ORIGINAL ARTICLE

Curcumin Attenuates Adipose Angiogenesis and Inflammation in Very High-Fat Diet-Induced Obesity Mice

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Objective: To investigate the effects of curcumin (CUR) on adipose angiogenesis and inflammation in a very high-fat diet (VHFD)-induced obesity mouse model, focusing on molecular mechanisms underlying its anti-obesity properties.

Materials and Methods: Male ICR mice (8 mice per group) were randomly assigned to three groups: low-fat diet (LFD), VHFD + vehicle, and VHFD + CUR (300 mg/kg/day). Treatments were administered orally for six weeks. Body weight (BW) and visceral white adipose tissue (vWAT) weight were recorded. Adipose angiogenesis was evaluated by CD31 immunostaining. The expressions of vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 alpha (HIF-1α), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-alpha (TNF-α), and nuclear factor-kappa B (NF-κB) in vWAT were assessed by immunohistochemistry.

Results: VHFD-fed mice exhibited significant increases in body weight, visceral fat weight, microvascular density (MVD), and the expression of VEGF, HIF-1α, MMP-2, MMP-9, TNF-α, and NF-κB compared with controls. CUR supplementation tended to reduce body weight and visceral fat weight and significantly suppressed MVD as well as the expression of VEGF, HIF-1α, MMP-2, and MMP-9. Moreover, CUR markedly reduced the pro-inflammatory markers TNF-α and NF-κB, thereby attenuating the inflammatory microenvironment in adipose tissue.

Conclusion: CUR attenuates obesity-associated adipose remodeling by suppressing angiogenesis, inflammation, and extracellular matrix remodeling enzymes through inhibition of the HIF-1α, VEGF, TNF-α, and NF-κB axis, underscoring its potential as a natural therapy for obesity.

Keywords: Curcumin; Adipose angiogenesis; Anti-inflammation; Vascular endothelial growth factor; Tumor necrosis factor-alpha

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Overweight and obesity have become rapidly escalating threats to public health across many countries. In Thailand, recent surveys indicate that 48.28% of the working-age population is classified as obese (BMI greater than 25), highlighting its significance as a national health concern[1]. Obesity is strongly associated with multiple chronic diseases, including type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, and certain cancers, leading to reduced quality of life and substantial healthcare costs. Despite advances in lifestyle interventions and pharmacotherapy, effective long-term strategies to prevent or reverse obesity remain limited, necessitating further investigation into its underlying mechanisms.

Adipose tissue expansion, the hallmark of obesity, occurs through both hypertrophy and hyperplasia[2]. These processes are tightly coupled with angiogenesis, the formation of new blood vessels from existing vasculatures. Angiogenesis ensures adequate oxygen and nutrient delivery to proliferate and differentiate adipocytes while facilitating waste removal[3]. Insufficient vascularization results in adipose hypoxia, inflammation, and fibrosis, whereas excessive angiogenesis supports pathological fat accumulation and obesity progression[4]. Pro-angiogenic mediators such as vascular endothelial growth factor (VEGF)[5,6], platelet-derived growth

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factor (PDGF)[6], and tumor necrosis factor-alpha (TNF-α)[2], along with extracellular matrix (ECM) remodeling enzymes like matrix metalloproteinases (MMPs)[7], play central roles in regulating adipose angiogenesis. Transcriptional regulators such as hypoxia-inducible factor-1 alpha (HIF-1α) further link hypoxia to angiogenic signaling in white adipose tissue (WAT).

Therefore, targeting angiogenesis has emerged as a potential therapeutic approach for obesity. Recent evidence summarized in a comprehensive review indicates that pharmacologic and herbal anti-angiogenic agents suppress adipose vascularization, thereby limiting adipose expansion and protecting against diet-induced obesity in animal models[8]. These findings highlight the pivotal role of vascular remodeling in adipose tissue growth and provide a rationale for evaluating natural compounds with anti-angiogenic properties as safer alternatives to synthetic drugs.

Curcumin, the principal bioactive polyphenol derived from *Curcuma longa* L. (turmeric), has long been recognized for its broad pharmacological activities. Extensive research has demonstrated its antioxidant, anti-inflammatory, metabolic regulatory, and anti-angiogenic effects[9-11]. Mechanistically, curcumin interferes with angiogenic signaling by downregulating VEGF expression, inhibiting endothelial cell proliferation and migration, and suppressing matrix-degrading enzymes such as MMP-2 and MMP-9[12,13]. While most studies have focused on cancer and inflammatory models, emerging evidence suggests that curcumin also modulates lipid metabolism, insulin sensitivity, and adipocyte differentiation, indicating potential benefits in obesity management[14,15]. The previous study demonstrated the short-term effects of tetrahydrocurcumin on adipose tissue angiogenesis in a very high-fat diet-induced obesity mouse model. While that study provided important evidence supporting the anti-angiogenic potential of curcumin derivatives, the specific signaling pathways through which curcumin modulates adipose angiogenesis remained unclear[16]. To address this limitation, the current study investigates the molecular mechanisms underlying curcumin-mediated regulation of adipose angiogenesis, with a particular focus on the HIF-1α, VEGF, TNF-α, and NF-κB signaling axis, which plays a central role in hypoxia-induced angiogenesis and inflammation in obese adipose tissue. By elucidating these mechanisms, this study provides novel insights into curcumin-induced modulation of adipose vascular remodeling and highlights its potential as a natural therapeutic strategy for obesity management.

Materials and Methods

Preparation of curcumin

Curcumin was isolated from crude curcuminoids purchased from Thai-China Flavours and Fragrances (TCFF). The crude curcuminoids were subjected to column chromatography using silica gel as the adsorbent and CH_2Cl_2-MeOH as the mobile phase under gradient elution, yielding curcumin with a 60% yield and a purity of 99.5% or better. The spectroscopic data were compared with previously reported values[17].

Animals and experimental model

All experimental procedures were approved by the Animal Ethics Committee of Thammasat University (020/2021). Male ICR mice weighing 20 to 25 g were obtained from Siam Nomura International Co. Ltd. and housed at the Animal Laboratory Center, Thammasat University. The animals were maintained under standard laboratory conditions, with free access to food and water, for a one-week acclimatization period. After acclimation, mice were randomly assigned to three groups (eight mice per group): 1) low-fat diet (LFD) group, received a low-fat diet (7% kcal from fat, CP082G, National Laboratory Animal Center, Thailand), 2) very high-fat diet (VHFD) group, received a very high-fat diet (60% kcal from fat, MP Biomedicals, USA), plus 1% DMSO in corn oil orally for 6 weeks, and 3) VHFD+CUR treated group, VHFD-fed mice treated with curcumin (300 mg/kg, orally, once daily for 6 weeks). Body weight and food intake were monitored weekly throughout the experiment. At the end of treatment, visceral white adipose tissues (vWATs) from retroperitoneal and mesenteric depots were excised and weighed. Relative adipose tissue weight was calculated as total vWATs normalized to final body weight. Tissue samples were then fixed in 10% formalin for subsequent analyses. Although a similar dietary model was employed in the previous study[16], all experiments and analyses in the present study were conducted to address distinct mechanistic questions, and the data were collected and analyzed specifically for the objectives of this investigation under the same approved ethical protocol.

Immunohistochemistry for CD31 expression and microvascular density determination

To evaluate angiogenesis, microvascular density

(MVD) was determined by immunohistochemical staining with an anti-CD31 antibody. Sections of vWAT were incubated with a ready-to-use monoclonal CD31 antibody (DAKO Cytomation, USA) according to a previously described method[18]. Tissue sections were examined under low magnification (40x), and the regions with the highest vessel density were identified. From these regions, three to five independent fields per mouse were imaged. The proportion of CD31-positive immunoreactive area relative to the total tissue area was quantified using ImageJ, version 1.38 (National Institutes of Health, USA).

Immunohistochemistry for angiogenic biomarkers and MMPs

Paraffin-embedded vWAT sections were incubated with primary monoclonal antibodies against VEGF (ready-to-use; DAKO Cytomation, USA), HIF-1α (1:100; nb100-131, Novus Biologicals, USA), MMP-2 (1:500; ab86607, Abcam, USA), and MMP-9 (1:500; ab288402, Abcam, USA) at 4°C for one hour. Following PBS washes, the sections were processed using the EnVision/HRP detection system (DAKO Cytomation, USA) for 30 minutes, followed by incubation with a DAB substrate-chromogen solution for 10 minutes at room temperature. Quantification was performed by calculating the percentage of immunopositive areas for VEGF, HIF-1α, MMP-2, and MMP-9 relative to the total tissue area using ImageJ, version 1.38 (National Institutes of Health, USA).

Immunohistochemistry for inflammatory biomarkers

Paraffin-embedded vWAT sections were incubated with primary monoclonal antibodies against TNF-α (1:100; ab1793, Abcam, USA) and NF-κB (1:800; ab16502, Abcam, USA) at 4°C for one hour. After washing with PBS, the sections were developed using the EnVision/HRP system (DAKO Cytomation, USA) for 30 minutes and visualized with DAB chromogen for 10 minutes at room temperature. Quantification was performed by calculating the percentage of TNF-α and NF-κB-positive areas relative to the total tissue area using ImageJ, version 1.38 (National Institutes of Health, USA).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Analysis of variance (ANOVA) in conjunction with Tukey's post hoc test was used to compare multiple groups, and a difference of p-value less than 0.05 was considered to be statistically significant. The data are presented as the means ± standard error of the mean (SEM).

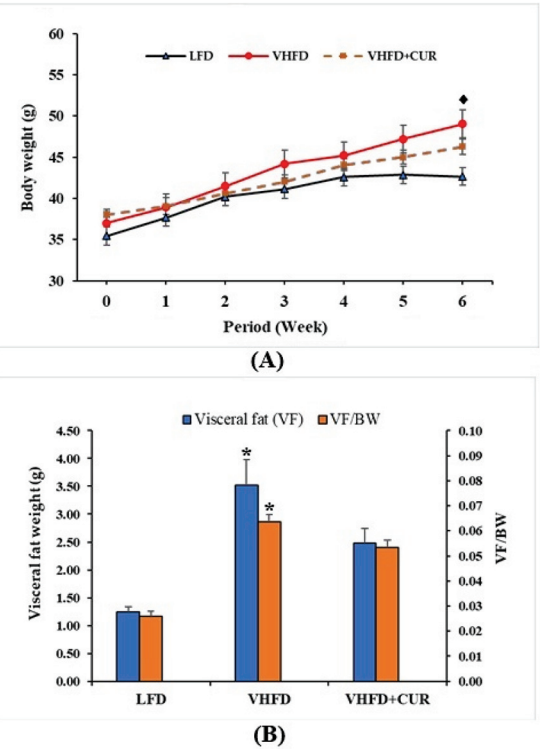

Figure 1. Effect of CUR on body weight and visceral adiposity. (A) Body weight, (B) Visceral fat weight and visceral fat weight/body weight ratio.

Data are expressed as mean ± SEM, ♦ $p<0.05$ vs. LFD group, * $p<0.001$ vs. LFD group.

Results

Effect of curcumin on body weight and visceral adiposity

Figure 1A shows the changes in body weight across the experimental groups. At week 6, mice in the VHFD group exhibited a significantly higher body weight (49.05±1.56 g) compared with the LFD control group (42.67±0.63 g) ($p<0.05$). In the VHFD+CUR group, body weight (46.29±0.95 g) was lower than that of the VHFD group. However, the difference was not statistically significant.

As illustrated in Figure 1B, both visceral fat weight and the visceral fat weight-to-body weight ratio were markedly elevated in the VHFD + vehicle group (3.52±0.46 and 0.066±0.003) compared with the control group (1.24±0.01 and 0.028±0.002)

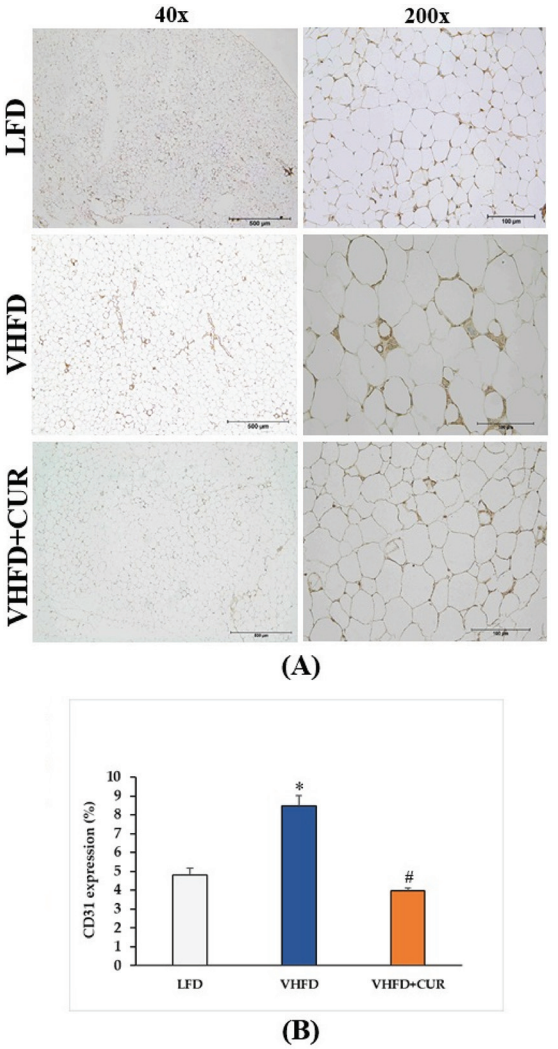

Figure 2. Effect of CUR on adipose tissue angiogenesis. (A) Representative CD31 immunostaining in vWAT (left: 40x, scale bar=500 µm; right: 200x, scale bar=100 µm), (B) Quantification of microvascular density (% of CD31-positive staining).

Data are expressed as mean ± SEM, * p<0.001 vs. LFD group; # p<0.001 vs. VHFD group.

(p<0.001). Curcumin treatment tended to attenuate these increases, as indicated by reductions in both parameters (2.48±0.27 and 0.053±0.003) compared with the VHFD + vehicle group.

Effect of curcumin on adipose tissue angiogenesis

Figure 2A demonstrates that adipose tissue from VHFD-fed mice was highly vascularized, whereas curcumin-treated mice exhibited reduced vascularization. The MVD, quantified as the percentage of CD31 expression, was significantly elevated in the VHFD-fed group (8.49±0.53),

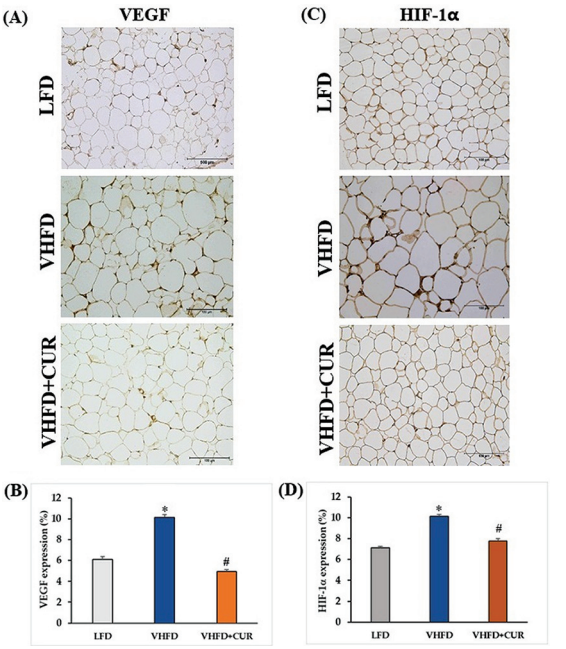

Figure 3. Effect of CUR on VEGF and HIF-1α expression. (A) Representative VEGF immunostaining (200x, scale ba r=100 µm), (B) Quantification of VEGF-positive staining (%), (C) Representative HIF-1α immunostaining (200x, scale bar =100 µm), (D) Quantification of HIF-1α-positive staining (%).

Data are expressed as mean ± SEM, * p<0.001 vs. LFD group, # p<0.001 vs. VHFD group.

compared with the LFD group (4.81±0.37) (p<0.001). Notably, curcumin treatment significantly reduced MVD in adipose tissue (3.99±0.14) compared with the untreated VHFD-fed mice (p<0.001) (Figure 2B).

Effect of curcumin on the expression of VEGF and HIF-1α in adipose tissue

Immunohistochemical analysis revealed that VEGF expression was markedly higher in the VHFD group compared with the LFD group. Interestingly, curcumin treatment attenuated VEGF expression (Figure 3A). As shown in Figure 3B, VEGF expression, at 10.14±0.29%, was significantly elevated in the VHFD group relative to the LFD group (6.12±0.25%) (p<0.001). Importantly, curcumin-treated mice exhibited a significant reduction in VEGF-positive staining (4.96±0.17%) (p<0.001).

HIF-1α, a key transcription factor that mediates hypoxia-induced angiogenesis, was markedly overexpressed in the VHFD group compared with the LFD group. However, curcumin treatment attenuated HIF-1α expression (Figure 3C). As shown in Figure 3D, HIF-1α expression (10.11±0.43%) was

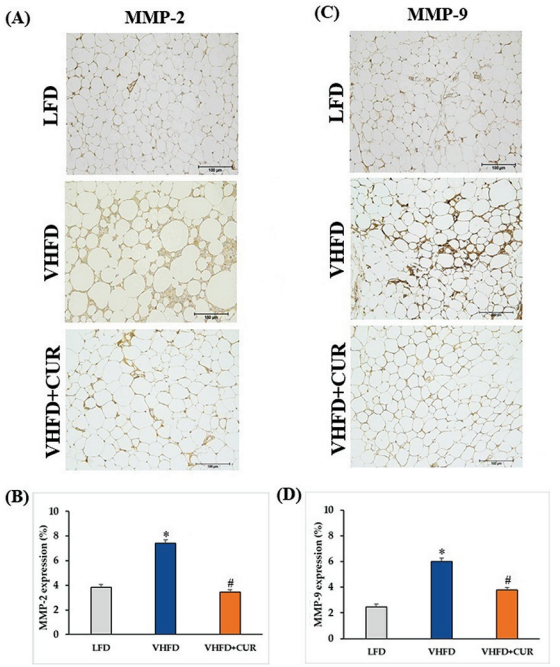

Figure 4. Effect of CUR on MMPs expression. (A) Representative MMP-2 immunostaining (200x, scale bar=100 µm), (B) Quantification of MMP-2-positive staining (%), (C) Representative MMP-9 immunostaining (200x, scale bar=100 µm), (D) Quantification of MMP-9-positive staining (%).

Data are expressed as mean ± SEM, * p<0.001 vs. LFD group, # p<0.001 vs. VHFD group.

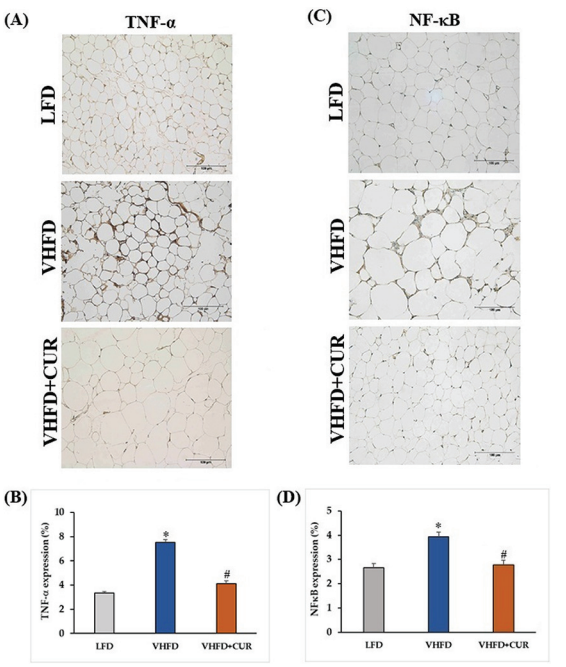

Figure 5. Effect of CUR on TNF-α and NF-κB expression. (A) Representative TNF-α immunostaining (200x, scale bar=100 µm), (B) Quantification of TNF-α-positive staining (%), (C) Representative NF-κB immunostaining (200x, scale bar=100 µm), (D) Quantification of NF-κB-positive staining (%).

Data are expressed as mean ± SEM, * p<0.001 vs. LFD group, # p<0.001 vs. VHFD group.

significantly higher in the VHFD group than in the LFD group (7.11±0.22%) (p<0.001). Importantly, curcumin-treated mice exhibited a significant reduction in HIF-1α-positive staining (7.79±0.34%) (p<0.001) relative to the VHFD group.

Effect of curcumin on the expression of MMPs in adipose tissue

MMP-2 and MMP-9 expressions were markedly increased in the VHFD group, whereas both were notably reduced following curcumin treatment (Figures 4A and 4C). Quantitative analysis of positive staining is presented in Figure 4B and 4D. In the VHFD group, MMP-2 (7.42±0.40%) and MMP-9 (5.98±0.25%) expression levels were significantly higher than those in the LFD group, with MMP-2 (3.83±0.20%) and MMP-9 (2.45±0.25%) (p<0.001). In contrast, the VHFD+CUR group exhibited significantly lower percentages of MMP-2 (3.46±0.16%) and MMP-9 (3.77±0.24%) positive staining compared with the VHFD group (p<0.001).

Effect of curcumin on the expression of TNF-α and NF-κB in adipose tissue

As shown in Figure 5A, TNF-α expression was markedly elevated in the VHFD group, whereas it was significantly reduced following curcumin treatment. Figure 5B illustrates the percentage of TNF-α-positive staining. In the VHFD group, TNF-α expression (7.53±0.21%) was significantly higher than in the LFD group (3.35±0.14%) (p<0.001). In contrast, the VHFD+CUR group exhibited a significant reduction in TNF-α-positive staining (4.13±0.22%) compared with the VHFD group (p<0.001).

Immunohistochemical analysis revealed that NF-κB expression was markedly higher in the VHFD group compared with the LFD group. In contrast, the VHFD+CUR group exhibited weaker NF-κB expression than the VHFD group (Figure 5C). As shown in Figure 5D, NF-κB expression (3.93±0.20%) was significantly elevated in the VHFD group relative to the LFD group (2.65±0.18%) (p<0.005). Importantly, curcumin supplementation significantly reduced NF-κB-positive staining (2.78±0.19%) compared with untreated VHFD mice (p<0.005).

Discussion

Previous reports have suggested that the growth and development of adipose tissue are closely associated with angiogenesis and ECM remodeling[19]. Neovascularization in adipose tissue depends on continuous angiogenesis, and inhibition of angiogenic pathways significantly reduces body weight and adipose tissue mass[3,19-21], supporting a critical role for angiogenesis in adipose expansion. The previous study demonstrated that tetrahydrocurcumin suppresses adipose angiogenesis by downregulating angiogenic factors (VEGF and TNF-α) and reduces ECM remodeling via decreased MMP-2 and MMP-9 expression in VHFD-induced obese mice[16]. However, the molecular mechanisms underlying the anti-angiogenic effects of curcumin, the parent compound, in VHFD-induced obesity remain incompletely understood. Therefore, the present study aimed to explore the potential molecular mechanisms of curcumin on adipose angiogenesis in mice with obesity induced by a very high-fat diet.

In the present study, curcumin supplementation attenuated obesity-associated adipose tissue remodeling in VHFD-induced obese mice through multiple mechanisms. Although curcumin did not significantly reduce body weight, it tended to decrease visceral fat mass and the visceral fat-to-body weight ratio, indicating a modest effect on adiposity. These findings are consistent with previous reports showing that natural polyphenols, including curcumin, exert anti-obesity effects primarily by modulating adipose tissue metabolism, inflammation, and angiogenesis rather than by directly inducing weight loss[22-24]. Notably, body weight reflects the combined mass of multiple tissues and is influenced by overall energy intake, energy expenditure, and metabolic adaptation. Therefore, although inhibition of adipose angiogenesis might restrict adipocyte hypertrophy and hyperplasia at the tissue level, this effect alone might be insufficient to induce a significant reduction in body weight within the experimental timeframe. Collectively, these results suggest that curcumin exerts its anti-obesity effects by improving adipose tissue quality, inflammatory status, and metabolic function rather than by directly promoting overt weight loss.

A key novel observation of the present study is that curcumin significantly reduced adipose angiogenesis, reflected by a decrease in CD31 expression and microvascular density (MVD). Consistent with the previous observations[16], the VHFD group in the present study exhibited increased adipose tissue angiogenesis compared with the LFD group, supporting the validity of the dietary obesity model in the present study. Since angiogenesis provides essential vascular support for adipocyte hypertrophy and hyperplasia, suppression of angiogenesis represents an important strategy for limiting adipose tissue expansion. Mechanistically, curcumin downregulated VEGF and HIF-1α, two critical angiogenic mediators activated under hypoxic conditions in expanding white adipose tissue. In addition, CUR inhibited MMP-2 and MMP-9 expressions, suggesting that it targets both the signaling axis of VEGF and HIF-1α, and ECM remodeling enzymes (MMPs).

HIF-1α plays a central role in coordinating hypoxic responses in adipose tissue. Under low oxygen conditions, HIF-1α induces VEGF-driven angiogenesis and promotes TNF-α-mediated inflammation[25,26]. In addition, crosstalk between the HIF-1α and NF-κB pathways amplifies these responses, as NF-κB, activated by inflammatory stimuli such as TNF-α, enhances HIF-1α expression even under normoxic conditions. This interaction establishes a feed-forward loop linking hypoxia and inflammation, in which NF-κB acts as a master regulator of pro-inflammatory gene expression, and TNF-α serves as a key driver of adipose inflammation and systemic metabolic dysfunction[26]. Consequently, chronic low-grade inflammation driven by the HIF-1α, VEGF, TNF-α, and NF-κB axis represents a hallmark of obesity and contributes critically to the development of insulin resistance and metabolic syndrome.

Consistent with this mechanism, a previous study demonstrated that VHFD-fed mice exhibited overexpression of inflammatory cytokines in WAT, including TNF-α, accompanied by adipocyte hypertrophy and crown-like structure (CLS) formation[16]. In line with these observations, the present study demonstrated that curcumin supplementation significantly suppressed NF-κB and TNF-α, highlighting its ability to attenuate the pro-inflammatory microenvironment within adipose tissue. Although curcumin exhibits low oral bioavailability, several mechanisms may explain its observed biological effects. Curcumin can exert local intestinal actions, influence gut-derived inflammatory signaling, and be metabolized into active derivatives such as tetrahydrocurcumin. Notably, the previous finding demonstrated that tetrahydrocurcumin significantly attenuated adipose tissue angiogenesis in a VHFD-induced obesity mouse model[16], supporting

the notion that curcumin metabolites contribute to its in vivo anti-angiogenic effects. Moreover, tissue accumulation and repeated exposure may enable curcumin and its active metabolites to modulate adipose tissue angiogenesis and inflammation despite low plasma concentrations.

The observed reduction in angiogenic and inflammatory markers is mediated, at least in part, by the anti-inflammatory activity of curcumin. Curcumin inhibits NF-κB signaling and downstream TNF-α expression, which may in turn attenuate HIF-1α stabilization and VEGF activation. In addition, its antioxidant properties may further limit hypoxia-driven signaling pathways, collectively contributing to reduced adipose angiogenesis and inflammation. Together with its inhibition of HIF-1α and VEGF, these findings suggest that curcumin disrupts the inflammatory-angiogenic axis in obesity. By simultaneously modulating hypoxia-induced angiogenic signaling and NF-κB-mediated inflammation, curcumin interrupts the synergistic pathways driving pathological adipose expansion and chronic inflammation.

Limitation

The present study has limitations, including:

First, this was conducted solely in a VHFD-induced obese mouse model, which may not fully reflect the complex pathophysiology of human obesity, limiting the generalizability of the findings.

Second, only male mice were used in the present study, leaving potential sex-specific differences in adipose angiogenesis and inflammatory responses unexamined.

Third, although curcumin was shown to downregulate angiogenic (VEGF and HIF-1α), inflammatory (TNF-α and NF-κB), and ECM remodeling (MMP-2 and MMP-9) markers, the underlying molecular pathways were not fully elucidated. Further mechanistic studies, including transcriptomic or proteomic profiling, are needed to confirm downstream targets.

Finally, the intervention period was short (six weeks), and the long-term effects of curcumin on obesity progression and metabolic complications remain unclear.

Conclusion

Curcumin mitigates obesity-associated adipose tissue remodeling by inhibiting angiogenesis, inflammation, and ECM remodeling enzymes through suppression of the HIF-1α, VEGF, TNF-α, and NF-κB axis in a very high-fat diet (VHFD)-induced obesity mouse model. These integrated effects support curcumin's potential as a natural therapeutic candidate for obesity management.

What is already known about this topic?

1. Obesity is a global health concern characterized by excessive adipose tissue expansion, which occurs through both adipocyte hypertrophy and hyperplasia. These processes are tightly linked to angiogenesis, as new blood vessels are required to support nutrient and oxygen supply in expanding adipose tissue.

2. Angiogenesis in white adipose tissue is essential for fat mass expansion. Inhibition of angiogenesis in experimental models has been shown to reduce adipose tissue mass and body weight, highlighting angiogenesis as a therapeutic target in obesity.

3. Key pro-angiogenic and inflammatory mediators in adipose tissue include VEGF, HIF-1α, TNF-α, and NF-κB, together with ECM remodeling enzymes such as MMP-2 and MMP-9. Importantly, crosstalk between hypoxia and inflammation, mediated through the HIF-1α/VEGF and NF-κB/TNF-α axes, drives pathological adipose tissue expansion and dysfunction.

4. Previous studies have suggested that curcumin and its metabolites (e.g., tetrahydrocurcumin) may modulate adipose tissue metabolism and suppress angiogenesis, but direct evidence of curcumin's role in adipose angiogenesis in the VHFD-induced obesity mouse model remains limited.

What does this study add?

This study demonstrates that curcumin supplementation attenuates obesity-associated adipose tissue remodeling in VHFD-fed mice. Curcumin suppresses angiogenesis, inflammation, and ECM remodeling in adipose tissue by downregulating VEGF, HIF-1α, TNF-α, NF-κB, MMP-2, and MMP-9 expression. These findings provide novel evidence that curcumin disrupts the angiogenic and inflammatory pathways driving adipose tissue expansion, highlighting its potential as a natural therapeutic candidate for obesity management.

Authors' contributions

US, PP, ND, NS, PT, CC, and BY contributed to the conception and design of the study. US, NM, NP, CC, AK, BK, and BY contributed to data acquisition, analysis, and interpretation. CC and BY provided research resources. US, PP, ND, PT, and BY drafted

the manuscript, critically revised it, and approved the final version for publication. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability statement

The data analyzed during this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All experimental procedures were approved by the Animal Ethics Committee of Thammasat University (Approval No. 020/2021) and were conducted in accordance with relevant institutional guidelines and regulations for the care and use of laboratory animals.

Clinical trial registration

Not applicable, as this study did not involve a clinical trial.

Use of artificial intelligence

The authors did not use artificial intelligence (AI) tools for data analysis or interpretation. AI-assisted tools (ChatGPT, version 5, OpenAI) were used only for language editing. All content was critically reviewed and approved by the authors.

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Conflicts of interest

The author declares no conflict of interest.

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