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The effect of Piceatannol on Liver function and TGF-β1 expression in Diabetic Rats

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ABSTRACT

To investigate the effect of piceatannol (PIC) on liver function and the expression of transforming growth factor-β1 (TGF-β1) in diabetic rats, and to provide a basis for future research on the liver-protective effects of PIC in diabetic rats based on TGF-β1.

Methods: 40 male healthy SD rats were selected, and 30 of them were used to establish a diabetic nephropathy (DN) model by intraperitoneal injection of streptozotocin. The 30 successfully modeled SD rats were randomly divided into a model group, a PIC-L group (50 mg/kg), and a PIC-H group (100 mg/kg). The remaining 10 rats were normally raised as the control group . All groups started receiving medication after successful modeling. The PIC-L and PIC-H groups were given the corresponding doses of PIC by gavage, while the control group and model group were given 10 ml/kg of saline by gavage. All rats were treated continuously for 4 weeks, once daily. During the medication period, the physiological conditions of the rats were observed. 12 hours after the last administration, the body weight of the rats was measured, urine was collected, and the rats were anesthetized and euthanized. Blood and liver tissues were collected from each group to measure and compare serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP),and TGF-β1 lever in liver tissues.Observe the pathological changes in the liver.

Results After 28 days of treatment, the levels of ALT, AST, AKP, and TGF-β1 were highest in the model group, followed by the PIC-L group, and lowest in the PIC-H group and the control group. The differences among the four groups were statistically significant ($P < 0.05$).PIC can significantly improve the pathological changes in the liver of NAFLD rats**.**

Conclusion PIC treatment can improve liver function in diabetic rats, and its liver-protective effects may be mediated by reducing TGF-β1 levels.

Keywords: *diabetic rats; piceatannol; liver function; TGF-β1*

1. INTRODUCTION

Diabetic liver injury refers to the pathological changes in liver histology and function caused by diabetes mellitus, a chronic complication of diabetes. The fundamental pathological manifestations include significant hepatic steatosis, inflammatory cell infiltration, hepatocyte apoptosis, and fibrosis. However, when liver injury progresses to later stages such as cirrhosis, the condition is often irreversible [1]. To date, there is no effective method to prevent its progression and deterioration, making the effective prevention and treatment of diabetic liver disease a common concern among medical researchers. The pathogenesis of diabetic liver disease is not fully understood, but the relationship between inflammatory theory and oxidative stress with diabetic chronic complications is currently a hot and cutting-edge research topic. Transforming growth factor-β1 (TGF-β1) is an inflammatory product of macrophage activation under high glucose conditions and is a central cytokine in the promotion of hepatic fibrosis, involved in cell growth, apoptosis, and differentiation. Piceatannol (PIC), a polyphenolic compound, has been shown to have free radical scavenging, anti-inflammatory, and antioxidant effects [2]. This experiment establishes a diabetic rat model to explore the impact of PIC on the expression of TGF-β1 in the liver of diabetic rats, providing reliable experimental data and theoretical basis for the further development and application of PIC.

2. MATERIALS AND METHODS

1.1 Experimental Animals

40 healthy male rats weighing 190-210 g, aged 6-8 weeks, were purchased from the Henan Experimental Animal Center. The rats were housed under the following conditions:12-hour light/dark cycle,temperature maintained at 20°C-25°C,humidity at 60%-70%, noise below 80 decibels, and clean, ventilated cages.

1.2 Main Reagents and Instruments

PIC,(No:P0453) and streptozotocin injection (No:111607-200301, purity > 98%) were purchased from Sigma.ELISA kits for serum alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (AKP) were purchased from Shanghai Bangjing Industrial Co., Ltd. ELISA kits for serum creatinine (Scr) were purchased from Shanghai Lianmai Bioengineering Co., Ltd. Fasting blood glucose (FBG) ELISA kits were purchased from Shanghai Bangjing Industrial Co., Ltd. Real-time fluorescence quantitative PCR (RT-PCR) instrument (Model 2720) was purchased from Beiden Medical Research.

1.3 Research Methods

1.3.1 Animal Grouping

After 1 week of acclimatization, the 40 rats were randomly divided into 4 groups (n=10 per group): control group, model group, PIC-H group, and PIC-L group.

1.3.2 Animal Model Establishment

The control group was fed a standard diet. The model group, PIC-H group, and PIC-L group were fed a high-fat, high-sugar diet and injected intraperitoneally with 65 mg/kg streptozotocin (STZ). After 72 hours, blood glucose levels were measured via tail vein sampling for 3 consecutive days. Rats with blood glucose levels ≥ 16.7 mmol/L, urine output ≥ 150% of baseline, and 24-hour urine protein (UP) excretion > 30 mg were considered successfully modeled.

1.3.3 Drug Administration

The PIC-H group and PIC-L group were administered PIC at 100 mg/kg and 50 mg/kg, respectively, by gavage once daily for 4 weeks. The control group and model group were administered saline by gavage.

1.3.4 Specimen Collection

After 4 weeks of treatment, rats were fasted for 24 hours, and body weight was recorded. Urine was collected, and rats were anesthetized with 3% sodium pentobarbital and euthanized. Blood (3 mL) was collected from the abdominal aorta. Urine and blood samples were centrifuged at 3000 rpm for 10 minutes, and the supernatant was stored at -20°C.Take 0.5g of liver tissue, homogenize it using a tissue homogenizer, and centrifuge to separate the mixture. Collect the supernatant and store it at -80°C. The remaining liver tissue is cut into small pieces and fixed in 4% neutral formaldehyde solution..

1.4 Observation Indicators

1.4.1 Fasting Blood Glucose and Serum Creatinine Measurement

Serum supernatant from 1.3.4 was thawed at 4°C, and FBG and Scr levels were measured using ELISA kits according to the manufacturer's instructions.

1.4.2 Measurement of ALT, AST, AKP, and TGF-β1 Expression

Serum ALT, AST, and AKP levels were measured using ELISA. TGF-β1 expression in liver tissues was detected using RT-PCR.

1.4.3 The liver tissues of rats from each group.

Fixed in 4% neutral formaldehyde solution as described in sections 1.3.4 for 24 hours, were processed through conventional clearing, paraffin embedding, and sectioning to a thickness of 5 μm. Following the instructions provided with the HE staining kit, the sections were stained, dehydrated, cleared, and then mounted. The prepared slides were examined under an optical microscope to observe histopathological changes.

1.5 Statistical Analysis

Data were analyzed using SPSS 26.0 software. Measurement data were expressed as mean standard deviation ($\overline{X} \pm s$). Comparisons among multiple groups were performed using one-way anova, with $P < 0.05$ considered statistically significant.

3. RESULTS

2.1 The effects of PIC on FBG and serum Scr levels in rats.

Compared with the control group, FBG and serum Scr levels were significantly higher in the model group ($P < 0.05$). Compared with the model group, FBG and serum Scr levels were significantly lower in the PIC-L and PIC-H groups ($P < 0.05$), showing a dose-dependent effect. **(Table 1)**

Table 1 Comparison of FBG and Scr levels in each group of rats（$\bar{x} \pm s$， n=10）

Group	Scr(umol/L)	FBG(mol/L)
Control Group	2736.17±253.41	5.72±1.13
Model Group	4366.75±265.84[a]	24.18±3.62[a]
PIC-L Group	3953.89±225.07[ab]	18.23±2.15[ab]
PIC-H Group	3135.49±203.26[abcd]	10.45±1.48[abcd]

Note:Compared with the normal control group, [a]$P<0.05$; Compared with the DN group,[c]$P<0.05$; Compared with the low-dose PIC group,[c]$P<0.05$; Compared with the medium-dose PIC group,[d]$P<0.05$.

2.2 The effects of PIC on the levels of ALT, AST, AKP in rat serum and TGF-β1 in rat liver tissue.

After 4 weeks of treatment, the levels of ALT, AST, AKP, and TGF-β1 were highest in the model group, followed by the PIC-L group and the PIC-H group, with the control group showing the lowest levels. The differences among the four groups were statistically significant (P < 0.05). (Table 2)

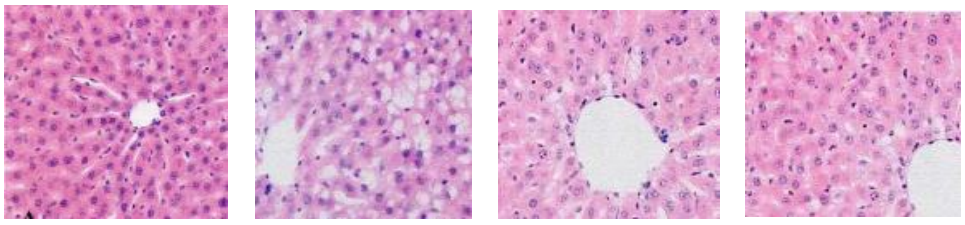
Table 2 Comparison of liver function and TGF-β1 expression levels in rats after 4 weeks of drug administration.（$\bar{x}$ ±s,n=10）

Group	ALT/（U·L-1）	ASL/（U·L-1）	AKP/（U·L-1）	TGF-β1
Control Group	48.73±5.64	118.35±11.65	14.67±1.58	156.46±15.26
Model Group	168.24±14.33b	196.34±16.87b	39.54±4.98b	279.89±18.36b
PIC-L Group	83.24±8.32ab	135.34±13.43ab	26.24±2.76ab	218.46±19.26ab
PIC-H Group	65.25±5.38ab	122±12.45ab	22.65±1.95ab	185.46±19.26ab

Note: Compared with the normal control group, ([a]$P<0.05$);Compared with the model group,([b]$P<0.05$).

2.3 Effects of PIC on Liver Histomorphological Changes in NAFLD Rats

Observation of HE-stained sections under light microscopy:In the control group, the liver lobule structure of rats was intact,and the histomorphological appearance of the liver tissue was normal,with clear hepatic cell cords.In the model group,the lobular structure of the liver tissue was blurred,and hepatocytes exhibited extensive ballooning degeneration and steatosis.The nuclei were displaced to one side by lipid droplets,and the hepatic cell cords were disorganized,with mild fibrous tissue hyperplasia.Compared with the model group, both the PIC-H and PIC-L groups showed a certain degree of cellular degeneration and lobular structural changes in the liver tissue. However,the steatosis was alleviated to varying degrees,demonstrating a dose-dependent effect(Figure 1).



Control Group **Model Group** **PIC-L Group** **PIC-H Group**

Figure 1: Pathological changes in liver tissues of rats in each group

(HE staining, ×400).

4. DISCUSSION

In recent years, changes in dietary habits, such as high-fat and high-sugar diets, overnutrition, and reduced physical activity, have led to a gradual increase in the incidence of diabetes in China. According to global epidemiological analysis, it is estimated that by 2035, approximately 592 million people in China will suffer from diabetes. The pathogenesis of diabetes is closely related to the expression of TGF-β1. Current research indicates that TGF-β1 is a key cytokine promoting liver fibrosis. When the liver is injured, it secretes large amounts of TGF-β1, which is an inflammatory product of macrophage activation under high glucose conditions and plays a central role in the formation of liver fibrosis [3]. Prolonged exposure to a high-glucose environment in diabetic patients triggers oxidative stress and inflammatory responses in liver tissues, leading to hepatocyte damage.

PIC is primarily found in plants such as sugarcane, grapes, and rhubarb and is a metabolic derivative of resveratrol with excellent antioxidant activity. Due to its structural similarity to resveratrol, PIC also exhibits strong anti-inflammatory and anti-proliferative effects. Additionally, PIC has an extra hydroxyl group compared to resveratrol, giving it stronger antioxidant activity and free radical scavenging capabilities [4]. Wu Rongyan et al.found that PIC could improve renal tissue damage in diabetic nephropathy (DN) rats by inhibiting the expression of transforming growth factor-β/signal transduction proteins [5] .

The results of this study showed that after 4 weeks of treatment, the levels of ALT, AST, AKP, and TGF-β1 were highest in the model group, followed by the low-dose PIC group and the high-dose PIC group, with the normal control group showing the lowest levels. This suggests that PIC can improve liver function by inhibiting the expression of TGF-β1. Under normal conditions, free radical metabolism is balanced. However, when the body is in a prolonged high-glucose state, this balance is disrupted, leading to lipid peroxidation and cellular tissue damage. To counteract oxidative toxicity, the body neutralizes reactive oxygen species (ROS) through antioxidant mechanisms. However, excessive ROS production can accumulate and trigger inflammatory responses [6]. PIC, through its free radical scavenging ability, can reduce inflammatory responses in the body, decrease the activation of TGF-β1 protein expression, and thereby alleviate liver fibrosis in diabetic rats, delaying the progression of diabetes and liver tissue damage.

In conclusion, PIC treatment can improve liver function in diabetic rats, and its hepatoprotective effects may be mediated by regulating the expression of TGF-β1.

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