

Article

Effects of Cinnamaldehyde on Glucose and Lipid Metabolism in Type 2 Diabetic Mice via the FXR/FGF15 Signaling Pathway

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Abstract: Objective: To investigate the effects of cinnamaldehyde (CA) on glucose and lipid metabolism in streptozotocin (STZ)-induced diabetic mice and to explore the underlying mechanism involving the farnesoid X receptor (FXR) and fibroblast growth factor 15 (FGF15) signaling pathway. Methods: Forty-eight male C57BL/6 mice were randomly divided into six groups (n = 8 per group): normal control, model, metformin, and low-, medium-, and high-dose CA groups (20, 40, and 120 mg/kg, respectively). Diabetes was induced by intraperitoneal administration of STZ (150 mg/kg). Fasting blood glucose and serum lipid profiles were measured. Furthermore, the mRNA expression of CYP7A1, FGFR4, FXR, TGR5, FGF15, and Gcg in the liver and small intestine was determined by RT-qPCR. Results: Compared with the model group, medium-dose CA (40 mg/kg) significantly up-regulated hepatic CYP7A1, TGR5, and FXR mRNA expression, increased intestinal Gcg expression, reduced fasting blood glucose and serum triglyceride levels, and partially reversed the model-associated reduction in serum LDL-C. The medium dose produced the most pronounced improvement, whereas high-dose CA (120 mg/kg) aggravated glucolipid metabolic disorders and further suppressed CYP7A1 expression. Conclusion: Medium-dose cinnamaldehyde ameliorates glucolipid metabolic disorders in STZ-induced diabetic mice, likely by up-regulating hepatic CYP7A1 to promote de novo bile acid synthesis and by modulating the intestinal FXR/FGF15 and TGR5/GLP-1 signaling pathways, providing an experimental basis for developing cinnamaldehyde as a potential antidiabetic agent.

Keywords: cinnamaldehyde; type 2 diabetes; bile acids; farnesoid x receptor; glucose metabolism; lipid metabolism

1. Introduction

Bile acids, the principal functional components of bile, are synthesized from cholesterol in the liver via the classic and alternative pathways and represent the major metabolic route for cholesterol elimination from the body. After synthesis, bile acids are secreted into the intestine with bile, where they participate in the digestion and absorption of dietary lipids and fat-soluble vitamins, and are subsequently reabsorbed into the liver through enterohepatic circulation. The biological functions of bile acids are mediated by their receptors, including the nuclear receptors farnesoid X receptor (FXR), pregnane X receptor (PXR), and vitamin D receptor (VDR), as well as the membrane receptor G protein-coupled bile acid receptor 1 (TGR5/GPBAR1). In 1999, multiple research teams independently demonstrated that bile acids are endogenous ligands of FXR, thereby establishing bile acids as bona fide metabolic signaling molecules. Accumulating evidence now indicates that bile acids are not merely constituents of digestive fluid but also important metabolic signaling molecules involved in the regulation of glucose metabolism, energy balance, endocrine function, and immune responses; alterations in bile acid metabolism and signal transduction are closely associated with inflammation, tumors, cholestasis, liver fibrosis, gut microbiota dysbiosis, metabolic syndrome, and

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atherosclerosis. Therefore, in-depth investigation of bile acid actions in the liver and intestine, together with the exploration of disease mechanisms and novel therapeutic targets, is of considerable clinical significance and scientific value. Among these receptors, FXR is the central nuclear receptor governing bile acid, lipid, and cholesterol metabolism as well as energy homeostasis [1–3]. In bile acid metabolism, FXR fine-tunes de novo bile acid synthesis through feedback inhibition of the key rate-limiting enzymes CYP7A1, CYP8B1, and CYP27A1.

As a metabolism-related nuclear receptor, FXR has attracted increasing attention for its role in glucose metabolism. FXR-knockout mice exhibit abnormal hepatic expression of the gluconeogenesis-related genes PGC-1 α , PEPCK, and G-6-Pase, together with marked glucose intolerance and impaired insulin sensitivity, indicating that FXR is essential for maintaining normal glucose homeostasis [4–6]. FXR activation also modulates adiposity and peripheral insulin responsiveness in mice, and administration of the FXR agonist GW4064 significantly lowers blood glucose in diabetic mice [7, 8]. Notably, the intestinal actions of FXR are highly tissue-specific: intestinal FXR activation suppresses the secretion of glucagon-like peptide-1 (GLP-1) from ileal and colonic L cells; the intestine-selective FXR agonist fexaramine (FEX) promotes adipose tissue browning, reduces obesity, and ameliorates impaired insulin sensitivity, whereas intestine-selective FXR inhibitors likewise improve obesity-related metabolic dysfunction, suggesting that intestinal FXR signaling regulates glucolipid metabolism in a bidirectional and context-dependent manner. Cinnamaldehyde (CA), the major active constituent of the volatile oil of *Cinnamomum cassia* (Lauraceae), exerts significant hypoglycemic and hypolipidemic effects in db/db mice and streptozotocin (STZ)-induced diabetic animal models. Upon activation, intestinal FXR induces the transcription and secretion of fibroblast growth factor 15 (FGF15; the human ortholog is FGF19), which reaches the liver via the portal circulation, binds the FGFR4/ β -Klotho receptor complex on hepatocytes, and feedback-inhibits CYP7A1 expression, thereby constituting the enterohepatic negative-feedback loop that maintains bile acid homeostasis, namely the FXR/FGF15 signaling pathway. Building on previous genomic and metabolomic findings of bile acid enrichment, the present study focused on the FXR/FGF15 signaling pathway in an STZ-induced diabetic mouse model. We examined the effects of different doses of cinnamaldehyde on blood glucose, blood lipids, tissue total bile acid content, and the expression of FXR/FGF15 pathway-related genes, assessed the association between cinnamaldehyde intake and bile acid-FXR signaling, and further explored the potential links and targets through which cinnamaldehyde regulates blood glucose, with the aim of elucidating the mechanism by which cinnamaldehyde ameliorates glucolipid metabolic disorders in diabetes mellitus (DM).

2. Materials and Methods

2.1. Experimental Animals and Grouping

Forty-eight specific pathogen-free (SPF) male C57BL/6 mice, aged 4–5 weeks and weighing 14–16 g, were obtained from the Guangdong Medical Laboratory Animal Center (certificate No. 44007200062167; license No. SCXK (Yue) 2018-0002). After a 3-day acclimatization period on standard chow, body weights were recorded; following a 12-hour fast, approximately 0.5 mL of blood was collected from the tail vein of each mouse, and serum was isolated by centrifugation at 3,500 r/min for 15 min to determine fasting blood glucose levels [9, 10]. Mice were then randomly assigned to six groups ($n = 8$ per group): normal control (N), model (M), metformin (Met), low-dose cinnamaldehyde (LCA, 20 mg/kg), medium-dose cinnamaldehyde (MCA, 40 mg/kg), and high-dose cinnamaldehyde (HCA, 120 mg/kg), with no statistically significant differences in baseline blood glucose or body weight across groups [11, 12].

2.2. Main Reagents and Animal Modeling

A 1% streptozotocin (STZ) solution was prepared by dissolving 10 mg of STZ in 1 mL of 0.1 mol/L citric acid–sodium citrate buffer (pH 4.5), followed by sterile filtration

through a 0.22- μ m membrane filter; the solution was used immediately and stored at 4 °C in the dark [13–15].

Metformin tablets (brand name: Glucophage; specification: 0.5 g $\times$ 20 tablets) were obtained from Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd [16–18]. (approval number: H20023370); STZ was sourced from Sigma-Aldrich; assay kits for total bile acids, farnesoid X receptor (FXR), fibroblast growth factor 15 (FGF15), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were all supplied by Nanjing Jiancheng Bioengineering Institute [19, 20].

After one week of acclimatization, male C57BL/6 mice underwent model induction following a 12-hour fast with free access to water. Except for the normal control group, all animals received an intraperitoneal administration of STZ at a dose of 150 mg/kg, delivered bilaterally into the lower abdominal region at approximately the lateral one-third position to avoid the midline bladder area; the normal control group received an equivalent volume of citrate buffer. Post-administration, mice were maintained on standard chow with unrestricted water access, and daily observations included body weight, water consumption, spontaneous activity, behavioral responses, and survival status. Animals exhibiting signs of hypoglycemia within 72 hours post-administration were provided 10% glucose solution ad libitum. On day 10 after model establishment, all mice were fasted for 6 hours, and fasting blood glucose was measured from tail vein blood samples; a value exceeding 11.0 mmol/L was defined as successful model induction. Mice with fasting blood glucose below 11.0 mmol/L underwent re-administration of STZ on day 21 using the identical protocol [21, 22].

2.3. Determination of Total Bile Acid Content in Mouse Tissues

At the end of the experiment, the mice were euthanized, and serum, liver, small intestine, colonic contents, and fecal samples were collected. The small intestine was rinsed with pre-chilled phosphate-buffered saline and opened longitudinally; the intestinal mucosa was gently scraped off and immediately snap-frozen in liquid nitrogen. To assess bile acid excretion, the mice were housed individually in metabolic cages, and feces were collected continuously for three days, air-dried, weighed, and stored. Total bile acid content in each sample was determined strictly according to the manufacturer's instructions for the total bile acid assay kit; the sum of total bile acids in the liver and small intestinal contents was defined as the bile acid pool size [23, 24].

2.4. Detection of Fxr/fgf15 Signaling Pathway-Related Gene Expression

mRNA expression levels of the relevant genes were quantified using real-time quantitative PCR (RT-qPCR). Target genes included the hepatic gene encoding the rate-limiting bile acid synthetic enzyme CYP7A1, the fibroblast growth factor receptor 4 gene FGFR4, the nuclear receptor gene FXR, and the membrane bile acid receptor gene TGR5; in the small intestine, FXR, its downstream target gene FGF15, and the proglucagon gene Gcg (encoding GLP-1). GAPDH was used as the internal reference gene. Primer sequences are provided in Tables 1 and 2 (As shown in Table 1, 2).

Table 1. Primer Sequences for the Gcg (GLP-1) and TGR5 Genes

Gene	Forward/Reverse	Primer sequence (5'-3')
CYP7A1	F	GGAATGCCATTTACTTGGATC
	R	TATAGGAACCATCCTCAAGGTG
FGF15	F	AGACGATTGCCATCAAGGACG
	R	GTACTGGTTGTAGCCTAAACAG
FXR	F	GTTTCGGCGGAGATTTCAATAAG
	R	AGTCATTTGAGTTCTCCAACAC
FGFR4	F	CTCGATCCGCTTTGGGAATTC
	R	CAGGTCTGCCAAATCCTTGTC
GAPDH	F	CTGCGACTTCAACAGCAACT

	R	GAGTTGGGATAGGGCCTCTC
Table 2. Primer Sequences for the CYP7A1, FGF15, FXR, FGFR4, and Gapdh Genes		
Gene	Forward/Reverse	Primer sequence (5'-3')
CYP7A1	F	GGAATGCCATTTACTTGGATC
	R	TATAGGAACCATCCTCAAGGTG
FGF15	F	AGACGATTGCCATCAAGGACG
	R	GTACTGGTTGTAGCCTAAACAG
FXR	F	GTTCGGCGGAGATTTCAATAAG
	R	AGTCATTTGAGTTCTCCAACAC
FGFR4	F	CTCGATCCGCTTTGGAATTC
	R	CAGGTCTGCCAAATCCTTGTC
GAPDH	F	CTGCGACTTCAACAGCAACT
	R	GAGTTGGGATAGGGCCTCTC

2.5. Statistical Analysis

Quantitative data are presented as mean ± standard deviation and analyzed using SPSS Statistics 19.0. Multiple-group comparisons were conducted via one-way analysis of variance (one-way ANOVA), with post hoc pairwise comparisons performed using the LSD-t test. Statistical significance was defined as P < 0.05. All available data points were included without outlier removal; given the limited sample size, between-group differences were interpreted in conjunction with within-group variability [25–27].

3. Results

3.1. Effects of Cinnamaldehyde Intervention on Blood Glucose and Serum Lipid Levels in Diabetic Mice

The effects of different doses of cinnamaldehyde on blood glucose and serum lipids in the mice are shown in Figure 1. Compared with the normal control group, mice in the model group exhibited significantly elevated fasting blood glucose and serum triglyceride levels, indicating that streptozotocin treatment induced glucolipid metabolic disorders characterized by hyperglycemia and hypertriglyceridemia. Serum low-density lipoprotein cholesterol levels were significantly decreased in the model group, and total cholesterol levels also showed a decreasing trend without reaching statistical significance, which may reflect an imbalance between lipid synthesis and catabolism following streptozotocin-induced injury to pancreatic β cells. Collectively, these findings confirm successful establishment of the streptozotocin-induced diabetic mouse model [28, 29].

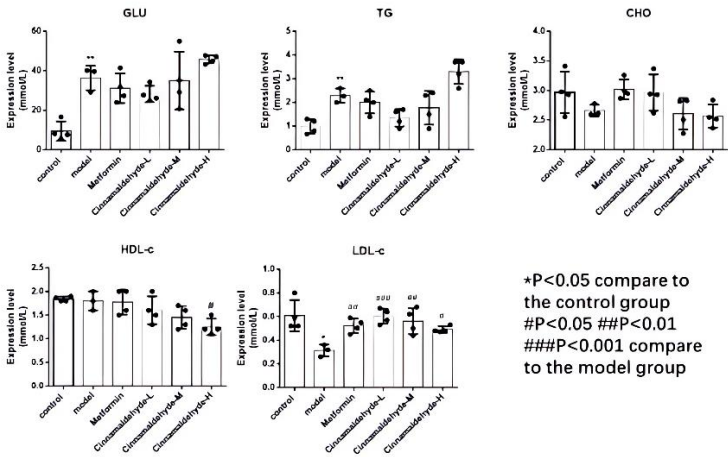


Figure 1. Effects of Different Doses of Cinnamaldehyde on Blood Glucose and Serum Lipid Levels in Diabetic Mice

Further intergroup comparisons revealed that, following administration of the test compounds, blood glucose and serum triglyceride levels tended to decrease in the metformin, low-dose cinnamaldehyde, and medium-dose cinnamaldehyde groups; however, the differences did not reach statistical significance, likely due to substantial interindividual variability. Total cholesterol levels tended to increase without statistical significance, while low-density lipoprotein cholesterol levels rebounded significantly [30, 31]. Notably, unlike the dyslipidemia typically observed in type 2 diabetes, this streptozotocin-induced model featured reduced rather than elevated low-density lipoprotein cholesterol; thus, the observed rebound should be interpreted as a partial restoration of the model-specific lipid profile rather than a conventional lipid-lowering effect. Based on changes in fasting blood glucose and serum triglycerides, metformin and low- and medium-dose cinnamaldehyde appeared to ameliorate hyperglycemia and hypertriglyceridemia to some extent, whereas high-dose (120 mg/kg) cinnamaldehyde failed to produce improvement and instead exacerbated these metabolic disturbances. Considering all parameters, medium-dose (40 mg/kg) cinnamaldehyde yielded the most pronounced overall effect on fasting blood glucose and serum triglycerides, and this dose was therefore selected for subsequent mechanistic studies.

3.2. Effects of Cinnamaldehyde Intervention on the Expression of Bile Acid Metabolic Pathway-Related Genes in Diabetic Mice

3.2.1. RNA Concentration and Purity

The OD260/280 ratio is a standard indicator of RNA sample purity, and high-quality RNA samples typically exhibit an OD260/280 ratio between 1.8 and 2.1. The measured values for total RNA extracted from liver tissue are presented in Table 3.

Table 3. Concentration and Purity of Total RNA from Liver Tissue

Sample	Conc. (ng/μL)	Vol. (μL)	OD260/280	Path (mm)
N-1	616.04	80	2.03	0.2
N-2	318.18	80	2.04	0.2
N-3	194.3	80	2.01	0.2
N-4	396.52	80	2.02	0.2
N-5	185.3	80	1.97	0.2
N-6	255.1	80	1.96	0.2
N-7	268.5	80	2.01	0.2
N-8	241.2	80	1.95	0.2

Per standard laboratory criteria, an OD260/280 ratio below 1.8 suggests potential contamination with protein, phenol, or other organic solvents, while a ratio substantially exceeding 2.1 may indicate residual DNA or other non-RNA components; RNA integrity is more accurately evaluated via electrophoresis or RNA integrity number (RIN) analysis. As shown in Table 3, all extracted total RNA samples exhibited OD260/280 ratios within the 1.8–2.1 range, confirming satisfactory purity and absence of detectable contamination by protein, DNA, or organic solvents—thus fulfilling the quality requirements for downstream RT-qPCR analysis.

3.2.2. Melting Curve Analysis

As shown in Figure 2, the melting temperatures of CYP7A1, FGFR4, hepatic FXR, GAPDH, FGF15, and intestinal FXR were (82.2 ± 0.2) °C, (87.8 ± 0.2) °C, (80.0 ± 0.2) °C, (85.8 ± 0.2) °C, (85.0 ± 0.2) °C, and (80.0 ± 0.2) °C, respectively. Each gene exhibited a single-peak melting curve, confirming high primer specificity and absence of nonspecific amplification or primer-dimer formation.

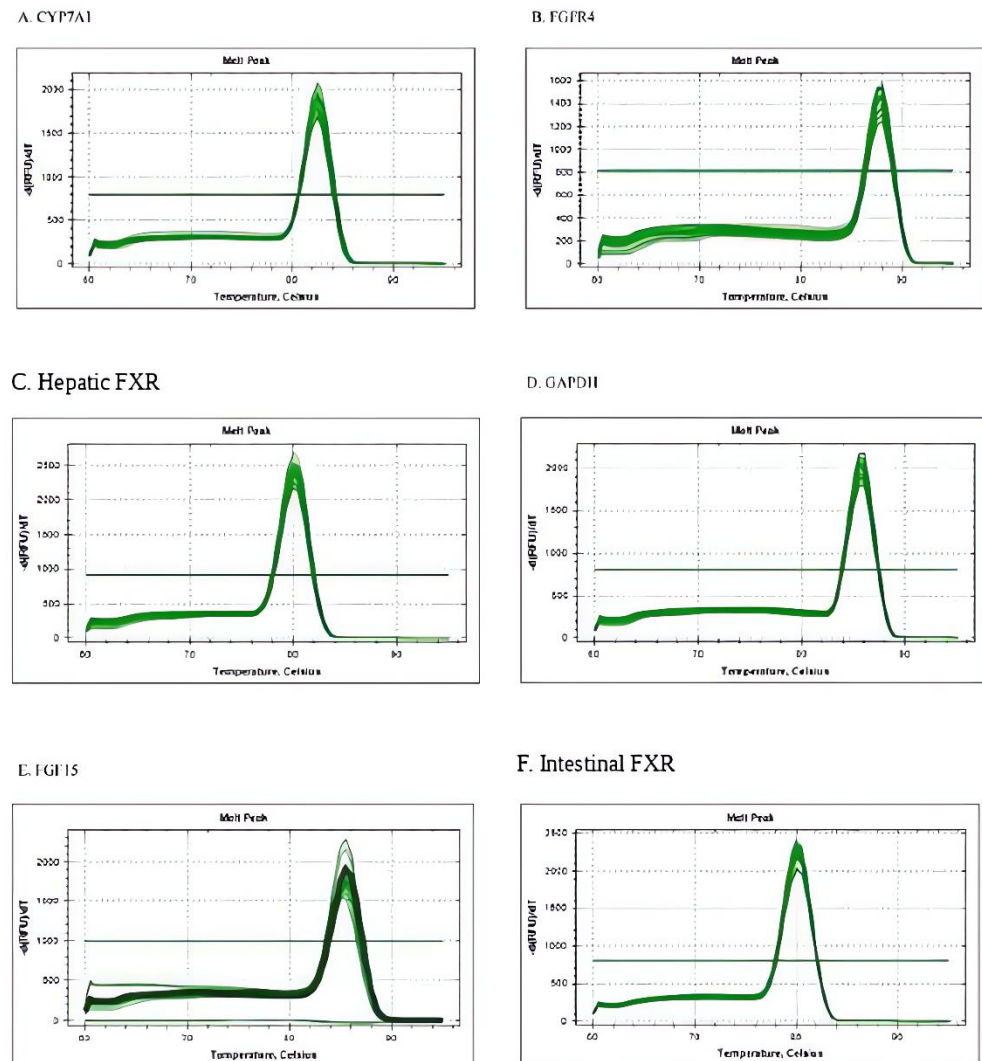


Figure 2. Melting Curves of the CYP7A1, FGFR4, FXR, FGF15, and Gapdh Genes

3.2.3. Effects of Cinnamaldehyde on Hepatic CYP7A1, TGR5, and FXR and Intestinal Fxr/fgf15 Gene Expression in Diabetic Mice

As shown in Figure 3A, hepatic CYP7A1 mRNA expression in the model group was lower than that in the normal control group and all drug-treated groups (differences not statistically significant), suggesting reduced activity of the key rate-limiting step in de novo hepatic bile acid synthesis and reduced cholesterol catabolism in the diabetic state. Hepatic CYP7A1 mRNA expression in the LCA and MCA groups was significantly higher than that in the model and normal control groups ($P < 0.05$), with the MCA group reaching a level comparable to that of the metformin group; the HCA group showed the lowest CYP7A1 expression, indicating that increasing the cinnamaldehyde dose beyond 40 mg/kg does not further enhance CYP7A1 expression and that excessive intake may inhibit the bile acid synthesis pathway [21, 32]. As shown in Figure 3B, intestinal Gcg (encoding GLP-1) mRNA expression in the model group was lower than that in all cinnamaldehyde-treated groups (differences not statistically significant), with the highest expression observed in the MCA group, suggesting that 40 mg/kg cinnamaldehyde may promote GLP-1 expression and secretion by intestinal L cells and thereby support improved glucose metabolism. As shown in Figure 3C, hepatic TGR5 mRNA expression in the model group was significantly lower than that in the normal control group and all drug-treated groups ($P < 0.05$). TGR5, the first identified membrane-bound G protein-coupled bile acid receptor, participates broadly in bile acid signal transduction and the modulation

of glucolipid metabolism; its down-regulation indicates impaired bile acid membrane receptor signaling in diabetic mice [33–35]. Comparisons among the treatment groups showed that hepatic TGR5 mRNA expression in the MCA group (40 mg/kg) was significantly higher than that in the other drug-treated groups ($P < 0.05$). As shown in Figure 3D, hepatic FXR mRNA expression in the model group was markedly lower than that in the normal control group, whereas expression in the metformin, LCA, and MCA groups was higher than that in the model group, suggesting that cinnamaldehyde treatment enhances hepatic FXR expression and promotes activation of downstream bile acid metabolic pathways. As shown in Figure 3E, intestinal FGF15 mRNA expression in the model group did not differ significantly from that in the normal control and metformin groups; comparisons among the cinnamaldehyde treatment groups showed that FGF15 expression was significantly increased only in the LCA group ($P < 0.05$); however, given the considerable within-group variability of FGF15 expression and the limited sample size, this result should be interpreted with caution and warrants confirmation at the protein level [36–38]. CYP7A1 is the initiating rate-limiting enzyme of cholesterol catabolism: it converts excess cholesterol into bile acids, promotes bile acid synthesis, and reduces cholesterol accumulation in the body [39]. Taken together, these results suggest that 40 mg/kg cinnamaldehyde may modulate glucolipid metabolism by enhancing hepatic CYP7A1 expression to accelerate de novo bile acid synthesis while simultaneously activating FXR/TGR5-mediated bile acid signal transduction [40].

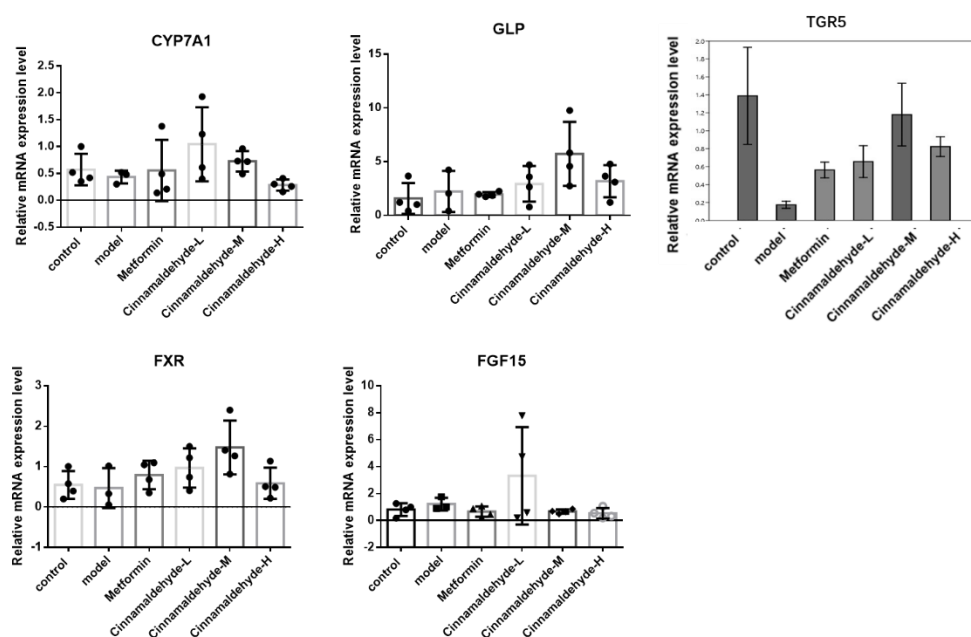


Figure 3. Effects of Cinnamaldehyde on the mRNA Expression of Bile Acid Metabolism- and Fxr/fgf15 Pathway-Related Genes in Diabetic Mice. (A) Hepatic CYP7A1; (B) Intestinal Gcg (GLP-1); (C) Hepatic TGR5; (D) Hepatic FXR; (E) Intestinal FGF15.

4. Discussion

Type 2 diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia that results from the combined effects of enhanced hepatic gluconeogenesis, reduced hepatic glycogen storage, insufficient insulin secretion, and decreased peripheral insulin sensitivity; it is frequently accompanied by dyslipidemia such as elevated triglycerides and decreased high-density lipoprotein cholesterol. Chronic hyperglycemia can cause complications involving multiple organ systems, seriously affecting patients' quality of life and life expectancy and imposing a heavy socioeconomic burden. Therefore, identifying agents with pronounced glucose- and lipid-lowering effects and good long-term safety has remained an important direction in drug

development for metabolic diseases. Bile acid metabolism plays an important role in the development and progression of type 2 diabetes: patients with diabetes commonly exhibit an imbalance in bile acid synthesis and enterohepatic circulation homeostasis, and alterations in bile acid pool size and composition can, in turn, affect glucolipid metabolism. Building on previous work, this study investigated the roles of CYP7A1 and the FXR/FGF15 signaling pathway in bile acid metabolism and glucolipid metabolism in diabetic mice during cinnamaldehyde treatment.

FXR is the most important nuclear receptor for bile acids, and its activation bidirectionally modulates bile acid synthesis and homeostasis through the hepatic SHP pathway and the intestinal FGF15/19 pathway. Activation of intestinal FXR promotes the transcription and secretion of FGF15, which acts via the portal circulation on the FGFR4/ β -Klotho receptor complex on the surface of hepatocytes to inhibit CYP7A1 gene transcription, thereby completing the enterohepatic negative-feedback control of bile acid synthesis; the human counterpart of this axis, FGF19, displays a pronounced diurnal rhythm and likewise participates in the control of hepatic bile acid synthesis. Beyond bile acid homeostasis, the FXR/FGF15 signaling pathway also plays important roles in energy metabolism, glucose metabolism, and liver regeneration. Results showed that hepatic CYP7A1, TGR5, and FXR mRNA expression all trended downward in STZ-induced model mice, consistent with the phenotype of impaired bile acid signaling and glucolipid metabolic disorders; medium-dose (40 mg/kg) cinnamaldehyde significantly up-regulated the expression of these genes while improving blood glucose and lipid levels, suggesting that cinnamaldehyde may restore the function of the hepatic FXR/CYP7A1 axis, promote the conversion of cholesterol into bile acids, and thereby reduce cholesterol accumulation and improve lipid metabolism.

GLP-1 is another important effector molecule of intestinal bile acid signaling. Secreted by ileal and colonic L cells, GLP-1 promotes insulin secretion and suppresses glucagon release in a glucose-dependent manner. Previous studies have shown that intestinal FXR activation inhibits GLP-1 production by L cells, whereas activation of the membrane receptor TGR5 promotes GLP-1 secretion and improves glucose homeostasis; bile acid activation of TGR5 also increases energy expenditure. In the present study, intestinal Gcg mRNA expression tended to increase after medium-dose cinnamaldehyde treatment, and hepatic TGR5 expression was significantly up-regulated, suggesting that cinnamaldehyde may synergistically improve glucose metabolism through the bile acid–TGR5–GLP-1 pathway. Recent studies have also confirmed that specific bile acids improve glucose homeostasis through a dual TGR5 and FXR signaling mechanism, corroborating these findings. Notably, although intestinal FXR activation has been reported to inhibit GLP-1 production by L cells, cinnamaldehyde up-regulated intestinal Gcg expression in the present study; this apparent discrepancy suggests that the GLP-1-related effect of cinnamaldehyde is mediated predominantly through TGR5 rather than intestinal FXR, although direct confirmation using intestine-specific FXR modulation is warranted. In addition, bile acid sequestrants have been clinically proven to improve glycemic control in patients with type 2 diabetes, and the clinical benefits of metformin are likewise associated with intestinal FXR signaling and bile acid metabolism, which may explain why the metformin and MCA groups performed similarly across multiple indices in this study.

It is noteworthy that the effects of cinnamaldehyde in this study exhibited clear dose dependence: the low- and medium-dose groups benefited significantly, whereas the high-dose (120 mg/kg) group showed aggravated glucolipid metabolic disorders, with CYP7A1 expression falling to its lowest level. This indicates the existence of an optimal dose window for cinnamaldehyde treatment; excessive intake may exacerbate metabolic disorders through over-activation of, or feedback inhibition on, the FXR/FGF15 pathway. Safety evaluation and dose optimization should therefore be priorities in future research.

This study has several limitations. First, a diabetic model induced by a single high dose of STZ (150 mg/kg) was used, which is characterized primarily by pancreatic β -cell injury and insufficient insulin secretion; this differs from the pathogenesis of clinical type

2 diabetes, in which insulin insensitivity is central and induction commonly requires combination with a high-fat diet. Future studies should validate findings using the classic type 2 diabetes model combining a high-fat diet with low-dose STZ. Second, expression of FXR/FGF15 pathway-related genes was examined only at the mRNA level; protein expression assays, targeted metabolomic profiling of the bile acid spectrum, and modulation with intestine-specific FXR agonists or antagonists are needed to further establish causality. Third, the gut microbiota, an important regulator of bile acid metabolism and FXR signaling, warrants in-depth investigation in the context of cinnamaldehyde treatment. Finally, the atypical lipid profile of the STZ-induced model (reduced rather than elevated LDL-C) should be considered when extrapolating the lipid-related findings to clinical type 2 diabetes.

In summary, medium-dose (40 mg/kg) cinnamaldehyde significantly ameliorates glucolipid metabolic disorders in STZ-induced diabetic mice, and its mechanism of action may be related to the up-regulation of hepatic CYP7A1 expression, the promotion of de novo bile acid synthesis, and the modulation of the intestinal FXR/FGF15 and TGR5/GLP-1 signaling pathways. This study provides an experimental basis for the further development of cinnamaldehyde as a potential natural antidiabetic agent.

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