ORIGINAL ARTICLE

Protective Mechanism Pathway of *Cinnamomum zeylanicum* at High Dosage against Liver and Renal Damage in STZ-Induced Diabetic Rats

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ABSTRACT

INTRODUCTION: *Cinnamon zeylanicum* (CZ) bark is widely used as supplement for diabetic management, there are concerns about its safety and potential toxicity at high doses, and limited evidence to support its efficacy. To investigate this further, this study examines the effects of *Cinnamon zeylanicum* aqueous extract (CZAE) on various factors in diabetic rats, including body weight, blood glucose level, biochemical parameters, histological changes, and gene expression. **MATERIALS AND METHODS:** In the study, 30 male Sprague-Dawley rats were divided into five groups of six animals each. Type 2 diabetes mellitus (T2DM) was induced in all groups except the negative control by a single intraperitoneal injection of streptozotocin (STZ). The rats in the intervention groups (Groups C, D, and E) were given CZAE at 1000, 1500, and 2000 mg/kg, dose respectively, for 28 days. The body weight and fasting blood glucose were monitored weekly, and their liver and renal profiles were analyzed. Histology was assessed with hematoxylin and eosin stain, and apoptotic gene expression was examined in liver and renal tissues. **RESULTS:** The body weight of rats in intervention groups increased compared to the control group. There was a significant decrease ($P<0.001$) in blood glucose levels. The extract significantly reduced ($P<0.05$) liver biochemical markers in the intervention groups compared to the control group. The histology of the liver & kidney improved ($p<0.001$) with upregulated Bcl-2 and down-regulated BAX genes in preventing apoptosis in the intervention groups. **CONCLUSIONS**: High doses of CZAE are safe and effective for T2DM.

Keywords
Cinnamon zeylanicum, Sprague Dawley rats, histopathology, liver profile, gene expression

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global cause of illness and death due to increased incidence resulting from pancreatic β-cell dysfunction and insulin resistance in peripheral tissues.[1] Malaysia has the highest prevalence of T2DM at 16.8% in the Western-Pacific region.[2] Diet is crucial for managing T2DM, leading to studies on dietary components as alternative treatment. Therefore, a study on diabetes and its alternative treatment is a priority to control the diabetes epidemic.[3] Both *in vitro* and *in vivo* studies have shown that cinnamon is one such dietary component that contains biologically active substances with insulin-mimetic properties.[4,5] Cinnamon increases glucose absorption by stimulating insulin receptor kinase activity, autophosphorylation, and glycogen synthase activity. The active substances in cinnamon regulate plasma glucose by initiating insulin receptor kinase, glycogen synthase, and insulin receptor auto-phosphorylation.[6]

There are two main types of cinnamon which are *Cinnamomum cassia* (CC) and *Cinnamomum zeylanicum* (CZ), which differs in their coumarin content.[4] CC has high coumarin levels and can have toxic side effects on the liver,[5] while CZ has negligible coumarin content.[6] CC has been restricted in some regions due to health risks,[4] and studies have examined its effects on T2DM *in vitro* and *in vivo*.[7] However, no studies have investigated the effects of higher doses of CZ on diabetes mellitus. The current study investigates the impact of high-dose CZ on liver and renal biochemical parameters, haematological parameters,

histological, and gene expression profiles due to its low coumarin content compared to other species.[4]

MATERIALS AND METHODS

Preparation of plant extracts

Cinnamomum zeylanicum (CZ) stem bark from Malaysia which was used for the study was verified by UPM botanist and stored at the UPM herbarium (voucher number UPM/IBS/UB/H24/21). CZ was processed by boiling with double-distilled water in a 1:4 ratio for 8 hours at 120℃, and later placed in a freeze dryer turbo extractor. The resulting extract was spray-dried into powder, packed in zip-lock bags, and refrigerated at 4℃.

Preparation of experimental animals

The study adhered to ethical standards of MSU (MSU-RMC-02/FR01/08/L3/007). Male Sprague-Dawley rats weighing 170-200g were obtained from the MSU animal house and acclimatised for one week in controlled conditions before the study, with free access to food and water.[8]

Induction of diabetes

Streptozotocin (STZ) was dissolved in citrate buffer and given to overnight fasted rats through a single intraperitoneal injection of 60 mg/kg body weight to induce diabetes.[9] T2DM was confirmed by measuring fasting blood glucose levels. Rats with fasting glucose levels above 250 mg/dL (13.9 mmol/L) were considered diabetic.[8]

Experimental Design

Thirty male Sprague-Dawley rats were divided into 5 groups (n=6 per group) as follows: Group A is negative control (rats fed with normal diet only), Group B is positive control (rats exposed to STZ only), Groups C, D, and E are intervention groups receiving CZ at 1000, 1500, and 2000 mg/kg, respectively via oral gavage for 28 days.[10] Weekly body weight was measured, and at the end of the study, the animals were sacrificed. Liver and kidney samples were collected, weighed, and stored at -80°C for histopathological and gene expression analysis. The liver was examined for spotty or zonal liver necrosis, swelling of hepatocytes, fatty changes, and inflammation. Kidneys were observed for tubular epithelial cell damage, presence of casts or crystals, glomerular changes, and inflammation. Tissue samples were embedded in paraffin, sectioned, stained with Haematoxylin and Eosin (H&E), and assessed for histological changes and gene expression analysis via RT-PCR amplification.

Evaluation of biochemical parameters

Baseline blood glucose was measured on Day 0 to confirm diabetes and then monitored weekly (on Days 7, 14, 21, and 28) using the On call Plus Glucometer. Blood urea, serum creatinine, alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin (TBIL) were examined using Biosystems biochemical kits (BioSystems S.A. Costa Brava, 30, 08030 Barcelona Spain) (www.biosystems.cs) according to the manufacture's guidelines.[10]

Histological analysis

Liver and kidney tissues were fixed in 10% neutral phosphate buffer formalin, dehydrated, and preserved in liquid paraffin. Tissue samples were sliced into 5 μm thick paraffin-soaked sections, deparaffinized, hydrated, and stained with H&E. Slides were then mounted with a coverslip using immersion oil and examined under a light microscope.

Evaluation of BAX &Bcl-2 gene expression

The gene expression study followed a specific protocol for RNA extraction protocol (Macarel Nagel, Germany), cDNA synthesize (OneScipt Hot Reverse Transcriptase kit (ABMgood, Canada), and analysis of gene expression. DNA sequencing was conducted using RT-PCR with the HotStar Taq Master Mix Kit (Qiagen, USA). Two primers, GAPDH (as control gene) and OPRM (as target gene) were used in this study. The primer designs were obtained from the (NCBI) website

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STATISTICAL ANALYSIS

Data on body weight were evaluated using Statistical Package for Social Science (SPSS) Version 28.0, IBM, (New York, USA). Values were expressed as Mean ± SE and evaluated by one-way analysis of variance (ANOVA) followed by Tukey's post hoc multiple comparison test with significance taken at $p \leq 0.05$.

RESULTS

Effect of *Cinnamon zeylanicum (CZ)* on body weight of rats

Table 1 summarizes weekly body weight changes in rats. The results show a decrease in body weight for the positive control group, while intervention groups showed an increase in body weight.

Table 1: Body weight (Mean±SD) of rats in each group from Day 0 to Day 28.

CZ extract	Body weight (Mean ± S.D)					
	Group (n=5)	Day 0	Day 7	Day 14	Day 21	Day 28
No	Group-A (Negative control)	187.17 ±7.44	197.50 ±8.3[b]	209.33 ±3.8[b]	209.83 ±5.7[b]	213.17 ±2.7[b]
	Group-B (Positive control)	192.33 ±7.94	185.00 ±43.35	175.33 ±5.61	168.33 ±5.35	155.67 ±4.55
	Group-C (CZ 1000mg/kg)	184.83 ±4.45	195.00 ±2.8[b]	199.33 ±3.2[b]	201.17 ±4.3[b]	206.83 ±2.5[b]
Yes	Group-D (CZ 1500mg/kg)	200.83 ±4.0[a]	207.33 ±5.2[b]	213.17 ±4.5[b]	217.83 ±4.0[b]	219.33 ±3.6[b]
	Group-E (CZ 2000mg/kg)	205.00 ±4.2[b]	211.33 ±4.2[b]	213.17 ±3.9[b]	214.17 ±4.3[b]	217.33 ±4.[b]

**b: p<0.001.*

Effect of *Cinnamon zeylanicum (CZ)* on fasting blood glucose

After the rats were induced with STZ, the blood glucose levels surged in all groups. However, Groups C, D, and E, which were treated with CZ extract showed a significant reduction compared to the positive control group in dose-dependent manner as shown in Table 2.

Effects of *Cinnamon zeylanicum* (CZ) on urea and creatinine

Figure 1 shows the urea and creatinine levels for rats in 5 groups. Group B had the highest levels. No significant difference was found in urea and creatinine levels among intervention groups.

Table 2: Blood glucose levels (Mean±SD) of rats in each group from Day 0 to Day 28.

CZ extract	Blood glucose level (mmols/L)					
	Group (n=5)	Day 0	Day 7	Day 14	Day 21	Day 28
No	Group-A (Negative control)	5.53± 0.12	5.53± 0.09[b]	6.13±0. 10[b]	5.50± 0.19[b]	4.75± 0.11[b]
	Group-B (Positive control)	16.62± 0.20	17.20± 0.10	18.67± 0.23	17.90± 0.46	17.80± 0.10
	Group-C (CZ 1000mg/kg)	16.86± 0.07	5.11± 0.08[b]	4.90±0. 03[b]	5.31± 0.11[b]	5.09± 0.06[b]
Yes	Group-D (CZ 1500mg/kg)	15.67± 0.16	5.13± 0.11[b]	5.15±0. 11[b]	5.38± 0.19[b]	5.09± 0.07[b]
	Group-E (CZ 2000mg/kg)	17.64± 0.11	5.87± 0.11[b]	5.68±0. 19[b]	5.38± 0.27[b]	5.66± 0.13[b]

**b: p<0.001.*

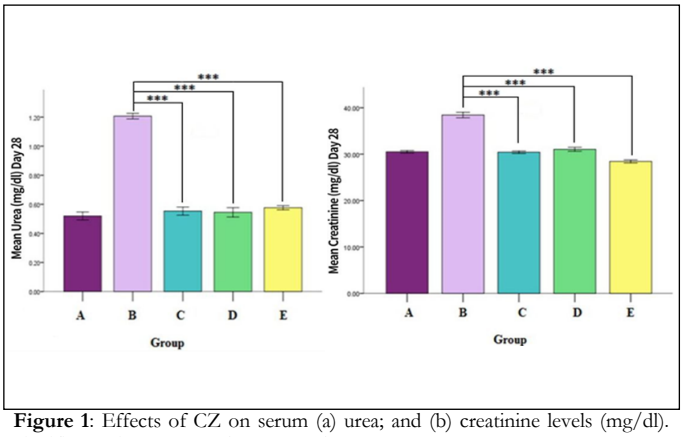

Figure 1: Effects of CZ on serum (a) urea; and (b) creatinine levels (mg/dl). Significance is represented as ***P value <0.001.

Effect of *Cinnamon zeylanicum* (CZ) on serum AST, ALT and total bilirubin

Figure 2 illustrates Day 28 serum level of AST, ALT and total bilirubin for rats in 5 groups. Positive control had higher serum AST, ALT and total bilirubin levels than other groups by the end of the study.

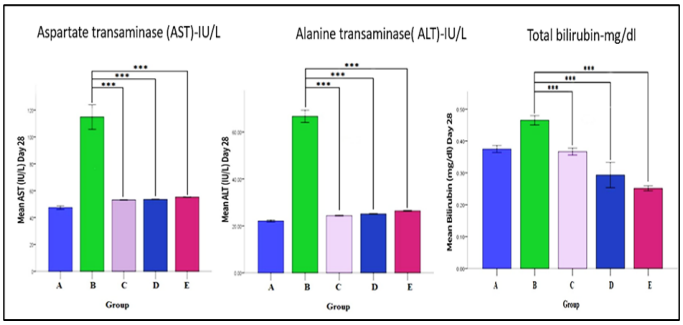

Figure 2: Effect of Cinnamon zeylanicum (CZ) on serum AST, ALT and total bilirubin. Group A is negative control, Group B is positive control, Group C-E are intervention group. *** (p<0.001).

Effect of Cinnamon zeylanicum (CZ) on relative organ weight.

Table 3: Organ weight and relative organ weight across the five groups at Day 28

CZ extract	Dosage in mg/kg	Organ weight (g)		Relative organ weight (g)	
		Liver	Kidney	Liver	Kidney
No	Group-A (Negative control)	9.86±0.08[b]	2.60±0.13 [b]	4.62± 0.06[b]	1.22±0.06[b]
	Group-B (Positive control)	11.91±0.39	3.65±0.17	7.66± 0.35	2.34±1.03
	Group-C (CZ 1000mg/kg)	9.56±0.25[b]	2.55±0.16[b]	4.62± 0.09[b]	1.23±0.08[b]
Yes	Group-D (CZ 1500mg/kg)	9.89±0.12[b]	2.62±0.19[b]	4.51± 0.05[b]	1.19±0.09[b]
	Group-E (CZ 2000mg/kg)	9.87± 0.11[b]	2.60±0.08[b]	4.54± 0.09 [b]	1.20±0.05[b]

[b] *p <0.001.*

Effect of *Cinnamon zeylanicum (CZ)* on the histological changes of kidney

Figure 3(a) shows kidney histology that were observed for tubular epithelial cell damage, presence of casts or crystals, glomerular changes, and inflammation. Results show changes in the positive control group (Group B) with evidence of congestion (CON). These changes were remarkably reduced in the CZ treated groups of rats almost close to the features in negative control groups.

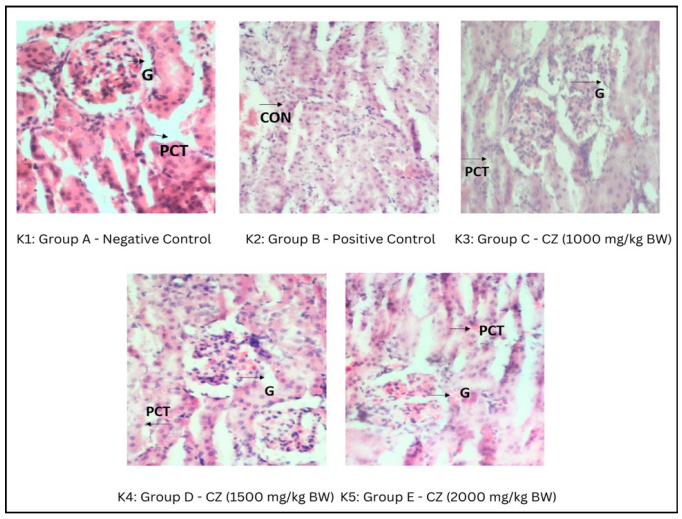

Figure 3(a): Histological section of kidney stained with haematoxylin and eosin at 40x magnification. (K1) Negative control, (K2) Positive control group, (K3, K4, K5) CZ-treated 1000,1500 and 2000 mg/kg respectively. G-Glomerulus; PCT- proximal convoluted tubule; CON-congestion, Blood vessel (BV).

Effect of *Cinnamon zeylanicum (CZ)* on the histological changes of liver

Figure 3(b) shows the liver histology that examined for spotty or zonal liver necrosis, swelling of hepatocytes fatty changes and inflammation. The positive control group shows distorted cellular architecture (DA), intracytoplasmic vacuolation (IV), nuclear karyopyknotic (K) and karyorrhexis (Kr), and congestion (CON) with inflammation (INF). These changes were reduced in all CZ-treated groups.

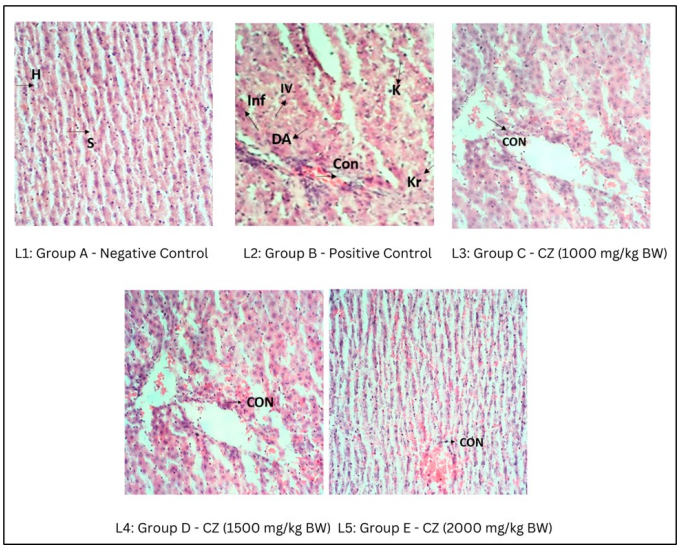

Figure 3(b): Shows liver tissue sections stained with H&E at 40x magnification. L1 represents the negative control, L2 represents the positive control group, and L3-L5 represents CZ-treated groups at different doses. S-sinusoids, H-hepatocytes, DA-distorted cellular architecture, IV-intracytoplasmic vacuolation, K-nuclear karyopyknotic, Kr-karyorrhexis, CON-congestion, INF-inflammation.

Effect of *Cinnamon zeylanicum (CZ)* on gene expression in kidney and liver

Figure 4(a) shows there was up-regulation of Bcl2 and down regulation of Bax gene suggesting no apoptosis seen in the kidney tissue across all intervention group when compared to positive treatment group. This suggest that treatment with CZ has no adverse effect on apoptotic gene expression in kidney tissue.

Figure 4(b) shows there was up-regulation of Bcl2 and down regulation of Bax gene suggesting no apoptosis seen in the liver tissue across all intervention group when compared to positive treatment group. This suggests that treatment with CZ has no adverse effect on apoptotic gene expression in liver tissue.

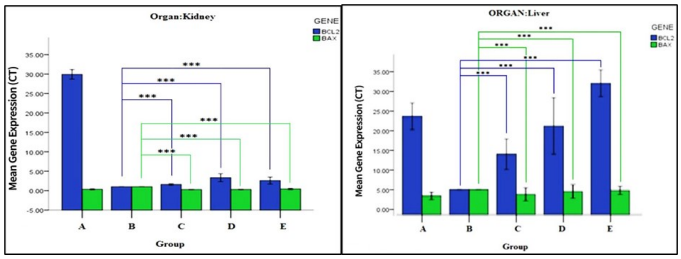

Figure 4: Gene expression graph for a) kidney and b) liver across groups. ***p <0.01.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder with various complications affecting patients' biochemical, histopathological, and haematological states.[11] The goal of treating T2DM is to reduce hyperglycaemia. Although modern medicine has produced synthetic drugs to treat T2DM, research continues to explore alternative plant-based remedies, such as cinnamon, due to their phytochemical content. The gold standard for T2DM animal study uses male Sprague-Dawley (SD) rats because female rats are less sensitive to STZ.[12] In this study the STZ-injected rats developed T2DM. The diabetic rats were treated with *Cinnamon zeylanicum* (CZ) extract, except for the positive control diabetic untreated group. After 28 days of treatment, all intervention groups showed significant weight gain compared to the positive control group, which had significant weight loss. This is consistent with previous reports.[13,14] Diabetes causes weight loss and it may be due to prolonged disease exposure, insulin deficiency, and catabolic effects which can lead to muscle wasting and protein degradation in diabetes.[15] Furthermore, weight loss may also be related to the conversion of glucose into glycogen, fat catabolism, and inhibited lipolysis, which are dependent on insulin action.[16] CZ extract prevents muscle wasting and protein loss, restoring the body weight of diabetic rats.[17] CZ treatment significantly reduce blood glucose levels in diabetic rats compared to positive control but still higher than negative control (Figure 2), which is consistent with previous findings.[18] The reduction in blood glucose is due to the stimulatory effect on cells in Islets of Langerhans and increasing glucose transfer to peripheral organs.[19] The antidiabetic effect of CZ is likely due to the presence of Methyl-hydoxychalone polymer (MHCP), which triggers insulin secretion from β islet cells and activates glycogen synthase while inhibiting glycogen synthase kinase-3.[20]

Phenolic and flavonoid compounds in CZ may prevent and treat T2DM[21] most likely from the enhanced liver enzyme activity, and controlled glucose metabolism, which leads to potential prevention and treatment of T2DM. Phenolic compounds in CZ may regulate glucose uptake by inhibiting carbohydrate digestion and absorption.[22]

Urea and creatinine are biomarkers for kidney disease,[23] and hyperglycaemia is one of the major causes of progressive renal damage. In CZ-treated diabetic rats, urea levels were significantly lower than in untreated rats, similar to the control group. Creatinine was significantly reduced in CZ-treated rats, particularly in the highest CZ dose group (Group E), indicating a greater improvement in hyperglycaemia-induced renal damage.

Total bilirubin, AST, and ALT levels were higher in the positive control group compared to the CZ-treated groups (Figure 2), suggesting increased hepatocellular damage and membrane permeability. Total bilirubin levels showed a dose-dependent change among the CZ-treated groups. Hepatocyte damage may be due to increased oxidative stress and enzyme production disruption.[24] The elevation of total bilirubin could be due to reduced liver reabsorption, conjugation, or an increased total bilirubin synthesis.[25] ALT is a more sensitive and specific indicator of hepatocellular injury in rats than AST.[26] CZ showed hepatoprotective effects on diabetic rats, as evidenced by the non-significant difference in ALT levels between the intervention and negative control groups, consistent with a previous study.[27]

Relative kidney weights were compared between treatment groups. All intervention groups had significantly lower relative kidney weights than the positive control group ($p<0.001$), but there was no significant difference between the negative control and treatment groups. This decrease in relative kidney weight observed in the treatment group is consistent with previous findings on the protection of the kidney from deterioration. Similar pattern of relative weight change was observed for the liver as well. In the present study, we investigated liver and kidney weights as markers of gross anatomy.

Alterations in these weights relative to organ size offer insights into structural attributes. This aids in comprehending potential organ health, including factors like growth or atrophy. CZ treatment caused a reduction in the relative liver weight, as reported by Ahmed et al. (2015).[27] However, Hussain et al. (2021)[26] found that rats treated with *Cinnamon cassia* extract at a dose of 2000 mg/kg had higher absolute liver weights than their respective negative control groups which contained more coumarin and is hepatotoxic. CZ used in this study has minimal coumarin content of 0.001% unlike *Cinnamon cassia* which has up to 1.218% of coumarin content which is more hepatotoxic.[28]

CZ compounds like cinnamaldehyde, phenols, and terpenes are believed to possess antioxidant activity, resulting in a decrease in lipid peroxidation, which may contribute to the decrease in liver weight observed in the study.[29] On the histopathological changes of the kidney, the positive control group showed mild thickening of the glomerular basement membrane and moderate vacuolation of tubular cells in the kidney, indicating the impact of hyperglycaemia and oxidative stress on the renal system as shown in Figure 3(a)-K2.[30] Cellular hypertrophy is likely due to the elevation of cytokines and growth factors in response to hyperglycaemia,[31] and these changes were observed to resolve following treatment with CZ [Figure 3(a): K3-K5]. The improvement in kidney parenchymal congestion following treatment with CZ, may be due to its antidiabetic effect from phenolic contents, as seen in prior study.[32]

A similar study by Qureshi et al. (2019) on alloxan-induced diabetic Wistar rats found that cinnamon can potentially restore kidney histological damages caused by diabetes, attributed to cinnamic acid, anhydride tannin, and methyl-hydroxy chalcone polymer.[18] However, in this study, streptozotocin (STZ) was used to induce type 2 diabetes (T2DM) in Sprague Dawley rats. Al Syaad et al. (2019) observed that 2000mg/kg oral cinnamon cassia showed no organ histopathologic changes, and lesions were incidental as the control group also showed similar changes.[27]

CZ-treated rats showed dose-dependent preservation of normal liver architecture, while the positive control group exhibited moderate fatty changes, congestion, inflammation, sinusoidal dilation, and inflammatory infiltrates. CZ treatment improved liver parenchyma, resolving inflammation in hepatocytes, though mild congestion persisted in all treatment groups. Improving tissue antioxidant state may prevent or ameliorate diabetic issues.[33]

Two previous studies found cinnamon extract to have a similar effect in improving liver damage with congestion.[34] Hyperglycaemia-induced oxidative stress is presumed to be the primary cause of degenerative changes in the liver and kidney in STZ-induced diabetes.[19,35] Improved tissue antioxidants may prevent or alleviate diabetic problems.[34] Flavonoids in cinnamon possess strong antioxidant properties which neutralise harmful free radicals. In a cell death pathway, Bcl-2 inhibits apoptosis, while BAX promotes apoptosis by countering Bcl-2. In diabetics, hyperglycaemia upregulates BAX and downregulates Bcl-2, leading to endothelial dysfunction. [36]

The activation of apoptosis in the liver tissues is one of the consequences of diabetes mellitus.[37] Here, we analyzed Bcl-2 and BAX gene expression in the liver and kidney of diabetic-induced rats and CZ-treated rats at varying doses. BAX and Bcl-2 are vital regulators in programmed cell death, called apoptosis, which maintains tissue balance, removes damaged cells, and prevents harmful mutations. Both belong to the Bcl-2 family, with BAX being pro-apoptotic, triggering cell death by causing mitochondrial membrane permeability and releasing factors like cytochrome c. Bcl-2 is anti-apoptotic, blocking cytochrome c release to maintain mitochondrial integrity and cell survival. The balance between BAX and Bcl-2 determines a cell's response to stress. Imbalances impact cell fate, influencing survival or death pathways. Altered BAX/Bcl-2 ratios are linked to cancer and neurodegenerative disorders.[38] Control samples were used as a reference to detect any changes in gene expression. After CZ treatment, Bcl-2 expression in the kidney was significantly upregulated in Groups C, D, and E compared to the positive control group ($p<0.001$) (Figure 4).

However, there was no significant difference between the negative control and intervention groups. CZ treatment also resulted in a dose-dependent downregulation of the pro-apoptotic gene BAX in the treated groups (Figure 4).

The BAX gene was upregulated in the positive control group, but Bcl-2 was not downregulated as expected. In the negative control and all intervention groups, Bcl-2 was upregulated. CZ treatment resulted in noticeable upregulation of Bcl-2 in Groups D and E, but there was no significant difference in the downregulation of BAX expression among the treated groups. Some studies suggest that herbal medicines may induce cell apoptosis at higher doses[39] however, this was not observed in our study. Certain herbal compounds have been investigated for their potential effects on inducing cell apoptosis, a natural process of programmed cell death that plays a crucial role in maintaining tissue homeostasis and removing damaged cells from the body. These studies often focus on specific compounds or extracts derived from plants, and the mechanisms by which these compounds induce apoptosis can vary.

Apoptosis is tightly regulated and involves various cellular pathways. *In vitro* research suggests that extracts of *M. indica* and its phytochemical components can hinder breast cancer cell growth, migration, and invasion. These compounds also appear to induce apoptosis to pause the cell cycle, and *in vivo* studies confirm reduced breast tumor xenograft growth.[40] Other studies have identified natural compounds with diverse anti-tumor effects, mainly in vitro and in vivo, using colorectal cell lines, experimental models, and a few clinical trials. These compounds induce cell cycle arrest or apoptosis in colorectal cancer cells (CRC cells), suppressing tumor growth. [41]

As reported earlier, these gene expressions were most significant in the convoluted part of the kidney.[42] However, locating the exact area of their expression is challenging, as these genes have roles in kidney and mitochondrial morphogenesis and apoptosis. Previous studies in animal models and cell cultures suggest that acute and chronic hyperglycaemia lead to oxidative stress, which triggers apoptosis in renal cells.[43] High glucose-induced oxidative stress is the main cause of renal glomerular and tubular cell death, leading to increased BAX protein expression and decreased Bcl-2 expression.[44]

These findings align with previous research indicating elevated expression of the pro-apoptotic BAX gene and downregulation of the anti-apoptotic Bcl-2 gene during diabetes.[45] BAX-mediated mitochondrial permeability caused by hyperglycaemia results in ROS-dependent apoptosis of mesangial cells and cytochrome C release.[46] In an intrinsic cell death pathway, Bcl-2 extends cell survival by inhibiting apoptosis. At the same time, BAX counters Bcl-2 activity and promotes entry into the apoptotic program upon receiving a death signal.[37] CZ treatment suppressed apoptosis by downregulating the pro-apoptotic gene and upregulating the anti-apoptotic gene Bcl-2 in a dose-dependent manner, as shown in Figure 4. The intervention Groups (C, D, and E) exhibited significant upregulation of Bcl-2 and downregulation of BAX compared to the positive control group (B) ($p < 0.001$).

Cinnamon modulates Bcl-2 and BAX in mice with acetaminophen-induced liver injury, similar to this study.[47] Apoptosis, characterised by cellular shrinkage, DNA fragmentation, and apoptotic body formation, plays a crucial role in T2DM pathophysiology, including β-cell apoptosis and pancreatic tissue remodelling. Glucose toxicity in insulin-resistant T2DM accelerates β-cell apoptosis.[48]

Apoptosis is regulated by BAX and Bcl-2 signaling pathways.[49] *Cinnamon zeylanicum* (CZ) was shown to protect against hepatotoxicity and nephrotoxicity in rats in this study. Bcl-2 is an anti-apoptotic protein, while BAX is a pro-apoptotic protein.[50] Previous studies have shown that cinnamon can regulate apoptotic pathways, thus preventing excessive cell death and promoting hepatocyte survival. Polyphenols and other bioactive compounds found in cinnamon have potent antioxidant properties. These compounds scavenge free radicals, reducing oxidative stress and preventing cellular damage in the liver.[47] The active components in cinnamon have

been shown to inhibit pro-inflammatory cytokines and enzymes, reducing inflammation within liver tissues and preventing inflammatory damage. Administration of cinnamon influences the phase I and phase II detoxification enzymes in the liver, enhancing the body's ability to metabolize and eliminate harmful substances, inhibit lipid peroxidation, preserve cell membrane integrity, and prevent hepatocellular injury.[48]

Similar to its hepatoprotective effects, the anti-inflammatory and antioxidant properties of cinnamon contribute to reducing oxidative stress and inflammation in renal tissues. Cinnamaldehyde, the bioactive compound found in cinnamon, may contribute to the relaxation of blood vessels, promoting better blood flow to the kidneys and aiding in blood pressure regulation. Furthermore, the vasodilatory potentiol of cinnamon, improves renal blood flow, enhances oxygen and nutrient delivery to renal tissues.[49] Cinnamon might inhibit kidney fibrosis development by influencing extracellular matrix deposition and tissue remodeling pathways. The various components in cinnamon may help maintain mitochondrial function and cellular health in renal cells, contributing to overall renal protection.[50] Overall, the present study suggests using cinnamon supplementation to attenuate oxidative stress, apoptosis, and inflammation in liver and renal tissues. It is important to note that while these mechanisms show promise in experimental and preclinical studies, further research is needed to fully elucidate the detailed mechanisms and establish the clinical applicability of *Cinnamon zeylanicum* for its hepatoprotective and renal protective effects.

CONCLUSIONS

Cinnamon zeylanicum (CZ) can improve diabetic complications through hypoglycaemic and antioxidant effects. It reduces fasting blood glucose, improves liver and kidney function, restores renal and liver histological changes, and regulates Bcl-2 and BAX genes to prevent apoptosis. CZ may reduce the risk of liver and renal complications, prevent pancreatic β-cell apoptosis, and be useful in treating diabetes and prediabetic states.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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