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Dioscorea batatas Extract Attenuates High-Fat Diet-Induced Obesity in Mice by Decreasing Expression of Inflammatory Cytokines

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The objective of the present study was to determine whether *Dioscorea batatas* (DB) extract reduces visceral fat accumulation and obesity-related biomarkers in mice fed a high-fat diet (HFD) and whether genes associated with adipogenesis and inflammation could be modulated by a diet containing DB extract.

Material/Methods: Male C57BL/6J mice were divided into 4 groups (n=10 per group): normal diet (ND), HFD, 100 mg/kg DB extract-gavage with HFD, and 200 mg/kg DB extract-gavage with HFD. The mice were fed the experimental diets for 14 weeks. At 12 weeks, micro-computed X-ray tomography (micro-CT) was performed.

Results: Supplementation of the diet with DB extract for 14 weeks significantly prevented HFD-induced increases in body weight, visceral adipose tissue, plasma lipid levels, and leptins. The area of visceral fat was reduced by DB extract supplementation when examined by micro-CT. Supplementation with DB extract resulted in the downregulation of the adipogenic transcription factor (C/ERBα) and its target gene (CD36) in epididymal adipose tissue, compared to HFD alone. DB extract decreased the expression of proinflammatory cytokines (TNF-α, MCP-1, and IL-6) in epididymal adipose tissue.

Conclusions: Our results suggest that DB extract may prevent HFD-induced obesity by downregulating the expression of genes related to adipogenesis and inflammation in visceral adipose tissue.

MeSH Keywords: Adipogenesis • Diet, High-Fat • Dioscorea • Obesity

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Background

Obesity is a major health problem in worldwide and is associated with increased risk of multiple complications such as cardiovascular disease, type 2 diabetes, and certain types of cancer [1–3]. Diet restriction, physical exercise, and medication are the major ways to reduce obesity, but their effectiveness remains limited [4–7]. Some studies have shown that certain herbal agents have anti-obesity effects [8,9]. Thus, the development of an alternative agent for the treatment of obesity is necessary. Evidence has accumulated indicating that obesity is associated with systemic inflammation characterized by the activation of inflammatory signaling pathways and abnormal cytokine production in adipose tissue [10,11]. The cytokines produced by adipocytes include several inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). These cytokines are associated with the development of cardiovascular disease and type 2 diabetes [12]. Yam (*Dioscorea batatas* [DB]) belongs to the Dioscoreaceae family and is found throughout East Asia, including China, Japan, Taiwan, and Korea. It has been traditionally used to treat inflammatory diseases such as asthma, rheumatoid arthritis, and bronchitis [13]. In a recent study, DB extract ameliorates insulin resistance in mice fed a high-fat diet [14]. However, the effect of DB extract on obesity and adipocytes has not been documented. The aim of this study was to investigate whether DB extract could reduce visceral fat accumulation and improve obesity-related biomarkers in mice fed a high-fat diet and whether its effects were exerted by the modulation of the expression of genes associated with adipogenesis and inflammation.

Material and Methods

Preparation of DB extract

The rhizome of DB was provided by Ahn-Dong city in Korea (Gyeong-buk Province). The dried rhizome of DB was homogenized to a fine powder. The powdered DB rhizome was soaked in a water-ethanol (1:1, v/v) solution (1:5, plant weight/solvent volume) for 24 h, with occasional shaking. After filtration, the extract was vacuum concentrated to yield 3.09% ethanol extract, which was stored at –4°C for later use.

Animals and experimental protocol

Male C57BL/6J mice (6 weeks old) were purchased from Raon Bio (Gyeonggi-do, Republic of Korea) and were maintained in 12-h light-dark with *ad libitum* access to food and water. After a 2-week acclimatization period, the mice were divided into 4 groups (n=10 per group): normal diet (ND), high-fat diet (HFD), 100 mg/kg DB extract-gavage with HFD (Y100), and 200 mg/kg DB extract-gavage with HFD (Y200). The ND was a purified diet based on the AIN-76 rodent diet composition. The HFD was identical to the ND but contained 200 g/kg fat (170 g of lard plus 30 g of corn oil) and 1% cholesterol. The mice were fed the experimental diets for 14 weeks. At 12 weeks, micro-computed X-ray tomography (micro-CT; described below) was performed. Diet consumption was monitored daily and body weight was monitored weekly. At the end of the feeding period, mice were anesthetized with a Zoletil™ (anesthetic) and Rumpun™ (muscle relaxant) mixture, and their blood samples were collected in EDTA-coated tubes. Blood was collected from the inferior vena cava. Plasma samples were isolated by centrifugation at 4000× g for 20 min and stored at –70°C for subsequent analysis. Adipose and liver tissues were collected, washed with phosphate-buffered saline, and frozen at –70°C. All animal experiments were performed in accordance with the Korean Food and Drug Administration guidelines. The Institutional Animal Care and Use Committee of the Soonchunhyang Laboratory Animal Research Center reviewed and approved the protocols.

Biochemical analysis

Plasma concentrations of triglycerides (TGs), total cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using commercial kits (Asan Pharmaco Co., Seoul, Korea). Leptin plasma levels were measured using a mouse ELISA kit (Crystal Chem Inc., Downers Grove, IL, USA).

Histological analysis

Liver tissue was fixed in neutral buffered formalin, embedded in paraffin, and sectioned into 5-μm sections onto slides. For histology, sections were stained with hematoxylin and eosin (H&E) stain. Steatosis, inflammation, and ballooning were assessed in the livers of mice by an experienced pathologist in a blinded fashion. Steatosis, inflammation, and ballooning were scored based on non-alcoholic fatty liver disease activity score (NAS).

Micro-computed X-ray Tomography

After 11 weeks of feeding, 5 mice from each group were selected and fasted for 24 h prior to anesthetization with isoflurane. Transverse micro-CT images of the abdomen from L1 to L5 were scanned using a micro-CT scanner (SkyScan 1176; SkyScan Co., Kontich, Belgium) with resolution of 30 μm, voltage of 100 kV, current of 100 μA, exposure of 474 ms, and rotation step (degree) of 0.500. Analysis of micro-CT images was performed using Nrecon software (SkyScan Co.). Subcutaneous and visceral fats were detected at a range of –543.37 to +598.19 Hounsfield units.

RNA extraction and quantitative PCR

Total RNA was isolated from mouse epididymal fat tissue using the RNeasy Tissue Mini Kit (Qiagen, Tokyo, Japan) according to

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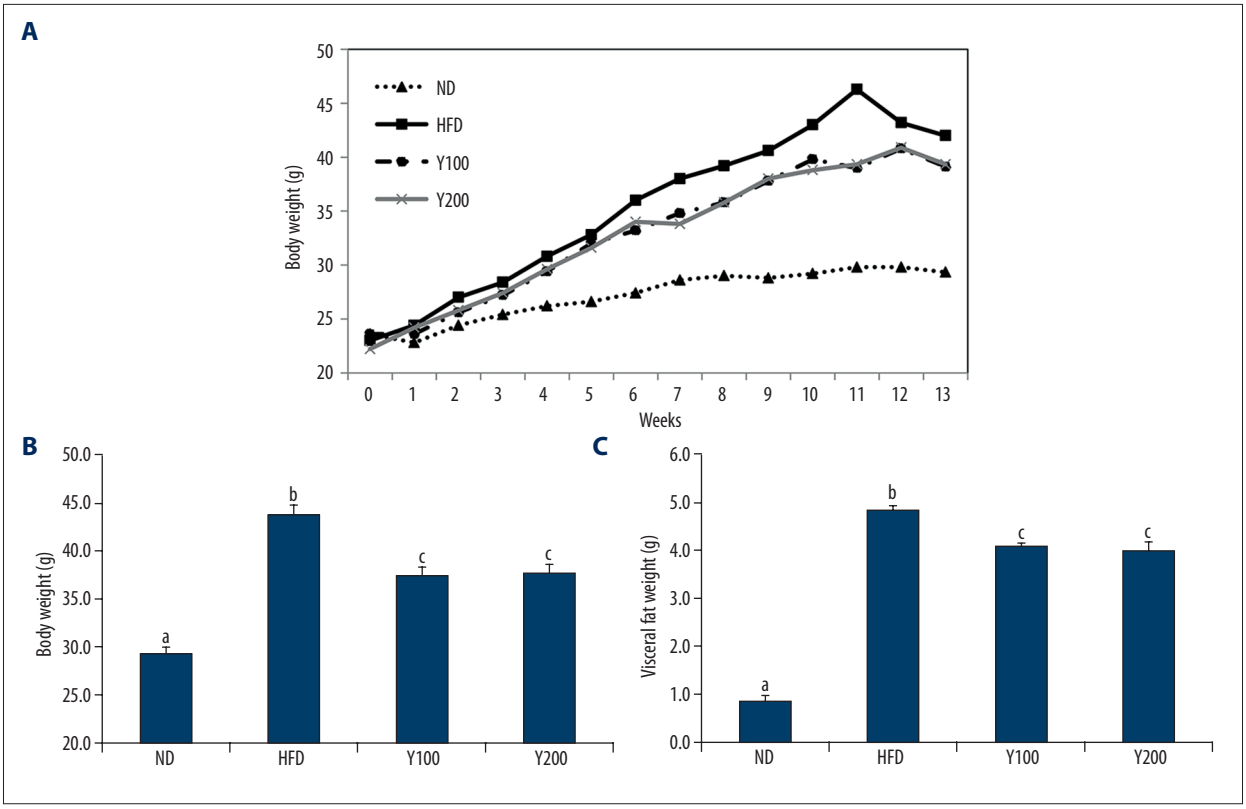

Figure 1. Body weight and visceral fat weight of mice fed the experimental diets for 13 weeks. (**A**) The change in body weight in the 4 groups. Sequential variation of body weight was significantly increased in the HFD, Y100, and Y200 groups relative to the ND group. (**B**) DB extract supplementation ameliorated the body weight gain compared to HFD at 13 weeks. (**C**) Visceral fat was significantly higher in the HFD, Y100, and Y200 groups relative to the ND group. DBV extract supplementation ameliorates the visceral fat weight gain. The data are presented as the mean ±SEM. Statistical analysis was performed using ANOVA and post hoc analysis using Tukey's B analysis. Values with different letters are significantly different (P<0.05).

the manufacturer's instructions. Total RNA (1 mg) was used as the template for cDNA synthesis in a 50-μL reaction using a reverse transcriptase-PCR kit (Toyobo Co., Osaka, Japan) according to the manufacturer's instructions. Real-time PCR was performed on a CFX96TM (Bio-Rad). Each PCR reaction consisted of Power SYBR Green PCR Master Mix (Applied Biosystems, UK), 0.1 mM (10 pM) specific primers, and 50 ng of cDNA. The primer sequences are as follows: C/EBPα, 5'-AAGGCCAAGAAGTCGGTGGA-3' and 5'-CCATAGTGGAAGCCTGATGC-3'; CD36, 5'-ATGACGTGGC AAAGAACAGC-3' and 5'-GAAGGCTCAAAGATGCCTCC-3'; TNFα, 5'-TGTCTCAGCCTCTTCTCATT-3' and 5'-AGATGATCTGAGTG TGAGGG-3'; IL-6, 5'-TTGCCTTCTTGGGACTGATG-3' and 5'-CCACGAT TTCCCAGAGAACA-3'; MCP1, 5'-CTGGATCGGAACCAAATGAG-3' and 5'-CGGGTCAACTTCACATTCAA-3'; GAPDH, 5'-AGAACATCATCCCT GCATCC-3' and 5'-TCCACCACCCTGTTGCTGTA-3'.

Statistical analysis

All results are expressed as the mean ± standard error of the mean (SEM) values. All analyses were performed using SPSS (version 14.0) statistics software. The mean values of the groups were compared by analysis of variance and post hoc analysis using Tukey's B analysis. P values less than 0.05 were considered statistically significant.

Results

Effect of DB extract on body weight and epididymal fat pad weight

The HFD group exhibited significantly accelerated weight gain and increased final body weight compared to the ND group (Figure 1A, 1B). Mice with diets supplemented with DB extract exhibited significantly decreased body weight compared to mice in the HFD group, but there was no difference between the Y100 and Y200 groups. DB extract-fed mice had increased body weight compared to the ND group. Visceral fat weight was significantly higher in the HFD, Y100, and Y200 groups than in the ND group. DB treatment affected the visceral fat weight of the HFD group during an experimental period in post hoc analysis (Figure 1C).

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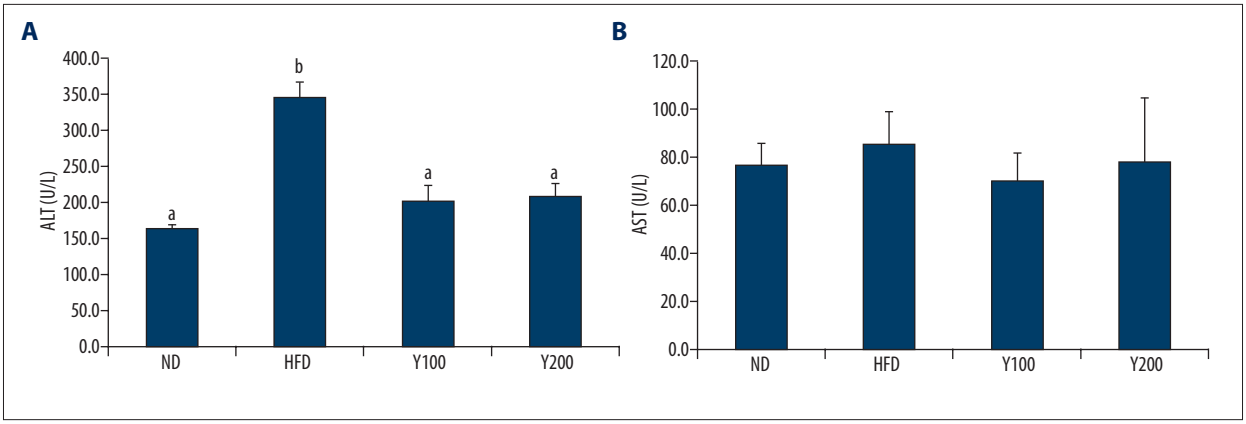

Figure 2. Liver enzyme (**A**) DB extract attenuated the increase of ALT compared with HFD. (**B**) AST was not increased in HFD compared with ND. Statistical analysis was performed using ANOVA and post hoc analysis using Tukey's B analysis. Values with different letters are significantly different (P<0.05).

Table 1. Effect of *Dioscorea batatas* extract supplementation on the lipid profile of mice fed with a high-fat diet.

	ND	HFD	Y100	Y200	P-value
Total cholesterol (mg/dl)	140.4±5.00	217.9±5.59	200.5±4.89	168.1±4.16	<0.001
Triglyceride (mg/dl)	94.30±4.98	140.82±7.34	87.85±1.99	102.90±5.11	<0.001
HDL (mg/dl)	119.93±13.16	98.77±8.53	119.00±3.54	123.87±4.90	<0.025

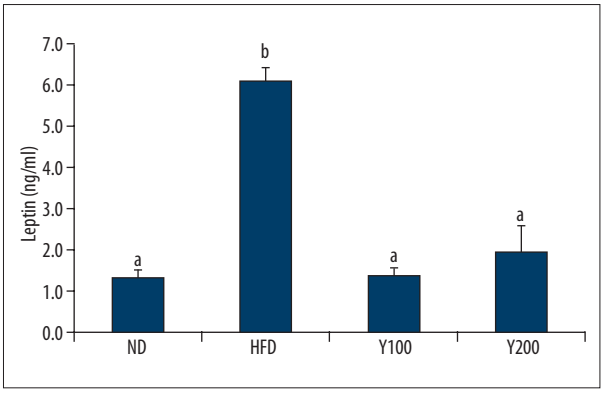

Figure 3. DB extract supplementation protects from high-fat-induced leptin elevation. Y200 significantly reduced serum leptin level compared to HFD. Values represent means ±SEM. Values with different superscripts are significantly different from one another (P<0.05).

Effect of DB extract on serum liver enzyme, lipid profile, and adipokines

The activity of liver enzymes is shown in Figure 2. As expected, the HFD group exhibited a marked increase in ALT levels, although AST did not increase in this group. Supplementation with DB extract reduced ALT levels but AST levels did not vary among the 4 groups. The serum lipid profile, including total cholesterol, high-density lipoproteins (HDL), and TGs, was measured and the concentration of low-density lipoprotein (LDL) cholesterol was calculated (Table 1). The average total cholesterol level in the HDF group was significantly higher than in the ND group (P<0.001). Supplementation with DB extract reduced the total cholesterol levels in a dose-dependent manner; however, the DB extract-supplemented group exhibited significantly higher levels than the ND group. Although TG levels in the HFD group were significantly higher than in the ND group, TG levels were reduced by supplementation with DB extract relative to the HFD group (P<0.001). Additionally, HDL levels were alleviated by supplementation with DB extract. Leptin levels were increased in the HFD group compared to the ND group and DB extract supplementation reduced leptin levels induced by HFD (Figure 3).

The effect of DB extract on visceral fat and liver tissue of mice

In vivo whole-body scans for abdominal fat deposition were performed using micro-CT. These results confirmed the changes in HFD mice, showing an increase in visceral and subcutaneous fat relative to the ND group (Figure 4). Supplementation with DB extract reduced visceral fat accumulation but did not reduce subcutaneous fat when compared to the HFD group.

HFD could induce non-alcoholic steatohepatitis. Histology was performed on liver tissue to determine the effect of the DB extract on the liver. The HFD group had increased hepatic steatosis

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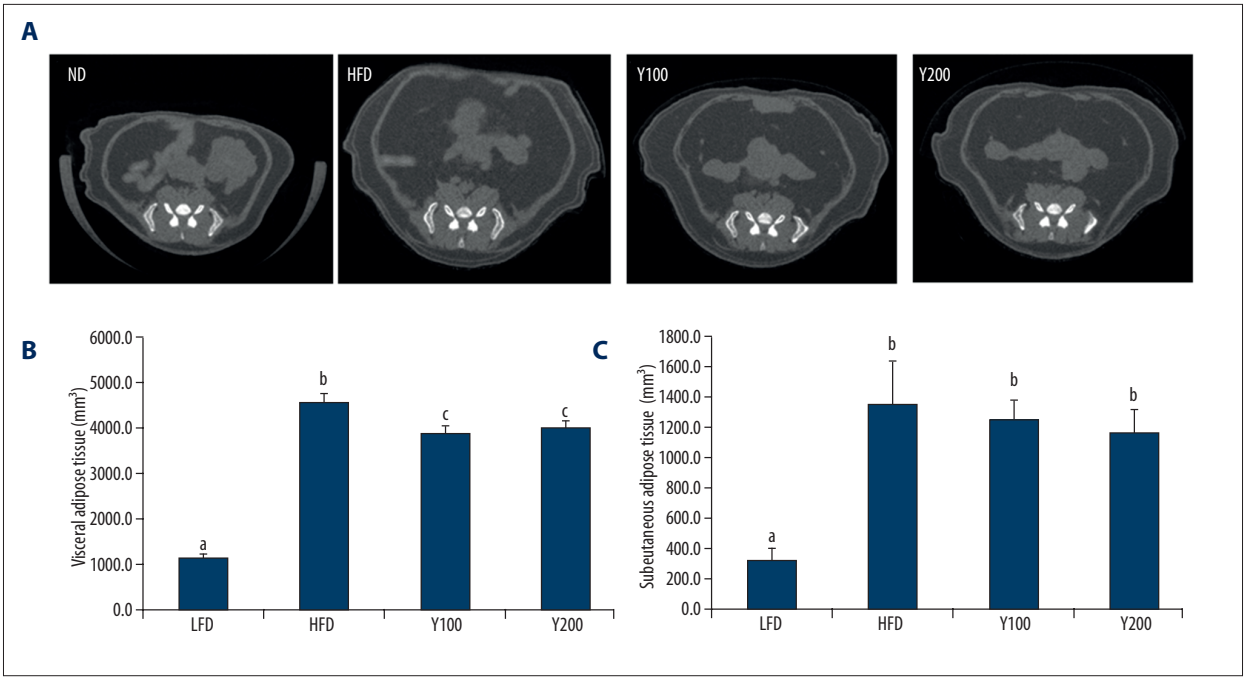

Figure 4. Transverse micro-CT images of the abdomen in C57BL6 mice fed with various diets (**A**). ND – normal diet, HFD – high-fat diet, Y100 DB extract-gavage with HFD, and Y200 DB extract-gavage with HFD. (**B**) DB extract supplementation reduced the visceral fat area from L1 to L5 in HFD-fed mice. (**C**) Subcutaneous fat area from L1 to L5 was not different among the HFD, Y100, and Y200 groups. DB extract supplementation did not prevent subcutaneous fat accumulation. Statistical analysis was performed using the ANOVA and post hoc analysis using Tukey's B analysis. Values with different letters are significantly different from one another (P<0.05).

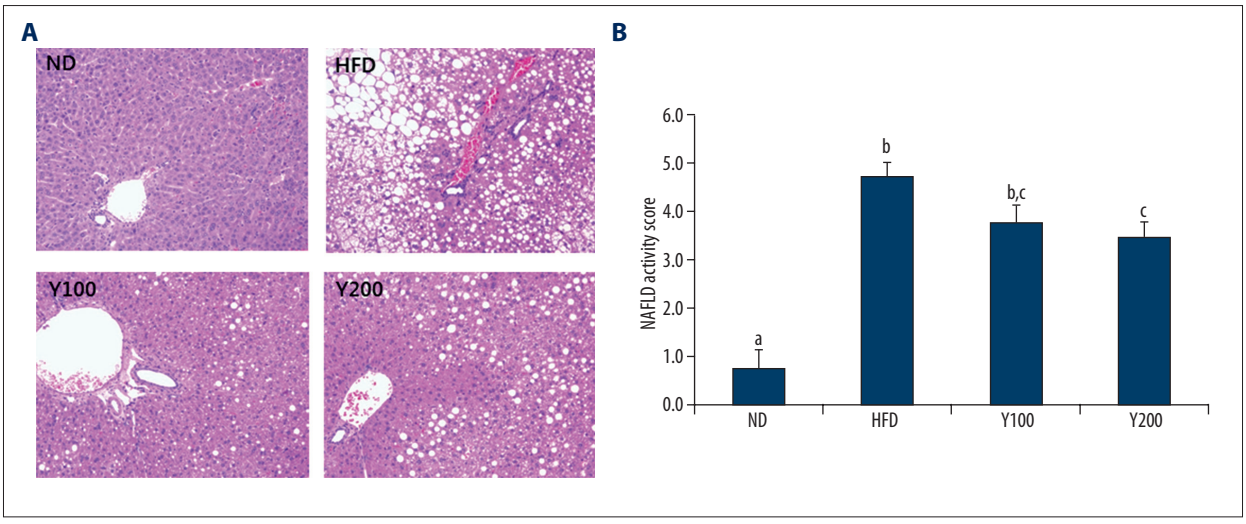

Figure 5. DB extract supplementation provided protection from high-fat-induced hepatic steatosis. (**A**) Representative images of H&E-stained livers of mice from ND or HFD groups (10×). (**B**) NAFLD activity score (NAS) was assessed by histopathology of H&E stained livers in a blinded fashion. The Y200 group exhibited significantly reduced NAS relative to the HFD group. Values represent means ±SEM. Values with different superscripts are significantly different from one another (P<0.05).

as assessed by H&E staining (Figure 5A). This response was reduced by supplementation with DB extract. Histopathological analysis revealed the NAS was greater in the HFD group than in the ND group (Figure 5B). The NAS of the Y200 group was significantly lower than that of the HFD group (3.44±0.34 *vs.* 4.70±0.30, P<0.001), although there was no difference between the NAS of the HFD and Y100 groups (4.70±0.30 *vs.* 3.78±0.36, P=0.430)

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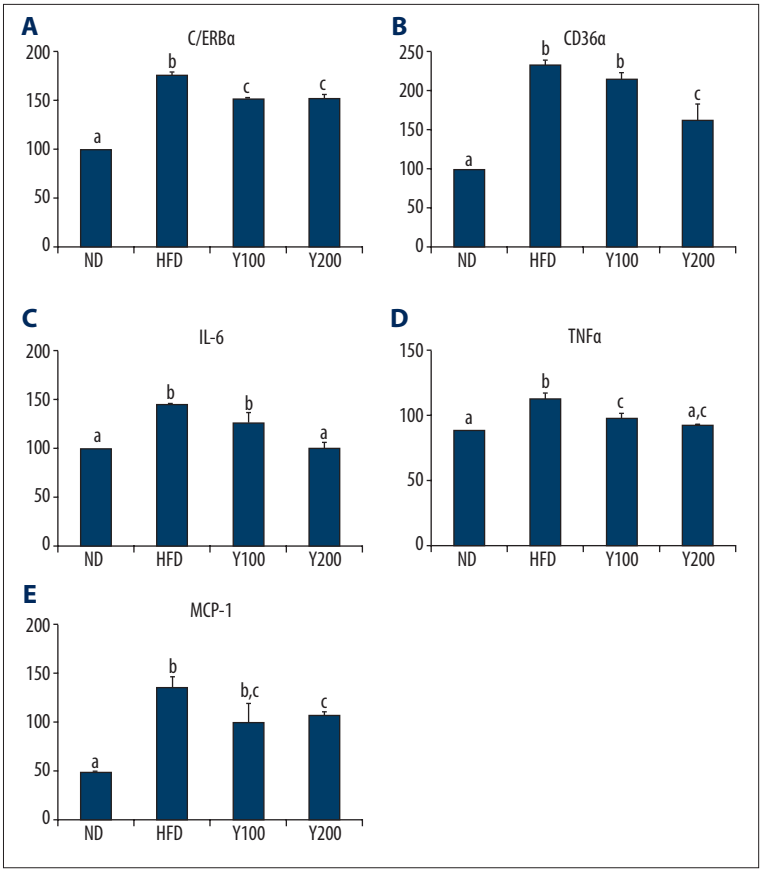

Figure 6. DB extract supplementation reduced high-fat-induced adipogenic and proinflammatory cytokines. (**A, B**) C/EBPα and CD36 are related with adipogenesis. DB extract (200 mg/dl) supplementation reduced expression of both cytokines. (**C–E**) TNF-α, IL-6, and MCP-1 in adipose tissue are proinflammatory cytokines that could be involved in systemic cardiovascular events due to obesity. DB extract (200 mg/dl) supplementation reduced both cytokines. Values represent means ±SEM. Values with different superscripts are significantly different from one another (P<0.05)

The effect of DB extract on the expression of genes related to adipogenesis and inflammation

Examination of adipogenic gene expression in epididymal adipose tissue showed that the mRNA levels of C/EBPα, a regulator of adipogenic factors, were significantly lower in DB extract-fed mice than in the HFD group (Figure 6A). The expression of the PPARγ2 target gene – cluster of differentiation 36 (CD 36) – was significantly decreased in the Y200 group compared to the HFD group (Figure 6B). We also examined the effect of DB extract supplementation on the expression of proinflammatory cytokines in epididymal adipose tissue. The proinflammatory cytokines in adipose tissue have been suggested to involve the cardiovascular event in obese patients [15]. Compared to HFD-fed mice, DB extract supplementation decreased the levels of HFD-induced TNF-α, IL-6, and MCP-1 in epididymal adipose tissue (Figure 6C–6E).

Discussion

Excessive dietary fat intake is one the most important environmental factors that causes obesity and chronic diseases such as hypertension, diabetes, and hyperlipidemia [16,17]. Some studies have demonstrated that a HFD can efficiently induce obesity, with an increase in body weight, adipose tissue weight, and hyperlipidemia in animals [18,19]. We investigated the ability of DB extract supplementation to exert an anti-obesity effect using a 14-week HFD feeding model. Kim et al. reported that the oral administration of 100 mg/kg of DB extract alleviated insulin resistance in a 4-week HFD feeding model [14]. In a previous study, an ethanol extract of *Dioscorea opposita* was reported to be effective in reducing the plasma glucose level in type 2 diabetic rats [20]. Based on these studies, DB extract concentrations of 100 mg/kg and 200 mg/kg were considered for this study. In the present study, the DB extract significantly decreased body weight gain and visceral adiposity in HFD-fed mice. The body weight did not vary significantly between the Y100 and Y200 groups. HFD-induced steatosis was not prevented by the 100-mg/Kg DB extract, but, the 200-mg/kg DB extract could reduce the HFD-induced steatosis. Regarding body weight, the high-dose DB extract was not necessary but was considered because of the potential improvement of liver function.

Circulating leptin is an ideal indicator for assessing obesity in both experimental animal models and humans [21–23]. In mice that became obese after being fed a HFD, leptin concentrations were, along with an increase in the expression of SOCS-3, a suppressor of cytokine signaling and a potent inhibitor of leptin signaling [24]. In our study, higher levels of DB supplement (Y200)

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prevented the HFD-induced increase of leptin, which could be attributable to the prevention of visceral adipocyte hypertrophy.

In obese states, adipocytes release cytokines, adipokines, and free fatty acids, which can act in a paracrine- or autocrine-dependent manner to amplify the proinflammatory state within adipose tissue [10–12]. Obesity increases the expression and secretion of TNFα, a prototypical inflammatory cytokine [25,26]. In turn, increased TNFα activates adipocytes, thereby further enhancing the expression of various proinflammatory genes such as MCP-1 and IL-6 [27,28]. IL-6 induces a hepatic acute-phase reaction with upregulated C-reactive protein and fibrinogen. In addition, MCP1 contributes to chronic inflammation. These cytokines could be involved the cardiovascular risk due to obesity, thus the cytokine response should be controlled in obesity. DB extract supplementation reduced the HFD-induced increase of IL-6 and MCP-1, which could be an additional benefit, independent of reducing body weight. On the other hand, C/EBPα is a key transcription factor involved in adipocyte differentiation and it transactivates adipocyte genes, including FAS, CD36, and aP2 [29]. CD36 facilitates the uptake of long-chain fatty acids in adipocytes, thereby increasing adipocyte and fat accumulation [30]. Supplementation with DB extract also inhibited the expression of adipogenesis genes. The anti-obesity effect of DB extract is likely related to these cytokines. We hypothesized that the high-dose DB extract would be more effective in reducing the expression of adipogenic genes and proinflammatory cytokines.

Conclusions

In conclusion, a diet containing DB extract suppressed body weight gain, fat accumulation, and hyperlipidemia. Furthermore, administration of DB extract improved leptin resistance and adipocyte cytokine expression. Therefore, dietary supplementation with this extract may be an effective adjunctive therapy for the prevention and/or treatment of obesity and related metabolic syndromes in mice. Further studies will be required to prove this effect of DB in humans.

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