

Original Article

The effect of Bailing capsules combined with losartan to treat diabetic glomerulosclerosis and the combination's effect on blood and urine biochemistry

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Abstract: Objective: This study aimed to explore the efficacy of Bailing capsules combined with losartan to treat diabetic glomerulosclerosis (DG) and the combination's effect on blood and urine biochemistry. Methods: 160 DG patients admitted to our hospital were recruited as the study cohort and randomly divided into a control group and an observation group (n=80 in each group). The control group was treated with losartan, and the observation group was treated with losartan and Bailing capsules. The efficacy, diastolic blood pressure (DBP), systolic blood pressure (SBP), blood creatinine (Scr), 24 h urine protein (24 h UP), blood urea nitrogen (BUN), urine microalbumin (mALB), urine β_2 microglobulin (β_2 -MG), glomerular filtration rates (GFR), TCM scores, serum superoxide dismutase (SOD), reactive oxygen species (ROS), 8-hydroxydeoxyguanine (8-OHdG), hypersensitive C-reactive protein (hs-CRP), transforming growth factor β_1 (TGF- β_1), and the serum amyloid A (SAA) levels were compared between the two groups. Results: The overall effective rate was higher in the observation group (91.25%) than it was in the control group (78.75%) ($P<0.05$). After the treatment, the DBP, SBP, Scr, 24 h UP, BUN, mALB, and β_2 -MG levels were lower, and the GFR was higher in the observation group than in the control group ($P<0.01$). The TCM points were lower in the observation group than they were in the control group ($P<0.01$). The observation group also showed higher serum SOD and lower ROS, 8-OHdG, hs-CRP, TGF- β_1 , and SAA levels than the control group ($P<0.01$). The differences in the incidences of adverse reactions between the two groups were not significantly different ($P>0.05$). Conclusion: Bailing capsules combined with losartan in the treatment of diabetic glomerulosclerosis can improve the therapeutic efficacy, improve the blood and urine biochemical indexes, the renal function, and the clinical symptoms, reduce the oxidative stress, improve the microinflammatory state, and delay the progression of the disease without increasing the adverse reactions.

Keywords: Diabetic glomerulosclerosis, Bailing capsules, losartan, biochemical parameters, microinflammatory state, adverse reactions

Introduction

The current number of diabetic patients in China has reached about 40 million, of which more than 90% suffer from type 2 diabetes [1]. Diabetic glomerulosclerosis is a common chronic microvascular complication of diabetes, and its prevalence ranges from 30% to 50% in Western countries and about 21.5% in China [2]. In the early stage of diabetic glomerulosclerosis, microalbumin excretions in the urine may be increased, and as the disease progresses, severe proteinuria may occur,

resulting in progressive renal function damage, which eventually develops into chronic renal failure and threatens patients' lives [3].

Studies have suggested that the development of diabetic glomerulosclerosis is closely related to hyperglycemia, protein kinase glycosylation, and oxidative stress, conditions that can lead to microcirculatory disorders, elevated net filtration pressure, and the disruption of the basement membrane charge, causing renal damage [4, 5]. Thus, the treatment options for diabetic glomerulosclerosis include controlling

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the blood glucose and blood pressure, regulating the lipids, and reducing the proteinuria. However, the clinical outcome is poor [6]. Traditional Chinese medicine has abundant clinical experience in the treatment of diabetic glomerulosclerosis. Clinical studies [7-9] explore ways to improve the clinical efficacy of Chinese medicine combined with losartan in the treatment of diabetic glomerulosclerosis. However, no consensus has been reached. Diabetic glomerulosclerosis is categorized as “emaciation-thirst” and “consumptive disease” in TCM. Since it originates from the kidneys, it should be treated via the kidneys. Bailing capsules have the effect of tonifying the lungs and kidneys and benefiting the essence. The present study observed the therapeutic effect of Bailing capsules combined with losartan in the treatment of diabetic glomerulosclerosis and the treatment’s effect on the blood and urine biochemistry, aiming to provide a clinical reference.

Materials and methods

General information

One hundred and sixty patients with diabetic glomerulosclerosis admitted to our hospital from January 2017 to September 2020 were recruited as the study cohort. The inclusion criteria: (1) patients who met the diagnostic criteria for DG established by the American Diabetes Association [10], (2) patients <75 years old, (3) patients without any diabetic complications, (4) patients with good compliance, and (5) patients who signed the informed consent. Exclusion criteria: (1) patients with allergic comorbidities, (2) patients also suffering from a mental illness or an unclear consciousness, (3) patients also suffering from liver, lung, or other organ dysfunction, (4) patients with malignant tumors, (5) patients with hematopoietic system disease, (6) patients with recent episodes of acute complications of diabetes mellitus or cardiovascular events, (7) patients not taking other traditional Chinese medicines, Chinese patent medicines, etc. that may affect the results of the study. The patients were randomly divided into a control group and an observation group (n=80 in each group). This study was approved by the medical ethics committee.

Methods

A fasting blood glucose level <7 mmol/L and a blood pressure level <140/90 mmHg were the health targets in both groups using controlled diets and appropriate exercise. The control group was given losartan (China Resources Double-Crane Pharmaceutical Co., Ltd., H20-143019) q.d. 50 mg in the morning, and the observation group was given Bailing capsules (Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., Z10910036) t.i.d. 5 capsules. Both groups were treated for 1 month.

Observational indicators

(1) The therapeutic efficacy was assessed in accordance using the *Diagnostic Efficacy Criteria for Traditional Chinese Medicine*. Markedly effective: the urine albumin excretion rate (AER) or the reduction of proteinuria was >50% or it returned to normal. Effective: the AER or the reduction of proteinuria ranged from 30%~50%. Ineffective: the AER or the reduction of proteinuria was <30%. Total effective rate = (Markedly effective + effective)/80 × 100%. (2) The diastolic blood pressure (DBP) and the systolic blood pressure (SBP) were measured before and after the treatment. (3) Blood and urine biochemical indexes. Before and after the treatment, the Scr, 24 h UP, BUN, mALB, and β₂-MG levels were measured. $GFR = 175 \times \text{standard creatinine}/88.4 (\mu\text{mol/L}) - 1.234 \times \text{age (years)} - 0.179 \times [\text{female} \times 0.793]$. (4) The symptoms of dry throat and thirst, frequent urination, shortness of breath, swelling of the lower limbs, and fatigue were evaluated according to the *Guidelines for Clinical Studies of New Chinese Medicines*, and each symptom was scored as 0, 1, 2, or 3 for none, mild, moderate, or severe, respectively. (5) Oxidative stress: venous blood was drawn before and after the treatment, the serum was separated, and the SOD, ROS, and 8-OHdG levels were measured using the enzymatic labeling method. (6) Before and after the treatment, serum samples were collected, and immunonephelometry was used to measure the serum high-sensitivity C-reactive protein (hs-CRP) levels, and an enzyme linked immunosorbent assay was used to measure the transforming growth factor beta 1 (TGF-β₁) levels, and the colloidal gold method was used to measure the serum amyloid A (SAA) levels. (7) The incidences of

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Table 1. Comparison of the general information [$\bar{x} \pm s, n$ (%)]

Grouping	n	Gender		Average age (years)	Average duration of diabetes (years)
		Male	Female		
Observation group	80	39	41	49.97±10.65	9.17±2.31
Control group	80	37	43	50.13±11.26	9.03±2.24
χ^2		0.100		0.092	0.389
P		0.752		0.927	0.700

Table 2. Comparison of the efficacy [n (%)]

Grouping	n	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	80	35 (43.75)	38 (47.50)	7 (8.75)	91.25
Control group	80	23 (28.75)	40 (50.00)	17 (21.25)	78.75
χ^2		-	-	-	4.902
P		-	-	-	0.027

the adverse reactions were compared between the two groups.

Statistical analysis

The data were analyzed using SPSS 25.0. The measurement data were expressed as $\bar{x} \pm s$, and compared using *t* tests. The count data were expressed as % and examined using χ^2 tests. $P < 0.05$ indicates a statistical significance.

Results

Comparison of the general information

The control group included 37 males and 43 females, aged 35-74 years, with a mean age of (50.13±11.26) years, and the observation group included 39 males and 41 females, aged 37-73 years, with a mean age of (49.97±10.65) years. The differences between the two groups in terms of gender, age, and the duration of diabetes were not significantly different ($P > 0.05$), so they were comparable (**Table 1**).

Comparison of the efficacy

The overall treatment response rate was higher in the observation group (91.25%) than it was in the control group (78.75%) ($P < 0.05$), suggesting that the combined regimen can improve the treatment efficiency (**Table 2**).

Comparison of DBP and SBP

After treatment, the DBP and SBP levels were decreased in both groups, and the levels in

the observation group were lower than they were the control group ($P < 0.001$). This suggests that combined regimen can improve patients' blood pressure levels (**Table 3**).

Comparison of the blood and urine biochemical parameters in the two groups

After the treatment, the Scr, 24 h UP, BUN, mALB, and β_2 -MG levels decreased in both groups and were lower in the observation group than in the control group.

The GFR levels were increased in both groups, and were higher in the observation group than in the control group ($P < 0.001$), indicating that the combined regimen can improve patients' blood and urine biochemistry as well as their renal function (**Figure 1**).

Comparison of the TCM points

After the treatment, the TCM symptom scores in both groups were reduced and were lower in the observation group than in the control group ($P < 0.001$), suggesting that combined regimen can reduce patients' TCM symptom points (**Table 4**).

Comparison of the oxidative stress indicators

After the treatment, the two groups' serum SOD levels were increased, and the levels in the observation group were higher than they were in the control group. The ROS and 8-OHdG levels were decreased in both groups, and the levels in the observation group were lower than they were in the control group ($P < 0.001$), showing that the combined regimen can reduce oxidative stress injuries (**Figure 2**).

Comparison of serum hs-CRP, TGF- β_1 , and SAA levels

The serum hs-CRP, TGF- β_1 and SAA levels decreased in the two groups following the treatment, and the levels in the observation group was lower than they were in the control group ($P < 0.001$), indicating that the combined regimen can reduce the hs-CRP, TGF- β_1 , and SAA

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Table 3. Comparison of the DBP and SBP levels ($\bar{x} \pm s$, mmHg)

Grouping	n	DBP		SBP	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	80	83.91±2.03	78.60±1.82**	138.92±1.03	133.20±1.39**
Control group	80	83.86±2.11	80.57±1.98**	138.73±1.11	135.94±1.34**
t		0.153	6.552	1.122	12.693
P		0.879	0.000	0.264	0.000

Note: Compared to the pre-treatment levels, **P<0.001.

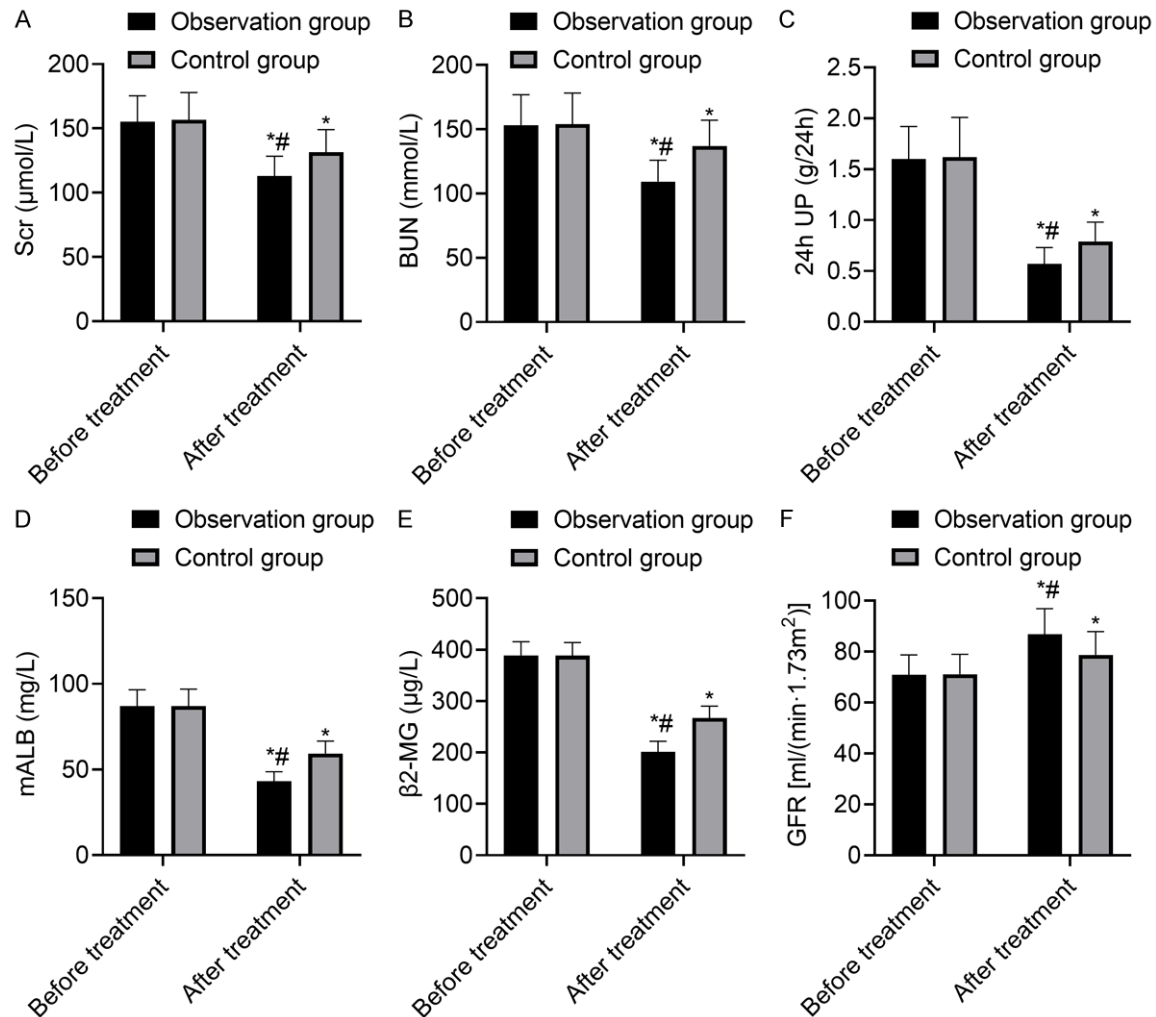


Figure 1. Comparison of the blood and urine biochemical parameters. Note: A: Scr; B: BUN; C: 24 h UP; D: mALB; E: β2-MG; F: GFR. Compared with pre-treatment, *P<0.05; compared with the control group, #P<0.05.

levels in patients and can exert anti-inflammatory and anti-fibrotic effects (Table 5).

Comparison of the adverse reactions

The incidences of adverse reactions (7.50% versus 3.75%) in the two groups were not significantly different ($P>0.05$), showing that com-

bined regimen did not increase the incidence of adverse reactions (Table 6).

Discussion

Current treatment options for diabetic glomerulosclerosis include glycemic control, blood pressure control, and lipid lowering [11, 12].

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Table 4. Comparison of the TCM symptom scores between two groups ($\bar{x} \pm s$, min)

Grouping	n	Timing	Dry throat and thirst	Frequent urination	Shortness of breath and lazy speech	Swelling of the lower limbs	Lack of energy
Observation group	80	pre-treatment	2.33±0.56	2.26±0.52	2.43±0.55	2.50±0.46	2.43±0.49
		post-treatment	0.75±0.24 ^{###}	0.85±0.30 ^{###}	0.71±0.19 ^{###}	0.92±0.25 ^{###}	0.79±0.34 ^{###}
Control group	80	pre-treatment	2.31±0.50	2.28±0.59	2.47±0.52	2.53±0.41	2.45±0.40
		post-treatment	1.14±0.35 ^{***}	1.21±0.34 ^{***}	1.04±0.21 ^{***}	1.16±0.39 ^{***}	1.11±0.36 ^{***}

Note: Compared with pre-treatment, ^{***}P<0.001; compared with the post-treatment control, ^{###}P<0.001.

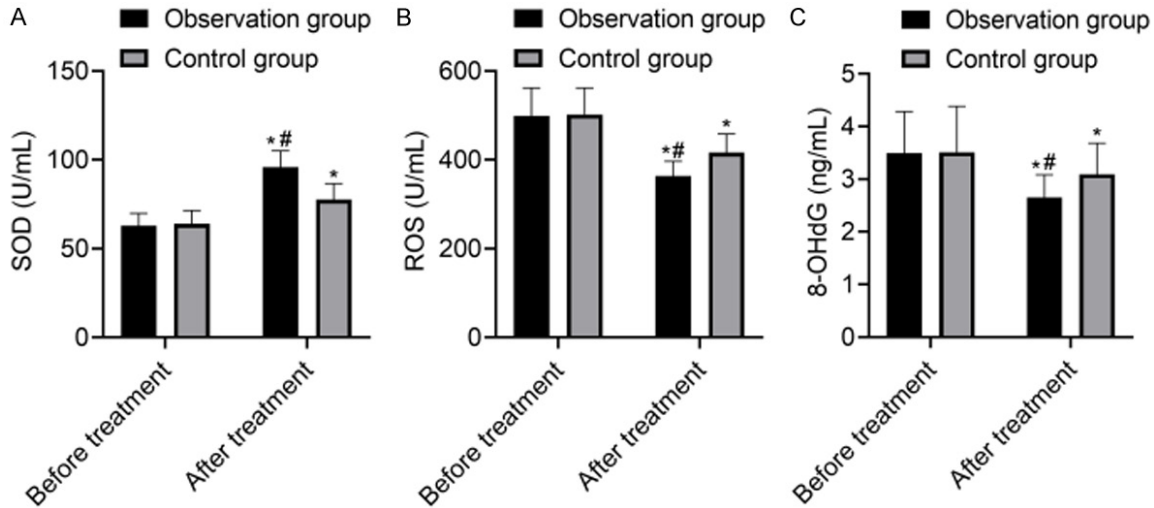


Figure 2. Comparison of the oxidative stress indicators. Note: A: SOD; B: ROS; C: 8-OHdG. Compared with pre-treatment, ^{*}P<0.05; compared with the control group, [#]P<0.05.

Table 5. Comparison of the serum hs-CRP, TGF- β_1 and SAA levels ($\bar{x} \pm s$)

Grouping	n	hs-CRP (mg/L)		TGF- β_1 (μ g/L)		SAA (μ g/L)	
		pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Observation group	80	4.09±1.01	1.36±0.78 ^{**}	52.33±6.45	40.64±5.06 ^{**}	17.69±2.20	9.23±0.94 ^{**}
Control group	80	4.11±1.05	2.53±0.99 ^{**}	51.97±7.02	46.95±5.27 ^{**}	17.72±2.17	12.26±1.02 ^{**}
t		0.123	8.303	0.338	7.725	0.087	19.538
P		0.902	0.000	0.736	0.000	0.931	0.000

Note: Compared to pre-treatment, ^{**}P<0.001.

Table 6. Comparison of the adverse reactions [n (%)]

Grouping	n	Headache and dizziness	Diarrhea	Skin rash	Decreased hemoglobin	The incidence
Observation group	80	1 (1.25)	2 (2.50)	1 (1.25)	2 (2.50)	7.50 (6/80)
Control group	80	1 (1.25)	1 (1.25)	0 (0.00)	1 (1.25)	3.75 (3/80)
χ^2		-	-	-	-	0.471
P		-	-	-	-	0.303

Losartan is an angiotensin II antagonist that acts on the type I (AT1) receptor of angiotensin II and regulates the level of angiotensin II. It stimulates the unclosed AT2 receptor, counteracts the effect of the AT1 receptor, dilates the

path of blood in the kidney, lowers the glomerular pressure, relieves hyper perfusion and hyperfiltration, and thus inhibits the proliferation of glomerular mesenteric cells and renal interstitial fibrosis. At the same time, it can

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interrupt the body's angiotensin system, reduce proteinuria, and delay chronic renal dysfunction.

In traditional Chinese medicine, DG is caused by a deficiency of kidney qi, qi malfunction, and unfavorable opening and closing. In addition, overeating, congenital deficiencies, external causes, and overwork causing yin deficiency and fluid depletion are all also closely related to the occurrence of diabetic glomerulosclerosis. Therefore, it should be clinically treated from the kidneys to tonify the kidneys and benefit qi. The ingredients of Bailing capsules are mainly the mycelium of *Ophiocordyceps sinensis*, which is effective in tonifying the lungs and kidneys and benefiting the essence and qi. Modern pharmacological studies have shown that *Ophiocordyceps sinensis* contains nucleosides, zingols, polysaccharides, mannitol, and other active ingredients that have hypoglycemic, immune modulating, anti-inflammatory, anti-oxidative damage, anti-fibrosis, and kidney protecting effects [13]. *Ophiocordyceps sinensis* can improve sugar metabolism, regulate blood sugar levels, scavenge superoxide anion radicals and hydroxyl radicals, inhibit lipid peroxidation, and reduce oxidative damage. The cordycepin in *Ophiocordyceps sinensis* is a nucleoside, with an anti-renal fibrosis effect. Studies [14, 15] show that Bailing capsules supplemented with losartan can significantly improve the efficacy and the renal function, and reduce the oxidative stress in patients with nephropathy. The results of this study show that the overall effective rate of the observation group (91.25%) was higher than the overall effective rate in the control group (78.75%), and the DBP and SBP levels in the observation group were decreased and were lower than they were in the control group ($P < 0.05$). Therefore, the combined regimen resulted in a higher efficacy and improved the blood pressure levels. This may be due to the synergistic effect of the combined regimen.

The main manifestations of diabetic glomerulosclerosis are proteinuria and impaired renal function. Scr, a small molecule that is mainly filtered by the glomerulus, and the creatinine produced every day are excreted in the urine. High Scr levels often indicate impaired renal function. The content of the urine protein is minimal in the healthy population, and elevated 24 h UP often suggests renal dysfunction.

BUN is excreted through glomerular filtration, and its elevated levels often indicate a decompensation of renal insufficiency. The large molecular weight of albumin does not allow it to pass through the glomerular basement membrane, so the mALB in urine is usually low, which can lead to an increased permeability of the glomerular basement membrane and elevated urinary mALB [16]. β 2-MG is an endogenous low-molecular-weight serum protein that can easily pass through the glomerular filtration membrane and is largely reabsorbed and degraded by proximal convoluted tubules. Under normal conditions, the β 2-MG release rate is constant, and a high concentration of β 2-MG in the urine indicates abnormal renal function [17]. Therefore, clinical measurements of the blood and urine biochemical parameters are helpful in determining the treatment and prognosis of diabetic glomerulosclerosis. Evidence [13] has shown that *Ophiocordyceps sinensis* can improve renal function and relieve the symptoms of proteinuria in patients with diabetic nephropathy. The results of this study show that the observation group had improved Scr, 24 h UP, BUN, mALB, and β 2-MG levels, GFR, and reduced TCM points, which was superior to the control group, suggesting the combined regimen can improve the blood and urine biochemical parameters as well as the renal function. The reason may be that losartan inhibits glomerular mesenteric cell proliferation and renal interstitial fibrosis by improving the glomerular pressure, and its high perfusion, high filtration state, resulting in improved renal function. Bailing capsules tonify the lungs and kidneys, benefit the essence to fill the marrow, which enhances the effects of losartan in improving kidney function.

Oxidative stress injuries play a key role in the development of diabetic glomerulosclerosis. Under hyperglycemia, renal tissues cause automatic glucose oxidation and protein non-enzymatic glycation due to disorders of the glucose metabolism, producing a large number of oxygen free radicals [18]. These oxygen free radicals can directly damage glomerular endothelial and mesenteric cells, promoting the aggregation of macrophages and inflammatory cell infiltration, altering the permeability of glomerular capillaries and basement membranes, thus causing proteinuria. SOD is an antioxidant metalloenzyme, and it is capable of scavenging oxygen free radicals. The

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generation of mitochondrial ROS mainly takes place at the electron transport chain located on the inner mitochondrial membrane during the process of oxidative phosphorylation. High blood sugar levels can lead to an increase in ROS, and excessive ROS can accelerate the release of the free radicals, and can aggravate the oxidative stress injuries in the kidneys. 8-OHdG is the most representative product of the oxidative modifications of DNA, and urinary 8-OHdG is potentially the best non-invasive biomarker of oxidative damage to DNA [19]. Evidence [20] has shown that the treatment of diabetic nephropathy with *Ophiocordyceps sinensis* can reduce the oxidative stress response. The results of the present study show that the serum SOD levels increased and the ROS and 8-OHdG levels decreased in the observation group and were better than the corresponding levels in the control group ($P < 0.05$), which is similar to the results of above studies, suggesting that the combined regimen can reduce oxidative stress damage. The reason may be that Bailing capsules inhibit lipid peroxidation and reduce oxidative damage by scavenging superoxide anion radicals and hydroxyl radicals.

A hyperglycemic state can increase the expression of macrophage chemotactic protein-1, activate macrophages, release a variety of inflammatory factors, cause inflammatory responses, and increase the release of TGF- β_1 [21]. hs-CRP is an acute phase protein. The inflammatory responses can lead to an increase in the hs-CRP levels. TGF- β_1 is a cytokine that regulates cell growth and differentiation and can transform the phenotype of normal fibroblasts [22]. Inflammatory responses can lead to elevated SAA levels. Evidence [23] has shown that *Ophiocordyceps sinensis* can improve the micro-inflammatory state in patients with diabetic nephropathy. Another study [24] showed that *Ophiocordyceps sinensis* extracts reduced the levels of TGF- β_1 in diabetic nephropathy patients and delayed the progression of the disease. The results of this study show that the serum hs-CRP, TGF- β_1 and SAA levels were decreased in both groups after treatment, and the observation group was lower than the control group ($P < 0.05$). It suggests that a combined regimen can improve the hs-CRP, TGF- β_1 , and SAA levels. The reason may be that Bailing capsules exert anti-inflammatory and anti-fibrotic effects and reduce the

hs-CRP, TGF- β_1 , and SAA levels. The results of this study also showed that there was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$), indicating that Bailing capsules do not increase the adverse reactions when combined with losartan.

In summary, Bailing capsules combined with losartan can improve therapeutic efficacy, blood and urine biochemical parameters, renal function, and clinical symptoms, reduce body oxidative stress, improve the microinflammatory state, and delay the progression of the disease, without increasing the adverse effects, so it is worth promoting. This study has the shortcomings of a small sample size, a short follow-up time and bias in the case selection. Moreover, the pharmacology of Bailing capsules is complex, and their mechanism of action in diabetic glomerulosclerosis still needs further exploration.

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Disclosure of conflict of interest

None.

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