

Article

Anti-Obesity Effects of a Standardized *Prunus persica* Flower Extract (HT099) Through the Regulation of Lipid Metabolism in High-Fat Diet-Induced Obese Mice

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Abstract

Background: Obesity is one of the most prevalent metabolic disorders worldwide, and its long-term management remains challenging due to the limited efficacy and adverse effects of current pharmacological treatments. Accordingly, there is growing interest in safe and effective anti-obesity strategies based on natural compounds. This study aimed to evaluate the anti-obesity effects of HT099, an extract derived from *Prunus persica* (peach blossom), and to investigate molecular changes associated with its metabolic effects in a high-fat diet (HFD)-induced obesity mouse model. **Methods:** Male C57BL/6N mice were fed an HFD and orally administered HT099 (50 or 100 mg/kg) or the positive control orlistat (40 mg/kg) for 12 weeks. Body weight, adipose tissue accumulation, food efficiency ratio, glucose tolerance, serum lipid profiles, and hepatic gene expression related to lipid metabolism were evaluated. **Results:** HT099 supplementation significantly attenuated body weight gain and reduced white adipose tissue accumulation while improving food efficiency ratio. HT099 also ameliorated HFD-induced glucose intolerance and favorably modulated serum lipid profiles, including reduced triglyceride levels, increased HDL-cholesterol levels, and improved non-HDL cholesterol indices. At the molecular level, HT099 administration was associated with an increased hepatic AMPK α 1 mRNA expression and decreased expression of adipogenic and lipogenic genes, including C/EBP α , PPAR γ , FAS, and SREBP-1c. **Conclusions:** These findings indicate that HT099 exerts anti-obesity effects in HFD-induced obese mice, accompanied by improvements in lipid and glucose metabolism and changes in adipogenesis- and lipogenesis-related gene expression. Collectively, the results support the potential of HT099 as a natural bioactive agent for obesity management.

Keywords: obesity; *Prunus persica* (peach blossom); HT099; adipogenesis; lipid metabolism; high-fat diet (HFD)

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1. Introduction

Obesity has emerged as one of the most serious public health challenges of the 21st century, with its prevalence increasing rapidly across all age groups, ethnicities, and socio-economic strata [1]. Large-scale epidemiological studies, including the Global Burden of Disease (GBD) 2021 analysis, have consistently demonstrated a continuous rise in adult overweight and obesity prevalence across most regions worldwide over recent decades, underscoring obesity as a major and ongoing global public health burden [2,3].

Although several pharmacological agents are available for obesity management, their long-term clinical utility remains limited due to adverse effects and poor treatment adherence. For example, glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide (Wegovy) have demonstrated substantial short-term weight reduction; however, significant weight regain has been reported following treatment discontinuation [4]. Similarly, sympathomimetic agents such as phentermine are associated with undesirable side effects, including cardiovascular and central nervous system symptoms, which restrict their long-term use [5,6]. These limitations highlight the need for alternative strategies that are more suitable for long-term obesity management.

In this context, natural compounds have attracted increasing attention as alternative or complementary approaches for obesity prevention and management, as they often exert broad metabolic effects while maintaining favorable safety profiles. Unlike single-target pharmacological agents, bioactive compounds derived from natural sources may influence multiple biological processes related to adipogenesis, lipid metabolism, and glucose homeostasis, which is particularly relevant for complex metabolic disorders such as obesity.

The flowers of *Prunus persica* (L.) Batsch, commonly referred to as “Do-hwa” in traditional Korean and Chinese medicine, have long been consumed as herbal teas and utilized for various health-related purposes. Classical medical texts, including Donguibogam [7] and Ben Cao Gang Mu [8], describe *P. persica* flowers as remedies for promoting circulation, alleviating constipation, regulating body fluids, and reducing edema. These historical records suggest a traditional association between *P. persica* flowers and metabolic or fluid homeostasis.

Consistent with these traditional uses, previous experimental studies have reported that *P. persica* flower extracts reduced body weight gain, abdominal fat accumulation, serum glucose levels, and hepatic enzyme activities in high-fat diet (HFD)-induced obesity models [9]. However, the specific molecular mechanisms and the efficacy of a standardized formulation have not been fully characterized.

In the present study, we evaluated the anti-obesity effects of HT099—an extract standardized for chlorogenic acid and enriched through enzymatic hydrolysis—in an HFD-induced obesity mouse model to investigate its impact on adipogenesis and lipid metabolism. We investigated changes in body weight, adipose tissue accumulation, glucose tolerance, serum lipid profiles, and the expression of genes related to adipogenesis and lipid metabolism. Our findings show that HT099 supplementation attenuated body weight gain and adipose tissue accumulation and was accompanied by improvements in glucose tolerance and serum lipid profiles, along with changes in adipogenic and lipogenic gene expression. Collectively, these results suggest that HT099 may represent a promising natural bioactive agent for obesity management.

2. Materials and Methods

2.1. Preparation of HT099

The dried flowers of *Prunus persica* (L.) Batsch (flower; origin: Zibo City, Shandong Province, China; harvest period: April–June 2025) were obtained from a commercial supplier. The plant material was botanically authenticated by Prof. Hocheol Kim based on morphological examination and DNA-based genetic analysis, and a voucher specimen (No. NMD202506PPB-1) was deposited at Neumed. The dried flowers of *Prunus persica* were subjected to a two-step extraction process. Briefly, the plant material was extracted with water at 95 ± 5 °C for 2 h, followed by a second extraction under the same conditions for an additional 2 h. The combined extracts were filtered and concentrated under reduced pressure. The concentrate was subsequently fractionated using a resin, after which the reaction mixture was adjusted to pH 3.0. β -D-glucosidase (Plantase C150P; Bision, Seoul, Republic of Korea) was then added at 3% (*w/w*, based on the solid content of the concentrate) to induce enzymatic hydrolysis at 40 °C for 15 h under continuous stirring. No buffer or additional additives were used. The enzymatic reaction was terminated by heating at 90 °C for 30 min to inactivate the enzyme. Finally, dextrin was added as a carrier (10%), and the solution was spray-dried to obtain the powdered form of HT099. Thus, the spray-dried HT099 powder contained 90% (*w/w*) HT099 extract solids and 10% (*w/w*) dextrin.

2.2. High-Performance Liquid Chromatography (HPLC) Analysis of Standardized HT099

For quality control of standardized HT099, chlorogenic acid—a primary marker compound of *Prunus persica* flowers—was quantified using high-performance liquid chromatography (HPLC). Briefly, 50 mg of HT099 powder was dissolved in 10 mL of 50% methanol, sonicated for 10 min, and filtered through a 0.45 μ m syringe filter prior to analysis. HPLC analysis was performed using an Agilent 1260 Infinity system (Agilent Technologies, Santa Clara, CA, USA) equipped with a quaternary pump (G7111A), diode array detector (G7155A), and autosampler (G7129A). Separation was achieved on a ZORBAX Eclipse Plus C18 reverse-phase column (4.6 $\times$ 250 mm, 5 μ m particle size) (Agilent, Santa Clara, CA, USA) maintained at 35 °C.

The mobile phase consisted of solvent A (distilled water containing 0.1% phosphoric acid) and solvent B (acetonitrile). Both solvents were filtered and degassed through a 0.45 μ m membrane filter prior to use. The gradient elution program was as follows: 0–3 min, 5% B; 3–30 min, 5–20% B; 30–35 min, 20–35% B; 35–50 min, 35–40% B; 50–51 min, 40–90% B; 51–56 min, 90% B; 56–57 min, 90–5% B; and 57–62 min, 5% B. The flow rate was maintained at 1.0 mL/min, the injection volume was 10 μ L, and UV detection was performed at 330 nm.

Chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, caffeic acid, p-coumaric acid, ferulic acid, rutin, multiflorin A, multiflorin B, naringenin, and kaempferol reference standards were purchased from Nature Standard (Shanghai, China). All analyses were conducted in triplicate to ensure analytical precision and reproducibility.

2.3. Determination of Total Phenolic Content

The total phenolic content (TPC) of HT099 was determined using the Folin–Ciocalteu colorimetric method and expressed as gallic acid equivalents (GAE).

Gallic acid (approximately 10.0 mg) (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in about 10 mL of distilled water (DW) with vortex mixing to obtain a stock solution (1000 μ g/mL). The stock solution was serially diluted 1:1 (*v/v*) with DW to prepare a set of four working standard solutions for calibration. Sodium carbonate solution (8%, *w/v*) was prepared by dissolving approximately 8.0 g of sodium carbonate (Sigma, Bellefonte, PA, USA) in 100 mL DW.

For sample preparation, approximately 1.5 mg of powdered raw material or HT099 extract was weighed into a microtube, and 1.5 mL of DW was added. The mixture was vortexed thoroughly and sonicated for 10 min to obtain a homogeneous sample working solution. An aliquot of 50 μ L of each gallic acid standard or sample solution was dispensed into wells of a 96-well microplate, followed by the addition of 50 μ L of Folin–Ciocalteu’s phenol reagent (Sigma-Aldrich, St. Louis, MO, USA). After incubation for 5 min at room temperature, 50 μ L of the 8% sodium carbonate solution was added to each well. The plate was then incubated for 1 h at room temperature in the dark, and the absorbance was measured at 765 nm using a microplate reader (BioTek Instruments, Winooski, VT, USA).

A calibration curve was constructed by plotting absorbance at 765 nm versus the gallic acid concentration of the standards. The TPC of each sample was calculated from the calibration curve and expressed as mg GAE/g sample (dry weight).

2.4. Animals and Experimental Design

Male C57BL/6N mice (4 weeks old, $n = 50$) were obtained from Narabio Co. (Seoul, Republic of Korea). Only male C57BL/6N mice were used in this study because they exhibit a stable and reproducible obese phenotype in response to HFD feeding. Female mice show substantial physiological variability due to estrous cycle-related hormonal fluctuations, which can influence adiposity, thermogenesis, food intake, and metabolic outcomes. As the primary aim of this study was to evaluate the anti-obesity efficacy of HT099 rather than sex-specific differences, male mice were selected to minimize hormonal variability and ensure consistency in metabolic parameters. Upon arrival, animals were housed under controlled environmental conditions (22 ± 1 °C, $55 \pm 5\%$ humidity, 12 h light/dark cycle) with ad libitum access to a HFD (D12492, Research Diets, Inc., New Brunswick, NJ, USA) and distilled water. The normal chow diet (D12450B, Research Diets, Inc.) provided 10% of total calories from fat, whereas the high-fat diet (D12492, Research Diets, Inc.) provided 60% of total calories from fat, according to the manufacturer’s specifications. All animals underwent a 7-day acclimatization period before the start of the experiment. All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Neumed Inc. (Approval No. KISTEM-IACUC-2022-002) and were conducted in accordance with the guidelines for the care and use of laboratory animals. Following acclimatization, mice were randomly divided into five groups ($n = 10$ per group) based on body weight (average ~ 17 g). The group size of $n = 10$ per group was determined with reference to previous studies using HFD-induced obesity mice, in which group sizes of 8–10 animals were sufficient to detect significant metabolic and physiological changes. Therefore, $n = 10$ was selected as an appropriate and commonly accepted group size for this experimental model.

1. Normal control (NC, fed normal chow; D12450B, Research Diets, Inc.);
2. HFD control (HFD-DW);
3. Orlistat 40 mg/kg (OS 40) (CKD Pharm, Chong Kun Dang Pharmaceutical, Cheonan, Republic of Korea);
4. HT099 50 mg/kg (HT-L);
5. HT099 100 mg/kg (HT-H).

The dose levels used in this study (50 and 100 mg/kg) were selected based on preliminary experiments conducted prior to the main study. In these pilot studies, multiple doses of HT099 were tested to identify a range that produced metabolic effects without signs of adverse responses. The 50 and 100 mg/kg doses were therefore chosen as effective and well-tolerated concentrations for evaluating the anti-obesity efficacy of HT099 in HFD-induced obese mice. All groups except NC continued on the HFD for 12 weeks.

Treatments were administered orally once daily, while NC and HFD-DW groups received distilled water. Body weight was recorded twice weekly, and food intake was measured three times weekly throughout the study. After 12 weeks, glucose tolerance testing (GTT) and computed tomography (CT) imaging were performed. Mice were fasted overnight before sacrifice at week 13 under humane conditions. Immediately after sacrifice, the liver and individual white adipose tissue depots (epididymal, mesenteric, subcutaneous, perirenal, and retroperitoneal fat) were carefully dissected, cleared of surrounding connective tissue, and weighed promptly using a calibrated analytical microbalance. All organ weights were recorded as wet weights.

2.5. Calculation of Food Efficiency Ratio (FER)

The food efficiency ratio (FER) is a commonly used index in rodent obesity models that quantifies the relationship between food intake and body weight gain, reflecting metabolic efficiency and obesity progression [10–12].

$$\text{FER (\%)} = (\text{Total body weight gain (g)} / \text{Total food intake (g)}) \times 100$$

2.6. Serum Biochemical Analysis

Blood samples collected at sacrifice were centrifuged to obtain serum. Serum triglycerides (TG), total cholesterol (TC), and HDL cholesterol (HDL-C) were measured using FUJI DRI-CHEM SLIDE kits and a FUJI DRI-CHEM NX700 analyzer (Fujifilm, Tokyo, Japan). Non-HDL cholesterol was calculated by subtracting HDL-C from TC.

2.7. Intraperitoneal Glucose Tolerance Test (ipGTT) Procedure

To evaluate the effects of HT099 on glucose metabolism, an intraperitoneal glucose tolerance test (ipGTT) was conducted at week 13, following 12 weeks of treatment. A glucose solution (2 g/kg body weight) was prepared in sterile saline and administered intraperitoneally. Mice were fasted for 4–6 h prior to the test to stabilize baseline glucose levels.

Blood glucose was measured from tail vein blood using a portable glucometer (Handok, Eumseong, Republic of Korea) at 0, 30, 60, 90, and 120 min after glucose injection. Tests were performed under constant environmental conditions (22 ± 1 °C, consistent illumination), and body temperature was maintained using a heating pad. All sampling and measurements were performed by the same investigator to minimize variability.

The area under the glucose curve (AUC, 0–120 min) was calculated using the trapezoidal rule in GraphPad Prism (GraphPad Software, San Diego, CA, USA). This method is a standardized approach for quantifying glucose tolerance and insulin sensitivity in rodent models [13–15].

2.8. Gene Expression Analysis

To investigate the molecular effects of HT099 on lipid metabolism, gene expression analyses were performed using hepatic and interscapular brown adipose tissue (iBAT) samples. Total RNA was extracted from tissues, and complementary DNA (cDNA) was synthesized using a commercial reverse transcription kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. The sequences and annealing temperatures of all primer sets used for amplification are provided in Table 1 [16–22].

Table 1. Primer sequences and annealing temperatures used for qPCR analysis. Forward and reverse primer sequences, target genes, and annealing temperatures employed for gene expression analysis in hepatic and brown adipose tissues.

Genes	Sets	Sequences (5'→3')	Annealing Tem.
ACO (<i>acox1</i>)	Forward	GTGCAGCTCAGAGTCTGTCCAA	59 °C
	Reverse	TACTGCTGCGTCTGAAAATCCA	
AMPK α 1 (<i>prkaa1</i>)	Forward	CTCTATGCTTTGCTGTGTGG	55.9 °C
	Reverse	GGTCCTGGTGGTGTTCCTGTG	
C/EBP α (<i>cebpa</i>)	Forward	GAACAGCAACGAGTACCGGGTA	61 °C
	Reverse	GCCATGGCCTTGACCAAGGAG	
CPT1 (<i>cpt1a</i>)	Forward	GTGACTGGTGGGAGGAATAC	56 °C
	Reverse	GAGCATCTCCATGGCGTAG	
FAS (<i>fasn</i>)	Forward	TGCGATTCTCCTGGCTGTGAA	59 °C
	Reverse	CAACAACCATAGGCGATTCTGG	
G6P (<i>g6pc</i>)	Forward	CTGCTTCCAGATAGTCTCCACTG	59.5 °C
	Reverse	TAGAGAAGGTGGTGTGAGAGACAG	
PGC1 α (<i>ppargc1a</i>)	Forward	AAGAGCTCCAAGACTCTAGACAAC	59.5 °C
	Reverse	CAAAGTCTCTCTCAGGTAGCACTG	
PPAR α (<i>ppara</i>)	Forward	ACCACTACGGAGTTCACGCATG	61 °C
	Reverse	GAATCTTGCAGCTCCGATCACAC	
PPAR γ (<i>pparg</i>)	Forward	GTACTGTCGGTTTCAGAAAGTGCC	60.5 °C
	Reverse	ATCTCCGCCAACAGCTTCTCCT	
SREBP1c (<i>srebf1</i>)	Forward	CGACTACATCCGCTTCTTGACG	59.5 °C
	Reverse	CCTCCATAGACACATCTGTGCC	
UCP1 (<i>ucp1</i>)	Forward	CGACTCAGTCCAAGAGTACTTCTCTTC	58 °C
	Reverse	GCCGGCTGAGATCTTGTTTC	
β -actin (<i>actb</i>)	Forward	TGCTGTCCCTGTATGCCTCTG	58 °C
	Reverse	TGATGTCACGCACGATTTC	

2.9. Micro-Computed Tomography (μ -CT) Analysis

Abdominal fat volume and distribution were evaluated using micro-computed tomography (μ -CT; SkyScan 1176, Bruker, Kontich, Belgium). The scan parameters were configured using the preset settings in the Scanner Setup. Scans were conducted in Standard resolution mode with an aluminum (Al) 1 mm X-ray filter, voltage of 65 kV, current of 373 μ A, pixel size of 35 μ m, exposure time of 100 ms, and a rotation step of 0.70°. In vivo scans were performed 5 days before the end of the experimental period, with three to four mice per group scanned daily under isoflurane anesthesia. Raw projection images were reconstructed using NRecon software (version 1.6.10.1, Bruker, Kontich, Belgium).

The volume of abdominal fat was quantified using CTAn software (version 1.17.7.2, Bruker). The volume of interest (VOI) was defined from the point where the lungs disappeared to the point just before vertebral bones other than the spine became visible. Approximately 400 cross-sectional slices (35 μ m per slice) were analyzed. Fat tissue was segmented using threshold-based segmentation, and the object volume (fat volume) and percent object volume (fat volume/VOI ratio) were calculated. Morphological parameters, including object surface area, surface-to-volume ratio, surface density, and surface convexity index, were also analyzed using the same software. All mice were subjected to μ -CT analysis, and the abdominal fat ratio was additionally expressed as the percentage of fat area relative to the total abdominal cross-sectional area. Each measurement was independently performed by two investigators, and the mean of their measurements was used as the final value.

2.10. Serum Adipokine Analysis

Serum adiponectin and leptin levels were measured using commercially available ELISA kits. Adiponectin was quantified using an ELISA kit from ALPCO (Salem, NH, USA), and leptin was measured using a Mouse Leptin ELISA kit from Enzo Life Sciences (Farmingdale, NY, USA). All assays were performed according to the manufacturers' instructions. Serum samples were diluted as recommended and loaded onto pre-coated plates, followed by incubation with detection antibodies and substrate solution.

2.11. Statistical Analysis

Statistical analyses were performed using GraphPad Prism software (version 8.4.2; GraphPad Software, USA). Normality of data distribution was verified using the Shapiro–Wilk test, and homogeneity of variance was assessed using the Brown–Forsythe test. Except for weekly body weight changes and the time-course data of the intraperitoneal glucose tolerance test (ipGTT), comparisons among groups were analyzed using one-way ANOVA followed by Dunnett's multiple comparison test. Weekly body weight data and ipGTT time-course results were analyzed using two-way ANOVA. Exact *p*-values are reported where appropriate, and statistical significance was set at *p* < 0.05. All data are presented as the mean ± standard error of the mean (SEM).

3. Results

3.1. Comprehensive Component Profiling of HT099

To obtain a comprehensive chemical profile of HT099, high-performance liquid chromatography (HPLC) analysis was performed using multiple reference standards. This approach enabled the detection and identification of major constituents present in the extract. By comparison with authentic standards, chlorogenic acid (CAS No. 327-97-9), neochlorogenic acid (CAS No. 906-33-2), crypto-chlorogenic acid (CAS No. 905-99-7), *p*-coumaric acid (CAS No. 501-98-4), caffeic acid (CAS No. 331-39-5), ferulic acid (CAS No. 1135-24-6), multiflorin B (CAS No. 52657-01-9), multiflorin A (CAS No. 1350028-90-8), rutin (CAS No. 153-18-4), kaempferol (CAS No. 520-18-3) and naringenin (CAS No. 480-41-1) were identified in HT099 (Figure 1, Supplementary Table S3). In addition, HT099 showed a total phenolic content of 298.3 ± 6.4 mg GAE/g extract, confirming that HT099 is a polyphenol-rich standardized formulation.

The identified compounds were classified into two major groups: flavonoids (multiflorin B, multiflorin A, rutin, kaempferol and naringenin) and phenolic acids (chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, *p*-coumaric acid, caffeic acid, and ferulic acid). Among these constituents, chlorogenic acid was selected as the marker compound for HT099 standardization due to its clear chromatographic profile and representative abundance in the extract.

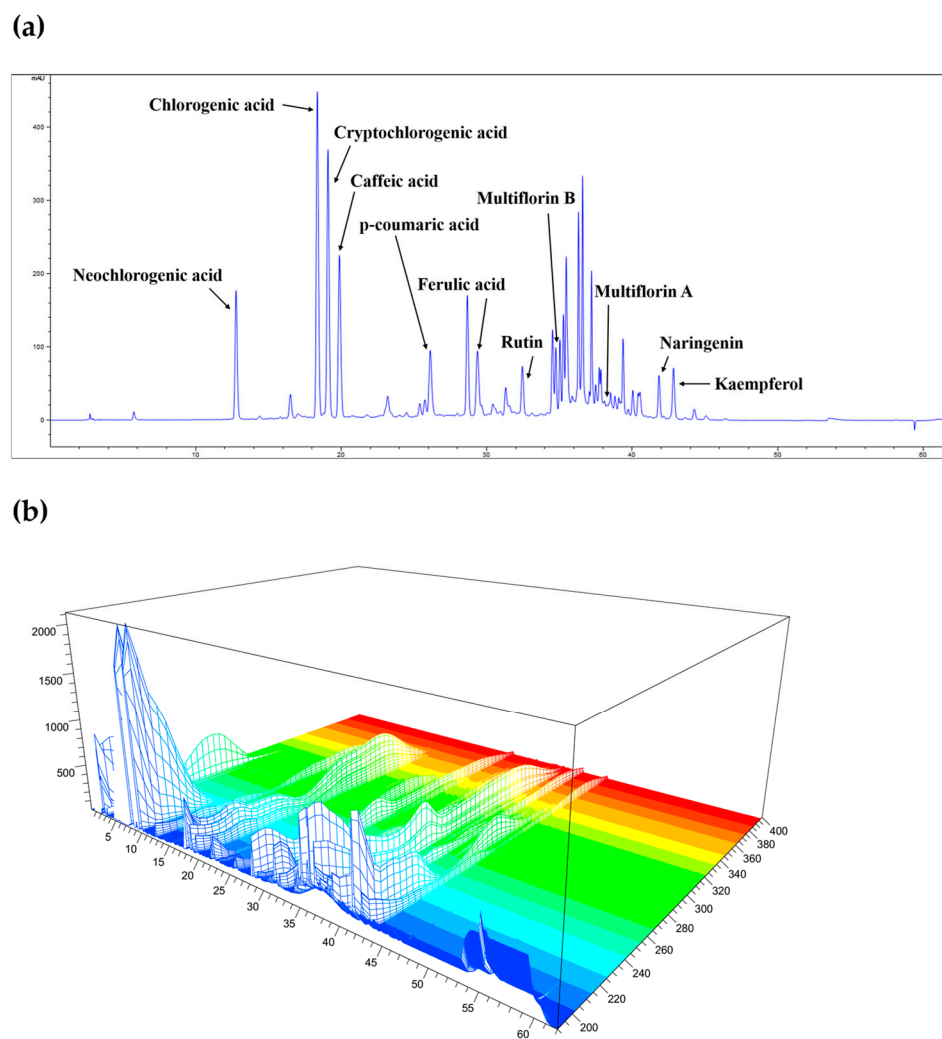


Figure 1. Comprehensive HPLC profiling of HT099. (a) Representative two-dimensional HPLC chromatogram of HT099 showing major phenolic and flavonoid constituents, including chlorogenic acid, p-coumaric acid, ferulic acid, multiflorin A, multiflorin B, rutin, and naringenin. (b) Three-dimensional HPLC chromatographic profile of HT099 illustrating the overall chemical fingerprint of the extract across retention time and detection wavelength.

3.2. Changes in Body Weight and Food Efficiency

Body weight gain differed markedly among experimental groups during the study period (Figure 2a). The HFD-DW group exhibited a pronounced increase in body weight compared with the NC group, whereas this increase was significantly attenuated in the OS 40- and HT099-treated groups. Among the HT099-treated groups, the HT-H group showed the lowest overall body weight gain, whereas the HT-L group also exhibited a significant reduction compared with the HFD-DW group. Detailed weekly body weight values are provided in Supplementary Table S1.

Food efficiency was highest in the HFD-DW group and was significantly reduced in both the OS 40- and HT099-treated groups (Figure 2d). No significant differences in cumulative food intake were observed among the HFD-fed groups during the experimental period (Supplementary Figure S1).

Consistent with the longitudinal body weight curves, the OS 40 group showed a significant reduction in body weight gain relative to the HFD-DW group beginning at week 3, whereas the HT-L group exhibited a significant reduction from week 5 onward ($p < 0.05$) (Figure 2a, Supplementary Table S1). The HT-H group showed a significant reduction in

body weight gain relative to the HFD-DW group at the end of the study period. In contrast, the HFD-DW group displayed a rapid increase in body weight beginning at week 3 ($p < 0.01$), resulting in a significantly higher final body weight compared with the NC group. Final body weight was significantly lower in the OS 40- and HT099-treated groups compared with the HFD-DW group (Figure 2b).

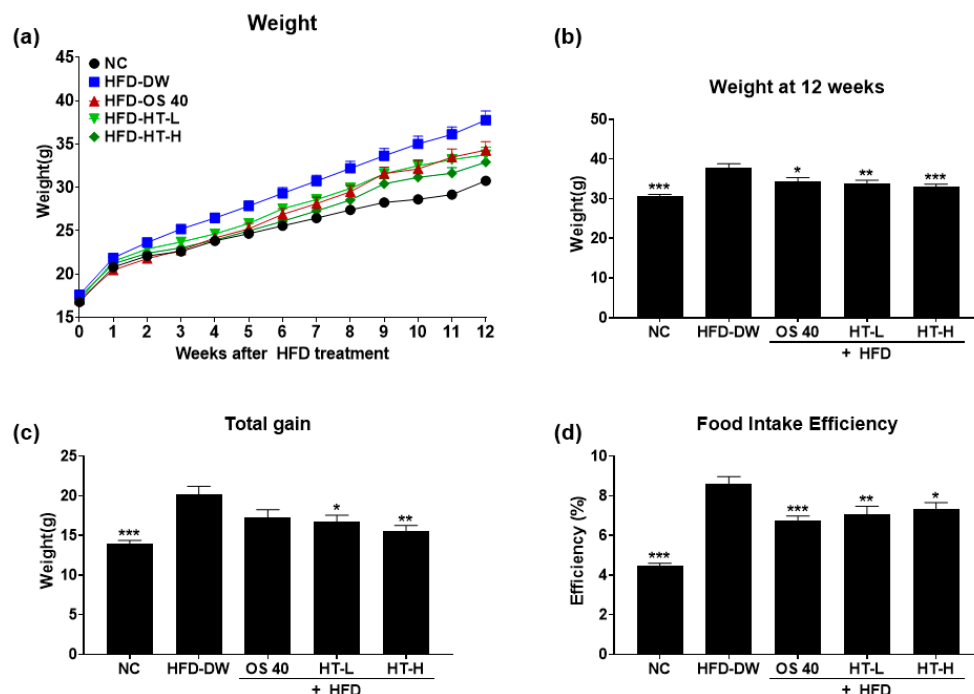


Figure 2. Effects of HT099 on body weight and food efficiency ratio (FER) in HFD-induced obesity mice. (a) Weekly body weight changes during the 12-week experimental period. (b) Final body weight after 12 weeks of treatment. (c) Total weight gain during the experimental period. (d) Food efficiency ratio (FER), calculated as total body weight gain divided by total food intake. Data are presented as mean $\pm$ SEM ($n = 10$ per group). Statistical analyses were performed using two-way ANOVA for weekly body weight changes and one-way ANOVA followed by Dunnett's multiple-comparison test for final body weight and FER. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

3.3. Regional Adipose Tissue Weight

To evaluate the effects of HT099 on HFD-induced fat accumulation, the weights of various white adipose tissue depots were measured (Figure 3a–e). The HFD-DW group exhibited significantly higher fat mass in all examined regions compared with the NC group ($p < 0.001$).

In epididymal adipose tissue (Figure 3a), the HFD-DW group showed a marked increase relative to the NC group ($p < 0.001$). This increase was significantly reduced in the OS 40 group and in both HT099-treated groups compared with the HFD-DW group ($p < 0.05$). No significant difference was observed between the HT-L and HT-H groups. Mesenteric adipose tissue weight (Figure 3b) was also significantly increased by HFD feeding. The OS 40 group showed a significantly lower value compared with the HFD-DW group ($p < 0.001$). Both the HT-L ($p < 0.01$) and HT-H ($p < 0.001$) groups exhibited significant reductions compared with the HFD-DW group. A similar pattern was observed in subcutaneous adipose tissue (Figure 3c). The HFD-DW group displayed a significant increase compared with the NC group ($p < 0.001$), whereas the OS 40, HT-L, and HT-H groups all showed significant reductions compared with the HFD-DW group ($p < 0.05$). In perirenal adipose tissue (Figure 3d), fat mass was significantly increased in the HFD-DW group

relative to the NC group ($p < 0.001$). The OS 40, HT-L, and HT-H groups all showed significantly lower values compared with the HFD-DW group ($p < 0.05$). Retroperitoneal adipose tissue weight (Figure 3e) was markedly elevated in the HFD-DW group compared with the NC group ($p < 0.001$). In contrast, the OS 40, HT-L, and HT-H groups each showed significantly lower values compared with the HFD-DW group ($p < 0.01$).

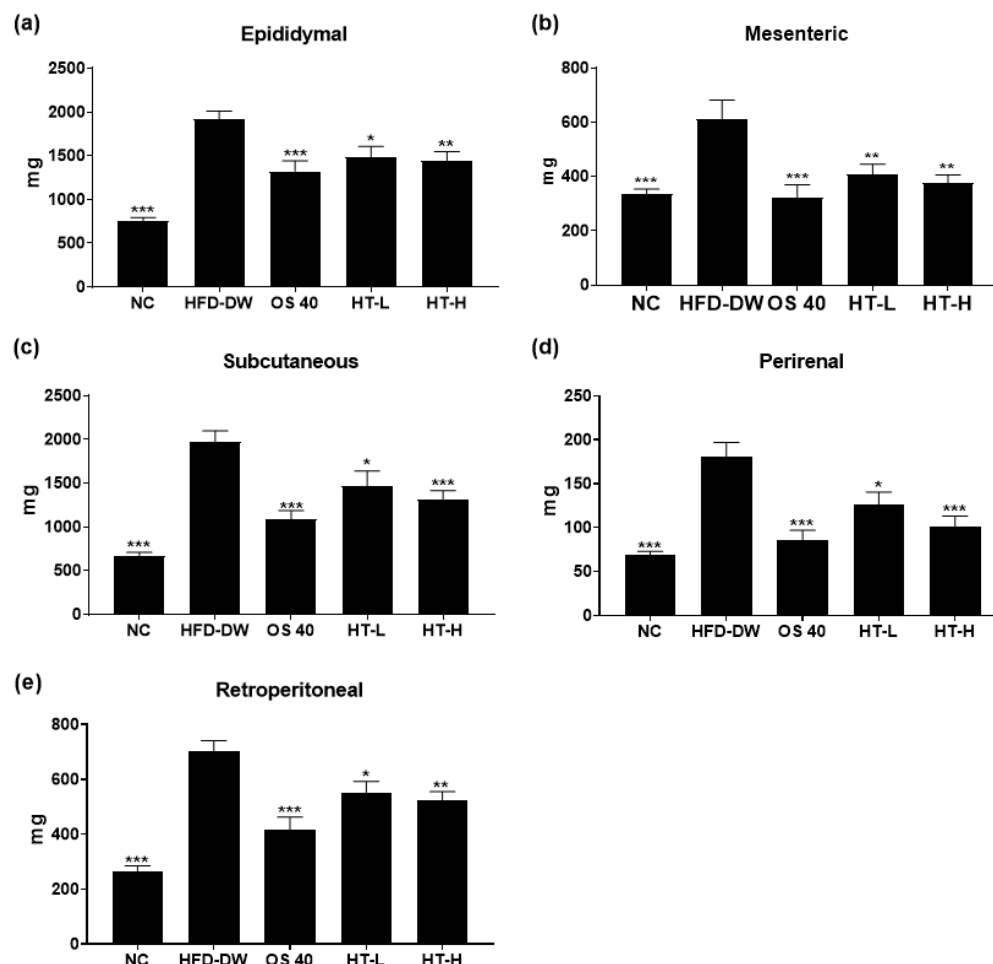


Figure 3. Regional adipose tissue weights after HT099 administration. Weights of epididymal (a), mesenteric (b), subcutaneous (c), perirenal (d), and retroperitoneal (e) adipose tissues were measured at sacrifice. HT099 significantly reduced fat accumulation across multiple depots. Data are presented as mean $\pm$ SEM ($n = 10$). One-way ANOVA followed by Dunnett's multiple comparison test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

When total white adipose tissue (Total WAT) was analyzed (Figure 4a), the HFD-DW group showed a significant increase compared with the NC group ($p < 0.001$), whereas the OS 40, HT-L, and HT-H groups exhibited significant reductions ($p < 0.001$, $p < 0.01$, and $p < 0.001$, respectively). Consistently, abdominal fat percentage assessed by computed tomography (CT) imaging (Figure 4b) was significantly reduced in the OS 40- and HT099-treated groups compared with the HFD-DW group ($p < 0.001$). Because body weight itself is a treatment-responsive outcome in this model, expressing adipose tissue depot weights as a percentage of the final body weight provides a more appropriate and conservative assessment of tissue-specific effects. Accordingly, %BW-normalized adipose tissue data are presented in the Supplementary Materials (Supplementary Figure S2).

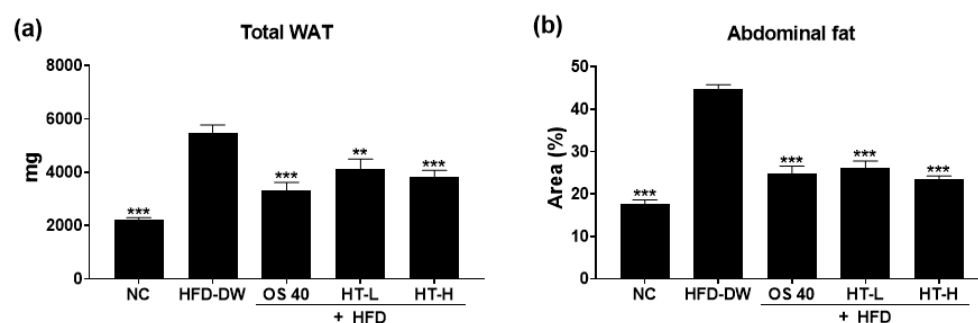


Figure 4. Total white adipose tissue (WAT) weight and abdominal fat ratio assessed by μ -CT. (a) Total WAT weight was calculated as the sum of dissected fat depots. (b) Abdominal fat area ratio was determined using micro-computed tomography (μ -CT). Data are mean $\pm$ SEM ($n = 10$). One-way ANOVA followed by Dunnett's multiple comparison test, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

3.4. Intraperitoneal Glucose Tolerance Test (ipGTT)

To assess glucose tolerance, blood glucose levels were measured for 120 min following an intraperitoneal glucose injection (2 g/kg) (Figure 5a, Supplementary Table S2). In the NC group, blood glucose levels transiently increased at 15 min and returned to baseline by 120 min. In contrast, the HFD-DW group exhibited significantly elevated glucose levels at all measured time points compared with the NC group ($p < 0.001$). The OS 40 group showed attenuated glucose elevations relative to the HFD-DW group, with significant reductions observed at 30 and 60 min ($p < 0.01$). HT099 treatment also resulted in reduced glucose levels, with the HT-H group showing significant reductions over a broader time window compared with the HFD-DW group. The HT-L group showed significantly lower glucose levels compared with the HFD-DW group at 30 and 60 min ($p < 0.05$), whereas the HT-H group exhibited significant reductions from 30 to 120 min ($p < 0.01$ and $p < 0.001$, respectively).

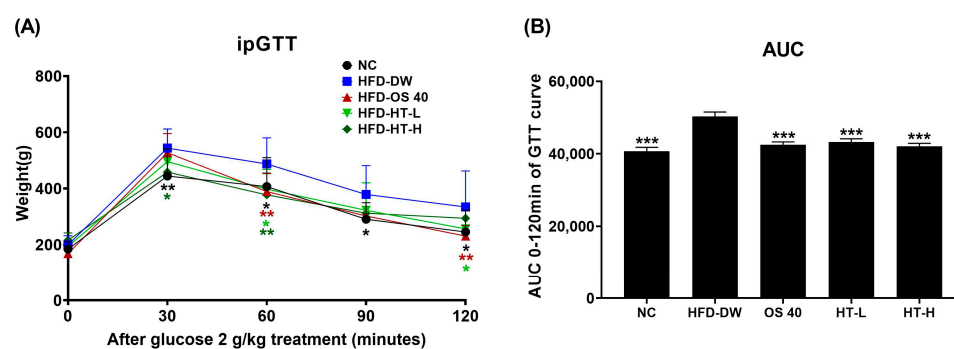


Figure 5. Intraperitoneal glucose tolerance test (ipGTT) and area under the curve (AUC). (a) Blood glucose levels were measured at 0–120 min after glucose (2 g/kg) injection. (b) AUC was calculated by the trapezoidal rule. Data are mean $\pm$ SEM ($n = 10$). Two-way ANOVA for time-course data and one-way ANOVA for AUC. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

Consistent with these findings, analysis of the area under the curve (AUC) revealed that the HFD-DW group had a significantly higher AUC compared with the NC group ($p < 0.001$) (Figure 5b, Supplementary Table S2). The OS 40 group showed a significant reduction in AUC relative to the HFD-DW group ($p < 0.001$). Both the HT-L and HT-H groups also exhibited significantly lower AUC values compared with the HFD-DW group ($p < 0.001$). The AUC value of the HT-H group was numerically lower than that of the OS

40 group; however, this difference was not statistically significant (Supplementary Table S2).

3.5. Serum Lipid Profiles

The effects of HT099 on serum lipid parameters were evaluated in HFD-induced obese mice. No significant differences in total cholesterol (TC) levels were observed among the experimental groups (Figure 6a). Serum triglyceride (TG) levels were significantly increased in the HFD-DW group compared with the NC group. This increase was significantly attenuated in the OS 40- and HT099-treated groups compared with the HFD-DW group, with both the HT-L and HT-H groups showing significant reductions (Figure 6b).

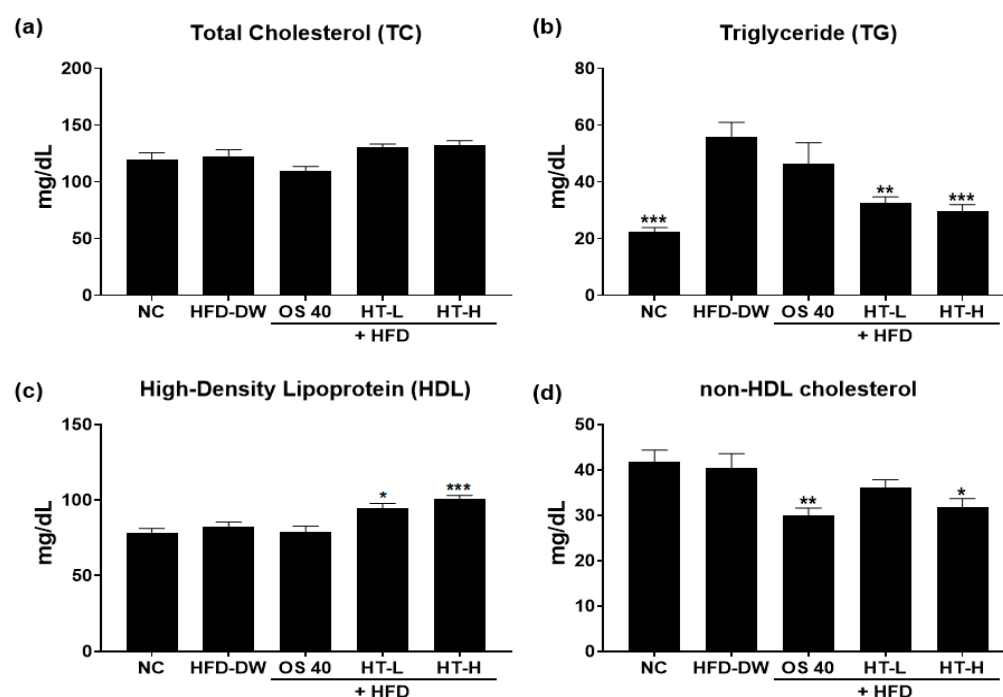


Figure 6. HT099 reduced TG and non-HDL cholesterol and increased HDL-C levels. Serum levels of (a) total cholesterol (TC), (b) triglycerides (TG), (c) HDL cholesterol (HDL-C), and (d) non-HDL cholesterol were analyzed. HT099 reduced TG and non-HDL cholesterol and increased HDL-C levels, indicating improved lipid metabolism. Data are presented as mean $\pm$ SEM ($n = 10$). One-way ANOVA followed by Dunnett's multiple comparison test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

High-density lipoprotein (HDL) cholesterol levels were significantly elevated in both the HT-L and HT-H groups, whereas no significant change was observed in the OS 40 group compared with the HFD-DW group (Figure 6c). Non-HDL cholesterol levels did not differ significantly between the NC and HFD-DW groups. However, non-HDL cholesterol levels were significantly reduced in the OS 40 and HT-H groups and showed a decreasing trend in the HT-L group compared with the HFD-DW group (Figure 6d).

3.6. Hepatic Gene Expression Related to Lipogenesis and Adipocyte Differentiation

While HFD feeding did not significantly alter hepatic AMPK α 1 mRNA levels, HT-H administration significantly upregulated its expression compared with the HFD-DW group ($p < 0.05$) (Figure 7a). The expression of C/EBP α was significantly elevated in the HFD-DW group compared with the NC group and was significantly reduced in the OS 40, HT-L, and HT-H groups (Figure 7b).

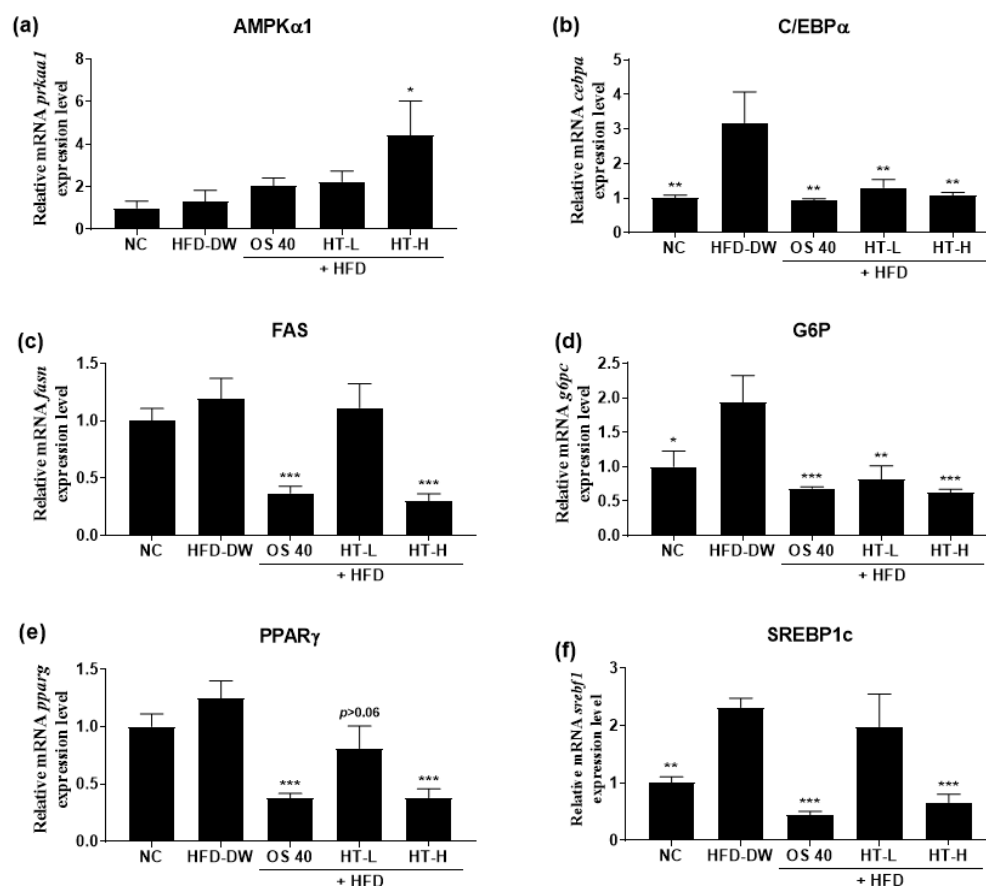


Figure 7. Hepatic gene expression associated with lipogenesis and adipocyte differentiation. Relative mRNA levels of (a) AMPK α 1, (b) C/EBP α , (c) FAS, (d) G6P, (e) PPAR γ , and (f) SREBP1c were determined using qPCR. HT099 increased AMPK α 1 expression while downregulating lipogenic and adipogenic genes. Data are mean $\pm$ SEM. One-way ANOVA followed by Dunnett's multiple comparison test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW control.

Hepatic PPAR γ and FAS expression levels were not significantly different between the NC and HFD-DW groups; however, both were significantly reduced in the OS 40- and HT099-treated groups compared with the HFD-DW group (Figure 7c,e).

By contrast, SREBP-1c and G6P expression levels were significantly increased in the HFD-DW group compared with the NC group and were significantly reduced by OS 40 and HT099 treatments (Figure 7d,f).

3.7. Effects of HT099 on Serum Adipokines

Serum adiponectin and leptin concentrations were measured to evaluate the effects of HT099 on adipokine levels (Figure 8). Serum adiponectin levels were significantly reduced in the HFD-DW group compared with the NC group ($p < 0.05$; Figure 8a). Treatment with OS 40 and both HT099 doses (HT-L and HT-H) resulted in significant increases in serum adiponectin levels compared with the HFD-DW group ($p < 0.01$; Figure 8a).

Serum leptin levels were significantly elevated in the HFD-DW group compared with the NC group and were significantly attenuated by OS 40 and HT099 treatments. Leptin concentrations were significantly lower than those in the HFD-DW group in the OS 40 ($p < 0.001$), HT-L ($p < 0.05$), and HT-H ($p < 0.01$) groups (Figure 8b).

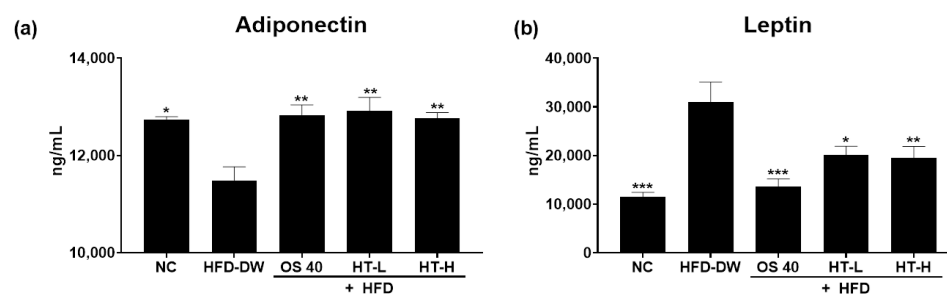


Figure 8. Effects of HT099 on serum adipokine levels in HFD-induced obesity mice. (a) Serum adiponectin levels and (b) serum leptin levels following 12 weeks of treatment. NC, normal control; HFD-DW, HFD with distilled water; OS 40, orlistat 40 mg/kg; HT-L, HT099 50 mg/kg; HT-H, HT099 100 mg/kg. Data are expressed as mean $\pm$ SEM ($n = 10$ per group). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test versus the HFD-DW group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. HFD-DW.

4. Discussion

Obesity is a major global health concern closely associated with metabolic disorders such as type 2 diabetes, dyslipidemia, and cardiovascular disease. Despite the availability of various pharmacological interventions, achieving sustained long-term weight reduction remains challenging, underscoring the need for alternative strategies based on natural products with favorable safety profiles. In this context, plant-derived polyphenol-rich extracts have attracted increasing attention due to their potential to exert broad metabolic effects. Extracts from *Prunus persica* flowers (PPF) have previously been reported to improve lipid metabolism and metabolic function [9], providing a rationale for the further investigation of standardized formulations derived from this botanical source.

In the present study, the food efficiency ratio (FER) was used as a supportive indicator to compare body weight gain relative to food consumption among HFD-fed groups. Although caloric intake is an important parameter for assessing energy balance, all HFD-fed groups received diets with identical caloric density. Consistent with this, cumulative food intake did not differ significantly among the HFD-fed groups (Supplementary Figure S1). Under these conditions, HT099 attenuated HFD-induced body weight gain. These findings are consistent with previous reports demonstrating that *Prunus persica* flower extracts reduce body weight without altering food intake [9]. In our study, HT099 reduced body weight gain without significant changes in food intake, resulting in a decreased food efficiency ratio (FER). However, because energy expenditure, physical activity, and nutrient absorption were not directly assessed, the physiological basis underlying the reduced FER cannot be conclusively determined.

HT099 administration also resulted in marked reductions in white adipose tissue (WAT) mass across multiple depots and decreased abdominal fat accumulation, as assessed through μ -CT imaging. Compared with the previous study using crude hot-water *Prunus persica* flower extract incorporated into the diet [9], the present work differs in several key aspects. Specifically, we evaluated a standardized and processed formulation (HT099) with batch-to-batch quality control based on chlorogenic acid content and enrichment via resin fractionation and enzymatic hydrolysis. In addition, HT099 was administered through oral gavage at defined doses (50 and 100 mg/kg) for a longer intervention period (12 weeks) with a positive control (orlistat), thereby strengthening translational relevance and exposure control. Furthermore, we expanded metabolic phenotyping by assessing abdominal adiposity using μ -CT, glucose tolerance (ipGTT), serum lipid profiles, adipokines, and hepatic transcriptional changes related to adipogenesis and lipogenesis,

providing a broader mechanistic and metabolic characterization than previously reported. Notably, HT099 improved multiple metabolic parameters at relatively lower oral doses, and this enhanced efficacy may be related, at least in part, to resin-based enrichment and enzymatic processing, which improve the uniformity and recovery of polyphenolic constituents [23,24]. The HT099 process (hot-water extraction → resin enrichment → β -D-glucosidase hydrolysis) was designed to recover and enrich polar polyphenols from *P. persica* flowers under food-compatible, scalable conditions while applying a mild enzymatic step to modulate glycosylated constituents and support batch-to-batch standardization. Consistent with this rationale, HT099 showed a high total phenolic content (298.3 ± 6.4 mg GAE/g extract) and contained multiple phenolic acids and flavonoids, including chlorogenic acids, as well as rutin, kaempferol, and naringenin. Although this study did not pinpoint a single active principle, we propose that the observed anti-obesity effects likely reflect the combined action of these phenolic constituents, with chlorogenic acid being one plausible contributor and a practical marker for standardization.

At the transcriptional level, HT099 administration was associated with increased hepatic AMPK α 1 mRNA expression and decreased expression of key adipogenic and lipogenic genes, including C/EBP α , PPAR γ , FAS, and SREBP-1c. These transcriptional changes provide molecular evidence consistent with the observed reductions in hepatic lipid accumulation. Nevertheless, because protein expression and phosphorylation status were not evaluated, further studies will be required to determine whether these transcriptional changes translate into a functional modulation of downstream metabolic processes.

Consistent with the hepatic gene expression profile, HT099 favorably modulated serum lipid parameters by reducing triglyceride levels, increasing HDL cholesterol, and improving non-HDL cholesterol profiles. These findings are in agreement with previous studies reporting lipid-lowering and hepatoprotective effects of polyphenolic compounds such as chlorogenic acid, ferulic acid, and rutin, several of which were identified in HT099 [25–27]. The combined presence of these bioactive constituents may contribute additively or synergistically to the observed improvements in lipid metabolism.

HFD feeding induced a pronounced adipokine imbalance characterized by decreased adiponectin and elevated leptin levels, a hallmark of obesity-associated metabolic dysfunction. HT099 administration restored adiponectin levels and attenuated HFD-induced hyperleptinemia. Given the established roles of adiponectin in insulin sensitivity and lipid oxidation, and of leptin dysregulation in obesity, these changes suggest an improvement in adipose tissue metabolic status. However, it should be noted that the observed changes in adipokine levels may be secondary to the reduction in adipose tissue mass rather than reflecting direct regulatory effects of HT099. In addition, leptin signaling and insulin sensitivity were not directly assessed, and thus these interpretations should be regarded as associative rather than causal.

With respect to brown adipose tissue (BAT), HT099 did not significantly alter the mRNA expression of thermogenesis- and mitochondria-related genes, including PGC-1 α , PPAR α , UCP1, and C/EBP α , although modest trends were observed for some markers (Supplementary Figure S3). Given the absence of significant changes in thermogenic markers like UCP1, the present study suggests that the anti-obesity effects of HT099 are primarily mediated through the regulation of white adipose tissue mass and hepatic lipogenesis rather than BAT thermogenesis under the experimental conditions employed. Instead, the collective findings suggest that the metabolic benefits of HT099 are more likely mediated through effects on WAT mass, hepatic lipid metabolism, and adipokine regulation.

Several limitations of this study should be acknowledged. First, only male C57BL/6N mice were used, which may limit the generalizability of the findings to females. Second, energy expenditure, substrate utilization, fecal energy loss, and insulin-based indices of

insulin sensitivity were not evaluated. Third, although human-equivalent doses were estimated based on body surface area normalization, the pharmacokinetic properties, bioavailability, and metabolite profiles of HT099 remain to be characterized. Because HT099 was administered as a spray-dried powder containing 10% dextrin, and orlistat acts locally in the gastrointestinal tract with minimal systemic absorption, differences in non-absorbed luminal components could, in principle, influence metabolic outcomes. Although the dextrin exposure from HT099 was small (5–10 mg/kg/day at the tested doses), this potential confounding factor should be considered when interpreting the in vivo results. Finally, although chlorogenic acid was used as a quality-control marker, HT099 is a chemically complex extract, and the individual or combined contributions of minor constituents remain to be elucidated. Future studies incorporating metabolic cage experiments, protein-level analyses, and well-designed human trials will be necessary to further clarify the metabolic actions and translational potential of HT099.

5. Conclusions

HT099, a standardized polyphenol-rich extract from *Prunus persica* flowers, attenuated HFD-induced obesity and associated metabolic disturbances in mice. HT099 reduced body weight gain, white adipose tissue accumulation, and dyslipidemia, while improving glucose tolerance and adipokine profiles. Collectively, these findings support the potential of HT099 as a natural bioactive agent for the management of diet-induced obesity and warrant further mechanistic and translational studies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/metabo16020132/s1>, Figure S1: Cumulative food intake was measured throughout the 12-week experimental period; Figure S2: Regional adipose tissue weights normalized to body weight after HT099 administration; Figure S3: Gene expression levels in brown adipose tissue after HT099 administration; Table S1: Effects of HT099 on weekly body weight in HFD-induced obesity mice; Table S2: Effects of HT099 on intraperitoneal glucose tolerance test (ipGTT) in HFD-induced obese mice; Table S3: Area under the curve (AUC) of blood glucose levels during the intraperitoneal glucose tolerance test (ipGTT); Table S4: HPLC retention times of the identified compounds in HT099 (corresponding to Figure 1).

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Abbreviations

The following abbreviations are used in this manuscript:

HFD	High-fat diet
FER	Food efficiency ratio
ipGTT	Intraperitoneal Glucose Tolerance Test
AMPK α 1	AMP-activated protein kinase alpha 1
C/EBP α	CCAAT/enhancer-binding protein alpha
FAS	Fatty acid synthase
G6P	Glucose-6-Phosphatase
PPAR α	Peroxisome Proliferator-Activated Receptor Alpha
PPAR γ	Peroxisome proliferator-activated receptor gamma
SREBP-1c	Sterol Regulatory Element-Binding Protein 1c
PGC-1 α	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
UCP1	Uncoupling protein 1

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