

# The Hypoglycaemic Mechanism of Camel Placenta Powder on Streptozotocin Induced Type 2 Diabetic Rats

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## ABSTRACT

The objective of this study was to explore the effects of camel placenta powder on associated symptoms, signs and indicators in type 2 diabetic rats. For this study sixty male Wistar rats were randomly divided into a normal group, model group, metformin group, and low-, medium- and high-dose camel placenta groups. A high-fat and high-sugar feed combined with intraperitoneal injection of STZ dissolved in a citric acid-sodium citrate buffer was used to establish a rat model of hyperglycaemia. Metformin hydrochloride tablets were used as a positive control to detect fasting blood glucose. The contents of glycated haemoglobin (HbA1c), insulin (INS) and glucose (GLUC3) as well as the protein expression and mRNA levels of sodium-glucose co-transporter 2 (SGLT2) and glucose transporter 2 (GLUT2) were used to study the mechanism of the hypoglycaemic effect of CPP on diabetic rats. We found that camel placenta produced no meaningful changes in the weight of hyperglycaemic rats or the weight of the liver, kidney, or pancreas. After STZ modelling, the blood glucose levels of rats noticeably increased. However, the blood glucose values of rats decreased substantially due to camel placenta treatment from the 4th to the 6th week. Camel placenta dramatically reduced the serum HbA1c and GLUC3 content in hyperglycaemic rats. Dry CPP had a down-regulating effect on the levels of SGLT2 and GLUT2 protein, SGLT2 mRNA and GLUT2 mRNA in the kidneys of hyperglycaemic rats. However, there was no meaningful difference between the metformin group and the high- and medium-dose camel placenta groups. To conclude camel placenta has a notable hypoglycaemic effect on diabetic rats induced by STZ with a high-fat and high-sugar feed.

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## Authors' Contribution

XC conceived of the study. BB participated in its design and coordination. MD helped to draft the manuscript. All authors read and approved the final manuscript.

## Key words

Camel placenta, Type 2 diabetic, Hypoglycaemic effect, SGLT2; GLUT2

## INTRODUCTION

In an aging global society, diabetes places a heavy burden on individual and public health in terms of the number of patients with the disease, diabetes-related complications (including frailty and disability) and expenditures for national health and social care systems (Sinclair *et al.*, 2019). The prevalence of diabetes is rising rapidly around the world, as recently confirmed by the finding that, in 2019, 9.5% of 488 million adults around the world aged 20–99 years have diabetes (Saeedi *et al.*, 2019).

Although various therapeutic medicines are commonly used to relieve diabetes, this problem has still not been

fully resolved by currently available treatments. Antidiabetic medicine like sulfonylureas show limited efficacy in many diabetic conditions and is severely limited by adverse effects (Gloyn *et al.*, 2018). Therefore, this unmet clinical need reflects a demand to develop novel classes of antidiabetic drugs than those currently available.

In Mongolian medicine, xihexixijing refers to a prolonged disease characterised by polydipsia, polyuria and emaciation. It is equivalent to diabetes in modern medicine. The treatment principle is to regulate three roots (heyi, xila and badagan) and tonify the kidney (Bai *et al.*, 1990). Modern medical and biological research has shown that the placenta contains a variety of hormones, immunoglobulins, growth factors, enzymes, interferons, lipopolysaccharides and other substances that have complex bioactive components and positive medicinal value (Nagae *et al.*, 2022; Prince *et al.*, 2018; Heo *et al.*, 2018). The placenta is non-toxic, non-irritating, convenient to consume and has meaningful efficacy on human immunity, antioxidant capacity and disease treatment (Zhang and Huang, 2018; Choi and Kim, 2019). Camel placenta is recommended for the treatment of diabetes in pastoral areas where camels are bred in large numbers and to have a

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preventive and therapeutic effect on some diabetic patients (Ao *et al.*, 2019). Previous studies indicated that the dried powder of camel placenta can noticeably reduce food intake, inhibit appetite, improve abdominal obesity and reduce blood glucose in spontaneous diabetic mice (Bao *et al.*, 2022). However, the hypoglycaemic mechanism of CPP remains unclear. By assessing the contents of HbA1c, INS and GLUC3, as well as the protein expression and mRNA levels of SGLT2 and GLUT2, we aim to reveal the mechanisms and characteristics of CPP on associated symptoms, signs and indicators in STZ-induced type 2 diabetic rats, providing a theoretical basis for exploring novel therapies for diabetic patients.

## MATERIALS AND METHODS

### *Experimental animals*

Specific pathogen-free (SPF) male Wistar rats weighing 180–200 g were purchased from Changchun Yisi Experimental Animal Technology Co., Ltd. (SCXK Ji –2018–0003) were housed in the animal room of key laboratory of the Ministry of Education of the State People's Committee. These rats were fed in standard cages (5 mice per cage) for 1 week under standard conditions (temperature: 22±2°C; humidity: 30–40% relative humidity; 12 h light/dark cycle) with free access to food and water prior to the experiment (Cui, 2016).

### *Main instruments, reagents and drugs*

H-2050R centrifuge (Cence), sunrise multiscan spectrum (Tecan), fluor chem HD2 chemiluminescent imaging system (Protein Simple), ABI 7500 fast real-time polymerase chain reaction (RT-PCR) (Applied Biosystems) (Dai *et al.*, 2021).

CPP (batch number: 20181024, provided by the Preparation Department of Alashan Mongolian Medical Hospital); metformin hydrochloride tablets (batch number: 14880466, Youcare Pharmaceutical); STZ (batch number: 917L038, Solarbio); rat HbA1c ELISA kit (batch number: 201904) and rat INS ELISA kit (201905) were purchased from Mlbio; glucose detection kit (batch number: 40879901, Sandhofer Strasse 116, 68305 Mannheim); anti-SGLT2 antibody (batch number: GR3211034-2) and anti-glucose transporter GLUT2 antibody (batch number: GR3249968-12) were purchased from Aibio; FastStart Universal SYBR Green Master (ROX; batch number: 41472600, Tiangen Biotech Co., Ltd.) (Dai *et al.*, 2021).

### *Preparation of camel placenta powder (CPP)*

A healthy camel placenta was selected according to the standardisation requirements of placenta products proposed by the Ministry of Health, and impurities, such

as foreign bodies and surface fat, were removed, and the blood attached to its surface was washed. The placenta was cut into small pieces and dried in a microwave oven until slightly yellow (dry) before being crushed with a medicinal pulveriser (Chen *et al.*, 2019).

### *Animal grouping and treatment*

Sixty male Wistar rats were randomly divided into a normal group, model group, metformin group, and low, medium and high-dose camel placenta groups. There were 10 rats in each group, and modelling began after 1 week of adaptive feeding. The normal group continued to be given a normal diet, and the other 5 groups were given a high-fat and high-sugar diet and were fasted for 12 h after 4 weeks (Zhang *et al.*, 2019). The normal group was administered a 30 mg/kg sodium citrate buffer intraperitoneally, and the other 5 groups were given STZ intraperitoneally for 3 consecutive days. Fasting blood glucose was measured after 3 days and again after 1 week of feeding. The fasting glucose should be >10.0 mmol/L (Lin *et al.*, 2021).

The positive control group (metformin hydrochloride tablets 120 mg/kg) was administered by gavage. The low-dose camel placenta group was administered 2.5 g/kg camel placenta. The medium-dose camel placenta group were administered with 5.0 g/kg and the high-dose camel placenta group were administered with 7.5 g/kg. The normal control group and model group were given an equal volume of saline. The experimental plan is shown in Figure 1.

### *Observed indices and methods of detection*

Experiments were performed according to the manufacturer's instructions and standard procedures, as previously described (Wen *et al.*, 2018). The rats weight was measured weekly. After 6 weeks of administration, the rats were anaesthetised by intraperitoneal injection of 30 mg/kg chloral hydrate. Blood was collected from the abdominal aorta, the serum was centrifuged at 3,000 rpm for 15 min, and the liver, kidney and pancreas were weighed and stored at –80°C. The rats were observed for the following general conditions: Activity, mental status, appetite, hair growth and presence of faecal matter. A drop of blood was taken from the tail vein each week to measure fasting blood glucose using a blood glucose meter, and the rats' weight change was measured. Serum triglyceride (TG), total cholesterol (TCHO), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and glucose tolerance, 3 h (GLUC3) levels were measured with a biochemical instrument. The levels of glycosylated haemoglobin and insulin in the serum were detected by enzyme-linked immunosorbent assay. The effect of camel placenta on the sodium-glucose cotransporter (SGLT2) and

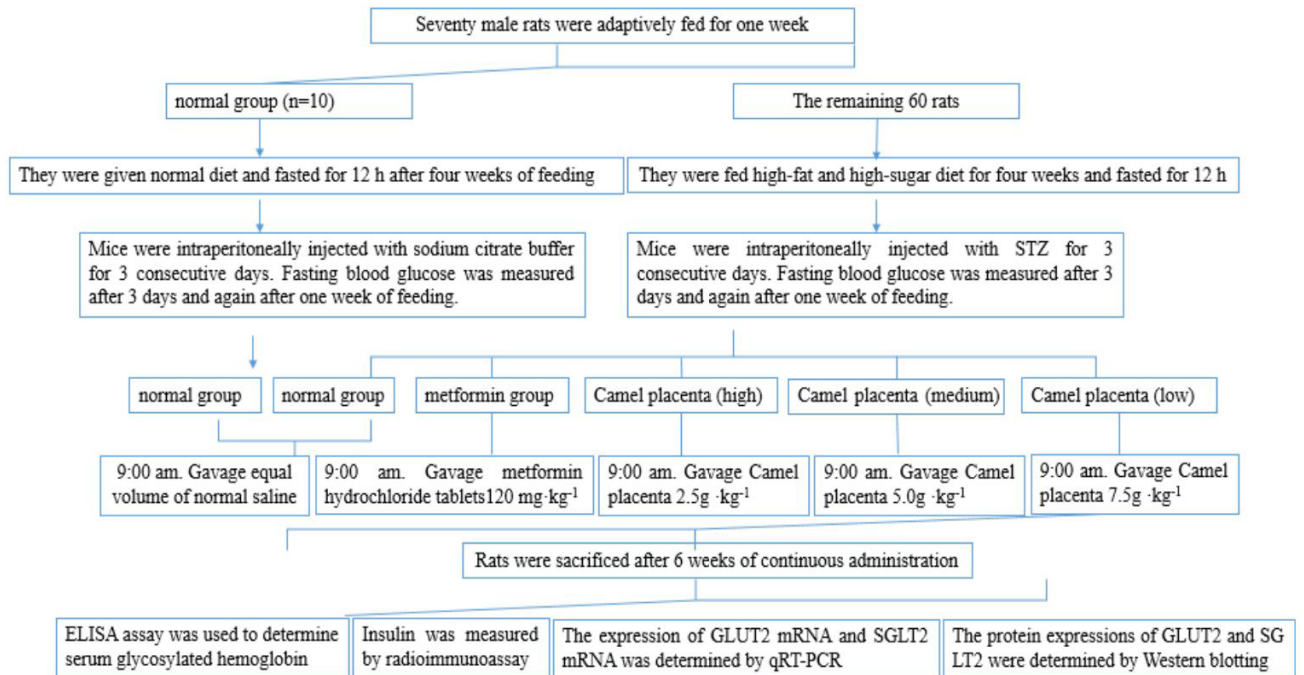


Fig. 1. Experimental plan of work.

**Table I.** Effect of CPP on the body weight of diabetic rats ( $\bar{x} \pm s$ ,  $n = 10$ ).

Groups	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
Normal group	416.2±19.3	430.3±16.2	442.5±16.7	459±16.5	474.4±18.8	490.7±15.0
Model group	331.2±19.0**	341.1±17.3**	353.2±21.4**	358.4±16.9**	366.4±15.0**	372.9±18.2**
Metformin group	324.5±14.3**	334.5±19.4**	345.8±17.0**	354.5±20.3**	359.7±16.6**	364.8±14.9**
Camel placenta (high)	322.3±16.3**	334.8±16.5**	347.8±18.4**	358.2±19.0**	361.1±17.2**	368.3±15.5**
Camel placenta (medium)	333.8±10.3**	343.6±17.4**	355.8±12.8**	354.1±20.9**	358.8±14.3**	360.2±13.9**
Camel placenta (low)	334.5±14.7**	344.5±19.6**	348.9±12.3**	357.5±12.0**	368.2±19.6**	366.4±19.1**

Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, ## $P < 0.01$ , # $P < 0.05$ .

rat kidney was detected by Western blot. The effect of the camel placenta on the expression of SGLT2 mRNA and GLUT2 mRNA in the diabetic rat kidney was detected by quantitative fluorescence PCR (QF-PCR). The primer sequences are as follows.

*SGLT2* F 5'-TCTGAACCTG GGGAGCAGAAG-3'  
R 5'-AACACCAATGACCAGCAGGAA-3'

*GLUT2* F 5'-CAACATGTT CAGAAGACAAGATCAC-3'  
R 5'-CACACCGATGTCATATCCGAACT-3'

*ACTB* F 5'-TCAGCAAGCAGGAGTACGATG-3'  
R 5'-GTGTA AACCGCAGCTCAGTAACA

#### Statistical analysis

Statistical analyses were conducted with SPSS19.0. Continuous variables were expressed as the means  $\pm$  standard deviations, and categorical variables were expressed as numbers and percentages. A one-way analysis

of variance was conducted for continuous variables, while analyses for categorical variables were performed using the  $\chi^2$  test or Fisher exact test.  $P < 0.05$  was statistically significant.

## RESULTS

#### Effect of CPP on the weight of diabetic rats

The body weight of rats in the model group after intraperitoneal injection of STZ decreased to varying degrees compared with the normal group ( $P < 0.01$ ). Compared with the model group, there was no relevant difference between the body weight of rats in the metformin group and the high-, medium-, and low-dose camel placenta treatment groups (Table I). Camel placenta and metformin had no demonstrable effect on the body weight of STZ-induced diabetic rats.

**Table II. Effect of CPP on blood glucose in diabetic rats ( $\bar{x} \pm s$ , n = 10).**

Groups	Week 1	Week 2	Week 3	Week 4	Week 15	Week 6
Normal group	5.4±1.3	4.0±0.2	4.5±0.7	4.9±1.5	4.4±0.8	5.6±1.0
Model group	18.2±3.0**	18.1±4.3**	19.6±2.4**	19.4±16.9**	18.4±15.0**	19.9±18.2**
Metformin group	17.5±4.3**	14.5±3.6**	12.8±3.7***	10.3±2.3***	8.7±2.1###	7.2±1.2###
Camel placenta (high)	17.3±1.3**	17.8±5.5**	17.8±5.1**	18.2±4.3**	16.1±17.2**	16.3±4.2**
Camel placenta (medium)	18.8±4.3**	16.2±3.4**	13.1±2.5***	13.0±2.9***	13.4±4.0***	11.2±3.1###
Camel placenta (low)	15.5±3.7**	14.5±1.6**	12.9±2.3***	11.5±1.1###	11.2±1.6###	9.8±2.7**

Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, ### $P < 0.01$ , # $P < 0.05$ .

#### Effect of CPP on blood glucose in diabetic rats

Changes in the rats' blood glucose were measured weekly before and after modelling, as well as after treatment with camel placenta and metformin (Table II). After STZ administration, the blood glucose level of each group rose noticeably compared with the normal group ( $P < 0.05$ ). Compared with the model group, the blood glucose value of the metformin treatment group decreased steadily from the 1st week to the 6th week of treatment, and dropped markedly from the 3rd week to the 6th week of treatment ( $P < 0.05$ ). After treatment with camel placenta, the blood glucose values of the low- and medium-dose group dropped noticeably from the 4th to the 6th week compared with the model group ( $P < 0.05$ ).

#### Effect of CPP on organ weights of diabetic rats

The weight of the liver, kidney and pancreas in the model and treatment groups was lower than that of rats in the normal group to varying degrees, but the difference was not statistically significant (Table III).

#### Effect of CPP on blood lipids and serum glucose in diabetic rats

Compared with the normal group, the levels of TG, TCHO and LDL-C of each model group increased to different degrees ( $P < 0.05$ ), while HDL-C was dramatically decreased ( $P < 0.05$ ). Compared with the model group,

the TG, TCHO and LDL-C values of the treatment group all went down, and HDL-C meaningfully increased ( $P < 0.05$ ). This indicates that both camel placenta and metformin tablets have hypolipidemic effects. The results of the serum glucose measurement showed that GLUC3 in the serum of each model group increased to varying degrees compared with the normal group ( $P < 0.05$ ). Compared with the model group, GLUC3 in the serum of the metformin group, mid- and low-dose camel placenta group decreased demonstrably ( $P < 0.05$ ) (Table IV). The metformin and low-dose CPP treatments were effective in reducing blood glucose in STZ-induced diabetic rats.

**Table III. Effect of CPP on the weight of liver, kidney and pancreas of diabetic rats ( $\bar{x} \pm s$ , n = 10).**

Groups/ Organ weight	Liver	Kidney	Pancreas
Normal group	4.11±0.61	14.79±2.49	2.92±0.46
Model group	3.20±0.80	11.74±2.11	2.09±0.46
Metformin group	3.69±0.48	12.48±1.20	2.85±0.22
Camel placenta (high)	3.91±0.59	12.20±1.55	2.57±0.13
Camel placenta (medium)	3.79±0.48	12.44±0.49	2.48±0.13
Camel placenta (low)	3.88±0.54	11.74±2.11	2.51±0.14

Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, ### $P < 0.01$ , # $P < 0.05$ .

**Table IV. Effect of CPP on blood lipids and serum glucose in diabetic rats ( $\bar{x} \pm s$ , n = 10, nmol/L).**

Groups	TG	TCHO	LDL-C	HDL-C	GLUC3
Normal group	2.51±0.12	0.62±0.02	0.41±0.03	1.82±0.42	4.68±1.06
Model group	4.76±1.11*	2.81±0.53*	2.36±0.69**	0.96±0.06*	21.84±5.0**
Metformin group	2.70±0.78##	1.56±0.44##	1.18±0.26###	1.37±0.23#	7.77±2.1###
Camel placenta (high)	3.28±1.13##	2.11±0.55*	1.33±0.16###	1.32±0.13#	16.1±4.2*
Camel placenta (medium)	3.16±1.02##	1.95±0.46##	1.47±0.21###	1.44±0.19#	11.4±4.0#
Camel placenta (low)	2.89±0.90#	1.78±0.52##	1.26±0.21###	1.64±0.30#	7.2±2.0#

Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, ### $P < 0.01$ , # $P < 0.05$ . TG, triglycerides; TCHO, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; GLUC3, glucose tolerance, 3 h.



### Effect of CPP on HbA1c and INS in the serum of diabetic rats

The HbA1c level in each model group rose to varying degrees compared with the normal group, while the HbA1c level in each treatment group fell to varying degrees compared with the model group, among which the metformin and high-, medium- and low-dose camel placenta groups all decreased distinctively ( $P < 0.01$ ). The fasting INS level in each model group increased to varying degrees compared with the normal group ( $P < 0.05$ ), while metformin and camel placenta did not affect the INS after treatment ( $P > 0.05$ ) (Table V).

**Table V. Effect of CPP on GHbA1c and INS in diabetic rats ( $\bar{x} \pm s$ , n = 10).**

Groups	GHbA1c (nmol·L <sup>-1</sup> )	INS (mU·L <sup>-1</sup> )
Normal group	900.2±219.5	15.8±3.2
Model group	3284.76±311.3*	44.6±5.3*
Metformin group	992.3±178.0 <sup>##</sup>	39.1±4.2*
Camel placenta (high)	1401.7±111.3 <sup>###</sup>	43.4±5.5*
Camel placenta (medium)	1136±152.0 <sup>##</sup>	45.7±9.6*
Camel placenta (low)	1010.9±209.4 <sup>##</sup>	38.8±7.2*

Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, <sup>##</sup> $P < 0.01$ , <sup>#</sup> $P < 0.05$ . GHbA1c, glycated hemoglobin A1c; INS, insulin (?).

**Table VI. Effect of CPP on the expression of SGLT2 and GLUT2 proteins and mRNA levels in the kidney of diabetic rats ( $\bar{x} \pm s$ , n = 10).**

Groups	SGLT2	GLUT2
<b>Expression of proteins</b>		
Normal group	0.42±0.05	0.68±0.21
Model group	2.18±0.30**	2.66±0.34*
Metformin group	1.83±0.41**	2.81±0.82*
Camel placenta (high)	1.73±0.43**	2.14±0.53*
Camel placenta (medium)	0.96±0.30 <sup>##</sup>	1.37±0.26 <sup>#</sup>
Camel placenta (low)	0.66±0.24 <sup>##</sup>	1.08±0.25 <sup>#</sup>
<b>mRNA levels</b>		
Normal group	11.54±3.01	3.87±1.21
Model group	24.18±6.23**	9.66±3.18*
Metformin group	24.93±8.11**	9.57±2.06*
Camel placenta (high)	17.32±5.48*	7.89±2.43*
Camel placenta (medium)	15.77±6.02*	8.22±2.62*
Camel placenta (low)	10.66±3.05 <sup>##</sup>	5.08±2.15 <sup>#</sup>

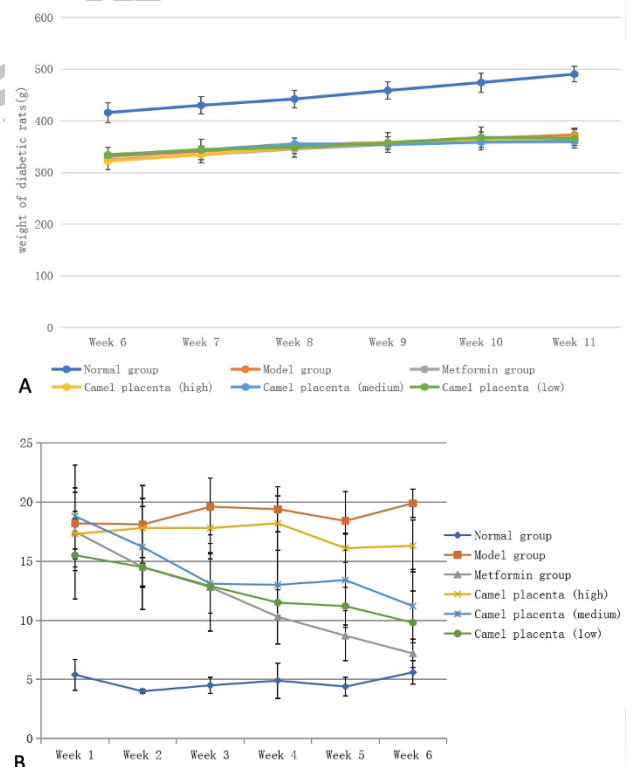
Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, <sup>##</sup> $P < 0.01$ , <sup>#</sup> $P < 0.05$ .

### Effect of CPP on the expression of SGLT2 and GLUT2 protein in the diabetic rat kidney

SGLT2 and GLUT2 protein expression in each model group expanded to varying degrees compared with the normal group and decreased markedly in the medium- and low-dose camel placenta treatment groups compared with the model group ( $P < 0.05$ ) (Table VI, Fig. 2). There was no statistically significant difference between the high-dose camel placenta and metformin groups ( $P > 0.05$ ).

### Effect of CPP on the expression of SGLT2 and GLUT2 mRNA in the diabetic rat kidney

The expression of SGLT2 mRNA and GLUT2 mRNA in the model and treatment groups was reduced to varying degrees compared with the normal group ( $P < 0.05$ ) (Table VI). Compared with the model group, the low-dose camel placenta group showed a statistical reduction ( $P < 0.05$ ). There was no notable difference between the metformin group and the high- and medium-dose camel placenta groups.



**Fig. 2. Effect of CPP on the expression of SGLT2 and GLUT2 proteins in the kidney of diabetic rats.**

A: Compared with normal group, \*\* $P < 0.01$ , \* $P < 0.05$ ; Compared with model group, <sup>##</sup> $P < 0.01$ , <sup>#</sup> $P < 0.05$ .

## DISCUSSION

Previous studies indicated that STZ combined with high-fat and high-sugar diets can establish a more stable animal model of type 2 diabetes (Gan *et al.*, 2020; Sang and Zhang, 2019; Li *et al.*, 2019). Our studies indicate that the rats represented a higher food intake and urine output as well as less weight with mental depression and a slightly yellowish coat, consistent with the symptoms of type 2 diabetic patients.

The pathogenesis of T2DM has not been fully clarified. The main pathophysiological changes associated with T2DM include  $\beta$  cell dysfunction and insulin resistance; glucose metabolism disorder, elevated blood glucose and multiple organ system damage are the main manifestations (Bian *et al.*, 2019). STZ leads to pancreatic cancer by reactive oxygen species mechanism, oxidative damage of cells and nitric oxide  $\beta$  cell cytotoxicity, resulting in  $\beta$  cell dysfunction and influencing insulin secretion (Rao and Mohan, 2017).

The kidney also plays an important role in blood glucose control (Pecoits-Filho *et al.*, 2016). Three membrane proteins are responsible for glucose absorption from the glomerular filtrate of the proximal tubule: the sodium-glucose cotransport proteins SGLT1 and SGLT2 in the parietal membrane and the single transporter GLUT2 in the basolateral membrane (Ghezzi *et al.*, 2018). SGLT1 is a glucose transporter in the apical membrane of the small intestine, which is responsible for transporting glucose from the intestinal cavity, while SGLT2 and GLUT2 in the proximal renal tubule play a key role in glucose reabsorption and are associated with the development of type 2 diabetes (Dalli *et al.*, 2021; Jiang *et al.*, 2019).

The study of Hussain *et al.* (2021) revealed that camel milk could act as an alternative treatment regimen for diabetes therapy. Previous studies indicated that dried CPP can dramatically reduce food intake, inhibit appetite, improve abdominal obesity and reduce blood glucose in spontaneous diabetic mice (Bao *et al.*, 2022). The results of our group show that STZ-induced type 2 diabetic rats treated with CPP meaningfully reduced blood glucose, glycated haemoglobin and renal SGLT2 and GLUT2 protein expression. Compared with the model group, both SGLT2 mRNA and GLUT2 mRNA expression within the treatment group were distinctively down-regulated, especially in the low-dose group. Notably, camel placenta fostered the analogous efficacy and characteristics to metformin in STZ-induced diabetic rats. The results of the present study suggest that CPP can effectively reduce blood glucose in STZ-induced experimental diabetic rats, and its hypoglycaemic mechanism may be related to the down-regulation of the expression of glucose transporter

proteins SGLT2 and GLUT2 in the kidney, specifically reducing the blood glucose by lowering the glucose reabsorption.

This study has some limitations, i.e., the mechanism is an animal experiment. In addition, a study showed that patients given SGLT2 inhibitors developed phenomena such as high anion gap acidosis, despite being in a normal glycaemic state (Wang and Isom, 2020). Therefore, in order to ensure the safety of clinical use, the question of lowering blood glucose through CPP causing a similar high anion gap acidosis, its specific dose and side effects need to be further studied. To sum up, this study provides a new idea and theoretical basis for the treatment of type 2 diabetes.

## CONCLUSION

In conclusion, this study shows that CPP has a hypoglycaemic effect, and its hypoglycaemic mechanism may reduce glucose reabsorption by inhibiting the expression of SGLT2 and GLUT2. Considering its satisfactory efficacy and hypoglycaemic mechanism, it is necessary to promote follow-up studies on clinical translation of CPP and explore novel therapies for diabetic patients. As a whole, we provided a novel theoretical basis for the application of CPP in reducing blood glucose.

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### Ethical statement

The study was approved by the Ethics Committee of Inner Mongolia Minzu University.

### Data availability

All data generated or analyzed during this study are included in this published article.

### Statement of conflict of interest

The authors have declared no conflict of interest.

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