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ORIGINAL RESEARCH

Protective Effect of Biochanin A on the Diabetes-Induced Renal Damage

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Objective: Angiogenesis and oxidative stress contribute to the pathogenesis of diabetic nephropathy (DN). The isoflavone biochanin A (BCA) has reported anti-inflammatory and antioxidant properties; we evaluated whether BCA modulates inflammatory and angiogenic markers in renal tissue of streptozotocin-induced diabetic rats.

Materials and Methods: Thirty-six male Wistar rats (180–200 g) were randomized into six groups (n = 6): non-diabetic control (vehicle), diabetic control (STZ 55 mg/kg, i.p.), and two diabetic groups treated with BCA (10 or 15 mg/kg; Oral). Treatments were administered for 42 days. On day 42 animals were sacrificed and blood and renal tissues collected. Renal VEGF, TNF-α, IL-1β, IL-6, IL-18, NF-κB, TGF-β, RAGE, CTGF, and MDA were measured by ELISA. Renal tissues evaluate histopathologically for mesangial expansion, cellularity, and angiogenesis.

Results: BCA treatment reduced fasting blood glucose in diabetic rats and significantly decreased renal VEGF, TNF-α, and IL-1β concentrations versus diabetic controls ($p < 0.05$). No clear dose-response was observed between 10 and 15 mg/kg; other markers showed non-significant trends toward improvement.

Conclusion/Discussion: BCA reduced key angiogenic and proinflammatory markers in diabetic rat kidney, suggesting potential nephroprotective effects; further studies are needed to define mechanisms, optimal dosing, and long-term safety.

Keywords: biochanin A, diabetic nephropathy, angiogenesis, inflammation, Wistar rat

Introduction

End-stage renal disease (ESRD) is a major complication of diabetes and diabetic nephropathy (DN). DN is among the most serious microvascular sequelae of long-standing hyperglycemia. Immune-mediated inflammatory processes, together with oxidative stress and dysregulated angiogenesis, drive the pathophysiology of DN. Numerous pro-inflammatory mediators, growth factors, cytokines, chemokines, and vasoactive substances promote DN development, and inflammatory cell infiltration is commonly observed in glomerular and tubulointerstitial compartments in experimental models.[1–4]

Hyperglycemia increases reactive oxygen species (ROS) production, which perturbs redox homeostasis and alters the balance of pro- and anti-angiogenic factors, thereby promoting abnormal endothelial proliferation, migration, and pathological angiogenesis. Hyperglycemia-driven oxidative stress also modifies gene expression programs that favor pro-inflammatory, pro-oxidant, and pro-angiogenic phenotypes.[2,5–8]

The inflammatory Interleukins like IL-1, IL-18, IL-6 and factors include transforming growth factor-beta 1 (TGF-β1), Connective tissue growth factor (CTGF), and tumor necrosis factor-alpha (TNF-α) are a few of these angiogenic promoting factors. Key mediators implicated in DN include proinflammatory cytokines (eg, IL-1β, IL-6, IL-18, TNF-α), profibrotic factors (TGF-β1, CTGF), and receptors such as Receptor for Advanced Glycation End products (RAGE). Reduced glomerular filtration rate and mesangial expansion driven by TGF-β1 overexpression contribute to progression toward ESRD. In addition to glycemic and blood-pressure control, interventions that target pro-angiogenic and inflammatory pathways are proposed to slow DN progression.[9,10]

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Preclinical studies indicate that flavonoids and polyphenols exert antidiabetic, anti-inflammatory, antioxidant, and antihypertensive effects that may retard DN progression. Biochanin A (BCA), an isoflavone, has been reported to modulate hyperglycemia, oxidative stress, inflammation, and angiogenesis in experimental models.[11–17]

Amri et al reported that BCA modulates expression of TGF-β1 and PAR-2, lowers serum fasting blood glucose (FBG), urea, and creatinine, decreases renal MDA, and restores SOD activity in diabetic rats, suggesting nephroprotective effects. BCA has also been reported to protect endothelial function and to influence angiogenesis-related genes (eg, VEGF, CTGF), although precise mechanisms remain incompletely defined. The compound's multi-target actions may support its evaluation in combination preclinical strategies.[18–20] However, the impact of BCA on key angiogenic (VEGF), receptor (RAGE), and additional cytokine (IL-18, IL-1β) pathways, alongside histopathological and cytokine changes on kidney tissue, has not been fully elucidated.

In this study, we examined the effects of six-week BCA administration on renal inflammatory, oxidative, and angiogenic markers (IL-6, IL-18, IL-1β, TNF-α, NF-κB, MDA, RAGE, CTGF, TGF-β, and VEGF) and performed histopathological assessment in STZ-induced diabetic and non-diabetic control rats.

Materials and Methods

All animal procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The study protocol was approved by the Ethical Committee of Arak University of Medical Sciences (Ethics No. IR.ARAKMU.REC.1395.238). Experiments and reporting followed ARRIVE guidelines. All animal procedures were performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th edition, 2011) and the AVMA Guidelines for the Euthanasia of Animals (2020 Edition). Streptozotocin (STZ), biochanin A (BCA), dimethyl sulfoxide (DMSO), and lysis-buffer reagents (HEPES, KCl, $MgCl_2$, EDTA, Triton X-100, dithiothreitol, protease inhibitor cocktail) were obtained from Sigma-Aldrich (Hamburg, Germany).

Thirty-six male Wistar rats (200–250 g) were obtained from the Central Animal House, Tehran University of Medical Sciences. Animals were housed under standard conditions (23 ± 2°C; 12 h light/12 h dark) with free access to water and standard pellet diet (approx. carbohydrate 60%, fat 12%, protein 17.5%, fiber 8% w/w). Body weight was recorded at baseline and at study end using a precision balance (Sartorius TE64, Germany). We randomized rats in 6 groups after diabetic confirmation for G4 to G6.

Rats were randomized into six groups (n = 6 per group):

- G1: Non-diabetic control (vehicle, 0.5% DMSO)
- G2: Non-diabetic + BCA 10 mg/kg/day
- G3: Non-diabetic + BCA 15 mg/kg/day
- G4: Diabetic control (vehicle, 0.5% DMSO)
- G5: Diabetic + BCA 10 mg/kg/day
- G6: Diabetic + BCA 15 mg/kg/day

Diabetes was induced by a single intraperitoneal injection of STZ (55 mg/kg) after overnight fasting. Seventy-two hours after STZ, animals with fasting blood glucose >250 mg/dL were considered diabetic and included in the study. BCA (dissolved in 0.5% DMSO) or vehicle was administered by oral gavage daily between 09:00 and 10:00 for six weeks starting after diabetes confirmation (10 and 15 mg/kg bw/day in G5 and G6 groups respectively) BCA doses were selected based on prior work.[18] Therandomization method was Simple randomization for diabetic rats to G4, G5 and G6 group and non-diabetic rats to G1, G2 and G3 group.

At study end, animals were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg, i.p.). Blood was collected via aortic puncture and animals were euthanized. Both kidneys were excised: the left kidney was rinsed in saline, snap-frozen in liquid nitrogen, and stored at −80°C for biochemical assays; the right kidney was fixed in 10% neutral buffered formalin for histology and immunohistochemistry.

Sampling

Blood samples were centrifuged (2,000 × g, 10 min, 4°C) and serum aliquots stored at −20°C. Fasting blood glucose (FBG), urea, and creatinine were measured using commercial enzymatic kits (Pars Azmun, Tehran, Iran) per manufacturer instructions; absorbance was read on a JENWAY 6505 spectrophotometer.

Frozen left kidney tissue was pulverized under liquid nitrogen and homogenized in lysis buffer (10 mM HEPES, 10 mM KCl, 1.5 mM $MgCl_2$, 1 mM EDTA, 0.5 mM dithiothreitol, 0.1% Triton X-100, protease inhibitor cocktail; pH 7.9). Homogenates were centrifuged (2,000 × g, 10 min, 4°C) and supernatants collected for analysis. Protein concentration was determined (eg, BCA assay) and cytokine/marker levels were normalized to total protein.

ELISA Measurement

Renal concentrations of VEGF, TNF-α, IL-1β, IL-6, IL-18, NF-κB, TGF-β, RAGE, CTGF, and MDA were quantified by ELISA using rat kits (Boster Bio Catalog No. EK0526 and Catalog No. EK0540). Readings were obtained on a BioTek ELx800 plate reader (USA). According to the manufacturer's instructions, both ELISA kits (Rat TNFα Kit, Catalog No. EK0526; Rat VEGF Kit, Catalog No. EK0540; Boster Bio, USA) have an assay range of 15.6 to 1000 pg/mL and a sensitivity of less than 1 pg/mL. The intra-assay coefficients of variation (CV) for the TNFα kit range from 3.1% to 5.3%, and the inter-assay CV range from 5.9% to 6.7%. For the VEGF kit, the intra-assay CV range from 3.7% to 5.2%, and the inter-assay CV range from 4.5% to 6.3%. All samples and standards were measured in duplicate. Briefly, 100 µL of standards or samples were added to pre-coated wells and incubated for 90 min at 37°C. After washing, 100 µL biotinylated antibody was added and incubated for 60 min at 37°C. Following another wash, 100 µL avidin-biotin-peroxidase complex (ABC) was added for 30 min at 37°C. After washing, 90–100 µL TMB substrate was added and incubated for 20–25 min (TNFα) or 25–30 min (VEGF) at 37°C in the dark. The reaction was stopped with stop solution, and absorbance was read at 450 nm using a microplate reader. Cytokine concentrations were calculated using a standard curve.

Histopathological Assay

Fixed kidneys were processed, paraffin-embedded, and sectioned at 4 µm. Sections were mounted on slides and stained with hematoxylin and eosin (H&E). Histological evaluation (glomerular and tubulointerstitial changes, mesangial expansion, cellularity, and angiogenesis) was performed at ×400 magnification by a blinded observer. The comparative scoring by expert pathologist was performed and the mesenchymal area, cellularity, and angiogenesis report in quantification.

Statistical Analysis

Data are presented as mean ± SD. Statistical analyses were performed using SPSS v16.0 (SPSS Inc., Chicago, IL) and GraphPad Prism v6.0 (GraphPad Software, San Diego, CA). One-way ANOVA was used to compare means among multiple groups. When a significant overall effect was detected ($p < 0.05$), post-hoc pairwise comparisons were performed using Tukey's Honestly Significant Difference (HSD) test to control for type I error due to multiple comparisons. No prespecified primary endpoint was designated; all endpoints (histological scores, TNFα, VEGF, etc.) were considered exploratory. However, to maintain scientific rigor, multiplicity adjustment was applied to all post-hoc comparisons. Normality (eg, Shapiro–Wilk) and homogeneity of variance were tested prior to ANOVA. A two-tailed $p < 0.05$ was considered statistically significant. Report exact p-values and sample sizes (n) for each analysis.

Results

Treatment with BCA affected fasting blood glucose (FBG), serum urea, and creatinine (Table 1). Compared with diabetic controls, BCA-treated diabetic rats showed significant reductions in FBG and serum urea ($p < 0.05$). Both 10 and 15 mg/kg doses produced similar decreases in FBG and urea; serum creatinine was significantly reduced at 10 mg/kg but not at 15 mg/kg.

Table 1 The Effect of BCA on the Serum FBG, Urea and Creatinine in Controls and Treated Groups

Groups	FBG (mg/dl) (P-value)	Urea (mg/dl) (P-value)	Creatinine (mg/dl) (P-value)
Control	83.33 ±7.03	33.16±8.23	0.32±0.06
Control +dose 10 mg/kg BCA	86.33 ±5.71	39.16±8.28	0.39±0.03
Diabetic Control	[a]690.33 ±16.26 **(0.0071)**	[a]80.66±9.0 **(0.0021)**	[a]0.63±0.9 **(<0.0001)**
Diabetic+ dose 10 mg/kg BCA	[b]404.83 ±27.00 **(0.0022)**	[b]47±5.51 **(0.0045)**	[b]0.46±0.6 **(0.0087)**
Diabetic+ dose 15 mg/kg	[b]416.66 ±13.70 **(<0.0001)**	[b]58.33±7.11 **(<0.0065)**	0.56±0.5

Notes: Each value is mean ± SD for 6 rats in each group. [a]$P < 0.05$ in comparison with normal rats. [b]$P < 0.05$ in comparison with diabetic rats. Bold values indicate statistical significance. Non-significant values have been omitted to avoid redundancy.

Renal VEGF levels were elevated in diabetic rats versus non-diabetic controls (Figure 1). Oral BCA (10 and 15 mg/kg) significantly reduced renal VEGF compared with diabetic controls ($p < 0.05$); the 10 mg/kg dose produced a greater reduction than 15 mg/kg ($p < 0.05$).

Renal TNF-α was increased in diabetic rats and was significantly reduced by BCA treatment at both doses (Figure 2; $p < 0.05$). The reduction did not follow a clear dose-response pattern.

Compared with non-diabetic controls, diabetic rats exhibited higher renal IL-18, IL-1β, MDA, RAGE, NF-κB, CTGF, and TGF-β (Table 2; $p < 0.05$). BCA at 10 mg/kg significantly reduced IL-18, IL-1β, MDA, RAGE, NF-κB, and CTGF ($p < 0.05$). At 15 mg/kg, BCA significantly decreased IL-1β, MDA, RAGE, and CTGF ($p < 0.05$), while reductions in IL-18 and NF-κB were smaller and did not reach significance ($p > 0.05$).

When diabetic rats were given BCA at both doses, the amount of TGF- and IL-6 in the kidneys reduced, but not significantly ($p > 0.05$).

Histopathology (H&E; Figure 3) showed increased mesangial expansion, cellularity, and angiogenesis in diabetic controls versus non-diabetic controls. BCA treatment reduced histological indices of angiogenesis and mesangial

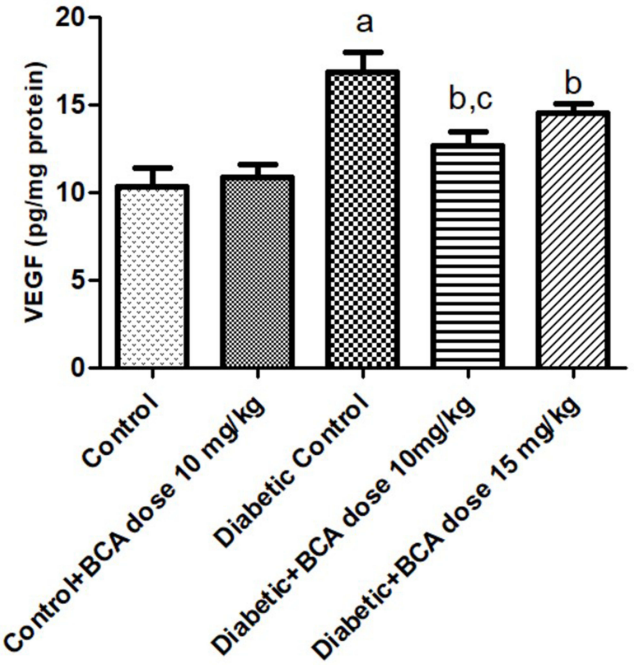

Figure 1 Renal VEGF concentration of control and diabetic rats that were treated with BCA for 6 weeks. Each value is mean ± SD for 6 rats in each group. (**a**) $P < 0.05$ in comparison with normal rats. (**b**) $P < 0.05$ in comparison with diabetic rats. (**c**) $P < 0.05$ in comparison with diabetic rats were treated with 15 mg/kg BCA. Since the results of G2 and G3 (non-diabetic + BCA 10 and 15 mg/kg) were virtually identical, they are combined in this figure as control + BCA. All six groups are detailed in the Methods.

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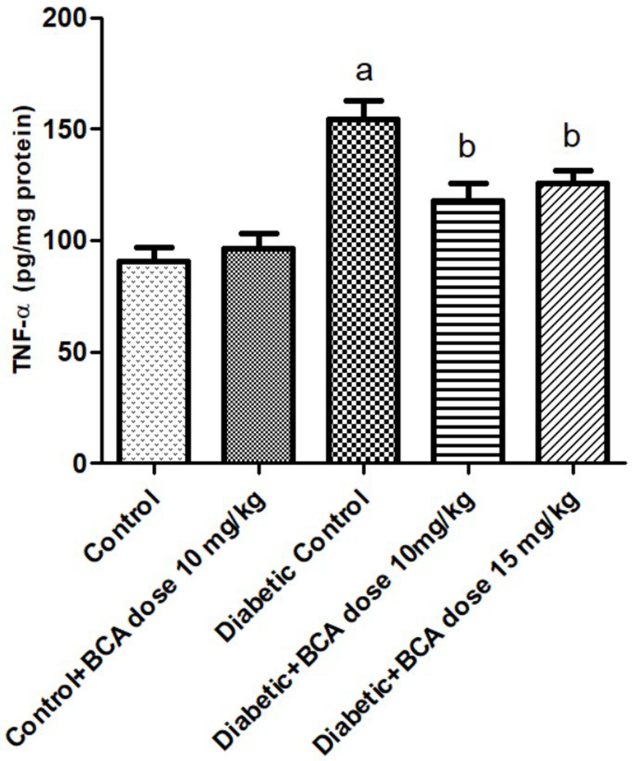

Figure 2 Renal TNF-α concentration of control and diabetic rats that were treated with BCA for 6 weeks. Each value is mean ± SD for 6 rats in each group. (**a**) $P < 0.05$ in comparison with normal rats. (**b**) $P < 0.05$ in comparison with diabetic rats. Since the results of G2 and G3 (non-diabetic + BCA 10 and 15 mg/kg) were virtually identical, they are combined in this figure as control + BCA. All six groups are detailed in the Methods.

expansion; angiogenesis was reduced in treated groups compared with diabetic controls. In diabetic control rats, a sharp increase (+++) in the number of vessels was observed according to the semi-quantitative scoring system (Table 3). The non-diabetic groups receiving BCA (both high and low dose) showed normal renal histology similar to the non-diabetic control group, therefore they are not shown separately in Figure 3.

Table 2 The Effect of BCA on the IL-6, IL-18, IL-1β, MDA, RAGE, NF-κB, CTGF, TGF-β in Kidney Tissue of Controls and Treated Groups

Groups	TGF-β (P- value)	CTGF (P- value)	NF-κB (P- value)	RAGE (P- value)	MDA (P- value)	IL-1β (P- value)	IL-18 (P- value)	IL-6 (P- value)
Control	375.75±58.92	51.75±5.90	39.25±7.93	161.25±3.86	21.87±2.78	2.08±0.24	24.02±2.09	0.985±0.34
Control +dose 10 mg/kg BCA	425±75.93	59.5±13.32	42.5±3.31	154.5±13.17	24.52±0.35	2.11±0.38	22.02±1.87	1.178±0.19
Diabetic Control	[a]702.5±142.44 **(0.0002)**	[a]75.2±9.75 **(0.0089)**	[a]59.0±16. **(0.018)**	[a]194±5.65 **(0.0018)**	[a]30.82±2.38 **(−0.002)**	[a]3.95±0.45 **(<0.0001)**	[a]31.2±3.72 **(−0.001)**	1.34±0.52
Diabetic+ dose 10 mg/kg BCA	642.5±87.70	[b]56.5±5 **(<0.0069)**	[b]34.75±6.07 **(<0.0057)**	[b]178.75±4.57 **(0.0041)**	[b]25.52±0.40 **(<0.0001)**	[b]2.83±0.60 **(0.0026)**	[b,c]23.88±4.85 **(<0.0076)** **(<0.0001)**	1.15±0.14
Diabetic+ dose 15 mg/kg	683.25±57.11	[b]56.32±7.03 **(0.0038)**	41.05±4.02 **(0.0089)**	[b]170.33±4.30 **(0.0024)**	[b]25.8±2.48 **−0.0065)**	[b]2.95±0.48 **(0.0091)**	30.12±1.07	1.16±0.12

Notes: Each value is mean ± SD for 6 rats in each group. [a]$P < 0.05$ in comparison with normal rats. [b]$P < 0.05$ in comparison with diabetic rats. [c]$P < 0.05$ in comparison with Diabetic+ dose 15 mg/kg. Bold values indicate statistical significance. Non-significant values have been omitted to avoid redundancy.

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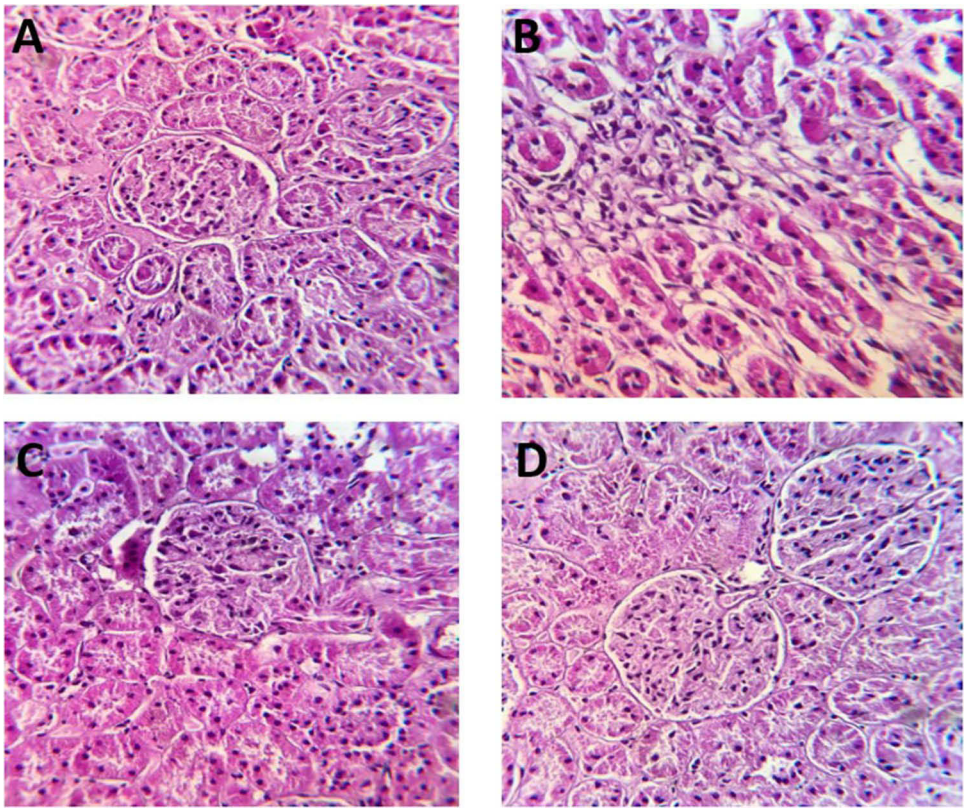

Figure 3 Effect of BCA on renal tissue sample (Hematoxylin and Eosin staining; magnification, × 400). (**A**) Control group, (**B**) Diabetic control group, (**C**) Diabetic group + 10 mg/kg BCA and (**D**) Diabetic group 15 mg/kg BCA.

Discussion

One of DN's pathogenic characteristics is aberrant angiogenesis, which contributes to progressive renal injury despite available therapies. Recent experimental research has found flavonoids to exert antidiabetic, anti-inflammatory, and antioxidant effects that may mitigate diabetes complications.

In this study, we evaluated the effects of biochanin A (BCA) on inflammatory and angiogenic markers in STZ-induced diabetic rats. BCA treatment reduced renal VEGF and several proinflammatory mediators and was associated with improved histological indices of angiogenesis and mesangial expansion.

STZ-induced diabetes increased fasting blood glucose (FBG) in our model, and BCA treatment significantly lowered FBG. These glycemic effects are consistent with prior reports that BCA improves glucose handling via multiple mechanisms, including upregulation of glycolytic enzymes, enhancement of insulin sensitivity (SIRT-1–related pathways), and modulation

Table 3 Pathological Changes in Kidney Tissue of Control and Treated Groups

Groups (Included Groups)	Number of Vessels	Diameter of Vessels
Control (non-diabetic+0.5% DMSO non-diabetic + high-dose BCA non-diabetic + low-dose BCA)	–	–
Diabetic Control (Diabetic control+ 0.5% DMSO)	+++	++
Diabetic + BCA 10 mg/kg (Diabetic + low-dose BCA)	++	+
Diabetic + BCA 15 mg/kg (Diabetic + high-dose BCA)	+	-

Notes: Scoring system: –, normal condition; +, slight increase; ++, moderate increase; +++, sharp increase.

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of lipid metabolism; such metabolic improvements likely contribute to downstream reductions in inflammatory and angiogenic signaling.[21–25] Our study confirms that BCA administration caused decrease in FBG, serum urea, renal VEGF, TNF-α, IL-18, IL-1β, MDA, RAGE, NF-κB, and CTGF ($p < 0.05$). BCA treatment reduced histological indices of angiogenesis and mesangial expansion; angiogenesis was reduced in treated groups compared with diabetic controls. In diabetic control rats, a sharp increase (+++) in the number of vessels was observed according to the semi-quantitative scoring system (Table 3).

Inflammation is central to DN pathogenesis. Diabetic controls showed elevated renal TNF-α, IL-6, IL-1β, IL-18, and NF-κB, and BCA treatment significantly reduced several of these markers. These anti-inflammatory effects align with BCA's reported modulation of inflammatory signaling pathways and may be mediated in part via PPAR-γ activation and suppression of NF-κB–driven transcription.[10,25,26]

Mechanistically, BCA has been reported to activate PPAR-γ and to modulate Nrf2 and NF-κB signaling, pathways that reduce proinflammatory gene expression and oxidative stress. While our data are consistent with these mechanisms, direct pathway readouts (eg, Western blot for NF-κB p65 nuclear translocation, Nrf2 target expression, or PPAR-γ activation assays) were not performed and should be included in future studies to confirm causality.[27–29]

Since abnormal angiogenesis in DN is known to be primarily caused by increased VEGF expression, we examined the effect of BCA on VEGF production in kidney tissue and discovered that oral administration of BCA decreased VEGF level in kidney. Renal histological analysis also revealed that BCA decreased angiogenesis in treated rats' kidney tissue. In a previous work, it was discovered that BCA, at a concentration of 35 μM, suppresses both HIF-1 and VEGF protein expression in C6 cells that have been exposed to the chemical stimulus of hypoxia, cobalt chloride (in vitro).[19]

Because VEGF-driven angiogenesis contributes to DN progression, we measured renal VEGF and performed histology. BCA reduced renal VEGF and histological indices of angiogenesis. These findings are supported by in vitro data showing BCA can suppress HIF-1 and VEGF expression under hypoxic stimulus, suggesting BCA may interfere with hypoxia-responsive angiogenic signaling; however, in vivo confirmation of HIF-1 modulation is needed. While Amri et al in 2022 demonstrated dose-dependent suppression of TGF-β1/PAR-2 genes and oxidative stress, our study extends these findings by showing BCA's impact on angiogenic (VEGF) and inflammasome-related (IL-18, NF-κB) pathways in kidney, with a potentially optimal dose at 10 mg/kg (18).

CTGF contributes to angiogenesis and fibrosis and is upregulated in diabetic kidneys. In our model, CTGF, TGF-β, and RAGE were elevated in diabetic controls; BCA reduced CTGF and RAGE, consistent with attenuation of profibrotic and pro-angiogenic signaling. These molecular changes likely underlie the improved histopathology observed with BCA treatment, but mechanistic links (eg, whether CTGF reduction is secondary to lowered TGF-β or direct transcriptional effects) remain to be established.

High AGE levels induce RAGE expression, activating NF-κB, increasing ROS, and worsening renal injury. We observed elevated renal RAGE and MDA in diabetic controls; BCA reduced both RAGE and MDA and is reported to enhance antioxidant defenses (eg, TAS, catalase, SOD) in other studies. These data suggest BCA may mitigate AGE/RAGE-mediated oxidative and inflammatory cascades, potentially via direct antioxidant activity and metabolites such as genistein. Direct measurements of AGE levels and RAGE signaling intermediates would strengthen this interpretation.

Limitations

This study has limitations: the sample size was modest, the STZ model primarily reflects insulin-deficient diabetes and may not capture all features of human type 2 diabetes, and mechanistic pathway analyses (eg, Western blots, phosphorylation assays, or gene knockdown) were not performed. Dose-response relationships were inconsistent (10 mg/kg sometimes more effective than 15 mg/kg) and warrant further investigation.

Conclusion

In summary, BCA reduced hyperglycemia, attenuated renal inflammation and oxidative stress, and decreased angiogenic and profibrotic markers in STZ-induced diabetic rats, with accompanying histological improvement. These findings support further mechanistic studies and longer-term evaluations to determine whether BCA or its derivatives have translational potential as adjunctive nephroprotective agents in diabetes.

Biochanin A (BCA) reduced renal angiogenic and proinflammatory markers and improved histopathological indices in streptozotocin-induced diabetic rats. These preclinical results indicate nephroprotective potential for BCA; however, translation to clinical practice requires additional work, including mechanistic validation, dose-optimization, long-term safety studies, and evaluation in models that better reflect human type 2 diabetes.

Highlights

The study aimed to investigate the effects of biochanin A (BCA) on Angiogenic response and Inflammation-associated factors in diabetic rats.

Results showed that BCA administration improved kidney function and reduced inflammation and angiogenesis in diabetic rats.

The study suggests that BCA could be a potential therapeutic agent for diabetic nephropathy.

Ethics Declaration

(No: IR.ARAKMU.REC.1395.238).

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Disclosure

All of the authors and co-authors declare that there is no conflict of interest regarding the concept and publication of this article. There are not any non-financial and other competing interest disclosures.

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