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Research Article

T-Fiber, A Highland Barley Fiber-Rich Powder, Alleviates Hyperglycemia and Improves Kidney Pathology in Db/db Mice

Yang Yang,[1] **Ma Yue**,[2] **Han Jing**,[2] **Peng Weijia**,[3] **Pi Rongbiao**,[1] **Yang Bo**,[2] **and Zhu Zeyu**[3]

[1]*School of Medicine, Sun Yat-Sen University, Shenzhen 518107, Guangdong, China*
[2]*Tibet Cheezheng Highland Barley Health Technology Co. Ltd., Lhasa 850000, Tibet, China*
[3]*School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, Guangdong, China*

Correspondence should be addressed to Zhu Zeyu; zhuzy23@mail2.sysu.edu.cn

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The role of dietary fiber in highland barley in lowering blood lipids has been continuously studied in recent years. However, its effects on diabetes and diabetic nephropathy are rarely studied. Considering that highland barley bran is rich in dietary fiber, the effective use of dietary fiber in highland barley bran can not only alleviate the symptoms of diabetes but also improve the local economy. This article aimed to study the effects of highland barley fiber-rich powder (**T-fiber**) with a high-quality natural dietary fiber ratio (insoluble fiber/soluble fiber = 3 : 1) on the symptoms of hyperglycemia in a diabetic mouse model. Compared with the model group's blood glucose level (30.80 mmol/L), glucose tolerance (28.57 mmol/L), and glycosylated serum protein (2.43 mmol/L), **T-fiber** presented significant reductions in blood glucose (23.69 mmol/L), better glucose tolerance (21.32 mmol/L), and glycosylated serum protein (1.78 mmol/L) in the diabetic mouse model. Meanwhile, **T-fiber** effectively alleviated hepatocellular lesions. In addition, **T-fiber** not only improved kidney function by reducing the 24-hour urine output (8.25 ml), urine protein levels (11.51 mg), and serum creatinine (13.80 μmol/L) but also alleviated renal pathology, including glomerular hypertrophy, mesangial expansion, and fibrosis. The above results proved the ability of **T-fiber** to reduce blood glucose and alleviate liver and renal function in diabetic mice. Altogether, **T-fiber** is a capable formula for utilizing highland barley bran dietary fiber, which alleviates diabetes symptoms and endows highland barley with promising value.

1. Introduction

Type 2 diabetes (T2DM) accounts for more than 90% of the total diabetic population and is often accompanied by various complications such as cardiovascular disease and diabetic nephropathy (DN); these symptoms often cause severe psychological and physical pain to patients [1]. How to effectively delay T2DM has become an urgent problem. Dietary interventions, especially diets rich in dietary fiber, are effective in preventing or delaying T2DM [2]. Dietary fiber includes insoluble dietary fiber and soluble dietary fiber. Insoluble dietary fiber can effectively improve the distribution of intestinal bacteria and regulate the digestive system, while soluble dietary fiber such as β-glucan has a good antioxidation and lipid-lowering effect [3, 4]. Interestingly, researchers found that a daily intake of 2 grams of dietary fiber from grains was associated with a 6% lower risk of T2DM [5]. Therefore, the intervention of a high dietary fiber diet for T2DM may be a potential treatment in the future.

Highland barley is one of the agricultural resources with export potential and one of the agricultural resources for sustainable economic development in the Tibet Plateau, China [6, 7]. Highland barley has the highest dietary fiber and nutrient content among high-altitude cereals, which also makes the largest contribution to the dietary fiber intake of people in high-altitude areas. Some epidemiological studies concluded that people in high-altitude areas have a low prevalence of diabetes, indicating that the dietary fiber of highland barley has a close relationship with human dietary health [8–10]. Highland barley dietary fiber includes

a variety of biological active ingredients, such as β-glucan, active polyphenols, etc. The above active ingredients have been found to have lipid-lowering, antioxidant, and other effects in recent years [11–13]. In addition, after microwaving, baking, and heat fluidization, treated highland barley dietary fiber displayed a higher antioxidant activity, β-glucan extractability, and improved liver injury of obese mice [14]. The above research indicates that the dietary fiber in highland barley is a potential cash crop. If the dietary fiber of highland barley can be further developed, it may have greater significance in the treatment of antidiabetes and diabetic nephropathy.

Highland barley fiber-rich powder (**T-fiber**) is a kind of natural nutritional powder rich in high-quality dietary fiber. **T-fiber** mainly consists of the dietary fiber from the highland barley bran in the Tibet Plateau, China. The ratio of high-quality natural dietary fiber is determined based on the Food and Drug Administration (FDA) (the ratio of insoluble dietary fiber to soluble dietary fiber = 3 : 1) [13]. Previous studies on the components of highland barley mainly focused on the hypoglycemic and lipid-lowering effects of β-glucan and polyphenols, while studies on the effects of dietary fiber in highland barley on T2DM and DN were limited. In this study, the classic T2DM model transgenic mice (Db/db mice) were used to explore the effect of **T-fiber** on hyperglycemia. Our research showed that **T-fiber** not only reduces blood glucose levels but also improves liver and renal function in Db/db mice. Altogether, **T-fiber** may be a formula that can effectively use highland barley bran dietary fiber to improve diabetes symptoms and improve the utilization value of highland barley.

2. Materials and Methods

2.1. Materials and Reagents. Whole grain power and highland barely rich fiber power (**T-fiber**) were provided by Tibet Cheezheng Highland Barley Health Technology Co., Ltd. (Tibet, China). Glycated serum protein (GSP) kit (Nitrotetrazolium blue chloride method, A037-2-1), urine protein quantitative detection kit (Coomassie brilliant blue G250 method, C035-2-1), urea nitrogen quantitative detection kit (Urease method, C013-2-1), and serum creatinine detection kit (Sarcosine oxidase method, C011-2-1) were purchased from Nanjing Jiancheng Biotechnology Research Institute (Nanjing, Jiangsu, China).

2.2. Animal Experiments. Male C57BL/KsJ$^{-db/m}$ (Wildtype, WT) and C57BL/KsJ$^{-Db/db}$ (Db/db) mice (8 weeks) (Yaokang Biotechnology Co., Ltd., Guangzhou, Guangdong, China) were housed at 24°C and a 12 h light-dark cycle in the Laboratory Animal Center of Sun Yat-sen University, during which the animals had free access to food and water. After the mice were adapted to the environment for 1 week, they were randomly divided into 5 groups (n = 10/group): (1) the control group (AIN-93M); (2) the model group (AIN-93M); (3) the whole grain power (WG) group (AIN-93M adjusted 44% whole grain power (w/w)); (4) the **T-fiber** low dosage group (T-L group) (AIN-93M adjusted 10% **T-fiber** (w/w)); and (5) the **T-fiber** high dosage group (T-H group) (AIN-93M adjusted 44% **T-fiber** (w/w)). All diets were manufactured by Xietong Organism Co., Ltd. (Jiangsu, China) in a cylindrical shape. In the WG and **T-fiber** groups, the composition of the diet was adjusted so that the final protein and fat percentages (by body weight) were nearly equal (Table 1). Weekly use of a calibrated scale and blood glucose meter (Accu-Chek; Roche Diagnostics, Mannheim, Germany) measured the body weight and blood glucose of the mice. Use metabolic cages to collect urine from mice for 24 hours and record the urine output. Whole blood was collected by the method of orbital blood collection, and serum was separated by centrifugation (3000 g, 15 min) and stored at −20°C. Then, liver and kidney tissues were collected, weighed, and frozen in liquid nitrogen for further studies. All protocols involving animal usage were approved by the Animal Ethical and Welfare Committee of Sericultural and Agri-Food Research Institute of Guangdong Academy of Agricultural Sciences and followed the Guiding Principles in the Care and Use of Animals.

2.3. Fasting Blood Glucose and Oral Glucose Tolerance Test (OGTT). Collections of tail vein blood were applied every week after an overnight fast for the testing of fasting blood glucose (n = 10 per group). The OGTT test was conducted as the final experiment of the study (n = 10 per group). In the OGTT test, after oral administration with 2 g/kg glucose, mice blood glucose were tested at 0, 30, 60, and 120 min. Blood glucose levels were quantified utilizing an Accu-Chek active blood glucose meter (Roche, Mannheim, Germany).

2.4. Biochemical Analysis. At the final stage of the experiment, urine was collected from the experiment mice after they had been housed in metabolic cages for 24 h. All mice were sacrificed after anesthesia, and serum separated from blood samples was stored at −20°C. Kidney and liver samples were quickly excised for weighting and fixed in 4% paraformaldehyde or frozen at 4°C afterwards. The measurement of glycated serum protein (GSP), blood urea nitrogen (BUN), serum creatinine (Cr), and 24 h urinary protein (UP) levels was detected utilizing commercially available kits (Jiancheng Biotech, China). After being fixed with 4% paraformaldehyde and embedded in paraffin, sections of the liver and kidney (4 μm thick) were stained with PAS, hematoxylin-eosin (HE), and Masson. The results were photographed by a light microscope, and the images were converted into digital images to analyze the pathological changes of the glomerulus. In addition, the immunohistochemical and immunofluorescence experiments on kidney tissue sections were performed by the Guangzhou Sevier Biology Company. The above results were tested by two researchers who were unaware of the experimental groups, and the results were consistent with the double-blind test criteria.

2.5. Statistical Analysis. All bar graphs were expressed as the mean ± SEM. Statistical comparisons among experimental groups were analyzed by one-way ANOVA, two-way ANOVA, and Duncan's multiple range test using

Table 1: Feed formulations and energy components.

Ingredient (g)	Control	Model	WG	T-L	T-H
Casein	140.000	140.000	95.239	123.500	58.211
L-cystine	1.800	1.800	1.800	1.800	1.800
Corn starch	495.682	495.692	180.927	446.692	241.303
Maltodextrin 10	125.000	125.000	125.000	125.000	125.000
Sucrose	100.000	100.000	100.000	100.000	100.000
Whole grain power	0	0	495.692	0	0
T-fiber*	0	0	0	100.000	507.192
Cellulose, BW200	50.000	50.000	50.000	50.000	50.000
Soybean oil	40.000	40.000	31.078	36.300	21.695
t-butylhydroquinone	0.008	0.008	0.008	0.008	0.008
Mineral mix S10022M	35.000	35.000	35.000	35.000	35.000
Vitamin mix V10037	10.000	10.000	10.000	10.000	10.000
Choline bitartrate	2.500	2.500	2.500	2.500	2.500
FD&C red dye #40	0	0.050	0	0	0.025
FD and C yellow dye #5	0	0	0.050	0	0
FD and C blue dye #1	0	0	0	0.050	0.025
Total	1000	1000.50	1127.294	1030.850	1152.759
Protein (kcal %)	14.7	14.7	14.7	14.7	15.0
Carbohydrate (kcal %)	75.9	75.9	75.9	75.9	75.5
Fat (kcal %)	9.4	9.4	9.4	9.4	9.5
Total	100	100	100	100	100

GraphPad Prism 7.0 software (version 17.0, GraphPad Inc., California, USA). *P*-values <0.05 were considered statistically significant.

3. Results

3.1. T-Fiber Changed the Diet and Water Intake but Did Not Affect Body Weight of Db/db Mice. To study the effect of **T-fiber** on hyperglycemia, **T-fiber** was coadministered with AIN-93M at two doses (low dose of 10%, T-L; high dose of 44%, T-H). Compared with the CT group, the diet, water intake, and body weight of the Db/db mice were significantly increased ($P < 0.001$) (Figures 1(a) and 1(b)). The above phenomena are consistent with the growth characteristics of polydipsia, hypereating, and obesity in Db/db mice [15]. In addition, compared with the model group, the T-H group significantly increased food and water intake from week 4 onwards ($P < 0.001$). However, the dietary intervention had no effect on the weight of the mice (Figure 1(c)). These results indicated that **T-fiber** altered the diet and water intake of Db/db mice but did not affect their body weight.

3.2. T-Fiber Decreased Fasting Blood Glucose Values, Oral Glucose Tolerance, and GSP Levels in Db/Db Mice. Further, we examined the effect of **T-fiber** on blood glucose in Db/db mice. The results showed that CT group retained the lowest fasting blood glucose level throughout the experiment (Figure 2(a)). The fasting blood glucose levels in different groups were similar at the initial stage of the experiment ($P > 0.05$) (Figure 2(a)), which is in line with the growth characteristics of Db/db mice with hyperglycemia [15]. After 2 weeks of intervention, the hypoglycemic effect of **T-fiber** was observed. From the fourth week, fasting blood glucose in T-H group was maintained at a lower level than that in model group ($P < 0.01$). In contrast, there was no significant difference in fasting blood glucose between WG group and model group after 8 weeks of dietary intervention (Figure 2(a)). In OGTT test, all groups reached a peak serum glucose level at 30 minutes and gradually decreased afterwards. The model and WG groups presented slowest serum glucose reduction, while T-H group exhibited the best intervention effect ($P < 0.001$) (Figure 2(b)). In the comparison of area under curve(AUC) in OGTT, T-L and T-H group exhibited a better hypoglycemic effect than model group but failed to reach significance. ($P > 0.05$) (Figure 2(c)). GSP was measured at the end of the experiment to reflect the average blood glucose level over the past 2–3 weeks. The GSP level of the T-L and T-H groups was significantly lower than that of the model group ($P < 0.001$) (Figure 2(d)). The above results indicated that **T-fiber** could ameliorate the dysregulation of glucose metabolism in Db/db mice.

3.3. T-Fiber Improved Liver Pathology in Db/Db Mice. Since **T-fiber** decreased the glucose level and glucose tolerance in Db/db mice, the hepatic pathology was next examined by immunohistochemistry (HE, PAS, Masson staining). The results showed that the liver weight (Figure 3(a)) and index(Figure 3(b)) of the model group increased significantly compared with the CT group ($P < 0.001$), and the liver weight and index of the T-L and T-H groups were decreased to a certain extent compared with model group ($P < 0.05$). HE staining was used to analyze the injury of hepatocytes in each group. Notably, hepatocytes in the model and WG group showed obvious vacuolar degeneration compared with the CT group. In contrast, the vacuolation of hepatocytes in Db/db mice was significantly reduced in the T-H group (Figure 3(c)). Next, we used PAS to detect glycogen accumulation in hepatocytes. The results

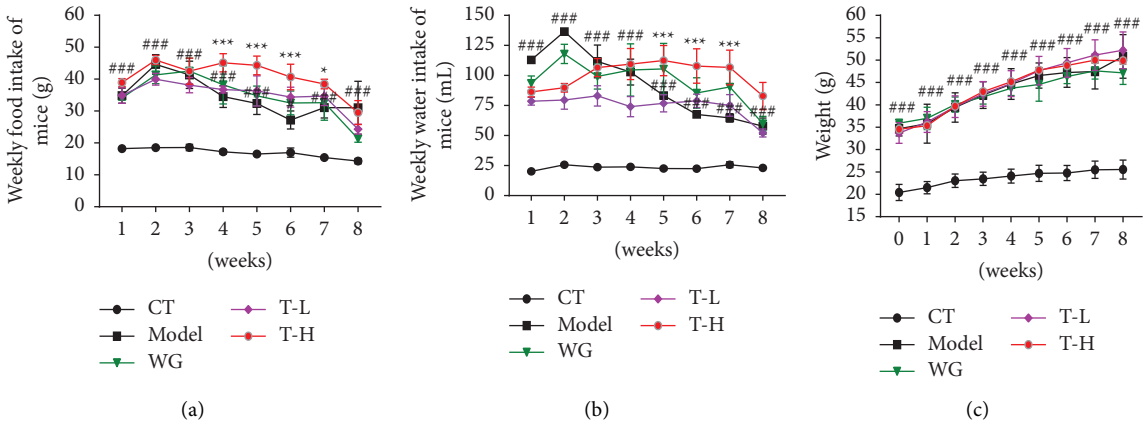

FIGURE 1: T-fiber changed the diet and water intake of Db/db mice but did not affect body weight. (a) and (b) Weekly food and water intake measurements of mice were recorded for each group; (c) weekly weight of mice measurements were recorded for each group; The data were showed as mean ± SEM and analyzed using two-way ANOVA followed by Dunnett's *t*-test. $N = 8–10$/group. $^{\#}P < 0.05$ vs. CT, $^{\#\#\#}P < 0.001$ vs. CT, $^{*}P < 0.05$ vs. model, $^{***}P < 0.001$ vs. model. $N = 8–10$/group.

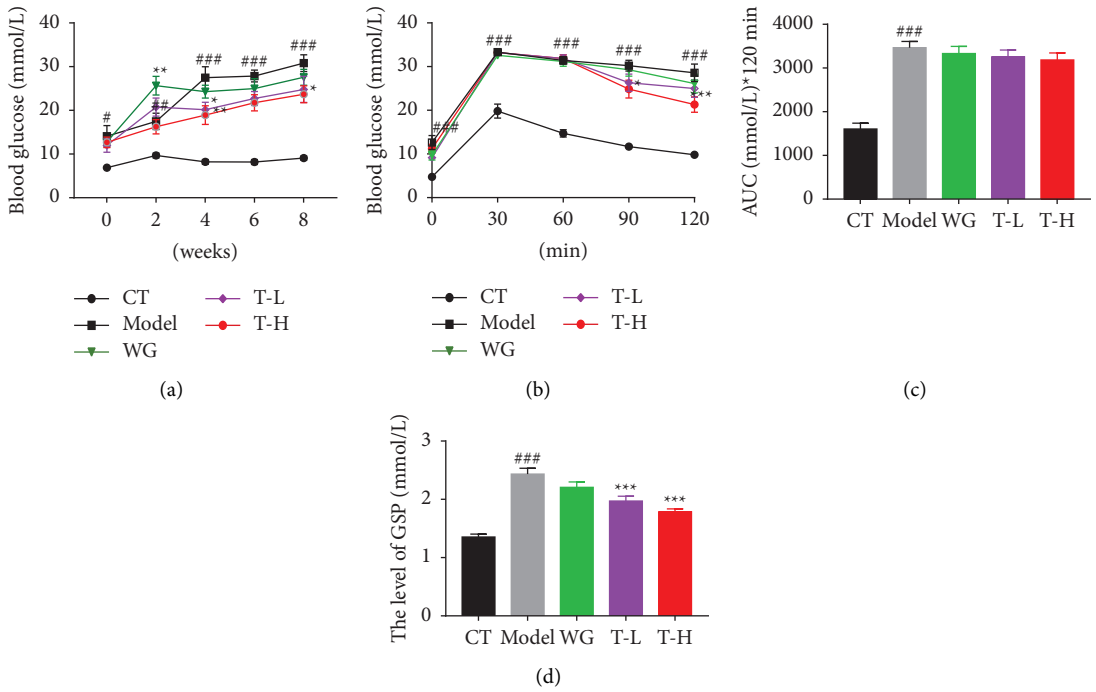

FIGURE 2: T-fiber improved hyperglycemia in diabetic mice in a dose-dependent manner. (a) Blood glucose, (b) OGTT, (c) AUC calculated for glucose levels during OGTT (d) GSP level detection. The data were showed as mean ± SEM and analyzed using Two-way ANOVA followed by Dunnett's *t*-test, $^{\#}P < 0.05$ vs. CT, $^{\#\#}P < 0.01$ vs CT, $^{\#\#\#}P < 0.001$ vs. CT,$^{*}P < 0.05$ vs. model, $^{**}P < 0.05$ vs. model, $^{***}P < 0.001$ vs. model. $N = 8–10$/group.

showed that the levels of glycogen in the hepatocytes of the model group and WG group were significantly increased, while **T-fiber** significantly reduced the levels of glycogen in the hepatocytes of diabetic mice (Figure 3(d)). The deposition of collagen fibers in liver tissue was detected by Masson's trichrome staining. The results showed that the hepatic lobule structure of CT group was normal, while collagen fiber proliferation was obvious in model and WG group. After **T-fiber** treatment, the proliferation of collagen fibers in liver tissue of Db/db mice was significantly decreased (Figure 3(e)). These results showed that **T-fiber** could improve liver weight gain, tissue degeneration, and fibrosis in Db/db mice.

3.4. T-Fiber Improved Renal Fibrosis and Renal Function in Db/Db Mice. Firstly, the effect of **T-fiber** on renal function of Db/db mice was investigated by detecting the kidney weight (Figure 4(a)), kidney index (Figure 4(b)), urine

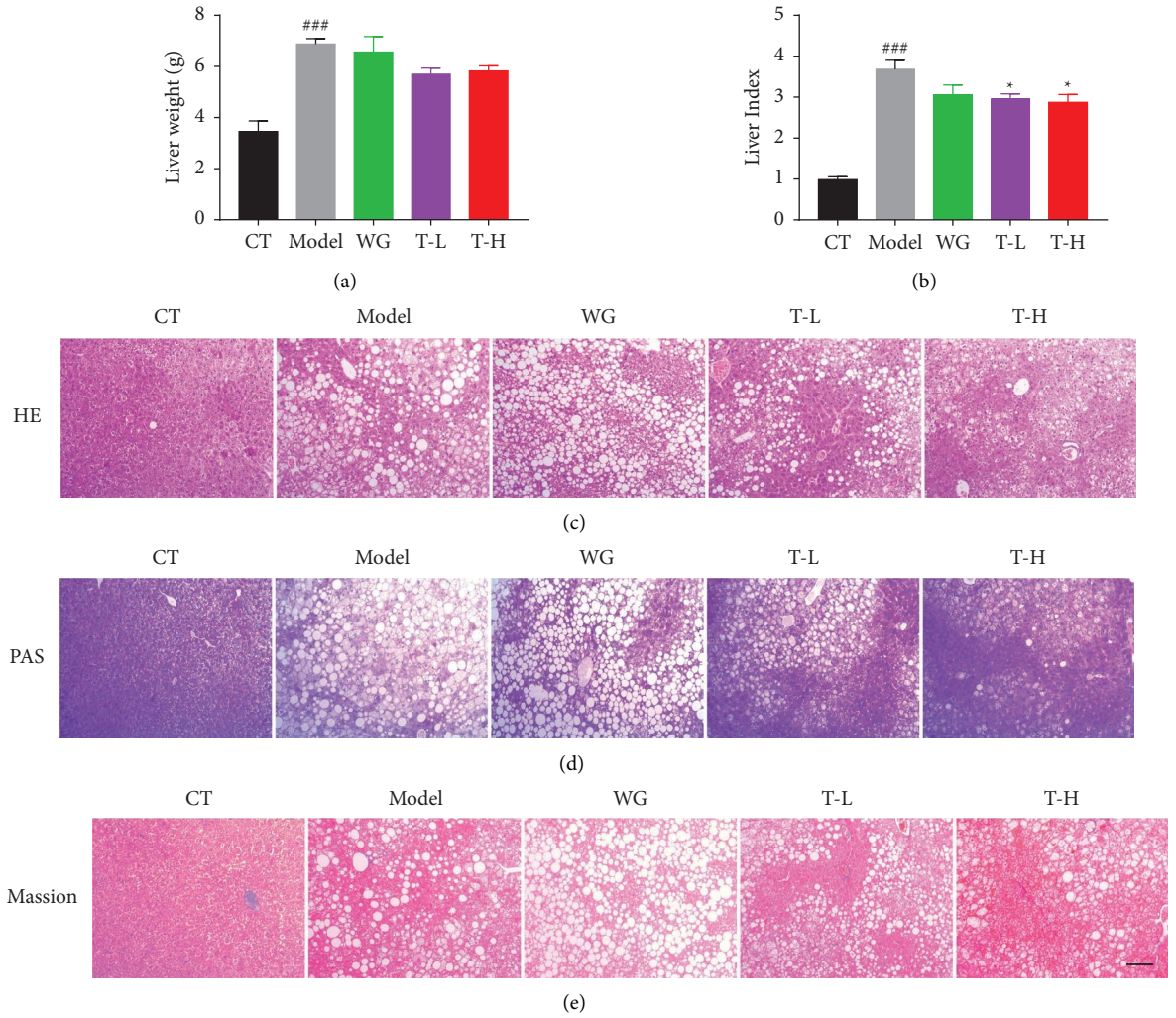

Figure 3: T-fiber improved liver pathology in Db/db mice. (a) and (b) Measurement of liver weight and liver index in each experimental group (c) histological observation of HE staining (200x magnification). (d) Representative pathological photographs show PAS staining of liver sections (200x magnification). (e) Histological observation of Masson trichrome sections (200x magnification). The data were expressed as mean ± SEM and analyzed using one-way ANOVA followed by Dunnett's *t*-test, $^{###}P < 0.001$ vs. CT, $^{*}P < 0.05$ vs. model, $N = 6$/group. (scale bar = 100 μm).

output (Figure 4(c)), 24 h-urinary protein (24 h UP) (Figure 4(d)), serum creatinine (Figure 4(e)), urea nitrogen (BUN) (Figure 4(f)).The results showed that treated with the high dosage of **T-fiber** could remarkably reverse the abnormal up-regulation of kidney weight and index, urine output, 24 h UP, CRE, BUN in Db/db mice. In the other hand, the results of HE and PAS staining showed that the glomeruli of diabetic mice were significantly hypertrophic, the glomerular clusters were locally adhered to Bowman's capsule, and the mesangial area was enlarged, in the contrast, T-H group significantly ameliorated the above renal pathological changes in diabetic mice (Figures 4(g) and 4(h)). Masson staining also revealed that a high dosage of **T-fiber** could decrease the generation of collagenous fibers in the glomeruli of Db/db mice and suppress the pathological process of renal fibrosis (Figure 4(i)). These results showed that **T-fiber** can not only effectively improve kidney function, but also improve kidney pathology.

4. Discussion

T2DM is a metabolic disease characterized by obesity, insulin resistance, and impaired glucose tolerance. Despite the increasing availability of hypoglycemic drugs in the clinic, diet and lifestyle changes remain the most promising, safe and cost-effective way to improve symptoms [16]. Intake of dietary fiber, defined as the edible portion of plants or similar carbohydrates, has been shown to significantly reduce the risk of T2DM and improve insulin resistance [17]. Due to the special geographical conditions of highland barley, the dietary fiber and nutrient content in cereals are the highest [6, 8]. Previous studies on the components of highland barley mainly focused on the liver injury, antioxidative stress and lipid-lowering effects of β-glucan and reactive polyphenols, while studies on the effects of dietary fiber in highland barley on hyperglycemia and DN were very limited [11–13]. If effectively studying the non-

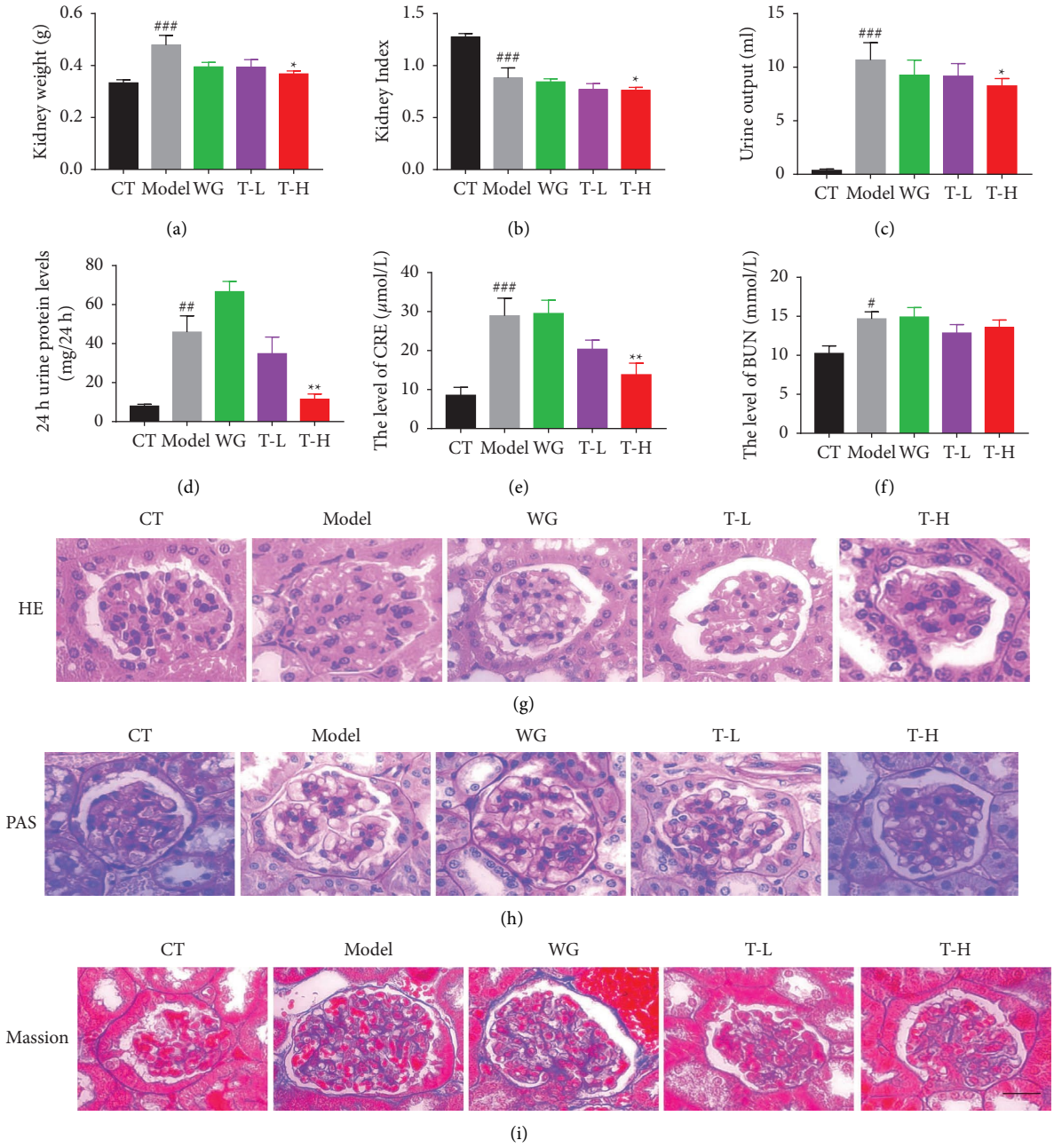

FIGURE 4: T-fiber improved kidney function and alleviated nephropathy in Db/db mice. (a) and (b) Kidney weight and index in each experimental group. (c) and (d) Urine output and urine protein of experimental animals. (e) and (f) Determination of the level of CRE and BUN in mice in each experimental group. (g) Histological observation of HE staining (h) representative photomicrographs images showed PAS staining of kidney sections. (i) Histological observation of Masson trichrome sections. The data were expressed as mean ± SEM and analyzed using one-way ANOVA followed by Dunnett's *t*-test, $^{\#}P < 0.05$ vs CT, $^{\#\#}P < 0.01$ vs CT, $^{\#\#\#}P < 0.001$ vs CT, $^{*}P < 0.05$ vs. model, $^{**}P < 0.01$ vs. model. $N = 6$–8/group. Scar bar = 400 μm.

pharmaceutical intervention effect of total dietary fiber in highland barley on diabetes, it will not only help clarify the role of highland barley dietary fiber in improving diabetes, but also improve the economic development of crops in Tibet, China. **T-fiber** is a high dietary fiber nutritional powder with highland barley as the raw material, comprising various cereal ingredients, as well as dietary fiber (the ratio of insoluble dietary fiber to soluble dietary fiber is 3 : 1). Our research aims to explore the effect of **T-fiber** on the improvement of T2DM hyperglycemia symptoms through non-drug pathways, and to further explore its mechanism of improving diabetes.

Obesity Gene Receptor is known as Diabetes Gene (db), and leptin receptor (Lepr) is closely related to obesity, hypertension, diabetes, lipid metabolism disorder r [18, 19]. In this study, leptin was knocked out in C57BL/KSJ^{-Nju} mice to

generate a C57BL/KSJ$^{-db/db}$ (Db/db) classical type 2 diabetic mouse model. It has been reported that obvious weight gain and dietary characteristics can be observed in such mice as early as 5 weeks [20]. Our results showed that high doses of **T-fiber** had no difference in body weight compared with the Model group, while the levels of blood glucose were significantly reduced by **T-fiber**. It is suggested that high dietary fiber intake will not affect the weight of mice, which is similar to previous report [21]. On the other hand, blood glucose, GSP and glucose tolerance levels were lower in the **T-fiber** group than the CT group. These preliminary results demonstrated that both whole grain powder and model group had severe hyperglycemia symptoms, but after adjusting the content and ratio of dietary fiber in the whole grain meal of barley, the blood glucose of Db/db mice was greatly reduced. **T-fiber** contains a 3 : 1 ratio of insoluble fiber to soluble fiber, which makes it difficult to be digested by human digestive enzymes after entering the body [22]. Several studies had reported the hypoglycemic activity of soluble dietary fiber primarily comprise pectin [23], arabinoxylan [24], and β-glucan [25]. Thus, we speculated that the hypoglycemic effect of **T-fiber** mainly attributes to the synergistic effect of these plant dietary fibers. Additionally, studies had found that the γ-oryzanol [26, 27], protein [28], in whole grains also has a positive effect on alleviating the symptoms of hyperglycemia [21, 22].

Hyperglycemia leads to various complications, including cirrhosis and eventually hepatocellular carcinoma [29]. Db/db mice have consistently elevated levels of liver weight and liver glycogen [30, 31], accompanied by liver steatosis, aggravated fibrosis [32]. Our results showed that **T-fiber** could improve the liver weight compared with the model group. Biochemical analysis indicated that high dose **T-fiber** alleviated lipid accumulation, degree of fibrosis, and inflammatory cell infiltration in the liver of Db/db mice. Researches showed that whole-grain dietary fiber could improve the hepatic pathology and ameliorate the symptoms of diabetes by activating the IRS1/PI3K/AKT pathway in Db/db mice [33]. Meanwhile, supplementing inulin rich in dietary fiber could improve liver damage in mice with liver damage [34]. Whole grain dietary fiber could reduce blood sugar by regulating the insulin signaling pathway. In our work, **T-fiber** could not effectively reduce the level of liver glucose, but also improve the liver pathology. Since IRS1/PI3K/AKT pathway is the key point in the insulin signaling pathway [35, 36], it suggests that **T-fiber** may play a hypoglycemic role by activating the insulin signaling pathway, and its specific mechanism is worthy of further study.

Diabetic nephropathy is a kind of chronic diabetes with complex pathogenesis. Its main pathological feature is renal fibrosis, including glomerular sclerosis and tubular interstitial fibrosis [37]. Studies found that the intervention of dietary fiber could effectively alleviate the occurrence and development of DN [38, 39]. Our results showed **T-fiber** could decrease the generation of collagenous fibers in the glomeruli and suppress the pathological process of renal fibrosis of Db/db mice. Meanwhile, a high dosage of **T-fiber** could remarkably reverse the abnormal upregulation of kidney weight and index, urine output, 24 h UP, CRE, BUN in Db/db mice. The above results suggest that **T-fiber** can effectively improve the renal function of diabetic mice. Some research studies showed that dietary fiber could improve DN by regulating intestinal flora [40]. The research found dietary fiber could prevent DN by changing the microbes in the intestines, thereby changing the content of short-chain fatty acids [41]. Recent studies have shown that inulin-type fructans (a dietary fiber) played a kidney-protective role by regulating the gut microbiome and increasing acetic acid production [42]. Our results found that **T-fiber** could effectively alleviate the related pathology of DN, but it has not been tested whether **T-fiber** can cause changes in the intestinal flora in Db/db mice. Therefore, whether **T-fiber** improves DN is further research is needed to improve the distribution of intestinal flora in the body.

5. Conclusion

Conclusively, the present study revealed the beneficial effects of **T-fiber** in lowering blood glucose and improving liver and kidney pathology in diabetic mice. The effect of high dose **T-fiber** was better (See Graphical Abstract). Further in vivo studies are needed to investigate the molecular mechanisms of **T-fiber** in improving diabetes and DN. In summary, these results indicated that **T-fiber** may be a potential nutrient for nondrug treatment of diabetes and DN.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

Yang Yang and Ma Yue are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yang Yang, Zeyu Zhu, and Rongbiao Pi designed the study and wrote the manuscript. Yue Ma, Jing Han, and Bo Yang provided supply and technical support for T-fiber. Weijia Peng contributed to the experiments and the data analysis. All authors discussed the results and approved the final manuscript. Yang Yang and Yue Ma contributed equally.

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