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Hypoglycemic effect of *Zingiber striolatum* bud extract in db/db mice

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Abstract

To evaluate the effectiveness of regulating insulin sensitivity via the insulin receptor substrate-1 of *Zingiber striolatum* bud extract in C57BL/KsJ-db/db mice. The C57BL mice were randomly divided into 5 groups (n=10), including normal control group, model group, metformin group, ZS-l (ZS low dose) group, and ZS-h (ZS high dose) group. The body weight and blood glucose were determined weekly. The oral glucose tolerance test, plasma insulin and biochemical parameters, pancreas histopathology, and the expression of insulin receptor substrate-1 were assayed at the end of experimental point. The results showed that *Z. striolatum* bud extract can significantly decrease the fasting blood glucose and glycated hemoglobin levels and insulin resistance (HOMA-IR) in C57BL mice. Western blot analysis demonstrated *Z. striolatum bud* extract could regulate the insulin sensitivity by upregulating the express of phospho-insulin receptor substrate-1. In conclusion, *Z. striolatum* bud extract could prevent the progression of diabetes and pancreatic fibrosis in C57BL mice.

Keywords: *Zingiber striolatum*; insulin receptor substrate-1; phospho-insulin receptor substrate 1; insulin resistance; type 2 diabetes mellitus.

Practical Application: The investigated *Z. striolatum* bud extract exhibits the well hypoglycemic activity *in vivo*. Moreover, the *Z. striolatum* bud extract is suitable for development as an effective natural functional component for T2DM patients.

1 Introduction

Diabetes mellitus is a complex chronic systemic disease including type 1 and type 2 diabetes mellitus (T1DM, T2DM), in which about 95% of them were T2DM (Thomas & Philipson, 2015). T2DM is mainly due to insufficiencies of insulin secretion or insulin resistance that can cause many complications and multiple organ injury even (DeFronzo, 2004; Forbes & Cooper, 2013). Traditional Chinese Medicine (TCM) has been frequently used to treat human diseases for thousands of years. In recent years, TCM have attracted more attentions to treat diabetes (He et al., 2016; Pang et al., 2014). Currently, in addition to TCM interventions, dietary interventions are recommended for, especially mild diabetes patients, such as switching to foods with a low glycemic index. Various functional foods may help control diabetes or make diabetes less likely to occur (Bai et al., 2021; Rehman et al., 2021; Yan et al., 2020). Indeed, the beneficial effects of functional food ingredients on diabetes have been demonstrated in experimental animal models as well as in human trials (Barros et al., 2021; Grom et al., 2020; Lin et al., 2021; Shafi et al., 2019).

Zingiber striolatum is a famous delicious vegetable and medicinal plant that widely distributed in China (Deng et al., 2018). In traditional Chinese medicine, it has been used to treatment diabetes and constipation. In previous studies, the chemical composition and pharmacological properties such as hypoglycemic, antioxidant, anticancer, nematicidal and antimicrobial activities were investigated (Cai et al., 2016; Hong et al., 2007; Tian et al., 2020). Its bud is a popular vegetable in southwest of China. Whereas, the research on the bud of *Z. striolatum* is still limited. The aim of this work is to evaluate the hypoglycemic function and mechanism of the bud of *Z. striolatum* in diabetic db/db mice.

2 Experimental

2.1 Chemicals and reagents

A One-Touch Ultra Blood Glucose Meter and strips (lot number: 3462320) were obtained from Johnson & Johnson Medical Equipment Co., Ltd. (Shanghai, China). A carboxyl methyl cellulose (0.5%) solution was used as the vehicle. Metformin (Met, Squib Pharmaceutical Co., Ltd., Shanghai, China) (suspended in 0.5% carboxyl methyl cellulose solution) was used as the positive drug. All antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA), and other chemicals were purchased from Sigma (St. Louis, MO).

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2.2 Plant materials and preparation of ZS

The buds of *Z. striolatum* were collected in Guizhou province in the summer. Plant material was botanically authenticated by Dr. Daopeng Tan, and a voucher specimen (*No*: ZS-190012~190015) was deposited in the School of Pharmacy, Zunyi Medical University. The buds were washed and soaked in purified water with a ratio of 1: 15 w/v overnight, and then boiled twice, each for 1 h. The extract was filtered and evaporated under reduced pressure. The residue was dried with spray dehydration apparatus yielding extract powder (the extract ratio 9.7%). This extract was used as raw plant materials for functional food development. Herein, this extract was used for bioassay.

2.3 Extract analysis

The extract was analyzed by UV-detector to determinate the content of flavonoids and polyphenols. The nutrient analysis of *Z. striolatum* extract was performed accrodingly. The nutrient and active components of ZS extract include the protein (11.9%), polysaccharide (44.1%), the polyphenols (6.3%), the flavonoids (2.7%) and saponins (0.3%).

2.4 Animals

Eight-week-old male C57BL/KsJ-db/db mice as the T2DM model (Fujimoto et al., 2010) were purchased from SLAC Laboratories Animal Co., Ltd. (Shanghai, China). Animals were housed in a 12-h light/dark cycles environment controlled at 23 ± 2 °C and 50 ± 5% humidity. The experiment procedures were strictly in accordance with the State Committee of Science and Technology of the People's Republic of China Order No. 2 on November 14, 1988 (revised 2011) and were approved by the Animal Experimentation Ethics Committee of the Zunyi Medical University.

2.5 Treatments

After 2 weeks of feeding, the mice were determined fasting blood glucose, and then randomly divided into five groups, ten mice each group, including normal control group, model group, metformin group (50 mg/kg, BW) and various concentrations of ZS (0.5 and 1.0 g/kg, BW) group. The normal control and model groups were received an equal volume of vehicle. Animals received the assigned intervention daily, per day continuously for 8 weeks. and their body weight, food, and water intake we measured weekly.

2.6 Serum biochemical factors

To determine fasting blood glucose levels, all mice were drawn blood from the tail vein every week. Approximately 50 μl fresh blood was added on test strips to determine the blood glucose content by a validated One-Touch Basic Glucose Monitoring System. At the end point of the experiment, all mice were fasted for 5 h and anesthetized with diethyl ether, and then taken blood for biochemical analysis. The blood samples were centrifuged 10 min by 3500 rpm to gain serum. The plasma insulin levels were detected by radioimmunoassay immediately. The plasma HbA1c level and lipid profile were measured by commercial kits and standard assay protocol. Homeostatic model assessment of insulin resistance (HOMA-IR) index was applied to estimate the change of insulin resistance in diabetic mice treated with ZS. The HOMA-IR calculation was performed using the following formula: HOMA-IR=fasting blood glucose (mmol/l) × insulin (μU/mL)/22.5 (Wallace et al., 2004).

2.7 Histopathology analysis

The pancreas tissues were fixed in 10% formalin solution for 24 h, and then dehydrated with alcohol and placed in xylene. The fixed pancreas samples were embedded in paraffin, and then cut into 6-8 μm thick sections by freezing microtome. Pancreas tissue sections were stained by hematoxylin and eosin (H&E) for examination by microscopy. Masson staining was operated to detect the islet fibrosis. Staining was performed according to the manufacturers' instructions.

2.8 Western blot analysis

To analyze the protein expression level related to insulin resistance, the insulin receptor substrate 1(IRS-1) and phospho-insulin receptor substrate 1(p-IRS-1) protein contents in the liver tissue were detected by Western blot. An appropriate amount of liver tissue was homogenized on ice with RIPA buffer and then treated with cell lysate and centrifuged to obtain the supernatant for separation by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The protein was transferred onto a nitrocellulose membrane in Tris-glycine buffer at 110 V for 1 h. The membranes were blocked with TBST containing 5% skim milk, and then incubated overnight with appropriate primary antibodies at 4 °C, washed twice with TBST, supplemented with the secondary antibodies, incubated for 2 h at room temperature. The images were obtained by enhanced chemiluminescence. β-actin was used as the reference protein. The relative band intensity was determined using a computerized densitometric analysis.

2.9 Statistical analysis

The statistical analyses were performed by SPSS software, version 18.0 (SPSS Inc., Chicago, USA). Statistical differences between groups were analyzed by one-way ANOVA. Values were expressed as means ± SD. Differences were considered to be significant, when p values<0.05.

3 Results

3.1 Effect of metabolic profiles in serum

At present, two doses of ZS and metformin did not significantly influence body weight, food and water intake, or feed efficiency ratio in db/db mice. As Figures 1A and 1C shown, compared to model group, ZS decreased significantly the fasting blood glucose and HbA1c levels in both ZS group. In oral glucose tolerance test, after intervention by ZS for 8 weeks, the blood glucose levels were significantly inhibited after a single high dose of glucose intake (Figure 1B) were decreased also.

Compared with the normal control group, the serum insulin level of db/db mice was significantly increased. Whereas, by

comparison with the model group, the HOMA-IR indexes were significantly decreased in various doses of ZS and metformin group (Figure 1D).

As shown in Table 1, The lipid profiles (TC, and TG) increased significantly, indicating dyslipidemia in db/db diabetic mice. Compared to model group, plasma concentrations of TC, and TG in ZS and metformin group decreased significantly. Malondialdehyde (MDA) was increased, however, the activity of SOD was decreased in diabetic mice by contrast with normal control group.

Controlling inflammation may promote insulin sensitivity and reduce the risk of developing T2DM patients (Qin et al., 2016; Shen et al., 2016). Our results showed that ZS intervention significantly lowered plasma levels of TNF-α and IL-1β compared with model group (Table 1.).

3.2 Effect of histopathology in pancreas

The results of histopathology were shown in Figure 2. Islet fibrosis played a major role in the progression and development of T2DM (Hayden & Sowers, 2007; Lee et al., 2011; Mizukami et al., 2008). The results of ZS in reducing fibrosis were shown as Figure 2. Masson staining indicated fibrosis in the islets of ZS groups (Figure 2D) decreased significantly compared with model group (Figure 2B).

3.3 Effect of protein expression in liver

The protein expression of IRS-1 and p-IRS-1 were detected by western blotting to clarify the mechanism of reducing insulin resistance and hyperglycemia of ZS (Karolina et al., 2011). Compared to normal control group, the protein expression level of phosphorylation of IRS-1 was decreased significantly

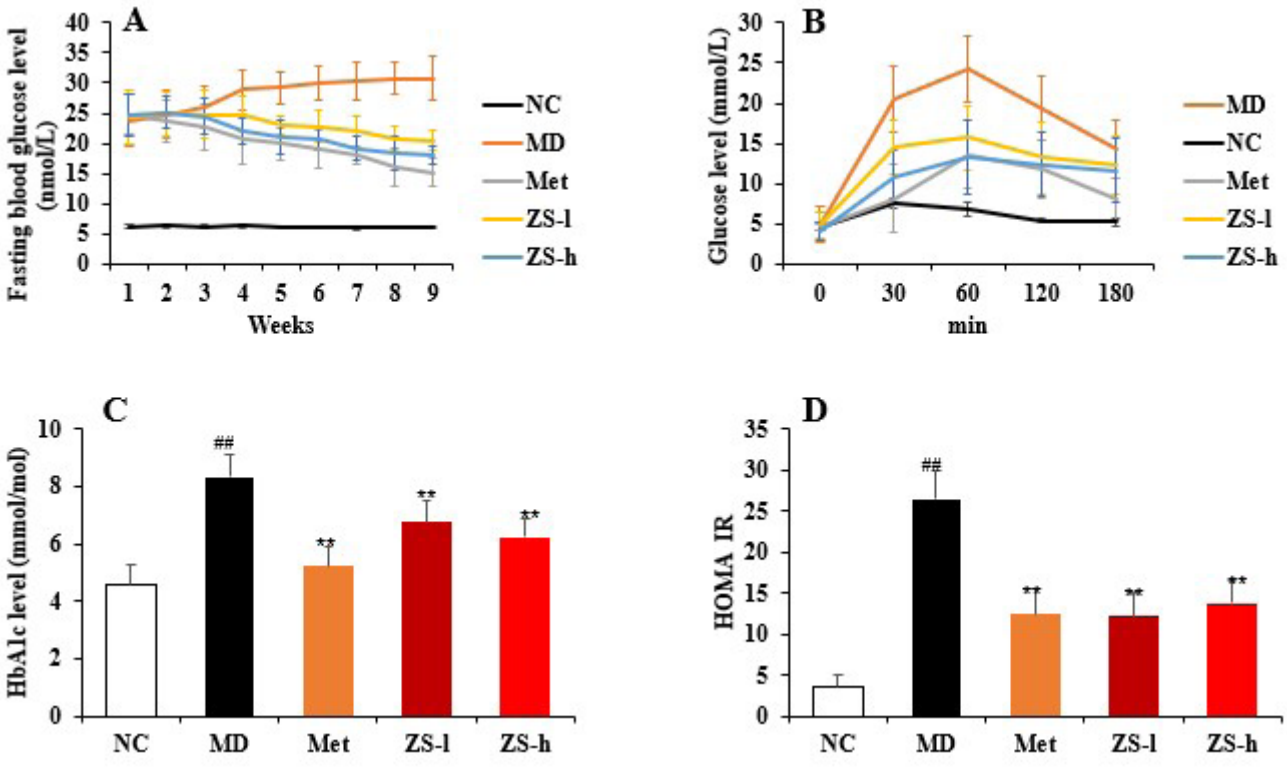

Figure 1. Blood glucose, HbA1c and HOMA-IR levels in db/db mice. Fasting blood glucose levels of db/db mice from week 1 to 8 (A). The blood glucose changing after administration ZS (B). The results of HbA1c in db/db mice at week 8 (C). The results of HOMA-IR in db/db mice at week 8 (D). NC: C57BL; DM: db/db mice untreated; Met: db/db mice treated with metformin (0.05 g/kg BW.); ZS-h, l: db/db mice treated with 1.0, and 0.5 g/kg b.w., respectively. ##p<0.05 compared with NC group; **p<0.01 compared with DM group.

Table 1. Effect of ZS on lipid profile in mice (n=10).

Groups	Dose (g/kg)	TC (mmol/L)	TG (mmol/L)	SOD (KU/mL)	MDA (mmol/L)	TNF-α (ng/L)	IL-1β (ng/mL)
NC	--	1.11 ± 0.54**	0.58 ± 0.31**	3.6 ± 0.3**	2.79 ± 0.23**	11.3 ± 1.1**	0.26 ± 0.13**
MD	--	2.47 ± 0.62	1.34 ± 0.43	0.9 ± 0.3	5.61 ± 0.22	36.0 ± 4.0	0.77 ± 0.22
Met	0.05	2.01 ± 0.57	1.13 ± 0.25*	2.2 ± 0.3**	3.52 ± 0.34**	35.4 ± 5.2**	0.32 ± 0.28**
ZS-l	0.5	2.13 ± 0.41*	1.15 ± 0.23*	2.8 ± 0.4**	3.71 ± 0.41**	25.7 ± 4.1**	0.35 ± 0.23**
ZS-h	1.0	2.07 ± 0.63*	1.09 ± 0.38*	2.2 ± 0.4**	3.49 ± 0.42**	26.8 ± 4.6**	0.36 ± 0.19**

Different from diabetic control group: *P < 0.05; **P < 0.01. serum total cholesterol (TC), triglyceride (TG), interleukin-1β (IL-1β), and tumor necrosis factor alpha (TNF-α), malondialdehyde (MDA), superoxide dismutase (SOD).

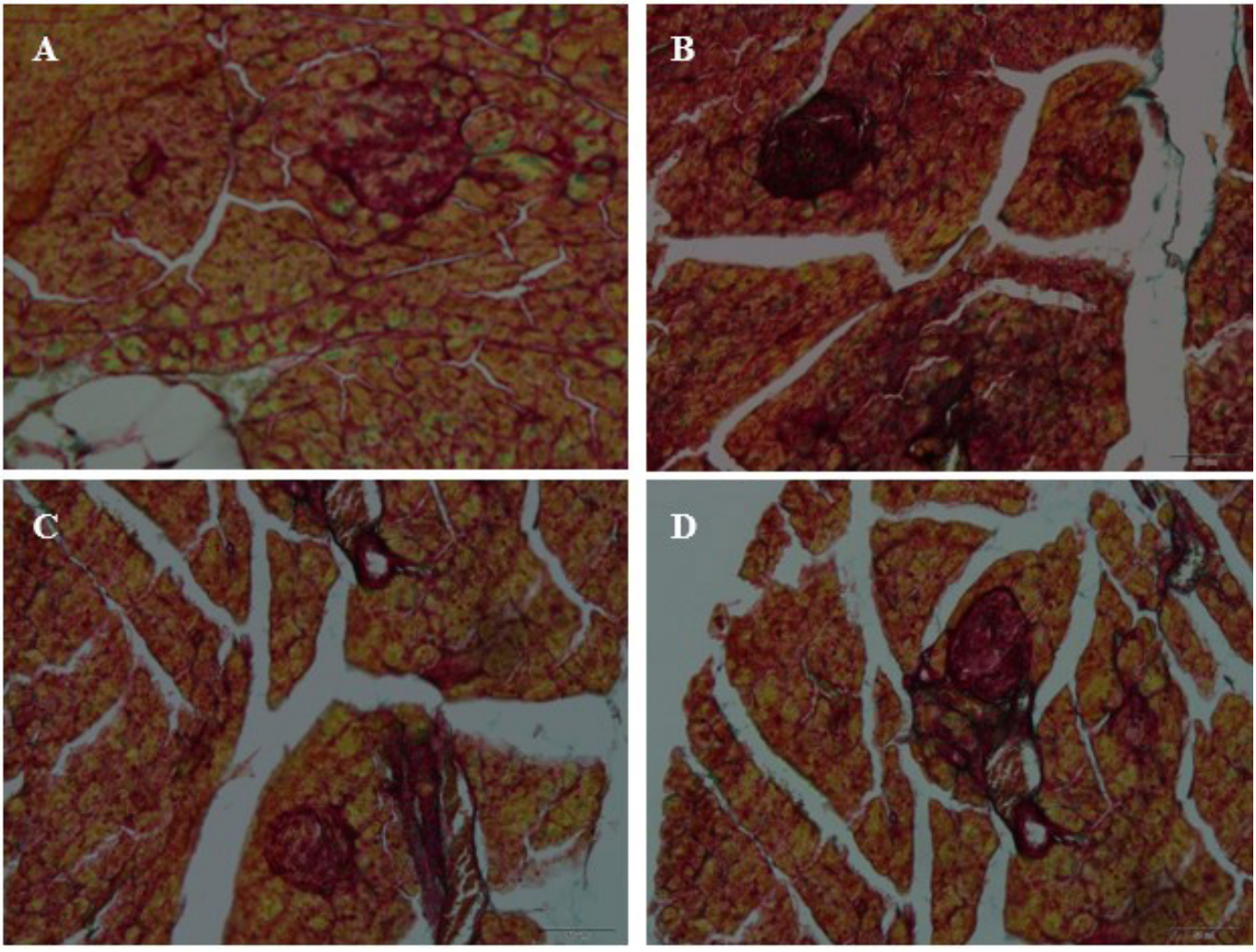

Figure 2. The islet fibrosis change of pancreas in db/db mice. (A) NC group, (B) DM group, (C) metformin group, (D) ZS-h group (1.0 g/kg BW).

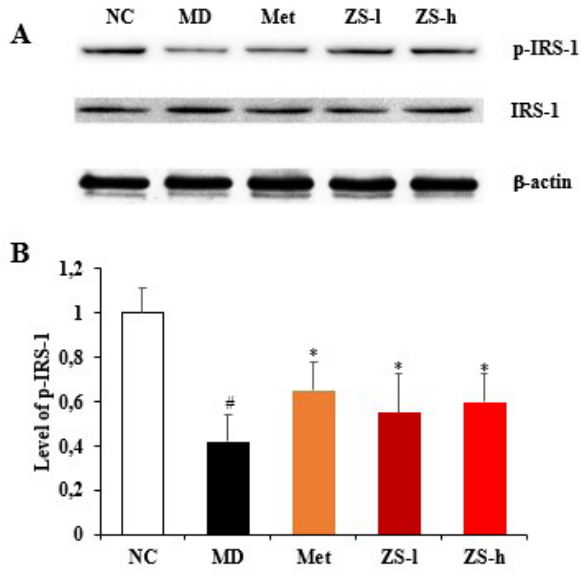

Figure 3. The protein expression levels of IRS-1 and p-IRS-1. (A) western blot image of IRS-1 and p-IRS-1, (B) relative expression levels of p-IRS-1. #p<0.05 compared with NC group; *p<0.05 compared with DM group.

in the liver of all db/db mice. Whereas the level of p-IRS-1 was increased in the ZS group by contrast to model group (Figure 3B).

4 Discussion

In the present study, the aim is to investigate the effects and mechanism of anti-diabetic function of ZS. Pancreatic β-cell failure plays a major role in the progress and development of T2DM (Jiang et al., 2014; Liu et al., 2017). Islet fibrosis may be an important result of progressive β-cell failure because it may accelerate the destruction of β-cells, such as that in chronic pancreatitis, or destroy β-cell (Gamble et al., 2004; Garner et al., 2004; Hayden et al., 2007). It has also been proposed that islet fibrosis is present in the late stage of β-cell dysfunction during the development of T2DM. Pancreatic fibrosis and parenchymal cell loss are central features of chronic pancreatitis, and pancreatic fibrosis was considered to be the cause of irreversible disease (Lee et al., 2011). It has been reported that oxidative stress is associated with fibrosis in various organs (Hayden & Sowers, 2007; Lee et al., 2011). High levels of ROS are intricately associated with obesity and related pathologies, especially insulin resistance and T2DM (Angiolillo et al., 2011; Kulkarni et al., 2003; Lee et al.,

2011). We evaluated the levels of oxidative stress marker (MDA) and antioxidant enzymes (SOD) activities. The results indicated that ZS could reduce blood glucose, protect islet cells, delay islet cell fibrosis, and resist oxidative stress. Even more significant, our work showed that ZS could reduce insulin resistance, which is verified by the decrease of HOMA-IR (Wallace et al., 2004).

IRS-1 is a key target of the insulin receptor tyrosine kinase and required for hormonal control of metabolism (Kulkarni et al., 2003; Wallace et al., 2004). The expression of IRS-1 was reduced in the liver and skeletal muscle of diabetic animal (Angiolillo et al., 2011; Karolina et al., 2011). Our work demonstrated that ZS could increase the expression of p-IRS-1 in liver tissue, which indicating that ZS could regenerate insulin signaling pathway. Our result suggested that the phosphorylation of IRS-1 induced by ZS is closely related to the amelioration of insulin resistance.

5 Conclusion

The results obtained in present study showed that the bud of *Z. striolatum* could reduce the blood glucose, insulin resistance and protect pancreatic fibrosis by regulating the phosphorylation of IRS-1 in db/db mice. Therefore, the bud of *Z. striolatum* may be an effective functional component for T2DM patients.

Abbreviations

Zingiber striolatum (ZS), C57BL/KsJ-db/db (db/db), Type 2 diabetes mellitus (T2DM), Glycated hemoglobin A1c (Hb1Ac), metformin (Met), Homeostatic model assessment of insulin resistance (HOMA-IR), Insulin receptor substrate 1 (IRS-1), phospho-insulin receptor substrate 1(p-IRS-1), Traditional Chinese Medicine (TCM), serum total cholesterol (TC), triglyceride (TG), interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), malondialdehyde (MDA), superoxide dismutase (SOD).

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Funding and research design: Xiangqian She. Conducted experiments: Daopent Tan, Jinguo Cui, Li Chen. Performed data analysis: Yuqi He, Yuhe Wang. Wrote or contributed to the writing of the manuscript: Daopeng Tan, Lin Qin.

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