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Extract of the aerial parts of *Aster koraiensis* reduced development of diabetic nephropathy via anti-apoptosis of podocytes in streptozotocin-induced diabetic rats

Eunjin Sohn, Junghyun Kim, Chan-Sik Kim, Young Sook Kim, Dae Sik Jang, Jin Sook Kim *

Diabetic Complications Research Center, Division of Traditional Korean Medicine (TKM) Integrated Research, Korea Institute of Oriental Medicine (KIOM), 483 Exporo, Yuseong-gu, Daejeon 305-811, South Korea

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ABSTRACT

Advanced glycation end products (AGEs) is produced from glycolysis *in vivo*, which may result in diabetic nephropathy. Podocyte loss has been implicated in the development of diabetic nephropathy. The aim of this study was to investigate the protective effects of *Aster koraiensis* extract (AKE), on the damage of renal podocytes in streptozotocin (STZ)-induced diabetic rats. AKE (100, 200 mg/kg per day) was given to diabetic rats for 13 weeks. Blood glucose, glycated haemoglobin (HbA1c), proteinuria and albuminuria were examined. Kidney histopathology, AGEs accumulation, apoptosis, and expression of Bax and Bcl-2 also were examined. In 20-week-old STZ-induced diabetic rats, severe hyperglycemia was developed, and proteinuria and albuminuria were markedly increased. TUNEL-positive signals were highly detected in glomeruli of STZ-induced diabetic rats. However, AKE reduced proteinuria and albuminuria in diabetic rats. AKE prevented AGEs deposition and podocyte apoptosis. Expression of Bax and Bcl-2 protein were restored by AKE treatment in the renal cortex. These results suggested that AKE has an inhibitory effect of AGE accumulation and anti-apoptotic effect in the glomeruli of diabetic rat. AKE could be beneficial in preventing the progression of diabetic nephropathy.

Diabetic nephropathy is an important complication of both type 1 and type 2 diabetic mellitus [1]. The clinical hallmarks of diabetic nephropathy include progressive albuminuria followed by a gradual decline in renal function. Glomerular basement thickening and mesangial expansion have been identified as pathological precursor of these clinical changes [2]. The loss of glomerular podocytes precedes and predicts the onset of clinical nephropathy and may be an early pathological manifestation of diabetic nephropathy [3,4]. Podocytes are one of the important ingredients of filtration barrier which has special cytobiological characteristic and physiological function. The injury of podocytes can unavoidably lead to the occurrence of proteinuria [5].

Advanced glycation end products (AGEs) are a complex, heterogeneous and sugar derived irreversible protein modifications that have been implicated in the pathogenesis of diabetic complications [6,7]. The irreversible formation of AGEs affects proteins and lipids, such as hemoglobin, collagen and lipoprotein, and causes damage to the kidney, eyes and blood vessels [8]. The levels of AGEs are much higher in patients with diabetes [6]. Moreover, it was reported that AGEs induced apoptosis of murine cultured podocytes. AGEs has been proposed for the potential causative factor of podocyte damage [9].

Some medicinal herbs have been used widely for the treatment of diabetes and diabetic complications for hundreds of years [10,11]. In the past few years, many herbal extracts have been screened for possible AGEs inhibitory effects *in vitro* in our laboratory. *Aster koraiensis* (*A. koraiensis*) is a valuable species as a Korean endemic perennial among many plants native to Korea. *A. koraiensis* is widely distributed in the southern and the central part of Korean peninsula and Jeju island, and it has also been cultivated and marketed as ground cover and bedding plant in Korea [12]. This herb has also been utilized as pot plant, vegetable and medicinal plants in traditional Korean medicine for a variety of medical purposes, such as pertussis, chronic bronchitis and pneumonia [13,14]. However, the effect of this herb on diabetes and diabetic complications is unclear. Therefore, in this study, we examined the preventive effect of an ethanol extract of the aerial parts of *A. koraiensis* on the injury of diabetic glomerular podocytes in streptozotocin (STZ)-induced diabetic rats.

Materials and methods

Plant materials. The aerial parts of *A. koraiensis* were collected from Euidang-myun, Gongju city, Chungchengnam-do, Korea, dur-

* Corresponding author. Fax: +82 42 868 9471.
E-mail address: jskim@kiom.re.kr (J.S. Kim).

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ing August 2007, and identified by Prof. Joo-Hwan Kim, Department of life science, Kyungwon University, Kyounggi-do 300-716, Korea. A voucher specimen (No. KIOM-83A) of the sample were deposited in the Herbarium of the Diabetic Complications Research Center, Korea Institute of Oriental Medicine (KIOM).

Preparation of A. koraiensis extract (*AKE*). The dried and ground plant material (2.5 kg) was extracted with EtOH (3 × 20 l) by maceration at room temperature for 3 days. The extracts were combined and concentrated *in vacuo* at 40 °C to give an EtOH extract (AKE, 303 g). For the standardization of AKE, the contents of the two major components, chlorogenic acid and 3,5-di-*O*-caffeoylquinic acid, in AKE were determined by HPLC analysis (data not shown). The contents of chlorogenic acid and 3,5-di-*O*-caffeoylquinic acid in AKE were 1.24 ± 0.02 and 2.25 ± 0.05%, respectively.

Animals and induction of diabetes. The experiments were performed according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and approved by the Korea Institute of Oriental Medicine Institutional Animal Care and Use Committee. Diabetes was induced by a single injection of streptozotocin (STZ, 60 mg/kg, i.p.) in rats. Age-matched control rats (aged 7 weeks) received an equal volume of vehicle (0.01 M citrate buffer, pH 4.5). Two days after injection, the blood glucose level was measured from the tail vein. Rats with a blood glucose level over 300 mg/dl were considered as diabetes-induced rats. To investigate the effects of AKE, treatment was begun 1 week after the onset of diabetes and the compound was administered to the rats a day orally for 13 weeks. The animals were divided into five groups: (1) normal SD rats (NOR, $n = 8$), (2) STZ-induced diabetic rats (DM, $n = 8$), (3) STZ-induced diabetic rats treated with aminoguanidine, a positive control for AGEs inhibitor (DM + AG, 100 mg/kg body weight, $n = 8$) (4) STZ-induced diabetic rats treated with AKE (DM + AKE-100, 100 mg/kg body weight, $n = 8$) and (5) STZ-induced diabetic rats treated with AKE (DM + AKE-200, 200 mg/kg body weight, $n = 8$).

Metabolic and morphological analysis. When the rats reached 20 weeks of age, blood glucose and HbA1c (A1C) were measured using an automated analyzer (Wako, Japan). Blood samples were collected from the tail vein after a 16-h fast. Individual rats were placed in metabolic cages to obtain 24-h urine collections, and urinary protein and albumin excretion levels were measured. Renal cortexes were fixed in 10% formaldehyde and embedded in paraffin, and 4 μm thick sections were prepared. The sections were stained with periodic acid-Schiff (PAS) reagent and haematoxylin as a counterstain.

Quantification of AGEs in serum. AGEs in serum were measured by a competitive enzyme-linked immunosorbent assay (ELISA). The assay was performed using a monoclonal AGEs antibody (6D12, Wako, Osaka, Japan) as previously described [15].

Immunohistochemical and immunofluorescent staining. Renal cortexes were fixed in 10% formaldehyde and embedded in paraffin, and 4 μm thick sections were prepared. Staining was performed as previously described [16]. Antibodies were mouse anti-AGEs (Transgenic Inc., Kobe, Japan), rabbit anti-synaptopodin (1:250, Santa Cruz, CA, USA) and rabbit anti-Wilms tumor antigen-1 (WT-1, 1:250, Santa Cruz), rabbit anti-Bax (1:200, Santa Cruz) and rabbit anti-Bcl-2 (1:250, Cell Signaling, MA, USA). For detection of AGEs, Bax and Bcl-2, the sections were incubated with the Envision kit (DAKO, CA, USA) and visualized by 3,3′-diaminobenzidine tetrahydrochloride. To detect synaptopodin and WT-1, the sections were incubated with fluorescein-conjugated goat anti-rabbit IgG (Santa Cruz) and Texas red-conjugated goat anti-rabbit IgG (Santa Cruz), respectively and detected by fluorescence microscopy (Olympus). Negative controls for immunohistochemistry were run by incubating the sections with nonimmune serum instead of the primary antibody. For morphometric analysis, the positive cell numbers or positive signal areas per one glomerulus in a total of 40 glomeruli was determined using Image J software (NIH, Bethesda, MD, USA).

TUNEL assay. TUNEL staining was performed with a kit (in situ cell death detection kit, AP, Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions. Apoptotic cells were detected with a color solution containing nitroblue tetrazolium (NBT, Roche Diagnostics) and 5-bromo-4-chloro-3-indolylphosphate (BCIP, Roche Diagnostics). For quantitative analysis, TUNEL-positive cells were then counted per one glomerulus in a total of 40 glomeruli.

Statistical analysis. Data are expressed as means ± SEM and analyzed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test or by unpaired Student's *t*-test using GraphPad *Prism 5.0* software (Graph pad, San Diego, CA, USA). Differences with a value of $P < 0.01$ were considered statistically significant.

Results

Body weight and metabolic parameters in blood

In STZ-induced diabetic rats at 20 weeks of age, body weight was decreased compared with normal rats and did not change compared with rats that treated AG or AKE. Blood glucose and HbA1c levels were significantly increased in STZ-induced diabetic rats ($P < 0.01$ vs. normal rats). However, no differences in blood glucose and HbA1c were noted between treated and untreated STZ-induced diabetic rats (Table 1).

Morphology and renal function

Mesangial matrix expansion is considered a hallmark of diabetic nephropathy. At 20 weeks of age, STZ-induced diabetic rats showed focal mesangial matrix expansion and proteinuria and albuminuria were significantly increased in STZ-induced diabetic rats compared to normal rats (Fig. 1A). AG and AKE treatment ameliorated mesangial expansion, proteinuria and albuminuria compared with the untreated STZ-induced diabetic rats (Fig. 1B,C).

Quantitation of AGEs in the renal glomerulus and serum

In our preliminary study, AKE exhibited inhibitory activity on AGEs formation *in vitro* (data not shown). Here, we evaluated

Table 1
Metabolic and physical parameters.

	NOR	DM	DM + AG	DM + AKE-100	DM + AKE-200
Body weight (g)	475.9 ± 10.7	208.5 ± 12.1*	210.3 ± 9.9	205.5 ± 23.1	206.0 ± 16.4
Blood glucose (mg/dl)	162.1 ± 11.3	587.3 ± 43.5*	494.9 ± 66.4	530.3 ± 58.1	474.2 ± 88.4
HbA1c (%)	3.86 ± 0.02	8.43 ± 0.20*	8.41 ± 0.29	8.72 ± 0.25	9.95 ± 0.94

NOR, normal rat; DM, STZ-induced diabetic rat; DM + AG, DM treated with AG (100 mg/kg); DM + AKE-100, DM treated with AKE (100 mg/kg); DM + AKE-200, DM treated with AKE (200 mg/kg). All data were expressed as means ± SEM. *$P < 0.01$ vs. NOR group.

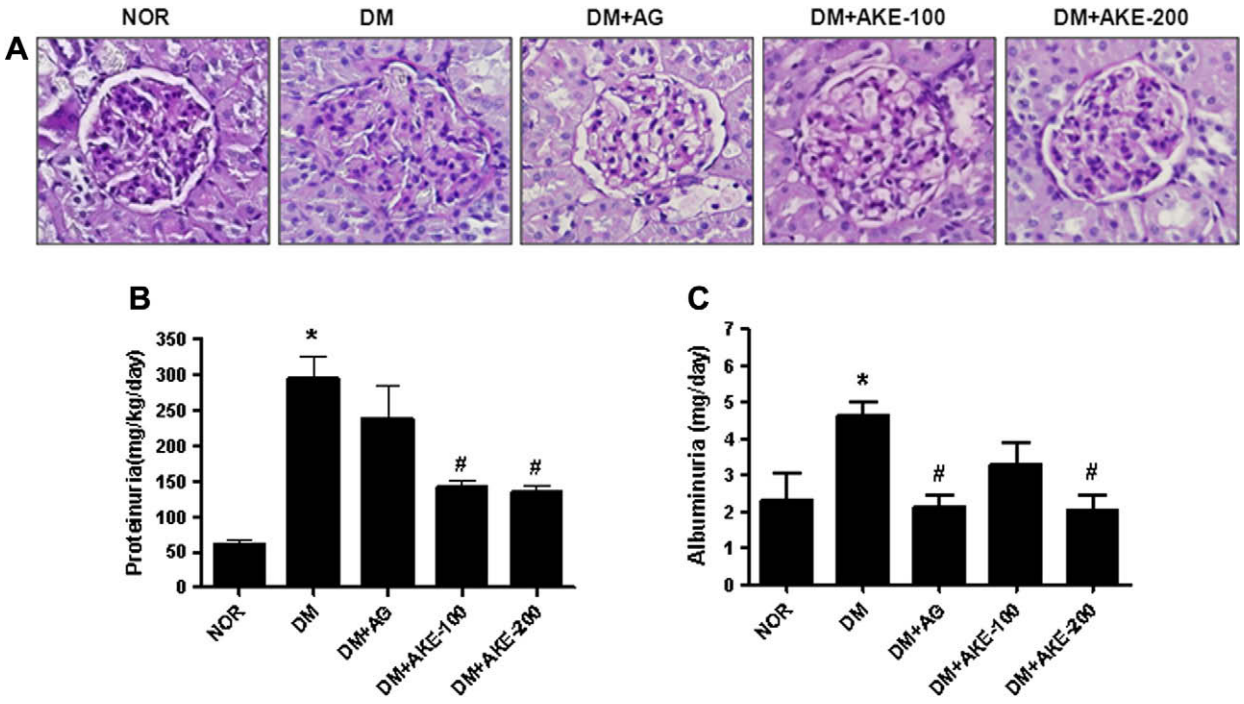

Fig. 1. Renal histopathology and function. (A) Periodic acid-Schiff staining of glomeruli. ×400 magnification. (B) Proteinuria and (C) albuminuria. NOR, normal rat; DM, STZ-induced diabetic rat; DM + AG, DM treated with AG (100 mg/kg); DM + AKE-100, DM treated with AKE (100 mg/kg); DM + AKE-200, DM treated with AKE (200 mg/kg). All data were expressed as means ± SEM ($n = 8$). $^{*}P < 0.01$ vs. NOR group, $^{\#}P < 0.01$ vs. DM group.

whether AKE has the preventive effect on formation of AGEs in renal glomerulus and serum. Immunohistochemical staining of AGEs in the glomeruli demonstrated a significant increase in STZ-induced diabetic rats as compared with normal rats. This was attenuated by AG as well as AKE (Fig. 2A). Serum AGEs levels were increased in the diabetic rats. AKE reduced these diabetes-induced increases in serum AGEs in a dose-dependent manner (Fig. 2B).

Apoptosis of renal podocytes in STZ-induced diabetic rats

To determine the anti-apoptotic effect of AKE, TUNEL assay was performed. In STZ-induced diabetic rats, TUNEL-positive cells per glomerular section were significantly increased compared with normal rats (Fig. 3A). AG and AKE treatment were effective in reducing apoptosis in STZ-induced diabetic rats. Average numbers of podocytes per glomerular section were determined by counting

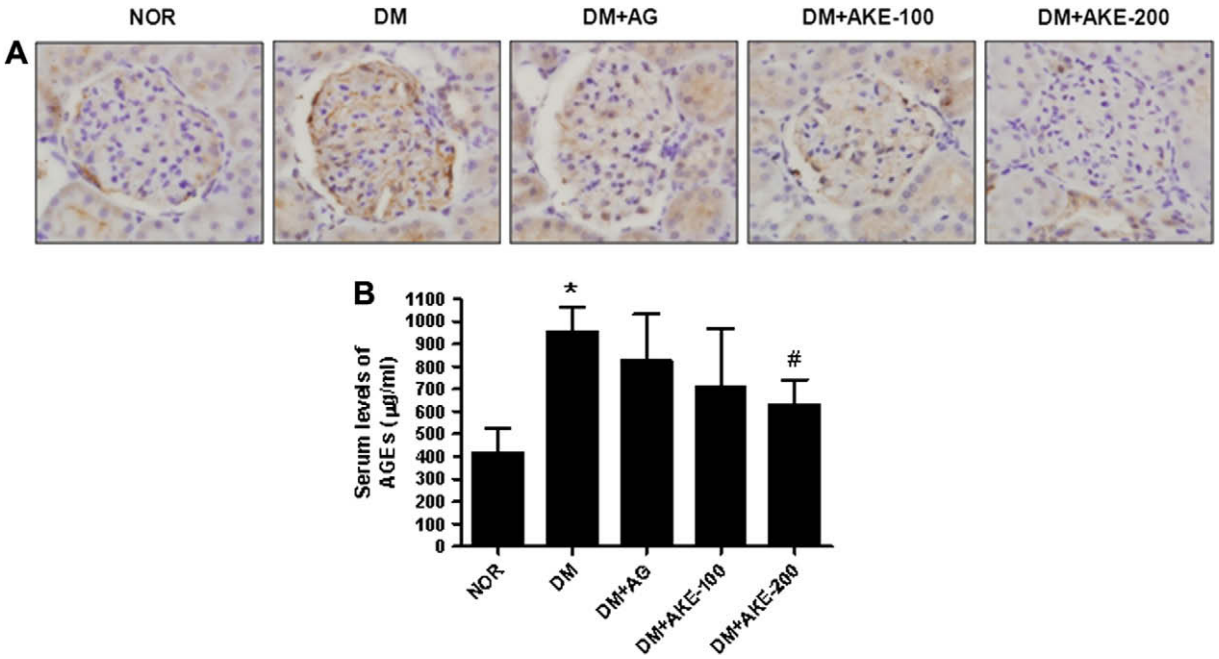

Fig. 2. Effect of AKE on AGEs accumulation in the renal glomerulus and serum. (A) Immunohistochemical staining for AGEs. ×400 magnification. (B) AGEs concentrations in serum were determined by ELISA. All data were expressed as means ± SEM ($n = 8$). $^{*}P < 0.01$ vs. NOR group, $^{\#}P < 0.01$, vs. DM group.

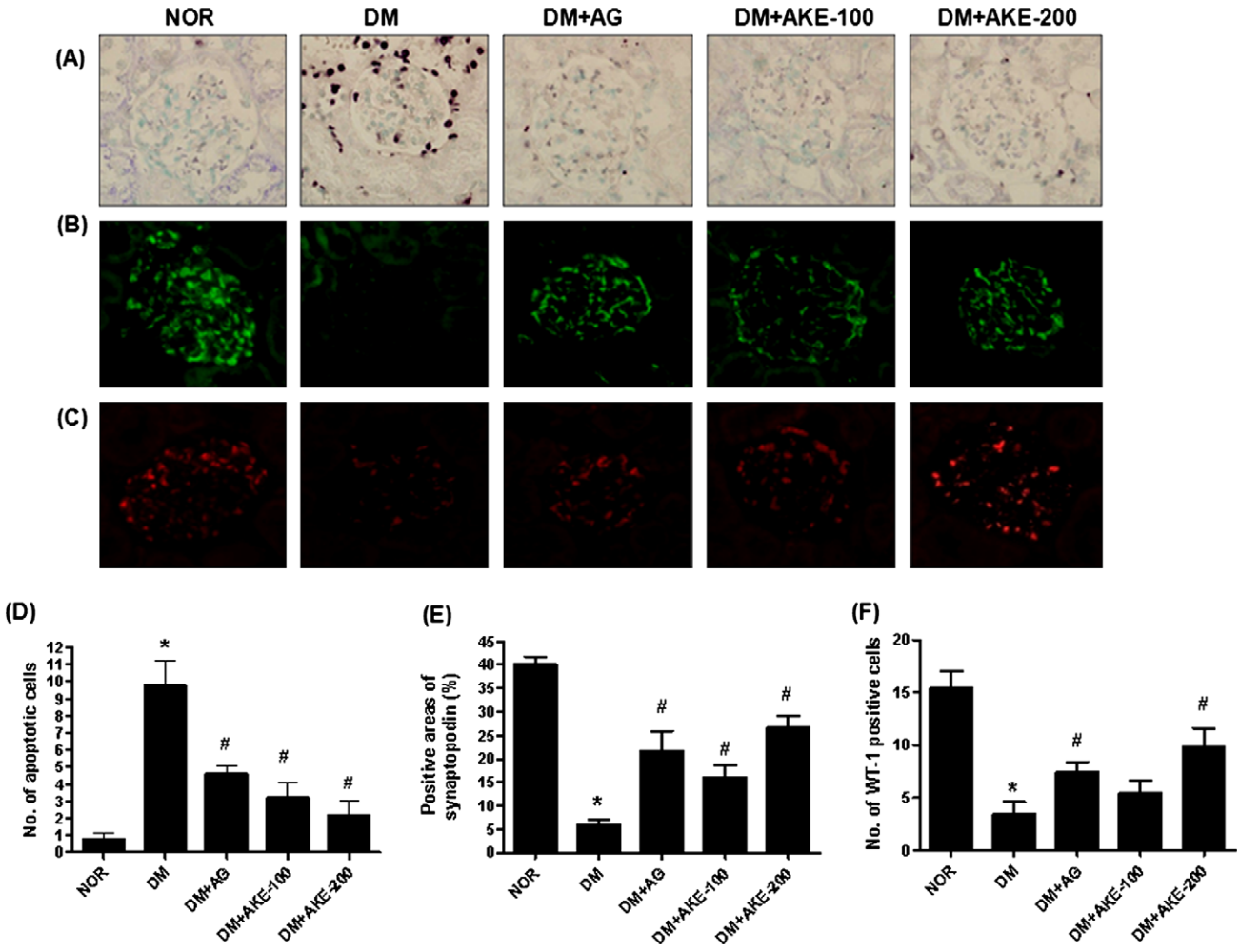

Fig. 3. Anti-apoptotic effect of AKE in the renal podocyte. A representative photomicrograph of (A) TUNEL, (B) synaptopodin, and (C) WT-1 in the glomerulus. ×400 magnification. Renal cortex from rats was stained using specific antibodies for synaptopodin and WT-1, which are specific markers of podocytes. Quantitative analyses of (D) apoptotic cells, (E) positive areas of synaptopodin and (F) positive cells of WT-1. All data were expressed as means ± SEM ($n = 8$). $^{*}P < 0.01$ vs. NOR group, $^{\#}P < 0.01$ vs. DM group.

cells and measuring areas that were positively labeled with two podocyte markers, such as synaptopodin and WT-1 [17,18]. In STZ-induced diabetic rats, synaptopodin and WT-1 positive cell counts tended to decrease compared with age-matched normal rats. Treatment with AG and AKE visibly increased the positive cells and areas in the kidney glomeruli (Fig. 3B,C).

Expression of Bax and Bcl-2 in renal glomeruli

To investigate the effect of AKE on apoptosis of renal podocytes, we measured the expression of pro-apoptotic Bax protein and anti-apoptotic Bcl-2 protein in renal glomeruli. In STZ-induced diabetic rats, the immunohistochemical staining for Bax revealed that the strong immunoreactivity of Bax was detected in renal glomeruli (Fig. 4A), and Bcl-2 immunoreactivity decreased (Fig. 4B). These proteins in the glomeruli were restored in diabetic rats treated with AG and AKE.

Discussion

A. koraiensis traditionally has been used for the purpose of food, medicine or health in Korea. Our previous studies showed that AKE exhibits stronger inhibitory activity against AGEs formation *in vitro* than AG (data not shown). The results of this study showed that AKE, an herbal inhibitor of AGEs formation, reduced the development of diabetic nephropathy in STZ-induced diabetic rats. Our current study confirmed that AKE-treated diabetic rats showed significant improvement in renal functions such as proteinuria and albuminuria. In addition, AKE prevented AGEs accumulation in the diabetic kidney, and reduced apoptosis of podocyte.

Although various initiators of diabetic nephropathy have been proposed, including glycation, polyol pathway and oxidative stress, one of the major consequences of hyperglycemia is the formation of AGEs. The formation of AGEs in renal tissue closely correlated with the development of diabetic nephropathy [19,20]. The loss of resident glomerular cells through apoptosis has recently been shown to occur in STZ-induced diabetic rats [21]. Hyperglycemia is present in STZ-induced diabetic rats, and diabetic nephropathy and podocyte loss progress rapidly in this model [22]. AGEs have been reported to induce apoptosis in mesangial cells [23], endothelial cells [24] and retinal pericytes [25]. It was recently reported that oxidative stress or pro-apoptotic cytokine through interaction AGEs and receptor for AGEs were involved in podocyte apoptosis under diabetic condition [24,26,27].

There is considerable interest in inhibitory compounds of AGEs formation because of their therapeutic potential [28,29]. Several natural and synthetic compounds have been proposed as inhibitors

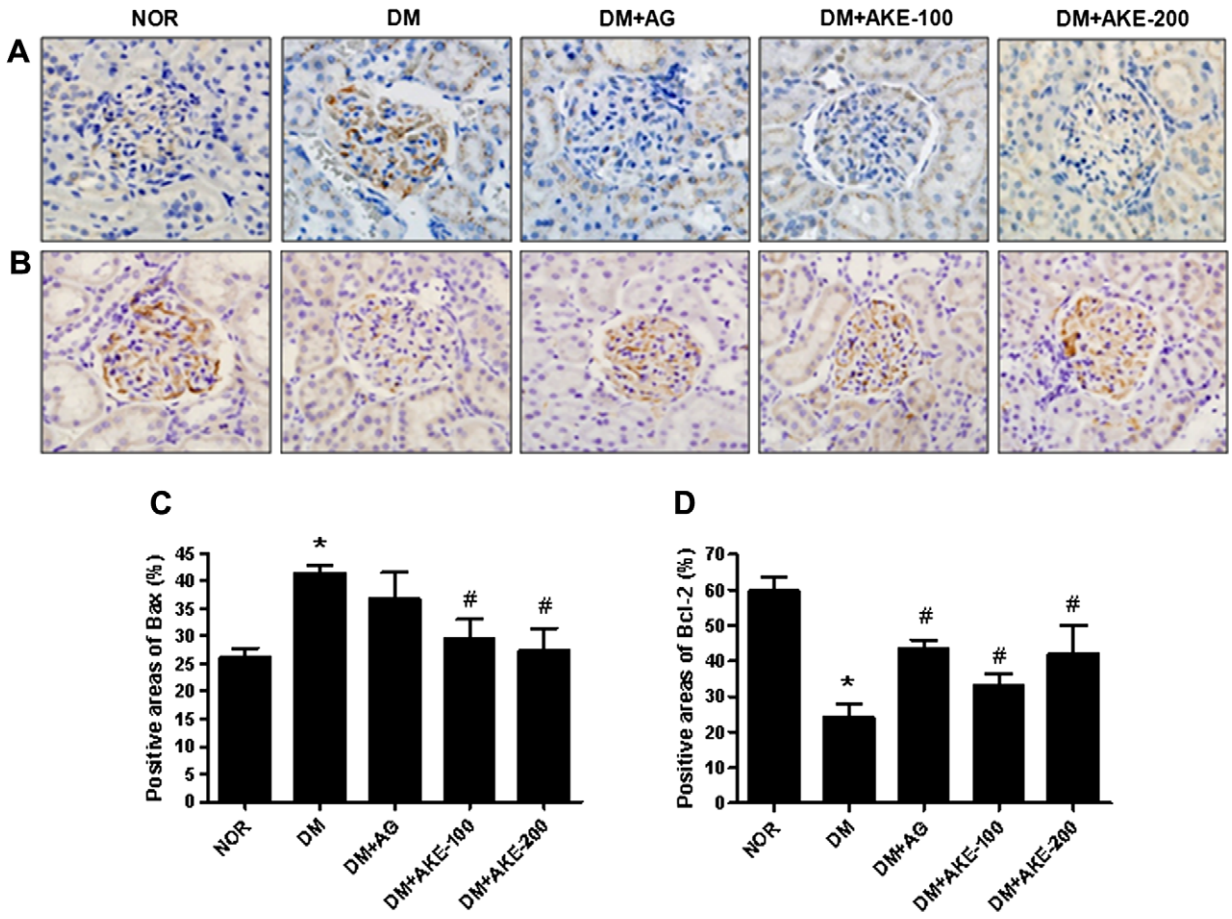

Fig. 4. Effect of AKE on the expression of Bax and Bcl-2 in the renal glomerulus. Immunohistochemical staining for (A) Bax and (B) Bcl-2. ×400 magnification. Morphometric analysis of (C) Bax and (D) Bcl-2-positive areas in renal glomerulus in each group. All data are expressed as means ± SEM ($n = 8$). $^{*}P < 0.01$ vs. NOR group; $^{\#}P < 0.01$ vs. DM group.

of AGEs formation. AGEs inhibitors, such as AG, ALT-946, and LR-90 attenuate mesangial expansion and albuminuria in animal models of diabetic renal disease [29–33]. Two caffeoylquinic acids, chlorogenic acid and 3,5-di-*O*-caffeoylquinic acid, are major compounds of AKE. There are some reports that caffeoylquinic acids like chlorogenic acid shows preventive effect on the formation of AGEs [34,35].

In this study, AGEs levels in glomerular section and serum were significantly reduced in AKE treated-STZ-induced diabetic rats. Furthermore, AKE had an anti-apoptotic effect on renal podocytes. High glucose-induced ROS promote podocyte apoptosis and AGEs accelerate podocyte injury by activation of the FOXO4 transcription factor [36]. In our previous study, KIOM-79, a natural AGEs inhibitor, prevents podocyte apoptosis in Zucker diabetic fatty rats, an animal model of type 2 diabetes [37]. Moreover, it was reported that chlorogenic acid and 3,5-di-*O*-caffeoylquinic acid are considered to have the anti-protective effect against neuronal cell apoptosis [38–42]. Therefore, the anti-apoptotic activity of AKE against diabetes-induced podocytes apoptosis may be considered to be due to effects of these compounds.

In this study, we also found that the treatment of AKE ameliorated the enhanced pro-apoptotic Bax and the decreased Bcl-2 protein in AGEs-accumulated glomeruli of STZ-induced diabetic rats. Bax and Bcl-2 are considered to be the principal factors in determining whether the execution of apoptosis proceeds [43]. Bcl-2 is an important anti-apoptotic proto-oncogene and Bax is a pro-apoptotic one. The ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2-like protein is believed to be important in determining cell survival versus cell death [44]. The ratio of Bax to Bcl-2 is altered in high glucose in a way that favors apoptosis [45]. The ratio of increased Bax/Bcl-2 damages the integrity of mitochondria, causing release of cytochrome *c* from mitochondria, thereby leading to the activation of caspase-3 and caspase-9 [46].

Although two major chemical standards of AKE are chlorogenic acid and 3,5-di-*O*-caffeoylquinic acid, the active compounds of AKE is still not clear. Based on our findings, the inhibition of AGEs accumulation in the kidney and the anti-apoptotic effect on podocyte by AKE might ameliorate diabetic nephropathy. It seems likely that the treatment with AKE is effective for treatment for diabetic nephropathy due to inhibition of AGEs accumulation in the kidney and serum, and could be a valuable therapeutic approach in diabetic nephropathy.

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