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# Slow-type Interval Training and Ethanol Extract of Sarang Semut (*Myrmecodia pendans*) can Improve the Early Lesions of Atherosclerosis in Type-2 Diabetes Mellitus Rats

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## Abstract

**BACKGROUND:** Macrovascular complications in diabetes mellitus (DM) are the most common cause of death in DM patients. The formation of foam cells on the endothelium is an early marker of atherosclerotic lesions. Physical exercise and antidiabetic agents are an integral part of the management of DM.

**AIM:** The purpose of this study was to analyze the synergistic effect of slow-type interval training (STIT) and ethanol extract of Sarang Semut (EESS) on the number of foam cells in type-2 DM (T2DM) rats.

**METHODS:** A total of 25 male Wistar rats were induced into a type-2 DM model with a high-fat diet and low-dose Streptozotocin injection. Rats were divided into four groups consisting of G1 (T2DM/T2DM), G2 (T2DM + STIT), G3 (T2DM + EESS), and G4 (T2DM + combination of STIT and EESS). The slow-type interval training exercise is done by running on a treadmill. Ethanol extract of Sarang Semut was given at a dose of 400 mg/kg BW for 8 weeks. Histopathological examination was performed with Hematoxylin-Eosin staining to examine the number of foam cells in the aorta. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara.

**RESULTS:** The results showed that there were differences in the average number of foam cells in each treatment group. The highest number of foam cells was found in the T2DM group. The average number of foam cells was the least in the group that received a combination of STIT and EESS which was statistically different from the group that received STIT (K2) and the group that received EESS (K3).

**CONCLUSION:** It can be concluded that the combination of slow-type interval training and ethanol extract of Sarang Semut can reduce the number of foam cells in T2DM rats.

## Introduction

The mechanism of microvascular and macrovascular complications in Type 2 diabetes mellitus (T2DM) begins with an increase in oxidative stress induced by hyperglycemia. Increased production of reactive oxygen species and oxidative stress induce endothelial dysfunction, which increases endothelial permeability and allows the entry of low-density lipoprotein (LDL) into the intima layer. LDL in the intima layer can be oxidized to oxidized LDL. Chemo-attractant expression in endothelial cells attracts monocytes from the lumen into the intima. Monocytes differentiate into macrophages and phagocytize oxidized LDL to form foam cells [1]. The results of a systematic study show that slow-type interval training can improve glycemic control (fasting blood sugar level, and HbA1c), improve body composition (weight, body fat composition, body mass index, and waist circumference), and improve cardiorespiratory fitness [2]. In addition, studies on slow-type interval training in humans and experimental animals have shown that this type of exercise is also able to reduce insulin resistance and increase the distribution of insulin receptors in skeletal muscle [3], [4]. Physical exercise has been shown to increase antioxidant production, so it can reduce oxidative stress [5]. One of the plants thought to have anti-diabetic properties is Sarang Semut (*Myrmecodia pendans*). Sarang Semut is widely used in West Papua as herbal medicine [6], [7], [8]. Ethanol extract of Sarang Semut contains flavonoids that function as antioxidants that can reduce free radical damage [9], [10]. This study aims to analyze the effect of the combination

**Table 1: Bodyweight of experimental animals before and after being given a high-fat diet**

| Groups | Median (minimum–maximum) | | p |
|---|---|---|---|
| | Before (g) | After (g) | |
| G1 (*n* = 7) | 198.00 (187–203) | 276.00 (253–286) | 0.018* |
| G2 (*n* = 6) | 197.50 (187–200) | 261.50 (238–305) | 0.027* |
| G3 (*n* = 6) | 194.00 (187–203) | 325.00 (294–399) | 0.028* |
| G4 (*n* = 6) | 197.00 (189–205) | 320.50 (265–415) | 0.028* |

*Significant. G1 (T2DM); G2 (T2DM+STIT); G3 (T2DM+EESS); G4 (T2DM+combination of STIT and EESS). T2DM: Type 2 diabetes mellitus, STIT: Slow-type interval training, EESS: Ethanol extract of Sarang Semut.

of slow-type interval training and ethanol extract of Sarang Semut on the number of foam cells in rats with the T2DM model.

## Methods

A total of 25 male Wistar rats were induced into the T2DM model with a high-fat diet and low-dose Streptozotocin injection [3]. Rats were divided into four groups consisting of G1 (T2DM), G2 (T2DM + STIT), G3 (T2DM + EESS), and G4 (T2DM +combination of STIT and EESS). Physical exercise in the form of slow-type interval training using a rat treadmill at a speed of 20 m/min for 2 minutes, 10 repetitions, with 60 seconds of active rest, 3 times a week, and for 8 weeks [11]. EESS was given at a dose of 400 mg/kg BW for 8 weeks [12]. Aortic histopathological examination was performed with Hematoxylin-Eosin staining to see the number of foam cells in the aorta. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara. Statistical analysis was carried out using statistical software.

## Results

The results showed a difference in median body weight before and after being given a high-fat diet in each group as listed in Table 1. Bodyweight increased by more than 20%, which means that obesity has occurred [13], [14]. The results of statistical tests showed a significant difference in body weight before and after being given a high-fat diet in each group ($p < 0.05$).

The results showed a significant difference in the number of foam cells between groups as listed in Table 2.

## Discussion

The results showed that there was no significant difference in the number of foam cells in the group that received only STIT compared to the T2DM group. Likewise, there was no significant difference in the number of foam cells in the group that received the EESS alone compared to the T2DM group. However, when combined, the number of foam cells in the group that received the combination of STIT and EESS was lower than the other three groups. This shows that the combination of slow-type interval training and ethanol extract of Sarang Semut plays a more potent role in reducing foam cell formation in T2DM rats. Physical exercise and ethanol extract of Ssarang Semut may play a role in increasing endogenous antioxidants through the Keap1-Nrf2 pathway. Activation of the transcription factor Nrf2 will increase the expression of genes encoding endogenous antioxidants and detoxifying enzymes so that they can counter the adverse effects of oxidative stress [9], [15], [16]. Nrf2 also plays a role in the regulation of lipoprotein transport protein expression in macrophages ([scavenger receptor Class A (SR-A), scavenger receptor Class B (CD36), lectin-type oxidized LDL receptor 1 (LOX-1), toll-like receptor 4 (TLR4), and chemokine (CXC motif) ligand 16 (CXCL16]). In addition, Nrf2 activation also increases cholesterol efflux from macrophages through increased expression of cholesterol transporter protein ([ATP-binding cassette transporter (ABCA1); ATP-binding cassette transporters sub-family G member 1 (ABCG1]). This accelerates the transport of cholesterol from macrophages to the liver thereby preventing the formation of foam cells [17], [18]. The flavonoid contained in the ethanol extract of Sarang Semut has the potential as antioxidants by inhibiting ROS production, increasing the translocation of Nrf2 to the cell nucleus and its ability to bind to DNA, as well as influencing Keap1-Nrf2 interactions and increasing Keap1 ubiquitination [9]. The Keap1-Nrf2/ARE signaling pathway is an important defense system that can fight oxidative stress to prevent complications of T2DM.

**Table 2: Effect of slow-type interval training, ethanol extract of Sarang Semut, and the combination of slow-type interval training and ethanol extract of Sarang Semut on the number of foam cells in Wistar rats model type 2 diabetes mellitus**

| Groups | G1 (*n* = 7) | G2 (*n* = 6) | G3 (*n* = 6) | G4 (*n* = 6) |
|---|---|---|---|---|
| Foam cell count, median (minimum–maximum) | 3.30 (0.90–11.50)[a] | 3.15 (1.60–4.40)[a] | 2.90 (2.40–4.40)[a] | 1.90 (1.50–2.10)[b] |

Kruskal–Wallis followed multiple comparison tests with Mann–Whitney. The treatment groups that were not significantly different ($p>0.05$) were marked with the same lowercase letters; treatment groups that were significantly different ($p<0.05$) were marked with different lowercase letters. G1 (Group 1 [T2DM]); G2 (Group 2 [T2DM+STIT]); G3 (Group 3 [T2DM+EESS]); G4 (Group 4 [T2DM+combination of STIT and EESS]). T2DM: Type 2 diabetes mellitus, STIT: Slow-type interval training, EESS: Ethanol extract of Sarang Semut.

## Conclusions

The combination of slow-type interval training and ethanol extract of Sarang Semut affects reducing the number of aortic foam cells in Wistar rats model T2DM. Further research is needed to examine biomarkers of early microvascular complications in T2DM.

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