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Sulforaphane attenuates high-fat diet-induced myocardial injury via AMPK/SIRT1/P65 signaling in mice

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Abstract: **Background**: Obesity-induced metabolic disorders are closely associated with myocardial injury, in which lipid accumulation and chronic inflammation play critical roles. Activation of the AMPK/SIRT1 pathway has been reported to suppress NF-κB–mediated inflammatory responses and protect cardiac function. Sulforaphane (SFN), a bioactive isothiocyanate derived from cruciferous vegetables, exhibits potent metabolic and anti-inflammatory properties; however, its protective effects and underlying mechanisms in obesity-related myocardial injury remain incompletely understood. **Objectives**: This study aimed to investigate whether SFN alleviates high-fat diet (HFD)–induced myocardial injury and to elucidate the involvement of the AMPK/SIRT1/NF-κB signaling pathway. **Methods**: Male C57BL/6 mice were fed a normal diet or HFD, with or without SFN treatment, for 16 weeks. Metabolic parameters, serum lipid profiles, myocardial injury markers, inflammatory cytokines and histopathological changes were evaluated. *In vitro*, palmitic acid-treated H9c2 cardiomyocytes were used to assess the mechanistic role of AMPK/SIRT1 signaling, with pharmacological inhibition of AMPK. **Results**: SFN significantly reduced body weight, fasting glucose, serum triglycerides, total cholesterol, free fatty acids, and LDL levels in HFD-fed mice. SFN markedly attenuated myocardial structural damage and decreased serum CK, CK-MB, and cTnI levels. Inflammatory cytokines (TNF-α, IL-1β, IL-6) were suppressed at both serum and myocardial mRNA levels. Mechanistically, SFN enhanced AMPK phosphorylation and SIRT1 expression while inhibiting p65 phosphorylation. *In vitro*, AMPK inhibition reversed the anti-inflammatory effects of SFN. **Conclusion**: SFN effectively alleviates HFD-induced myocardial injury by activating the AMPK/SIRT1 pathway and suppressing NF-κB–mediated inflammation, highlighting its potential as a therapeutic agent for obesity-related cardiac injury.

Keywords: AMPK/SIRT1; Inflammation; Myocardial injury; P65 phosphorylation; Sulforaphane

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INTRODUCTION

The global rise in obesity has increased the burden of related complications, among which obesity-related cardiomyopathy poses a significant threat to human health (Lin, *et al*., 2023, Zuo, *et al*., 2022). Researche indicates that obesity increases blood lipid levels, elevates hemodynamic load, leading to compensatory cardiac hypertrophy and exacerbating the risk of heart damage (Mouton, *et al*., 2020, Nishida and Otsu, 2017). Moreover, the disruption of lipid metabolism and the imbalance of myocardial inflammatory factors interact with each other, accelerating accelerating myocardial damage and forming a vicious cycle. (Carbone, *et al*., 2022, Halade and Lee, 2022). Adenosine monophosphate-activated protein kinase (AMPK) monitors cellular energy status and enhances SIRT1 function by modulating the NAD+/NADH ratio. Research has shown AMPK/SIRT1 pathway activation suppresses nuclear factor-kappa B (NF-κB) phosphorylation, thereby alleviating myocardial damage induced by disruptions in lipid metabolism and glucose (Tian, *et al*., 2016). Sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetables, exhibits potent anti-inflammatory properties (Zhang, *et al*., 2022). Studies have reported that SFN can improve ischemia-reperfusion injury and myocardial damage induced by angiotensin II (Ang II) in rodents (Taguchi, *et al*., 2021, Wang, *et al*., 2021). SFN is known to promote AMPK phosphorylation (Sun, *et al*., 2020). However, it is unclear whether SFN alleviates obesity-related myocardial injury through the AMPK/SIRT1 signaling pathway. This study therefore aimed to investigate the protective effect of SFN against HFD-induced myocardial injury and to elucidate its underlying mechanism, with a specific focus on the AMPK/SIRT1/NF-κB pathway. By integrating in vivo and in vitro models, we demonstrated the positive effects of SFN on metabolic and structural cardiac outcomes, and focused on the regulation of the AMPK/SIRT1/NF-κB pathway, preliminarily revealing the mechanism by which the SFN treats myocardial injury in a high-fat diet (HFD)-induced obese mouse model. This study addresses an important gap in the current understanding of obesity-related myocardial injury and provides a new perspective for the research on obesity-related cardiac injury.

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MATERIALS AND METHODS

Animals and cells

C57BL/6 male mice (n = 24, 20–22 g, SPF level) were sourced from Huafukang Biological Technology Co., Ltd., Beijing, China (License No. SCXK (Beijing) 2019-0008). The mice were housed under controlled temperature (22–24℃) and humidity (50%–60%) with a 12 h light/dark cycle and ad libitum access to food and water. All animal handling and experimental protocols were conducted in strict adherence to the ethical framework of Wenzhou University (Ethical Review Approval Number: WZU-2021-048). H9c2 myocardial cells, sourced from American Type Culture Collection (ATCC), cultured in DMEM medium (10% fetal bovine serum, 100 U/mL penicillin) and maintained at 37ºC in 5% CO_2. The cell line was regularly authenticated via STR profiling to confirm its identity. Additionally, the cell line was routinely tested for the absence of mycoplasma, chlamydia, as well as other common contaminants, to maintain culture purity.

Drugs and reagents

Sulforaphane (HY-13755), palmitic acid (HY-N0830) and the AMPK inhibitor (compound C, HY-13418A) were purchased from the American company MedChemExpress. The triglyceride (A110-1), total cholesterol (A111-1), free fatty acid (A042-2), high-density lipoprotein (A112-1), low-density lipoprotein (A113-1), creatine kinase (A032-1), creatine kinase isoenzyme (H197-2), cardiac troponin I (H149-2), tumor necrosis factor-α (H052-2), Interleukin-1β (H002-1) and IL-6 (H007-1) assay kits were purchased from Nanjing Biotech Co., Ltd. All remaining reagents used were of analytical purity.

Instruments and equipment

TissueLyser II electric homogenizer (QIAGEN, Germany), Synergy2 microplate reader (Biotek, USA), cell culture incubator (Binder, Germany), biosafety cabinet (Thermo, USA), electrophoresis system (Bio-Rad, USA) and LightCycler 96 PCR instrument (Roche, Switzerland).

Animal model establishment

A total of 24 mice were randomly assigned to three groups (n=8 per group): NCD group (normal diet), HFD group (high-fat diet) and HFD+SFN group (high-fat diet plus daily subcutaneous SFN injections at 0.5 mg/kg over 16 weeks). The HFD group received subcutaneous injections of an equivalent volume of saline.

Establishment of an in-vitro cell model

After overnight cell incubation in cell culture plates, after medium exchange, cells were exposed to 200 μM PA for 48 h. At the 24-hour mark of PA treatment, SFN (2.5 μM) or AMPK inhibitor (10 μM) was added to the cells.

Serum biochemical analysis and hematoxylin and eosin (HE) staining

After administering anesthesia via intraperitoneal injection of pentobarbital (50 mg/kg), blood was collected via orbital sinus. Serum was collected after allowing the blood to clot for 0.5 h followed by 15 min of low-speed centrifugation. Measurement of serum biochemical parameters and proinflammatory cytokine levels. Following humane euthanasia with 150 mg/kg pentobarbital (i.p.). Cardiac tissues were promptly harvested, settled in 4% paraformaldehyde (24 h), paraffin-embedded, sectioned, stained to observe myocardial tissue morphology under a microscope.

RT-qPCR analysis

Approximately 50 mg of cardiac tissue was homogenized and RNA was subsequently extracted using the Trizol method. RNA quality and quantity were evaluated before synthesizing cDNA with a reverse transcription kit (Vazyme, China), followed by SYBR Green (Vazyme, China) based RT-qPCR for gene expression analysis. Primer sequences were synthesized by Shanghai Sangon Biotech in Table 1. The $2^{-\Delta\Delta Ct}$method was employed to quantify target gene expression levels.

Western blot

RIPA protein lysis buffer (500 μL) was used to lyse the heart tissue (100 mg). The Bradford assay was used to evaluate protein concentration. 10% SDS-PAGE electrophoresis, transfer, blocking, antibody incubation and exposure followed by imaging (GE IA600, USA). Protein levels of p65, p-p65, AMPK, p-AMPK, SIRT1 were analyzed, reference protein GAPDH were detected. Primary antibodies were all purchased from Abcam, USA (lot numbers: ab32536, ab76302, ab32047, ab207442, ab110304, ab8245) and diluted to a ratio of 1:1000. Secondary antibodies were all purchased from Nanjing Biotech Co., Ltd. (lot numbers: A0208, A0216) and diluted to a ratio of 1:2000.

Statistical analysis

SPSS 18.0 software was used for data analysis. Values were presented as mean ± standard deviation (x ± s). Prior to conducting ANOVA, the Shapiro–Wilk test was applied to assess the normality of data distribution and Levene's test was used to examine the homogeneity of variances. One-way analysis of variance (ANOVA) was used for comparisons between various groups and post hoc Tukey analysis was used for pairwise group comparisons, with $P < 0.05$ considered statistically significant.

RESULTS

The effects of SFN on body weight and fasting blood glucose in HFD mice

Although there was no significant difference in food intake between the NCD group and the HFD group (Fig. 1A), the body weight (Fig. 1B-C) and fasting blood glucose (Fig. 1D) of the HFD group mice significantly increased (all $P < 0.01$). The treatment with SFN reversed these changes, leading to weight loss (Fig. 1B), a decrease in BMI (Fig. 1C), and a reduction in blood glucose levels (Fig. 1D) (all

$P < 0.01$), demonstrating the therapeutic potential of SFN in diet-induced obesity.

The influence of SFN on blood lipids in HFD mice

The HFD group showed notable elevated serum levels of total TC, TG and FFA compared with the NCD group ($P < 0.05$). In response to SFN intervention, HFD+SFN group displayed greatly lower serum lipid profiles compared with the HFD group ($P < 0.05$, Table 2), indicating that SFN alleviates hyperlipidemia in HFD mice, exerts anti-hyperlipidemic effects.

The impact of SFN on myocardial damage in HFD mice

H&E staining showed that compared with the NCD group, the myocardial fibers of HFD mice were fragmented, disordered, and myoplasmic dissolution was evident. However, the intervention of SFN significantly improved these conditions and alleviated the myocardial damage (Fig. 2). It also significantly reduced the pathological score ($P < 0.05$, Table 3). In addition, compared with the HFD group, the SFN intervention could also lower the levels of CK, CK-MB and cTnI in the serum (Table 3, $P < 0.05$). This provides strong evidence that SFN helps protect myocardial tissue from damage caused by obesity.

The effects of SFN on inflammation levels in HFD mice

Compared with the control group, the levels of TNF-α, IL-1β and IL-6 in the serum of HFD mice were increased ($P < 0.001$), but the intervention of SFN could effectively reduce the levels of these pro-inflammatory factors (Fig. 3A) ($P < 0.05$). Similarly, the mRNA levels of TNF-α, IL-1β and IL-6 in the myocardial tissue of HFD mice were significantly upregulated, while the intervention of SFN could downregulate the mRNA expression of these cytokines in the myocardial tissue (Fig. 3B) ($P < 0.05$). This indicates that SFN can significantly inhibit inflammation.

The effects of SFN on AMPK/SIRT1 and NF-κB signaling pathways in myocardial tissue of obese mice

Compared with the NCD group, the protein levels of p-AMPK and SIRT1 in the myocardial tissues of the HFD group were significantly decreased ($P < 0.05$), indicating that HFD inhibited the AMPK/SIRT1 pathway. The intervention of SFN effectively restored the expression of p-AMPK and SIRT1 (Fig. 4A-C) ($P < 0.01$), suggesting that SFN can enhance AMPK/SIRT1 signaling. Compared with the HFD group, SFN did not affect the expression level of p65 protein, but significantly reduced the phosphorylation level of p65 in the myocardial tissues (Fig. 4D-F) ($P < 0.01$), indicating that it inhibits the activation of NF-κB.

SFN suppresses myocardial inflammation by triggering the AMPK/SIRT1 pathway

To elucidate the mechanism underlying SFN's anti-inflammatory effect, H9c2 cells were treated with palmitic acid (PA) to model inflammation and assess AMPK/SIRT1 pathway involvement. PA exposure resulted in suppressed p-AMPK and SIRT1 expression within H9c2 cells while notably increasing p-p65 protein expression ($P < 0.05$). SFN treatment increased phosphorylated levels of AMPK and SIRT1 proteins and inhibited p65 phosphorylation (Fig. 5A-E) ($P < 0.05$). However, the co-administration of Compound C (CC, AMPK inhibitor) attenuated SFN's regulatory effect on the AMPK/SIRT1/P65 signaling axis.

Furthermore, following SFN administration, a notable suppression of pro-inflammatory factors Il-1β, Tnf-α, Il-6 mRNA transcription was observed when compared with the PA group ($P < 0.01$). However, CC substantially diminished SFN's ability to suppression of pro-inflammatory gene expression (Fig. 6) ($P < 0.01$), indicating that SFN alleviates PA-induced myocardial cell inflammation via the AMPK/SIRT1 pathway.

DISCUSSION

Obesity is a global health challenge that has adverse effects on multiple organs, among which heart damage is of particular concern. It increases cardiac workload, reduces contractility, and may lead to compensatory hypertrophy (Lavie, *et al*., 2013, Zuo, *et al*., 2022). As a small-molecule bioactive compound derived from natural sources, SFN plays a critical role in managing metabolic disease progression. It possesses potent anti-inflammatory properties and the ability to scavenge free radicals. SFN inhibits the accumulation of lipid peroxidation products such as 4-hydroxynonenal and MDA, thereby enhancing vascular resistance and permeability (Luo, *et al*., 2024). Previous studies have shown that SFN mitigates oxidative stress and activates the Nrf2/ARE pathway in metabolic disease models. (Zhang, *et al*., 2022). This study demonstrated that SFN can effectively inhibit the weight gain of obese mice induced by a HFD and reduce fasting blood glucose levels. Compared with the NCD group, long-term high-fat diet feeding significantly increased the levels of TC and TG in the circulation, leading to excessive accumulation of FFAs, which are known to cause cardiac toxicity. In contrast, SFN significantly reduced the levels of triglycerides, total cholesterol, and free fatty acids in the serum, indicating a significant improvement in systemic lipid metabolism. Serum CK, CK-MB, and cTnI are recognized biomarkers for assessing myocardial injury. Consistent with previous research results (Fu, *et al*., 2022, Hu and Li, 2013), long-term exposure to HFD led to significant myocardial structural abnormalities, including cell deformation, cell membrane damage, and fiber rupture. SFN treatment significantly alleviated these pathological changes, indicating that SFN has a beneficial repair effect on the myocardial injury of obese mice.

Elevated FFA levels in obese individuals are known to activate the NF-κB inflammatory signaling pathway in myocardial cells, thereby promoting inflammatory cell infiltration and aggregation. This mechanism has been

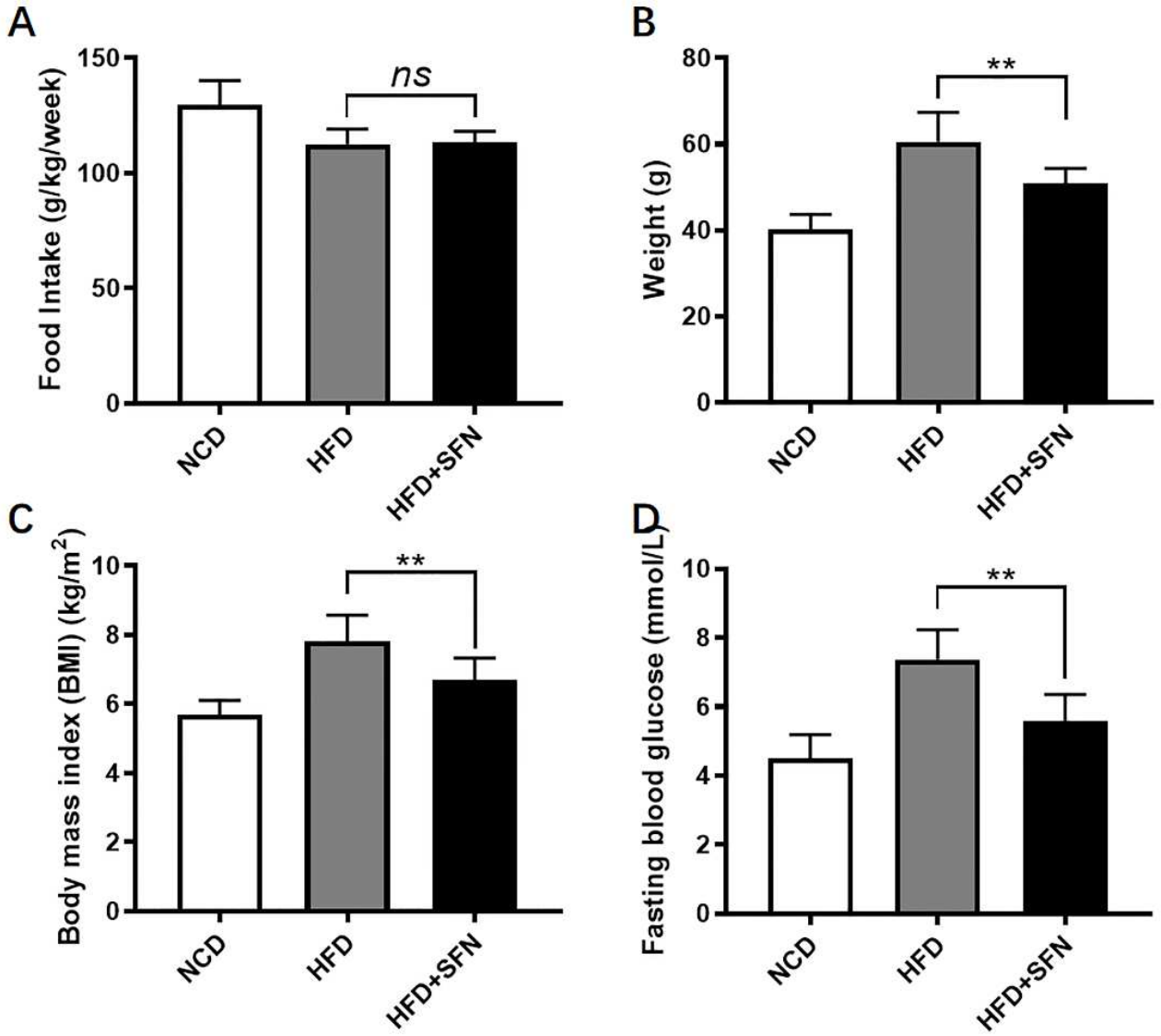

Fig. 1: Food intake, body weight, BMI, and fasting blood glucose values in each group (NCD: normal chow diet; HFD: high-fat diet; HFD+SFN: high-fat diet plus sulforaphane at 0.5 mg/kg/day, subcutaneous injection for 16 weeks)
(A: Weekly food intake per mouse; B: Body weight; C: Body mass index; D: Fasting blood glucose; compared to the HFD group, ns indicates no significant difference, $^{**}P < 0.01$).

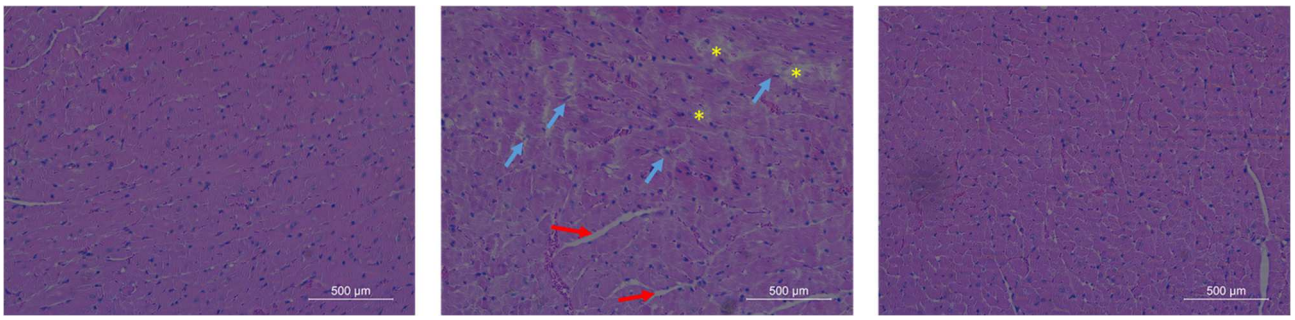

Fig. 2: Histological observation of myocardial tissue in various groups of mice (HE Staining ×200). (NCD, HFD, HFD+SFN as defined above; SFN dose: 0.5 mg/kg/day for 16 weeks) Red arrow indicates fiber fragmentation, apoptotic cardiac myocyte, blue arrow indicates myoplasmic dissolution, asterisk indicates disorganized arrangement.

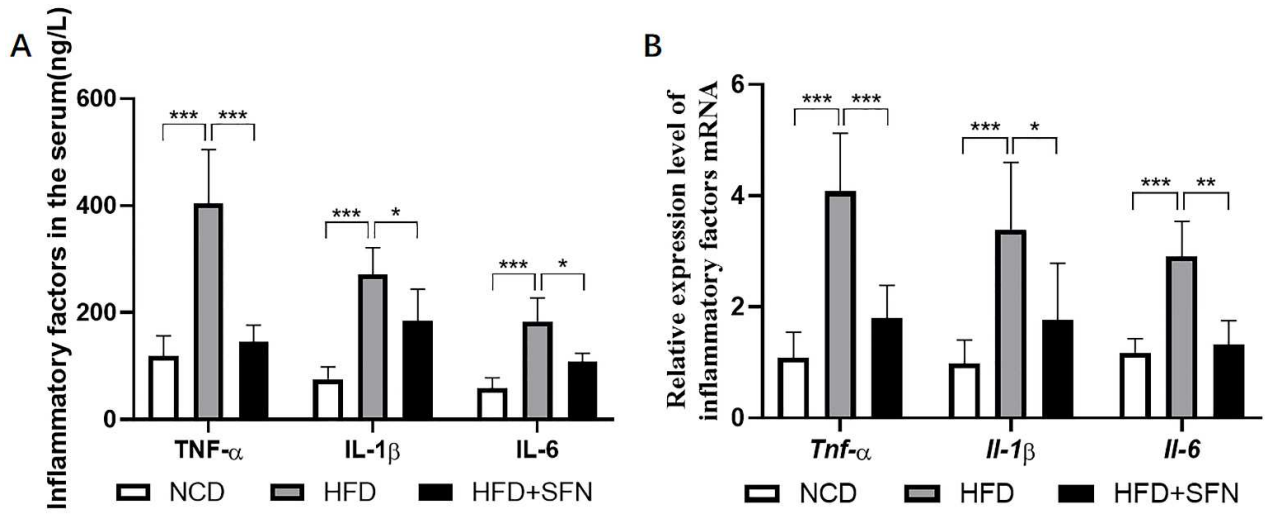

Fig. 3: Serum levels of inflammatory factors and myocardial tissue mRNA expression in various groups of mice (NCD, HFD, HFD+SFN as defined above)
(A: Levels of inflammatory factors in serum; B: Transcription levels of inflammatory factors in myocardial tissue; compared to the HFD group, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

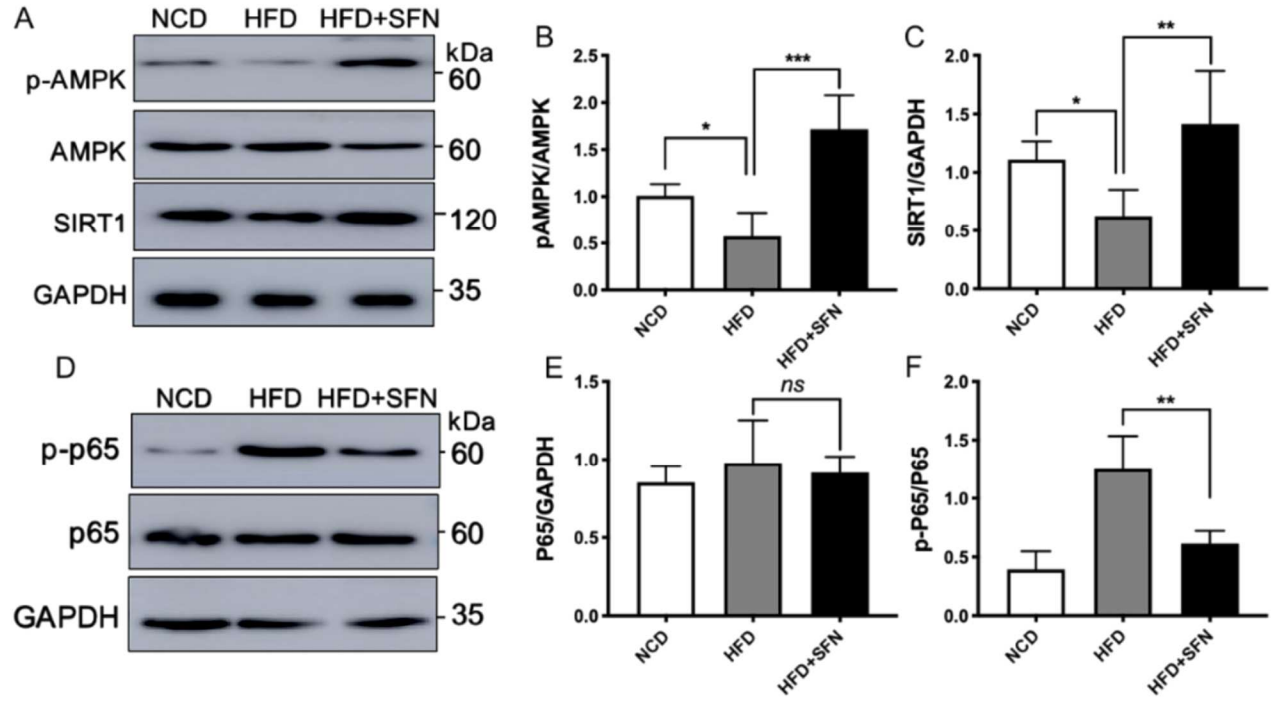

Fig. 4: Protein expression of p-AMPK, SIRT1, P65 and p-P65 in myocardial tissue of various groups of mice (NCD, HFD, HFD+SFN as defined above)
(A & D: Protein expression in mouse myocardial tissue detected by Western blot; B, C, E, & F: Relative protein expression levels; compared to the HFD group, ns, no significant difference, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

Table 1: Primer sequences

Gene	Forward primer (5'-3')	Reverse primer (3'-5')
Tnf-α	ACCACGCTCTTCTGTCTACT	AGGAGGTTGACTTTCTCCTG
Il-1β	GCAACTGTTCCTGAACTCAACT	ATCTTTTGGGGTCCGTCAACT
Il-6	CACATGTTCTCTGGGAAATCGTGGA	TCTCTCTGAAGGACTCTGGCTTTGT
β-actin	CGTGGGCCGCCCTAGGCACCA	TTGGCCTTAGGGTTCAGGGGG

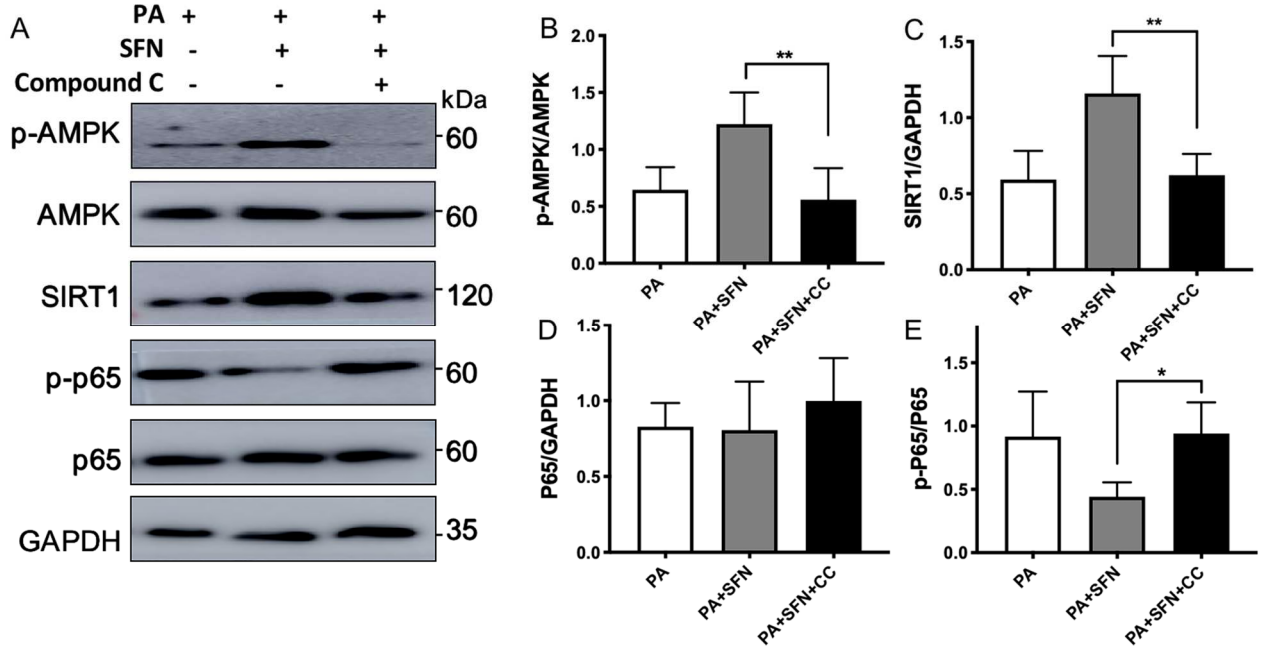

Fig. 5: Protein expression of p-AMPK, SIRT1, P65, and p-P65 in cells from various groups (Control, PA: palmitic acid-treated cells, PA+SFN: PA plus sulforaphane at 2.5 μM, PA+SFN+CC: PA plus sulforaphane and Compound C at 10 μM)
(A: Detection of protein expression in H9c2 cells using Western blot; B-E: Relative protein expression levels; compared to the HFD group, $^{*}P < 0.05$, $^{**}P < 0.01$).

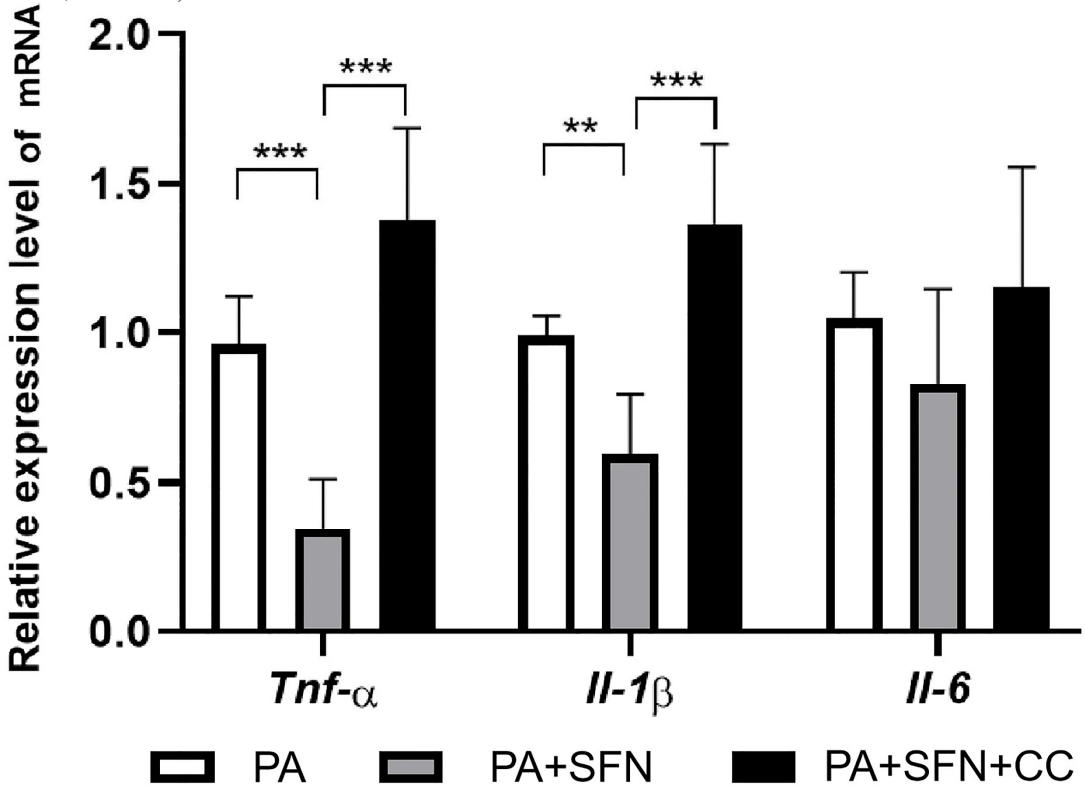

Fig. 6: AMPK inhibitor attenuates the anti-inflammatory effect of SFN(Control, PA: palmitic acid-treated cells, PA+SFN: PA plus sulforaphane at 2.5 μM, PA+SFN+CC: PA plus sulforaphane and Compound C at 10 μM) ($^{**}P < 0.01$, $^{***}P < 0.001$ compared to the HFD group.

Table 2: Blood lipid metabolism parameters in various groups of mice (n=8)

Lipid profiles (mmol/L)	NCD	HFD	HFD+SFN
TC	3.84 ± 0.76	10.29 ± 1.24***	8.49 ± 1.15$^{**\#}$
TG	2.134 ± 0.20	2.653 ± 0.34*	1.733 ± 0.43$^{*\#\#\#}$
FFA	1.798 ± 0.210	2.532 ± 0.202**	1.921 ± 0.241#
HDL-c	0.34 ± 0.053	0.271 ± 0.043	0.262 ± 0.023
LDL-c	1.452 ± 0.24	3.312 ± 0.34**	2.915 ± 0.32**

Note: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared to the NCD group. $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ as against with the HFD group. Data are presented as mean ± SD.

Table 3: Group-wise assessment of myocardial injury in mice (n=8)

Myocardial injury parameters	NCD	HFD	HFD+SFN
Pathological score	0.5 ± 0.29	2.0 ± 0.29**	1.0 ± 0.29$^{\#}$
CK (U/L)	804.2 ± 32.4	1210.9 ± 76.4***	894.3 ± 61.5$^{**\#\#}$
CK-MB (U/L)	612.4 ± 45.2	953.5 ± 50.4***	733.1 ± 55.3$^{*\#\#}$
cTnI (mg/ml)	1.01 ± 0.21	2.53 ± 0.22***	1.621 ± 0.24$^{*\#}$

Note: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared to the NCD group. $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ as against with the HFD group. Data are presented as mean ± SD.

identified as a key contributor to myocardial dysfunction (Bartekova, *et al*., 2018, Yu, *et al*., 2021). Concomitant with the increase in TG, TC and FFA levels, the content and mRNA expression of inflammatory factors rise myocardial expression and accumulation of inflammatory mediators. Furthermore, obese mice fed a HFD displayed enhanced NF-κB activation in cardiac tissue, as indicated by a higher p-p65/p65 ratio and concomitant upregulation of multiple inflammatory markers. AMPK functions as a central metabolic regulator essential for maintaining a balance between energy supply and demand. Upon activation, AMPK downregulates acetyl-CoA carboxylase (ACC) activity, thereby enhancing fatty acid β-oxidation and reducing lipid deposition (Peng, *et al*., 2022, Zang, *et al*., 2018). Simultaneously, activation of the AMPK pathway promotes SIRT1 phosphorylation, which in turn reduces histone acetylation levels and inhibits the transcription of pro-inflammatory factors (Li, *et al*., 2019). Conversely, excessive energy intake from a high-fat diet inhibits AMPK activation, leading to lipid accumulation and initiation of c-Jun N-terminal kinase (JNK)-mediated inflammatory signaling (Xie, *et al*., 2021). Results demonstrated treatment with SFN in obese mice resulted in lower serum FFA, increased phosphorylation of p-AMPK and SIRT1 expression, suppression of inflammatory cascades. *In-vitro* experiments confirmed that SFN can lower serum FFA levels and inhibit P65 phosphorylation by engaging the AMPK/SIRT1, thereby lower transcription of inflammatory factors. Previous research has further demonstrated that SFN can ameliorate mitochondrial dysfunction through activation of the AMPK/SIRT1/PGC-1α axis, thereby improving skeletal muscle morphology and function in sarcopenia (Guo, *et al*., 2024). Collectively, these findings suggest that SFN may enhance mitochondrial homeostasis via AMPK activation, representing a potential mechanism by which SFN mitigates HFD-induced myocardial injury and warranting further investigation.

This study acknowledges several limitations that may impact the interpretation of our findings. First, while this study focused on the AMPK/SIRT1/P65 signaling pathway, other potential mechanisms by which SFN exerts its protective effects were not explored. Investigating additional pathways may offer deeper insights into the diverse mechanisms through which SFN mitigates myocardial injury. Second, the present study evaluated sulforaphane at a single dose (0.5 mg/kg). Nevertheless, the absence of multiple dosing regimens limits the ability to characterize potential dose-response relationships and may affect the extrapolation of these findings to other contexts. Third, the effects of SFN on cardiac function remains to be examined. Evaluating parameters such as cardiac output, ejection fraction and other hemodynamic measures would enhance our understanding of how SFN influences cardiac performance in the context of obesity-related myocardial injury. Lastly, the study primarily used a mouse model, which may not entirely reflect human physiology and pathology. Further research in clinical settings is needed to corroborate these preclinical results and explore the therapeutic capability of sulforaphane in human subjects suffering from obesity-related myocardial injury.

CONCLUSION

In conclusion, SFN modulates the AMPK/SIRT1/P65 signaling axis, reducing inflammatory cytokine expression and secretion, effectively ameliorate metabolic disturbances and myocardial pathological damage in diet-induced obese mice. This study elucidates a new mechanism of cardiac protection for SFN, providing preliminary evidence to support the potential use of SFN as a therapeutic agent for obesity-related myocardial damage.

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Not applicable.

Author's contributions

Lipin Huang: Writing – review & editing, Methodology, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. Dingdao Chen: Writing – original draft, Investigation, Formal analysis, Data curation. Shengli Chen: Visualization, Investigation, Writing - original draft. Yongye Wang, Yunchao Hua and Zijiao Quan: Visualization, Investigation.

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Data availability statement

The datasets generated and analyzed during the current study are obtained from the corresponding author on request.

Ethical approval

All animal procedures were performed in strict compliance with the ethical guidelines of Wenzhou University. (WZU-2021-048).

Conflict of interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

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