



Research Article

Can cinnamon reduce endoplasmic reticulum stress in diabetic nephropathy?: An experimental rat model

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Abstract

Objectives: The aim was to investigate the effects of cinnamon on the kidney tissue serum endoplasmic reticulum (ER) stress marker, reticulone (RTN)1A, receptor for advanced glycation end products (RAGE) and the lipid peroxidation indicator, malondialdehyde (MDA) in an experimental diabetes mellitus (DM) rat model.

Methods: Twenty-eight male Wistar Albino rats (six months old and weighing 350–400 g) were divided equally into four groups: 1) Control group - citrate buffer (0.2 M, pH 4.4; ip); 2) Cinnamon group - cinnamon (600 mg/kg/day, orogastric tube); 3) DM group - STZ (35 mg/kg, ip); and 4) DM + cinnamon group; Cinnamon and STZ were given at the same doses and route as in Groups 2 and 3, respectively. At the end of the 12-week experiment period, serum, urine and kidney tissue samples were taken from all groups. Serum RTN 1A, RAGE, MDA, urea, blood urea nitrogen (BUN), creatinine levels and kidney tissue RTN 1A, RAGE and MDA levels were measured.

Results: Our biochemical results showed that there was a statistically significant decrease in RAGE and MDA levels in the DM + cinnamon group compared to the DM group ($p < 0.05$). In addition, the decrease in serum urea, BUN, and creatinine levels in the DM + cinnamon group was also remarkable ($p < 0.05$). Although histologically no widespread necrosis was observed, cortical interstitial vascular dilatation was observed in DM+cinnamon group.

Conclusion: Cinnamon was effective in reducing markers of oxidative stress and ER stress including RAGE and MDA, in kidney tissue in an animal model of diabetic nephropathy.

Keywords: Cinnamon, diabetic nephropathy, endoplasmic reticulum stress, malondialdehyde, receptor for advanced glycation end products, reticulone 1A

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Diabetic nephropathy (DN) is a major cause of end-stage renal disease worldwide. Between 20 and 40% of diabetic patients develop DN [1]. DN is characterized by thickening of the glomerular and basement membranes, renal inflammation, tubular interstitial fibrosis, and progressive decrease in kidney function. Proteinuria and microalbuminuria are important markers for evaluating the progression of DN [2, 3].

Chronic hyperglycemia is the main cause of metabolic, biochemical and vascular abnormalities in DN. Oxidative stress (OS) caused by increased levels of reactive oxygen species

(ROS) in the cell, triggered by chronic hyperglycemia, due to mitochondrial dysfunctional cellular respiration and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activity, can lead to DN [4–6]. As a result of OS, critical cellular components, especially protein, lipid, and DNA, are damaged and can lead to podocyte damage, endothelial cell dysfunction, mesangial cell damage, microalbuminuria, and apoptosis in the kidney [7]. Hyperglycemic states can also trigger an unfolded protein response (UPR) by inducing ER stress [5]. It has been suggested that hyperglycemia, protein-

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uria, and increased advanced glycation end products (AGEs) and free fatty acids in DN can trigger UPR in kidney cells, and chronic increased UPR response may result in cell death and increased kidney damage [6–8].

It is thought that the accumulation of AGEs has an important place in the pathophysiology of DN by contributing to the deterioration of ER homeostasis. AGEs show their abnormal effects by binding to their receptor, RAGE. Binding of AGEs with RAGE induces signal transduction and activates ROS production through dysregulation of NOX activity in endothelial cells. ER stress is induced not only in hyperglycemic states but also by hypoxia or oxidative stress, and UPR is triggered [9–11].

Reticulone 1 (RTN1)A is another molecule thought to contribute to ER stress-mediated kidney damage in DN [12]. Reticulones (RTNs) are proteins located in the ER membrane of the cell. There are three human RTN1 isoforms: RTN1A, RTN1B, RTN1C [13]. The human RTN1A protein consists of 776 amino acids, with a hydrophobic region in the ER membrane and hydrophilic regions extending out of the membrane (N-terminal and C-terminal) [14]. Increased expression of RTN1A has been reported to be associated with the progression of DN and the severity of kidney damage, but its mechanism is not yet clear [12, 15]. Increased expression of RTN1A in tubular epithelial cells induces apoptosis through the activation of ER stress [16]. Generally, agents that induce apoptosis at low doses induce necrosis at higher doses. Depending on the severity of exposure to the stimulus, apoptosis and cell necrosis may follow each other, both of which may copresent in most pathological conditions [17]. In this case, RTN1A cell content, indicated by increased renal expression, may be detected in the blood.

Cinnamon is widely consumed around the world as a spice and dietary supplement. The bark of cinnamon is peeled and dried from the body of a small tropical tree. Although there are about 250 types of cinnamon grown in the world, there are two types of cinnamon spices that humans consume: *Cinnamomum* (C.) *zeylanicum* and *C. cassia* [18]. Cinnamon has been shown to modulate glucose and lipid metabolism [19] and has shown pharmacological functions including inhibition of OS, and anti-inflammatory, antihypertensive, and antimicrobial effects [20, 21]. There are also studies suggesting that cinnamon is both preventive of the development of DN and protective against its progression by inhibiting the formation of AGEs [22, 23]. To date, no studies have investigated the impact of cinnamon on diabetic nephropathy (DN) in relation to RTN1A, an established marker of endoplasmic reticulum (ER) stress. In this study, we hypothesized that cinnamon would affect RTN1A, RAGE, and the lipid peroxidation indicator, MDA, in an animal model of DN.

Materials and Methods

Animals

Twenty-eight male Wistar Albino rats, six months old and weighing 350–400 g, were used. All rats were adapted for one week before the experimental procedure. During the adaptation and

treatment periods, all the animals were housed in cages at room temperature (22 ± 2 °C) and humidity ($55\pm 5\%$), and maintained under standard conditions with 12-hour light/dark cycles. They were fed a standard pellet diet and tap water ad libitum throughout the study. The study protocol was approved by the Institutional Animal Care and Ethical Committee of the University. (Approval Number: KOU HADYEK 2/1-2020). The study was designed in accordance with the Helsinki Declaration.

Experimental protocol

After the adaptation period, the rats were divided into four equally sized groups ($n=7/\text{group}$). These groups were: 1) the control group, which received the citrate buffer placebo (0.2 M, pH 4.4; Sigma Aldrich Co., St. Louis, MO., USA) intraperitoneally (i.p), in a single dose. 2) the cinnamon group which received cinnamon (stem barks of *C. Zeylanicum* (Ceylon cinnamon), 600 mg/kg/day) via orogastric tube suspended in distilled water, as previously described [24]; 3) the diabetes mellitus (DM) group, which received streptozotocin (STZ, Cat. No. S0130, Sigma Aldrich, St Louis, MO, USA) at a dose of 35 mg/kg dissolved in 0.2 M pH 4.4 citrate buffer i.p., was given as a single dose, as previously described [25]; And 4) the DM + cinnamon group: Diabetic rats were given cinnamon (600 mg/kg/day, orogastric tube) for 10 weeks.

Three days after STZ injection, rats with blood glucose levels of ≥ 300 mg/dL measured by glucometer (Accu-Chek, Roche, Basel, Switzerland) were considered diabetic and selected for the study [25]. This measurement was used solely as an inclusion criterion and was not part of the follow-up data. The experiment was continued for 12 weeks, including a two-week adaptation period [26]. Blood glucose levels were monitored at baseline and at the end of the first, third, and tenth weeks following STZ administration. Cinnamon was administered simultaneously with the STZ injection.

Collection of blood, urine and tissue samples

Spot urine samples of rats in all groups were collected into Eppendorf tubes and stored at -40 °C until tested. At the end of the experimental period, intracardiac blood was collected from rats in all groups under general anesthesia with 75 mg/kg ketamine + 15 mg/kg xylazine (90 + 12 mg/kg, i.p. single dose). Blood taken into a plain tube was centrifuged at 3500 g for 15 minutes and stored at -40 °C for biochemical analysis. Kidneys were perfused via abdominal aorta with 100 ml of phosphate buffered saline (PBS). Right kidney tissues were weighed, and 1/10 weight/volume PBS (0.1 M and pH 7.4) was added, and the tissues were homogenized. The homogenates were centrifuged at 3500 g for 15 minutes; the supernatants were separated, taken into Eppendorf tubes, and stored at -40 °C until analysis. Left kidney tissues were fixed with Bouin for 48 hours and prepared for routine light microscopy.

Biochemical measurements

In all groups, urea and creatinine levels of serum and urine were measured with an automated chemistry analyzer (AU

Table 1. Serum RTN1A, RAGE and MDA levels in all groups

Parameter	Control group (n=7)	Cinnamon group (n=7)	DM group (n=7)	DM+cinnamon group (n=7)
δ RTN1A (pg/mL)	307.34 $\pm$ 87.67	327.91 $\pm$ 74.40	428.28 $\pm$ 204.44	336.50 $\pm$ 23.68
ψ RAGE (ng/mL)	168.74 $\pm$ 4.27	179.98 $\pm$ 3.76*	186.19 $\pm$ 4.75*	181.26 $\pm$ 3.44*
δ MDA (nmol/mL)	0.76 $\pm$ 0.25	0.86 $\pm$ 0.13	1.48 $\pm$ 0.68**	0.96 $\pm$ 0.07

The values are expressed as mean $\pm$ standard deviation (SD). δ : p values are calculated with Mann-Whitney U test; ψ : p values are calculated with independent sample test; *: Compared with Control group; p<0.05, **: Compared with Cinnamon group; p<0.05. RTN1A: Reticulone 1 (RTN1)A; RAGE: Receptor for advanced glycation end products; MDA: Malondialdehyde; DM: Diabetes mellitus.

Table 2. Renal tissue RTN1A, RAGE and MDA levels in all groups

Parameters	Control group (n=7)	Cinnamon group (n=7)	DM group (n=7)	DM+cinnamon group (n=7)
ψ RTN1A (pg/mg protein)	31.50 $\pm$ 3.24	32.53 $\pm$ 3.17	48.92 $\pm$ 7.86**	36.45 $\pm$ 4.99
δ RAGE (ng/mg protein)	29.58 $\pm$ 1.84	30.69 $\pm$ 1.29	48.72 $\pm$ 8.48**	33.45 $\pm$ 3.06**
δ MDA (nmol/mg protein)	0.14 $\pm$ 0.04	0.15 $\pm$ 0.01	0.33 $\pm$ 0.09**	0.18 $\pm$ 0.10**

The values are expressed as mean $\pm$ standard deviation (SD). ψ : p values are calculated with independent sample test; δ : p values are calculated with Mann-Whitney U test; *: Compared with Control group, p<0.05; **: Compared with Cinnamon group, p<0.05; *: Compared with DM group, p<0.05.

5800, Beckman Coulter Inc., Brea, CA, USA). Rat RTN1A and rat RAGE concentrations in kidney tissue and serum were measured by rat-specific ELISA (Cat. No: 201-11-4817 and Cat. No: 201-11-4438, Sunred Biological Technology Co., Shanghai, China). Serum and kidney tissue malondialdehyde (MDA) concentrations were measured using the method of Buege and Aust [27]. Protein concentrations of tissues were determined by the method of Lowry et al. [28].

Light microscope procedures

Sections were trimmed into 20 μ m sections up to the beginning of the kidney tissue using a Leica SM2000 R microtome (Leica microsystems, Wetzlar, Germany). When the tissue was reached, serial sections of 4–6 μ m were taken. Five preparations were made by skipping ten sections from each kidney. The sections were taken from a hot water bath set at 450°C and mounted on standard glass slides. Then, the sections were stained with either hematoxylin and eosin (H&E) or periodic acid Schiff (PAS). The microscopic structure of kidney tissue was routinely evaluated with H&E. The development of diabetic nephropathy in rats was evaluated according to histopathological criteria. Histologically, necrotic changes in the renal cortex were quantified according to 5 parameters: 1. Interstitial Edema, 2. Epithelial Changes, 3. Tubular Degeneration, 4. Capillary Congestion, 5. Leukocyte Infiltration. PAS stains glomerular capillaries, mesangium, basement membranes of tubules, and Bowman capsules as positive (+). Examination using PAS thus allows for evaluation of the thickness of the basement membrane and possible defects in renal structures. Renal sections from all groups stained with H&E and PAS, were examined under an Olympus Light Microscope (Olympus CX41RF, Olympus Corporation, Tokyo, Japan) and photographed with an Olympus DP26 (Olympus Corporation, Tokyo, Japan) camera.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 10 (GraphPad Software Inc.; San Diego, CA, USA). Normality of data distribution was assessed using the Shapiro–Wilk test. Descriptive statistics were expressed as mean $\pm$ standard deviation (SD) for normally distributed variables. Independent sample t test was employed for normally distributed data, for non-parametric variables, Mann-Whitney U test was performed.

In addition, two-way ANOVA followed by Tukey's post hoc multiple comparison test was conducted to evaluate changes in glucose levels across four time points. All tests were two-tailed, and a p value<0.05 was considered statistically significant.

Results

Effects of cinnamon on serum RTN1A, RAGE and MDA levels

The effects of cinnamon on serum RTN1A, RAGE and MDA levels in this diabetic rat model are shown in Table 1. In the DM group, serum RAGE and MDA levels significantly increased compared to the control group (p<0.05). No statistically significant difference was found between the DM + Cinnamon group and the DM group in terms of any parameter.

Effect of cinnamon on kidney tissue RTN1A, RAGE and MDA levels.

The effects of cinnamon on kidney tissue RTN1A, RAGE, and MDA levels in this diabetic rat model are shown in Table 2. In the DM group, RTN1A, RAGE, and MDA levels were significantly increased compared to the control group (p<0.05). In the DM + Cinnamon group compared to the DM group, a statistically significant decrease was found in RAGE and MDA levels (p<0.05).

Table 3. Effect of cinnamon on serum urea, BUN and creatinine, and urinary albumin and creatinine levels in all groups

Parameters		Control group (n=7)	Cinnamon group (n=7)	DM group (n=7)	DM+cinnamon group (n=7)
Serum	^o Urea (mg/dL)	38.83±2.07	36.65±5.32	57.88±8.55 ^{*&}	39.59±2.27 ⁺
	^o BUN (mg/dL)	18.42±1.13	16.43±2.99	29.58±7.99 ^{&}	17.43±2.99 ⁺
	^ψ Creatinine (mg/dL)	0.34±0.04	0.29±0.08	0.47±0.06 ^{*&}	0.38±0.06 ⁺
Urine	^o Albumin (mg/dL)	2.69±1.13	4.26±1.45	21.85±15.47 ^{*&}	22.33±19.48 ^{*+}
	^o Creatinine(mg/dL)	28.92±10.79	23.32±8.97 [*]	25.84±6.72 [*]	36.15±12.60 [*]

The values are expressed as mean±standard deviation (SD). ^o: p values are calculated with Mann-Whitney U test; ^ψ: p values are calculated with independent sample test;

^{*}: Compared with Control group; p<0.05; [&]: Compared with Cinnamon group, p<0.05; ⁺: Compared with DM group; p<0.05. BUN: Blood urea nitrogen; DM: Diabetes mellitus.

Table 4. Blood glucose concentrations (mean±SD, mg/dL) in control and experimental groups of rats measured at baseline and at 1, 3, and 10 weeks following STZ injection

Experimental groups	Baseline	1 st week after STZ injection	3 rd week after STZ injection	10 th week after STZ injection
Control group	86.6±12.8	81.6±14.2	87.2±13.4	85.4±14.7
Cinnamon group	86.7±9.4	79.6±9.6	88.6±7.2	85.4±8.7
DM group	85.4±6.9	403.6±31.6	410.5±26.2	420.6±21.6
DM+cinnamon group	87.6±8.7	352.8±28.7	342.8±24.6	345.6±26.1
Group comparison	Baseline	1 st week	3 rd week	10 th week
Control vs. cinnamon	NS	NS	NS	NS
Control vs. DM	NS	p<0.001	p<0.001	p<0.001
Control vs. DM+cinnamon	NS	p<0.001	p<0.001	p<0.001
Cinnamon vs. DM	NS	p<0.001	p<0.001	p<0.001
Cinnamon vs. DM+cinnamon	NS	p<0.001	p<0.001	p<0.001
DM vs. DM+cinnamon	NS	p<0.001	p<0.001	p<0.001

The values are expressed as mean±standard deviation (SD). Results of two-way ANOVA followed by Tukey's post hoc multiple comparison test. SD: Standard deviation; STZ: Streptozotocin; DM: Diabetes mellitus; NS: Non-significant.

Effect of cinnamon on serum and urine parameters

Serum urea, BUN, and creatinine, and urine albumin and creatinine levels in the four groups are shown in Table 3. DM group: Serum urea, BUN, creatinine and urinary albumin levels significantly increased compared to the control group, while urinary creatinine levels decreased (p<0.05). Serum urea, BUN, and creatinine levels were significantly decreased in the DM + Cinnamon group compared to the DM group (p<0.05).

Blood glucose levels were analyzed after the STZ injection, at the 1st, 3rd, and 10th weeks, and it was determined that diabetes developed in the rats. Two-way ANOVA with Tukey's post-hoc multiple comparison test demonstrated that baseline glucose values did not differ among groups. From week 1 onward, diabetic (DM) animals exhibited markedly elevated glucose levels compared with controls (p<0.001). Cinnamon supplementation in DM animals produced a significant, progressive reduction in glucose concentrations versus DM alone (week 1: -50.8; week 3: -67.7; week 10: -75.0 units; all p<0.001), while no differences were observed between Control and Cinnamon groups at any time point (Table 4).

Histological evaluation

Normal parenchymal morphology of glomeruli, Bowman's capsular spaces, and tubules were observed in the kidney sections of the Control group under light microscopy. Tubules and arterioles were observed in the areas between the glomeruli. Larger arteries and vessels were traced at the interface between cortex and medulla. Only tubules and blood vessels were observed in the medulla. PAS staining revealed that the basement membranes in the tubules the Bowman capsule surrounding the glomeruli were thin (Fig. 1a-d). Similar morphological findings were observed in the Cinnamon group (Fig. 1e-h).

Granulo-vacuolar epithelial cell degeneration areas, and desquamation in tubules, hyaline cast, and leukocytic infiltration were observed in the DM and DM + cinnamon groups (Fig. 1i-p). PAS staining enabled examination of basement membrane thickness of renal tubules and Bowman capsules. PAS (+) areas in both the DM and DM + cinnamon group kidney sections, and PAS (+) staining in glomerulo-basement membranes were increased in comparison to tissues obtained from control animals (Fig. 1d, h, l, p).

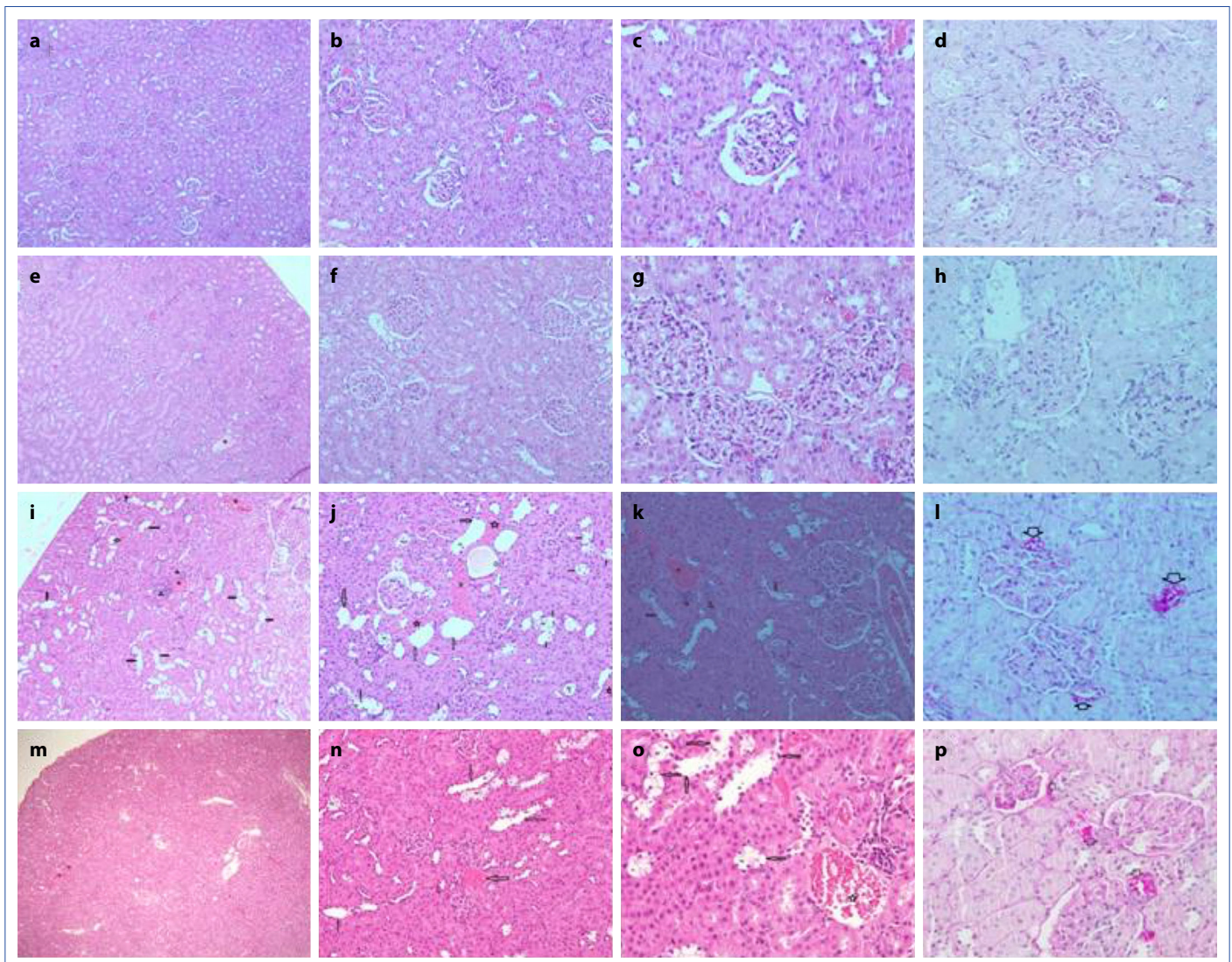


Figure 1. Photomicrographs of diabetic rats showing the effects of cinnamomum zeylanicum treatment on renal histology.

Histopathological changes were more prominent in the DM group (Fig. 1i-l) compared to the DM + cinnamon group (Fig. 1m-p). Although no widespread necrosis was observed, cortical interstitial vascular dilatation was observed in the DM+cinnamon group, (Fig. 1m-o).

These histological results suggest that cinnamon ingestion in the DM + cinnamon group did not completely eliminate microscopic renal damage. However, renal damage was not as common as in the DM group.

Discussion

This study demonstrates that cinnamon supplementation has significant effects on endoplasmic reticulum (ER) stress and oxidative stress (OS) in diabetic nephropathy (DN). In particular, RAGE and MDA levels in renal tissue were found to be significantly lower in the DM + cinnamon group compared with the DM group, suggesting an improvement in stress-related molecular pathways. Histologically, renal tissue damage such as tubu-

lar degeneration, leukocytic infiltration, vascular dilatation, and PAS(+) thickening of the glomerular basement membrane was observed in the diabetic groups; however, the severity of these changes was less pronounced in the DM + cinnamon group. Overall, these findings indicate that cinnamon intake reduced necrotic areas and alleviated renal damage in diabetic rats.

DN is one of the major microvascular complications of DM. The formation of AGEs, associated with hyperglycemia, is thought to play a central role in the pathophysiology of DN [29]. RAGE, a transmembrane receptor belonging to the immunoglobulin superfamily and found in almost all cell types in the kidney, plays key roles in innate immunity and inflammatory processes [30, 31]. It has been shown that increased AGEs due to DM stimulate RAGE expression in the kidneys [32]. It is thought that RAGE activation induces OS, ER stress, and UPR activation by stimulating NOX-mediated ROS production, causing inflammation, glomerular hypertrophy, podocyte damage and renal fibrosis. NOXs are sources of ROS, induced ER stress in kidney cells, and NOX

activity is induced by hyperglycemia, aggregation of AGEs, and activation of protein kinase C (PKC) [33]. UPR consists of three main signaling pathways initiated by the activation of three ER membrane receptors: Activating transcription factor 6 (ATF 6), enzyme 1 α that requires inositol (IRE1 α), and pancreatic ER eIF2 α kinase (PERK) [34]. These UPR-transducer proteins form the inflammatory signal cascade and regulate the expression of pro-inflammatory gene products through nuclear factor- κ B (NF- κ B) as well as other ER stress-inducible transcription factors that modulate ER functions [35]. Consistent with our study, Neto et al. [36] also concluded that cinnamaldehyde treatment reduced ER stress.

An interaction between ER stress and OS has been shown during the development and progression of DN [37]. OS can cause chronic inflammation in kidney tissue, tubule-interstitial fibrosis, and renal hypertrophy. It may also contribute to thickening of tubular and glomerular membranes, podocyte dysfunction, and development of apoptosis [38]. OS caused by chronic hyperglycemia can lead to metabolic and cellular disorders, including lipid peroxidation, protein oxidation, and DNA damage. Non-enzymatic glycosylation of endogenous antioxidants may also contribute to increased OS. Consequently, an imbalance between pro-oxidant and antioxidant processes in DN results in an increase in ROS [39]. The mechanisms of ROS formation in chronic hyperglycemia include oxidative phosphorylation of glucose, which may inhibit regeneration of reduced glutathione and increase superoxide production due to excessive consumption of NADPH in the polyol pathway, AGEs production, mitochondrial respiratory processes, and separation of NOX [40]. In a study investigating the effects of cinnamon on DN, it was reported that procyanidin-B2, one of the active metabolites of cinnamon, inhibited the accumulation of AGEs in diabetic rat kidney, caused a decrease in urinary albumin and creatinine levels, and that it had a curative effect on AGEs-mediated pathogenesis of DN. Recent reports have shown that accumulation of AGEs induced apoptosis through ER stress in various cell types, including glomerular mesangial cells [41, 42]. In agreement with these studies, our results suggest that cinnamon has a protective effect against ER stress by reducing the RAGE level.

Recent studies have suggested that RTN1A analysis plays a critical role in the development of renal tubular cell damage and renal fibrosis [16]. In our study, RTN1A levels in kidney tissue were significantly higher in the DM group compared to the control groups. However, there was no lowering effect of cinnamon on RTN1A levels. These results may be due to the dose, and duration of the cinnamon applied to the experimental groups. The increased expression of RTN1A was associated with progression of DN and the severity of kidney damage [15]. RTN1A has been shown to contribute to both glomerular and tubular cell damage in DN through regulation of ER stress. Fan et al. [6] showed that RTN1A interacts with PERK through its N-terminal and C-terminal domains, and mutation of these PERK domains prevents ER

stress [12]. PERK is known as an important UPR sensor in ER and is activated by phosphorylation under ER stress. Overexpression of RTN1A is thought to increase PERK phosphorylation in kidney cells, leading to the expression of the C/EBP homologous protein (CHOP), a transcription factor that is activated during ER stress [43].

Cinnamon is thought to modulate the production of antioxidant glutathione and phase II detoxifying enzymes, and can prevent the initiation and progression of DN by removing ROS through the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) [44, 45]. In agreement with these studies, in our study, the concentrations of the lipid peroxidation product, MDA, in the DM + cinnamon group were significantly lower than in the DM group. Similarly, Mishra et al. [46] showed that cinnamon reduces lipid peroxidation products and increases antioxidant capacity in a dose-dependent manner (5, 10, 20 mg/kg; i.p.) in the DN model.

In our study, cinnamon administration markedly improved serum markers of renal dysfunction, including serum urea, BUN, and creatinine, in diabetic rats. These findings are consistent with previous experimental studies demonstrating that cinnamon or its active components, such as cinnamaldehyde, reduce serum urea and creatinine levels and ameliorate renal histopathology in STZ-induced diabetic models [47–49]. This effect of cinnamon may be attributed to its antioxidant and anti-inflammatory properties, which alleviate oxidative stress and metabolic disturbances commonly associated with diabetic nephropathy [50].

However, despite the improvements in serum biochemical parameters, urinary albumin excretion remained elevated in the cinnamon-treated diabetic group compared with the DM group. This finding contradicts some studies reporting that cinnamon or its bioactive fractions reduced albuminuria in diabetic rats [23, 51], but it may indicate that the impact of cinnamon on glomerular permeability depends on the formulation, dose, and duration of treatment. Our results suggest that, at the dose and duration applied in our study, cinnamon ameliorated metabolic and oxidative stress-related damage but showed limited ability to reduce proteinuria.

We have shown both biochemical and histopathological changes in kidney tissues in diabetic animals supplemented with cinnamon. Our histological results suggested that cinnamon ingestion in the DM cinnamon group did not eliminate completely microscopic renal damage. However, it should be kept in mind that biochemical changes are likely to be detectable before histopathological changes are evident using basic light microscopy. Therefore, we believe that further studies are warranted using different cinnamon doses and different measures of ER stress and OS in DN models. In addition, performing histological evaluations by more sensitive methods, such as electron microscopy, may allow us to both observe the damage in more depth and show the possible protective effect of cinnamon in more detail.

Conclusion

These data suggest that cinnamon exerts a protective effect against DN in STZ-induced diabetic rats by reducing the ER stress response and OS. Cinnamon may have a role as an additional supportive agent in preventing the development of diabetic complications, especially those caused by the AGEs and the OS-mediated pathologies such as diabetic nephropathy. However, larger prospective animal studies followed by clinical trials would be necessary to confirm and expand upon these findings.

Ethics Committee Approval: The study was approved by the Kocaeli University Institutional Animal Care Local Ethics Committee (no: 2/1-2020, date: 27/02/2020).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest Statement: The authors have declared that no competing interests exist.

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