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EFFECTS OF THE ETHANOL EXTRACT OF *Coleus scutellarioides* ON BODY WEIGHT GAIN, ABDOMINAL CIRCUMFERENCE, AND LIVER INDEX IN HIGH-FAT DIET-FED MICE

Dwi Lista Ligarsari[1]*, Eli Halimah[2], Sri Adi Sumiwi[2], Jutti Levita[2]

[1]Master Program in Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia

[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia

*Email: dwi24016@mail.unpad.ac.id

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ABSTRACT

Insulin resistance (IR) is characterized by a reduced responsiveness of insulin-sensitive tissues to endogenous insulin. Excessive caloric intake promotes the accumulation of free fatty acids in skeletal muscle and the liver, resulting in the formation of lipotoxic metabolites that impair insulin signaling and glucose uptake. Although *Coleus scutellarioides* has demonstrated antihyperglycemic activity, its potential to ameliorate obesity-associated metabolic disturbances, particularly high-fat diet-induced insulin resistance, remains largely unexplored. IR is also associated with visceral fat accumulation, which is strongly correlated with increased body weight. Flavonoids such as quercetin have been reported to ameliorate IR in high-fat diet-fed mice. This study aimed to evaluate the effects of ethanolic extract of *C. scutellarioides* on body weight gain, abdominal circumference, and liver index in high-fat diet-induced mice. Twenty-five male *Swiss Webster* mice were randomly divided into five groups (n = 5/group), including normal control, negative control, metformin-treated, EECS 250 mg/kg, and EECS 500 mg/kg. Data were analyzed using one-way ANOVA followed by the LSD post hoc test. EECS at doses of 250 mg/kg and 500 mg/kg significantly attenuated body weight gain by 15.06% and 13.34%, respectively, while also reducing abdominal circumference and liver index compared with the negative control group ($p < 0.05$). These findings suggest that EECS possesses anti-obesity activity and may ameliorate metabolic alterations associated with high-fat diet feeding.

Keywords: *Coleus scutellarioides* Ethanol Extract, Insulin Resistance, Obesity, High-fat Diet

INTRODUCTION

Diabetes mellitus (DM) continues to represent a substantial public health burden worldwide. In Southeast Asia, DM was responsible for approximately 374 thousand deaths in 2024, with the highest mortality occurring in the West Pacific region at 1.2 million deaths (International Diabetes Federation, 2025). World Health Organization (2025) estimated that around 830 million individuals are affected by DM globally, most of whom reside in low- and

middle-income countries. The development of DM is closely related to insulin resistance (IR). Physiologically, IR is a condition in which target tissues exhibit a lower sensitivity to physiological insulin levels, resulting in an inability to achieve normal glucose uptake. IR disrupts glucose and lipid metabolism by reducing insulin responsiveness within tissues central to glucose and lipid metabolism, including skeletal muscle, the liver, and adipose depots, preventing them from removing glucose from the blood, disrupting systemic energy regulation, and often accelerating chronic metabolic diseases like type 2 DM (T2DM) (Zhao et al., 2023).

Excessive caloric intake and obesity, particularly those associated with long-term consumption of a high-fat diet, enhance lipid deposition within non-adipose tissues such as hepatic tissue, heart, pancreas, and skeletal muscle, causing damage through cellular oxidative stress (Mota et al., 2016; Lipke et al., 2022). High-fat diets disrupt substrate metabolism in the liver and extrahepatic tissues, increase glucose production, and eventually lead to excessive insulin secretion. Enhanced hepatic glucose production, driven by increased gluconeogenesis and glucose release from the liver, is considered a major contributor to IR progression (Zhang et al., 2017).

High-fat diet-induced obesity is characterized by excessive body weight gain, increased visceral adiposity, and hepatic lipid accumulation, leading to obesity-associated metabolic disorders. Accordingly, body weight gain is widely used to monitor obesity progression, whereas abdominal circumference reflects central adiposity. In addition, the liver index, expressed as the ratio of liver weight to body weight, serves as an indicator of hepatomegaly associated with hepatic lipid deposition. Therefore, these parameters are commonly employed to evaluate obesity severity and the efficacy of therapeutic interventions in experimental animal models (Srnic et al., 2025; Wen & Zhang, 2022; Radhakrishnan et al., 2021).

Indonesia, a tropical country rich in biodiversity, has long been recognized for its traditional herbal medicines, including *Coleus scutellarioides*. Previous studies have demonstrated that the ethanol extract of *C. scutellarioides* (EECS) is rich in flavonoids, with a total flavonoid content of 88.917 mg QE/g, and contains quercetin at a concentration of 3.122 mg/g (0.312%). In addition, EECS has demonstrated antidiabetic activity at a dose of 200 mg/kg body weight (Segara & Kurniawan, 2023; Sukmawati et al., 2019). Although the antihyperglycemic activity of *C. scutellarioides* has been reported previously,

its effects on obesity-related parameters and metabolic alterations associated with high-fat diet-induced IR have not been thoroughly investigated.

Quercetin has been reported to reduce lipid accumulation by downregulating key transcription factors involved in adipogenesis, including C/EBPβ, C/EBPα, and PPARγ (*Peroxisome Proliferator-Activated Receptor Gamma*). Quercetin also reduces matrix metalloproteinases (MMP-2 and MMP-9) expression required for adipose expansion (Song et al., 2023). Based on the reported presence of quercetin in *C. scutellarioides*, the present study aimed to investigate the effects of EECS on body weight gain, abdominal circumference, and liver index in mice fed a high-fat diet.

METHODS

Tools and Materials

Tools were an analytical digital balance (Ohaus Pioneer PA 114), macerator, oral gavage (sonde), a glucometer (EasyTouch), a rotatory evaporator (IKA 0010000403 RV 8), beaker glass (Pyrex), volumetric flasks and other chemical glasswares (Pyrex), blender (Sharp), evaporating disk, steel cabinet oven (Shel Lab), waterbath (Memmert), surgical blade (GEA), mice cage equipped with drink bottle, disposable syringe 1 mL (OneMed).

Materials were *C. scutellarioides* stem and leaf, metformin tablet 500 mg (Generik), sodium carboxymethyl cellulose (Na-CMC), 70% ethanol, aluminium chloride, sodium acetate 1 M, distilled water, glucometer strip (EasyTouch), and insulin (Novorapid).

Animals were Swiss-Webster mice weighing approximately 20 g. All animal experimental procedures were conducted in accordance with institutional ethical guidelines and approved by the Research Ethics Committee of Universitas Padjadjaran (Approval No. 92/UN6.KEP/EC/2026).

Research Path

1. Extract Preparation

The stems and leaves of *C. scutellarioides* were collected from Kebun Manoko, located in Cikahuripan Village, Lembang District, West Bandung Regency, West Java, Indonesia. The plant material was authenticated by Arifin Surya Dwipa Irsyam, S.Si., M.Si., at the Herbarium Bandungense, Biology Study Program, School of Life Sciences and Technology, Institut Teknologi Bandung, Indonesia. Plant identification was confirmed under certificate No. 7700/IT1.C11.2/TA.00/2025. The fresh materials were sorted, washed, and sun-dried for 5 days. The dried plant materials (1620 g) were ground into a coarse powder using a laboratory blender. The dried plant powder was extracted by maceration using 70%

ethanol. The powder was macerated three times, each for 24 hours, with fresh solvent replacement after each extraction cycle. The extract was then filtered and concentrated using a rotary evaporator at 50°C and 40 rpm to remove the solvent, followed by further evaporation in a water bath maintained at 50°C to obtain the ethanolic extract of *C. scutellarioides* (EECS), yielding 220.136 g of extract with an extraction yield of 13.59% (w/w).

2. Analysis of Total Phenolic Content (TPC) and Total Flavonoid Content (TFC)

TPC and TFC were assessed following the procedures presented in the Indonesian Herbal Pharmacopoeia 2017. For TPC analysis, gallic acid (50, 60, 70, 80, and 90 µg/mL) was used to construct the calibration curve. Briefly, the extract was reacted with Folin–Ciocalteu reagent, followed by the addition of sodium carbonate solution and incubation for 30 min at room temperature. The absorbance was measured at 730 nm using a UV–visible spectrophotometer. For TFC determination, quercetin (50, 60, 70, 80, and 90 µg/mL) served as the reference standard. The extract was mixed with aluminum chloride ($AlCl_3$) reagent and incubated for 30 min at room temperature before measuring the absorbance at 432,5 nm. The results were expressed as milligrams of gallic acid equivalents (mg GAE/g extract) for TPC and milligrams of quercetin equivalents (mg QE/g extract) for TFC.

3. Effects of EECS on Body Weight Gain, Abdominal Circumference, and Liver Index in a High-Fat Diet-Mice Model

Twenty-five male *Swiss Webster* mice (20–30 g) were randomly divided into five groups (n = 5/group), including normal control, negative control, metformin-treated, EECS 250 mg/kg, and EECS 500 mg/kg.

A high-fat diet-induced obesity model was established by feeding mice a commercially available high-fat diet (Biocalorix, Indonesia) for 14 days. The semi-purified grain-based diet (HFD60-GB) contained 60% high-fat content supplemented with 0.75% cholesterol, with tallow fat as the primary lipid source and a metabolizable energy of approximately 5,131 kcal/kg. This diet was specifically formulated to induce obesity, hyperlipidemia, and IR in experimental animals.

The normal control group received standard chow and Na-CMC suspension, whereas the negative control group received a high-fat diet along with Na-CMC suspension. The positive control group was treated with metformin at a dose of 100 mg/kg suspended in Na-CMC while

receiving the high-fat diet. Mice in the treatment groups were fed a high-fat diet concurrently with oral administration of EECS at doses of 250 mg/kg and 500 mg/kg throughout the experimental period. Body weight and waist circumference were monitored daily in the morning before feeding throughout the study period.

4. Statistical Analysis

Data are expressed as mean ± standard deviation (SD). The assumptions of normality and homogeneity of variance were verified using the Shapiro–Wilk and Levene's tests, respectively, before performing one-way analysis of variance (ANOVA). When a significant difference was detected, multiple comparisons were conducted using the least significant difference (LSD) post hoc test. Statistical significance was defined as $p < 0.05$.

RESULTS AND DISCUSSION

The TPC and TFC of EECS were 156.6677 mg GAE/g extract and 13.1194 mg QE/g extract, respectively. Although the flavonoid content of the present extract was lower than that reported by Segara and Kurniawan (2023), EECS remained a rich source of phenolic and flavonoid compounds, including quercetin, which has been widely recognized for its anti-obesity and metabolic regulatory properties. Previous studies have demonstrated that quercetin can attenuate body weight gain, reduce adipose tissue accumulation, and improve lipid metabolism by modulating adipogenesis, enhancing fatty acid oxidation, and suppressing inflammatory responses associated with obesity. Therefore, the anti-obesity effects observed in the present study, including the reductions in body weight gain, abdominal circumference, and liver index, may be partly attributed to the presence of flavonoids, particularly quercetin, in EECS.

The progression of body weight throughout the study period is shown in Table 1 and Figure 1; the figure depicts the percentage change in body weight recorded during the experimental period.

Table 1. Effects of EECS on initial body weight, final body weight, and body weight gain in high-fat diet-fed mice

Treatment Group	Initial Body Weight (g)	Final Body Weight (g)	Body Weight Gain (%)
Normal	26.8	29.6	9.45
Negative	26	35.6	26.96
Positive	25.8	27.2	11.03
EECS 250 mg/kg	24.8	26.6	15.06
EECS 500 mg/kg	26	27.6	13.34

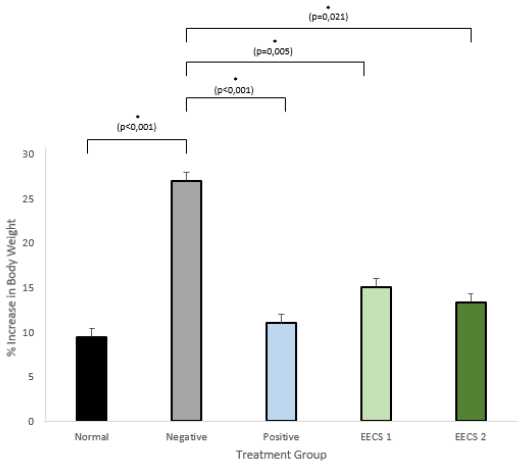

Figure 1. Effect of EECS on body weight gain (%) in mice fed a high-fat diet

Values are presented as mean ± SD (n = 5). (*) indicates a statistically significant difference compared with the negative control group ($p < 0.05$), as determined by one-way ANOVA followed by the LSD post hoc test.

Weight gain is frequently connected with increased concentrations of circulating free fatty acids (FFAs). Excess FFAs may be deposited in tissues not primarily intended for fat storage, particularly the liver and skeletal muscle, resulting in ectopic lipid accumulation. According to Hardy et al. (2012), intracellular lipid accumulation may trigger the activation of stress-related mediators and protein kinases that interfere with the integrity of *insulin receptor substrate-1* (IRS-1). As a consequence, insulin signaling becomes impaired, resulting in a reduced capacity of cells to uptake glucose efficiently.

Flavonoids have been reported to contribute to body weight regulation through their ability to inhibit the maturation of adipocytes by suppressing the differentiation of preadipocytes into mature fat cells. This activity may be attributed to the suppression of major adipogenic transcription factors, including PPARγ, a pivotal transcriptional regulator governing adipogenesis and lipid sequestration (Scarpa et al., 2025; Pan et al., 2016).

Flavonoids may also restrict the intestinal availability of dietary nutrients by interfering with pancreatic lipase and the carbohydrate-metabolizing enzymes, including α-amylase and α-glucosidase. The inhibition of these enzymes reduces the intestinal absorption of both lipids and carbohydrates, thereby contributing to a significant attenuation of body weight gain (Oliveira et al., 2022).

The results showed that all groups of mice exhibited an increase in body weight following 14 days of high-fat diet induction. The negative control group exhibited the most pronounced increase in body weight, with a gain of 26.96%, likely due to the absence of therapeutic intervention. Conversely, mice treated with metformin showed the smallest increase, with body weight rising by only 11.03% during the study period. This finding suggests that

metformin was effective in limiting body weight gain in mice. Such an effect may be attributed to its ability to enhance the production of satiety-related hormones, including GLP-1 (Glucagon-Like Peptide-1), while also influencing appetite-regulating centers in the brain, thereby reducing daily caloric intake (Yerevanian & Soukas, 2020).

Compared with the negative control group, mice receiving EECS experienced a more moderate increase in body weight. Treatment with EECS at 250 mg/kg and 500 mg/kg resulted in body weight increases of only 15.06% and 13.34%, respectively. Statistical analysis demonstrated that both EECS-treated groups and the metformin-treated group differed significantly from the negative control group ($p < 0.05$). These findings were consistent with the waist circumference measurements, which demonstrated a positive relationship between body weight and abdominal circumference, with heavier animals tending to exhibit larger waist circumferences. The percentage increase in waist circumference for each experimental group is presented in Figure 2.

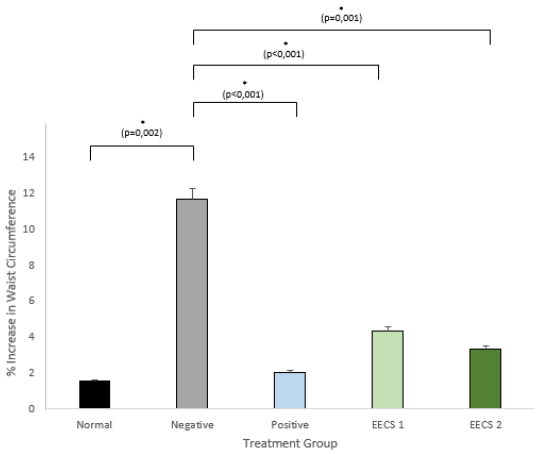

Figure 2. Effect of EECS on abdominal circumference (%) in mice fed a high-fat diet

The negative control group showed the greatest increase in body weight after high-fat diet feeding, confirming the successful establishment of the obesity model. Increased body weight in high-fat diet-fed mice is commonly associated with the accumulation of visceral adipose tissue, a hallmark of diet-induced obesity. Visceral adipose tissue is highly metabolically active and contributes to chronic low-grade inflammation, adipokine dysregulation, and ectopic lipid deposition, all of which promote obesity-associated metabolic disturbances. Progressive visceral fat accumulation also drives the development of central obesity, a major risk factor for metabolic disorders and insulin resistance. Compared with the negative control group, EECS-treated mice exhibited significantly lower body weight gain, suggesting that EECS may help attenuate obesity progression and improve

obesity-associated metabolic alterations (Khanna et al., 2022; He et al., 2020). Overall, the findings suggest that treatment with either metformin or EECS effectively mitigated the increases in body weight and abdominal circumference established through high-fat diet feeding.

Liver index measurements were included in the study parameters. High-fat diet induction is known to alter metabolic homeostasis, as reflected by changes in liver index values. The liver index measurements for all experimental groups are presented in Figure 3.

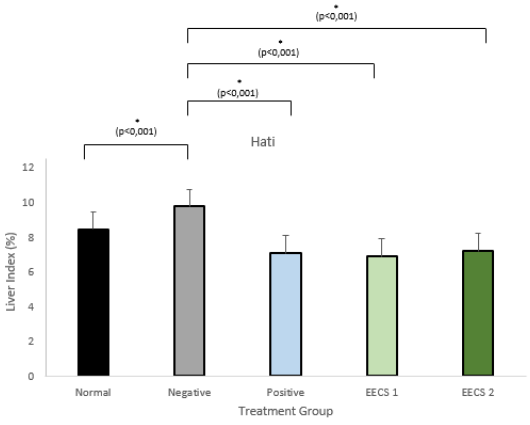

Figure 3. Effect of EECS on liver index (%) in mice fed a high-fat diet

The data showed that the negative control group exhibited the highest liver index among all experimental groups, with a value of 9.76%. This elevation is likely attributable to excessive lipid deposition in the liver as a consequence of prolonged exposure to a high-fat diet. An elevated liver index is indicative of triglyceride deposition within hepatocytes, which may ultimately lead to lipotoxicity (Kvitnitskaya-Ryzhova et al., 2021).

Figure 3 shows that treatment with metformin or EECS at 250 mg/kg and 500 mg/kg resulted in markedly different outcomes from the negative control group ($p < 0.05$). The elevated liver index observed in the negative control group likely reflects excessive hepatic lipid accumulation following prolonged high-fat diet (HFD) feeding. Chronic exposure to a lipid-rich diet increases the influx of free fatty acids into hepatocytes, exceeding the liver's capacity to oxidize or export lipids as very-low-density lipoproteins, thereby promoting triglyceride accumulation, hepatic steatosis, and liver enlargement (Lu et al., 2025). In contrast, EECS treatment significantly reduced the liver index, with the 500 mg/kg group showing a greater reduction than the 250 mg/kg group, suggesting a dose-dependent protective effect against HFD-induced hepatic alterations. This effect may be attributed to the higher availability of bioactive compounds, particularly flavonoids such as quercetin, at the higher dose. Quercetin has been reported to inhibit de novo lipogenesis, stimulate fatty acid β-oxidation, and attenuate oxidative stress and inflammation, thereby reducing hepatic lipid accumulation and preserving liver

morphology (Markowska et al., 2024). These observations imply that treatment with metformin and EECS at both tested doses was effective in reducing the liver index in insulin-resistant mice.

CONCLUSION

The influence of the ethanolic extract of *C. scutellarioides* (EECS) was assessed in a mouse model characterized by insulin resistance following high-fat diet feeding. EECS administration effectively attenuated body weight gain, limiting weight increases to 15.06% and 13.34% in the 250 mg/kg and 500 mg/kg groups, respectively. Furthermore, EECS significantly reduced abdominal circumference and liver index compared with the negative control group ($p < 0.05$). These findings suggest that EECS may improve obesity-associated metabolic alterations. However, further studies evaluating insulin sensitivity biomarkers are required to confirm its effects on insulin resistance.

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