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# Tetrahydropalmatine Prevents High-Fat Diet-Induced Hyperlipidemia in Golden Hamsters (*Mesocricetus Auratus*)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** Hyperlipidemia is a major cause of atherosclerotic cardiovascular disease. Tetrahydropalmatine (THP) can exhibit hepatoprotective, anti-arrhythmic, and anti-inflammatory activities. The mechanism of THP on the hyperlipidemia remains unknown; therefore, the present study explored the role of THP in hyperlipidemia.

**Material/Methods:** We established an animal model of hyperlipidemia by high-fat diet (HFD) feeding. Blood samples were obtained for determination of serum cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), pro-inflammatory cytokines, and CYP7A1 expression. Histology was performed and inflammation was detected in the liver using hematoxylin-eosin (HE) staining and enzyme-linked immunosorbent assay (ELISA), respectively. The mRNA and protein levels of TLR4 and TRAF-6 were determined by quantitative real-time PCR (qPCR) and Western blot, respectively.

**Results:** THP suppressed hepatic lipid accumulation and reduced serum levels of TC, TG, LDL-c, and HDL-c in HFD-fed golden hamsters. THP increased cholesterol 7 α-hydroxylase (CYP7A1) expression and prevented inflammation by the limited reduction in interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) expressions in serum and liver. THP slightly increased the ratio of the body/liver weight. THP inhibited the mRNA and protein levels of Toll-like receptor 4 (TLR4) and TNF-receptor associated factor-6 (TRAF-6).

**Conclusions:** These results suggest that THP attenuates hyperlipidemia by multiple effects, including hepatoprotective and anti-inflammatory effects. Moreover, THP also suppressed the expressions of TLR4 and TRAF-6 in golden hamsters.

**MeSH Keywords:** Anti-Inflammatory Agents • Hyperlipidemias • Tetrahydropapaveroline

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## Background

Hyperlipidemia, a major cause of cardiovascular disease, is a common disturbance of lipid metabolism, which appears as increased blood total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-c), as well as reduced high-density lipoprotein cholesterol (HDL-c) [1]. Moreover, hyperlipidemia induced by high-fat diet (HFD) is reported to result in non-alcoholic fatty liver disease (NAFLD) [2], which is characterized by deposition of fat in the liver. As a metabolic hazard, hyperlipidemia plays an important role in cardiovascular and cerebrovascular diseases involving formation of atheromatous plaques [3].

Multiple animal species can be used as models to mimic hyperlipidemia in humans. Rats and mice have good tolerance to cholesterol, so they are not suitable for the establishment of hyperlipidemia [4]. Rabbits were originally used for establishing a hyperlipidemia model, but rabbits are herbivores and are thus unsuited for an animal fat diet [5]. Golden hamsters has been used to establish a hyperlipidemia model in recent years [6,7]; therefore, we chose golden hamsters to establish the hyperlipidemia model in the present study.

Cholesterol 7α-monooxygenase or cytochrome P450 7A1 (CYP7A1) is a rate-limiting enzyme that metabolizes cholesterol to bile acid via the classic pathway [8]. Recently, CYP7A has been regarded as a critical feature in lipid regulation and was reported to be involved in the prevention and treatment of diseases caused by lipid metabolism [9]. A previous study revealed that a long-term HFD may cause obesity accompanied by low level of systemic inflammation in animals [10]. Moreover, adipose tissue has been reported as the primary source of pro-inflammatory factors and can exert a crucial effect on inflammation and metabolic dysfunction [11,12].

Toll-like receptors (TLRs) are reported to play an important role in regulation of innate and adaptive immune responses and are related to inflammatory liver diseases [13]. TLR4, a critical transmembrane recognition receptor, is associated with development of non-alcoholic steatohepatitis [14,15]. Tumor necrosis factor receptor-associated factor-6 (TRAF-6) is a key downstream target of TLR pathways [16]. TRAF6 has been reported to activate and translocate nuclear factor-kappa B/p65 (NF-κB) from cytoplasm to nucleus, thus leading to increased levels of pro-inflammatory cytokines [17,18].

Several drugs, such as fibrates and statins, are revealed to effectively and rapidly lower lipid levels. However, the pesticide effects are limited due to the potential side effects, individual differences of hyperlipidemia patients, and drug addiction [19]. Recently, plant extracts have been confirmed to have minor adverse responses and various targets for the prevention and treatment of hyperlipidemia [20]. Tetrahydropalmatine (THP), an alkaloid extracted from the plant *Corydalis yanhusuo*, has been found to exert hepatoprotective, anti-inflammatory, anti-oxidant, anti-nociceptive, anti-coagulant, antiviral, anti-hyperalgesic, and anti-arrhythmic properties [21,22]. Additionally, THP has been indicated to be a neuroprotective agent that exerts multiple favorable effects on the nervous system [23–26]. However, the effect of THP on hyperlipidemia remains poorly understood and reports are rare. Therefore, we explored the potential mechanism of THP in hyperlipidemia in golden hamsters.

## Material and Methods

### Animals and ethics statement

Male golden hamsters (7 weeks old) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). Hamsters were acclimatized for 1 week before feeding with HFD, with free access to water and food. All the related animal experiments were approved by the Animal Care and Use Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University.

### Materials

THP was obtained from Institute of Chinese Materia Medica, Chinese Academy of Medical Sciences (Beijing, China). Fenofibrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). The common diet was provided by Zhejiang Medical College (Hangzhou, China). Commercial kits for the detections of TG and TC were obtained from Abbott Laboratories (Chicago, USA) and HDL-c and LDL-c were purchased from Biosino Biotechnology and Science (Beijing, China). Enzyme-linked immunosorbent assay (ELISA) kits for the quantitation of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and CYP7A1 were obtained from Meibiao Bioscience Co., Ltd. (Yancheng, China). Trizol reagents were purchased from ComWin Biotech (Beijing, China). PrimeScript™ RT reagent kit and SYBR Green qPCR kit were purchased from Takara (Dalian, China). RIPA lysis buffer was obtained from Beyotime (Shanghai, China). BCA protein assay kits were purchased from Solarbio (Beijing, China). Antibodies used for Western blot analysis were anti-TLR4 (Proteintech, Chicago, IL, USA), anti-TRAF6 (Affinity Biosciences Inc., Amherst, NH), and β-actin (Huaan Biotechnology, Hangzhou, China) and secondary antibodies were obtained from Huaan Biotechnology (Hangzhou, China). All primers were synthesized by Sangon Biotech Co., Ltd. (Shanghai, China).





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### Animals model and diet

After acclimatization, the hamsters were randomized into 6 groups: a control group (n=8), an HFD group (n=8), a positive-control group (fenofibrate, 100 mg/kg/day) (n=8), and 3 THP-treated groups (6.3, 12.6 and 25.2 g/kg/day) (n=8). The control group was fed standard feed. The other groups were given the HFD (containing 10% lard, 5% custard powder, 2% cholesterol, and 0.5% bile salt) for another 2 weeks. The 4 drug treatment groups were given the same high-fat diet and dosed daily via intragastric gavage with 6.3, 12.6, and 25.2 g/kg/day THP or 100 mg/kg/day fenofibrate. The food/water intake and weight were measured at 8 and 9 days, respectively. Fresh blood was collected and settled for 30 min, followed by centrifugation at 3000 rpm for 10 min. The supernatant was collected for serum TG, TC, HDL-c, LDL-c, and pro-inflammatory cytokines determination. After 6 weeks of treatment, the animals were sacrificed and we determined the ratio of body/liver weight. Histology, ELISA, quantitate real-time PCR, and Western blot analysis were performed on liver samples.

### Histology

Liver tissues were fixed in phosphate-buffered formaldehyde solution for 48 h at room temperature. Thereafter, samples were incubated in 70% ethanol, then were dehydrated and embedded in paraffin and sections of the tissue were stained with hematoxylin-eosin (HE). Images of HE-stained sections were captured with an inverted fluorescence microscope (Nikon Eclipse TI-SR, Nikon Corporation, Japan) with a digital camera (DS-U3; Nikon, Japan).

### Detection of biochemical indicators

Biochemical factors including serum and hepatic levels of TC, TG, HDL-c and LDL-c were determined using an automatic biochemical analyzer (Abbott Laboratories, North Chicago, IL, USA)

### Measurement of inflammatory cytokines by ELISA

The levels of IL-6 and TNF-α were detected according to the manufacturer's protocol. Briefly, samples were seeded and incubated for 2 h at room temperature. Then, the antibodies were added for another 2 h at room temperature, and the working dilution of streptavidin-HRP was added and incubated for 20 min at room temperature, followed addition of stop solution. The optical density was measured at 450 nm on a microplate reader (Thermo Scientific, Pittsburgh, PA).

### RNA extraction, cDNA synthesis, and quantitative real-time PCR (qPCR)

Total RNA of liver tissues was isolated using Trizol extraction reagent. Briefly, liver tissues were homogenized in 700 µL Trizol reagent followed by addition of 300 µL chloroform. Then, the samples were mixed for 5 min. After centrifugation (12 000 g for 15 min at 4°C), the supernatant was carefully drawn into a new tube. An equal volume of isopropyl alcohol was added and incubated at room temperature for 20 min. Following the centrifugation (12 000 g at 4°C for 10 min), the supernatants were removed completely and the precipitate was washed twice with 75% ethanol. Finally, nuclease-free DEPC water was added to elute the RNA. The concentration and purity were detected by Shimadzu UV-2550 UV-visible spectrophotometer (Suzhou, China). The cDNA (totally 20 µL) was obtained by 1 µg RNA according to the kit protocol. The RNA was incubated with M-mlv, 5× RT Buffer, RnaseA inhibitor, OligdT, and dNTP at 42°C for 45 min followed by 70°C for 10 min. The expressions of TLR4 (forward: 5'-CTC AGA GAG AGC CAG TGG AA-3' and reverse: 5'-GGA GCA TTA GTG AAC CCT CG-3'); TRAF-6 (forward: 5'-CAA CTT GTC AGC CCT CCT TT-3' and reverse: 5'-TGG AAG AAT AGC CAG TGC TCT-3') and GAPDH (forward: 5'-AAC AGG GTG GTG GAC CTC AT-3' and reverse: 5'-TGC TCT CAG TAT CCT TGC TG-3') were conducted in the CFX-96 Touch Thermocycler (Bio-Rad, Hercules, CA) with the following conditions: 94°C for 1 min, 40 cycles of 95°C for 10 s, 58°C for 10 s and 72°C for 10 s. GAPDH served as a reference gene and the data were analyzed by the $2^{-\Delta\Delta Ct}$ method.

### Western blot

Liver tissues were washed by phosphate-buffered saline (PBS) and lysed. Then, the lysates were incubated on ice for 30 min and oscillated for 30 s. After centrifugation (10 000 g for 30 min at 4°C), the supernatant was obtained and the protein concentrations were determined by use of a bicinchoninic acid (BCA) kit. After sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), the separated proteins were transferred onto polyvinylidene difluoride membranes (GE Healthcare, Little Chalfont, United Kingdom). After blocking for 1 h, the membranes were incubated overnight at 4°C with following primary antibodies: TLR4 (1: 100), TRAF6 (1: 500), and β-actin (1: 500). The membranes were then incubated with secondary antibodies (1: 3000). The bands were determined by use of the Molecular Imager VersaDoc MP 5000 System (Bio-Rad, Hercules, CA). The densitometry was determined with Quantity One software (Bio-Rad).

### Statistical analysis

Data are expressed as mean ±SD and were assessed by one-way ANOVA followed by Newman-Keuls test using GraphPad





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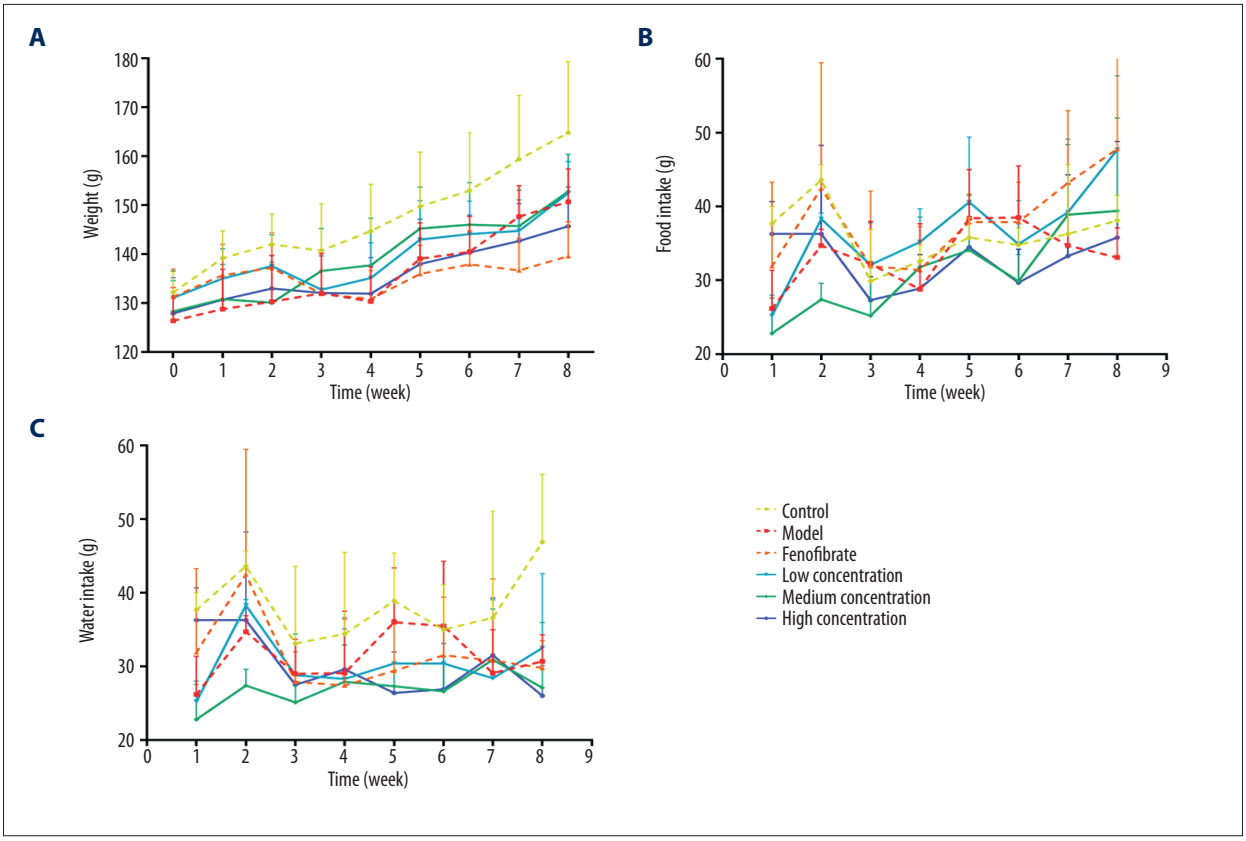


**Figure 1.** Effect of THP on weight gain, food consumption, and water intake. (**A**) The weights of golden hamsters in each group from 0 to 8 weeks. (**B**) The food consumptions of golden hamsters in each group from 1 to 8 weeks. (**C**) The water intake of golden hamsters in each group from 1 to 8 weeks.

Prism 5 software (San Diego, CA, USA). A value of $p<0.05$ was considered different significantly.

## Results

### Effect of THP on the HFD-induced weight, food consumption, and water intake

The weights of hamsters fed regular chow in the control group were increased by approximately 24.7% during the 8 weeks while those in model group were increased by nearly 19.2%. Moreover, after the drug treatment, the weights of hamsters in the fenofibrate group and the 3 THP groups improved more slowly than those in the model group. Weights of hamsters in the fenofibrate, low, medium, and high concentration of THP groups were increased by 2.2%, 11.8%, 16.9%, and 9%, respectively, which were less than those in the model group (Figure 1A). Moreover, the differences in food and water intake among all groups were not obvious (Figure 1B, 1C).

### THP alleviated the HFD-induced hepatic adipose infiltration

Livers from hamsters in each group at the end of the eighth week were analyzed by light microscopy (Figure 2). Long-term HFD caused inflammation, steatosis, and necrosis in the model group, but these pathological changes were markedly inhibited by fenofibrate and by medium and high concentrations of THP in the liver. Both size and number of lipid inclusions were significantly decreased in the livers of drug-treated hamsters.

### THP improved HFD-induced hyperlipidemia

The levels of serum TC were remarkably increased by HFD ($p<0.01$). However, the high serum TC levels were significantly reduced by fenofibrate and THP (Figure 3A). Moreover, the changes of serum TG and LDL-c were similar to the trend of TC (Figure 3B, 3C). The HFD-induced high HDL-c concentrations were also suppressed by THP, although HDL-c levels were increased slightly after fenofibrate treatment (Figure 3D). However, THP slightly inhibited the levels of TNF-α and IL-6 induced by HFD and enhanced CYP7A1 expression in a dose-dependent manner (Figure 3E–3G).





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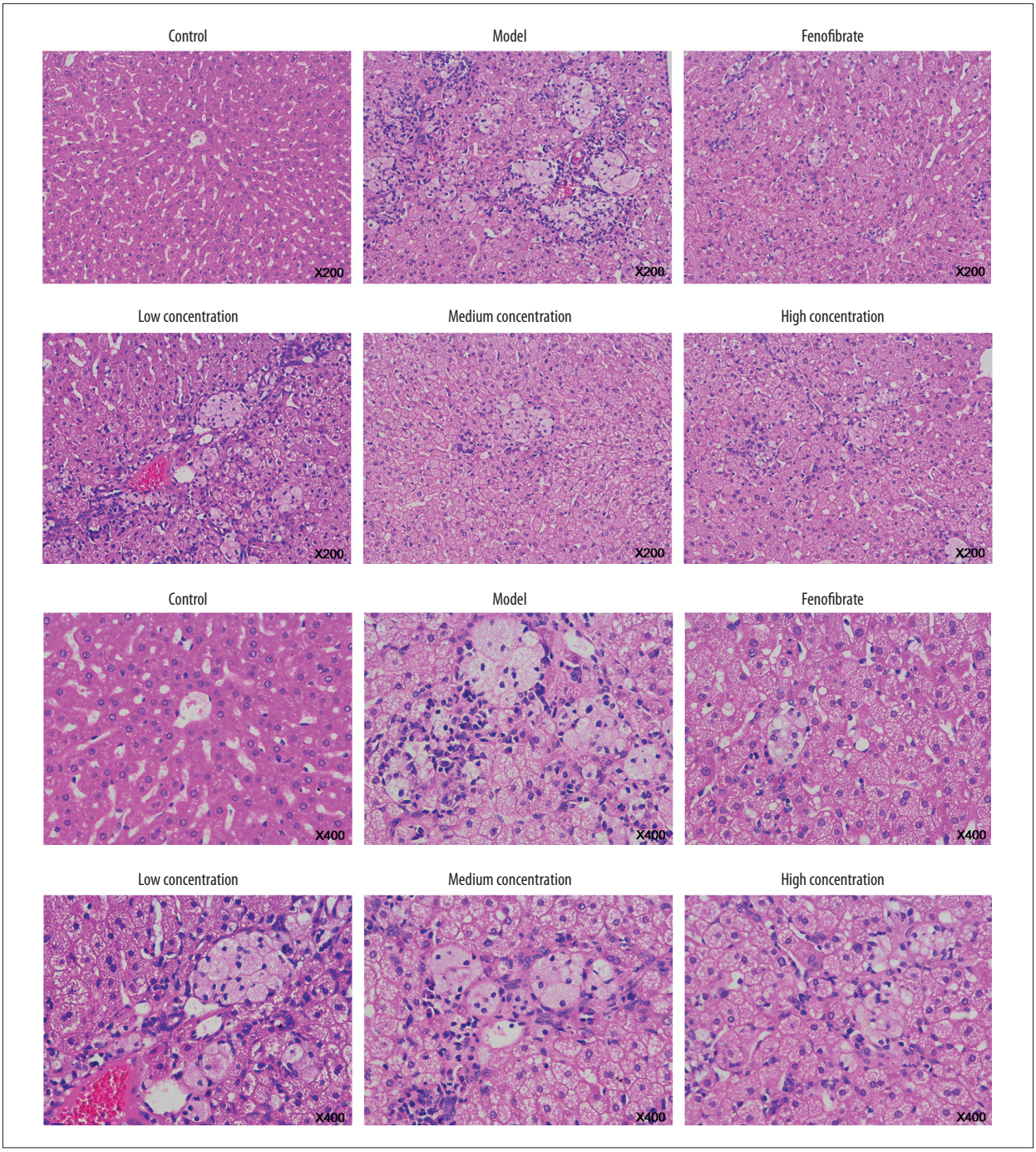


**Figure 2.** HE staining of liver tissues from HFD-induced hyperlipidemic golden hamsters under light microscope (×200 and ×400). Lipid obviously accumulated in the livers from golden hamsters in the model group according to the presence of circular lipid droplets in the HE-stained sections, but the pathological changes were reduced in drug-treated animals.





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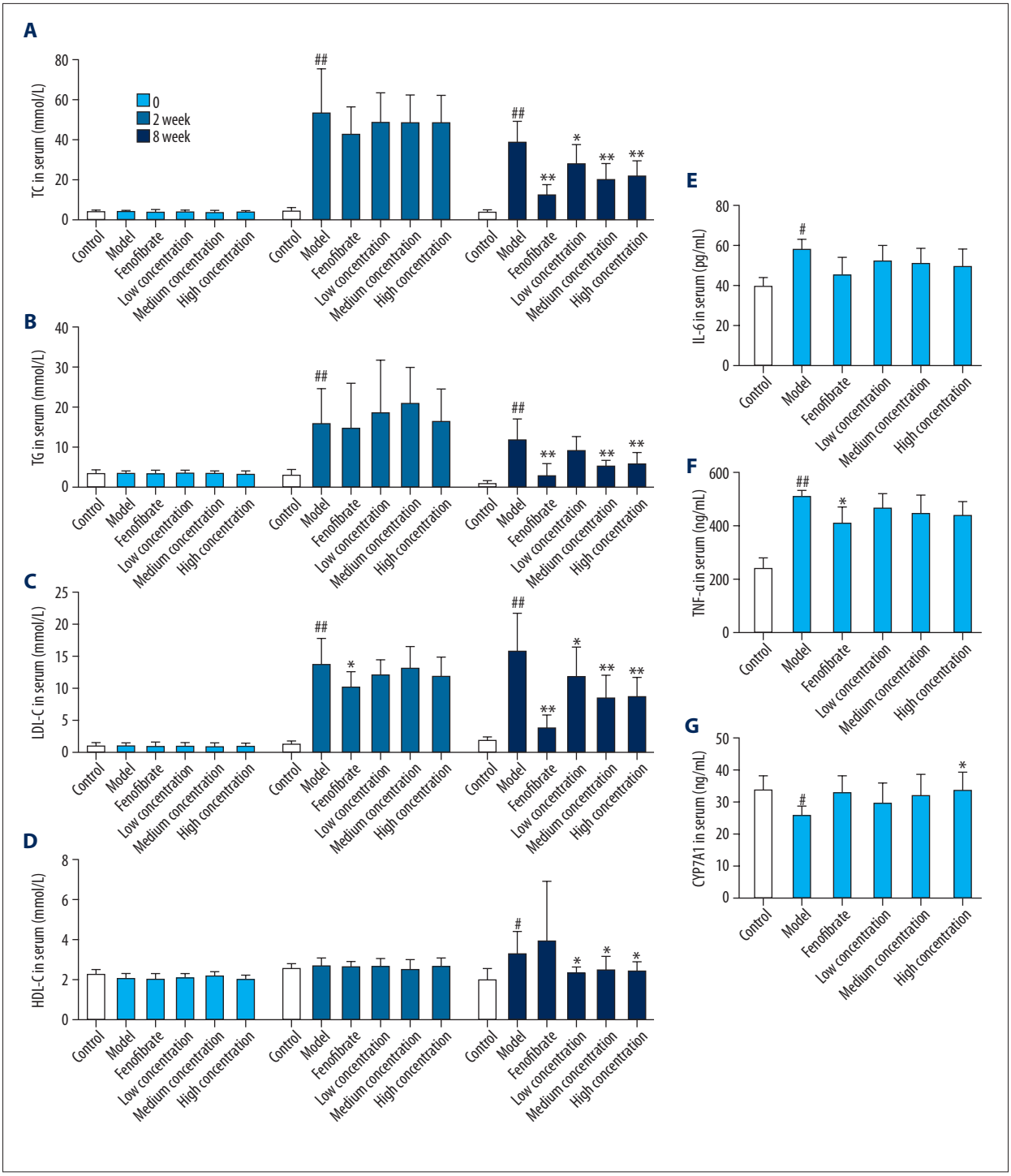


**Figure 3.** Effects of THP on the lipid metabolism and inflammation in the serum. The THP decreased the levels of (**A**) TC, (**B**) TG, (**C**) LDL-c, and (**D**) HDL-c in the serum. The serum (**E**) IL-6 and (**F**) TNF-α levels were slightly reduced while the serum (**G**) CYP7A1 expression was improved by THP. # $P<0.05$, ## $P<0.01$ versus control group, * $P<0.05$, ** $P<0.01$ versus model group.





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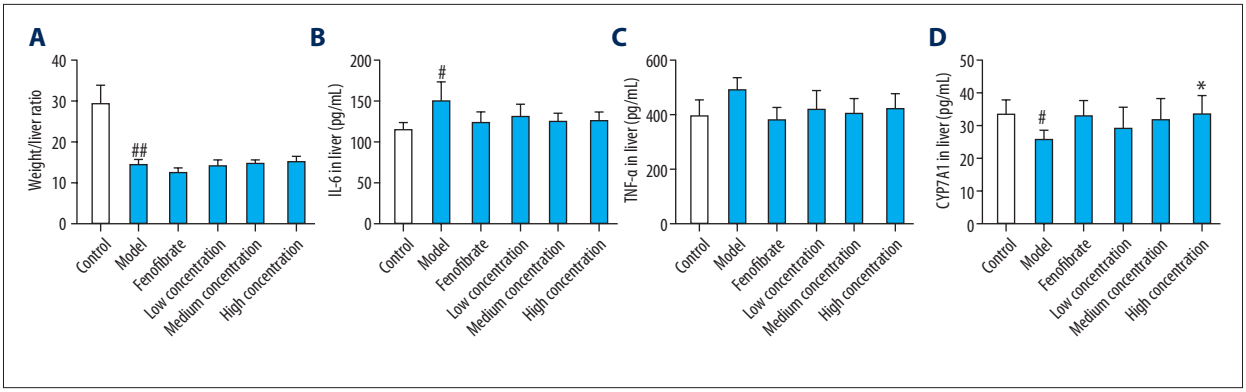


**Figure 4.** Effects of THP on livers from golden hamsters. (**A**) The decreased ratios of body/liver weight were slightly improved by THP. The levels of hepatic (**B**) IL-6 and (**C**) TNF-α were slightly reduced while the hepatic (**D**) CYP7A1 expression was improved by THP. # $P<0.05$, ## $P<0.01$ versus control group, * $P<0.05$ versus model group.

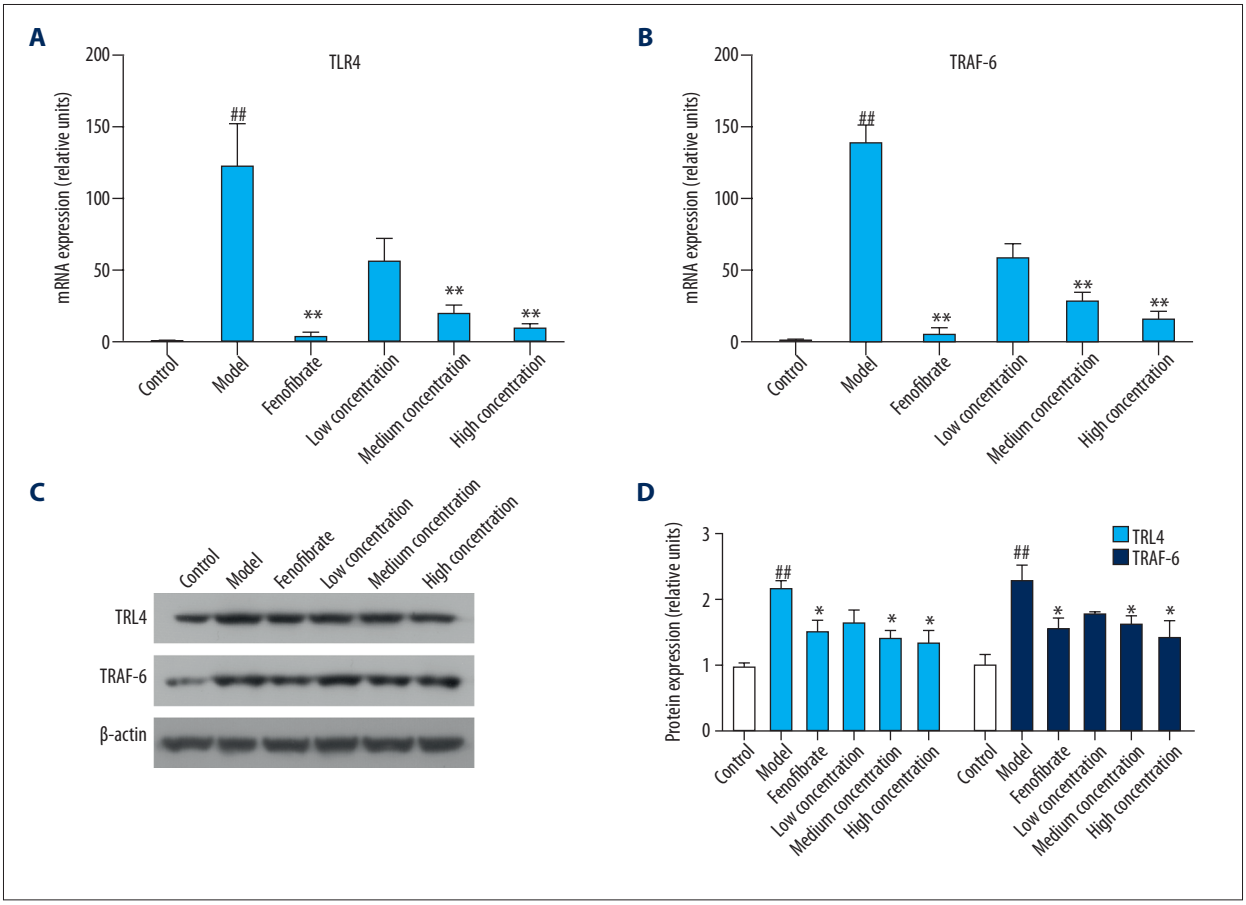


**Figure 5.** THP inhibited the expressions of TLR4 and TRAF-6. The high mRNA expressions of (**A**) TLR4 and (**B**) TRAF-6 induced by HFD were decreased by THP. (**C**) Western blot results showed that the HFD-induced protein levels of TLR4 and TRAF-6 were suppressed by THP. ## $P<0.01$ versus control group, * $P<0.05$ versus model group.





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### Effect of THP on the livers of golden hamsters

HFD markedly inhibited the body/liver weight ratio while THP has almost no effect on the ratio (Figure 4A). Moreover, the hepatic expression pattern of TNF-α and IL-6 was similar to that in serum (Figure 4B, 4C) and THP upregulated the CYP7A1 expression in a concentration-dependent manner in the liver (Figure 4D).

### THP suppressed the expressions of TLR4 and TRAF-6

The HFD evidently increased the mRNA levels of TLR4 and TRAF-6 but the expressions were inhibited by THP in a dose-dependent manner (Figure 5A, 5B). The HFD-induced protein levels of TLR4 and TRAF-6 were also decreased by medium and high concentrations of THP (Figure 5C).

## Discussion

The liver maintains a stable environment through regulating the synthesis and decomposition of carbohydrate, lipid, and protein [27]. In this study, we found that THP improved HFD-induced hyperlipidemia in golden hamsters. THP reduced the serum and hepatic levels of TC, TG, and LDL-c. These results proved that THP protected against the HFD-induced hyperlipidemia. However, the level of HDL-c was increased compared to in the control group. The increased HDL-c level may be a protective response of animals to HFD treatment. When the animals were treated by THP, this response was blunted. Additionally, THP slightly inhibited the pro-inflammatory factors and evidently enhance the CYP7A1 expression in serum and liver. Furthermore, THP suppressed the mRNA and protein expressions of TLP4 and TRAF-6 in the livers of golden hamsters.

Fatty liver is a common pathology of excessive fat deposition in hepatocytes induced by multiple diseases [28,29]. It has been demonstrated that long-term HFD results in lipid deposition, hyperlipidemia, and NAFLD [30]. In our study, HFD had little effect on the appetite of the golden hamsters and THP inhibited the weight gain, attenuated the HFD-induced fatty liver, and reduced the TC, TG, and LDL-c levels in liver and serum. Interestingly, THP obviously inhibited the HDL levels of hamsters, which is similar to human LDL due to the different blood lipid spectrum [31]. The results suggest that THP reduces cholesterol and lipid levels. HFD also results in the down-regulation of CYP7A1, which can initiate cholesterol catabolism and bile acid synthesis [32]. Furthermore, the increased CYP7A1 expression caused by high concentrations of THP may decrease the hepatic free cholesterol, which conversely reduces blood cholesterol levels by stimulating LDL receptor expression to bind with LDL [33]. The decreased levels of serum and hepatic cholesterol in DHP-treated groups might be associated with improved CYP7A1 expression.

HFD can trigger systemic and hepatic inflammation, activate hepatic NF-κB, and induce insulin resistance in mice [34]. Our study found that HFD significantly increased the levels of IL-6 and TNF-α in serum and liver. However, THP slightly reduced the levels of IL-6 and TNF-α, suggesting that THP might be not mainly involved in the release of IL-6 and TNF-α. Additionally, HDL exerts an important anti-inflammatory effect and can suppress hepatic inflammation in mice fed an HFD [34,35]. Therefore, we assumed the low HDL-c level in golden hamsters might lead to the increased IL-6 and TNF-α levels, while THP has a finite effect on these pro-inflammatory cytokines, but this requires further study. We also found that HFD led to increased liver weight and significantly decreased the ratio of body/liver weight. Moreover, THP improved the ratios in a dose-dependent manner, indicating that THP might play a role in fatty liver disease.

To explore whether THP was associated with inflammation, we assessed the expressions of TLR4 and TRAF-6. TLR4, which is expressed in hepatocytes, can alter hepatic lipid metabolism in obesity [36]. It was reported that deficiency of TLR4 alleviates obesity-induced hepatic steatosis and inflammation in mice [37]. The activated myeloid differentiation primary-response protein 88 (MyD88), a downstream effector of TLR4, can recruit TRAF-6 and TGF-β-activated kinase 1 (TAK1) to translocate NF-κB from cytoplasm to nuclei, leading to the generation of pro-inflammatory factors [38]. In the present study, the mRNA and protein levels were sharply increased by HFD, and THP inhibited the TLR4 expression in a dose-dependent manner. Similarly, THP reduced the high TRAF-6 level increased by HFD, suggesting that TLR4 and TRAF-6 are involved in HFD-induced hyperlipidemia in the golden hamsters.

## Conclusions

Our study demonstrates that THP exerts a critical effect in HFD-induced hyperlipidemic hamsters. THP enhanced the expression of CYP7A1 and inhibited the levels of TC, TG, LDL-c, and HDL-c. Pro-inflammatory factors were slightly inhibited by THP while the levels of TLR4 and TRAF-6 were suppressed by THP in a concentration-dependent manner. Hence, our results suggest that THP is a n effective natural agent for use in treatment of hyperlipidemia.

### Conflict of interest

None.





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