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Coffee pulp improves glucose and lipid metabolism disorder in high-fat diet-induced diabetic mice

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ABSTRACT

Background: Coffee berry extracts are anti-lipogenic and lipolytic. This study aims to investigate the effect and mechanism of coffee pulp on high-fat diet (HFD)-induced glucose and lipid metabolism disorder in mice.
Methods: The type 2 diabetes (T2D) mouse model was established by feeding the C57BL/6 J mice with HFD. Mice were administered with coffee pulp diluted in drinking water before or after the establishment of the T2D mouse model. After treatment, the body weight and fasting blood glucose (FBG) of mice were monitored; the intraperitoneal glucose tolerance test (IPGTT) of mice was performed; plasma insulin was determined by ELISA; serum total cholesterol (TC), triglyceride (TG) and liver TG were determined by biochemical analysis; hematoxylin-eosin (H&E) staining was used to evaluate organ histomorphology. Gene expression of key genes in de novo lipogenesis (DNL) in the liver was examined by quantitative reverse transcription PCR (RT-qPCR).
Results: Mice that consumed coffee pulp after modeling showed reduced FBG and liver TG, improved IPGTT, and alleviated fatty liver. Consuming coffee pulp before modeling prevented HFD-induced blood glucose and plasma TG increases. Mice consuming coffee pulp also had lower body fat and liver TG compared to the model group. qPCR results showed that the expression of transcription factors (Srebp1, PPARγ) and genes (Fasn, CideA, Plin3, Plin4, Plin5) related to DNL and lipid droplets (LD) formation in the liver of mice consuming coffee pulp were significantly lower than those of the control group.
Conclusions: Our study demonstrated that coffee pulp can attenuate HFD-induced disorders of glucose and lipid metabolism, and this effect may be related to the key pathways of lipid synthesis DNL and LD formation pathways in the liver.

1. Introduction

The prevalence of age-standardized obesity (body mass index (BMI) $> 30\ kg/m^2$) in adults aged 18 years and over has been increasing over the past few decades, and the Report on Nutrition and Chronic Disease Status of Chinese Residents (2020) states that more than half of the adult residents in China are overweight or obese, and the overweight and obesity rates of children under 6 years old and aged 6–17 years have reached 10.4 % and 19 % respectively. Obesity-induced disorders of glucose and lipid metabolism also quietly affect people's health. The incidence of chronic diseases such as hypertension, diabetes, and hypercholesterolemia has increased compared with 2015. Currently, 537 million people are suffering from diabetes worldwide, and this number is expected to reach 783 million in 2045 [1]. Facing the current severe situation, it is of great significance to explore the preventive and therapeutic effects of dietary intervention on glucose and lipid metabolism disorders.

Coffee is a widely consumed beverage worldwide with typical flavor, aroma, color, and beneficial health effects [2]. Epidemiological findings suggest that drinking coffee may help prevent a variety of chronic diseases, including T2D, Parkinson's disease and liver disease (cirrhosis and hepatocellular carcinoma) [3]. As one of the most traded commodities in the world, whether its by-products have the potential to

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Abbreviations

HFD	high-fat diet
T2D	type 2 diabetes
FBG	fasting blood glucose
IPGTT	intraperitoneal glucose tolerance test
TC	total cholesterol
TG	triglyceride
H&E	hematoxylin-eosin
DNL	de novo lipogenesis
RT-qPCR	quantitative reverse transcription PCR
LD	lipid droplets
TMCG	therapeutic model control group
CPTG	coffee pulp therapeutic group
CPPG	coffee pulp preventive group
PMCG	preventive model control group
PPAR	peroxisome proliferator-activated receptor
LDAPs	LD-associated proteins
PLIN	perilipin

provide biologically active substances in the context of a bio-based economy has gradually become a topic of concern in the coffee industry [4]. Studies have shown that coffee fruit extract can enhance the response of B lymphocytes and has a certain anti-tumor effect [5]. Coffee fruit is rich in high phenolic antioxidants and phytonutrients and has antioxidant effects [6,7]. Different colored coffee berry extracts have anti-lipogenic and lipolytic properties that may contribute to anti-obesity effects [8].

In this study, a model of glucose and lipid metabolism disorder induced by HFD was used in C57BL/6 J mice. By measuring body weight, food intake, FBG, IPGTT, blood lipid level and morphology, this study explored the potential of coffee pulp to ameliorate glucose and lipid metabolism disorders to establish a theoretical basis for the development of coffee pulp's health value and use in functional foods.

2. Material and methods

2.1. Material

Coffee Pulp is provided by Redfruit biotechnology (Jinhua) CO., LTD. Rodent diet with 60 kcal% fat (HFD) is bought from Research Diets, Inc. LabAssay™ Cholesterol kit is bought from FUJIFILM Wako Pure Chemical Corporation. Serum triglyceride determination kit is bought from Sigma-Aldrich LLC. Ultra-Sensitive Mouse Insulin ELISA Kit is bought from Crystal Chem.

2.2. Animals

Animal experiments were carried out in accordance with protocols approved by the Institutional Animal Care and Use Committee of Zhejiang University and conducted in accordance with the policies of institutional guidelines on the care and use of laboratory animals. Mice were housed under 12/12 h light/dark cycles in pathogen-free conditions with free access to mouse chow and water. 8-week-old male specific pathogen-free C57BL/6 J mice were purchased from the GemPharmatech Co., Ltd (Jiangsu, China).

2.3. Establishment of the T2D mouse model and experimental groups

For therapeutic experiment, all mice were fed with a regular chow diet for one month upon arrival. After acclimation, mice were fed with HFD for 6 months to induce T2D and randomly divided into 2 groups. Therapeutic model control group (TMCG) was given distilled water while the coffee pulp therapeutic group (CPTG) was given diluted coffee pulp (10 g/400 ml) for one month.

For preventive experiment, all mice were fed with regular chow diet for one month upon arrival. After acclimation, the mice were randomly divided into 2 groups and fed with HFD for 4 months. Coffee pulp preventive group (CPPG) was given diluted coffee pulp (10 g/400 ml) three weeks before and during HFD feeding, while preventive model control group (PMCG) kept drinking distilled water.

2.4. Glucose tolerance test

Glucose tolerance test was performed as previously described [9]. Mice were injected glucose (0.9 g/kg bw) intraperitoneally after an overnight starvation. Tail vein blood glucose was measured before (0 min) or 15, 30, 60, and 120 min after glucose administration.

2.5. Metabolic parameters

Blood samples were obtained by tail bleeding in 16-h-fasted mice, and the plasma samples were stored at −80 °C until analysis. Plasma concentrations of triglycerides, glycerol and cholesterol were measured using commercial assay kits according to the manufacturer's protocols. Plasma insulin concentrations were measured using an ELISA kit from Crystal Chem.

2.6. Histological analysis

For histological analysis, samples were fixed in 4 % (v/v) paraformaldehyde over 24 h, dehydrated and embedded in paraffin blocks. Histological sections were prepared using a microtome and then stained with hematoxylin and eosin (H&E) to reveal cellular morphology. The stained sections were photographed under a light microscope (BX53, Olympus, Japan).

2.7. Hepatic triglyceride measurement

Hepatic triglyceride was measured as previously described [10]. Briefly, Frozen livers were homogenized in homogenization buffer containing 50 mmol/L Tris, 5 mmol/L EDTA, and 300 mmol/L mannitol and mixed with potassium hydroxide. The crude extract was extracted by chloroform:methanol (2:1) with vigorous vortexing and short incubation. After washed with chloroform/MeOH/H2O (3:48:47 by volume), samples were centrifuged at 10,000 g for 10 min. The bottom layer was dried and resuspended in butanol/[(Triton-X114:MeOH) (2:1)](3:2) by volume before assayed with a Serum Triglyceride Determination Kit (Sigma-Aldrich).

2.8. Quantitative real-time PCR (qRT-PCR)

The total RNA extraction and reverse transcription were performed as previous described [11]. Total RNA was isolated from the indicated tissues with TRIzol (Ambion). cDNA was synthesized with HiScript II Q RT SuperMix for qPCR (Vazyme). The PCR was performed on a Roche LightCycler®480 II using a DNA Master SYBR Green I mix (Roche) according to the manufacturer's protocols. The specific primers for qRT-PCR were synthesized by Sangon Biotech (Shanghai) Co., Ltd. Primers' sequences are listed in Supplementary Table 1.

2.9. Statistics

Statistical analyses were carried out using GraphPad Prism 10. Statistical differences were evaluated using two-tailed unpaired Student t-test for comparisons between the two groups. For GTT studies, two-way ANOVA with multiple comparisons was used for statistical analysis. A P value of less than 0.05 ($^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$) was considered statistically significant.

Table 1
Water intake, food intake and liver index of HFD mice.

	TMCG	CPTG	PMCG	CPPG
water intake (ml/mice/day)	3.967 ± 0.054	6.750 ± 0.331[a]	3.572 ± 0.078	5.498 ± 0.157[c]
food intake (g/mice/day)	2.500 ± 0.101	2.633 ± 0.109	2.787 ± 0.045	2.939 ± 0.028[b]
liver index (%)	5.100 ± 0.415	4.855 ± 0.657	5.416 ± 0.279	5.522 ± 0.364

[a] $P < 0.001$ vs TMCG.
[b] $P < 0.05$ vs PMCG.
[c] $P < 0.001$ vs PMCG.

3. Results

3.1. Safety assessment of coffee pulp

In both the treatment and prevention experiments, the water intake of the mice was significantly increased (Table 1). The body weight of the CPTG mice was significantly greater than that of the model control group after drinking coffee pulp (Fig. 1 A), and this difference in body weight may be due to the increased water intake. In the prevention experiment, although the CPPG mice consumed significantly more food than the model control group, their body weights did not differ significantly from the control group when both water and food intake were

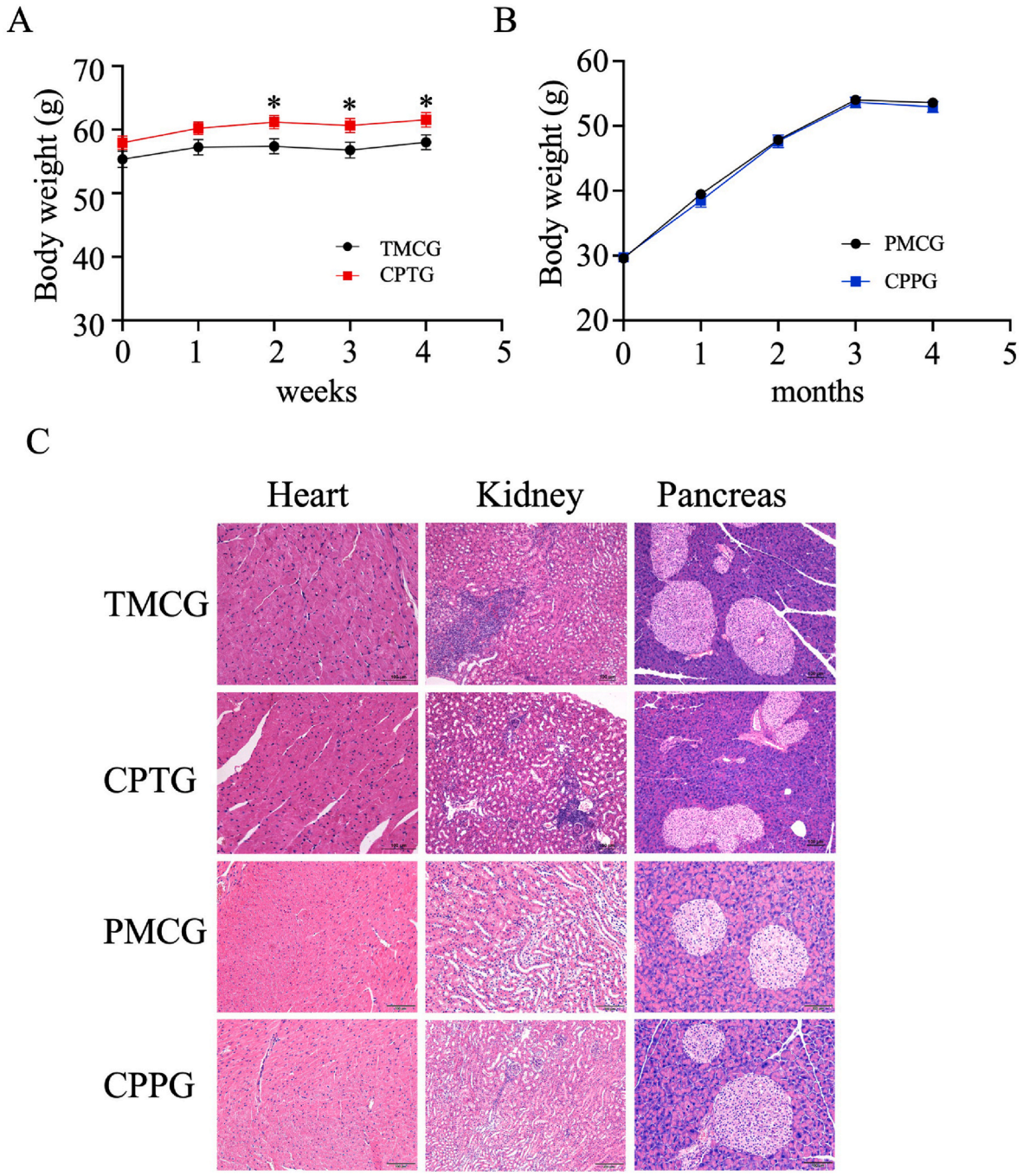

Fig. 1. Safety study of coffee pulp. Effects of coffee pulp on body weight of HFD mice in therapeutic experiment (A) and preventive experiment (B). The mice were weighed at the indicated time points after adding coffee pulp. Values are mean ± SEM, n = 10 mice per group. *P < 0.05 compared with the control group by unpaired Student's t-test. (C) H&E staining of heart, kidney and pancreas (scale bars, 100 μm).

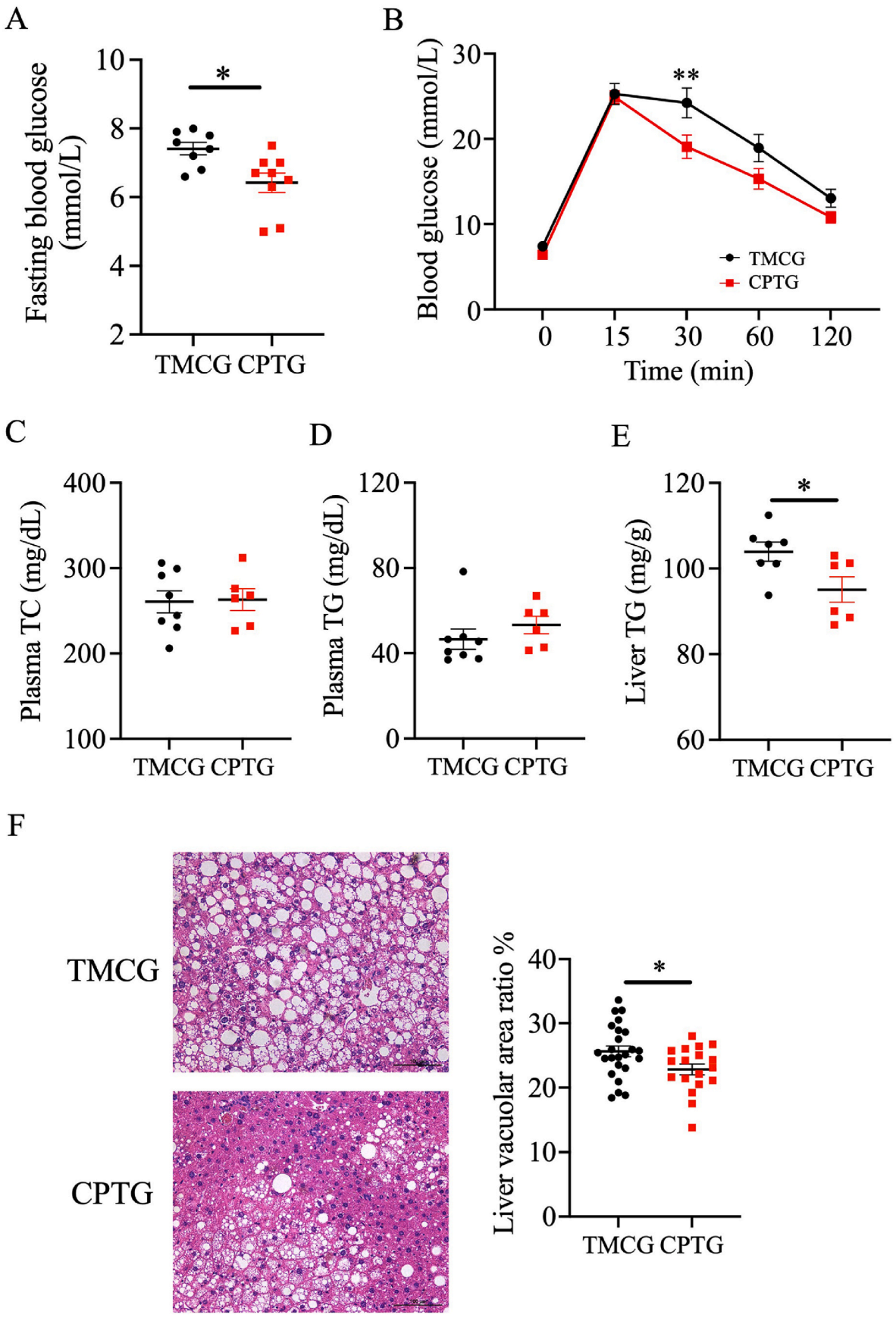

Fig. 2. Therapeutic effects of coffee pulp on glucose and lipid metabolism disorder of HFD mice. FBG (A), GTT (B), plasma TC (C), and TG (D) in mice fed with HFD for 6 months, n = 8 to 9 mice per group. Liver TG content (E) in *ad lib* HFD-fed mice, n = 6 to 7 mice per group. (F) H&E staining of liver (scale bars, 100 μm). Values represent mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ by unpaired Student's t-test.

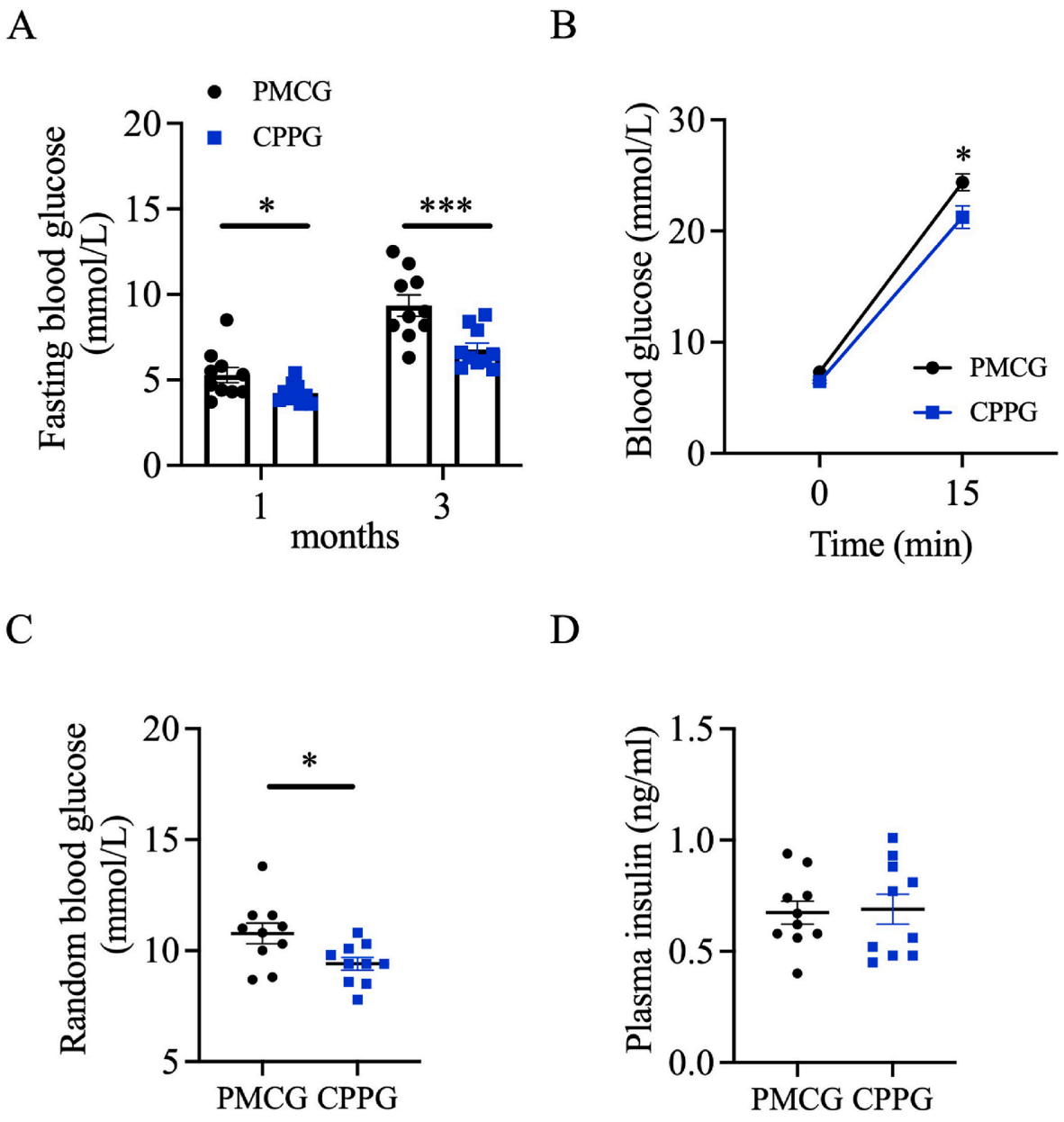

Fig. 3. Preventive effects of coffee pulp on glucose metabolism disorder of HFD mice. FBG (A) in mice fed with HFD for 1 or 3 months, n = 10 mice per group. GTT (B) in mice fed with HFD for 4 months, n = 5 to 8 mice per group. Random blood glucose (C) in mice fed with HFD for 5 months, n = 10 mice per group. Fasting plasma insulin (D) in mice fed with HFD for 4 months, n = 10 mice per group. Values represent mean ± SEM. *$P < 0.05$, ***$P < 0.001$ by unpaired Student's t-test.

significantly increased (Fig. 1 B). In both experiments, there was no significant change in the liver coefficients of the mice, and the organs (e.g. heart, kidney and pancreas) of CPTG and CPPG mice showed no noticeable difference in their organ sections compared to their respective model controls (Fig. 1 C), suggesting that coffee pulp has a superior safety profile.

3.2. Therapeutic effects of coffee pulp on glucose and lipid metabolism disorder of HFD mice

The HFD-fed mice in TMCG were diabetic at the terminus of experiment, as indicated by the FBG level (>7 mmol/L). The FBG of mice in CPTG group was significantly lower than that in TMCG group, which is under 7 mmol/L (Fig. 2A). Furthermore, the IPGTT performed as an in vivo measure of β-cell function showed that, the mice in CPTG group had significantly lower blood glucose than that in TMCG group after 30 min of intraperitoneal injection of glucose (Fig. 2B).

Fatty liver is one of the manifestations of lipid metabolism disorders. Although the lipid assays in mice showed no significant difference in plasma TC and plasma TG between CPTG and TMCG (Fig. 2C and D), the TG content in the liver of mice consuming coffee pulp 6 months after modeling was significantly reduced (Fig. 2E). Pathological analysis of the liver also revealed that CPTG mice had a lower liver LD percentage and smaller LD than TMCG (Fig. 2F). Collectively, these results suggest that coffee concentrate beverage has a therapeutic effect on fatty liver in mice, but it is limited in improving hyperlipidemia.

3.3. Preventive effects of coffee pulp on glucose metabolism disorder of HFD mice

In preventive experiment, the FBG of mice in CPPG was significantly lower than that in PMCG after fed with HFD for 1 month as well as 3 months (Fig. 3A). Especially, the FBG of mice in PMCG reached over 7 mmol/L after 3 months of feeding with HFD, while mice in CPPG did not

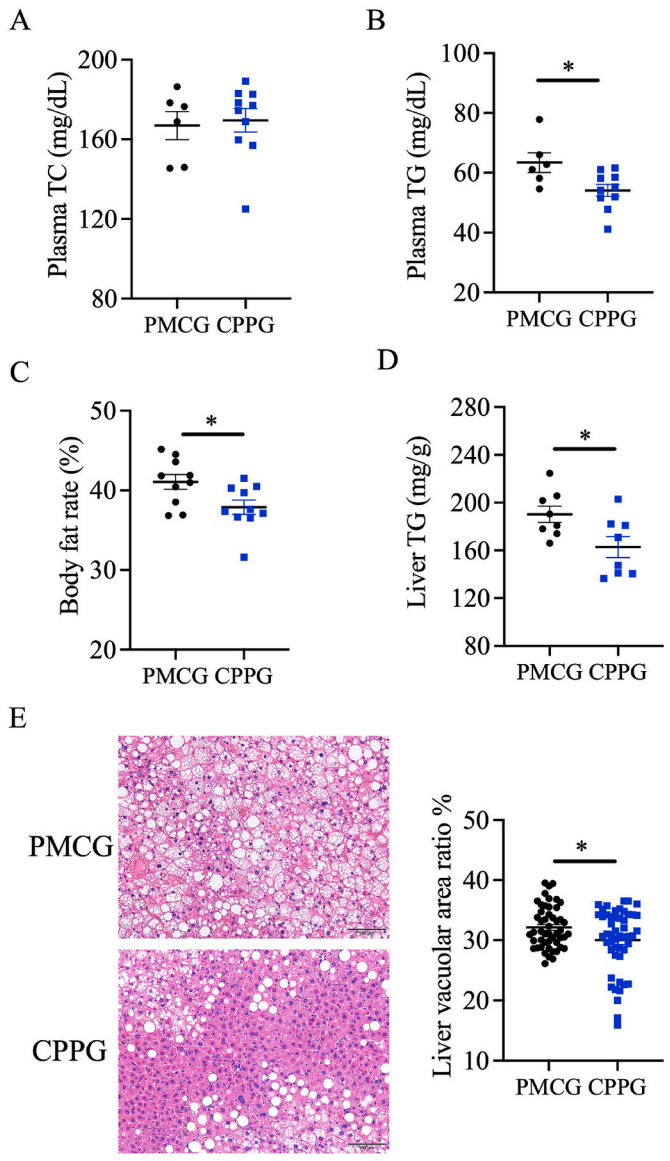

Fig. 4. Preventive effects of coffee pulp on lipid metabolism disorder of HFD mice. Fasting plasma TG (A) and TC (B) in mice fed with HFD for 4 months, n = 10 mice per group. Body fat rate (C) and liver TG (D) in mice fed with HFD for 5 months, n = 10 mice per group. (E) H&E staining of liver (scale bars, 100 μm). Values represent mean ± SEM. *$P < 0.05$ by unpaired Student's t-test.

(Fig. 3A). In IPGTT, the mice in CPPG group had significantly lower blood glucose than that in PMCG group after 15 min of intraperitoneal injection of glucose (Fig. 3B). Additionally, mice in CPPG experienced a significant decrease in their random blood glucose levels compared to those in PMCG after being fed HFD for 5 months (Fig. 3C). However, the fasting plasma insulin did not show any significant difference between CPPG and PMCG (Fig. 3D).

3.4. Preventive effects of coffee pulp on lipid metabolism disorder of HFD mice

The plasma TG levels of mice in CPPG group were significantly lower than that in PMCG group (Fig. 4A) while the plasma TC levels did not change significantly (Fig. 4B). After five months of HFD, body fat percentage analysis revealed that CPPG mice had a significant difference in body fat percentage compared to PMCG (Fig. 4C). The TG content in the liver of CPPG mice was significantly lower than that of PMCG (Fig. 4D), which was consistent with the significant reduction in the size and number of LDs in the liver of CPPG mice compared with PMCG, as observed by H&E staining results (Fig. 4E).

3.5. Effect of coffee pulp on genes related to hepatic lipid metabolism in mice

To investigate the mechanism of glucose and lipid metabolism disorder prevention and treatment in mice, livers of mice fed with HFD for 5 months were extracted for mRNA expression assay of glucose and lipid metabolism-related genes. The results of real-time qPCR showed that the expression levels of glucose and lipid metabolism-related transcription factors such as Srebp1c, PPARγ2, PPARγ1+2, PPARα, and Pgc1α were significantly lower in the livers of CPPG mice than in the control group (Fig. 5A). Among the genes related to fatty acid synthesis and triglyceride synthesis, the expression of Fas was significantly lower in CPPG than in the control group (Fig. 5B). LD formation-related genes such as Vldlr, CideA, Plin3, Plin4, and Plin5 were significantly lower in the liver of CPPG mice than in the control group (Fig. 5C). There was no significant difference in the expression of genes related to lipolysis and gluconeogenesis between the two groups (Fig. 5D and E).

4. Discussion

Glucose and lipids are essential nutrients, and their metabolism is accurately regulated in healthy individuals. Disorders of glucose and lipid metabolism can lead to a variety of diseases such as atherosclerosis, diabetes mellitus and fatty liver [12]. In T2D, the pancreas produces insulin in response to glucose stimulation, but is unable to properly absorb glucose due to insulin resistance in the liver, leading to hyperglycemia. Glucose tolerance tests are employed to assess how well individuals can process their glucose load. Mice in the coffee pulp treatment and prevention groups showed significantly decreased FBG and better blood glucose control compared to the model group in the glucose tolerance test, indicating an improvement in glucose metabolism.

Lipids are synthesized mainly in liver and adipose, and lipogenesis in the liver is more efficient than adiposity [13]. DNL is a complex and highly regulated metabolic pathway. Under normal conditions, DNL converts excess carbohydrates into fatty acids, which are then esterified into stored TG [14]. In hyperinsulinemic patients, this homeostasis of maintaining normal glucose concentrations disrupts hepatic lipid metabolism by increasing TG concentrations, which themselves may exacerbate insulin resistance and create a vicious cycle [15]. DNL occurs primarily in the liver and adipose, it is generally considered a secondary factor in maintaining serum TG homeostasis. Serum TG is mainly derived from diet; however, several studies have shown that hepatic DNL may have a significant effect on blood lipid levels in individuals on a high-carbohydrate diet [16]. Therefore, studies nowadays often use blood and liver lipid levels as an indicator of lipid metabolism in animal organisms. Coffee pulp reduced FBG in mice fed an HFD, prevented the appearance of hypertriglyceridemia, prevented and treated HFD-induced fatty liver, and showed preventive and control effects on disorders of glucose and lipid metabolism.

To identify potential mechanisms by which coffee pulp prevents HFD-induced disorders of glucose and lipid metabolism, we investigated key genes associated with DNL. Fasn, which is a crucial enzyme in DNL, is recognized as a marker of adipogenesis and is referred to as a housekeeping protein in the liver [17]. It is regulated by the key transcription factor Srebp-1a transcriptional regulation. Overexpression of Srebp-1a leads to overproduction of fatty acids and enlarged livers in mice [18,19]. Here, our results found that coffee pulp consumption had no impact on fasting insulin levels in mice, but maintained significantly lower mRNA expression levels of Srebp-1 and Fasn in the liver under HFD than in model controls, thereby affecting DNL in the liver, suggesting that the effect may not be insulin-dependent. Coffee pulp is rich

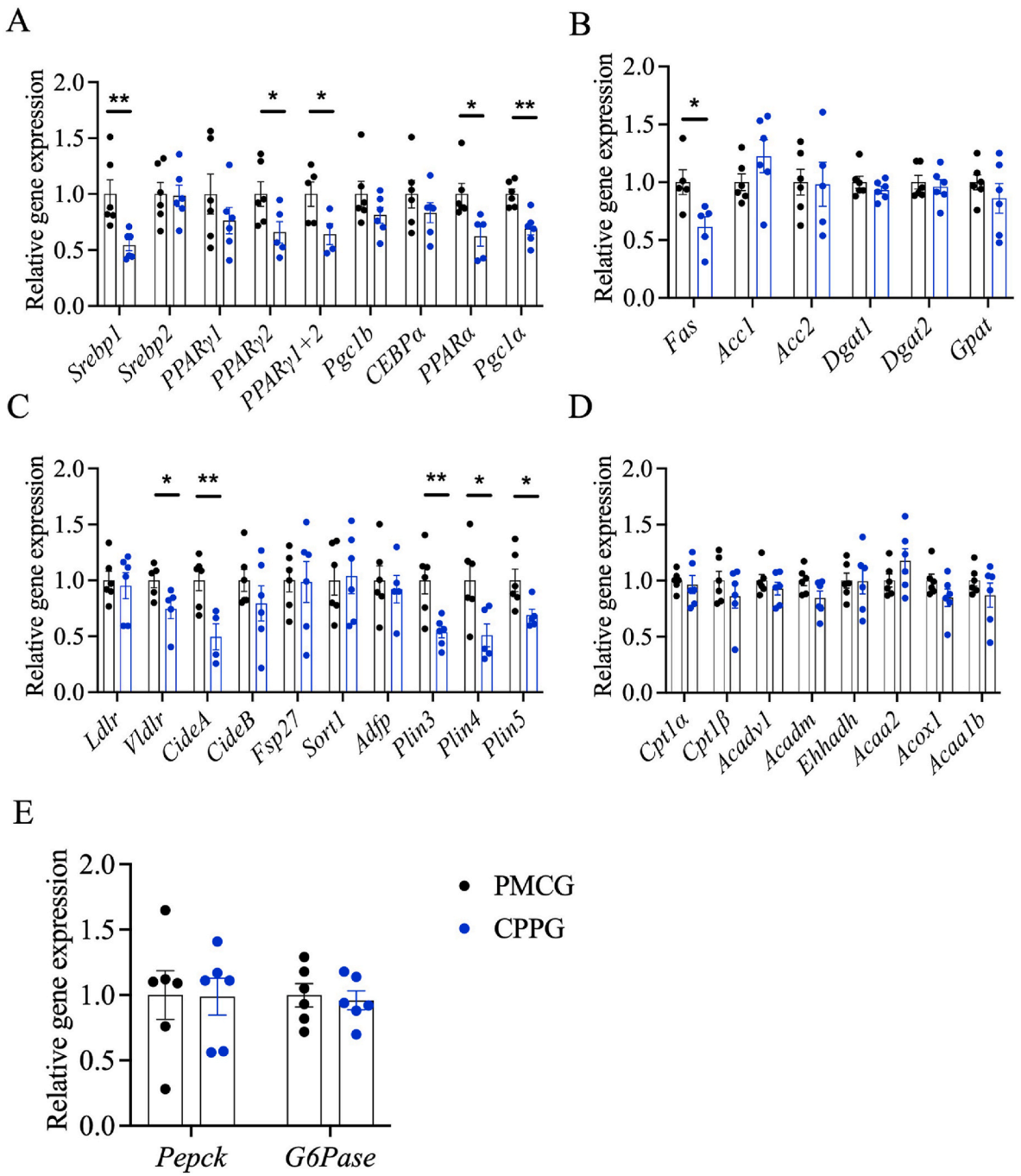

Fig. 5. MRNA expression of lipid metabolism-related genes in liver. The expression of transcription factors (A) and genes related to DNL (B), LD formation (C), lipolysis (D) as well as gluconeogenesis (E) were measured in the liver from mice fed with HFD for 5 months, n = 5 to 6 mice per group. Values represent mean ± SEM. *$P < 0.05$ by unpaired Student's t-test.

in caffeine, tea polyphenols, total flavonoids and crude polysaccharides. In agreement with our results, it was shown that caffeine significantly down-regulated the expression of Srebp gene in HepG2 cells and significantly inhibited the accumulation of hepatic lipids such as TG and cholesterol [20]. In a study on fat diet-induced obese rats, oolong tea extracts rich in caffeine and tea polyphenols reduced body weight and decreased lipid accumulation in visceral fat by decreasing the expression of adipogenesis-related proteins Srebp1 and Fasn [21]. Another study showed that tea polyphenols may inhibit adipogenesis by attenuating the expression of Srebp-1 and Fasn in Western diet-fed mice [22].

The liver is the primary organ responsible for keeping the body's nutrients and energy balanced. Liver abnormalities may lead to hepatic steatosis, steatohepatitis, fatty fibrosis and liver cancer. Peroxisome proliferator-activated receptor (PPAR) α, β/δ and γ regulate lipid homeostasis, with PPARα regulating lipid metabolism in the liver, PPARβ/δ mainly promoting fatty acid β-oxidation in extrahepatic organs, and PPARγ storing triacylglycerols in adipocytes [23]. Previous studies have indicated that PPARγ has complex and diverse biological functions, including the regulation of lipid and carbohydrate metabolism, energy homeostasis, and PPARγ is activated and induced in the liver during nutritional excess and obesity and is responsible for storing fatty acids by promoting LD formation [24,25].

LDs are dynamic subcellular organelles consisting of a phospholipid monolayer envelope, a neutral lipid core, and an array of specific LD-

associated proteins [26]. Intracellular LD are wrapped by various LD-associated proteins (LDAPs) from the CIDE (cell death-induced DNA fragmentation factor-α-like effector) family and PLIN (perilipin) family, which regulate LD synthesis and hepatic lipid homeostasis [26,27]. Among the three proteins of the CIDE family, only Cideb is highly expressed in the liver under normal dietary conditions, while Cidea and Cidec transcripts are undetectable, but both hepatic Cidea and Cidec transcripts are significantly elevated under conditions of obesity or HFD [26,28,29]. Deficiency of Cidea or Cidec in animals results in reduced hepatic lipid stores and resistance to HFD-induced fatty liver formation [25,30,31]. Studies have shown that PLIN2, PLIN3 and PLIN5 are elevated in human fatty liver and their ablation attenuates steatosis in mouse models [32,33]. Among the studies on natural dietary modulation of hepatic lipid accumulation, one study on matcha found that matcha downregulated PLIN4 gene expression in the liver and improved lipid accumulation and steatohepatitis associated with obesity [34].

The results of this study on genes related to gluconeogenesis and lipolysis showed that coffee pulp had no significant effect on hepatic gluconeogenesis and lipolysis in HFD-fed mice. The expression levels of LDAPs such as CideA, Plin3, Plin4, Plin5 and the transcription factor PPARγ, which is involved in the regulation of these genes, were significantly lower in the livers of HFD-fed mice after coffee pulp consumption than in the control group, indicating that coffee pulp consumption was mainly used to prevent fatty liver development in HFD-fed mice by inhibiting DNL and LD formation.

In this study, we found that HFD induced significant obesity symptoms and hepatic lipid accumulation, and the resulting lipotoxicity promoted the progression of fatty liver in mice. Upon analysis of biochemical parameters, histopathology and liver gene expression , it was found that long-term coffee pulp consumption has a good safety profile and can effectively reduce plasma glucose and plasma TG levels in HFD-fed C57BL/6 J mice and significantly improve obesity-related lipid accumulation. Fundamentally, DNL-related genes such as Fasn, LDAP such as Cidea, Plin3, Plin4 and Plin5, and related transcription factors such as Srebp1 and PPARγ expression levels were downregulated, suggesting that coffee pulp may exert an inhibitory effect on lipid accumulation mainly through a pathway that inhibits lipid synthesis and LD formation.

These findings indicate that coffee pulp can be utilized as a nutritional supplement to reduce obesity and fatty liver caused by HFD. However, the interaction between key genes in the glucose and lipid metabolic pathways during coffee pulp consumption is still unclear, and more research is needed to uncover the molecular mechanisms involved.

5. Limitations

Further research is needed to explore the specific mechanism of the regulation of coffee pulp consumption. Moreover, this is only an animal study, and it is better to prove it in clinical trials.

Funding

No funding was received.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Animal experiments were carried out in accordance with protocols approved by the Institutional Animal Care and Use Committee of Zhejiang University and conducted in accordance with the policies of institutional guidelines on the care and use of laboratory animals.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Shuaishuai Zhu: Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – original draft. **Chenying Wang:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. **Zhuo-Xian Meng:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2024.100303.

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