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Original article

Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the diabetic nephropathy rats model

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ABSTRACT

Objective: Study the effect of the 3:7 ratio of Astragalus total saponins and Curcumin on the model of diabetic nephropathy rats, and explore its mechanisms.
Methods: Diabetic nephropathy rats model was established by high-fat and high-sugar feed feeding combined with streptozotocin (STZ) injection in sublingual vein. Measured fasting blood glucose of rats on the 10, 20 and 30th day, and measured urine protein content in urine of rats on 30th days. Two hours after the last administration, measured glycated serum protein (GSP), insulin antibody (IA), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), malondialdehyde (MDA), insulin, superoxide dismutase (SOD), glutathione (GSH), urea nitrogen (BUN), creatinine (Cr) in the serum and calculated the renal index of rat. Take the viscera of pancreas and kidney, and HE staining, so as to observe pathological changes.
Result: Astragalus total saponins and Curcumin 3:7 compatibility each dose group can significantly reduce the diabetic nephropathy rats blood glucose of 30th days, significantly reduce the level of GSP, IA, TG, TC, LDL ($P < 0.01$), and reduce MDA levels with different degrees ($P < 0.01$ or $P < 0.05$), and significantly increase the level of insulin ($P < 0.01$), increase the level of HDL, SOD and GSH with different degrees ($P < 0.01$ or $P < 0.05$ or $P > 0.05$); Astragalus total saponins and Curcumin 3:7 compatibility each dose group also can decrease renal index, UN, and Cr levels with different degrees and improve the pathological changes of pancreatic tissue and kidney tissue in diabetic nephropathy rats with different degrees ($P < 0.01$ or $P < 0.05$ or $P > 0.05$).
Conclusion: The 3:7 ratio of Astragalus total saponins and Curcumin can achieve the treatment and protection effects on diabetic nephropathy rats by improve the glycometableolism, insulin resistance, lipid metableolism, oxidative stress levels, and pathological changes.

1. Introduction

Diabetes and its chronic complications are serious chronic metabolic disorder that seriously threatens human health, and its incidence is second only to malignant tumors and cardiovascular diseases (Tekce et al., 2014). Diabetic nephropathy (DN) is the most serious complication of diabetic microangiopathy with high morbidity and mortality. DN was characterized by high glomerular filtration and urinary microalbumin in the early stage, and gradually developed glomerular atrophy, renal tubular basement membrane thickening, and mesangial swelling and deformation, and eventually developed chronic renal insufficiency (Ni et al., 2015). DN is the result of the combined action of various factors such as abnormal glucose metabolism, lipid metabolism disorder, oxidative stress, and renal hemodynamic changes, and the control of blood glucose level is currently the most important treatment method in clinic (Tang et al., 2014). In the treatment of DN, traditional Chinese medicine (TCM) often use activating blood circulation and removing blood stasis, invigorating qi and strengthening spleen drugs, and achieved good curative effect. Moreover, their medicinal properties are mainly warm and cold, with most of them taste sweet (Liu, 2012). Astragalus total saponins has the function of tonifying middle-jiao and invigorating qi, strengthening spleen and tonifying lung. Rhizoma curcumae has the action of moving qi, dispersing wind and promoting blood circulation, passing

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meridian and relieving pain. Astragalus total saponins is one of the main active components of Astragalus, which can inhibit aldose reductase activity and thus reduces the incidence of diabetic complications (Wang et al., 2015). Curcumin is one of the main active components of Rhizoma curcumae. According to the literature, it has a good effect on DN rats (Wang et al., 2017). In view of the new model of the research of component chinese medicine, the previous study in our laboratory used the different ratio (10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10) of Astragalus total saponins and Curcumin to study the protection effect on DM rat model and mice model, which was finally determined that the optimum ratio of Astragalus total saponins to Curcumin was 3:7 (Yan et al., 2017; Miao et al., 2017). Therefore, on the basis of the previous research, our laboratory applied for the national major new drug development-jiangqi capsule pharmacodynamics research and obtained national funding. In order to further verified the effect of 3:7 ratio of Astragalus total saponins and Curcumin on DN rat model, we adjusted the dose up and down to find the best dose for the development of Jiangqi capsule. Based on the previous research results, the efficacy of 3:7 different dose was confirmed from 5 aspects: glucose metabolism and insulin resistance, lipid metabolism, oxidative stress, renal function and pathological changes.

2. Experimental materials

2.1. Animal

Wistar rats, male, SPF, weighing 200–220 g, provided by Shandong lu kang pharmaceutical co. LTD. Animal qualification number: 0013468. Certificate number of laboratory qualification: SYXK (He Nan) 2010-001. Experimental animal ethic approval letter: DWLL17010025.

2.2. Reagents and drugs

Curcumin, provided by Chemistry Laboratory of Henan University of traditional Chinese medicine, contains > 90%, batch number: 110809; Astragalus total saponins, provided by Chemistry Laboratory of Henan University of traditional Chinese medicine, contains > 50%, batch number: 111008; Metformin hydrochloride tablets, provided by Shanghai Xinyi Pharmaceutical Co. Ltd., batch number: 120523; STZ, provided by Sigma company, batch number Z120315; Citric acid, Sodium citrate, provided by Shanghai Pudong Chemical Co. Ltd., batch number: 20081019 and 20100502; Blood glucose test-kit, provided by Biosino Bio-Technology and Science Inc, batch number: 120521; SOD and MDA test-kit, provided by Nanjing Jiancheng Bioengineering Institute, batch Number: 20130119; GSH, Cr, GSP, BUN, and Proteinuria test-kit, produced by Nanjing Institute of biological engineering, batch number: 20130117, 20130115, 20130123, 20130121 and 20130105; Insulin and IA test-kit, produced by American R&D company, batch number: 20130101A; TG, TC, HDL, and LDL test-kit, produced by Beijing Beihua Kangtai clinical Reagent Co. Ltd., batch number: 20121212, 20121203, 20120827 and 20121106.

2.3. Experimental apparatus

BIORAD-680 Enzyme labeling instrument, provided by United States; KDC-160HR high-speed freezing centrifuge, provided by Hkust innovation co. LTD. Zhongjia branch; UV-2000 ultraviolet visible spectrophotometer, provided by Shanghai TianMei Scientific Instrument Co. LTD.; OLYMPUS BX61 electric microscope, provided by Japan OLYMPUS.

2.4. Test solution preparation

Preparation of 3:7 ratio of Astragalus total saponins and Curcumin different dose: 3:7 high dose group (0.270 g/kg): 0.081 g Astragalus total saponins and 0.189 g Curcumin; 3:7 middle dose group (0.135 g/kg): 0.0405 g Astragalus total saponins and 0.0945 g Curcumin; 3:7 low dose group (0.0675 g/kg): 0.02025 g Astragalus total saponins and 0.04725 g Curcumin.

3. Experimental method

3.1. Mold making and drug delivery

From 124 rats, 12 were randomly selected as blank groups, and the rest were used to prepare the diabetic nephropathy rat model. Diabetic nephropathy rat model were fed feeding high-fat and high-sugar (sucrose: lard: milk powder: egg: common feed = 30: 20: 4: 2: 63) for 4 weeks. After fasting 12 h, 112 rats were injected with STZ 25 mg/kg (dissolve in citric acid buffer) in sublingual vein. The blank group was feed with common feed and injected with equal volume citric acid buffer in sublingual vein. Fasting blood glucose was measured after 7 days, whose blood glucose levels were in the range of 16.7–21 mmol/L, and have obvious symptoms of polydipsia, polyphagia and polyuria were selected as diabetic nephropathy model rats. The 60 rats selected were randomly divided into 5 groups according to the blood glucose value: Model group, Metformin group (0.33 g/kg), Astragalus total saponins and Curcumin 3:7 high dose group (0.270 g/kg), 3:7 middle dose group (0.135 g/kg) and 3:7 low dose group (0.0675 g/kg). The model group and blank group were given the same volume of normal saline, once a day for 30 d.

3.2. Detection index

Fasting blood glucose was measured on the 10th, 20th, 30th day of administration. At the morning of the 30th day of administration, urine of rats was collected from the metabolic cage for 24 h, and urine protein content was measured. After the last administration of 2 h, take blood and centrifuge to determine the level of GSP, IA, TG, TC, LDL, HDL, MDA, insulin, SOD, GSH, BUN, Cr in the serum. Take the left kidney to weigh and calculate the renal index. Then 10% formalin fluid was used to immobilized the pancreas and the left kidney. HE staining was used to observe the morphological changes of pancreas and kidney under light microscope. Renal index = kidney weight/rat weight.

3.3. Statistics processing method

The data were analyzed by SPSS 17.0 for windows statistical software, measurement data are expressed by mean ± SD value, single factor variance analysis was used among the groups, the least significant difference (LSD) method was used to test the variance homogeneity and the Games-Howell method was used to test the heterogeneity of variance, ranked data using *Ridit* test.

4. Experimental results

4.1. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the level of blood glucose in DN model rats

We can see from Table 1: Except the blank group, there was no significant difference in blood glucose before administration, indicating that the group was uniform. Compared with the blank group, the level of blood glucose increased significantly in model group on 10th, 20th and 30th day ($P < 0.01$). Compared with the

Table 1
Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the levels of blood glucose in DN rats (mean ± SD, $n = 12$).

Group	Dose	Fasting blood glucose (mmol/L)			
	(mg/kg)	Initial	Tenth days	Twentieth days	Thirtieth days
Black	–	5.265 ± 0.211	5.512 ± 0.273**	5.485 ± 0.392**	6.162 ± 0.235**
Model	–	16.704 ± 0.519	20.746 ± 2.140	23.203 ± 2.032	23.279 ± 2.363
Metformin	0.33	16.909 ± 0.527	18.767 ± 1.547**	19.222 ± 1.827**	15.162 ± 1.440**
3:7 high dose	0.27	16.902 ± 0.622	19.427 ± 1.787	20.682 ± 1.868**	16.277 ± 1.439**
3:7 middle dose	0.14	16.961 ± 0.689	20.205 ± 2.288	20.867 ± 1.663**	17.430 ± 1.813**
3:7 low dose	0.07	16.689 ± 0.437	20.551 ± 1.493	21.849 ± 2.185	20.109 ± 1.641**

Compared with model group,
*P < 0.05.
** P < 0.01.

model group, the Metformin group could significantly reduce the blood glucose level on the 10th, 20th and 30th day ($P < 0.01$). On the 20th day of administration, the 3:7 middle and high dose groups could significantly reduce the blood glucose level of DN model rats ($P < 0.01$). On the 30th day of administration, the 3:7 low, middle and high dose groups all could significantly reduce the blood glucose level of DN model rat ($P < 0.01$).

4.2. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the levels of GSP, IA and insulin in DN model rats

Compared with the model group, the Metformin, 3:7 high, middle and low dose groups could significantly reduce the levels of GSP (Fig. 1) and IA (Fig. 2) and significantly increased the level of Insulin (Fig. 3) in DN model rats ($P < 0.01$).

4.3. Estimation of plasma lipid parameters in DN model rats

Compared with the model group, the Metformin, 3:7 high, middle and low dose groups could significantly reduce the TG (Fig. 4), TC (Fig. 5) and LDL (Fig. 6) levels ($P < 0.01$), 3:7 high and middle dose groups could significantly increased HDL (Fig. 7) level ($P < 0.01$) and low dose groups could obviously increase HDL (Fig. 7) level of DN model rats ($P < 0.05$).

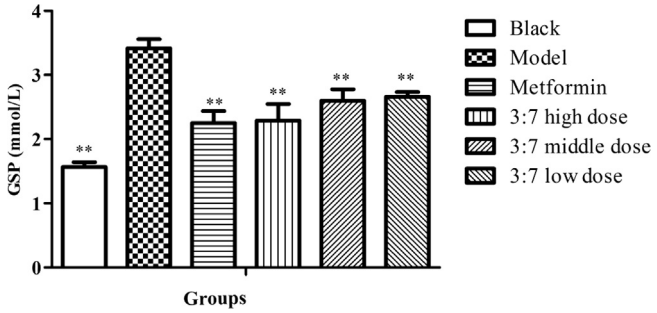

Fig. 1. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the GSP of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

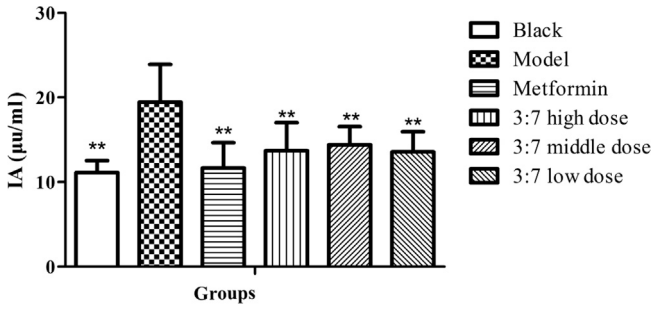

Fig. 2. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the IA of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

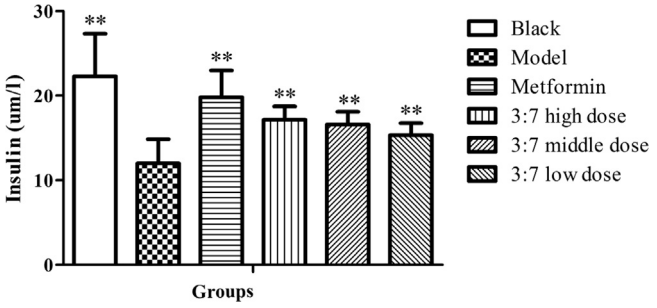

Fig. 3. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the Insulin of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

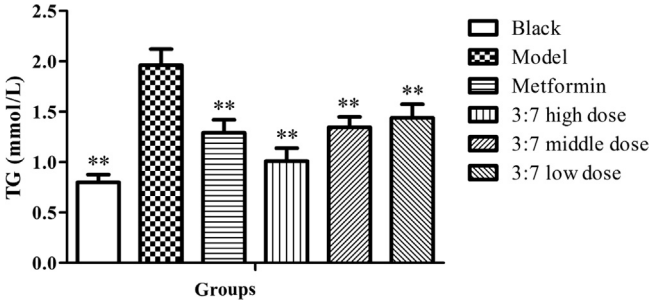

Fig. 4. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the TG of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

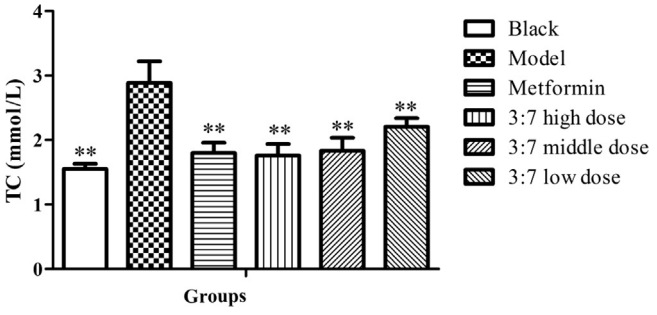

Fig. 5. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the TC of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

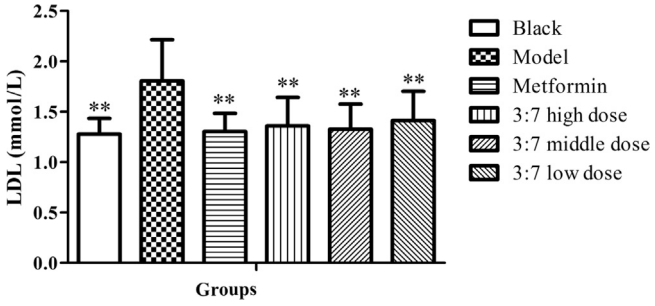

Fig. 6. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the LDL of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

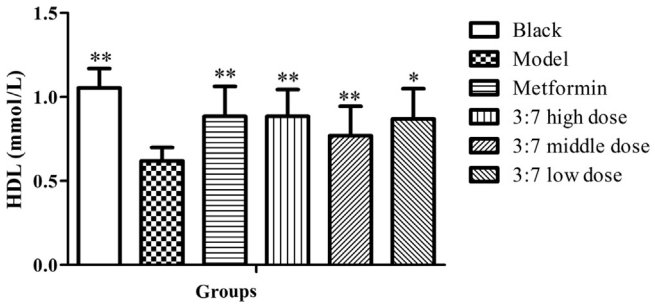

Fig. 7. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the HDL of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

4.4. Estimation of oxidative stress in DN rats

Compared with the model group, the Metformin, 3:7 high, middle dose groups could significantly reduce the MDA (Fig. 8) level, and significantly increase the GSH (Fig. 9) and SOD (Fig. 10) levels ($P < 0.01$), the 3:7 low dose group could obviously reduce the MDA (Fig. 8) level ($P < 0.05$), and significantly increase the SOD (Fig. 10) level of DN rats ($P < 0.05$).

4.5. Estimation of renal function in DN rats

Compared with the model group, the Metformin, 3:7 high, middle and low dose groups could significantly reduce the renal index (Fig. 11) of DN rats ($P < 0.01$), the Metformin, 3:7 high and middle dose groups could significantly reduce BUN (Fig. 12) and Cr (Fig. 13) levels of DN rats ($P < 0.01$), obviously reduce the level of proteinuria (Fig. 14) of DN rats ($P < 0.05$).

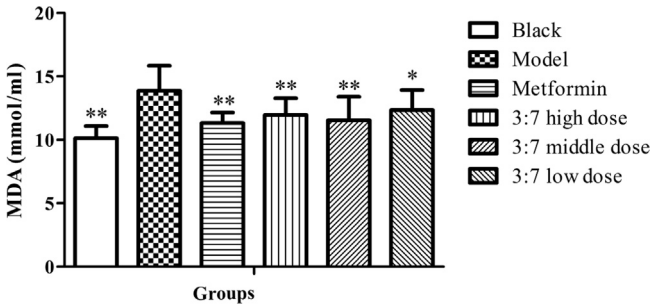

Fig. 8. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the MDA of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

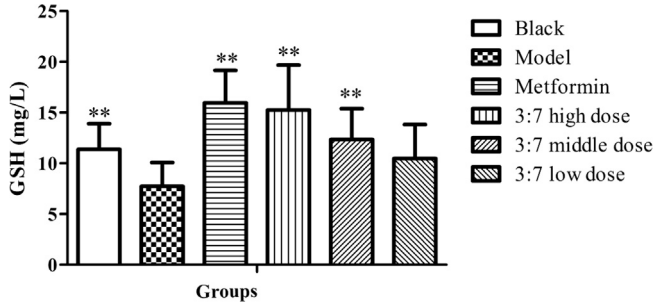

Fig. 9. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the GSH of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

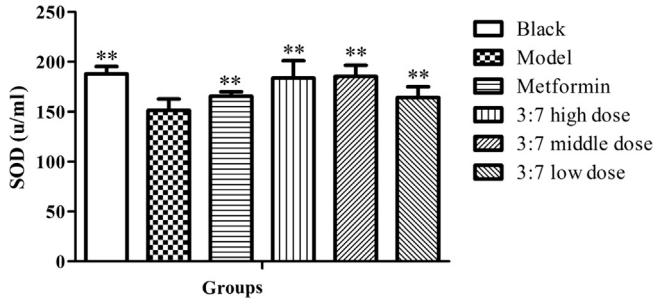

Fig. 10. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the SOD of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

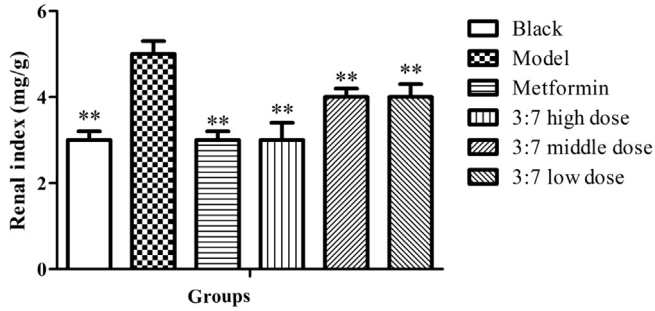

Fig. 11. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the Renal index of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

4.6. Effects of Astragalus total saponin and curcumin 3:7 ratio on pancreatic tissue in DN rats

As we can see from Table 2 and Fig. 15: Compared with the blank group, in model group, there was significant pathological changes in pancreatic tissue ($P < 0.01$); As we can see from Fig. 15B, the islet nuclei of the rats showed a dense state, and the cytoplasm of most islet cells atrophy. Compared with the model group, the Metformin, 3:7 high and middle dose groups could significantly reduce the pathological changes of pancreatic tissue in DN rats ($P < 0.01$); As we can see from Fig. 15C, D and E, the small fraction of rat islet cells showed a dense state, and the cytoplasm of less islet cells showed a atrophy state. The 3:7 low dose group could obviously reduce the pathological changes of pancreatic tissue ($P < 0.05$); As we can see from Fig. 15F, the nucleus of a few islet cells was dense, and the cytoplasm of most islet cells was atrophic and morbid.

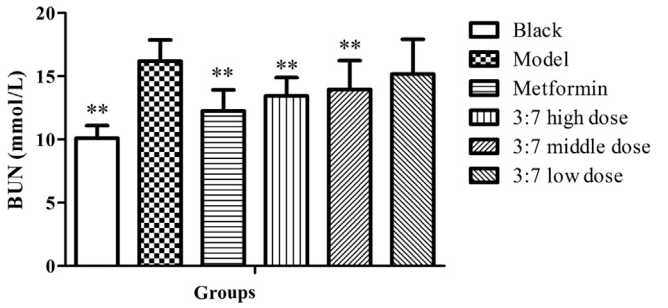

Fig. 12. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the BUN of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

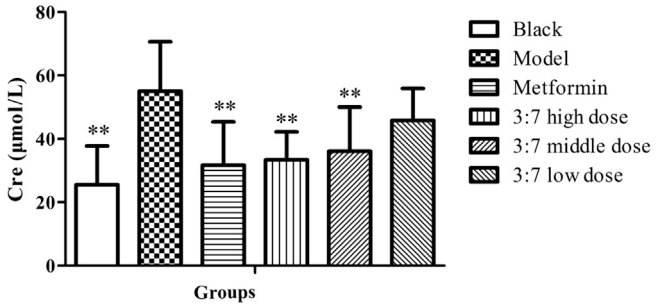

Fig. 13. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the Cre of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

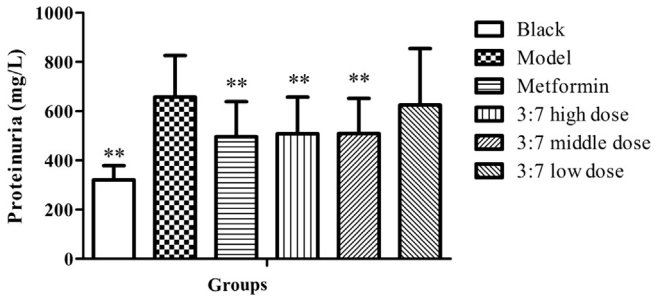

Fig. 14. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on the Proteinuria of all group rats (mean ± SD value, $n = 12$). Compared with model group, $^{**}P < 0.01$, $^{*}P < 0.05$.

4.7. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on kidney tissue in DN rats

From Table 3 and Fig. 16: Compared with the blank group, in model group, there was significant pathological changes in kidney tissue ($P < 0.01$); As we can see from Fig. 16B, the glomerular cells were obviously proliferated and the renal cyst cavities disappeared. Compared with the model group, the Metformin, 3:7 high and middle dose groups could significantly reduce the pathological changes of kidney tissue in DN rats ($P < 0.01$); As we can see from Fig. 16C, D and E, the proliferation of glomerular cells was not obvious, and the renal cyst space was slightly narrowed. The 3:7 low dose group could obviously reduce the pathological changes of kidney tissue ($P < 0.05$); As we can see from Fig. 16F: The proliferation of glomerular cells was obvious, and part of the renal cyst cavities became narrow or disappeared.

5. Discussion

DN is one of the common and serious long-term complications of diabetes, which can eventually develop into diabetic renal failure (Sidaway, 2014; Zhang et al., 2018). Although traditional Chinese medicine has definite curative effect in treating diseases, its composition is trace, the pretreatment method of administration is inconsistent, and the dissolution of effective components is also inconsistent. The development and research of component traditional Chinese medicine can make up for the above disadvantages, so that the selectivity is relatively improved and the dosage is relatively accurate (Liu et al., 2016). Under the new model of component traditional Chinese medicine research, the total saponin of astragalus and curcumin were studied in different proportions. Our laboratory has found that 3:7 has the best curative effect, and the best ratio of 3:7 obtained by previous screening is verified by this experiment. And the efficacy of total saponins from Astragalus total saponins and curcumin 3:7 ratio of different doses was confirmed from 5 aspects: glucose metabolism and insulin resistance, lipid metabolism, oxidative stress, renal function and pathological changes, so as to lay a foundation for the development and application of Jiangqi capsule.

The pathogenesis of DN is not yet clear, which involves various factors such as glycometableolism disorder, abnormal expression of various cytokines, oxidative stress, and renal function impairment. Glycometableolism disorder is the most important pathological manifestation of diabetes, so the determination of blood glucose changes is the primary index of evaluation model and efficacy. The level of GSP was directly proportional to the blood glucose concentration, which could be used to evaluate the blood glucose level within 2–3 weeks. Insulin resistance is the hallmark of type 2 diabetes, and insulin resistance or sensitivity reduce can inhibit glucose conversion to fat and can lead to brain dysfunction in a variety of ways (Ghareeb et al., 2013; Ge et al., 2017). Insulin is one of the main drugs for diabetes mellitus, and endogenous insulin level is a manifestation of islet β-cell function (AD, 2005). The experimental results show that Astragalus total saponins and curcumin 3:7 ratio could decrease GSP, blood glucose, IA and increase insulin, thus significantly improve the glucose metabolism disorder and insulin resistance in DN rats. Lipid meta-

Table 2
Effect of 3:7 ratio of Astragalus total saponins and Curcumin on pancreatic tissue in DN rats.

Group	Dose (mg/kg)	–	+	++	+++	*P*
Black	–	12	0	0	0	<0.01
Model	–	0	0	4	8	–
Metformin	0.33	0	8	4	0	<0.01
3:7 high dose	0.27	1	7	4	0	<0.01
3:7 middle dose	0.14	0	8	4	0	<0.01
3:7 low dose	0.07	0	2	4	6	<0.05

"–" There are more than 4 islet cells in the pancreatic tissue, islet cells are rich in cytoplasm and nucleus loosening. "+" There are more than 4 islet cells in the pancreatic tissue, cytoplasm atrophy of a few islet cells and nuclear concentration. "++" There are 2–3 islet cells in the pancreatic tissue, cytoplasm atrophy of some islet cells and nuclear concentration. "+++" There are 0–1 islet cells in the pancreatic tissue, cytoplasm atrophy of all islet cells and nuclear concentration.

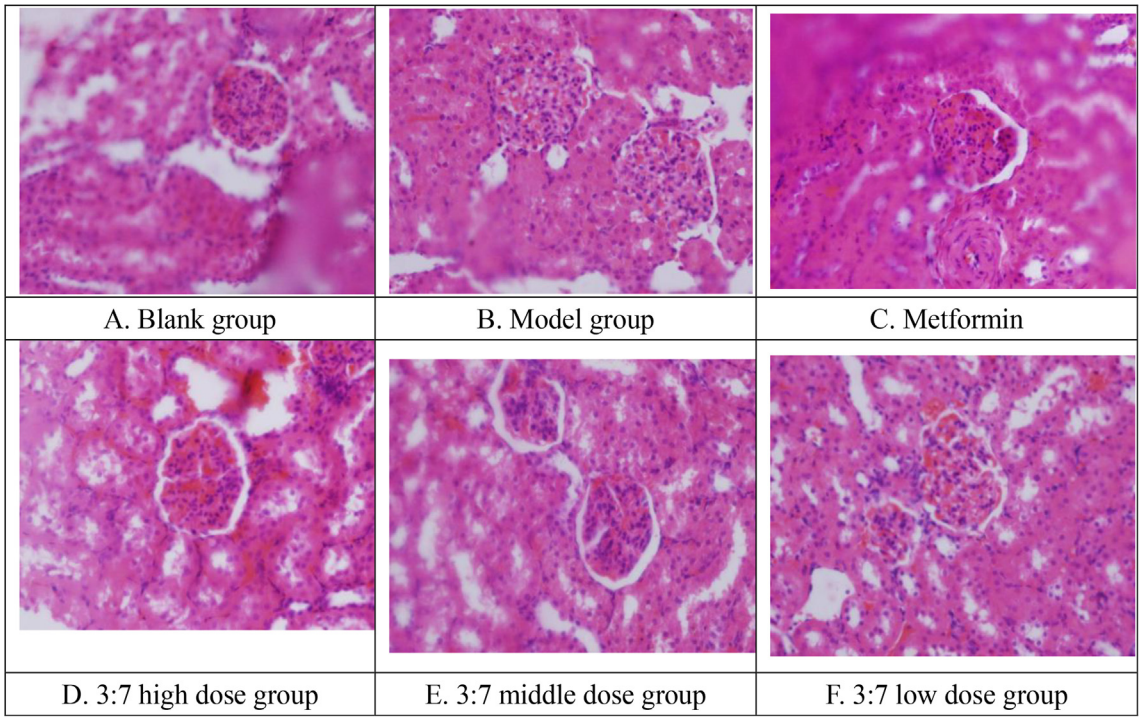

Fig. 15. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on pancreatic tissue in DN rats (HE × 400).

Table 3
Effect of 3:7 ratio of Astragalus total saponins and Curcumin on kidney tissue in DN rats.

Group	Dose (mg/kg)	–	+	++	+++	*P*
Black	–	12	0	0	0	–
Model	–	0	0	0	12	<0.01
Metformin	0.33	1	7	4	0	<0.01
3:7 high dose	0.27	2	7	3	0	<0.01
3:7 middle dose	0.14	0	6	6	0	<0.01
3:7 low dose	0.07	0	0	7	5	<0.05

"–" Normal glomerular cells and normal capsular space; "+" The glomerular cells were slightly proliferated and the capsular space was narrowed slightly. "++" glomerular cell proliferation and capsular space narrowing. "+++" Obvious glomerular cell proliferation and capsular space disappearing.

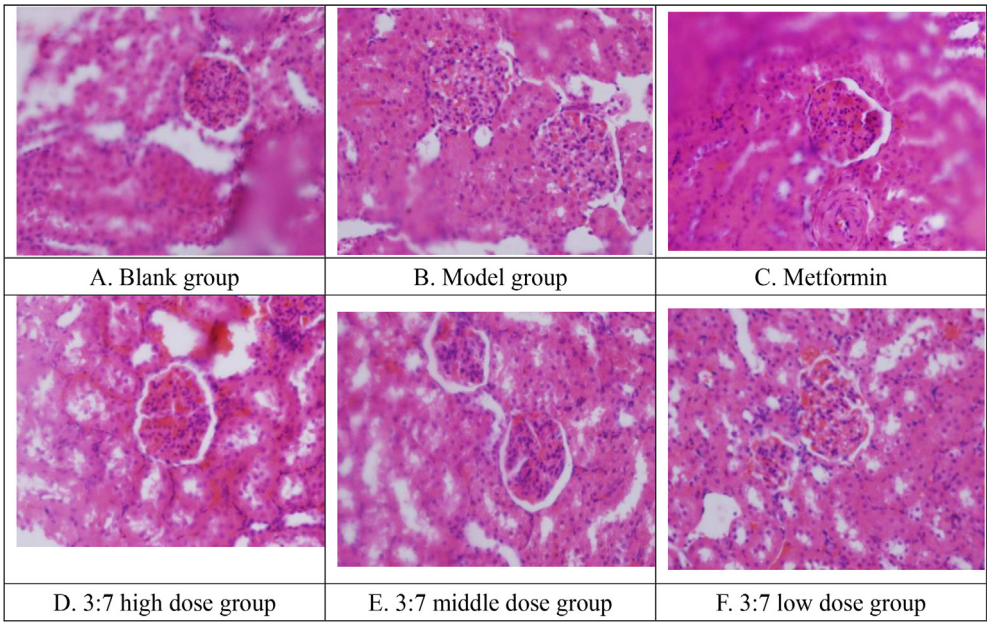

Fig. 16. Effect of 3:7 ratio of Astragalus total saponins and Curcumin on kidney tissue in DN rats (HE × 400).

bolism disorder is secondary to glucose metabolism disorder, and the two promote each other, forming a vicious cycle in the pathogenesis of DN, and regulating the lipid metabolism disorder on the basis of controlling blood sugar is an effective method to delay the complications of diabetes. The experimental results show that Astragalus total saponins and curcumin 3:7 ratio different doses could reduce the TC, TG and LDL of DN rats, and raise the level of HDL. Activation of oxidative stress reaction is an important pathologic link that causes DN occurrence. Poor blood glucose control can promote the generation of oxygen free radicals, and the overgenerated oxygen free radicals can cause oxidative damage to various cells in the glomerular structure (Aghadavod et al., 2016). GSH is an important antioxidant and free radical scavenger in the body, which can effectively alleviate the oxidative damage in the body. SOD is an important enzyme of lipid peroxidation, which can effectively remove superoxide anion free radicals produced by biological oxidation and has the effect of stopping radical chain reaction. MDA is one of the most important products of lipid peroxidation, and its accumulation can cause damage to cell structure and function. Therefore, GSH, SOD and MDA can be used as indicators to reflect the body's antioxidant capacity and scavenge free radical ability (Brezniceanu et al., 2008; Peng et al., 2014). The experimental results show that Astragalus total saponins and curcumin 3:7 ratio could decrease MDA content in diabetic nephropathy rats and increase the content of SOD and GSH, and significantly improve the oxidative stress level of DN rats. Renal failure, nephritis, urinary tract obstruction can increase blood urea nitrogen content. Proteinuria is the main characteristic of early DN, and the monitoring of microalbumin content has guiding significance to the prognosis of DN (Kaur et al., 2014). The experimental results show that Astragalus total saponins and curcumin 3:7 ratio different doses could reduce the kidney index, Cr and Proteinuria, indicating that it has protective effect on the renal function of DN rats. DN involves the pathological changes of viscera, kidney and pancreas is closely related to the course of disease, the experimental results show that Astragalus total saponins and curcumin 3:7 ratio different doses have the effect of improving the pathological changes of kidney and pancreas in DN rats.

To sum up, Astragalus total saponins and curcumin 3:7 ratio can reach the intervention effect by improve DN rats glycometableolism, insulin resistance, lipid metabolism, oxidative stress levels, renal function and pathological changes of the kidney and pancreas. The results of this experiment further verified the optimal proportion of the two components for the treatment of DN, and the effect was best in the 3:7 high-dose group, further promoted the research basis for the subsequent development and clinical application of Jiangi capsules.

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