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Study on the Effects of Aqueous Extracts of *Actinidia chinensis* Planch and *Mucuna macrocarpa* on Type 2 Diabetic Rats

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Abstract

Objective: To investigate the potential therapeutic effects of *Actinidia chinensis* Planch (*A. chinensis*) and *Mucuna macrocarpa* (*M. macrocarpa*) extracts alone and in combination on type 2 diabetes mellitus (T2DM) rats induced by a high-sugar and high-fat diet combined with streptozotocin (STZ). Methods: Forty-eight 8-week-old Sprague-Dawley (SD) rats were selected, with 8 rats assigned as the blank control group. The remaining 40 rats were fed a high-fat and high-sugar diet for 7 weeks combined with STZ injection to establish a T2DM rat model. Rats with successful modeling were randomly divided into 5 groups (n = 8 per group): the model group, Positive drug group (metformin, 75 mg/kg/d), *A. chinensis* Planch treatment group (4.5 g/kg/d), *M. macrocarpa* treatment group (2.25 g/kg/d), and Combination treatment group (*A. chinensis* Planch, 4.5 g/kg/d; *M. macrocarpa*, 2.25 g/kg/d). All groups received corresponding interventions for 6 weeks. The differences in drug efficacy were systematically evaluated by determining the levels of relevant biochemical indicators in rats, including fasting blood glucose(FBG), postprandial blood glucose(PBG), insulin (INS), total cholesterol (TC), triglycerides (TG), high-density lipoprotein Cholesterol (HDL-C), low-density lipoprotein Cholesterol (LDL-C), total superoxide dismutase (T-SOD), malondialdehyde (MDA), nitric oxide (NO), and total antioxidant capacity (T-AOC), combined with the observation of pathological changes in liver, kidney, and spleen tissues via hematoxylin-eosin (HE) staining. **Results**: Compared with the model group, the aqueous extracts derived from *A. chinensis* and *M. macrocarpa*, administered

as alone or in combination, significantly reduced the fasting and PBG levels of rats, ameliorated insulin resistance, regulated lipid metabolism, decreased the levels of TC, TG and LDL-C, and elevated the level of HDL-C. Furthermore, these extracts enhanced the antioxidant capacity, increased the activities of T-SOD and T-AOC, reduced the MDA level, and alleviated the pathological damage of liver, kidney and spleen tissues to varying degrees. Among the treatment groups, *M. macrocarpa* treatment group exhibited a superior hypoglycemic effect to both the combination group and *A. chinensis* treatment group; *A. chinensis* treatment group showed a more prominent lipid-lowering effect. In contrast, the combination group exerted the optimal synergistic protective effect on the pathological repair of liver, kidney and spleen tissues, which was superior to those of the monotherapy groups and the positive drug group. ConclusionThe aqueous extracts of *A. chinensis* and *M. macrocarpa* both exert significant hypoglycemic, lipid-regulating, antioxidant, and organ-protective effects on T2DM rats. The combined administration of these two extracts exerts a prominent protective effect in the repair of organ damage. The underlying mechanism may be associated with ameliorating insulin resistance, regulating lipid metabolism, and inhibiting oxidative stress. This study provides novel insights into natural herbal combinations and experimental evidence for the clinical treatment of T2DM and its complications.

Keywords

Actinidia chinensis Planch, *Mucuna macrocarpa*, Aqueous Extracts, Type 2 Diabetes Mellitus, Protective Effect

1. Introduction

Diabetes mellitus is a common clinical metabolic disease, whose pathogenesis is mainly associated with genetic and environmental factors. Currently, the incidence and prevalence of T2DM are increasing year by year worldwide. In recent years, the number of T2DM cases in China has risen to the highest globally. Studies have demonstrated that T2DM is often accompanied by dyslipidemia and oxidative stress responses, whereas dyslipidemia can exert an inhibitory effect on insulin secretion in the body [1]-[3]. *M. macrocarpa*, belonging to the genus *Mucuna* (Fabaceae), has roots and stems as its medicinal parts. It exerts pharmacological effects including nourishing blood, promoting blood circulation, relaxing muscles and tendons, and regulating menstruation [4]-[7]. *A. chinensis*, which is rich in various chemical components such as volatile compounds, multiple vitamins, actinidine, polysaccharides, as well as a variety of essential amino acids and trace elements for the human body. It exhibits therapeutic benefits including lowering blood lipids, resisting lipid peroxidation, preventing cancer, and enhancing immunity, and shows favorable curative effects on symptoms such as dysphoria with smothery sensation, diabetes-induced thirst, dry cough due to lung-heat, and hemorrhoids [8] [9]. Numerous studies have demonstrated that plant polysaccha-

rides possess prominent hypoglycemic and lipid-lowering activities with minimal toxic and side effects [10]. Therefore, an increasing number of researchers are committed to developing safe, cost-effective and potent natural drugs for hypoglycemic and lipid-lowering purposes using natural plants [11]-[13]. Through complementary advantages and combined application of multiple drugs, a comprehensive therapeutic effect on diseases can be achieved to fulfill the treatment goals. In this experiment, a rat model of T2DM was employed to investigate the hypoglycemic, lipid-lowering and antioxidant effects of *A. chinensis* and *M. macrocarpa*. when used alone or in combination, thereby providing new insights for diabetes research [14]-[17].

2. Materials and Methods

2.1. Animals

A total of 48 6-week-old male SD rats, with a body weight of 200 ± 25 grams, were used in this study. These rats were provided by Changsha Tianqin Biotechnology Co., Ltd., and the feed, Ethics Approval No.: 2024090601. Certificate No. SYXK (Gui) 2022-0004 and bedding were provided by the Animal Center of Youjiang Medical University for Nationalities. The high-sugar and high-fat feed was formulated with the following composition: 77.1% basal feed, 10% lard, 10% sucrose, 2.5% cholesterol, and 0.4% sodium cholate. All 48 male SD rats were given standard pellet feed for a 1-week adaptive feeding period, and then randomly divided into a blank control group (n = 8) and a model group (n = 40). The blank control group was continuously fed with normal feed, while the remaining rats were given high-sugar and high-fat feed. After 7 weeks of feeding, blood pressure and blood glucose levels were measured. To establish a T2DM model, rats fed with the HSHF diet were fasted for 12 h and then intraperitoneally injected with a single dose of 35 mg/kg streptozotocin (STZ) dissolved in 0.1 mol/L citric acid-sodium citrate buffer (pH 4.4). On the 7th day after STZ injection, fasting blood glucose (FBG) was measured using a glucometer. Blood samples were collected from the tail vein after 12 h of fasting, and rats with FBG ≥ 11.1 mmol/L were considered to have successful modeling. Subsequently, the successfully modeled rats were randomly allocated into 5 groups (8 rats per group): the model group, Positive drug treatment group, *A. chinensis* treatment group, *M. macrocarpa* treatment group, and Combination treatment group. The administration lasted for 6 weeks. At the end of the experiment, the rats were fasted for 12 h with free access to water, then anesthetized via intraperitoneal injection of urethane. The abdominal cavity was incised along the midline, and blood samples were collected from the abdominal aorta using a blood collection needle. The rats were then euthanized with all efforts made to minimize animal suffering. The liver, kidney and spleen tissues were quickly harvested. The specimens were fixed in 10% neutral formaldehyde solution following snap-freezing in liquid nitrogen, and then subjected to histopathological analysis.

2.2. Medicinal Materials and Drug Dosages

M. macrocarpa. was sourced from Donglan County, Guangxi in 2019, and *A. chinensis* were sourced from Leye County, Guangxi. The roots and stems of *M. macrocarpa* and the fruits of *A. chinensis* were extracted successively with 90% ethanol (room temperature, 3 repetitions, 3 days per repetition), 50% ethanol (room temperature, 3 repetitions, 3 days per repetition), and boiling water (2 repetitions, 0.5 hours per repetition), respectively. The extracts obtained from each of the two medicinal materials were pooled separately and subjected to vacuum concentration to obtain the *M. macrocarpa* root and stem extract and *A. chinensis* fruit extract. In this study, the dosage regimen was established strictly following the principle of interspecies equivalent dose conversion based on traditional folk monotherapeutic experience. According to the Guangxi Traditional Chinese Medicine Materials Standard and documented local folk medicinal practices, the conventional crude herb dosage of *M. macrocarpa* for treating chronic diseases ranges from 15 to 30 g daily for a 60-kg adult, while that of *A. chinensis* ranges from 30 to 60g daily. Considering safety profiles observed in preliminary experiments, we employed a conservative dosing strategy, and the human-to-rat equivalent dose conversion was calculated using a conversion factor of 6.2. Accordingly, the dosage for the *M. macrocarpa* group was derived from the median value of the traditional dose range (22.5 g), corresponding to 0.375 g/kg for a 60-kg human: $0.375 \times 6.2 \approx 2.3$ g/kg, thus set at 2.25 g/kg/d; the dosage for the *A. chinensis* group was calculated based on the customary dosage of 45 g (0.73 g/kg): $0.73 \times 6.2 \approx 4.5$ g/kg/d. The grouping and drug administration regimens for rats were as follows: *M. macrocarpa* treatment group (*M. macrocarpa* extract, 2.25 g/kg/d), *A. chinensis* treatment group (*A. chinensis* fruit extract, 4.5 g/kg/d), Positive drug group (metformin, 75 mg/kg/d), and Combination treatment group (*M. macrocarpa* extract, 2.25 g/kg/d; *A. chinensis* extract, 4.5 g/kg/d). During the administration period, the model group was given an equal volume of distilled water via intragastric gavage.

2.3. Instruments and Reagents

Cholesterol and STZ were purchased from Beijing Solarbio Science & Technology Co., Ltd. Kits for the detection of TC, TG, LDL-C, and HDL-C were obtained from Maccura Biotechnology Co., Ltd. The T-SOD assay kit was supplied by Medicalsystem Biotechnology Co., Ltd., while the kits for MDA, NO, and T-AOC detection were procured from Nanjing Jiancheng Bioengineering Institute. Urethane was provided by Shanghai Hengyuan Biotechnology Co., Ltd. Sodium citrate buffer and citric acid were purchased from Tianjin Guangfu Technology Development Co., Ltd. and Tianjin Damao Chemical Reagent Partnership Enterprise (Limited Partnership) respectively. For the histological analysis of liver, spleen, and kidney tissues, the Motic BA210 digital biological microscope and Motic BA600 virtual slide scanning system were supplied by Motic China Group Co., Ltd. (Xiamen, China). The LB941 multi-functional microplate reader (Berthold Technologies GmbH & Co. KG) was obtained from Hunan Xiangyi Laboratory

Instrument Development Co., Ltd. The B-100 rotary evaporator was manufactured by BUCHI Labortechnik AG (Switzerland), and the FA1204B electronic analytical balance was produced by Shanghai Techcomp Precision Instruments Co., Ltd. Both the SHB-III circulating water multi-purpose vacuum pump and DLSB-5/10 low-temperature cooling liquid circulation pump were products of Zhengzhou Greatwall Scientific Industrial and Trade Co., Ltd.

2.4. Data Analysis

Statistical analysis was performed using IBM SPSS Statistics 26 software. Quantitative data were expressed as mean ± standard deviation ($\overline{x} \pm s$). One-way analysis of variance (ANOVA) was employed to compare the differences among multiple groups. A value of $P < 0.05$ was considered to indicate a statistically significant difference. GraphPad Prism 8 and Microsoft Excel were used for graph construction.

3. Results

3.1. Prepare a Model of Type 2 Diabetes in Rats

In this experiment, a T2DM model was established in 40 male SD rats. A total of 48 male SD rats were used in the present study, among which 8 rats were assigned to the blank control group, and the remaining 40 rats were subjected to T2DM model induction. The blood glucose levels of the rats are shown in Table 1. All 40 rats were successfully modeled, with no deaths or dropouts observed throughout the experimental period. Finally, the 40 successfully modeled rats were randomly divided into four experimental groups, resulting in a final sample size of n = 8 per group across all five groups. Compared with the levels before model establishment, the blood glucose levels of the rats increased significantly after model preparation ($P < 0.01$), indicating the successful establishment of the T2DM rat model.

Table 1. Establishment of T2DM rat model ($\overline{x} \pm s$, n = 40).

	Number of rats (n)	Blood glucose level (mmol/L)
Before model establishment	40	4.67 ± 0.55
After model establishment	40	19.72 ± 3.74**
t		28.15
P		<0.0001

Note: Compared with the values before model establishment, *P < 0.05; **P < 0.01. Among the 48 rats, another 8 were used as the control group.

3.2. Effects of Aqueous Extracts on Glucose Homeostasis

The purpose of this experiment was to investigate the effects of the aqueous extracts of *A. chinensis*) and *M. macrocarpa* on glucose homeostasis in T2DM rats. As shown in Table 2, compared with the blank control group, the FBG levels in the model group were significantly elevated. After administration, compared with

the model group, the FBG levels in the Positive drug group and *M. macrocarpa* treatment group decreased significantly ($P < 0.01$), followed by a marked reduction in the combination treatment group ($P < 0.01$), and a decrease in the *A. chinensis* treatment group ($P < 0.05$). As shown in Table 3, compared with the blank control group, the PBG levels in the model group were significantly elevated ($P < 0.01$). In contrast, compared with the model group, the PBG levels in the Positive drug group decreased significantly ($P < 0.01$). Meanwhile, significant reductions in PBG levels were also observed in the *A. chinensis* treatment group, *M. macrocarpa* treatment group and combination treatment group ($P < 0.01$). Among these three groups, the *M. macrocarpa* treatment group showed the most pronounced reduction, though this effect was less potent than that of the positive drug group. As shown in Table 4, compared with the blank control group, the INS levels in the model group were significantly increased ($P < 0.01$). After intervention, compared with the model group, the INS levels of T2DM rats in the positive treatment drug group decreased, yet without significant statistical difference. In contrast, the serum INS levels of rats in the other three treatment groups all decreased with significant statistical differences ($P < 0.01$).

Table 2. Fasting blood glucose levels in rats ($\overline{x} \pm s$, n = 8).

	FBG (mmol/L)
Blank control group	3.65 ± 0.22
Model group	19.40 ± 1.78**
Positive drug group	10.23 ± 1.95##
A. chinensis treatment group	17.05 ± 1.84#
M. macrocarpa treatment group	10.42 ± 1.85##
Combination treatment group	15.64 ± 1.45##
F	124.8
P	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; compared with the model group, #P < 0.05, ##P < 0.01.

Table 3. Postprandial blood glucose levels in rats ($\overline{x} \pm s$, n = 8).

	PBG (mmol/L)
Blank control group	4.39 ± 0.84
Model group	24.93 ± 2.63**
Positive drug group	11.42 ± 1.69##
A. chinensis treatment group	20.51 ± 2.23##
M. macrocarpa treatment group	18.42 ± 3.59##

Continued

Combination treatment group	19.31 ± 2.18##
F	98.34
P	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; compared with the model group, #P < 0.05, ##P < 0.01.

Table 4. Serum insulin levels in rats ($\overline{x} \pm s$, n = 8).

	INS (mIU/L)
Blank control group	16.38 ± 0.97
Model group	20.01 ± 1.43**
Positive drug group	19.03 ± 1.39
A. chinensis treatment group	17.94 ± 1.07##
M. macrocarpa treatment group	17.93 ± 1.04##
Combination treatment group	16.86 ± 0.91##▲▲
F	13.59
P	<0.0001

Note: Compared with the blank control group, *P<0.05; **P<0.01; Compared with the model group, #P < 0.05, ##P < 0.01. Compared with the positive drug group, ▲P < 0.05, ▲▲P < 0.01.

3.3. Effects of Aqueous Extracts on Lipid Profiles

The present study aimed to investigate the effects of *A. chinensis* and *M. macrocarpa* aqueous extracts on dyslipidemia in T2DM rats. As shown in Table 5, compared with the blank control group, the TG and TC levels in the model group were significantly elevated (P < 0.01), indicating lipid accumulation and metabolic abnormalities. Compared with the model group, the TG and TC levels in all treatment groups exhibited significant reductions (P < 0.01). Specifically, the TG levels in *A. chinensis* treatment group were significantly lower than those in the Positive drug group (P < 0.01), while the TG levels in the *M. macrocarpa* treatment group were also significantly lower than those in the Positive drug group (P < 0.05). In terms of TC regulation, the levels in all treatment groups decreased to values close to those of the blank control group, with no significant differences observed among these groups. As shown in Table 6, compared with the blank control group, the HDL levels in the model group were significantly decreased (P < 0.01), whereas the LDL levels were significantly elevated (P < 0.01), indicating impaired lipid transport function under T2DM conditions. Compared with the model group, the LDL levels in all treatment groups were significantly reduced (P < 0.01). Specifically, the HDL levels in the *A. chinensis* treatment group were significantly in-

creased ($P < 0.01$) and were also significantly higher than those in the Positive drug group ($P < 0.01$). Although the HDL levels in the remaining treatment groups exhibited an upward trend, this trend did not reach statistical significance. Additionally, the HDL and LDL levels in the combination treatment group showed no significant differences from those in the monotherapy groups, with all indicators maintained within the normal physiological range.

Table 5. Effects of aqueous extracts on serum TG and TC levels in rats ($\overline{x} \pm s$, n = 8).

	TG (mmol/L)	TC (mmol/L)
Blank control group	0.11 ± 0.02	3.23 ± 0.48
Model group	0.27 ± 0.05**	4.94 ± 0.53**
Positive drug group	0.18 ± 0.03##	3.49 ± 0.63##
A. chinensis treatment group	0.12 ± 0.03##▲▲	3.68 ± 0.61##
M. macrocarpa treatment group	0.13 ± 0.03##▲	3.32 ± 0.67##
Combination treatment group	0.13 ± 0.02##▲	3.74 ± 0.62##
F	36.67	11.03
P	<0.0001	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; Compared with the model group, #P < 0.05, ##P < 0.01. Compared with the positive drug group, ▲P < 0.05, ▲▲P < 0.01.

Table 6. Effects of aqueous extracts on serum HDL and LDL levels in rats ($\overline{x} \pm s$, n = 8).

	HDL (mmol/L)	LDL (mmol/L)
Blank control group	0.86 ± 0.12	0.92 ± 0.06
Model group	0.70 ± 0.12**	1.12 ± 0.12**
Positive drug group	0.67 ± 0.12	0.87 ± 0.11##
A. chinensis treatment group	0.98 ± 0.11##▲▲	0.81 ± 0.09##
M. macrocarpa treatment group	0.81 ± 0.13	0.82 ± 0.10##
Combination treatment group	0.80 ± 0.14	0.96 ± 0.09##
F	8.227	14.10
P	<0.0001	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; Compared with the model group, #P < 0.05, ##P < 0.01. Compared with the positive drug group, ▲P < 0.05, ▲▲P < 0.01.

3.4. Effects of Extracts on Lipid Peroxidation Levels in Rats

The present study aimed to investigate the effects of *A. chinensis* and *M. macrocarpa* aqueous extracts on oxidative stress and inflammatory status in T2DM rats. As

shown in Table 7, compared with the blank control group, the T-SOD activity in the model group was significantly decreased ($P < 0.01$), while the MDA level was significantly elevated ($P < 0.01$), indicating decreased antioxidant enzyme activity and accumulation of lipid peroxidation products in T2DM model rats. Compared with the model group, all treatment groups improved the above indicators to varying degrees. Specifically, the *A. chinensis* treatment group exhibited a significant increase in T-SOD activity, which was significantly superior to that of the positive drug group ($P < 0.01$), along with a marked reduction in MDA levels ($P < 0.01$). The *M. macrocarpa* treatment group also showed significant improvements in both T-SOD activity and MDA levels ($P < 0.01$). In the combination treatment group, T-SOD activity was significantly increased ($P < 0.01$) and MDA levels were decreased ($P < 0.05$). These results indicated that both natural medicines could alleviate oxidative stress damage by enhancing antioxidant enzyme activity and reducing the production of lipid peroxidation products, with the *Actinidia chinensis* treatment group demonstrating the optimal efficacy. As shown in Table 8, compared with the blank control group, the model group rats exhibited a significant reduction in serum NO levels and a marked decrease in T-AOC. These findings are highly consistent with the well-established pathological features of diabetes, including enhanced oxidative stress and impaired endothelial function. The aqueous extract of *A. chinensis* showed a trend toward increasing NO levels in diabetic rats, although this effect did not reach statistical significance. In contrast, it significantly enhanced T-AOC ($P < 0.05$), suggesting a prominent role in improving endothelial function and antioxidant defense. Conversely, the other treatment groups were less effective in improving both NO and T-AOC compared to the *A. chinensis* treatment group. This indicates that their protective effects may not be primarily mediated through the modulation of NO or T-AOC, but rather through alternative pathways such as anti-inflammatory and anti-apoptotic mechanisms.

Table 7. Effects of aqueous extracts on serum T-SOD and MDA levels in rats ($\overline{x} \pm s$, n = 8).

	T-SOD (U/mL)	MDA (mmol/L)
Blank control group	2.33 ± 0.04	1.60 ± 0.14
Model group	1.83 ± 0.05**	2.64 ± 0.38**
Positive drug group	1.96 ± 0.05##	2.46 ± 0.28
A. chinensis treatment group	2.15 ± 0.04##▲▲	2.23 ± 0.17##
M. macrocarpa treatment group	2.02 ± 0.07##	2.14 ± 0.25##
Combination treatment group	2.03 ± 0.07##	2.27 ± 0.16#
F	97.42	20.95
P	<0.0001	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; Compared with the model group, #P < 0.05, ##P < 0.01. Compared with the positive drug group, ▲P < 0.05, ▲▲P < 0.01.

Table 8. Effects of aqueous extracts on serum NO and T-AOC levels in rats ($\bar{x} \pm s$, n = 8).

	NO (mmol/L)	T-AOC (mmol/L)
Blank control group	94.12 ± 8.69	0.16 ± 0.05
Model group	67.91 ± 5.83**	0.11 ± 0.02**
Positive drug group	65.21 ± 5.94	0.09 ± 0.03
A. chinensis treatment group	73.32 ± 5.46	0.15 ± 0.02#
M. macrocarpa treatment group	67.12 ± 9.42	0.13 ± 0.02
Combination treatment group	62.55 ± 6.91	0.12 ± 0.02
F	25.71	8.000
P	<0.0001	<0.0001

Note: Compared with the blank control group, *P < 0.05; **P < 0.01; Compared with the model group, #P < 0.05, ##P < 0.01. Compared with the positive drug group, ▲P < 0.05, ▲▲P < 0.01.

3.5. Pathological Effects of Aqueous Extracts on Liver Tissues of Rats

The purpose of the present experiment was to investigate the pathological effects of aqueous extracts on liver tissues of T2DM rats (Figure 1). HE staining results of rat liver tissue sections showed that the liver tissues of the blank control group were structurally intact, with neatly arranged hepatocytes and distinct nuclei, and no pathological changes such as fatty degeneration or inflammatory cell infiltration were observed. In contrast, the hepatocytes of the model group presented obvious fatty degeneration, with numerous vacuoles observed around the central veins; the cells were swollen and disordered, accompanied by mild inflammatory cell infiltration. Both the *A. chinensis* and *M. macrocarpa* aqueous extract treatment groups alleviated hepatocyte injury to varying degrees, characterized by reduced vacuole numbers and mitigated inflammatory infiltration, among which the *M. macrocarpa* monotherapy group exhibited a more significant improvement effect. Notably, in the combination treatment group, hepatocyte morphology was close to normal, with almost no fatty degeneration, regularly arranged cells, distinct central vein structure and no obvious inflammatory cell infiltration. Its liver tissue repair effect was significantly superior to that of the monotherapy groups and the positive drug treatment group, demonstrating a synergistic protective effect.

3.6. Pathological Effects of Aqueous Extracts on Spleen Tissues of Rats

The purpose of the present experiment was to investigate the pathological effects of aqueous extracts on Spleen tissues of T2DM rats (Figure 2). In the blank control group, the boundaries between the white pulp and red pulp of rat spleens were distinct, lymphocytes were orderly arranged, and no hyperemia or inflammatory cell infiltration was observed. In contrast, the spleens of the model group pre-

sented white pulp atrophy, decreased number and reduced volume of lymphoid follicles, obvious red pulp hyperemia, and accompanied by massive inflammatory cell infiltration, indicating immune dysfunction. Both the *A. chinensis* and *M. macrocarpa* treatment groups promoted the structural restoration of white pulp, increased the number of lymphoid follicles, and alleviated red pulp hyperemia and inflammatory infiltration to varying degrees, among which the *M. macrocarpa* treatment group showed a more pronounced improvement. Notably, in the combination treatment group, the splenic white pulp exhibited intact structure, the lymphoid follicles were abundant and orderly arranged, the red pulp showed no obvious hyperemia, and inflammatory cell infiltration was minimal. Its efficacy in repairing splenic immune structure and inhibiting inflammation was superior to that of the monotherapy groups, demonstrating a synergistic protective effect on splenic function.

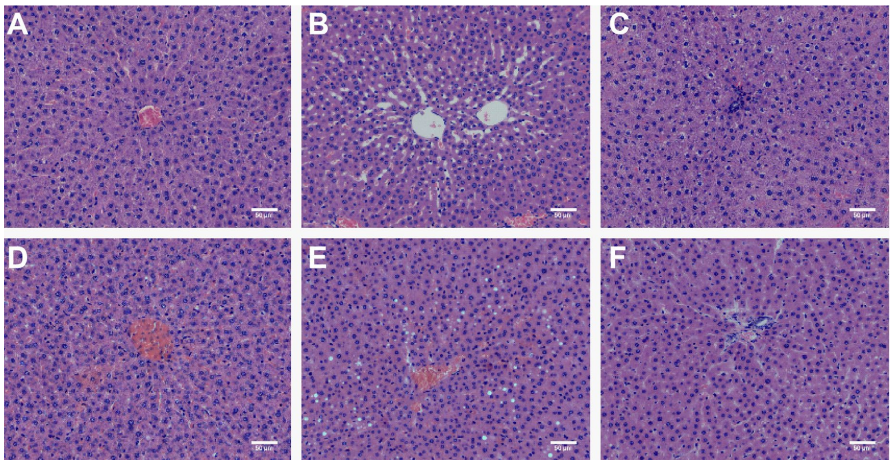

Figure 1. HE staining results of rat liver tissues in each group (×200). Note: A. Blank control group; B. Model group; C. Positive drug group; D. *M. macrocarpa* treatment group; E. *A. chinensis* treatment group; F. Combination treatment group.

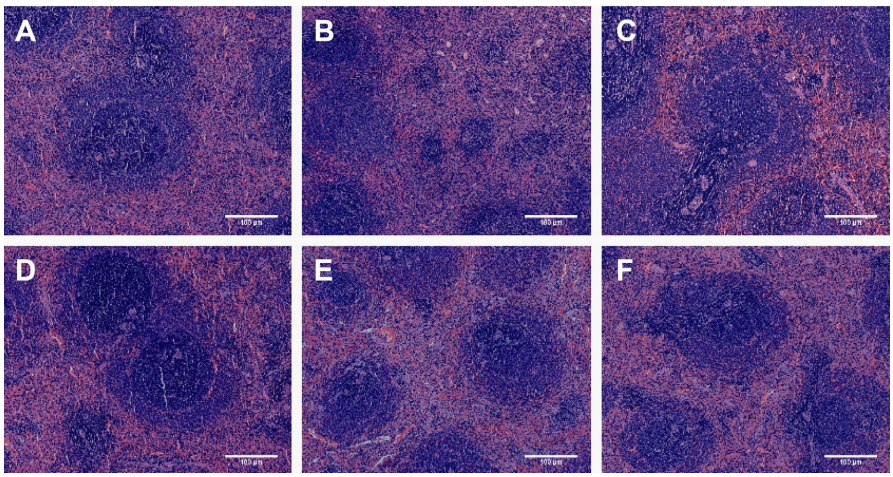

Figure 2. HE staining results of rat Spleen tissues in each group (×100). Note: A. Blank control group; B. Model group; C. Positive drug group; D. *M. macrocarpa* treatment group; E. *A. chinensis* treatment group; F. Combination treatment group.

3.7. Pathological Effects of Aqueous Extracts on Kidney Tissues of Rats

The purpose of the present experiment was to investigate the pathological effects of aqueous extracts on Kidney tissues of T2DM rats (Figure 3). In the blank control group, the renal glomeruli were structurally intact, the capillary loops were distinct, the number of mesangial cells was normal, the renal tubular epithelial cells were orderly arranged, and no inflammatory cell infiltration was observed in the interstitium. In contrast, the model group exhibited swollen glomerular capillary loops, widened mesangial regions, and massive inflammatory cell infiltration in the interstitium. Both the *A. chinensis* and *M. macrocarpa* treatment groups alleviated the above pathological damages, as evidenced by reduced glomerular swelling and mesangial widening, regularized renal tubular structure, and decreased inflammatory infiltration. Notably, the renal tissue morphology of the combination treatment group was the closest to that of the blank control group, with intact glomerular capillary loop structure, orderly arranged renal tubular epithelial cells, unexpanded lumens, and no obvious inflammatory cell infiltration in the interstitium. Its efficacy in protecting and repairing renal filtration function and tissue structure was superior to that of the monotherapy interventions.

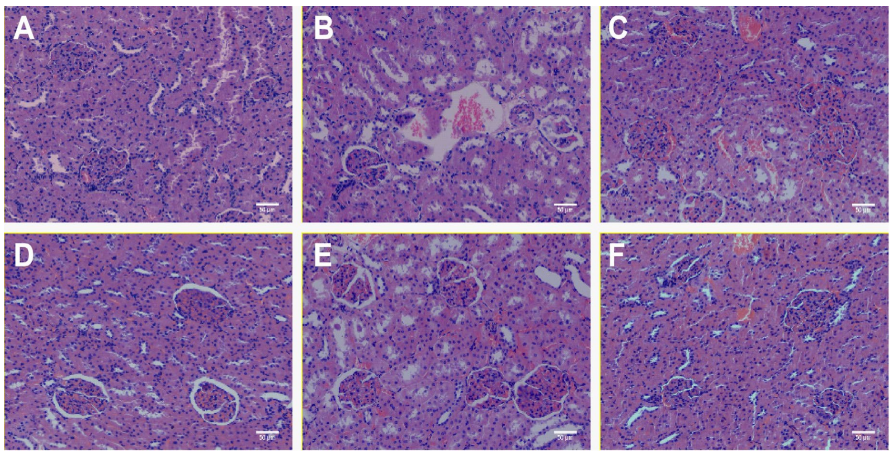

Figure 3. HE staining results of rat kidney tissues in each group (×200). Note: A. Blank control group; B. Model group; C. Positive drug group; D. *M. macrocarpa* treatment group; E. *A. chinensis* treatment group; F. Combination treatment group.

4. Discussion

T2DM, a globally prevalent metabolic disease, has a complex pathological mechanism and is often characterized by glucose and lipid metabolism disorders, oxidative stress, chronic inflammatory responses, and multi-organ damage. Owing to the advantages of multiple components, multi-targeting effects, and low toxic and side effects, natural medicines have attracted considerable attention in the comprehensive treatment of T2DM [18] [19]. In this study, aqueous extracts of *A. chinensis* and *M. macrocarpa* were used as intervention agents. Using a T2DM rat model, we systematically investigated their therapeutic effects when administered

alone and in combination, thereby providing experimental evidence for the combined application of natural medicines.

With respect to the regulation of glucose and lipid metabolism, the results of this study demonstrated that these two natural medicines exhibited distinct advantages. The *M. macrocarpa* treatment group showed a significant hypoglycemic effect: the FBG level in this group was comparable to that in the positive drug group, accompanied by a significant reduction in serum insulin level, indicating prominent hypoglycemic activity and efficacy in improving islet function [20]. In contrast, *A. chinensis* treatment group exhibited outstanding performance in lipid-lowering, with its TG and HDL levels superior to those in other groups. This might be attributed to the abundant polysaccharides, polyphenols and flavonoid compounds in its fruits, which can regulate blood lipids by modulating intestinal flora and inhibiting lipid absorption [21] [22]. Notably, the combination treatment group exhibited no obvious protective effect in regulating glucose and lipid metabolism. It is speculated that this may be related to the partial overlap in their mechanisms of action or a suboptimal dose ratio, and subsequent gradient dose experiments are required to optimize the compatibility ratio. In terms of antioxidant and anti-inflammatory effects, both the *A. chinensis* treatment group and *M. macrocarpa* treatment group aqueous extracts demonstrated definite protective effects. Under T2DM conditions, hyperglycemia-induced ROS can reduce the activity of antioxidant enzymes, cause the accumulation of oxidative products, and activate inflammatory pathways, which in turn lead to organ damage. In this study, the *A. chinensis* treatment group exhibited significantly higher T-SOD activity and markedly lower MDA levels than the other groups, demonstrating its prominent antioxidant properties. There was no significant difference in NO levels between the *M. macrocarpa* treatment group and the model group ($P = 0.78 > 0.05$), The single-dose intervention regimen may not have achieved the optimal dosage for NO modulation, and serum NO levels could also be affected by other factors such as the detection time point and the degree of inflammation.

Notably, organ protection represents the core finding of this study, and the combination treatment group exhibited significant synergistic advantages. The combination treatment exhibited a superior organ protective effect to monotherapies, yet failed to exceed the theoretical additive effect. Pathological results indicated that both the *M. macrocarpa* treatment group and the *A. chinensis* treatment group exerted certain reparative effects on organ damage repair: they were able to alleviate hepatocyte steatosis induced by T2DM, reduce glomerular mesangial widening and inflammatory infiltration, promote the structural restoration of splenic white pulp, and alleviate red pulp congestion and inflammatory infiltration. In addition, the morphological features of liver, kidney and spleen tissues in the combination treatment group were the closest to those in the blank control group, with no significant hepatocyte steatosis, intact glomerular structure, and regular splenic immune structure. By comparison, although metformin, the positive control drug, showed remarkable hypoglycemic efficacy, its performance in

organ protection was inferior to that of natural medicines. This finding suggests that T2DM treatment should balance blood glucose control and complication prevention.

This study has certain limitations: the core active components responsible for the efficacy of the two agents have not been identified; in addition, only a single ratio was adopted in the experiment, failing to maximize the protective effect. Future research should further investigate the optimal dose ratio of *M. macrocarpa* and *A. chinensis* extracts to maximize their protective effect. Meanwhile, it is necessary to further isolate and identify the core components such as polysaccharides from *M. macrocarpa* and *A. chinensis*, so as to clarify their main pharmacodynamic ingredients. Moreover, network pharmacology and molecular biology techniques should be employed to reveal the synergistic action pathways [23]-[26]. This will provide more precise theoretical support and clinical reference for the combined natural medicine therapy of T2DM and its complications.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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