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Original Research

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p-Coumaric acid alleviates metabolic dysregulation in high-fructose diet-fed hamsters

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Conflict of Interest
The authors declare no potential conflicts of interests.

ABSTRACT

BACKGROUND/OBJECTIVES: *p*-Coumaric acid (CA), a 4-hydroxycinnamic acid derivative, is widely distributed in nature and exerts various beneficial biological effects. However, the effects of CA on metabolic abnormalities triggered by excessive fructose intake, such as dyslipidemia, hyperglycemia, non-alcoholic fatty liver disease (NAFLD), and insulin resistance, have not been sufficiently investigated. Our objective was to investigate whether CA ameliorates high-fructose diet (HFrD)-induced metabolic dysregulation.
MATERIALS/METHODS: Golden Syrian hamsters were randomly assigned to 3 groups and were fed diets containing 60% cornstarch (CON group), 60% fructose (HFrD group), or 60% fructose with CA (0.02%) (HFrD+CA group) for 5 weeks.
RESULTS: HFrD feeding significantly increased the levels of plasma triglyceride, apolipoprotein (apo)-CIII, fasting blood glucose, and homeostatic model assessment insulin resistance, and tended to increase plasma total cholesterol (TC) and low-density lipoprotein/very low-density lipoprotein cholesterol (LDL/VLDL-C) compared with the CON group. In HFrD-fed hamsters, CA supplementation significantly decreased plasma TC, LDL/VLDL-C, apo-CIII, and fasting blood glucose levels. Moreover, CA significantly decreased the hepatic lipid levels and fibrosis induced by HFrD. The plasma and hepatic lipid-lowering effects of CA were associated with decreased enzyme activity and mRNA expression of genes involved in fatty acid, triglyceride, and cholesterol synthesis as well as increased activity of carnitine palmitoyltransferase, a rate-limiting enzyme in fatty acid oxidation, in the liver. CA-treated hamsters also exhibited decreased hepatic gluconeogenic enzyme activity and increased hepatic glycolytic enzyme activity, with mRNA expression changes similar to these activity patterns.
CONCLUSION: Our findings indicate that CA potentially improves metabolic abnormalities associated with excessive fructose intake, such as hyperglycemia, dyslipidemia, and NAFLD.

Keywords: Fructose; hyperglycemia; dyslipidemias; non-alcoholic fatty liver disease; *p*-coumaric acid

INTRODUCTION

Metabolic syndrome, which encompasses obesity, abnormalities in lipid and glucose metabolism, and an increased risk of cardiovascular disease, is a growing global health concern [1]. Many of these diseases co-occur, share common risk factors, and are associated

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Author Contributions

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with increased risk of disability, cancer, and premature mortality [1]. Unhealthy lifestyle choices, including physical inactivity and poor diet, significantly increase the risk of metabolic syndrome. Among these, dietary factors, such as high-fat diet (HFD) and high-fructose diet (HFrD), are particularly noteworthy contributors to their heightened risk. Fructose consumption has surged over the past century, largely because of its widespread use in commercially available soft drinks, juices, and baked goods [2]. Extensive evidence suggests that excessive fructose consumption is a critical factor in the development of metabolic syndrome, exacerbating abnormalities in lipid metabolism and insulin sensitivity [2-4]. Fortunately, metabolic syndrome can be prevented or managed by identifying its risk factors and adopting healthy lifestyles.

Phytochemicals have gained significant attention as dietary factors that can help prevent and improve metabolic syndrome. These naturally occurring compounds in plants have been shown to exhibit a range of beneficial health effects, including anti-inflammatory, antioxidant, and lipid-lowering properties. One such phytochemical is *p*-coumaric acid (CA), a phenolic acid widely found in fruits, vegetables, cereals, and other natural ingredients [5]. Previous studies have demonstrated that CA positively affects metabolic syndrome by improving lipid profiles, reducing oxidative stress and inflammation, and enhancing insulin sensitivity [5]. Recently, our research group revealed that CA protected against HFD-induced metabolic disturbances, including adiposity, non-alcoholic fatty liver disease (NAFLD), inflammation, and insulin resistance, in mice [6]. However, its effects on lipid and glucose metabolism under high-fructose conditions remain underexplored.

The increasing consumption of fructose, especially in the form of high-fructose corn syrup, necessitates further investigation into the metabolic effects of CA. Investigating the potential of mitigating the adverse effects of HFrD may contribute to the development of dietary strategies and interventions aimed at reducing the burden of diet-induced metabolic diseases. Therefore, the current study investigated the efficacy of CA in improving fructose-induced metabolic disturbances in hamsters fed a HFrD. To elucidate the mechanisms underlying the amelioration of metabolic abnormalities by CA, hepatic lipid and glucose metabolism-controlling enzyme activity, gene mRNA expression, and fecal lipid excretion were analyzed.

MATERIALS AND METHODS

Experimental animals, diets, sampling procedures

Five-week-old golden Syrian hamsters (male, n = 25), purchased from Hana BioTech Inc. (Pyeongtaek, Korea), were housed in separate cages at a maintained temperature of 24 ± 2°C and humidity of 50 ± 5% under 12-h light/dark cycle. For acclimation after arrival, we provided a commercial chow diet for 1 week. Thereafter, they were randomly divided into 3 groups and fed their respective experimental diets for 5 weeks, each containing 60% cornstarch or fructose as the carbohydrate source: control diet (CON, 60% cornstarch, n = 7), high-fructose diet (HFrD, 60% fructose, w/w, n = 9), and high-fructose diet + CA (HFrD+CA, 0.02% CA, w/w, n = 9) (CA purity ≥ 98%; Sigma, St. Louis, MO, USA). The experimental diets were prepared by mixing the components in the proportions described in **Table 1**, and all diets were composed of 63% kcal of carbohydrate, 23% kcal of protein, and 14% kcal of fat. The animals were had free access to food and water throughout the experimental period. Body weight was measured weekly, and food consumption, accounting for spilled food, was measured thrice weekly.

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Table 1. Diet ingredient composition (% of diet, w/w)

Ingredient	CON group	HFrD group	HFrD+CA group
Casein	22	22	22
Cornstarch	60		
Fructose		60	60
Corn oil	6	6	6
Cellulose	7.1	7.1	7.1
Cholinebitartrate	0.2	0.2	0.2
L-arginine	0.1	0.1	0.1
L-tryptophan	0.1	0.1	0.1
Mineral mix (AIN-76)[1)]	3.5	3.5	3.5
Vitamin mix (AIN-76)[2)]	1	1	1
Total (g)	100	100	100
p-Coumaric acid			0.02

Golden Syrian hamsters randomly divided into 3 groups and were fed diets containing 60% cornstarch (CON group), 60% fructose (HFrD group), or 60% fructose with CA (0.02%) (HFrD+CA group).
[1)]Mineral mixture AIN-76 (g/kg): sucrose, fine ground 118.03, calcium phosphate dibasic 500, sodium chloride 74, potassium citrate monohydrate 220, potassium sulfate 52, magnesium oxide 24, manganous carbonate 3.5, ferric citrate 6, zinc carbonate 1.6, cupric carbonate 0.3, potassium iodate 0.01, sodium selenite pentahydrate 0.01, chromium potassium sulfate dodecahydrate 0.55.
[2)]Vitamin mixture AIN-76 (g/kg): thiamin (81%) 0.6, riboflavin 0.6, pyridoxine HCl 0.7, niacin 3, calcium pantothenate 1.6, folic acid 0.2, biotin 0.02, vitamin B_{12} (0.1% in mannitol) 1, vitamin A palmitate (500,000 IU/g) 0.8, vitamin E, DL-α tocopheryl acetate (500 IU/g) 10, vitamin D_3, cholecalciferol (400,000 IU/g in sucrose) 0.25, vitamin K, MSB complex 0.15, sucrose fine ground 981.08.

Five weeks after administering the experimental diets, the hamsters were anesthetized with CO_2 gas following a 12-h fasting period. Blood samples, collected into heparin-treated syringes from the inferior vena cava, were centrifuged at 3,000 rpm and 4°C for 15 min to isolate plasma for plasma biomarker analysis. The liver and epididymal white adipose tissue (WAT) were removed and weighed. All samples were stored at −80°C for further study. All animal experiments were reviewed and approved by the Animal Ethics Committee of Pukyong National University (approval No. 2020-09).

Determination of plasma, hepatic, and fecal lipids

Commercial enzymatic kits were used to determine the concentrations of plasma triglyceride (TG), total-cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein/very low-density lipoprotein-cholesterol (LDL/VLDL-C) and apolipoprotein (apo)-CIII levels by measuring spectrophotometrically (TG, TC from Asan Pharm Co., Seoul, Korea; HDL-C, LDL/VLDL-C from Cell Biolabs Inc., San Diego, CA, USA; apo-CIII from Abcam, Cambridge, UK). The HDL-C to TC ratio (HTR) and atherogenic index (AI) were calculated using the following formulas:

$$\text{HTR (\%)} = \{(\text{HDL-C})/(\text{TC})\} \times 100$$

$$\text{AI} = (\text{TC} - \text{HDL-C})/\text{HDL-C}$$

Hepatic and fecal lipid extraction was performed by modifying the method of Folch *et al.* [7]. During the final week of dietary manipulation, fecal samples were collected to determine fecal lipids. The same commercial kits (Asan Pharm Co.) used to measure plasma lipid levels were used to determine the concentrations of TG and TC in the liver and feces.

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Determination of blood glucose, plasma insulin, and homeostasis model assessment of insulin resistance

Before sacrifice, all animals were fasted for 12 h. Fasting blood glucose levels were measured using a blood glucose meter (Accu-Chek Performance; Roche, New York, NY, USA). Plasma insulin levels were measured using the Milliplex Map Kit (Merck, KGaA, Darmstadt, Germany). The homeostatic index of insulin resistance (HOMA-IR) was calculated using the following equation:

$$\text{HOMA-IR} = \{\text{Insulin (mU/L)} \times \text{Fasting Blood Glucose (mmol/L)}\}/22.5.$$

Hepatic enzyme activity analysis and Oleson's protocol

Hepatic mitochondrial, cytosolic, and microsomal fractions were isolated according to the protocol outlined by Hulcher and Oleson [8], and protein concentrations were assessed using the Bradford method [9]. Enzyme activities related to lipid metabolism, including carnitine palmitoyltransferase (CPT), fatty acid β-oxidation, and phosphatidate phosphohydrolase (PAP), were assessed in hepatic mitochondria or microsomes using distinct methods outlined by Bieber and Fiol [10], Lazarow [11], and Walton and Possmayer [12], respectively. Glucose metabolism-related enzyme activities, including those of cytosolic glucokinase, microsomal glucose-6-phosphatase (G6Pase), and cytosolic phosphoenolpyruvate carboxykinase (PEPCK), were evaluated using the methods described by Davidson and Arion [13], Alegre *et al.* [14], and Bentle and Lardy [15], respectively. All enzyme activities were normalized to the protein concentration.

RNA isolation and quantitative reverse transcription polymerase chain reaction (qRT-PCR)

Liver tissue was homogenized in TRIzol reagent to extract total RNA. For quality control, RNA purity and integrity were evaluated using Gen5 3.04 software program (BioTek Inc., Winooski, VT, USA). Subsequently, qRT-PCR was conducted using a high-capacity cDNA reverse transcription kit (Applied Biosystems Inc., Foster City, CA, USA). The qRT-PCR was conducted with TOPreal™ qPCR 2X PreMix (Enzynomics Inc., Daejeon, Korea) on the StepOnePlus™ Real-Time PCR System (Applied Biosystems Inc.). β-Actin was used as the housekeeping gene, and the relative expression of each gene was determined using the $2^{-\Delta\Delta Ct}$ method. The primer pairs were as follows: β-actin, 5′-TGCTGTCCCTGTATGCCTCTG-3′ and 5′-AGGGAGAGCGTAGCCCTCAT-3′; acetyl-CoA carboxylase (ACC), 5′-ACACTGGCTGGCTGGACAG-3′ and 5′-CACACAACTCCCAACATGGTG-3′; fatty acid synthase (FAS), 5′-CACAGATGATGACAGGAGATGG-3′ and 5′-TCGGAGTGAGGCTGGGTTGAT-3′; stearoyl-CoA desaturase 1 (SCD1), 5′-TGGGTTGGCTGCTTGTG-3′ and 5′-GCGTGGGCAGGATGAAG-3′; sterol regulatory element-binding protein-1c (SREBP1c), 5′-GCTGTTGGCATCCTGCTATC-3′ and 5′-TAGCTGGAAGTGACGGTGGT-3′; peroxisome proliferator-activated receptor (PPAR)-γ, 5′-GGAAGACCACTCGCATTCCTT-3′ and 5′-GTAATCAGCAACCATTGGGTCA-3′; sterol regulatory element-binding protein-2 (SREBP2), 5′-GAGAGCTGTGAATTTTCCAGTG-3′ and 5′-CTACAGATGATATCCGGACCAA-3′; 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), 5′-GACGGTGACACTTACCATCTGT-3′ and 5′-GATGCACCGTGTTATGGTGA-3′; 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMGCS), 5′-TTTGATGCAGCTGTTTGAGG-3′ and 5′-CCACCTGTAGGTCTGGCATT-3′; carnitine palmitoyltransferase 1a (CPT1a), 5′-CTCAGTGGGAGCGACTCTTCA-3′ and 5′-GGCCTCTGTGGTACACGACAA-3′; PPAR-α, 5′-TGAGGAAGCCGTTCTGTGAC-3′ and 5′-GGTGTCATCTGGATGGTTGC-3′; Glucokinase, 5′-AGAGCAGATCCTGGCAGAGT-3′ and

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5′-TGGTTCCTCCCAGGTCTAAG-3′; G6pase, 5′-CATCAATCTCCTCTGGGTGGC-3′ and 5′-TGTTGCTGTAGTAGTCGGTGTCC-3′; PEPCK, 5′-GAGTTCCTGCCTCTCTCCAC-3′ and 5′-TTCCACGAACTTCCTCACTG-3′.

Histopathological examination

A small portion of the liver was fixed in 10% formaldehyde and embedded in paraffin. Liver tissues were subsequently stained with 3 different dyes: hematoxylin and eosin (H&E) for histopathological evaluation and Sirius red and Masson's trichrome staining for collagen accumulation and fibrosis analysis. The stained samples were analyzed under a microscope (Eclipse E200; Nikon, Tokyo, Japan) at 400× magnification.

Statistical analysis

The data were presented as mean ± SE of the mean. Statistical analyses were performed using the SPSS (ver. 27; IBM Corporation, Armonk, NY, USA). Student's *t*-test was used to assess significant differences between groups, with statistical significance set at $P < 0.05$.

RESULTS

Effects of CA on food intake, body weight, and adipose tissue weight

The HFrD group consumed significantly less food than the CON group (**Fig. 1A**); however, there were no notable differences in body weight or epididymal WAT weight between the 2 groups (**Fig. 1B, D, and E**). Therefore, the food efficiency ratio (FER) in the HFrD group was 15.4% higher than that of the CON group, although the difference was not statistically significant (**Fig. 1C**).

In HFrD-fed hamsters, CA supplementation did not affect food intake compared to the HFrD group (**Fig. 1A**). However, the HFrD+CA hamsters gained significantly less weight than the HFrD animals, resulting in significant decreases in FER and body weight gain (**Fig. 1B-D**). Furthermore, the epididymal WAT weight was significantly lower in the HFrD+CA group than in the HFrD group (**Fig. 1E**).

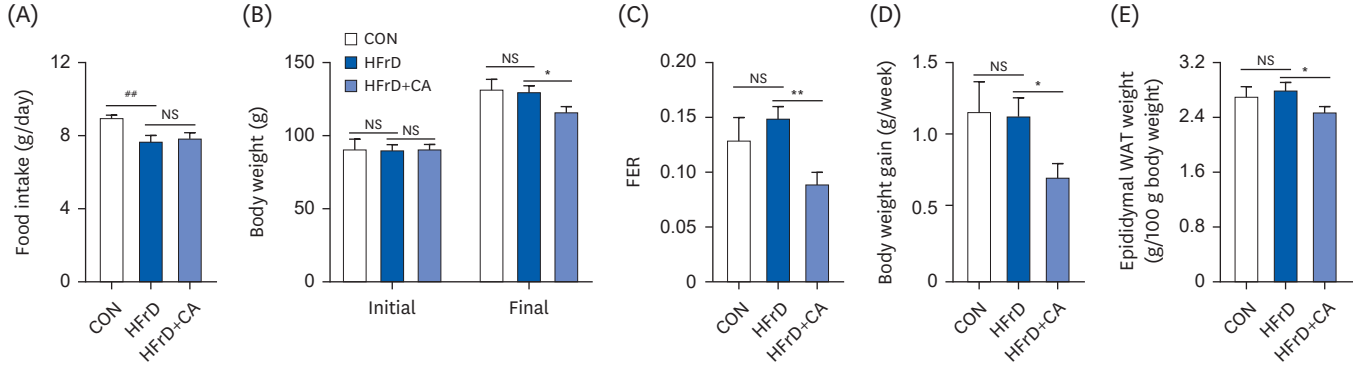

Fig. 1. Effects of CA supplementation on food intake (A), body weight (B), food efficiency ratio (C), body weight gain (D), and epididymal white adipose tissue weight (E) in Golden Syrian hamsters fed a HFrD. Data are presented as mean ± SE of the mean. Values are compared between groups using Student's *t*-test.
CA, *p*-coumaric acid; HFrD, high-fructose diet; CON, control diet; FER, food efficiency ratio; WAT, white adipose tissue; NS, no significant.
$^{\#\#}P < 0.01$, CON group versus HFrD group; $^{*}P < 0.05$, $^{**}P < 0.01$, HFrD group versus HFrD+CA group.

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Effects of CA on fasting blood glucose, plasma insulin levels, and homeostasis model assessment of insulin resistance

The HFrD group showed significantly increased fasting blood glucose levels and a tendency to increase plasma insulin levels by almost 24% compared to the CON group (**Fig. 2A and B**). Similarly, HOMA-IR values were higher in hamsters fed the HFrD than in those fed the CON diet (**Fig. 2C**).

In HFrD-fed hamsters, CA supplementation significantly reduced fasting blood glucose levels (**Fig. 2A**). Furthermore, CA decreased plasma insulin levels and HOMA-IR by 14%, and 31%, respectively, compared with HFrD alone (**Fig. 2B and C**).

Effects of CA on plasma lipid profiles

The HFrD induced significant increases in plasma TG and apo-CIII levels compared with those in the CON group (**Fig. 2D and K**). Additionally, HFrD-fed hamsters tended to have higher plasma TC, LDL/VLDL-C levels, and AI values, along with lower HDL-C levels and HTR compared to the CON group (**Fig. 2E-G, I, and J**).

In contrast, the HFrD+CA group showed significantly lower plasma TC, LDL/VLDL-C, and apo-CIII levels than the HFrD group (**Fig. 2E, F, and K**). Although there was no significant difference in HDL-C levels between the 2 groups, the HFrD+CA group tended to have higher HTR and lower AI values than the HFrD group (**Fig. 2G, I, and J**). CA also tended to decrease plasma TG levels compared to thoe in the HFrD group ($P < 0.08$; **Fig. 2D**). Regardless of the type of dietary carbohydrate or CA supplementation, plasma free fatty acid (FFA) levels were not altered (**Fig. 2H**).

Effects of CA on liver weight, hepatic lipids levels, hepatic histopathological changes, and fecal lipids levels

We investigated whether CA ameliorates HFrD-induced NAFLD. Although the HFrD group did not show a significant increase in liver weight compared with the CON group, it showed markedly increased hepatic TG and TC levels (**Fig. 3A-C**). Additionally, the HFrD group exhibited notable hepatic lipid droplet deposition and massive perivascular collagen accumulation compared to the CON group, as evidenced by H&E, Sirius red, and trichrome staining (**Fig. 3E**). In fecal samples, the levels of TC were significantly decreased in hamsters fed the HFrD compared to those in the CON animals (**Fig. 3G**). There also tended to be a decrease in fecal TG levels in the HFrD group compared to those in the CON group (**Fig. 3F**).

In HFrD-fed hamsters, CA supplementation significantly decreased hepatic TG and TC contents and tended to decrease liver weight by 5.6% compared to the HFrD group (**Fig. 3A-C**). Moreover, CA supplementation alleviated lipid droplets and collagen deposition compared to that in the HFrD group (**Fig. 3E**). CA supplementation did not significantly alter fecal lipid excretion; however, in HFrD-fed hamsters, CA supplementation tended to increase fecal TG excretion by approximately 20% compared to that in the HFrD group (**Fig. 3F and G**). Similar to plasma FFA levels, hepatic FFA levels did not differ between the groups (**Fig. 3D**).

Effects of CA on hepatic lipid metabolic enzymes activities and genes expression

The activities of enzymes and mRNA expression of genes involved in lipid synthesis and decomposition were analyzed in the liver to elucidate the mechanism by which CA ameliorates HFrD-induced NAFLD and dyslipidemia. When hamsters were fed a HFrD,

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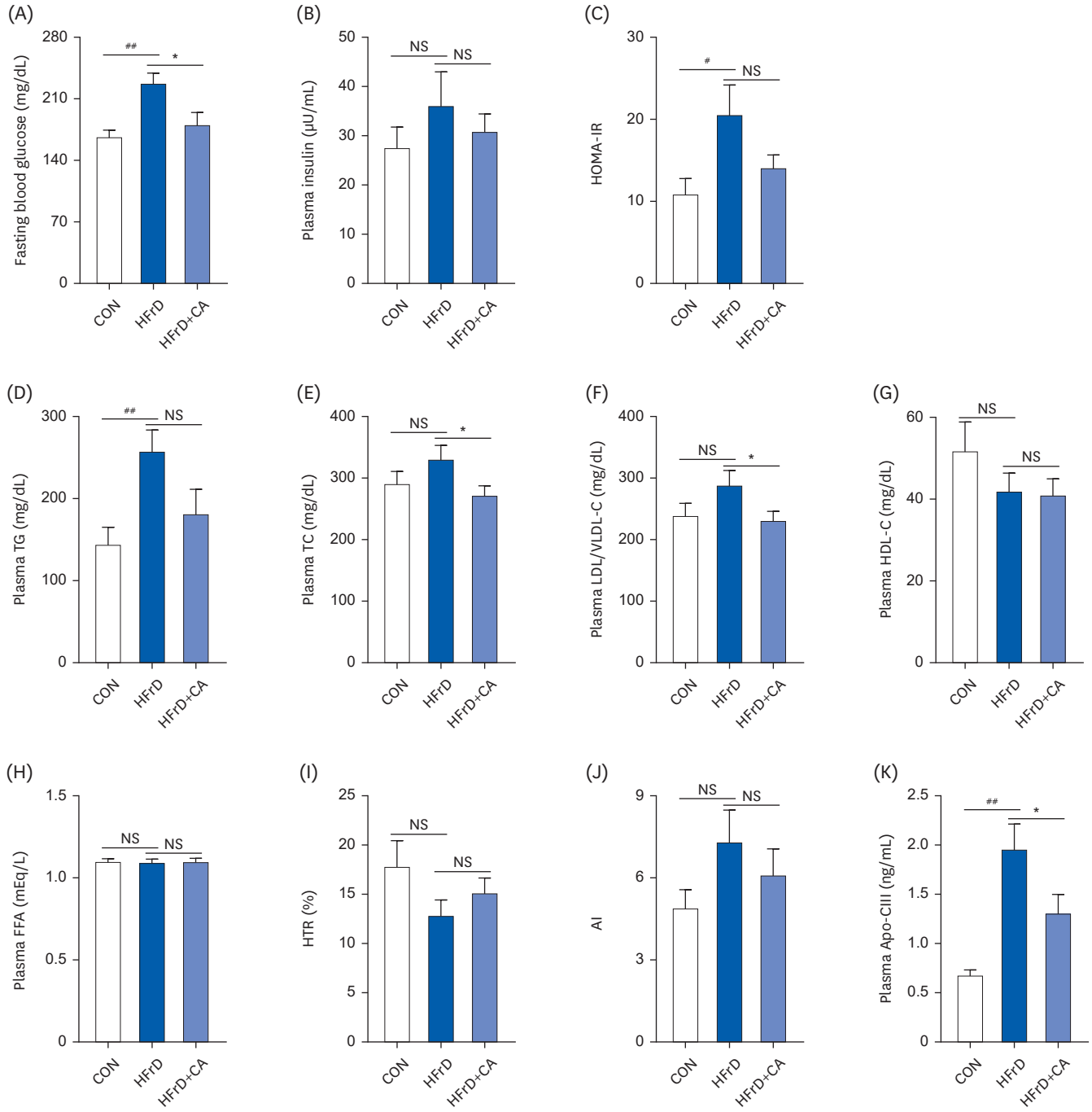

Fig. 2. Effects of CA supplementation on fasting blood glucose (A), plasma insulin (B), HOMA-IR (C), plasma TG (D), TC (E), LDL/VLDL-C (F), HDL-C (G), FFA (H), HTR (I), AI (J), and Apo-CIII (K) levels in Golden Syrian hamsters fed a HFrD. Data are presented as mean ± SE of the mean. Values are compared between groups using Student's *t*-test.

CA, *p*-coumaric acid; HOMA-IR, homeostatic index of insulin resistance; TG, triglyceride; TC, total cholesterol; LDL/VLDL-C, low-density lipoprotein/very low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; FFA, free fatty acid; HTR, ratio of HDL-C to TC; AI, atherogenic index; apo-CIII, apolipoprotein CIII; CON, control diet; HFrD, high-fructose diet; NS, no significant.

$^{*}P < 0.05$, $^{**}P < 0.01$, CON group versus HFrD group; $^{*}P < 0.05$, HFrD group versus HFrD+CA group.

there was a tendency for lipogenic PAP activity to increase ($P < 0.08$) and for β-oxidation to decrease by 12% in the liver compared to the CON group (**Fig. 4A and C**). Additionally, the HFrD triggered a significant upregulation of SCD1 mRNA expression and tended

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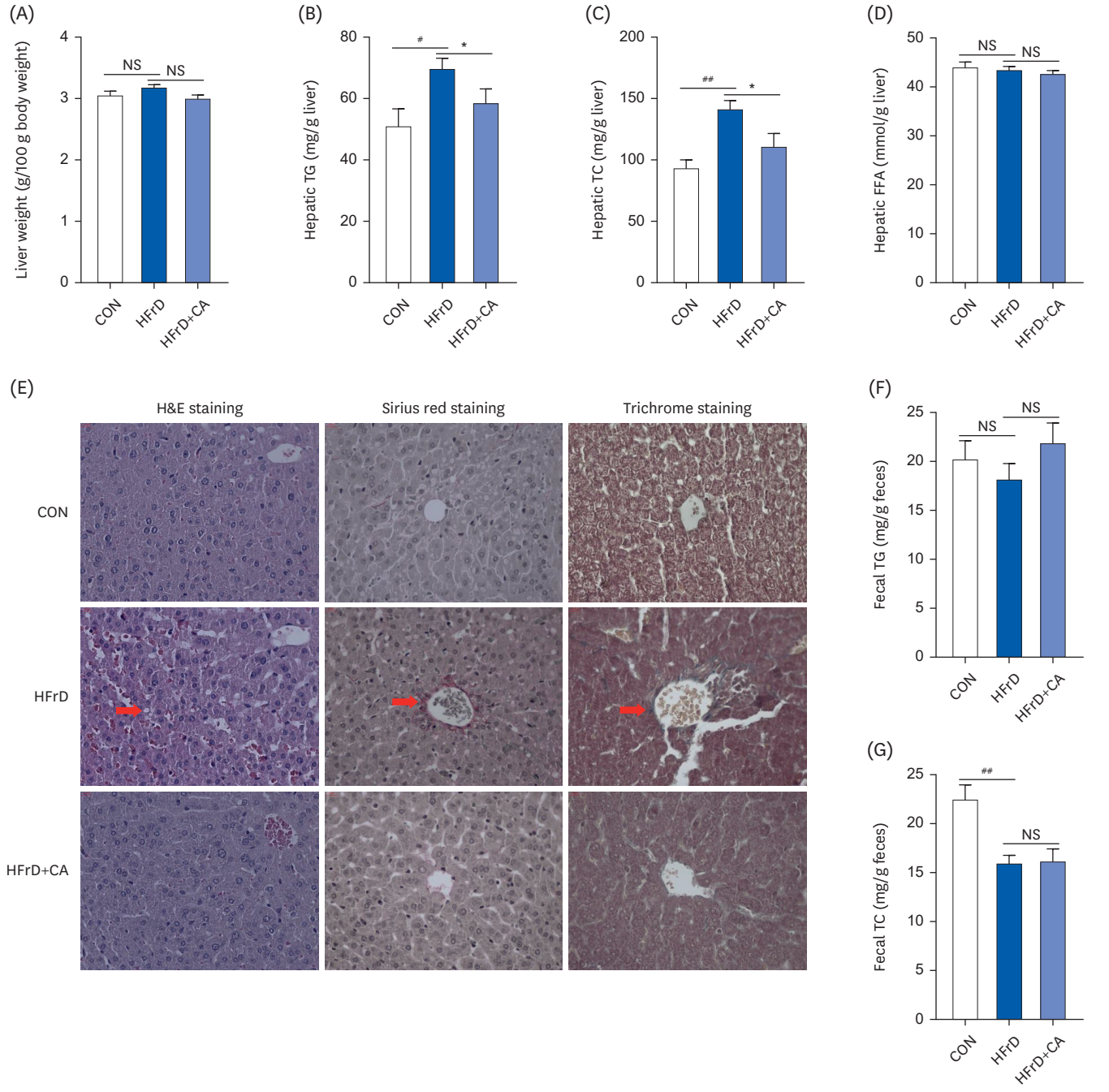

Fig. 3. Effects of CA supplementation on liver weight (A), hepatic TG (B), hepatic TC (C), hepatic FFA (D), histopathological staining of liver section (E), fecal TG (F), and fecal TC (G) in Golden Syrian hamsters fed a HFrD. Data are presented as mean ± SE of the mean. Values are compared between groups using Student's *t*-test.
CA, *p*-coumaric acid; TG, triglyceride; TC, total cholesterol; FFA, free fatty acid; CON, control diet; HFrD, high-fructose diet; NS, no significant.
$^{\#}P < 0.05$, $^{\#\#}P < 0.01$, CON group versus HFrD group; $^{*}P < 0.05$, HFrD group versus HFrD+CA group.

to upregulate the mRNA expression of other lipogenic genes, including ACC, FAS, and SREBP1c, in the liver compared to the CON diet (**Fig. 4D-G**). HMGCR and SREBP2 mRNA expression also tended to be upregulated by HFrD (**Fig. 4I and J**).

Interestingly, in HFrD-fed hamsters, CA supplementation significantly inhibited hepatic PAP activity (**Fig. 4A**). In contrast, hepatic CPT activity, which facilitates the rate-limiting

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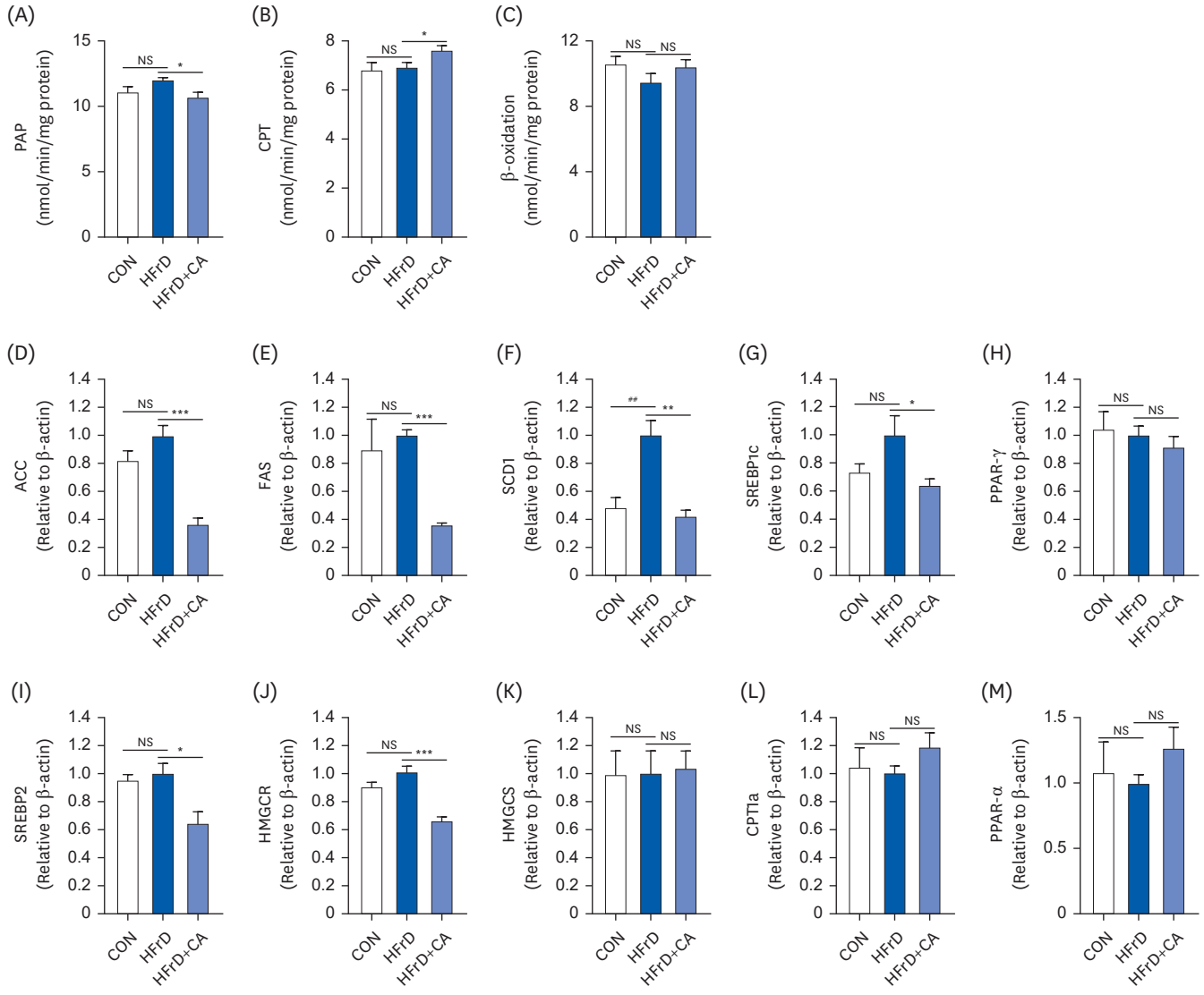

Fig. 4. Effects of CA supplementation on activities of enzymes (A-C) and mRNA expression of genes (D-M) involved in lipid synthesis or decomposition in the liver of Golden Syrian hamsters fed a HFrD. Data are presented as mean ± SE of the mean. Values are compared between groups using Student's *t*-test.
CA, *p*-coumaric acid; HFrD, high-fructose diet; CON, control diet; PAP, phosphatidate phosphatase; CPT, carnitine palmitoyltransferase; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; SREBP1c, sterol regulatory element-binding protein-1c; PPAR-α, peroxisome proliferator-activated receptor alpha; SREBP2, sterol regulatory element-binding protein-2; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HMGCS, 3-hydroxy-3-methylglutaryl coenzyme A synthase; CPT1a, carnitine palmitoyltransferase 1a; NS, no significant.
$^{\#\#}P < 0.01$, CON group versus HFrD group; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, HFrD group versus HFrD+CA group.

step of fatty acid oxidation by transporting long-chain fatty acids from the cytoplasm into the mitochondria, was significantly increased, and *β*-oxidation was somewhat higher (10%) in the HFrD+CA group compared to the HFrD group (**Fig. 4B and C**). Similarly, the mRNA expression of genes involved in fatty acid, TG, and cholesterol synthesis, such as ACC, FAS, SCD1, HMGCR, SREBP1c, and SREBP2, was significantly downregulated in the liver of the HFrD+CA group compared with that in the HFrD group (**Fig. 4D-G, I, and J**). In contrast, the mRNA expression of hepatic PPAR-α and CPT1a tended to be upregulated by 27% and 19%, respectively, with CA supplementation in HFrD-fed hamsters (**Fig. 4L and M**).

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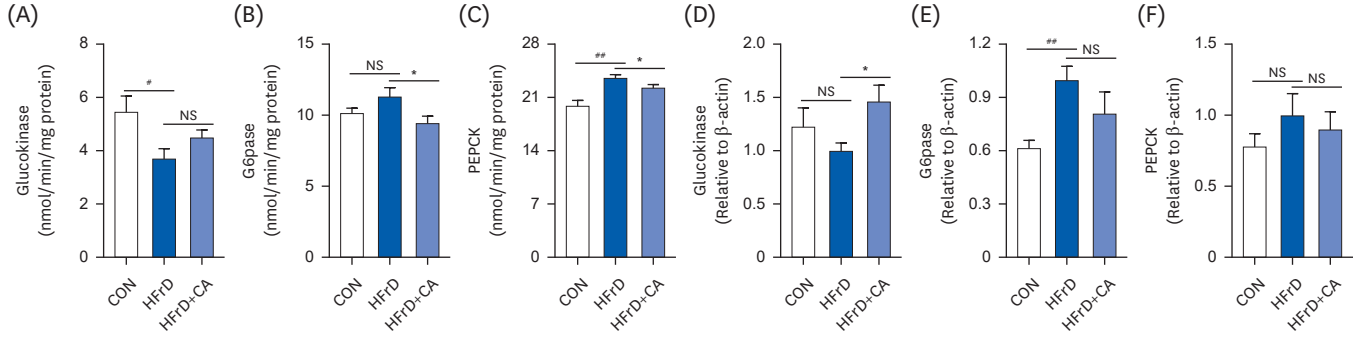

Fig. 5. Effects of CA supplementation on hepatic glucose metabolic enzymes activities (A-C) and genes mRNA expression (D-F) in Golden Syrian hamsters fed a HFrD. Data are presented as mean ± SE of the mean. Values are compared between groups using Student's *t*-test.
CA, *p*-coumaric acid; HFrD, high-fructose diet; CON, control diet; G6pase, glucose 6-phosphatase; PEPCK, phosphoenolpyruvate carboxykinase; NS, no significant.
$^{\#}P < 0.05$, $^{\#\#}P < 0.01$, CON group versus HFrD group; $^{*}P < 0.05$, HFrD group versus HFrD+CA group.

Effects of CA on hepatic glucose metabolic enzymes activities and genes expression

We also assessed the activities of glucose metabolic enzymes and mRNA expression of related genes in the liver. Hamsters fed the HFrD showed a significant reduction in hepatic glucokinase activity compared to those fed the starch-based CON diet. In contrast, the HFrD significantly increased PEPCK activity and tended to increase G6Pase activity by 11% in the liver (**Fig. 5A-C**). Similarly, the mRNA expression of hepatic glucokinase tended to be lower by 18% in the HFrD group than in the CON group, whereas hepatic G6pase mRNA expression was significantly upregulated and hepatic PEPCK mRNA expression tended to be upregulated by 28% with HFrD feeding (**Fig. 5D-F**).

In HFrD-fed hamsters, CA supplementation significantly inhibited the activities of gluconeogenic enzymes such as G6pase and PEPCK, while it tended to activate the activity of glucokinase, a glycolytic enzyme, compared with the HFrD group ($P < 0.09$) (**Fig. 5A-C**). Moreover, the mRNA expression of glucokinase was significantly upregulated by CA supplementation compared to that in the HFrD group, while G6pase and PEPCK mRNA expression tended to be downregulated by 19% and 10%, respectively, with CA supplementation (**Fig. 5D-F**).

DISCUSSION

Although several *in vitro* and *in vivo* studies have reported the protective effects of CA against obesity, diabetes, NAFLD, and other metabolic disorders [5,6,16-30], there is limited research on its efficacy against metabolic dysregulation induced by HFrD. Therefore, the present study investigated whether CA could alleviate HFrD-induced metabolic dysregulation in hamsters, which exhibit lipid metabolism characteristics that are more similar to humans than mice or rats [31,32] and develop many features of metabolic syndrome, such as insulin resistance, dyslipidemia, and hepatic steatosis, when fed an HFrD [33-36].

In a previous study comparing the short-term effects of carbohydrate-enriched diets containing either 60% fructose or 60% cornstarch in hamsters, an HFrD containing 60% fructose for 2 weeks significantly increased plasma triglyceride and cholesterol levels compared to a diet containing an equivalent amount of cornstarch and a chow diet [37].

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HFrD-fed hamsters also showed significantly increased liver weight and plasma insulin levels, a tendency towards lower food intake, and unchanged body weight [37]. Consistent with a previous study, we observed that feeding an HFrD (containing 60% fructose) for 5 weeks significantly increased plasma TG, apo-CIII (a major apolipoprotein attached to TG-rich lipoproteins), hepatic TG and cholesterol, fasting blood glucose, and HOMA-IR, and tended to increase plasma TC, LDL/VLDL-C, insulin, and liver weight, while tending to decrease plasma HDL-C levels compared to a diet containing a similar high carbohydrate content from cornstarch (60%). HFrD did not affect body weight or epididymal WAT weight, despite significantly decreased food intake. Thus, the present study supports previous evidence linking excessive fructose consumption to hyperglycemia, insulin resistance, hypertriglyceridemia, and intrahepatic lipid accumulation [37-41].

In HFrD-fed hamsters, CA did not alter food intake, but significantly decreased body weight gain and epididymal WAT. These results support our previous findings regarding the anti-adiposity effects of CA in HFD-induced obese mice [6], confirming its protective effects against body fat accumulation caused by high-energy diets rich in fats or fructose. Additionally, CA-supplemented hamsters exhibited decreased fasting blood glucose levels, plasma insulin levels, and HOMA-IR, all of which were increased by HFrD feeding.

Several factors are likely to contribute to hyperglycemia in HFrD-fed animals. Fructose administration induces hyperglycemia by increasing hepatic glucose production in humans and rats [42,43], which is consistent with our findings. In the present study, HFrD-fed hamsters showed significantly increased enzyme activity and mRNA expression of genes involved in hepatic gluconeogenesis, such as PEPCK and G6Pase, compared to the CON group. CA supplementation significantly inhibited the increased activity of hepatic PEPCK and G6Pase induced by the HFrD, and gene expression exhibited similar patterns of change. Conversely, HFrD significantly inhibited hepatic glucokinase activity which plays an important role in blood glucose homeostasis via hepatic glucose utilization [44]. Hepatic glucokinase activity was slightly increased in the HFrD+CA group relative to the HFrD group, with a corresponding significant increase in mRNA expression. Taken together, these results suggest that CA counteracts HFrD-induced hyperglycemia, possibly by enhancing glucose utilization and reducing glucose production in the liver under conditions of fructose-induced energy overload.

It is well established that fructose is a potent inducer of hepatic *de novo* lipogenesis (the generation of fatty acids from alternative carbon sources such as dietary carbohydrates), which promotes fat deposition in the liver as well as in circulating blood [45]. In the liver, *de novo* lipogenesis is a vital pathway involved in lipid storage that significantly contributes to the pathogenesis of NAFLD. The key enzymes involved in this process are ACC and FAS. ACC, the first rate-limiting enzyme in *de novo* lipogenesis, converts acetyl-CoA to malonyl-CoA, a key precursor for fatty acid synthesis. This precursor is then converted into long-chain saturated fatty acids (palmitate) by FAS [46]. Fatty acids synthesized through *de novo* lipogenesis in the liver can be utilized for energy via fatty acid oxidation, or they can be converted into TG through the action of enzymes such as SCD and PAP. SCD converts saturated fatty acids into monounsaturated fatty acids, which are involved in TG synthesis. PAP catalyzes the dephosphorylation of phosphatidic acid to produce diacylglycerol (DAG), a key intermediate in TG synthesis. The conversion of phosphatidic acid to DAG by PAP is a critical step in the lipid metabolic pathway, as it facilitates energy storage in the form of TG. TG can be stored in the liver or released into the bloodstream for use in other tissues. SREBP1c is a crucial

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transcription factor that regulates the expression of genes involved in *de novo* lipogenesis and TG synthesis, including SCD1, ACC and FAS [47].

In the present study, we observed a significant up-regulation of mRNA expression of SCD1 in HFrD-fed hamsters compared to the CON group. This finding is consistent with previous studies reporting that HFrD upregulates the expression of SCD1 in rats [48-50]. Miyazaki *et al.* [50] demonstrated that SCD1 deficiency in mice protected against HFrD-induced fatty liver disease. In the present study, HFrD-fed hamsters also showed a tendency for increased activity of PAP, and decreased β-oxidation, along with slightly upregulated expression of other lipogenic genes such as ACC, FAS, and SREBP1c. These changes reflect the hepatic environment, favoring lipid synthesis over lipid degradation.

Conversely, CA supplementation in the HFrD-fed hamsters significantly inhibited hepatic PAP activity and increased CPT activity, thereby facilitating fatty acid oxidation. This was corroborated by a slight increase in β-oxidation in the HFrD+CA group compared to the HFrD group. The CPT catalyzes the transfer of free fatty acids into the mitochondria, an essential step for the β-oxidation of long-chain fatty acids. Additionally, CA supplementation significantly downregulated mRNA expression of hepatic lipogenic genes, including ACC, FAS, SCD1, and SREBP1c, while tending to upregulate CPT1a and PPAR-α mRNA expression in the liver. These results indicate that the beneficial effects of CA on plasma and hepatic TG levels in HFrD-fed hamsters may be due to decreased lipogenesis and increased fatty acid oxidation in the liver.

In addition, CA supplementation significantly downregulated the mRNA expression of HMGCR, a rate-limiting enzyme in cholesterol synthesis, and its transcription factor SREBP2 in the liver, suggesting a mechanism for the marked decrease in plasma and hepatic TC levels in the HFrD+CA group. Moreover, the H&E, Sirius red, and Masson's trichrome staining results suggested that CA effectively alleviated the extent of hepatic collagen deposition and lipid droplet accumulation induced by HFrD in hamsters. The pathophysiology of hepatic fibrosis, which is mainly characterized by the deposition of collagen-rich scar tissue, appears to be multifactorial. Hepatic free cholesterol overload is a mechanistic driver of fibrosis in humans and animals [51]. HMGCR mRNA expression was increased in subjects with NAFLD (both biopsy-proven nonalcoholic fatty liver and biopsy-proven nonalcoholic steatohepatitis) compared to lean or obese controls with normal liver histology [52]. Additionally, HMGCR inhibitors, such as statins, not only decrease cardiovascular risk, but also ameliorate liver fibrosis [53]. Similar to our results, a recent study reported the protective effects of CA against hepatic fibrosis induced by high-fat and high-sucrose diets in mice [54]. However, further research is needed to elucidate the detailed mechanisms underlying the anti-fibrotic effects of CA.

Besides this, the present study has several limitations. First, the research was conducted on hamsters, which may limit the generalizability of the findings to humans. Although hamsters are commonly used as a model for studying metabolic diseases, physiological differences between species could affect the applicability of the results. Second, while we demonstrated significant effects of CA supplementation on various metabolic parameters, the duration of the intervention was relatively short. Long-term studies are needed to fully understand the sustained effects and potential side effects of CA. Third, the mechanisms by which CA improves glucose and lipid metabolism were not fully elucidated. Although we observed changes in enzyme activities and gene expression related to glucose and lipid metabolism,

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further mechanistic studies are required to investigate the specific pathways involved. Finally, dietary intake was monitored, but the absorption and bioavailability of CA were not directly measured. Future studies should consider assessing the pharmacokinetics of CA to better understand its metabolism and efficacy.

In conclusion, our study demonstrates that HFrD induces significant hyperglycemia, dyslipidemia and NAFLD in hamsters, whereas CA supplementation effectively mitigates these effects. CA appears to exert its beneficial effects by modulating the hepatic glucose and lipid metabolic pathways, reducing gluconeogenesis and lipogenesis, and enhancing glucose utilization and fatty acid oxidation. These findings suggest that CA has potential therapeutic value in the management of HFrD-induced metabolic complications, warranting further investigation in clinical settings.

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