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Dietary Sinapic Acid Alleviates Adiposity and Inflammation in Diet-Induced Obese Mice

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ABSTRACT: Sinapic acid (SA), a hydroxycinnamic acid, is known to confer protection against oxidative stress, inflammation, diabetes, and liver disease. However, the effectiveness of SA in improving obesity remains obscure. Therefore, this study evaluated anti-obesity efficacy of SA and to elucidate its mechanism of action. Male mice were maintained for 16 weeks on high-fat diet (HFD) alone or with SA (0.004%, w/w) and bodyweight, fat mass, adipocyte size, food intake, and biochemical and molecular markers were evaluated. SA-supplemented mice demonstrated markedly decreased fat mass and adipocyte size compared to unsupplemented group, without any changes in bodyweight and food intake between the two groups. Plasma adipocytokines levels including leptin, resistin, monocyte chemoattractant protein (MCP)-1 and interleukin-6 were also markedly reduced by SA supplementation. SA tended to lower plasma insulin level and improved homeostatic index of insulin resistance and intraperitoneal glucose tolerance test in HFD-induced obese mice. The anti-adiposity effect of SA was maybe owing to down-regulation of the mRNA expression of lipogenic genes, including *acetyl coenzyme A (CoA) carboxylase, fatty acid synthesis, stearoyl-CoA desaturase 1*, and *phosphatidate phosphatase*, and *peroxisome proliferator-activated receptor γ*, a transcription factor responsible for governing lipid metabolism, in adipose tissues. SA significantly down-regulated pro-inflammatory *nuclear factor kappa B, MCP-1, tumor necrosis factor-α,* and *Toll-like receptor 4* mRNA expression in adipose tissue. Thus, SA could be beneficial for the development of functional foods or herbal medications to combat obesity.

Keywords: inflammation, insulin resistance, lipogenesis, obesity, sinapic acid

INTRODUCTION

Obesity is a serious health issue of the 21st century as its prevalence has been augmenting globally over past decades (World Health Organization, 2021) and is linked to several co-morbidities leading to disability and death (Jung and Choi, 2014). Excess adiposity is a major obesity characteristic and is developed by prolonged positive energy balance, due to surplus on the balance between energy intake and expenditure. Fat rich diet is a principal contributor to positive energy balance as fat is the most energy-efficient food source (Hill et al., 2000). In obesity research employing rodent animal models, high-fat diet (HFD) is a frequently adopted diet to induce obesity and its associated co-morbidities (Preguiça et al., 2020). These animals have characteristics like human obesity compared to genetic models (Preguiça et al., 2020). C57BL/6J mouse strain is especially vulnerable to adiposity, weight gain, and glucose homeostasis disruptions when fed with HFD (Surwit et al., 1995).

With growing prevalence of obesity and its associated health issues, various natural bioactive compounds from fruits and vegetables have attracted attention as adjunctive therapies to satisfy the demand for safe and effective anti-obesity agents (Sandner et al., 2020). Sinapic acid (SA, 3,5-dimethoxy-4-hydroxycinnamic acid) is a bioactive compound prevalent in fruits, vegetables, grains, seeds, seaweed, and other plant varieties and therefore can be commonly consumed through a healthy diet (Nićiforović and Abramovič, 2014; Cotas et al., 2020). SA is believed to make a valuable contribution towards curtailing the risk of inflammation, oxidative stress, cancer, and anxiety (Nićiforović and Abramovič, 2014). It also exerted protective effects against diabetes and diabetic atherosclerosis in rats (Cherng et al., 2013; Han et al. 2018). Lately, an *in vitro* study exhibited that SA up-regulated expression

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of markers involved in thermogenesis and mitochondrial biogenesis and triggered lipolysis in brown adipocytes (Hossain et al., 2020). SA (0.03%, w/w) supplementation for 12 weeks reduced bodyweight and augmented fat accumulation by HFD in hamsters (Wang et al., 2022). Contrastingly, SA (200 mg/kg body weight, for 8 weeks replenishment) did not modify bodyweight in HFD-fed rats (Yang et al., 2019). Thus, the role of SA in improving obesity remains controversial and is still obscure *in vivo* model. To our knowledge, no studies have yet inspected effects of low-dose SA supplement on HFD-induced adiposity, inflammation and insulin resistance in C57BL/6J mice.

Hence, this study explored the impact of SA (0.004%, w/w) on obesity in HFD-fed C57BL/6J mice. SA efficacy on food intake, bodyweight, fat accumulation, plasma leptin level, and expression of adipose tissue genes linked to lipid metabolism were estimated. We also measured its efficacy on HFD-induced hyperglycemia, hyperinsulinemia, insulin resistance, and inflammation.

MATERIALS AND METHODS

Animal procedures

C57BL/6J mice (four-week-old male, n=16, Hana Bio-Tech Inc., Pyeongtaek, Korea) were housed in separate cages under controlled surroundings (24±2°C, 12-h light-dark cycle). Immediately upon arrival, animals were permitted to adapt to the new conditions for one week before the experiments; during which, they were fed with a chow diet. Mice were then randomly segregated into two groups: HFD (containing approximately 40 kcal% fat from lard (85% of total fat, w/w) and corn oil (15% of total fat, w/w), 18 kcal% proteins, and 42 kcal% carbohydrates, n=8) and HFD+SA (0.004%, w/w, approximately 3 mg/kg bodyweight, Sigma-Aldrich Co., St. Louis, MO, USA, n=8). Under *ad libitum* feeding conditions, the mice were given diets for 16 weeks. Bodyweight and food intake were supervised daily and weekly, throughout the experimental period.

At the end of the experimental period, each mouse was anesthetized with ether post 12-h fasting period, and their plasma samples were acquired by collecting blood from the inferior vena cava with a heparinized syringe. Post blood collection, epididymal, mesenteric, perirenal, retroperitoneal, and subcutaneous white adipose tissue (WAT) were isolated, rinsed with physiological saline, and weighed. Epididymal WAT were snap-frozen in liquid nitrogen and stored at −70°C for later analyses. All animal experiments were conducted according to procedures approved by the Animal Ethics Committee of Pukyong National University (no. PKNUIACUC-2022-33).

Histological analysis

For histological examination, a portion of the epididymal WAT was fixed in 10% formalin and processed routinely for paraffin embedding and sectioning. Sections with a thickness of 4 μm were stained with hematoxylin & eosin (H&E) and observed employing an optical microscope (Nikon, Tokyo, Japan) at 100× magnification.

Analyses of plasma glucose, insulin, adipocytokine, and homeostatic model assessment-insulin resistance (HOMA-IR) levels

The concentrations of plasma glucose and insulin were estimated using commercial kits produced by the Asan Pharm Co., Ltd. (Seoul, Korea) and Merck KGaA (Darmstadt, Germany), respectively. Concentrations of plasma adipocytokines [leptin, resistin, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), and interleukin (IL)-6] were measured employing Milliplex Map Kit (Merck KGaA, Germany). HOMA-IR was calculated from fasting glucose and insulin concentrations as:

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mmol/L)} \times \text{Fasting insulin } (\mu\text{LU/mL})}{22.5}$$

Intraperitoneal glucose tolerance test (IPGTT)

IPGTT was conducted in all mice post 15 weeks of experimental diet feeding. Prior to IPGTT, mice were fasted for 4 h, and glucose (1 g/kg body weight) was administered via intraperitoneal injection. Blood glucose concentrations were monitored from the tail-tip utilizing a glucose analyzer (Accu-Chek Performa, Roche AG, Basel, Switzerland) at baseline, mid, and endpoint (30, 90, and 120 min post glucose administration).

RNA extraction and quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) analysis

Total RNA was isolated from epididymal WAT employing TRIzol reagent (Invitrogen Life Technologies, Waltham, MA, USA), and the RNA was reverse transcribed using a high-capacity cDNA reverse transcription kit (Applied Biosystems Inc., Foster City, CA, USA) for cDNA synthesis. mRNA expression of the target genes was estimated using qRT-PCR, which was conducted using SYBR green PCR Master Mix (Applied Biosystems Inc.) and StepOnePlus™ Real-Time PCR System (Applied Biosystems Inc.). mRNA expression levels of each gene were normalized to those of glyceraldehyde 3-phosphate dehydrogenase (internal control) adopting the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

Data from all the experiments were evaluated using the

SPSS package version 27 (SPSS Inc., Chicago, IL, USA). The Student's *t*-test was employed to compare means of the experimental groups. A *P*-value<0.05 was considered statistically significant. All data are expressed as the mean with the standard error of the mean.

RESULTS

Food intake, bodyweight, adipocyte size, and adipose tissue weight

Food intake and initial and final bodyweights did not significantly differ between HFD and HFD+SA groups (Fig. 1A and 1B). However, HFD+SA group demonstrated smaller adipocyte size compared to that of HFD group (Fig. 1C). Moreover, SA supplementation significantly diminished epididymal WAT weight (Fig. 1D). The weights of visceral WAT (combined weight of epididymal, perirenal, retroperitoneal, and mesenteric WAT) and total WAT (combined weight of visceral and subcutaneous WAT) were also significantly lower in HFD+SA group than in HFD group (Fig. 1D), although the difference in subcutaneous WAT weight between the two groups was statistically insignificant (data not depicted).

Plasma adipocytokine, glucose, insulin, HOMA-IR, and IPGTT

Subsequently, we assessed the effect of SA on plasma adipocytokine levels in obese mice. Like fat mass, plasma leptin levels were significantly lowered by SA supplementation (Fig. 2A). Furthermore, plasma pro-inflammatory marker levels, including MCP-1 and IL-6, were significantly lower in HFD+SA group compared to those in the HFD group, and plasma TNF-α levels also depicted a similar trend (Fig. 2B).

SA did not affect fasting glucose levels, but it significantly reduced plasma resistin levels (Fig. 2C and 2D). There was a trend of decreased HOMA-IR, an insulin re-

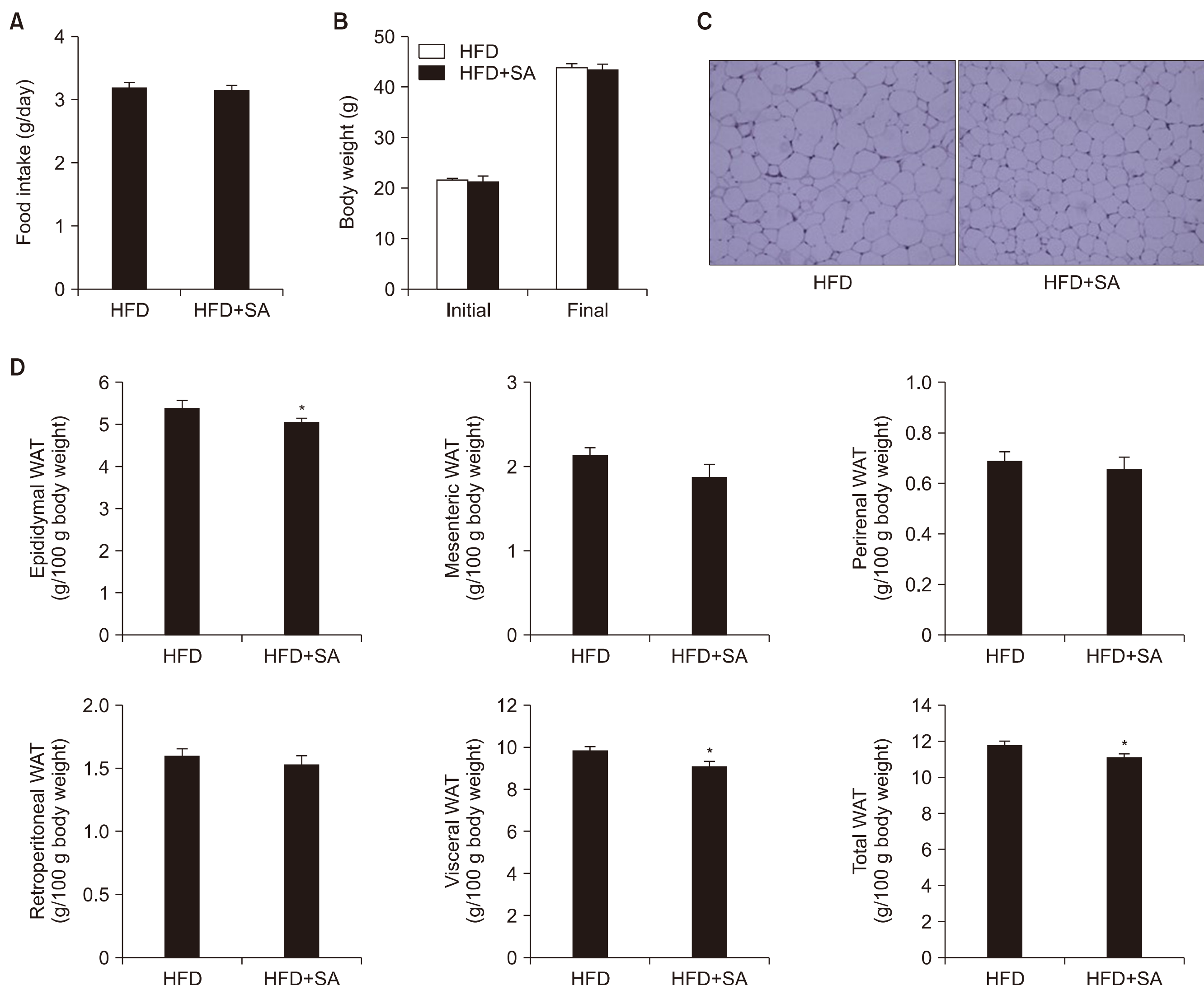

Fig. 1. Impact of sinapic acid (SA) on food intake (A), bodyweight (B), epididymal white adipose tissue (WAT) morphology (hematoxylin & eosin, 100×) (C), and fat mass (D) in high-fat diet (HFD)-induced obese mice. (A, B, and D) Data are presented as mean± SEM (n=8). *P<0.05 vs. HFD control group.

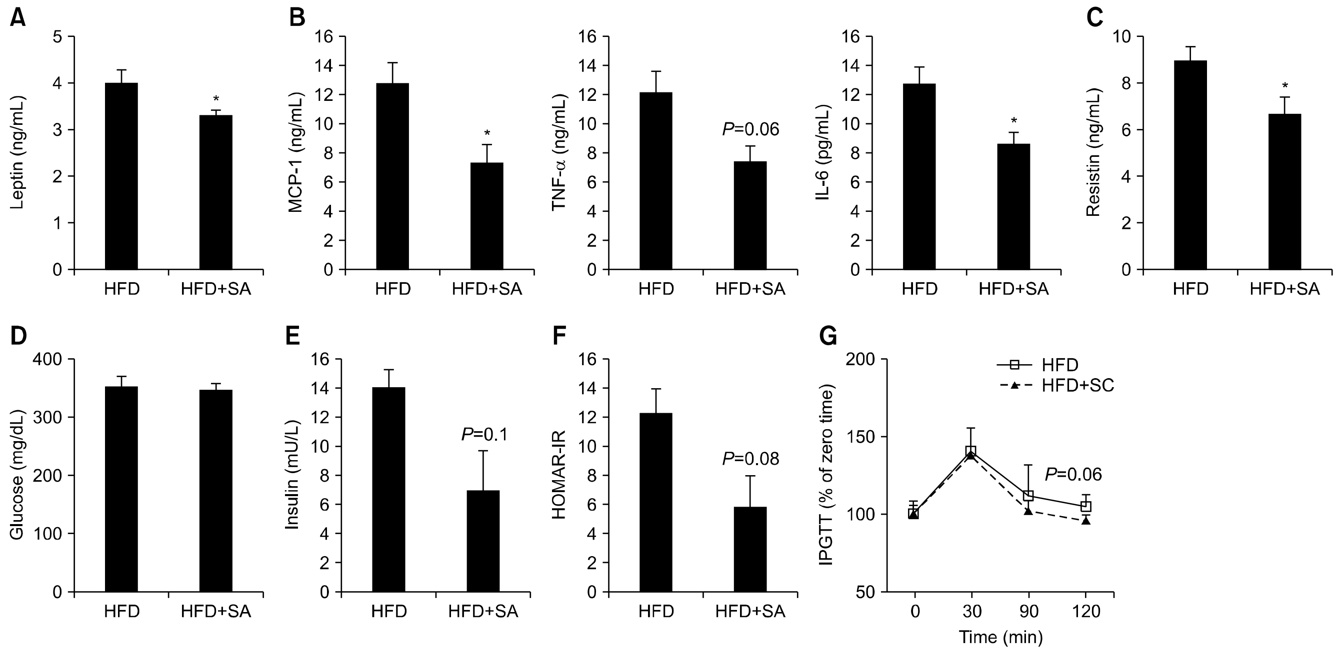

Fig. 2. Impact of sinapic acid (SA) on plasma leptin levels (A), pro-inflammatory chemokine and cytokines (B), resistin (C), glucose (D), insulin (E), homeostatic model assessment-insulin resistance (HOMA-IR) (F), and intraperitoneal glucose tolerance test (IPGTT) (G) in high-fat diet (HFD)-induced obese mice. Data are presented as mean±SEM (n=8). *$P<0.05$ vs. HFD control group. MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α; IL, interleukin.

sistance marker, and plasma insulin levels (Fig. 2E and 2F). During IPGTT, blood glucose reached peak levels at 30 min post glucose injection and thereafter began to decline in both groups (Fig. 2G). However, SA-supplemented mice tended to have slightly lower blood glucose levels at 120 min than in HFD control mice, indicating that SA supplementation may help improve glucose tolerance in HFD-induced obese mice.

Lipid metabolism and inflammation associated gene expression in WAT

qRT-PCR was conducted to analyze differentially expressed genes associated with lipid metabolism and inflammation. HFD+SA group demonstrated significantly down-regulated mRNA expression of *de novo* lipogenic genes, including *acetyl coenzyme A (CoA) carboxylase (ACC)*, *fatty acid synthase (FAS)*, *stearoyl-CoA desaturase 1 (SCD1)*,

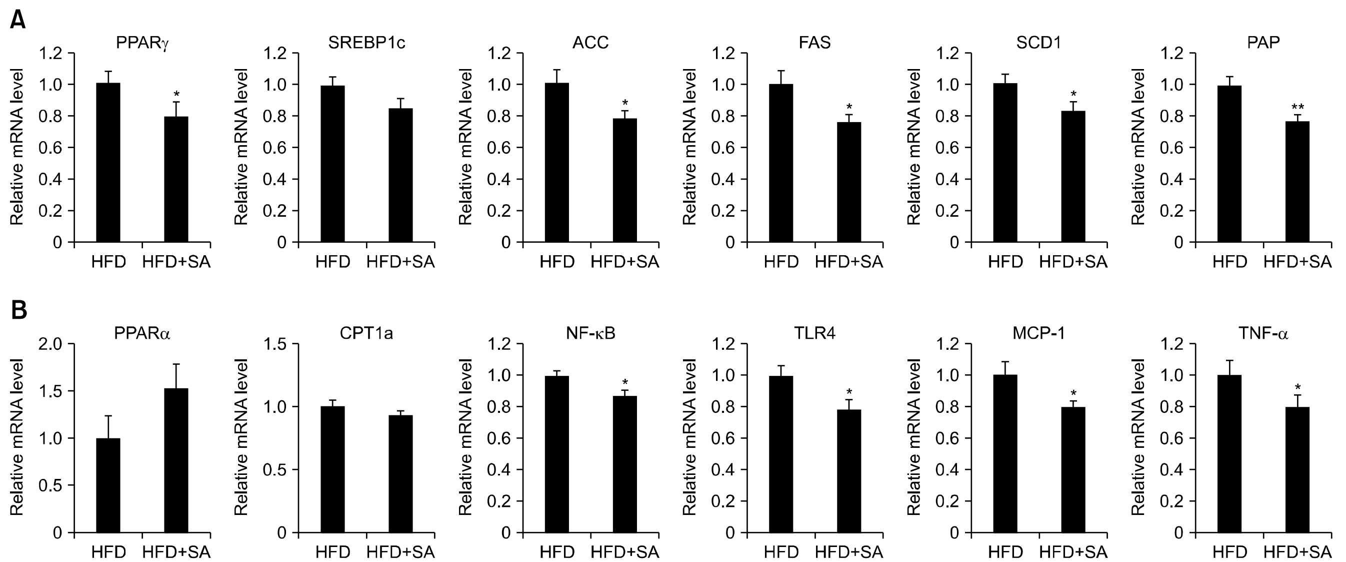

Fig. 3. Impact of sinapic acid (SA) on mRNA expression of markers involved in lipogenesis (A), fatty acid oxidation (B), and inflammation (C) in white adipose tissue (WAT) of high-fat diet (HFD)-induced obese mice. Data are presented as mean±SEM (n=8). *$P<0.05$ and **$P<0.01$ vs. HFD control group. PPAR, peroxisome proliferator-activated receptor; SREBP1c, sterol-regulatory element binding protein 1c; ACC, acetyl coenzyme A (CoA) carboxylase; FAS, fatty acid synthesis; SCD1, stearoyl-CoA desaturase 1; PAP, phosphatidate phosphatase; CPT1a, carnitine palmitoyltransferase 1a; NF-κB, nuclear factor kappa B; TLR4, Toll-like receptor 4; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α.

and *phosphadidate phosphatase* (*PAP*), and transcription factor peroxisome proliferator-activated receptor (PPAR) γ in WAT compared to that in the HFD group (Fig. 3A). SREBP1c mRNA expression also tended to be lower in WAT of HFD+SA than in the HFD group (P=0.1), although the difference was statistically insignificant. Contrary to its effect on the expression of *de novo* lipogenic genes, the difference in the mRNA expression of PPARα, a key regulator of fatty acid oxidation, was statistically insignificant, although HFD+SA group tended to up-regulate PPARα mRNA expression in WAT by 24% in comparison to that in the HFD group (Fig. 3B). SA also did not markedly affect its target gene *CPT1a* in WAT. Contrastingly, mRNA expression of pro-inflammatory transcription factor (nuclear factor kappa B, NF-κB), its target genes (*MCP-1* and *TNF-α*), and its upstream activator and receptor (Toll-like receptor 4, TLR4) was significantly down-regulated in WAT by SA supplementation.

DISCUSSION

In this study, we established that SA supplementation significantly reduced fat mass and adipocyte size in HFD-fed mice. Fat deposit is regulated by the balance between lipid synthesis and breakdown (Kersten, 2001). Herein, SA did not alter mRNA expression of *CPT1a*, a gene regulating transportation of fatty acids to the mitochondrial matrix for oxidation, in WAT. However, mRNA expression of genes controlling fatty acid and triglyceride synthesis (*ACC, FAS, SCD1*, and *PAP*) was significantly down-regulated in WAT by SA supplementation. Consistent with this, mRNA expression of PPARγ, a transcriptional factor regulating lipid storage (Tontonoz and Spiegelman, 2008), was markedly down-regulated in WAT of SA-supplemented mice. *De novo* lipogenesis is a metabolic process wherein carbon precursors are converted to fatty acids that are utilized to form triglycerides or other lipids. Several enzymes are involved in *de novo* lipogenesis regulation and many are regulated predominantly during transcription in a coordinated manner. The metabolic pathway commences with the generation of malonyl-CoA from an acetyl-CoA by ACC. FAS converts malonyl-CoA to palmitate, the initial fatty acid formed in lipogenesis, which is a key rate-limiting step. SCD1 and PAP are also crucial enzymes for lipid synthesis, catalyzing desaturation of saturated fatty acids including palmitate and diacylglycerol generation. Abnormal lipogenesis elevation is linked to development of obesity and its comorbid condition like insulin resistance and type 2 diabetes (Batchuluun et al., 2022). Conversely, mice lacking FAS in adipose tissue demonstrated protective effects against HFD-induced obesity, insulin resistance, and inflammation (Wueest et al., 2010; Lodhi et al., 2012). Besides FAS, inhibition of enzymes or genes controlling fatty acid and triglyceride synthesis, including *ACC, SCD1*, and *PAP*, represents an attractive therapeutic option for resisting obesity (Phan et al., 2004; Nadra et al., 2012; ALJohani et al., 2017; Lee et al., 2020; Liu et al., 2020; Batchuluun et al., 2022). Therefore, the protective mechanisms of SA against adiposity may be through the inhibition of lipogenic metabolic pathways. Some phytochemicals have also been verified as lipogenic inhibitors and this inhibition in WAT was linked to their anti-obesity effects (Borah et al., 2021).

Besides serving as an energy reservoir, WATs are accepted as endocrine organs that secrete several adipocytokines. Leptin is one of the adipocytokines secreted by adipocytes, and there is a positive relationship between circulating leptin and fat mass (Considine et al., 1996). In SA-supplemented mice, lower plasma leptin levels were noted in comparison to those in the unsupplemented group, and this may reflect the reduced fat mass that accompanies SA supplementation. Additionally, SA supplementation reduced plasma pro-inflammatory chemokine and cytokine levels and down-regulated mRNA expression of transcription factor NF-κB, its target genes *MCP-1* and *TNF-α* and its upstream activator and receptor TLR4 in WAT. WAT is a crucial site that mediates inflammatory response to obesity through the secretion of pro-inflammatory adipocytokines (Cinti et al., 2005). In chronic positive energy balance conditions, WAT expansion can induce the release of pro-inflammatory adipocytokines, and WAT inflammation is believed to cause obesity-related metabolic dysfunction (Lumeng and Saltiel, 2011). Numerous chemokines and cytokines, including MCP-1 and IL-6, are generally augmented in obese animals and human plasma compared to that in lean controls (Catalán et al., 2007; Breslin et al., 2012; Shin et al., 2016; Naowaboot et al., 2021). Expression of *TLR4, NF-κB, MCP-1*, and *TNF-α* in WAT correlates positively with adiposity (Hotamisligil et al., 1995; Kamei et al., 2006; Ko and Kim, 2013; Tian et al., 2017; Wang et al., 2017). Conversely, prevented or delayed obesity is linked to down-regulated *TNF-α* and *MCP-1* mRNA expression in WAT (Hotamisligil et al., 1995; Kern et al., 1995; Ko and Kim, 2013), and lacking TLR4 protects from HFD-induced obesity in mice (Pierre et al., 2013). Collectively, it appears that SA can effectively improve systemic inflammation by inhibiting the pro-inflammatory genes expression in WAT, which may be associated with beneficial effect of SA on fat accumulation.

Previous studies have indicated a potential role of obesity-induced inflammation in the development of insulin resistance (Uysal et al., 1997; Kamei et al., 2006; Saberi et al., 2009; Pierre et al., 2013). Prolonged ingestion of HFD (8∼16 months, 40∼60% energy from fat) in C57BL/6J mice leads to hyperglycemia, hyperinsulinemia, and im-

paired insulin sensitivity in addition to a significant rise in bodyweight, fat mass, and inflammation (Do et al., 2011; Avtanski et al., 2019; Munkong et al., 2022). van der Heijden et al. (2015) have implied that obesity-associated insulin resistance is possibly more linked to inflammation in adipose tissue rather than other tissues such as the liver. In this study, SA did not affect fasting glucose levels, but tended to reduce fasting insulin levels in HFD-induced obese mice. Furthermore, there has been a trend toward improving glucose tolerance in SA-supplemented mice, as evidenced by the declined glucose levels during IPGTT when compared to those in the HFD controls. In support of the glucose tolerance results, SA supplementation tended to reduce HOMA-IR and significantly decreased levels of resistin, an adipocytokine that confers a pivotal role in insulin resistance, obesity, and inflammation (Steppan et al., 2001; Acquarone et al., 2019). Plasma resistin levels are increased in HFD-induced obese mice, and anti-resistin antibody administration in obese mice ameliorates insulin resistance (Steppan et al., 2001). As high circulating resistin levels are indicated to exert pro-inflammatory effects (Acquarone et al., 2019), there is also a probability that a decline in plasma resistin observed in SA-supplemented mice could be associated with advantageous effectiveness on inflammation and insulin resistance.

Overall, we provide evidence that dietary SA supplementation significantly reduces fat mass by down-regulating lipogenic genes mRNA expression in WATs of HFD-fed mice. Also, marked drop in circulating pro-inflammatory cytokine and chemokine levels and WAT inflammatory genes mRNA expression were observed in SA-supplemented mice. Therefore, SA may help control adiposity and inflammation in diet-induced obesity by controlling expression of genes linked to lipogenesis and inflammation in WAT. Moreover, SA-supplemented mice demonstrated an improving tendency of insulin resistance. Collectively, our data supports that SA may be beneficial as a functional food or medicine which focuses on resolving the burgeoning obesity problem, although more pre-clinical and clinical studies need to be performed to comprehend the role of SA on obesity and its co-morbidities.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: HJB, BK, UJJ. Analysis and interpretation: all authors. Data collection: HJY, DSY. Writing the article: HJY. Critical revision of the article: HJB, BK, UJJ. Final approval of the article: all authors. Statistical analysis: UJJ. Obtained funding: HJB, BK, UJJ. Overall responsibility: UJJ.

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