ORIGINAL ARTICLE

Sesamol intervention ameliorates obesity-associated metabolic disorders by regulating hepatic lipid metabolism in high-fat diet-induced obese mice

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Popular scientific summary
- Sesamol significantly lowered body weight and ameliorated dyslipidemia, insulin resistance, and hepatic steatosis in high-fat diet-induced obese mice; and it might be due to the regulation of hepatic lipid metabolism by sesamol.
- The liver is known to involve in lipid metabolism, including lipid uptake, lipid synthesis, and lipid catabolism. Sesamol reduced hepatic lipogenesis and increased lipolysis and fatty acid β-oxidation, which in turn reduce lipid accumulation in the body to alleviate obesity and obesity-associated metabolic disorders.

Abstract

Background: Obesity has currently become a serious social problem to be solved. Sesamol, a natural bioactive substance extracted from sesame oil, has shown multiple physiological functions, and it might have an effect on the treatment of obesity.

Objective: This study was conducted to investigate the therapeutic effect and potential mechanisms of sesamol on the treatment of obesity and metabolic disorders in high-fat diet (HFD)-induced obese mice.

Methods: C57BL/6J male mice were fed HFD for 8 weeks to induce obesity, followed by supplementation with sesamol (100 mg/kg body weight [b.w.]/day [d] by gavage) for another 4 weeks. Hematoxylin and eosin staining was used to observe lipid accumulation in adipose tissues and liver. Chemistry reagent kits were used to measure serum lipids, hepatic lipids, serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels. ELISA kits were used to determine the serum insulin and free fatty acid (FFA) levels. Western blotting was used to detect the protein levels involved in lipid metabolism in the liver.

Results: Sesamol significantly reduced the body weight gain of obese mice and suppressed lipid accumulation in adipose tissue and liver. Sesamol also improved serum and hepatic lipid profiles, and increased insulin sensitivity. In the sesamol-treated group, the levels of serum ALT and AST decreased significantly. Furthermore, after sesamol treatment, the hepatic sterol regulatory element binding protein-1 (SREBP-1c) decreased, while the phosphorylated hormone sensitive lipase (p-HSL), the carnitine palmitoyltransferase 1α (CPT1α), and the peroxisome proliferator-activated receptor coactivator-1α (PGC1α) increased, which were responsible for the fatty acid synthesis, lipolysis, and fatty acid β-oxidation, respectively.

Conclusions: Sesamol had a positive effect on anti-obesity and ameliorated the metabolic disorders of obese mice. The possible mechanism of sesamol might be the regulation of lipid metabolism in the liver.

Keywords: *sesamol; obesity; liver; lipid metabolism*

Obesity has become a serious public health concern that threatens human health worldwide (1, 2). The incidence of obesity-associated metabolic diseases, such as hypertension, type 2 diabetes, and hepatic steatosis, is rapidly increasing (3–5). Therefore, effective prevention and treatment strategies are needed to halt the development of obesity.

For the treatment of obesity, promoting lipid metabolism is an attractive way (6–8). It is well-known that liver is one of the main organs responsible for lipid metabolism,

including lipid uptake, lipid synthesis, and lipid catabolism (9–12). Previous studies have demonstrated that regulating the factors responsible for lipid metabolism in liver could protect the body against obesity (13–15).

Sesamol, a natural bioactive substance extracted from sesame oil (16), has been reported to exhibit multiple biological effects (17–20). Recently, it is reported that the administration of sesamol significantly reduced the body weight in HFD-induced obese mice and decreased lipid droplets accumulation in 3T3-L1 adipocytes (21, 22). These findings suggested that sesamol had a potential anti-obesity effect. However, the detailed mechanism remains unclear, especially the effect of sesamol on hepatic lipid metabolism has not been clearly defined. In this study, we investigated the effects of sesamol on the aspect of hepatic lipid metabolism in HFD-induced obese mice in order to elucidate the underlying mechanism of sesamol in the treatment of obesity and obesity-associated metabolic disorders.

Materials and methods

Animals and diet

Male C57BL/6J mice (4–6 weeks old) were purchased from Central South University (Hunan, Changsha, China). The mice were housed in the standard animal room (humidity: 40%–70%, temperature: $22 \pm 2°C$, light and dark cycle: 12 h/12 h, free feeding and drinking water). After acclimatization, one group of the mice were fed with the normal-fat diet (NFD, 10 kcal% fat; rodent diet D12450B, Research Diets, New Brunswick, NJ, USA), and all the other mice were fed with a HFD (60 kcal% fat; rodent diet D12492, Research Diets, New Brunswick, NJ, USA). After 8 weeks, mice weighing 20% more than the average weight of mice in the NFD group were considered obese mice, and then, the obese mice were divided into two groups: HFD group (fed a HFD) and HFD+sesamol group (fed a HFD and administered with sesamol by gavage). All three groups with eight mice in each were fed for another 4 weeks. Sesamol (Sigma-Aldrich, St. Louis, MO) was dissolved in a vehicle (0.5% carboxylmethyl cellulose) and administered at a dose of 100 mg/kg b.w./d by gavage, and mice in the NFD and HFD groups were given the equal volume of vehicle by gavage. The mice were allowed free access to water and food. Everyday food-intake and every-week body weight of the mice were recorded. The project was approved by the Animal Care and Use Committee of Central South University (IACUC Approval Number: 2019sydw0025), and all experiments were performed in accordance with the committee's guidelines.

Intraperitoneal glucose tolerance test (IPGTT), fasting blood glucose (FBG), serum insulin, and the insulin resistance index (HOMA-IR)

The IPGTT was performed in the 12th week, and mice were fasted for 12 h before the experiment. The FBG was measured with tail vein blood using a glucose analyzer (Contour TS, Bayer, Germany). Then, the mice were intraperitoneally injected with 2 g/kg body weight glucose, and then, the blood glucose levels were measured with tail vein blood at 15, 30, 60, and 90 min. ELISA assay was used to measure the serum insulin concentration (cusabio, WuHan, China). The homeostasis model assessment of HOMA-IR was calculated as follows: fasting insulin concentration (mU/L) × fasting glucose concentration (mmol/L)/22.5.

Serum and tissue collection

After 12 weeks, the mice were anesthetized with ether. Blood samples were taken from the femoral artery and placed at room temperature for 30 min and centrifuged at 2,500 × rpm for 10 min, and separated serum samples were stored at −80°C. Then, the mice were killed by cervical dislocation. The livers and adipose tissues (epididymal, perirenal, and inguinal white adipose tissue [WAT]) were dissected, rinsed, and weighed. Then, the livers and adipose tissues were divided into two parts: one was quickly fixed in 4% formalin solution for histological analysis, and the other was quickly frozen in liquid nitrogen and immediately stored at −80°C until use.

Histological analysis

Fixed liver and adipose tissue were removed from formalin solution and embedded in paraffin wax. Paraffin-embedded sections (5 μm) were stained with hematoxylin and eosin (HE). Then, the sections were analyzed by an optical microscope (EVOSTM Auto2, Thermo Fisher Scientific, WA, USA). Adipocyte size was determined by measuring the area of 100 adipocytes in stained sections and analyzed with Image J software.

Serum biochemical analyses

Serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum-free fatty acid (FFA), ALT, and AST were measured using chemistry reagent kits (Nanjing Jiancheng, Nanjing, China).

Hepatic lipid concentration

The liver samples were homogenized with normal saline (1:9, w/v) and centrifuged at 2,500 rpm for 10 min. Hepatic triglycerides (TG), TC, and LDL-C levels were assayed using the same kits used for serum analysis.

Western blotting analysis

Liver tissues were harvested in a cold RIPA buffer containing proteinase inhibitor (Ding Guo Changsheng Biotechnology Co., Ltd., Beijing, China). All protein extracts were then centrifuged at 12,000 rpm at 4°C for 15 min. The protein concentration of supernatants was measured

with BCA Protein Assay Kit (Beyotime Biotechnology, Shanghai, China).

The protein was separated by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (Bioleader, Maine, USA). After blocked in 5% skim milk in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 1 h at room temperature, the membranes were incubated overnight at 4°C with primary antibodies and secondary antibody for 1 h at room temperature. With an ECL method, protein bands were detected using the chemiluminescence imager (Tanon-5500, Tanon Science & Technology Co., Ltd., Shanghai, China). The primary antibodies used in this study were SREBP-1c (A15586), CPT1α (A5307), PKA-C (A7715), and β-actin (AC026), which were purchased from Abclonal (Wuhan, China); and HSL (AF6403) and Phospho-HSL (p-HSL, AF8026) were purchased from Affinite (OH., USA). The secondary antibody was HRP Goat Anti-Rabbit IgG (AS014) purchased from Abclonal.

Statistical analysis

Data are expressed as the mean ± standard deviations (SD). Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used for comparisons among group. Significant differences between the mean values were assessed using least-significant difference t-test (LSD-t). Results were considered statistically significant at $P < 0.05$.

Results

Effect of sesamol on body weight in obese mice

After 8 weeks, the weights of the mice fed with HFD were significantly higher than the mice fed with NFD, and the 4-week treatment with sesamol markedly decreased the weights of the mice (Fig. 1a), and the body weight gain of HFD+sesamol group was significantly lower than that of the HFD group (Fig. 1b). In addition, there was no significant difference in the food intake among the three groups (Fig. 1c).
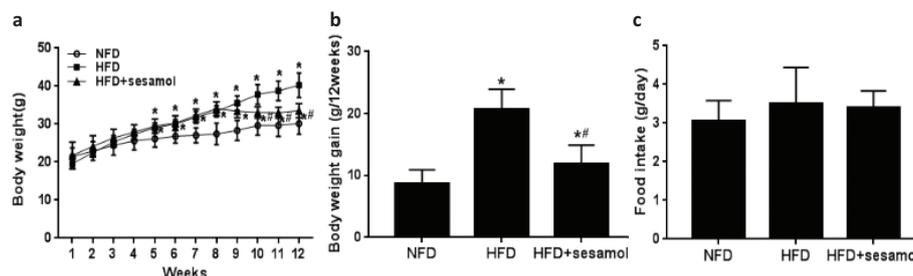
Effects of sesamol on adipose tissue in obese mice

The epididymal, perirenal, and inguinal WAT weights were significantly reduced by sesamol compared with the HFD group (Fig. 2a). Adipose tissues were smaller in terms of appearance after sesamol treatment, and sections showed that the sizes of adipocytes were also smaller in the HFD+sesamol group than that in the HFD group (Fig. 2b–d). Furthermore, the cell size distributions of representative WATs were quantified. We found that there was a shift from larger cell area to smaller cell area in adipose tissues in sesamol-treated mice (Fig. 2e, f). These results indicated that sesamol might reduce lipid storage in adipose tissues in HFD-induced obese mice.

Effect of sesamol on IPGTT, FBG, serum insulin, and the HOMA-IR in obese mice

Glucose disposal was delayed in IPGTT, and FBG was significantly increased in the HFD group compared with the NFD group, which indicated that HFD feeding induced glucose intolerance in mice, and sesamol improved glucose tolerance by promoting glucose disposal and decreasing FBG (Fig. 3a–c). The serum insulin level and HOMA-IR were significantly higher in the HFD group than that in the NFD group, whereas sesamol markedly reduced serum insulin levels and HOMA-IR (Fig. 3d, e), which indicated an improvement of insulin sensitivity after sesamol treatment.

Effects of sesamol on serum lipid profile in obese mice

The levels of serum TC and LDL-C were dramatically lower in the HFD+sesamol group compared with the HFD group (Fig. 4a, b). The level of HDL-C was significantly higher in the HFD+sesamol group (Fig. 4c). Additionally, the level of serum FFA was significantly decreased by sesamol compared with the HFD group (Fig. 4d). These data suggested that HFD-induced dyslipidemia was significantly improved by sesamol.

Effects of sesamol on liver function and lipid profile in obese mice

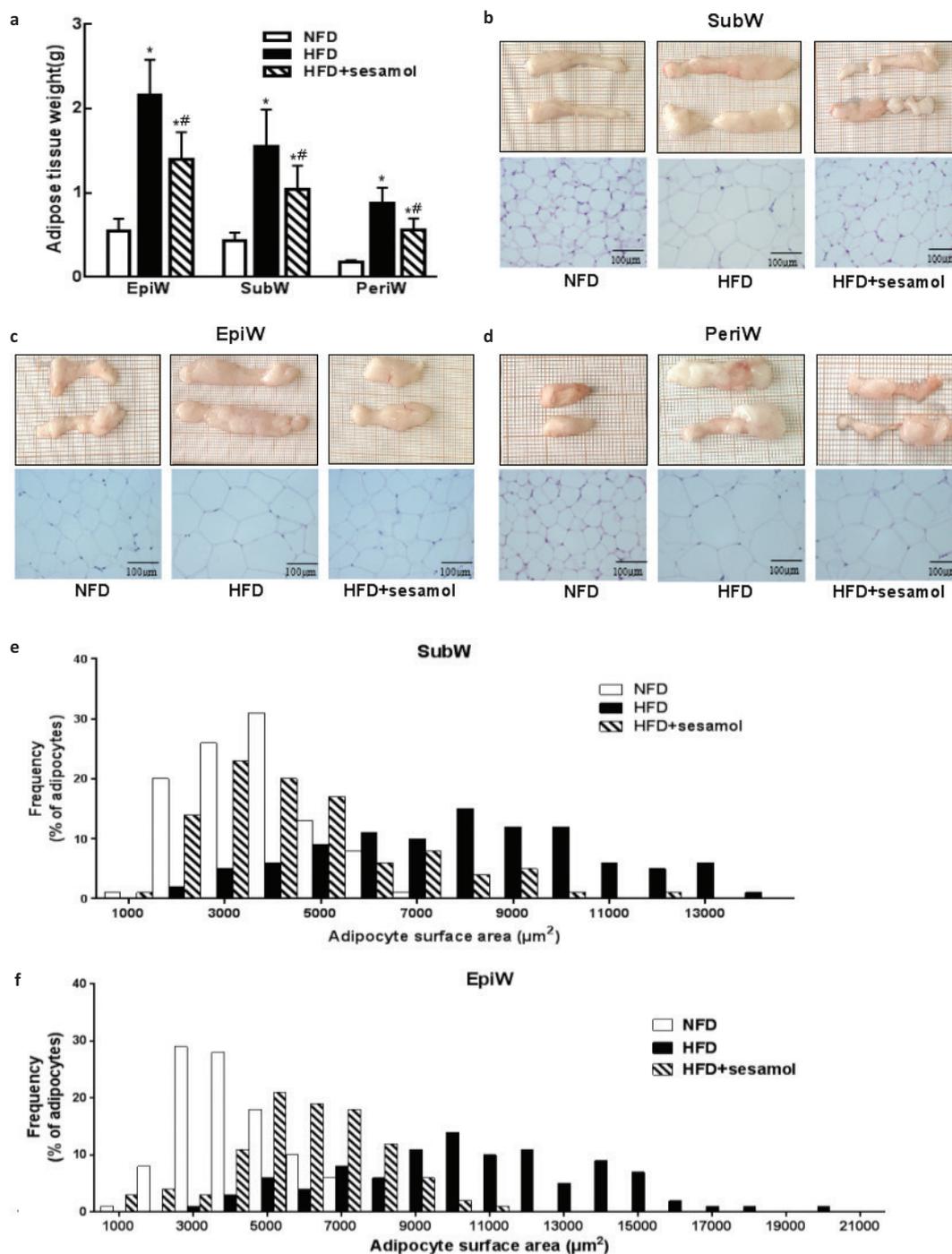The liver weight was obviously decreased in the HFD+sesamol group compared with the HFD group

Fig. 1. Effect of sesamol on the body weight in HFD-induced obese mice. (a) Body weight, (b) body weight gain, and (c) food intake based on food consumption per day per mouse. Data are shown as mean ± SD ($n = 8$). * $P < 0.05$ compared with the NFD group; # $P < 0.05$ compared with the HFD group.

Fig. 2. Effects of sesamol on white adipose tissue (WAT) weights and histological analysis in HFD-induced obese mice. (a) The weights of WATs. (b) SubW, (c) EpiW, and (d) PeriW morphology and H&E staining (400×), scale bar = 100 μm. (e) The size distribution of adipocytes in SubW. (f) The size distribution of adipocytes in EpiW. SubW: inguinal WAT; EpiW: epididymal WAT; PeriW: perirenal WAT. Data are shown as mean ± SD (n = 8). * $P < 0.05$ compared with the NFD group; # $P < 0.05$ compared with the HFD group.

(Fig. 5a). In terms of liver morphology, the livers were pale and larger in the HFD group, which was improved after sesamol treatment, and liver sections showed that hepatic fat vacuoles were also much fewer in the HFD+sesamol group than the HFD group (Fig. 5b). Serum ALT and AST levels were markedly reduced in the HFD+sesamol group (Fig. 5c). Furthermore, the levels of hepatic TG and LDL-C were also significantly
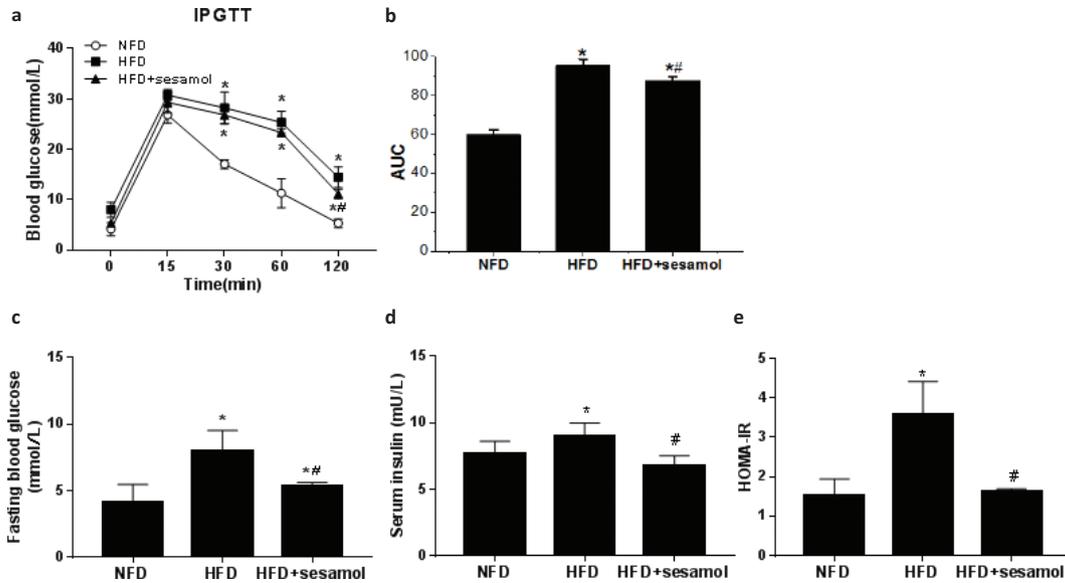
Fig. 3. Effect of sesamol on glucose tolerance and insulin resistance in HFD-induced obese mice. (a) The blood glucose concentration at the indicated times (0, 15, 30, 60, and 120 min) after intraperitoneal injection of glucose. (b) Area under the curve (AUC) of blood glucose levels after the IPGTT. (c) Blood glucose levels after 12-h fasting. (d) Serum insulin levels after 12-h fasting. (e) HOMA-IR calculated by fasting blood glucose and insulin levels. Data are shown as mean ± SD (n = 3). * $P < 0.05$ compared with the NFD group; # $P < 0.05$ compared with the HFD group.
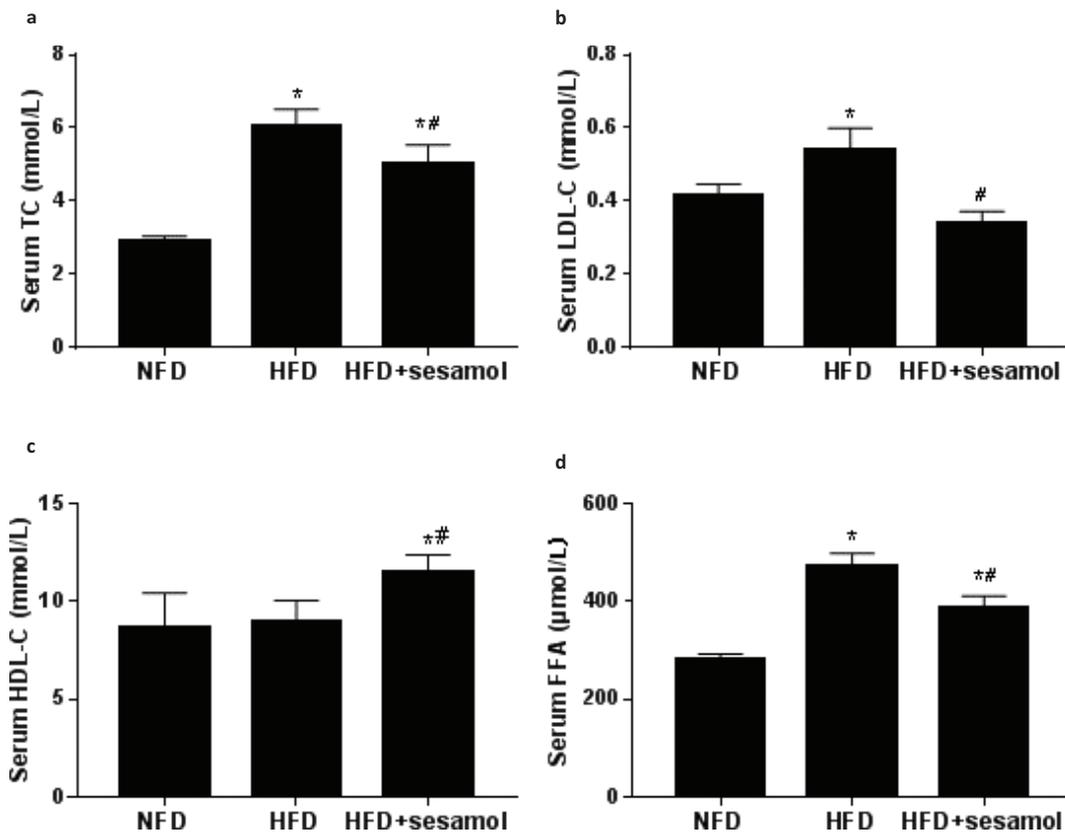

Fig. 4. Effects of sesamol on serum lipid levels in HFD-induced obese mice. (a) Serum TC, (b) serum LDL-C, (c) serum HDL-C, and (d) serum FFA. Data are shown as mean ± SD (n = 3). * $P < 0.05$ compared with the NFD group; # $P < 0.05$ compared with the HFD group.
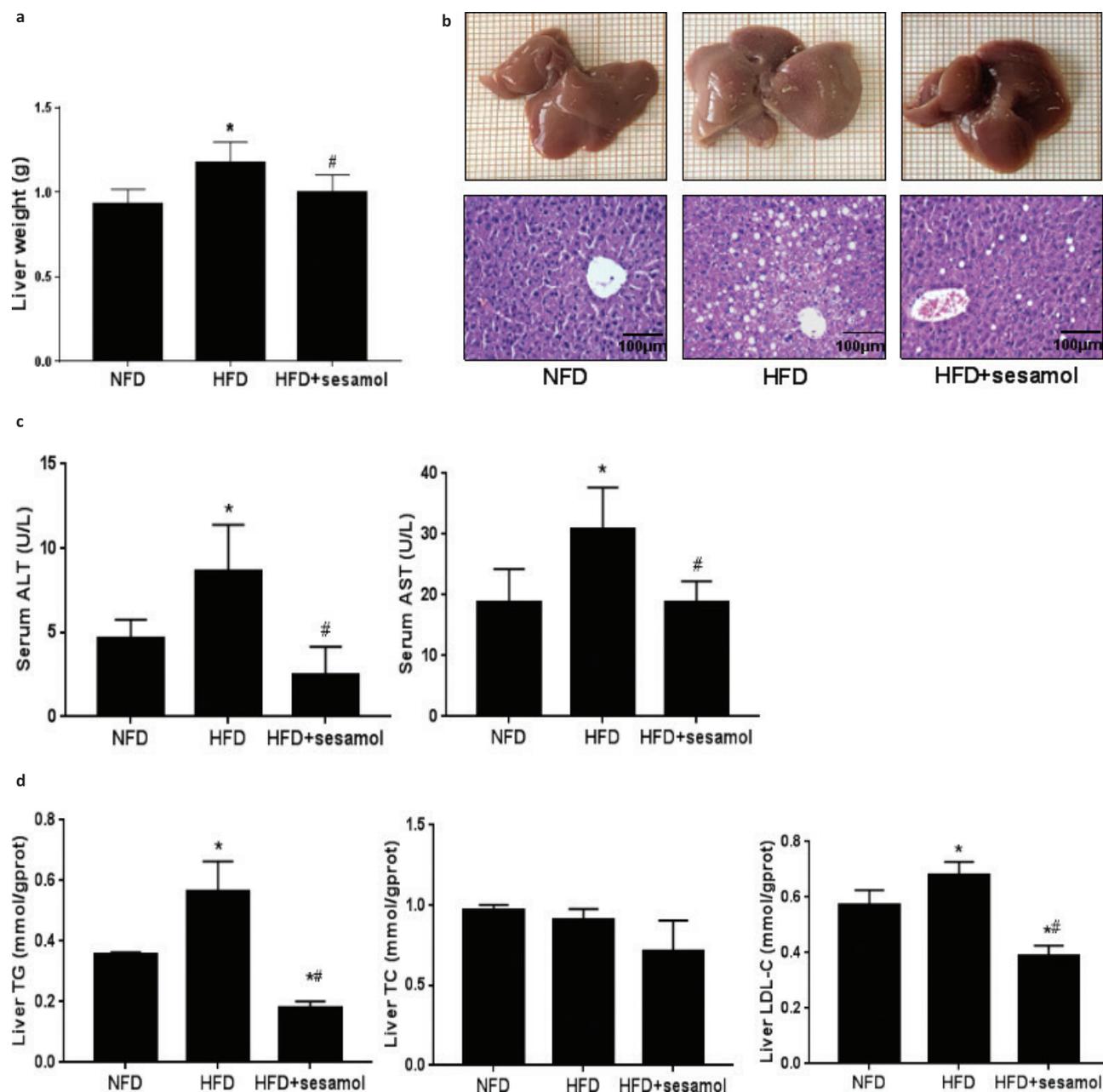
Fig. 5. Effects of sesamol on liver histology, liver weight, liver function, and liver lipid profiles in HFD-induced obese mice. (a) Liver weight (*n* = 8). (b) Liver morphology and sections of H&E staining (400×), scale bar = 100 μm. (c) Serum ALT and AST. (d) Liver TG, TC, and LDL-C. Data are shown as mean ± SD (*n* = 3). * P < 0.05 compared with the NFD group; # P < 0.05 compared with the HFD group.

lower after sesamol treatment (Fig. 5d). Thus, we concluded that sesamol could decrease lipid accumulation in the liver and improve liver function.

Effects of sesamol on hepatic lipid metabolism regulators in obese mice

Since liver plays a critical role in metabolism, several representative hepatic lipid metabolism regulators were detected to explore the anti-obesity mechanism

of sesamol. The expression of SREBP-1c was significantly reduced in the HFD+sesamol group compared with the HFD group (Fig. 6a), which indicated a decrease in fat synthesis. The expression of p-HSL was markedly increased by sesamol (Fig. 6b); in addition, PGC1α and CPT1α expression levels were higher in the HFD+sesamol group than that in the HFD group (Fig. 6c, d), which demonstrated the enhancement of lipolysis and fatty acid oxidation. Collectively, these
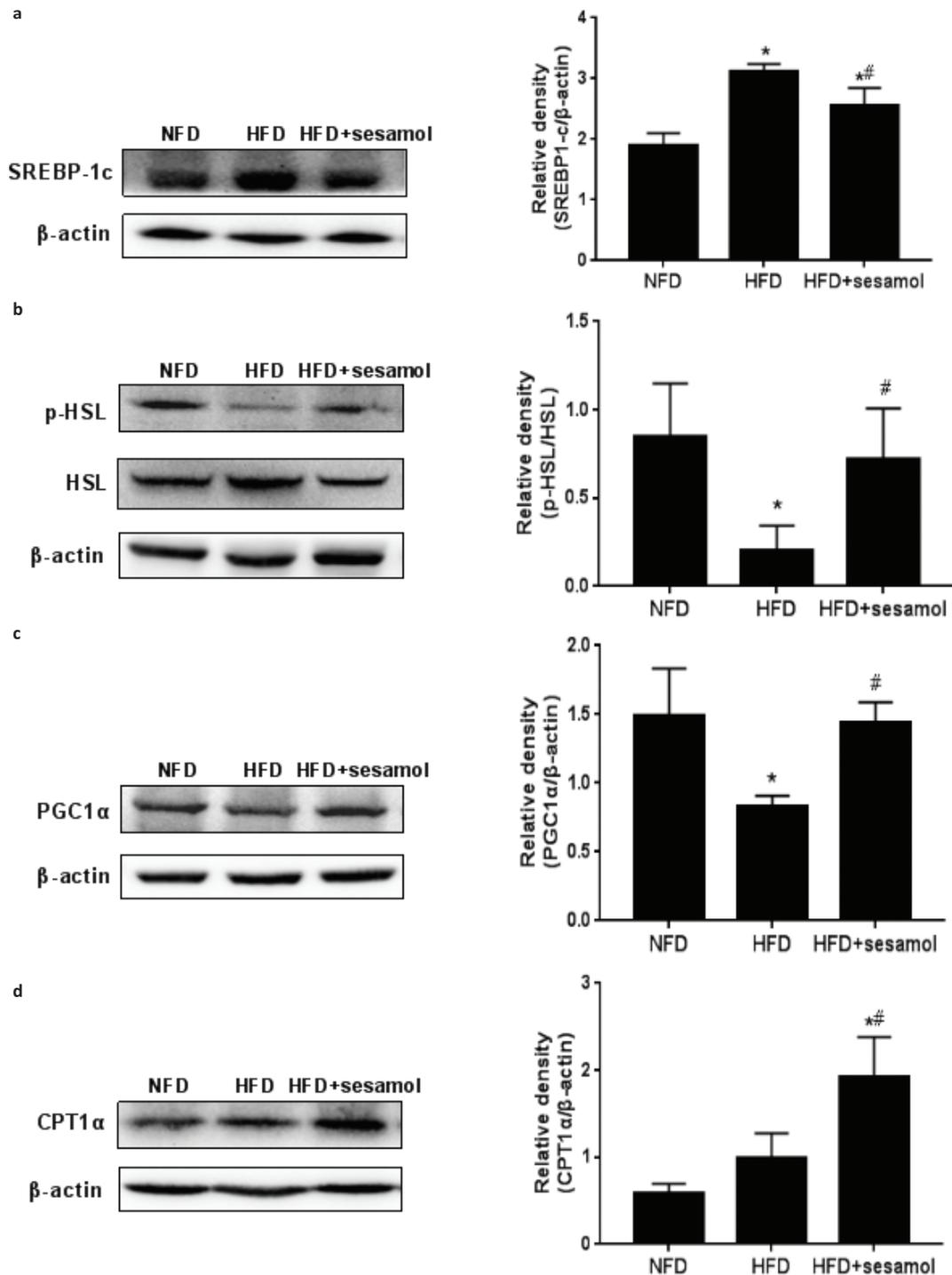
Fig. 6. Effects of sesamol on protein expression levels related to lipid metabolism in HFD-induced obese mice. Protein expression levels and density analysis of (a) SREBP-1c, (b) p-HSL and HSL, (c) PGC1α, and (d) CPT1α. Data are shown as mean ± SD ($n = 3$). * $P < 0.05$ compared with the NFD group; # $P < 0.05$ compared with the HFD group.

data suggested that sesamol might be involved in hepatic lipid metabolism.

Discussion

Increasing attentions have been paid to phytochemicals that serve as alternative strategies for obesity treatment (23, 24). In this study, we investigated the effects of sesamol on HFD-induced obese mice and explored the underlying mechanisms. For the first time, we demonstrated that sesamol could reduce body weight gain and improve obesity-associated metabolic disorders, which were dependent on the regulation of lipid metabolism in the liver, and

the detailed mechanism was that sesamol down-regulated SREBP-1c and up-regulated p-HSL, PGC1α, and CPT1α in the liver.

Obesity is characterized by increased lipid storage in an expanded adipose tissue mass (25). In this study, we found that sesamol markedly reduced the body weight gain of HFD-induced obese mice without affecting the food intake of mice, and it also reduced weights of epididymal, perirenal, and inguinal WAT and diminished adipocyte size. These results directly proved that sesamol had an anti-obesity effect. Notably, it has been reported that obesity is closely related to the development of metabolic disorders, including dyslipidemia, insulin resistance, and hepatic steatosis (26). Our results showed that sesamol decreased the levels of serum TC and LDL-C and increased serum HDL-C level to alleviate dyslipidemia in obese mice. Additionally, sesamol promoted glucose disposal and decreased FBG level, which suggested that sesamol improved the glucose tolerance of obese mice. Sesamol also decreased serum insulin level and HOMA-IR, which indicated that sesamol could enhance insulin sensitivity. These results illustrated that sesamol had an effective anti-obesity effect and ameliorated obesity-associated metabolic disorders.

The liver plays a key role in lipid homeostasis (27); however, excessive fat tends to accumulate in the liver in a state of obesity, which impairs liver function and further exacerbates obesity-associated metabolic disorders (28, 29). Therefore, we sought to determine whether sesamol could reduce fat accumulation in the liver to treat obesity and obesity-associated metabolic disorders. The results showed that livers weight and fat vacuoles in liver sections were obviously reduced, which indicated that sesamol alleviated obesity-associated hepatic steatosis. We also found that serum ALT and AST were decreased by sesamol, and liver TG and LDL-C levels were significantly reduced by sesamol, which suggested that the recovery of liver function benefited from the reduction of hepatic lipid accumulation in the presence of sesamol.

Since the liver is involved in fat synthesis, lipolysis, and oxidation (30, 31), we next investigated whether sesamol could directly regulate hepatic lipid metabolism regulators to reduce lipid accumulation in the whole body, which further clarified the mechanism of sesamol in anti-obesity. It is well-known that lipogenesis is transcriptionally regulated by SREBP-1c, which is a critical transcription factor and stimulates the expression of lipogenic enzymes involved in lipid synthesis in the liver (32). In this study, we found higher expression of SREBP-1c in the liver of obese mice, and sesamol markedly down-regulated SREBP-1c expression level. Given previous studies have demonstrated that decreasing lipid synthesis in the liver ameliorated obesity and hepatic steatosis (33, 34), we

believed that sesamol might reduce fat accumulation in the whole body by reducing fat synthesis in the liver of obese mice.

Except for a decrease in fat synthesis, the reduction of fat accumulation in the liver might also be contributed by an increase in lipolysis. Thus, we detected the expression of HSL in the liver. It is well-known that HSL, a rate-limiting enzyme for TG decomposition, needs to be phosphorylated for lipolysis (35, 36). Furthermore, it has been proved that HSL-mediated lipolysis can ameliorate hepatic steatosis (37). In our study, sesamol obviously increased p-HSL expression level in the liver, which proved that sesamol could indeed promote lipolysis in the liver.

Furthermore, lipolysis releases FFA that is partly eliminated by β-oxidation, and the rest goes into the blood circulation (38). However, an increase in lipolysis releases excessive FFA that leads to lipotoxicity by impairing cellular signaling and function, which results in decreasing insulin sensitivity (39, 40). In our study, although lipolysis in the liver was enhanced by sesamol, we observed a decrease in serum FFA and improvement in insulin sensitivity, so we hypothesized that sesamol might increase fatty acid β-oxidation in the liver. As is known, fatty acid β-oxidation occurs in mitochondria (41), PGC1α is related to mitochondrial biosynthesis (42, 43), and CPT1α is a key enzyme for fatty acid β-oxidation in the mitochondria, which catalyzes the transport of fatty acid to mitochondrial matrix for oxidation (44, 45). Therefore, we detected the expressions of PGC1α and CPT1α in the liver and found that sesamol up-regulated PGC1α and CPT1α expression levels. These results confirmed that sesamol indeed enhanced fatty acid β-oxidation in the liver.

Our findings demonstrated that sesamol decreased the expression of SREBP-1c and increased the expressions of p-HSL, PGC1α, and CPT1α, which promoted lipid metabolism in the liver to ameliorate obesity and obesity-associated metabolic disorders. Notably, obesity is simultaneously caused by internal (genetic) and external factors (dietary or lifestyle) in some cases, and it was reported that ob/ob mice, a hereditary obesity model caused by genetic mutation, had hepatic steatosis related to the increase of SREBP-1c level and the decrease of PGC1α and CPT1α levels in the liver (46–48). Considering the positive effects of sesamol on these proteins in the liver of HFD-induced obese mice, we suspect that these effects could be expected in ob/ob mice. In future research, we would further determine the therapeutic effect of sesamol on obesity in ob/ob mice. Moreover, in this study, we chose mice to be the experimental subject in line with numerous studies about lipid metabolism in obesity state (5, 49); however, the results in animal experiments do not necessarily reflect the situation in

human beings. Therefore, incorporating in vivo and in vitro experiments that we would like to perform using human hepatic cell lines, such as HepG2 and L02 cells, will provide a basis for clinical experiments of sesamol in order to develop sesamol as a drug for human obesity treatment in the future.

Conclusions

Collectively, this study revealed that sesamol could ameliorate obesity and obesity-associated metabolic disorders through regulating hepatic lipid metabolism, including decreasing lipogenesis and increasing lipolysis and fatty acid β-oxidation in the liver of obese mice. Our results suggested that sesamol might serve as a versatile drug to treat obesity.

Author contributions

H.Q., J.H.C., and H.Y.X. conceived, designed, and performed the experiments. H.Q. and H.Y.X. wrote the manuscript. L.Y. and L.N.Y. contributed to the discussion and revised the manuscript. C.L. analyzed the data. All authors approved the final manuscript.

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