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Diverse Mechanisms of Antidiabetic Effects of the Different Procyanidin Oligomer Types of Two Different Cinnamon Species on *db/db* Mice

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Supporting Information

ABSTRACT: The procyanidin oligomers are thought to be responsible for the antidiabetic activity of cinnamon. To investigate the hypoglycemic effects of different procyanidin oligomer types, the procyanidin oligomer-rich extracts were prepared from two different cinnamon species. Using high-performance liquid chromatography with purified procyanidin oligomers as reference compounds, we found that the *Cinnamomum cassia* extract (CC-E) and *Cinnamomum tamala* extract (CT-E) were rich in B- and A-type procyanidin oligomers, respectively. In the experiment, 8-week-old diabetic (*db/db*) mice were gavaged with CC-E and CT-E (both 200 mg/kg per day) for 4 weeks. Both CC-E and CT-E exhibited antidiabetic effects. Moreover, histopathological studies of the pancreas, liver, and adipose tissue showed that CC-E promoted lipid accumulation in the adipose tissue and liver, whereas CT-E mainly improved the insulin concentration in the blood and pancreas.

KEYWORDS: *Cinnamom, Cinnamomum cassia, Cinnamomum tamala, diabetes mellitus, procyanidin oligomers*

INTRODUCTION

Diabetes mellitus type 2, in which 90−95% of patients do not properly use or do not produce enough insulin, has increased rapidly worldwide and has a major impact on public health.[1] The mechanisms of the hypoglycemic activity of several medicinal plants that have antidiabetic potentials are currently being studied, offering great potential in discovering new antidiabetic drugs.[2,3] Cinnamon, a commonly consumed spice, is currently being investigated as a potential preventive supplement in improving glucose metabolism.[4−6]

Interests in cinnamon being a potentially useful treatment for type 2 diabetes began nearly 20 years ago.[7] Then, the effects of cinnamon on insulin signal transduction have been reported by numerous *in vitro* and *in vivo* studies.[8−12] Anderson et al. claimed that cinnamon is a natural insulin sensitizer.[13] Another study has revealed that cinnamon can inhibit advanced glycation of end products.[14,15] Although numerous trials have been conducted in humans using cinnamon to manage diabetes, the results remained controversial.[16] The intake of water-soluble cinnamon extracts can decrease fasting glucose and HbA1c levels.[17,18] However, some other clinical studies have demonstrated that cinnamon supplementation had no significant hypoglycemic effects.[19,20]

The ingredients of the cinnamon samples or extracts used in most studies were undefined. Procyanidin oligomers are the active compounds in the plant extracts.[21] A series of polyphenolic compounds have been presented as individual monomeric or oligomeric units from cinnamon. There are two main types of procyanidin oligomers (double-linked A type and single-linked B type) existing in the plants.[22] A-type polymers of cinnamon possess potent antioxidant properties and can increase insulin sensitivity.[21] However, the antidiabetic mechanism of the different types of procyanidin oligomers is poorly understood. Our previous studies have demonstrated that the different cinnamon species are rich in different types of procyanidin oligomers.[23] Thus, the controversial results are presumed to be caused by the use of different cinnamon species with undefined ingredients. Thus, preparing well-defined ingredients of cinnamon extracts before evaluating the mechanism of action of cinnamon regarding its therapeutic potential in diabetic care is crucial.

In this study, *Cinnamomum cassia* (aromaticum), popularly used as common cinnamon, and *Cinnamomum tamala*, popularly used in southwestern China, were chosen as raw materials to investigate whether different species of cinnamon have different antidiabetic effects. The procyanidin oligomer-rich extracts were obtained after purification. First, the procyanidin oligomer in the extracts were analyzed and compared to reference compounds. Then, the quantum of these constituents was surveyed using high-performance liquid chromatography (HPLC) fingerprint. Given the well-defined ingredients of the extracts, their antidiabetic effects were investigated on a genetic type 2 diabetic *db/db* mice model.

MATERIALS AND METHODS

Plants and Sample Preparation. Two cinnamon samples were collected from different areas in China. *C. cassia* (Chinese name *rou-gui*) and *C. tamala* (Chinese name *chai-gui*) were collected from Yunnan and Guangxi provinces, respectively. The samples were botanically

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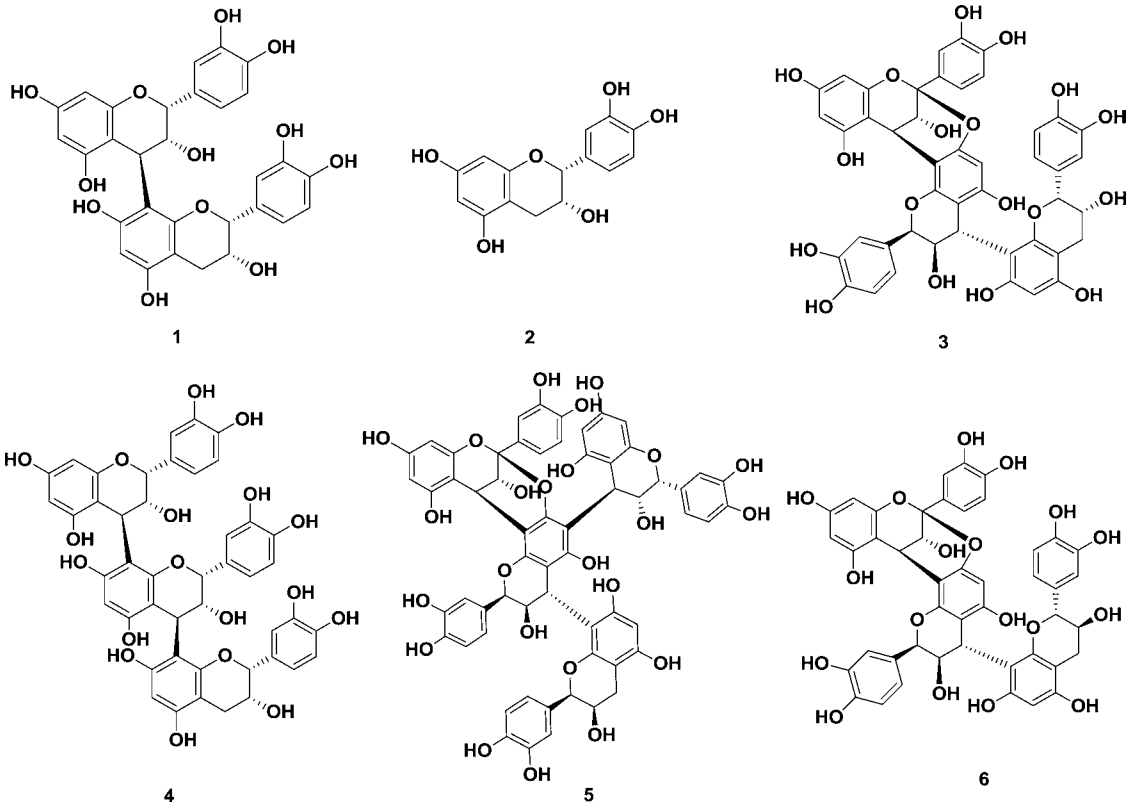

Figure 1. Structure of compounds **1**–**6**.

authenticated by Prof. Guanyun Gu from the School of Pharmacy, Fudan University, Shanghai, China. The voucher specimen (numbers RG006 and RG007) were deposited at the Herbarium of the Department of TCM Chemistry, School of Pharmacy, Shanghai University of Traditional Chinese Medicine (Shanghai, China).

Air-dried and powdered *C. cassia* bark (1 kg) was ground continuously with a 10 L 50% acetone–water solution at room temperature for 2 h. After filtration, the bark was ground for the second time with the same solvent under similar conditions. The two extracts were combined, concentrated *in vacuo* (40 °C) to 500 mL, and subsequently partitioned with diethyl ether (500 mL × 3) and ethyl acetate (500 mL × 6). The ethyl acetate fraction was concentrated and lyophilized to yield a 24 g EtOAc layer, named CC-E (bark extract from *C. cassia* Presl. tree). The *C. tamala* bark was processed using the same steps as those of CC-E extraction to yield a 35 g EtOAc layer, named CT-E [bark extract from *C. tamala* (Buch.-Ham.)].

Reference Compounds. Six compounds were isolated from these two extracts to investigate the chemical constituents in the cinnamon samples. Their structures were elucidated using spectroscopy methods and are known as procyanidin B2 (**1**), (−)-epicatechin (**2**), cinnamtannin B1 (**3**), procyanidin C1 (**4**), parameritannin A1 (**5**), and cinnamtannin D1 (**6**) (Figure 1). The purity of the compounds was checked using HPLC. The results showed that they can be used as reference compounds in CC-E and CT-E HPLC fingerprint map marking.

HPLC and Electrospray Ionization–Mass Spectrometry (ESI–MS) Analysis of Polyphenols. The principal components of the extracts were detected using HPLC. Then, 5 mg of CC-E or CT-E powder was dissolved in 5 mL of MeOH. Compounds **1**–**6** were also dissolved in MeOH. The methanolic solutions were then filtered through a 0.45 μm membrane for HPLC injection.

The analysis of procyanidins of the CC-E/CT-E using reversed-phase (RP)-HPLC was performed on an Agilent 1200 series HPLC instrument equipped with a hand sampler/injector, quaternary HPLC pump, column heater, diode array detector, and Agilent Chem-Station for data collection and manipulation. An Agilent Extend C18 column (5 μm, 4.6 × 250 mm) was used in this experiment. The samples were analyzed with a linear gradient from 92% solvent A (water) and 8% solvent B (100% acetonitrile) to 75% solvent A and 25% solvent B in 20 min and then to 10% solvent A and 90% solvent B for 30 min at a flow rate of 1.0 mL/min with an ultraviolet (UV) diode array detector at 280 nm. ESI–MS was recorded on a Thermo LCQ FLEET (Thermo Scientific) with negative-ion mode. Scan range was m/z 200–2000.

Animal Experiments. Male C57BL/KsJ-Lep^{db} mice (*db/db*, Jackson Laboratories) were maintained in a 12:12 light/dark cycle with a normal chow diet and free access to water. At 8 weeks of age, the *db/db* mice were randomly divided into 3 groups (n = 8 per group). Then, they were gavaged once daily with the vehicle (0.5% carboxymethyl cellulose), CC-E (200 mg/kg of body weight), and CT-E (200 mg/kg of body weight) for 4 weeks. After 6 h of fasting, blood glucose was monitored using tail vein blood with a glucometer (Accu-CHEK, Roche) every week. On days 26 and 28 post-drug administration, the mice were fasted for 12 and 6 h to perform oral glucose tolerance test (OGTT) and insulin tolerance test (ITT), respectively. At the end of the experimental period, the blood, pancreas, liver, and adipose tissues were collected for further studies. Serum insulin was measured using an insulin enzyme-linked immunosorbent assay (ELISA) kit (Millipore). Serum triglyceride (TG) and total cholesterol (TC) levels were assayed with commercial enzyme assay kits (Rongsheng, Shanghai, China). All animal experiments were permitted by the Institutional Animal Care and Use Committee of Shanghai Institute of Materia Medica (accreditation number SIMM-2011-WHY-04).

Histomorphology and Immunohistochemistry. Tissue samples were fixed in a 4% buffered paraformaldehyde solution and embedded in paraffin wax. After dehydration, the 5 μM thick sections were stained with hematoxylin and eosin (HE staining). For immunohistochemistry, the pancreas sections were washed in phosphate-buffered saline and incubated overnight at 4 °C with a monoclonal rabbit anti-insulin antibody (Cell Signaling Technology, Inc., Danvers, MA). The sections were then treated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG for 1 h at room temperature followed by incubation with diaminobenzidine. The slides were counterstained with hematoxylin. The images were captured using a microscope (DP70, Olympus).

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Statistical Analysis. Data were all expressed as the mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Dunnett's test analysis was performed, and a value of $p < 0.05$ was considered significant.

RESULTS

Identification of the Main Oligomeric Procyanidins in CC-E and CT-E. Cinnamon contains two main types of procyanidin oligomers. A-type procyanidin oligomers contain (+)-catechin and/or (−)-epicatechin units that form double links through carbon and C2 → O → 7 ether bonds, such that their trimers and tetramers have molecular masses of 864 and 1152 Da, respectively. B-type procyanidin oligomers contain flavan-3-ol units that form a single link through C4 → C8 and/or C4 → C6 bonds, such that their trimers and tetramers have molecular masses of 866 and 1154 Da, respectively.[23]

The HPLC chromatographic profiles (Figures 2 and 3) illustrated that the main components in CC-E were significantly different from those of CT-E, revealing an obvious difference between the constituents of *C. cassia* and *C. tamala*. The retention times (Rt) of main chromatographic peaks in CC-E were at 11.56, 12.76, 13.79, 14.10, and 15.23 min. These peaks were marked as P1−P5 (Figure 2). In comparison to the reference compounds isolated from CC-E, these peaks were identified as follows: P1 was compound **1**; P2 was compound **2**; P3 was compound **3**; and P4 was compound **4**. ESI−MS data of these peaks further identified that P1−P4 were compounds **1**−**4**. However, P5 cannot be identified by a single purified compound. The compounds from P5 exhibited three molecular ions at m/z 577, 865, and 1153 in the negative-ion mode of ESI−MS. This result suggested that P5 was a B-type procyanidin mixture. Hence, the main peaks in CC-E were P1, P4, and P5 (Table 1). B-type procyanidins could be the main ingredient in CC-E.

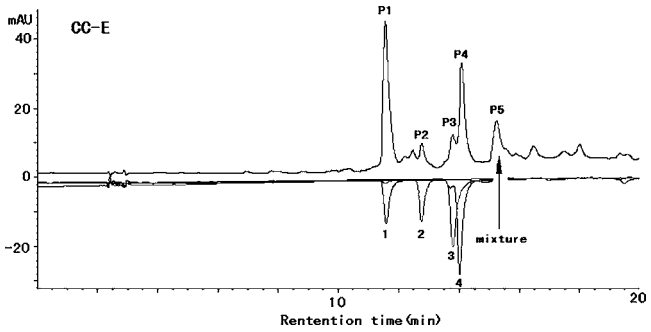

Figure 2. RP-HPLC chromatographic profile of CC-E polyphenolics detected at 280 nm.

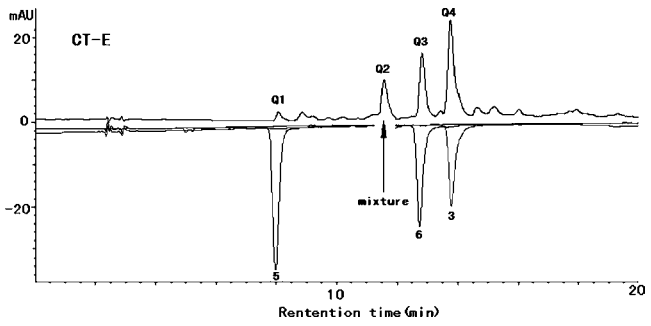

Figure 3. RP-HPLC chromatographic profile of CT-E polyphenolics detected at 280 nm.

The Rt values of the main chromatographic peaks in CT-E were at 8.05, 11.54, 12.80, and 13.77 min. These peaks were marked as Q1−Q4 (Figure 3). In comparison to the reference compounds isolated from CT-E, these peaks were identified as follows: Q1 was compound **5**; Q3 was compound **6**; and Q4 was compound **3**. ESI−MS data of these peaks further identified that Q1, Q3, and Q4 were compounds **5**, **6**, and **3**. Q2 showed the presence of molecular ions at m/z 1151 and 577 in the negative-ion mode of ESI−MS. Thus, Q2 can contain compound **1** and another unknown A-type tetramer procyanidin.[24] Hence, CC-E may primarily contain A-type procyanidins because the main peaks in CT-E were Q2, Q3, and Q4 (Table 1).

Effects of CC-E and CT-E on Blood Glucose, Serum Insulin, TG, and TC of *db/db* Mice. After 4 weeks of CC-E and CT-E treatments in *db/db* mice, no evident alteration in overall body weight gain and food intake was found (data not shown). However, the fasting blood glucose levels of CC-E- and CT-E-treated mice were lower than that of the vehicle group during the fourth week. CT-E administration showed a more evident hypoglycemic effect (Figure 4A). In the measurement of serum insulin, TG, and TC, we found that both CC-E and CT-E have increased the serum insulin concentration after 4 weeks of treatment. Moreover, CT-E-treated mice exhibited higher values compared to the CC-E-treated mice (Figure 4B). CC-E reduced the serum TG of *db/db* mice (Figure 4C). No evident change in the TC level was observed in the CC-E- or CT-E-treated mice (Figure 4D).

Effect of CC-E and CT-E on Blood Glucose Levels in OGTT and ITT in *db/db* Mice. OGTT and ITT were performed 4 weeks post-treatment to investigate further the antidiabetic effect of CC-E and CT-E on *db/db* mice. Both CC-E- and CT-E-treated mice had increased glucose tolerance (Figure 5A) and insulin sensitivity (Figure 5B). The areas under the curve (AUCs) in the CC-E and CT-E groups were lower than that of the vehicle-treated group (Figure 5C).

Histopathology and Immunohistochemistry. Immunohistochemical staining for insulin on pancreas sections from each group revealed that the CC-E and CT-E treatments increased insulin expression in the pancreas (Figure 6). This phenomenon is in agreement with the blood insulin measurement result. CC-E evidently increased the volume of adipocytes in adipose tissues, but CT-E had a weaker effect on the adipose tissues (Figure 6). Furthermore, a more remarkable hepatic lipid accumulation was observed in the CC-E-treated mice than in the CT-E-treated mice compared to the vehicle group (Figure 6).

Table 1. Peak Area of P1−P5 in CC-E and Q1−Q4 in CT-E

sample	CC-E					CT-E			
peak	P1	P2	P3	P4	P5	Q1	Q2	Q3	Q4
Rt (min)	11.56	12.76	13.79	14.10	15.25	8.07	11.57	12.82	13.76
area (mAU)	584.7	73.8	116.8	411.0	233.8	23.2	115.2	194.3	358.5
area (%)	33.1	4.1	6.6	23.3	13.3	2.8	13.8	23.3	43.0

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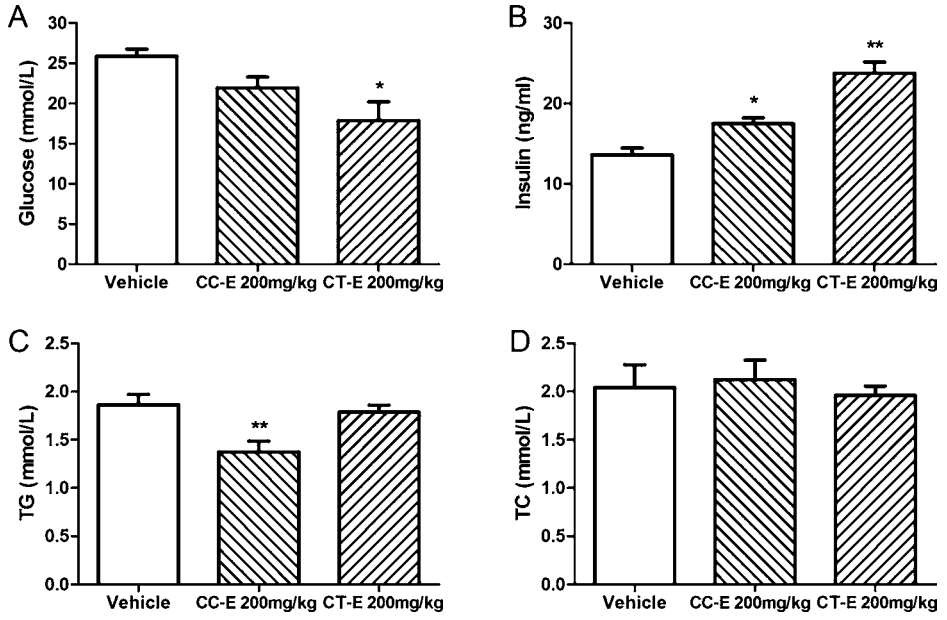

Figure 4. Effect of CC-E and CT-E on blood glucose, insulin, TG, and TC levels in *db/db* mice. The *db/db* mice were treated with the vehicle, 200 mg/kg of CC-E, and 200 mg/kg of CT-E for 4 weeks. Then, the (A) fasting blood glucose, (B) insulin, (C) TG, and (D) TG levels were measured. Values are the mean ± standard error (SE) (n = 8). (*) $p < 0.05$ and (**) $p < 0.01$ indicate the significant differences compared to the vehicle group.

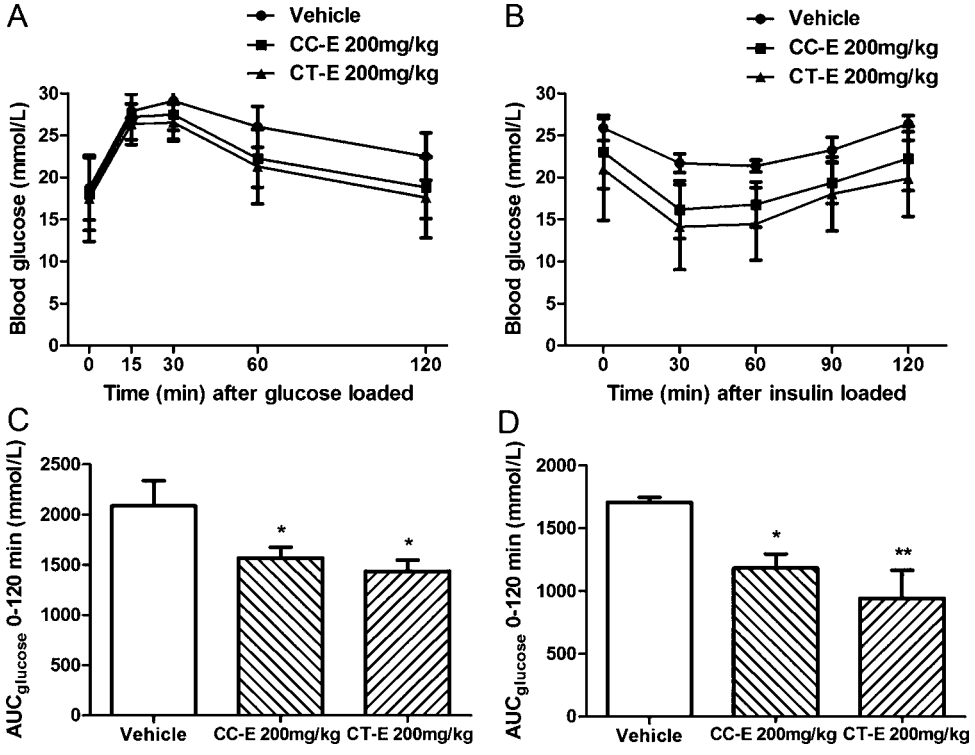

Figure 5. Effect of the 4 week administration of CC-E and CT-E in the (A) OGTT and (B) ITT in *db/db* mice. (A) After 12 h of fasting, 2 g of dextrose per kilogram of body weight was gavaged into mice and calculated as 0 min. Blood glucose levels were measured at the indicated times shown in the graph. (B) After 6 h of fasting, blood glucose concentrations were measured at the indicated time following intraperitoneal injection of 1 unit of insulin per kilogram of body weight. AUCs for (C) OGTT and (D) ITT are shown in the graph. Values are the mean ± SE (n = 8). (*) $p < 0.05$ and (**) $p < 0.01$ indicate the significant differences compared to the vehicle group.

DISCUSSION

Cinnamon has antidiabetic properties *in vitro* and *in vivo*. However, the underlying mechanisms are not fully understood. *C. cassia* can improve insulin sensitivity[25] and increases glucose uptake in 3T3-L1 adipocytes.[26] *C. tamala* promotes peripheral use of glucose and increases muscle glycogen storage.[27] In addition, this compound also has antidiabetic effects in both streptozotocin-induced diabetic rats[28] and *db/db* mice.[29]

Our previous studies have also revealed that the extracts from different cinnamon species have hypoglycemic effects in streptozotocin-induced diabetic rats.[23,30] In the present experiment, we found that the *C. cassia* and *C. tamala* extracts have

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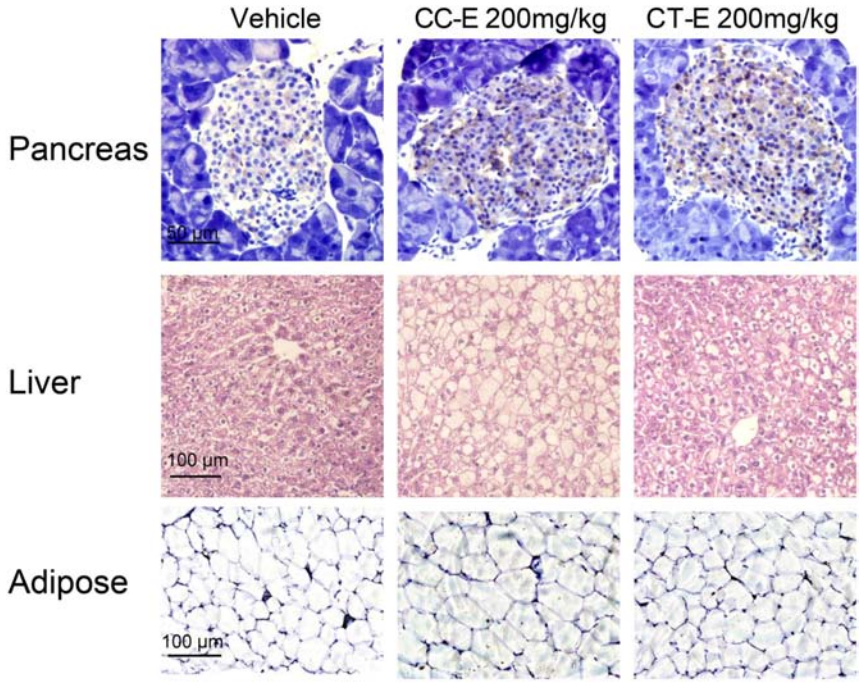

Figure 6. Immunohistochemical staining for insulin on pancreas sections. HE staining of the liver and white adipose tissues from the vehicle-, CC-E-, and CT-E-treated *db/db* mice. Tissues of 6 animals from each group and 4−6 random sections were selected for comparison. Scale bars are shown in graphs and refer to the same line.

significant antidiabetic effects in *db/db* mice. However, several differences between the two species were observed. After 4 weeks of CC-E and CT-E administration at 200 mg/kg of body weight on *db/db* mice, reduced blood glucose levels and improved OGTT and ITT were observed in the CC-E- and CT-E-treated mice compared to the vehicle group, in which CT-E showed more effective results. CT-E administration increased the blood insulin concentration remarkably. However, the CC-E-treated animals had a lower blood TG concentration compared to the vehicle group. CT-E had no effect on the TG.

Hence, we performed morphological studies to investigate the possible mechanism of the observed *in vivo* effect of CT-E and CC-E. Although both extracts could increase the insulin content in the pancreas, CT-E had a stronger effect on both the pancreatic insulin content and blood insulin concentration than CC-E. Chandola et al. speculated that the *C. tamala* leaf extract might promote insulin release or has an insulin-like action.[31] The phenomenon is in accordance with our present study that the extracts might increase the insulin concentration by improving insulin production in the pancreas.

Several studies have reported that *C. cassia* can improve insulin sensitivity[13,25,26] and elevate the expression of peroxisome proliferator-activated receptors (PPARs) as well as their target genes.[32] These receptors play important roles in dyslipidemia and diabetes.[33] The activation of PPARα leads to a lower plasma TG,[34] whereas PPARγ activation increases insulin sensitivity and induces lipid accumulation in adipose tissues and the liver.[35] We found that CC-E induced an obvious lipid accumulation in adipose tissue and fatty liver infiltration in the *db/db* mice compared to the vehicle group. However, no similar effect was observed in the CT-E- treated mice.

These results suggest that CC-E and CT-E contain different active ingredients. We found that the peak areas of procyanidin oligomers in CC-E and CT-E were over 80.6 and 82.9%, respectively. These results were further approved with the HPLC fingerprint under LC−MS ion current detection (see the Supporting Information). With purified procyanidin oligomers as reference compounds, the HPLC fingerprint showed that CC-E contained mainly B-type procyanidin dioligomer (P1) and trioligomer (P4), whereas CT-E from *C. tamala* contained mainly A-type procyanidin trioligomers (Q3 and Q4). These ingredients in different species of cinnamon may contribute to the difference in the mechanisms of their metabolic effects. Some reports have indicated that cinnamon species with A-type procyanidin oligomers may have a hypoglycemic effect, whereas other cinnamon species have no biological activities.[21] These results show that the ingredients of cinnamon extracts should be well-defined. In addition, cinnamon extracts need to have good quality control to ensure effectiveness and repeatability in biological assay tests.

In conclusion, the metabolic effects of *C. cassia* and *C. tamala* in diabetic *db/db* mice models were investigated and differences between the antidiabetic mechanisms of these species were found. The primary ingredients of the two species were identified. In addition, the diverse procyanidin oligomer components in *C. cassia* and *C. tamala* may crucially contribute to the different antidiabetic effects. The antidiabetic effects of the purified procyanidin oligomer compounds need further investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

LC−MS analysis of CC-E and CT-E, positive- and negative-ion current maps of CC-E and CT-E, and peak identification in the negative-ion current map of CC-E and CT-E. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†These authors contributed equally to this work.

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Notes

The authors declare no competing financial interest.

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