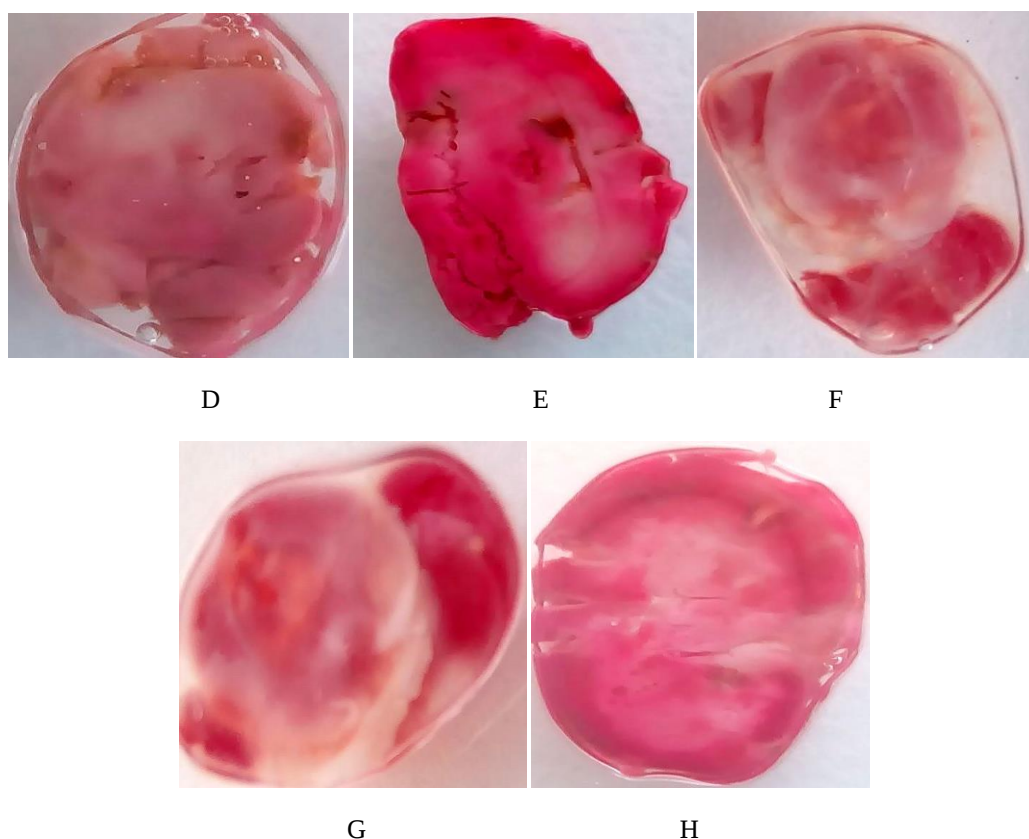


Figure 1: Neuroprotective effect of *Cinnamomum zeylanicum* extract against Global cerebral ischemia reperfusion damage in diabetic mice evaluated by 2,3,5-triphenyltetrazolium chloride (TTC) staining. Brain coronal sections were prepared and then each section was stained with TTC. (A) Normal control, (B) sham control, (C) Diabetic control, (D) Diabetes +stroke, (E) Standard (insulin treated), (F) CZ(75 mg/kg), (G) CZ(150 mg/kg), (H) CZ(300 mg/kg). The infarction was markedly reduced in the mice brain treated with CZ(150 mg/kg), CZ(300 mg/kg) and Standard(insulin treated).

Discussion

In the present study an attempt was made to evaluate the neuroprotective effect of *Cinnamomum zeylanicum* in streptozotocin induced and global cerebral ischemia/reperfusion injury induced mice. It is well known that Diabetes mellitus (DM), is a most common problem around the world & contributes to the development of different types of complications due to various pathological changes like change in thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation. Diabetes mellitus also represents a strong independent risk factor for stroke.[2] Different types of molecular signaling mechanism activated by hyperglycaemia are Protein kinase C, polyol pathway flux, Hexosamine pathway flux and Advanced glycation end products (AGEs) formation which can further leads to stroke.[19]

Oxidative stress plays a key role in brain damage after cerebral ischemia. When an imbalance occurs either by increasing free radicals or decreased antioxidant defence, the accumulation of free radicals is known as the state of oxidative stress.[20] ROS are small oxygen-derived molecules, including the superoxide anion radical ($O_2^{\cdot-}$),

hydroxyl radical ($OH^{\cdot}$), and certain non-radicals that are either oxidizing agents or easily converted into radicals, such as hydrogen peroxide (H_2O_2) and the oxygen singlet ($1O_2$). [8] The primary source of free radical generation in cells during cerebral ischemia is due to a decrease in mitochondrial redox potential causing ROS production from the Endothelial cell, mainly at the level of cytochrome III (Ramassamy C., 2006). After ischemia, an excess of cytosolic free Ca^{++} due to excitotoxicity may overload the mitochondrial proton circuit, which leads to failure in oxidation together with increased ROS production.⁷ Overproduction of ROS by mitochondria causes the impairment of the ETC, which leads to decreased ATP production, increased formation of free radicals, altered calcium homeostasis and mitochondrial dysfunction.[21] Transient middle cerebral artery occlusion (MCAO) in rats induces ROS production and mitochondrial dysfunction, including the inactivity of ETC enzymes.[22]

In this study we investigated the antidiabetic as well as neuroprotective effect of *Cinnamomum zeylanicum* in diabetic mice. Many synthetic drugs protect against oxidative damage, but they have side effects. An alternative solution to the problem is to consume natural antioxidants from food supplements and traditional medicines. Hence tremendous

input is made worldwide, in search of the antioxidant rich herbal plants to combat diseases.[23] In this study cinnamon bark extract was used as a test drug in mice. As per the previous reports it can be concluded that the extracts of Cinnamon barks exhibited higher antioxidant activity than other parts of cinnamon and ethanol is the best solvent to obtain the main antioxidant constituents. All these findings indicate that Cinnamon extracts possess antioxidant activity.[9] Antioxidant activity of cinnamon is due to phenolic compound such as hydroxycinnamaldehyde, hydroxycinnamic acid present in the cinnamon extract act as a scavenger of peroxide radical and prevents oxidative damage.[24] A proanthocyanidine found in *Cinnamomum zeylanicum* i.e cinnamatannin B1 exhibit antioxidant activity. It is an active compound which inhibit lipid peroxidation and also an active scavenger of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals.[10] Antidiabetic and antioxidant activity of cinnamon was investigated by the induction of diabetes mellitus and global cerebral ischemia reperfusion injury in mice.

Diabetes mellitus(Type I) was chemically induced in mice by administering single dose of streptozotoin (STZ, 65 mg/kg, i.p), which produces cytotoxicity to β cells of islets of langerhans by increasing the activity of xanthine oxidase and poly ADP-ribose polymerase (PARP), which consequently cause apoptotic and necrotic cell death in pancreatic β cells. STZ was used in this study because of its properties such as selective β cell toxicity and minimal toxic to other organs. Half life of streptozotocin is also high as compared to alloxan.[25]

Global cerebral ischemia was induced by both common carotid artery occlusion for 10 min and reperfusion for 24 hr[11], as indicated by the formation of cerebral infarction, increase in the malondialdehyde level, and decrease in the glutathione level. Pretreatment with *Cinnamomum zeylanicum* 21 days prior to ischemic insult significantly inhibited the malondialdehyde level and cerebral infarction.

In this study antidiabetic effects of *Cinnamomum zeylanicum* was also evaluated because diabetes is the leading cause of brain damage due to several mechanism.[26] There was a significant increase in the markers of diabetes i.e serum glucose level, Serum triglycerides level, decreased body weight and also increase in the markers of brain damage i.e percent cerebral infarction, TBARS level, glutathione level after the administration of STZ as compared to non diabetic group.

Cinnamomum zeylanicum (75 mg/kg, 150 mg/kg and 300 mg/kg, p.o) showed reduction in the serum glucose level, serum triglyceride level, MDA (Malondialdehyde), cerebral infarct size and increase in body weight and glutathione level as compared to diabetic control and diabetes+ stroke group. Low dose shows less effect as compared to medium dose and high dose. *Cinnamomum zeylanicum* (75 mg/kg, 150 mg/kg and 300 mg/kg, p.o) did not showed any effect on body weight on day 0 and day 7, but it showed a significant increase in body weight on day 14 and day 21.Diabetic control group showed a significant difference as compared to normal control

and sham control group when the increased level of markers of oxidative stress(brain damage) was observed and this finding of the present study strongly suggest the diabetes mellitus plays a key role in the pathogenesis of oxidative stress and brain stroke.Results indicates that *Cinnamomum zeylanicum* is a good neuroprotective and could be used as a therapeutic treatment in brain stroke.The phenolic constituents of CZ are likely to be responsible for the anti-oxidant and free radical scavenging activity observed.

Conclusion

From the above discussion and results it can be concluded that:

- *Cinnamomum zeylanicum* bark extract shows a neuroprotective as well as antidiabetic effect in streptozotocin induced diabetes in mice.
- Treatment with *cinnamomum zeylanicum* (75 mg/kg, 150 mg/kg and 300 mg/kg) seems to lower blood glucose and triglycerides level and also it has antioxidant and free radical scavenging properties.
- Out of the results there was a significant decrease in MDA level and increase in glutathione level which are the main markers of brain damage.
- In conclusion this study is the main evidence for the therapeutic potential of *Cinnamomum zeylanicum* in global cerebral ischemia reperfusion injury.The study supports an important concept that the onset of neurodegeneration due to diabetes may be delayed or mitigated with use of dietary antioxidants and antidiabetic drugs that protect against oxidative stress and neurodegeneration.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgement

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