Window of Health Jurnal Kesehatan
journal homepage : www.jurnal.fkmumi.ac.id

ARTICLE RESEARCH
URL artikel: http://jurnal.fkmumi.ac.id/index.php/woh/article/view/woh9208

Effect of Hypoxic MSC Exosome on IL-10 and SOCS3 Expression

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and persistent inflammation. Increased expression of Suppressor of Cytokine Signaling 3 (SOCS3) and decreased Interleukin-10 (IL-10) contribute to the progression of inflammation and impaired insulin signaling. Mesenchymal stem cell-derived exosomes under hypoxic conditions (EH-MSCs) have shown potential anti-inflammatory effects and may improve inflammatory responses in T2DM. Objective: This study aimed to determine the effect of hypoxic mesenchymal stem cell exosomes (EH-MSCs) on IL-10 and SOCS3 expression in Wistar rats with type 2 diabetes mellitus. Methods: This was an in vivo experimental study using a randomized post-test only control group design. Twenty-eight Wistar rats were divided into four groups (n=7 each): negative control (K1), positive control (K2), treatment with intravenous injection of EH-MSCs 250 µL (K3), and treatment with intravenous injection of EH-MSCs 500 µL (K4). IL-10 and SOCS3 expression levels were measured using qRT-PCR on day 30. Data were analyzed using One-Way ANOVA followed by Post Hoc LSD test with a significance level of $p<0.05$. Results: The mean IL-10 expression was highest in K3 (1.99 ± 0.39), followed by K4 (1.47 ± 0.49), K2 (1.37 ± 0.54), and K1 (1.12 ± 0.31), with a statistically significant difference among groups ($p = 0.009$). Meanwhile, the mean SOCS3 expression was highest in K1 (1.09 ± 0.41) and lowest in K3 (0.56 ± 0.11), with significant differences among groups ($p = 0.018$). These findings indicate that EH-MSC administration increased IL-10 expression and decreased SOCS3 expression, particularly at the 250 µL dose. Conclusion: Hypoxic mesenchymal stem cell-derived exosomes significantly increased IL-10 expression and decreased SOCS3 expression in T2DM model rats, with the 250 µL dose showing the most effective anti-inflammatory response. EH-MSCs have potential as a therapeutic strategy for reducing inflammation in T2DM.

Keywords: EH-MSCs; IL-10; SOCS3; Type 2 Diabetes Mellitus; Exosomes

PUBLISHED BY :
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Article history)
Received 28 August 2025
Received in revised form 26 March 2026
Accepted 24 April 2026
Available online 26 April 2026

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent chronic metabolic diseases worldwide. The primary underlying mechanism is insulin resistance, which is exacerbated by chronic inflammation. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) contribute to impaired insulin signaling, while anti-inflammatory cytokines such as interleukin-10 (IL-10) play a protective role by improving insulin sensitivity. In addition, Suppressor of Cytokine Signaling 3 (SOCS3) acts as a negative regulator of the JAK/STAT pathway, and its overexpression has been shown to worsen insulin resistance.

Pathophysiologically, T2DM involves the overexpression of SOCS3, which inhibits insulin signaling pathways through suppression of insulin receptor substrate (IRS) phosphorylation and downstream phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) activation. This disruption contributes to insulin resistance, a hallmark of T2DM. Chronic inflammation in T2DM also leads to decreased anti-inflammatory cytokines such as IL-10, reducing the body's ability to control inflammation and maintain metabolic balance.

Globally, the prevalence of diabetes continues to rise significantly. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes in 2021, and this number is projected to reach 783 million by 2045. In Indonesia, Basic Health Research (Riskesdas) data showed an increase in diabetes prevalence from 6.9% in 2013 to 8.5% in 2018, with T2DM accounting for around 90–95% of cases. This condition poses a significant burden due to its complications, including damage to the retina, kidneys, nerves, and increased risk of neurodegenerative disorders.

Therapeutic approaches using mesenchymal stem cell-derived exosomes (MSC-Exos) have shown promising results in tissue repair by modulating inflammation and improving pancreatic beta-cell function. Previous studies have demonstrated that exosomes derived from bone marrow stromal cells can suppress inflammation and reduce oxidative stress, both of which play important roles in T2DM progression.

Hypoxic preconditioning further enhances the therapeutic potential of MSC-derived exosomes by increasing their bioactive components, including microRNAs (miRNAs), which regulate gene expression and improve insulin sensitivity. In addition, hypoxic MSC-derived exosomes have been shown to promote anti-inflammatory responses, including macrophage polarization toward the M2 phenotype.

Despite these promising findings, studies specifically investigating the effects of hypoxic MSC-derived exosomes on key inflammatory regulators such as IL-10 and SOCS3 in in vivo models of T2DM remain limited. Therefore, this study aims to evaluate the effect of hypoxic MSC-derived exosomes on IL-10 and SOCS3 expression in a T2DM rat model, in order to explore their potential as a novel therapeutic strategy.

METHOD

This study was a quantitative in vivo experimental study with a post-test only control group design,conducted at the Stem Cell and Cancer Research (SCCR) Laboratory, Faculty of Medicine, Universitas Islam Sultan Agung, Indonesia, from May to July 2025. Ethical approval for this study was obtained from the Institutional Ethics Committee (No: 218/2025/Komisi Biotik). A total of 24 male Wistar rats (Rattus norvegicus), aged 8–10 weeks and weighing 200–250 g, were used in this study. The sample size was determined based on Federer's formula. The animals were randomly divided into four groups (n=6 per group): (K1) normal control group receiving NaCl 0.9%, (K2) positive control group receiving metformin at a dose of 45 mg/kg body weight, (K3) treatment I group receiving MSC-derived exosomes at a dose of 250 µg, and (K4) treatment group receiving MSC-derived exosomes at a dose of 500 µg.

Type 2 diabetes mellitus was induced using a combination of streptozotocin (STZ) and nicotinamide(NA). Fasting blood glucose levels >200 mg/dL were considered diabetic. Mesenchymal stem cells (MSCs) were cultured and characterized based on surface markers (CD44+, CD90+, CD34−, CD45−) and confirmed for multipotency through adipogenic, osteogenic, and chondrogenic differentiation assays. Exosomes were isolated using tangential flow filtration (TFF) under controlled conditions.

Exosome therapy was administered on days 15, 18, and 21. The treatment groups received MSC-derived exosomes according to their respective doses, while the control group received NaCl and the positive control group received metformin. At the end of the treatment period, pancreatic tissues were collected for immunohistochemistry (IHC) analysis to evaluate IL-10 and SOCS3 expression.
Data were analyzed using one-way ANOVA followed by LSD post hoc test, with a significance level set at $p < 0.05$.

RESULTS

MSCs used in this study were isolated and cultured in a specialized medium at the Stem Cell and Cancer Research Laboratory. The cultured MSCs, after reaching the fourth passage, were subjected to hypoxic conditions and exhibited a characteristic spindle-shaped morphology, consistent with the typical fibroblast-like appearance seen in MSCs under low oxygen tension. To validate the identity and multipotency of these cells, hypoxia-conditioned MSCs were further cultured in osteogenic and adipogenic induction media to assess their ability to differentiate into osteocytes and adipocytes, respectively. This differentiation assay served as a crucial step in confirming the functional properties of MSCs for subsequent experimental applications (Figure 1).

The isolation of MSCs was validated using flow cytometry to assess their ability to express specific surface markers. The analysis revealed that the MSCs exhibited minimal expression of the hematopoietic marker CD45 (0.4%) and the endothelial marker CD31 (3.92%), confirming their negative status for these markers.

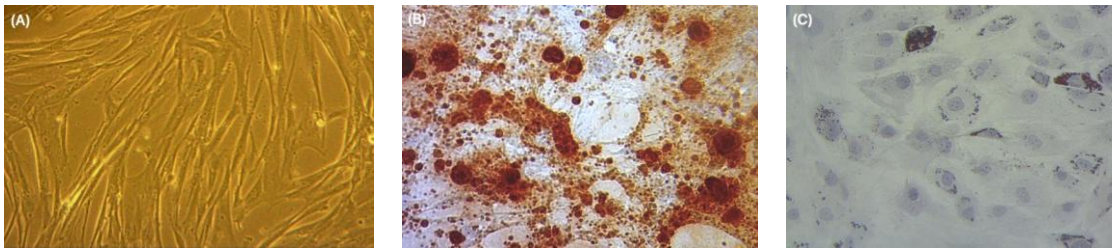


Figure 1. MSCs Validation. (a) spindle-shaped morphology of MSCs (b) Osteogenic differentiation (c) Adipogenic differentiation.

In contrast, the cells showed strong positive expression for mesenchymal markers CD90 (98.7%) and CD29 (99.9%). These results confirm the successful isolation and characterization of MSCs based on their distinctive surface marker profile.

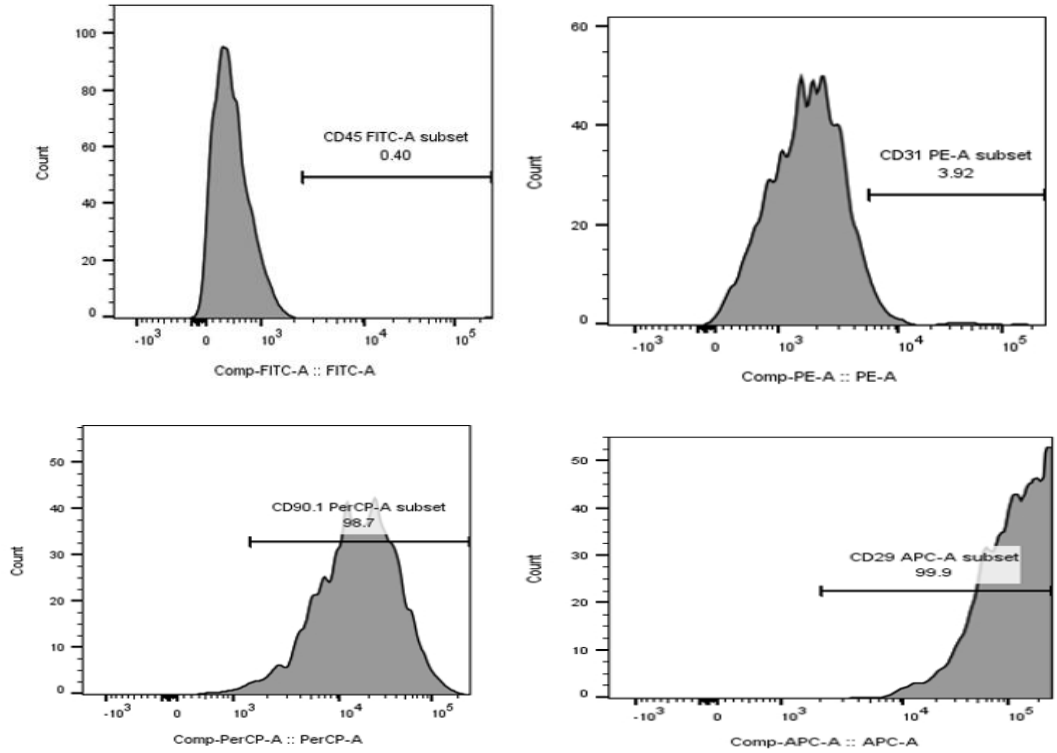


Figure 2. MSCs Validation using flow cytometry (A) CD45 0.4% (B) CD31 3.92% (C) CD90 98.7% (D) CD29 99.9%

Characteristics of EH-MSCs

Hypoxia-preconditioned mesenchymal stem cells were validated and subsequently subjected to filtration using tangential flow filtration (TFF) to obtain exosome-rich fractions, referred to as EH-MSCs. The filtration process yielded EH-MSCs at a concentration of 7.5 µg/mL. To confirm the identity and purity of these exosomes, flow cytometry analysis was performed, demonstrating that 9.1% of the EH-MSCs population expressed the surface marker CD9, a characteristic exosomal marker (Figure 3).

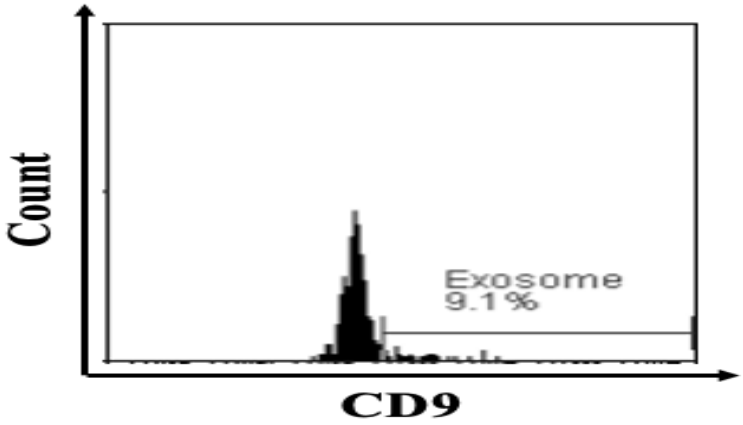


Figure 3. EH-MSCs Validation.

T2DM validation

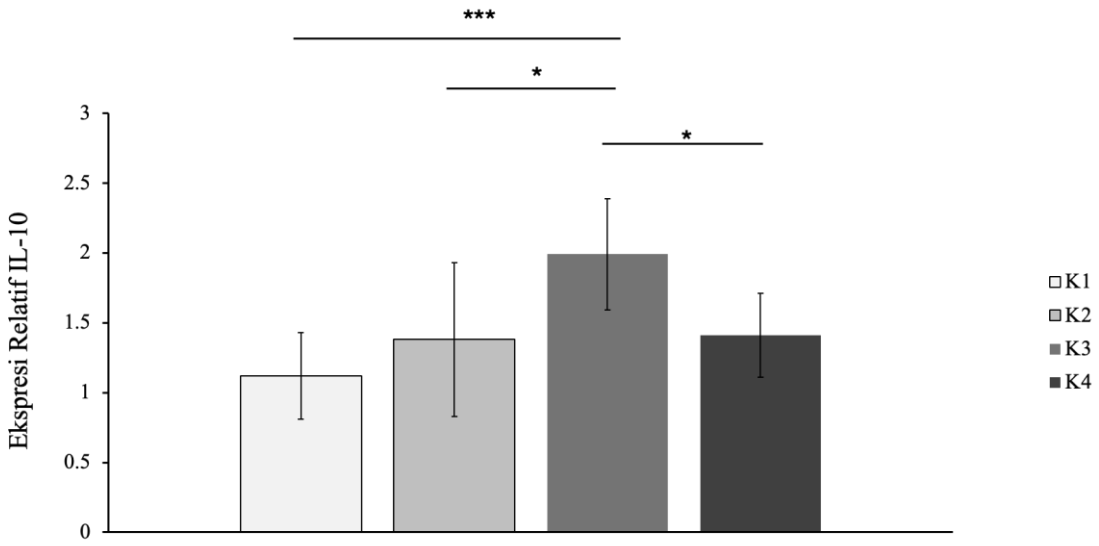
Male Wistar rats were used as subjects in this study to establish a type 2 diabetes mellitus (T2DM) model, induced with STZ at 65 mg/kgBW and nicotinamide (NA). Validation of T2DM was performed by analyzed both random and fasting blood glucose levels. Prior to induction, the rats exhibited a blood glucose level of 111 mg/dL, which increased to 334 mg/dL after induction, confirming the development of hyperglycaemia. Histological examination of pancreatic tissue revealed cytoplasmic degeneration, loss of cellular granules, and irregular islet morphology in the STZ-induced rats, indicating significant pancreatic damage. These findings collectively demonstrate that the Wistar rats successfully developed T2DM, as evidenced by both biochemical and microscopic assessments.

Figure 4. Validation of Wistar Rats Model T2DM. (A) Initial random blood glucose levels in the rats were measured at 111 mg/dL, establishing the baseline prior to induction (B) Following induction, fasting blood glucose levels rose significantly to 334 mg/dL, indicating the onset of hyperglycaemia characteristic of T2DM (C) Microscopic analysis of pancreatic tissue sections stained with hematoxylin and eosin (H&E) revealed classic features of diabetes, including marked damage to pancreatic beta cells.

EH-MSCs effects on IL-10 and SOCS3 in T2DM

The highest mean IL-10 expression was observed in group K3 at 1.99±0.39, followed by group K4 at 1.47±0.49 and group K2 at 1.37±0.54. The lowest IL-10 expression was found in group K1, the negative control group, at 1.12±0.31. Both the negative and positive control groups showed a significant difference compared to group K3, which received EH-MSCs at a dose of 250 µL ($p<0.05$). In contrast,

group K4, which received EH-MSCs at a dose of 500 µL, did not show a significant difference compared to either the negative or positive control groups (p>0.05). The comparison of IL-10 expression between the two EH-MSCs groups (K3 vs. K4) also showed a significant result, with a p-value of 0.021 (p<0.05). Based on these data, it can be concluded that EH-MSCs at a dose of 250 µL significantly increased IL-10 expression compared to the negative control, positive control, and the 500 µL EH-MSCs group. There is a pattern of increased IL-10 expression as a result of EH-MSCs treatment, as illustrated in the figure 5a.



*p<0.05 **p<0.01 p<0.001

Figure 5a. The results of the gene expression of IL-10 in the pancreatic tissue of each group (from left K1,K2,K3 and K4).

The highest mean SOCS3 expression was observed in group K1 (1.09±0.41), followed by group K2 (0.86±0.17). The lowest SOCS3 expression was found in the EH-MSCs treatment groups, with group K3 (0.56±0.11) and group K4 (0.73±0.26). The negative control group showed a significant difference compared to both EH-MSCs treatment groups—250 µL in group K3 and 500 µL in group K4 (p<0.05). Conversely, there was no significant difference between the positive control group (K2) and the EH-MSCs treatment groups (p>0.05). Additionally, the comparison of SOCS3 expression between the two EH-MSCs groups (K3 vs. K4) was not significant, with a p-value of 0.270 (p>0.05).

Based on these data, it can be concluded that EH-MSCs significantly affected SOCS3 expression compared to the negative control group, but not when compared to the positive control group. Furthermore, there was no significant difference in the effect between the 250 µL and 500 µL EH-MSCs doses, although the mean reduction in SOCS3 expression was lower in the 250 µL group (K3) than in the 500 µL group (K4). These results indicate a pattern of decreased SOCS3 expression following EH-MSCs treatment, as illustrated in the corresponding figure 5b.

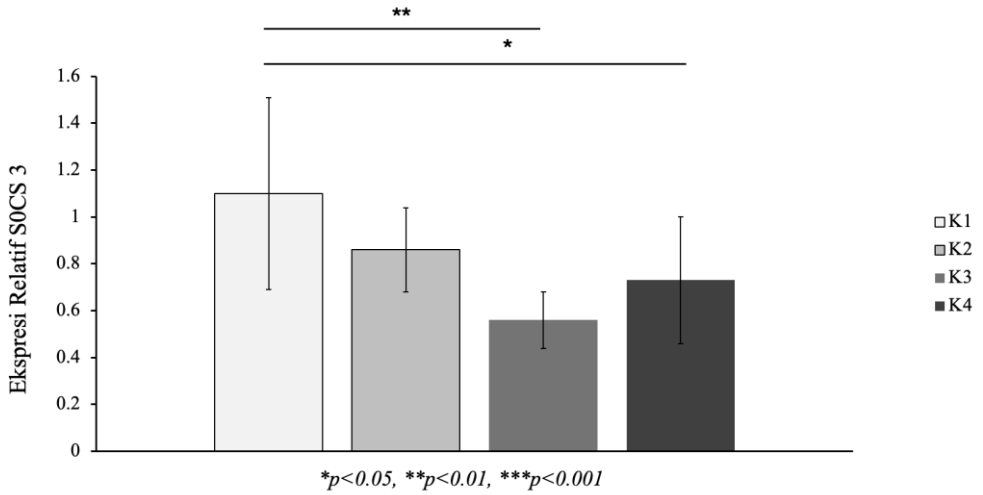


Figure 5b. The results of the gene expression of SOCS3 in the pancreatic tissue of each group (from left K1,K2,K3 and K4)

DISCUSSION

This study demonstrated that administration of hypoxic mesenchymal stem cell-derived exosomes (EH-MSCs) significantly modulates inflammatory markers in a T2DM rat model by increasing IL-10 expression and decreasing SOCS3 expression.

The increase in IL-10 expression observed in the treatment groups, particularly at the 250 µL dose (K3), indicates an enhancement of anti-inflammatory responses. IL-10 is a key anti-inflammatory cytokine that suppresses pro-inflammatory pathways and improves insulin sensitivity. The higher IL-10 levels in the EH-MSC-treated groups suggest that exosomes derived from hypoxic MSCs can effectively regulate immune responses and reduce chronic inflammation associated with T2DM.

Conversely, SOCS3 expression was significantly reduced following EH-MSC administration. SOCS3 is known to inhibit insulin signaling pathways and contribute to insulin resistance when overexpressed. The decrease in SOCS3 expression in the treatment groups indicates that EH-MSCs may help restore insulin signaling and reduce metabolic dysfunction. This finding supports previous evidence that modulation of SOCS3 plays an important role in improving inflammatory and metabolic conditions. Interestingly, the 250 µL dose (K3) demonstrated the most optimal effect compared to the 500 µL dose (K4). This suggests that higher doses do not necessarily lead to better therapeutic outcomes, possibly due to saturation effects or biological feedback mechanisms. Additionally, no significant difference was observed between the two treatment groups (K3 vs K4), indicating that the lower dose may already achieve maximal therapeutic benefit.

Furthermore, the significant differences between the negative control group and treatment groups confirm the effectiveness of EH-MSCs in reducing inflammation. However, the absence of significant differences between the positive control group and treatment groups suggests that EH-MSCs may have comparable effects to existing interventions.

Overall, these findings indicate that EH-MSCs have strong potential as an anti-inflammatory therapy in T2DM by enhancing IL-10 expression and suppressing SOCS3. This dual mechanism may contribute to improved insulin sensitivity and better metabolic regulation.

CONCLUSIONS AND RECOMMENDATIONS

The administration of hypoxic mesenchymal stem cell-derived exosomes (EH-MSCs) significantly affected inflammatory markers in a Type 2 Diabetes Mellitus (T2DM) rat model. EH-MSC treatment increased IL-10 expression and decreased SOCS3 expression compared to the control groups, indicating an improvement in anti-inflammatory response and potential restoration of insulin signaling. The 250 µL dose demonstrated the most optimal effect, as reflected by the highest increase in IL-10 and the greatest reduction in SOCS3 expression. Increasing the dose to 500 µL did not provide additional significant benefits, suggesting that the lower dose is sufficient to achieve the desired therapeutic effect. These findings indicate that EH-MSCs have potential as a therapeutic strategy for reducing inflammation in T2DM through modulation of IL-10 and SOCS3 pathways.

ACKNOWLEDGEMENT (Optional)

The authors thank Stem Cell and Cancer Research (SCCR) Indonesia, the supervising lecturer, and my family.

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