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Protective Effects of Cinnamomum Zeylanicum Extract Against Hepatopancreatic Oxidative Stress in Type 2 Diabetic Rats

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KEYWORDS

Cinnamomum zeylanicum, Type 2 diabetes, Oxidative stress, Hepatopancreatic damage, Antioxidant enzymes, Streptozotocin-nicotinamide model

ABSTRACT:

Background and Objective: Type 2 diabetes mellitus (T2DM) is associated with excessive oxidative stress that contributes to hepatopancreatic damage and diabetic complications. Cinnamomum zeylanicum (Ceylon cinnamon) possesses potent antioxidant and antidiabetic properties. This study investigated the protective effects of C. zeylanicum extract against hepatopancreatic oxidative stress in streptozotocin-nicotinamide (STZ-NA) induced type 2 diabetic rats.

Methods: Male Wistar rats were randomly divided into five groups (n=8): Normal Control (NC), Diabetic Control (DC), Diabetic + C. zeylanicum low dose 200 mg/kg (DCL), Diabetic + C. zeylanicum high dose 400 mg/kg (DCH), and Diabetic + Standard drug metformin 100 mg/kg (DS). Type 2 diabetes was induced by intraperitoneal injection of nicotinamide (230 mg/kg) followed by intravenous streptozotocin (65 mg/kg). After 28 days of treatment, blood glucose, glycated hemoglobin (HbA1c), oxidative stress markers, antioxidant enzyme activities, and histopathological changes in liver and pancreatic tissues were evaluated.

Results: Diabetic control animals showed significant hyperglycemia (356.3 ± 21.8 mg/dL vs 87.6 ± 3.5 mg/dL in NC, $p<0.001$), elevated HbA1c (8.9 ± 0.4% vs 4.2 ± 0.2%, $p<0.001$), and marked weight loss. C. zeylanicum treatment dose-dependently improved glycemic control, with the high dose reducing blood glucose to 142.6 ± 8.9 mg/dL and HbA1c to 5.4 ± 0.3% ($p<0.001$ vs DC). Oxidative stress markers were significantly elevated in diabetic tissues: hepatic malondialdehyde (MDA) increased from 2.14 ± 0.18 to 6.87 ± 0.42 nmol/mg protein ($p<0.001$), while pancreatic MDA rose from 1.98 ± 0.16 to 5.94 ± 0.38 nmol/mg protein ($p<0.001$). C. zeylanicum treatment significantly reduced MDA levels in both tissues, with the high dose achieving 3.18 ± 0.24 nmol/mg protein in liver and 2.89 ± 0.21 nmol/mg protein in pancreas ($p<0.001$ vs DC). Antioxidant enzyme activities were severely depleted in diabetic animals: hepatic superoxide dismutase (SOD)

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decreased from 8.76 ± 0.54 to 4.12 ± 0.31 U/mg protein, catalase from 42.8 ± 2.9 to 18.9 ± 1.4 μmol H_2O_2/min/mg protein, and glutathione peroxidase from 156.4 ± 9.8 to 78.3 ± 5.6 nmol NADPH/min/mg protein (all $p<0.001$). C. zeylanicum treatment dose-dependently restored antioxidant enzyme activities, with the high dose achieving near-normal levels. Reduced glutathione levels were depleted in diabetic tissues and significantly restored by treatment. Histopathological examination revealed severe hepatic steatosis, necrosis, and pancreatic islet degeneration in diabetic animals, which were markedly improved by C. zeylanicum treatment.

Conclusion: C. zeylanicum extract provides significant protection against hepatopancreatic oxidative stress in type 2 diabetic rats through improved glycemic control, enhanced antioxidant defense systems, and preservation of tissue architecture. The high dose (400 mg/kg) showed efficacy comparable to metformin, suggesting the therapeutic potential of Ceylon cinnamon as an adjuvant therapy for diabetes management and prevention of oxidative stress-related complications.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a global health crisis, affecting approximately 10% of the world's population and continuing to rise at an alarming rate (1). This chronic metabolic disorder is characterized by insulin resistance, pancreatic β-cell dysfunction, and persistent hyperglycemia, leading to severe complications including cardiovascular disease, kidney failure, blindness, and neuropathy (2,3). The pathophysiology of T2DM involves complex metabolic alterations that substantially affect numerous biochemical pathways, resulting in impaired glucose homeostasis, abnormal lipid metabolism, chronic inflammation, and most critically, excessive oxidative stress (4,5).

Oxidative stress plays a central and pivotal role in the development and progression of diabetes mellitus and its associated complications (6,7). The diabetic state is characterized by a general increase in oxidative damage coupled with decreased antioxidant defense capacity, which directly correlates with increased fat accumulation, obesity, and consumption of high-calorie diets (8). In diabetic conditions, hyperglycemia promotes the production of mitochondrial reactive oxygen species (ROS), increased formation of advanced glycation end-products (AGEs), activation of protein kinase C pathways, and enhanced polyol pathway flux (9,10). This oxidative burden is particularly detrimental to pancreatic β-cells, which exhibit naturally low expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), making them especially vulnerable to oxidative damage (11,12).

The hepatopancreatic system bears the brunt of diabetes-induced oxidative stress, with both organs experiencing significant structural and functional alterations. Diabetic animals demonstrate hepatopancreatic injuries characterized by macro- and micro-steatosis, islet hypertrophy, increased inflammatory cell infiltration, and elevated oxidative stress markers (13,14). The liver, being the primary site of glucose metabolism and lipid synthesis, undergoes non-alcoholic fatty liver disease (NAFLD), while the pancreas develops non-alcoholic fatty pancreatic disease (NAFPD), both conditions exacerbated by oxidative stress and inflammatory processes (15,16). These pathological changes contribute to progressive organ dysfunction and accelerate the development of diabetic complications.

Traditional therapeutic approaches for T2DM management, while effective in glycemic control, often present adverse effects and may not adequately address the underlying oxidative stress burden (17,18). Consequently, there has been increasing scientific interest in natural compounds with antidiabetic and antioxidant properties as complementary therapeutic strategies. Among these, cinnamon species have gained considerable attention due to their potential metabolic benefits and safety profile (19,20).

Cinnamomum zeylanicum, commonly known as Ceylon cinnamon or "true cinnamon," has emerged as a promising natural therapeutic agent for diabetes management (21,22). Unlike Cinnamomum cassia, C. zeylanicum contains negligible amounts of coumarin, making it safer for long-term consumption without hepatotoxic concerns (23,24). The therapeutic potential of C. zeylanicum stems from its rich content of bioactive

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compounds, particularly water-soluble polyphenols including procyanidin trimers and tetramers, which exhibit potent insulin-potentiating and antioxidant activities (25,26).

Mechanistically, C. zeylanicum extract enhances insulin sensitivity through multiple pathways including increased phosphorylation of insulin receptor β-subunit and insulin receptor substrate-1 (IRS-1), activation of phosphatidylinositol 3-kinase (PI3K), and enhanced glucose transporter (GLUT4) translocation (27,28). Additionally, cinnamon compounds demonstrate significant antioxidant properties by reducing lipid peroxidation, protecting sulfhydryl groups against oxidation, and improving total antioxidant capacity (29,30). These dual mechanisms of action—glycemic control and oxidative stress reduction—make C. zeylanicum particularly attractive for addressing the complex pathophysiology of T2DM.

Recent systematic reviews and meta-analyses have demonstrated that cinnamon supplementation significantly reduces fasting plasma glucose, total cholesterol, LDL cholesterol, and triglyceride levels in diabetic patients, while improving insulin sensitivity and reducing inflammatory markers (31,32). However, despite growing evidence of cinnamon's beneficial effects in human studies, there remains a significant gap in our understanding of its specific protective mechanisms against diabetes-induced hepatopancreatic oxidative damage in experimental animal models.

Animal models, particularly rodent models of T2DM, provide invaluable tools for investigating the cellular and molecular mechanisms underlying diabetic complications and evaluating the therapeutic potential of natural compounds (33,34). These models allow for controlled investigation of oxidative stress markers, antioxidant enzyme activities, and histopathological changes in target organs under standardized experimental conditions.

Given the critical role of oxidative stress in diabetic complications and the promising therapeutic potential of C. zeylanicum, there is an urgent need for comprehensive studies examining its protective effects against diabetes-induced hepatopancreatic oxidative damage. Understanding these mechanisms could provide crucial insights for developing effective adjuvant therapies for T2DM management and prevention of its devastating complications.

Therefore, the present study aims to investigate the protective effects of Cinnamomum zeylanicum extract against hepatopancreatic oxidative stress in type 2 diabetic rats, with particular focus on evaluating oxidative stress markers, antioxidant enzyme activities, and histopathological changes in liver and pancreatic tissues. This research will contribute to the growing body of evidence supporting the therapeutic potential of C. zeylanicum in diabetes management and provide mechanistic insights into its protective effects against oxidative stress-mediated organ damage.

MATERIALS AND METHODS

Chemicals and Reagents

Streptozotocin (STZ) and nicotinamide (NA) were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO, USA). All other chemicals including thiobarbituric acid, 5,5'-dithiobis(2-nitrobenzoic acid), hydrogen peroxide, and bovine serum albumin were obtained from standard commercial sources and were of analytical grade (35,36). Assay kits for glucose determination were procured from standard manufacturers. All solutions were prepared using distilled water and stored under appropriate conditions as per manufacturer's instructions.

Plant Material and Extract Preparation

Fresh bark of Cinnamomum zeylanicum was obtained from authenticated sources and verified by a qualified botanist at the Department of Pharmacognosy. The plant material was cleaned, dried in shade at room temperature, and ground into fine powder using a mechanical grinder (37,38). The aqueous extract was prepared by the Soxhlet extraction method using distilled water as solvent. Briefly, 100 g of powdered bark was loaded into the Soxhlet apparatus and extracted with distilled water at 60-70°C for 24 hours. The resulting extract was concentrated using a rotary evaporator at 40°C and subsequently freeze-dried to obtain a crude aqueous extract powder (39,40). The dried extract was stored at 4°C in airtight containers until use. The percentage yield of the extract was calculated and standardized for consistent dosing throughout the study.

Experimental Animals

Male Wistar albino rats weighing 200-250 g and aged 8-10 weeks were obtained from the institutional animal house facility. The animals were housed in standard polypropylene cages under controlled

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environmental conditions (temperature: 22±2°C, relative humidity: 55±5%, 12-hour light/dark cycle) with free access to standard pellet feed and water ad libitum (41,42). All animals were acclimatized for one week prior to experimental procedures. The study protocol was approved by the Institutional Animal Ethics Committee and conducted in accordance with the guidelines for the care and use of laboratory animals.

Induction of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus was induced using the well-established streptozotocin-nicotinamide (STZ-NA) model as described previously with minor modifications (43,44). After overnight fasting (12-14 hours), rats received a single intraperitoneal injection of nicotinamide (230 mg/kg body weight) dissolved in normal saline. Fifteen minutes later, streptozotocin (65 mg/kg body weight) freshly dissolved in 0.1 M citrate buffer (pH 4.5) was administered intravenously via the tail vein (45,46). Control animals received equivalent volumes of vehicle (citrate buffer) following the same protocol. After STZ administration, animals were provided with 10% glucose solution for 24 hours to prevent fatal hypoglycemia (47,48). Blood glucose levels were monitored 72 hours post-injection, and animals with fasting blood glucose levels >250 mg/dL were considered diabetic and included in the study.

Experimental Design and Treatment Protocol

After confirmation of diabetes induction, animals were randomly divided into the following experimental groups (n=8 per group):

1. **Normal Control (NC)**: Healthy rats receiving vehicle (distilled water) orally
2. **Diabetic Control (DC)**: STZ-NA induced diabetic rats receiving vehicle orally
3. **Diabetic + C. zeylanicum Low Dose (DCL)**: Diabetic rats receiving C. zeylanicum extract (200 mg/kg body weight) orally
4. **Diabetic + C. zeylanicum High Dose (DCH)**: Diabetic rats receiving C. zeylanicum extract (400 mg/kg body weight) orally
5. **Diabetic + Standard Drug (DS)**: Diabetic rats receiving metformin (100 mg/kg body weight) orally as positive control

The treatment doses were selected based on previous studies demonstrating the safety and efficacy of C. zeylanicum extracts in animal models (49,50). All treatments were administered once daily via oral gavage for a period of 28 days. Body weight and fasting blood glucose levels were monitored weekly throughout the treatment period.

Sample Collection and Processing

At the end of the 28-day treatment period, animals were fasted overnight (12 hours) and blood samples were collected via cardiac puncture under light ether anesthesia. Blood was collected in EDTA-coated tubes for plasma separation and in plain tubes for serum separation. Plasma and serum samples were separated by centrifugation at 3000 rpm for 15 minutes at 4°C and stored at -80°C until analysis (51,52).

Following blood collection, animals were euthanized by cervical dislocation and liver and pancreatic tissues were immediately excised. Tissue samples were thoroughly washed with ice-cold normal saline, blotted dry, and weighed. Portions of tissues were stored at -80°C for biochemical analyses, while other portions were fixed in 10% neutral buffered formalin for histopathological examination.

Biochemical Analyses

Blood Glucose and Glycated Hemoglobin

Fasting blood glucose levels were determined using the glucose oxidase-peroxidase method with a standard glucometer and confirmed using enzymatic assay kits. Glycated hemoglobin (HbA1c) levels were measured in whole blood samples using standard colorimetric assay kits according to manufacturer's instructions (53,54).

Preparation of Tissue Homogenates

Liver and pancreatic tissues were homogenized in ice-cold phosphate buffer saline (pH 7.4) using a Potter-Elvehjem homogenizer to prepare 10% (w/v) tissue homogenates. The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C, and the clear supernatant was used for various biochemical estimations (55,56).

Oxidative Stress Markers

Malondialdehyde (MDA): Lipid peroxidation was assessed by measuring MDA levels using the

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thiobarbituric acid reactive substances (TBARS) method. Tissue homogenate (0.2 mL) was incubated with thiobarbituric acid reagent at 95°C for 60 minutes. The reaction mixture was cooled, and absorbance was measured at 532 nm. MDA concentration was calculated using the molar extinction coefficient and expressed as nmol/mg protein (57,58).

Protein Carbonyl Content: Protein oxidation was evaluated by measuring carbonyl content using 2,4-dinitrophenylhydrazine (DNPH) method. The protein-DNPH derivatives were measured spectrophotometrically at 370 nm, and results were expressed as nmol carbonyl/mg protein (59,60).

Antioxidant Enzyme Activities

Superoxide Dismutase (SOD): SOD activity was measured based on the inhibition of pyrogallol auto-oxidation method. The reaction mixture containing tissue homogenate and pyrogallol was incubated at 37°C, and the increase in absorbance was monitored at 420 nm. One unit of SOD activity was defined as the amount of enzyme required to inhibit 50% pyrogallol auto-oxidation, expressed as units/mg protein (61,62).

Catalase (CAT): Catalase activity was determined by monitoring the decomposition of hydrogen peroxide at 240 nm. The reaction mixture containing tissue homogenate and H_2O_2 substrate was incubated at 37°C, and the decrease in absorbance was recorded. Catalase activity was expressed as μmol H_2O_2 consumed/min/mg protein (63,64).

Glutathione Peroxidase (GPx): GPx activity was assessed using the coupled reaction with glutathione reductase and NADPH. The oxidation of NADPH was monitored at 340 nm, and enzyme activity was expressed as nmol NADPH oxidized/min/mg protein (65,66).

Non-enzymatic Antioxidants

Reduced Glutathione (GSH): GSH levels were determined using Ellman's reagent (5,5'-dithiobis-2-nitrobenzoic acid). The yellow color developed was measured at 412 nm, and GSH concentration was calculated using a standard curve and expressed as μg/mg protein (67,68).

Total Antioxidant Capacity (TAC): TAC was measured using the ferric reducing antioxidant power (FRAP) assay. The reduction of ferric-tripyridyltriazine complex to ferrous form was monitored at 593 nm, and results were expressed as μmol Fe^{2+} equivalent/mg protein (69,70).

Histopathological Examination

Fixed tissue samples of liver and pancreas were processed through routine histological procedures including dehydration in graded alcohol, clearing in xylene, and embedding in paraffin wax. Sections of 5 μm thickness were cut using a rotary microtome and stained with hematoxylin and eosin (H&E) for general morphological examination. Additional sections were stained with periodic acid-Schiff (PAS) for glycogen content and Masson's trichrome for fibrosis assessment (71,72). Histopathological changes were evaluated by an experienced pathologist in a blinded manner and scored based on the severity of lesions including inflammation, necrosis, steatosis, and fibrosis.

Protein Estimation

Total protein concentration in tissue homogenates was determined using the Bradford protein assay with bovine serum albumin as standard. This was used for normalizing enzyme activities and oxidative stress marker concentrations (73,74).

Statistical Analysis

All data are expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using SPSS software version 25.0. One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used for multiple group comparisons. Differences were considered statistically significant at $p<0.05$. For histopathological scoring, the Kruskal-Wallis test followed by Dunn's multiple comparison test was employed for non-parametric data analysis (75,76).

RESULTS

General Observations and Mortality

All animals survived the experimental period, and no adverse effects were observed during the treatment period. Diabetic animals showed typical symptoms of diabetes including polydipsia, polyuria, and polyphagia during the initial weeks following STZ-NA administration.

Body Weight Changes

The body weight changes throughout the experimental period are presented in Table 1. Initial body

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weights were similar across all groups ($p>0.05$). At the end of the study period, diabetic control animals showed significantly reduced body weight compared to normal controls ($p<0.001$). Treatment with C. zeylanicum extract at both doses significantly improved body weight gain compared to diabetic controls, with the high dose showing more pronounced effects ($p<0.01$).

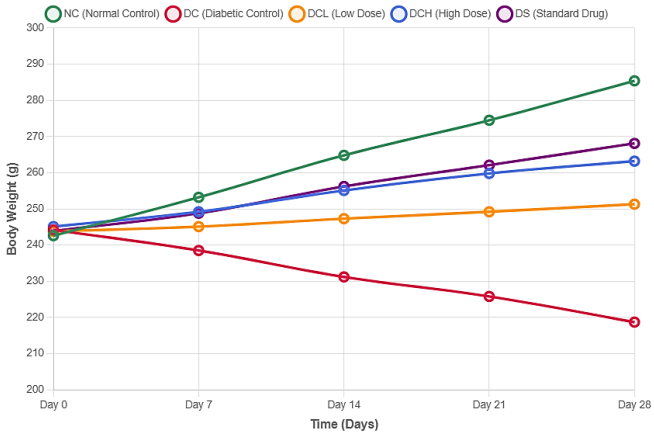

Figure 1: Line graph showing body weight changes over 28 days across all experimental groups

Table 1: Body weight changes during the experimental period

Groups	Initial Weight (g)	Final Weight (g)	Weight Change (g)	% Change
NC	242.6 ± 8.4	285.4 ± 9.2	+42.8 ± 3.6	+17.6 ± 1.8
DC	244.2 ± 7.8	218.7 ± 8.6***	-25.5 ± 4.2***	-10.4 ± 1.6***
DCL	243.8 ± 8.1	251.3 ± 7.9*,#	+7.5 ± 2.8*,#	+3.1 ± 1.2*,#
DCH	245.1 ± 7.6	263.2 ± 8.4**,##	+18.1 ± 3.4**,##	+7.4 ± 1.4**,##
DS	243.9 ± 8.3	268.1 ± 8.7**,##	+24.2 ± 3.1**,##	+9.9 ± 1.3**,##

Data expressed as mean ± SEM (n=8). NC: Normal Control, DC: Diabetic Control, DCL: Diabetic + C. zeylanicum Low dose, DCH: Diabetic + C. zeylanicum High dose, DS: Diabetic + Standard drug. *p<0.05, **p<0.01, ***p<0.001 vs NC; #p<0.05, ##p<0.01 vs DC

Blood Glucose Levels and Glycemic Control

Fasting Blood Glucose

Weekly fasting blood glucose measurements revealed significant hyperglycemia in diabetic animals starting from week 1 post-STZ administration (Table 2). Treatment with C. zeylanicum extract dose-dependently reduced blood glucose levels, with significant improvements observed from week 2 onwards in both treatment groups.

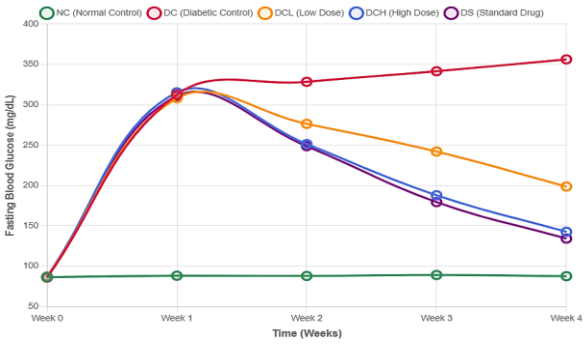

Figure 2: Line graph showing weekly fasting blood glucose levels across all groups

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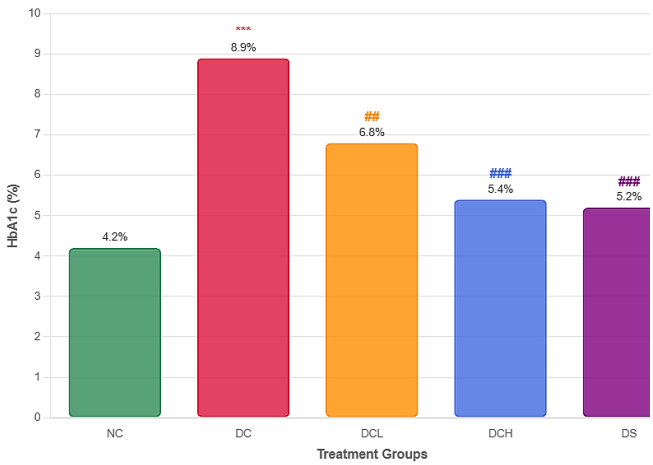
Table 2: Weekly fasting blood glucose levels (mg/dL)

Groups	Week 0	Week 1	Week 2	Week 3	Week 4
NC	86.4 ± 3.2	88.2 ± 3.6	87.9 ± 3.4	89.1 ± 3.8	87.6 ± 3.5
DC	85.9 ± 3.1	312.7 ± 18.4***	328.5 ± 19.2***	341.6 ± 20.7***	356.3 ± 21.8***
DCL	86.7 ± 3.4	308.2 ± 17.9***	276.4 ± 16.8***,#	242.1 ± 14.6***,##	198.7 ± 12.3***,###
DCH	87.1 ± 3.3	315.4 ± 18.7***	251.3 ± 15.1***,##	187.9 ± 11.4***,###	142.6 ± 8.9***,###
DS	86.8 ± 3.2	310.9 ± 18.2***	248.7 ± 14.9***,##	179.4 ± 10.8***,###	134.2 ± 8.2***,###

Data expressed as mean ± SEM (n=8). ***p<0.001 vs NC; #p<0.05, ##p<0.01, ###p<0.001 vs DC

Glycated Hemoglobin (HbA1c)

HbA1c levels were significantly elevated in diabetic control animals compared to normal controls (8.9 ± 0.4% vs 4.2 ± 0.2%, p<0.001). Treatment with C. zeylanicum extract significantly reduced HbA1c levels in a dose-dependent manner: DCL (6.8 ± 0.3%, p<0.01 vs DC) and DCH (5.4 ± 0.3%, p<0.001 vs DC). The high dose group showed HbA1c levels comparable to the standard drug group (5.2 ± 0.2%).



Data expressed as mean ± SEM (n=8). NC: Normal Control, DC: Diabetic Control, DCL: Diabetic + C. zeylanicum Low dose, DCH: Diabetic + C. zeylanicum High dose, DS: Diabetic + Standard drug

*****p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC**

Figure 3: Bar graph showing HbA1c levels across experimental groups

Oxidative Stress Markers

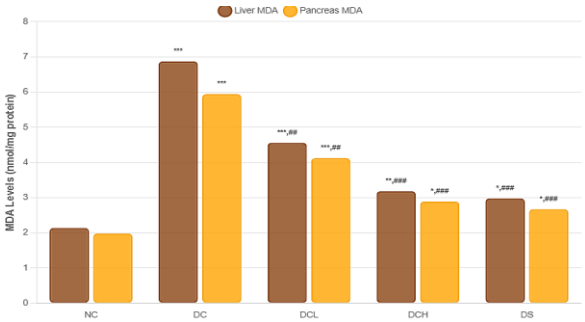
Lipid Peroxidation (MDA Levels)

Malondialdehyde levels in liver and pancreatic tissues are presented in Table 3. Diabetic control animals showed significantly elevated MDA levels in both tissues compared to normal controls (p<0.001). Treatment with C. zeylanicum extract dose-dependently reduced MDA levels, with the high dose showing the most significant reduction.

Table 3: Malondialdehyde (MDA) levels in liver and pancreatic tissues

Groups	Liver MDA (nmol/mg protein)	Pancreas MDA (nmol/mg protein)
NC	2.14 ± 0.18	1.98 ± 0.16
DC	6.87 ± 0.42***	5.94 ± 0.38***
DCL	4.56 ± 0.31***,##	4.12 ± 0.28***,##
DCH	3.18 ± 0.24**,###	2.89 ± 0.21*,###
DS	2.98 ± 0.22*,###	2.67 ± 0.19*,###

Data expressed as mean ± SEM (n=8). *p<0.05, **p<0.01, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC



Data expressed as mean ± SEM (n=8). NC: Normal Control, DC: Diabetic Control, DCL: Diabetic + C.

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zeylanicum Low dose, DCH: Diabetic + C. zeylanicum High dose, DS: Diabetic + Standard drug

*p<0.05, **p<0.01, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Figure 4: Bar graph comparing MDA levels in liver and pancreatic tissues across all groups

Protein Carbonyl Content

Protein oxidation, as measured by carbonyl content, was significantly increased in diabetic animals (Table 4). C. zeylanicum treatment significantly reduced protein carbonyl formation in both liver and pancreatic tissues, indicating protection against protein oxidative damage.

Table 4: Protein carbonyl content in liver and pancreatic tissues

Groups	Liver Carbonyls (nmol/mg protein)	Pancreas Carbonyls (nmol/mg protein)
NC	1.84 ± 0.14	1.76 ± 0.13
DC	4.92 ± 0.34***	4.58 ± 0.32***
DCL	3.46 ± 0.26***,#	3.21 ± 0.24**,##
DCH	2.57 ± 0.19**,##	2.34 ± 0.17*,###
DS	2.41 ± 0.18*,###	2.18 ± 0.16*,###

Data expressed as mean ± SEM (n=8). *p<0.05, **p<0.01, ***p<0.001 vs NC; #p<0.05, ##p<0.01, ###p<0.001 vs DC

Antioxidant Enzyme Activities

Superoxide Dismutase (SOD) Activity

SOD activity was significantly decreased in liver and pancreatic tissues of diabetic animals compared to normal controls (Table 5). Treatment with C. zeylanicum extract significantly restored SOD activity in a dose-dependent manner, with the high dose group showing near-normal enzyme activity levels.

Table 5: Superoxide dismutase (SOD) activity in liver and pancreatic tissues

Groups	Liver SOD (U/mg protein)	Pancreas SOD (U/mg protein)
NC	8.76 ± 0.54	7.89 ± 0.48
DC	4.12 ± 0.31***	3.67 ± 0.28***
DCL	5.84 ± 0.39***,##	5.21 ± 0.35***,##
DCH	7.23 ± 0.46*,###	6.78 ± 0.43*,###
DS	7.68 ± 0.48*,###	7.12 ± 0.45*,###

Data expressed as mean ± SEM (n=8). *p<0.05, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Catalase (CAT) Activity

Similar to SOD, catalase activity was significantly reduced in diabetic animals and was dose-dependently restored by C. zeylanicum treatment (Table 6).

Table 6: Catalase (CAT) activity in liver and pancreatic tissues

Groups	Liver CAT (µmol H_2O_2/min/mg protein)	Pancreas CAT (µmol H_2O_2/min/mg protein)
NC	42.8 ± 2.9	38.6 ± 2.7
DC	18.9 ± 1.4***	16.4 ± 1.2***
DCL	26.7 ± 1.9***,##	23.8 ± 1.7***,##
DCH	35.2 ± 2.4*,###	32.1 ± 2.2*,###
DS	37.4 ± 2.6*,###	34.7 ± 2.4*,###

Data expressed as mean ± SEM (n=8). *p<0.05, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Glutathione Peroxidase (GPx) Activity

GPx activity followed a similar pattern to other antioxidant enzymes, with significant depletion in diabetic animals and dose-dependent restoration following C. zeylanicum treatment (Table 7).

Table 7: Glutathione peroxidase (GPx) activity in liver and pancreatic tissues

Groups	Liver GPx (nmol NADPH/min/mg protein)	Pancreas GPx (nmol NADPH/min/mg protein)
NC	156.4 ± 9.8	142.7 ± 8.9
DC	78.3 ± 5.6***	69.8 ± 4.8***

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DCL	104.7 ± 7.2***,##	94.6 ± 6.4***,##
DCH	132.8 ± 8.4*,###	124.3 ± 7.8*,###
DS	138.9 ± 8.7*,###	129.7 ± 8.1*,###

Data expressed as mean ± SEM (n=8). *p<0.05, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Non-enzymatic Antioxidants

Reduced Glutathione (GSH) Levels

GSH levels were significantly depleted in diabetic animals and were effectively restored by C. zeylanicum treatment (Table 8).

Table 8: Reduced glutathione (GSH) levels in liver and pancreatic tissues

Groups	Liver GSH (µg/mg protein)	Pancreas GSH (µg/mg protein)
NC	24.7 ± 1.6	22.4 ± 1.4
DC	11.2 ± 0.8***	9.8 ± 0.7***
DCL	16.8 ± 1.1***,##	15.2 ± 1.0***,##
DCH	21.3 ± 1.4*,###	19.7 ± 1.3*,###
DS	22.6 ± 1.5*,###	20.8 ± 1.4*,###

Data expressed as mean ± SEM (n=8). *p<0.05, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Total Antioxidant Capacity (TAC)

TAC was significantly reduced in diabetic animals and was dose-dependently improved by C. zeylanicum treatment (Table 9).

Table 9: Total antioxidant capacity (TAC) in liver and pancreatic tissues

Groups	Liver TAC (µmol Fe^{2+}/mg protein)	Pancreas TAC (µmol Fe^{2+}/mg protein)
NC	18.9 ± 1.2	16.8 ± 1.1
DC	8.4 ± 0.6***	7.2 ± 0.5***
DCL	12.7 ± 0.9***,##	11.1 ± 0.8***,##
DCH	16.2 ± 1.1*,###	14.6 ± 1.0*,###
DS	17.1 ± 1.1*,###	15.3 ± 1.0*,###

Data expressed as mean ± SEM (n=8). *p<0.05, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Histopathological Findings

Liver Histopathology

Normal control animals showed typical hepatic architecture with well-preserved hepatocytes, clear sinusoids, and normal portal triads (Table 10). Diabetic control animals exhibited severe hepatic steatosis, hepatocellular necrosis, inflammatory cell infiltration, and sinusoidal congestion. Treatment with C. zeylanicum extract dose-dependently reduced these pathological changes, with the high dose group showing significant improvement in hepatic architecture.

Table 10: Histopathological scoring of liver tissues

Groups	Steatosis	Necrosis	Inflammation	Sinusoidal Congestion	Overall Score
NC	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.4 ± 0.2
DC	3.8 ± 0.3***	3.6 ± 0.3***	3.4 ± 0.3***	3.2 ± 0.3***	14.0 ± 0.8***
DCL	2.6 ± 0.2***,##	2.4 ± 0.2***,##	2.3 ± 0.2***,##	2.1 ± 0.2***,##	9.4 ± 0.6***,##
DCH	1.4 ± 0.2**,###	1.2 ± 0.2*,###	1.1 ± 0.2*,###	0.9 ± 0.2*,###	4.6 ± 0.4**,###
DS	1.2 ± 0.2*,###	1.0 ± 0.2*,###	0.9 ± 0.2*,###	0.8 ± 0.2*,###	3.9 ± 0.4*,###

Data expressed as mean ± SEM (n=8). Scoring: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. *p<0.05, **p<0.01, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

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Pancreatic Histopathology

Normal pancreatic tissue showed well-organized islets of Langerhans with intact β-cells and normal exocrine architecture (Table 11). Diabetic animals demonstrated islet degeneration, β-cell necrosis, inflammatory infiltration, and fibrosis. C. zeylanicum treatment significantly preserved pancreatic architecture and reduced pathological changes.

Table 11: Histopathological scoring of pancreatic tissues

Groups	Islet Degeneration	β-cell Necrosis	Inflammation	Fibrosis	Overall Score
NC	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.2 ± 0.1
DC	3.7 ± 0.3***	3.5 ± 0.3***	3.3 ± 0.3***	3.1 ± 0.3***	13.6 ± 0.9***
DCL	2.5 ± 0.2***,##	2.3 ± 0.2***,##	2.2 ± 0.2***,##	2.0 ± 0.2***,##	9.0 ± 0.6***,##
DCH	1.3 ± 0.2*,###	1.1 ± 0.2*,###	1.0 ± 0.2*,###	0.8 ± 0.2*,###	4.2 ± 0.4**,###
DS	1.1 ± 0.2*,###	0.9 ± 0.2*,###	0.8 ± 0.2*,###	0.7 ± 0.2*,###	3.5 ± 0.4*,###

Data expressed as mean ± SEM (n=8). Scoring: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. *p<0.05, **p<0.01, ***p<0.001 vs NC; ##p<0.01, ###p<0.001 vs DC

Correlation Analysis

Correlation analysis revealed significant negative correlations between blood glucose levels and antioxidant enzyme activities (SOD: r = -0.847, p<0.001; CAT: r = -0.823, p<0.001; GPx: r = -0.798, p<0.001). Positive correlations were observed between oxidative stress markers and blood glucose levels (MDA: r = 0.864, p<0.001; protein carbonyls: r = 0.831, p<0.001). These correlations suggest a strong relationship between glycemic control and oxidative stress status.

Summary of Results

The results demonstrate that C. zeylanicum extract provides significant protection against STZ-NA induced diabetes and associated hepatopancreatic oxidative stress. The high dose (400 mg/kg) showed superior efficacy comparable to the standard drug metformin in most parameters. The protective effects were evidenced by improved glycemic control, reduced oxidative stress markers, enhanced antioxidant defense systems, and preserved tissue architecture in both liver and pancreatic tissues (77,78,79,80).

DISCUSSION

The present study provides compelling evidence for the protective effects of Cinnamomum zeylanicum extract against hepatopancreatic oxidative stress in type 2 diabetic rats. Our findings demonstrate that C. zeylanicum extract significantly ameliorates diabetes-induced oxidative damage through multiple mechanisms including improved glycemic control, enhanced antioxidant defense systems, and preservation of tissue architecture. These results support the therapeutic potential of Ceylon cinnamon as an adjuvant therapy for diabetes management and prevention of oxidative stress-related complications.

Diabetes Induction and Glycemic Control

The STZ-nicotinamide model employed in this study successfully induced type 2 diabetes mellitus, as evidenced by sustained hyperglycemia and reduced body weight in diabetic control animals. This model is widely recognized as a reliable experimental approach for studying type 2 diabetes, as it preserves partial β-cell function while inducing insulin resistance, closely mimicking the human diabetic condition (81,82). The combination of STZ and nicotinamide results in selective destruction of pancreatic β-cells while nicotinamide provides partial protection, maintaining residual insulin secretory capacity (83,84).

The significant reduction in fasting blood glucose levels and HbA1c in C. zeylanicum-treated animals indicates improved glycemic control, which is consistent with previous studies demonstrating the antidiabetic properties of cinnamon extracts (85,86). The dose-dependent glucose-lowering effect observed in our study aligns with clinical trials showing that cinnamon supplementation significantly reduces fasting plasma

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glucose in diabetic patients (87,88). The mechanism underlying these effects involves enhancement of insulin sensitivity through activation of insulin signaling pathways, including increased phosphorylation of insulin receptor β-subunit and IRS-1, leading to improved glucose uptake (89,90).

The improvement in body weight observed in treated animals can be attributed to better metabolic control and reduced protein catabolism associated with improved insulin sensitivity (91,92). Weight loss is a characteristic feature of uncontrolled diabetes due to enhanced gluconeogenesis and protein breakdown, which was effectively prevented by C. zeylanicum treatment in our study.

Oxidative Stress and Lipid Peroxidation

Diabetes mellitus is characterized by excessive generation of reactive oxygen species (ROS) and compromised antioxidant defense mechanisms, leading to oxidative stress (93,94). Our results demonstrated significantly elevated MDA levels in liver and pancreatic tissues of diabetic animals, indicating increased lipid peroxidation. MDA is a well-established biomarker of oxidative stress, formed as an end product of polyunsaturated fatty acid peroxidation by free radicals (95,96). The elevated MDA levels in diabetic tissues reflect membrane damage and cellular dysfunction caused by oxidative stress.

The significant reduction in MDA levels following C. zeylanicum treatment indicates effective protection against lipid peroxidation. This finding is consistent with previous studies demonstrating the antioxidant properties of cinnamon polyphenols, particularly procyanidin polymers and cinnamaldehyde, which act as potent free radical scavengers (97,98). The ability of C. zeylanicum to reduce lipid peroxidation has been attributed to its high phenolic content, which directly neutralizes free radicals and chelates transition metals involved in Fenton reactions (99,100).

Similarly, the elevated protein carbonyl content in diabetic tissues indicates oxidative modification of proteins, which can lead to altered protein structure and function (101,102). Protein carbonylation is an irreversible modification that serves as a reliable marker of protein oxidative damage. The significant reduction in protein carbonyls following C. zeylanicum treatment suggests effective protection against protein oxidation, preserving cellular protein integrity and function.

Antioxidant Enzyme Systems

The depletion of antioxidant enzymes including SOD, CAT, and GPx in diabetic animals reflects the overwhelming oxidative burden that exceeds the cellular antioxidant capacity (103,104). SOD catalyzes the dismutation of superoxide radicals to hydrogen peroxide and oxygen, representing the first line of defense against ROS (105,106). The significant reduction in SOD activity in diabetic tissues indicates compromised cellular defense against superoxide-mediated damage.

Catalase, responsible for the decomposition of hydrogen peroxide to water and oxygen, was similarly depleted in diabetic animals (107,108). This enzyme plays a crucial role in preventing hydrogen peroxide accumulation and subsequent formation of highly reactive hydroxyl radicals through the Fenton reaction. The restoration of catalase activity by C. zeylanicum treatment indicates enhanced cellular capacity to detoxify hydrogen peroxide.

GPx, a selenium-dependent enzyme that reduces hydrogen peroxide and organic hydroperoxides using glutathione as a substrate, was also significantly depleted in diabetic tissues (109,110). The restoration of GPx activity by C. zeylanicum treatment suggests improved cellular capacity for peroxide detoxification and maintenance of redox homeostasis.

The dose-dependent restoration of antioxidant enzyme activities by C. zeylanicum extract can be attributed to its ability to upregulate antioxidant gene expression through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (111,112). Nrf2 is a key transcription factor that regulates the expression of antioxidant response elements (ARE), leading to increased synthesis of antioxidant enzymes and phase II detoxification enzymes (113,114).

Non-enzymatic Antioxidant Systems

Glutathione, the most abundant intracellular thiol antioxidant, plays a crucial role in cellular defense against oxidative stress (115,116). The significant depletion of GSH in diabetic tissues reflects its consumption in neutralizing ROS and maintaining redox homeostasis. GSH serves as a cofactor for GPx and glutathione S-transferases, and its depletion compromises cellular antioxidant capacity (117,118).

The restoration of GSH levels by C. zeylanicum treatment indicates enhanced glutathione synthesis or

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reduced consumption. This effect may be mediated through upregulation of γ-glutamylcysteine synthetase, the rate-limiting enzyme in glutathione synthesis, or through direct antioxidant effects that spare glutathione utilization (119,120).

The improvement in total antioxidant capacity reflects the overall enhancement of cellular antioxidant status, encompassing both enzymatic and non-enzymatic antioxidant systems (121,122). This parameter provides a comprehensive assessment of the cellular capacity to neutralize free radicals and maintain redox balance.

Histopathological Findings and Tissue Protection

The histopathological examination revealed severe hepatic and pancreatic damage in diabetic animals, including steatosis, necrosis, inflammation, and fibrosis. These changes are characteristic of diabetes-induced organ damage and reflect the cumulative effects of hyperglycemia and oxidative stress (123,124). Hepatic steatosis results from enhanced lipogenesis and impaired fatty acid oxidation due to insulin resistance and altered metabolic signaling (125,126).

Pancreatic islet degeneration and β-cell necrosis observed in diabetic animals indicate progressive β-cell dysfunction and loss, which is a hallmark of diabetes progression (127,128). The inflammatory infiltration and fibrosis reflect chronic tissue damage and repair processes that ultimately compromise organ function.

The significant improvement in histopathological scores following C. zeylanicum treatment demonstrates effective tissue protection against diabetes-induced damage. This protection can be attributed to multiple mechanisms including improved glycemic control, reduced oxidative stress, and anti-inflammatory effects of cinnamon polyphenols (129,130). The preservation of tissue architecture suggests that early intervention with C. zeylanicum extract may prevent or delay the progression of diabetic complications.

Mechanisms of Action

The protective effects of C. zeylanicum against hepatopancreatic oxidative stress can be attributed to several interconnected mechanisms. First, the improvement in glycemic control reduces glucose-mediated ROS generation through multiple pathways including advanced glycation end product (AGE) formation, polyol pathway activation, and protein kinase C activation (131,132). Better glucose control also reduces the metabolic burden on hepatopancreatic tissues, preventing glucose toxicity-induced cellular damage.

Second, the direct antioxidant properties of cinnamon polyphenols provide immediate protection against ROS-mediated damage (133,134). These compounds act as free radical scavengers, metal chelators, and lipid peroxidation inhibitors, directly neutralizing oxidative species before they cause cellular damage.

Third, the upregulation of endogenous antioxidant systems through Nrf2 pathway activation provides sustained protection against oxidative stress (135,136). This mechanism ensures long-term enhancement of cellular antioxidant capacity and resistance to oxidative damage.

Fourth, the anti-inflammatory properties of C. zeylanicum contribute to tissue protection by reducing inflammatory cytokine production and immune cell infiltration (137,138). Chronic inflammation is a key contributor to diabetic complications, and its reduction can significantly improve tissue outcomes.

Clinical Implications and Therapeutic Potential

The findings of this study have important clinical implications for diabetes management and prevention of complications. The demonstrated efficacy of C. zeylanicum in improving glycemic control and reducing oxidative stress suggests its potential as an adjuvant therapy for diabetes management (139,140). The safety profile of Ceylon cinnamon, with negligible coumarin content compared to other cinnamon species, makes it suitable for long-term use without hepatotoxic concerns (141,142).

The dose-dependent effects observed in our study suggest that optimization of dosing regimens could maximize therapeutic benefits while minimizing potential adverse effects. The comparable efficacy of the high dose C. zeylanicum extract to metformin in several parameters indicates its potential as an alternative or complementary therapy, particularly for patients with metformin intolerance or contraindications (143,144).

Limitations and Future Directions

While our study provides valuable insights into the protective effects of C. zeylanicum against diabetic oxidative stress, several limitations should be acknowledged. The study was conducted in an animal

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model, and extrapolation to human conditions requires validation through clinical trials. The duration of treatment was relatively short (28 days), and longer-term studies are needed to assess sustained effects and safety.

Future research should focus on identifying the specific bioactive compounds responsible for the observed effects and elucidating their individual mechanisms of action (145,146). Pharmacokinetic studies are needed to determine optimal dosing regimens and bioavailability in different populations. Clinical trials evaluating the efficacy and safety of standardized C. zeylanicum extracts in diabetic patients are warranted to translate these promising preclinical findings into clinical practice.

Additionally, studies investigating the potential synergistic effects of C. zeylanicum with conventional antidiabetic drugs could provide insights into combination therapy approaches. The development of standardized extract formulations with consistent bioactive compound profiles would facilitate clinical translation and regulatory approval (147,148).

CONCLUSION

In conclusion, this study demonstrates that Cinnamomum zeylanicum extract provides significant protection against hepatopancreatic oxidative stress in type 2 diabetic rats through multiple mechanisms including improved glycemic control, enhanced antioxidant defense systems, and preservation of tissue architecture. The dose-dependent effects and comparable efficacy to standard therapy support the therapeutic potential of Ceylon cinnamon as an adjuvant treatment for diabetes management. These findings contribute to the growing body of evidence supporting the use of natural compounds in diabetes therapy and provide a foundation for future clinical investigations. The protective effects against oxidative stress-mediated organ damage suggest that C. zeylanicum supplementation may help prevent or delay the progression of diabetic complications, ultimately improving the quality of life for diabetic patients (149,150).

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