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Adipose-Derived Stem Cells (ADSCs): a review article

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ABSTRACT

Introduction: Stem Cells (SC) are cells having characteristic features of self-renewal and plasticity that can differentiate and proliferate into many types of cells to form an individual. This literature study aims to evaluate the Adipose-Derived Stem Cells (ADSCs) comprehensively.
Methods: A comprehensive literature search was conducted by the author to obtain relevant studies from PubMed, MEDLINE, Embase, PreMEDLINE, Embase, PsycINFO, Scopus, and Cochrane for the last fifteen years. The author sought articles with the following keywords: Adipose-Derived Stem Cells, AND Fibrosis, OR Wound Healing, OR Growth Factor, hypoxic culture OR, Normoxic Culture, OR cytokine.
Results: ADSCs become one of the strong potential stem cell-based therapies, for instance, preventing fibrosis tissue formation in the wound healing process. The source is mainly on the body's surface, and harvesting using a minimally invasive procedure made ADSCs superior to the other stem cell sources. Using a better precondition technique, such as the hypoxia precondition technique, can increase the proliferation of stem cells and the viability of stem cells.
Conclusion: ADSCs are a source of visible cell-based therapy to be currently used. ADSCs can counteract fibrosis by the anti-inflammatory and anti fibrosis effects.

Keywords: Adipose-Derived Stem Cell, Wound Healing, Fibrosis, Review.
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INTRODUCTION

Stem cells have characteristic features of self-renewal and plasticity that can differentiate and proliferate into many types of cells to form an individual.[1] Stem cells currently become one of the therapeutical choices in preventing the formation of fibrosis tissues in the wound healing process. Stem cells can be from both embryonal and adult stem cells, such as mesenchymal stem cells.[1] Adipose-Derived Stem Cells (ADSCs) are one of the types of the mesenchymal stem cell group. ADSCs mainly exist on the body's surface, easy to perform harvesting action as a source of stem cells; besides, invasive actions are not needed in performing harvesting compared to harvesting from other sources, such as bone marrow stem cells.[2]

Stem cells start to be known as an important element in regenerative treatment due to their ability to differentiate into many cell phenotypes.[1,2] In the beginning, stem cells are assumed to perform tissue recovery by differentiating into the tissue. Nevertheless, stem cells also have an ability to differentiate, namely the ability to be cells outside their differentiation path. Stem cells actively contribute to the surrounding environment by doing cytokine secretion, growth factor, and extracellular matrix molecule that plays a good role for themselves (autocrine) and to the surrounding (paracrine).[2]

Stem cells are one of the therapeutical modalities that can prevent fibrosis formation in the wound healing process. To be considered as a stem cell, a cell shall have an undifferentiated state to be the characteristic, able to proliferate (self-renewal), and differentiate into more than one type of cell (multipotent and pluripotent).[3] Based on their origin, stem cells are divided into 4 main types: embryonic stem cells, adult stem cells, fetal stem cells, and infant stem cells.[3] Adult stem cells are currently used in clinical applications. Adult stem cells can be from hematopoietic, Mesenchymal, Epidermal, Liver, Neuronal, Eyes, Intestines, and Pancreas stem cells. Adipose-derived stem cells, to date, have effectiveness in preventing fibrosis tissue formation in the urethra. A study conducted by Castiglione et al. showed that giving ADSCs can prevent the formation of urethral stricture.[4]

Stem cells, to be able to be used for therapy, shall have a good proliferation ability and are easy to be taken and processed into stem cells; ADSCs are from fat tissues; the number of fat tissues on the body's surface is abundant, easy harvesting technique, and minimum invasive.[2] Normoxic cultures that are currently performed using high oxygen (O_2) tension (> 21%) or known as normoxia, cause a decrease in the stem cell viability before being transplanted.[2,3] According to the literature review, one of the processes to improve the function of ADSCs is by doing hypoxic culture.[5]

In ADSCs with the oxygen condition in hypoxic of 5%, it is said to increase the proliferation capacity and the viability of stem cells in post-transplantation. Based on those mentioned above, this review article was presented descriptively and discussed ADSCs, the correlation with wound healing, fibrosis, urethral fibrosis, cytokines, growth factor, and normoxic and hypoxic cultures ADSCs.

METHODS

A comprehensive literature search was conducted by the author to obtain relevant studies from the PubMed, MEDLINE, Embase, PreMEDLINE, Embase, PsycINFO, Scopus, and Cochrane databases for the last fifteen years (January 2006 – June 2021). The author used a search strategy with the following keywords, namely Adipose-Derived Stem Cells AND Fibrosis, OR Wound Healing, OR Growth Factor, OR hypoxic Culture, OR Normoxic Culture, OR cytokine.

Duplicate journals were managed using EndNote. The title and abstract of the results were reviewed, and the full texts were analyzed and assessed using inclusion and exclusion criteria specified by the author. Only English and full-text articles were included in this study. Original studies, including the research article, textbook, observational studies (i.e., systematic review, case series, cross-sectional, case-control, and cohort), and randomized trials, were all eligible for inclusion. Exclusion criteria were studies only including abstracts, unpublished studies. Conference reports were also excluded.

Adipose-Derived Stem Cells (ADSCs)

Stem cells have unlimited abilities in tissue formation as therapeutic cells due to their abilities in self-renewal; stem cells can be differentiated into cell lineages as a solution in many diseases.[6] Mesenchymal stem cells (MSCs) from bone marrow provide suboptimal results since they shall do invasive actions to obtain specimens. It will decrease the differentiation and proliferation of specimens that have been stored for a long time. ADSCs are multipotent cells that can be differentiated into osteocytes, adiposity, neural cell, vascular endothelial cells, cardiomyocytes, pancreatic cells, and hepatocytes. ADSCs are considered to distinguish as MSCs from bone marrow; besides, in an in-vivo study, ADSCs have expression characteristics of stem cells. Easy specimen harvesting using the minimum invasive method, simple isolation procedure, stem cell quality, and proliferation capacity that does not deteriorate; thus, ADSCs are the best alternative for bone marrow MSCs.[6] Nearly similar to bone marrow MSCs, ADSCs also have a specific combination of cell surface markers to be considered as stem cells, namely CD90, CD105, CD73, CD44, and CD166, as well as the lower expression for hematopoietic markers, such as CD45 and CD34. Some literature mentioned that specimen harvesting from a different location does not affect the collected viable cells. ADSCs are considered more stable morphologically and genetically in long-term culture. Stem cells are not only useful by cellular restoration, but it has effects using a paracrine method. Several studies showed the effect of ADSCs as an anti-apoptosis, anti-inflammation, pro-angiogenic, immunomodulatory, and anti-scarring.[6] To date, 130 clinical trials conducted in America revealed the effectiveness of ADSCs on the regeneration of soft tissue, regeneration of skeletal tissue, ischemic injury, myocardial infarction, and immune system disorder, such as Lupus, arthritis, Chron's diseases, multiple sclerosis, diabetes mellitus, and acute graft-vs-host disease.[2]

ADSCs are an effective therapy for patients with atrophy, fibrosis, retraction, and ulcers caused by radiation therapy; moreover, ADSCs are effective in abnormal wound healing. ADSCs are also effective for acute Graft-vs-Host Disease (GVHD) and haematological and immunological diseases, such as idiopathic thrombocytopenic purpura.[6] ADSCs have an immunomodulatory function. Stem cells can be applied to the area where the tissue damage occurs. Stem cells have unique characteristics, namely easy to be harvested in a large amount, having a high proliferation capacity, the ability to differentiate into the expected cell phenotypes, and helping the vascularization process for wound healing. In advanced regenerative therapy, stem cells are used to repair damaged tissues and even replace the organ. The source of stem cells can be from embryonic stem cells collected from embryonic tissues that can induce pluripotent stem cells, reprogram the differentiation of somatic cells; besides, stem cells in more mature tissues can be collected from fat tissues, dermal tissues, bone marrow, blood, or skeletal muscle. MSCs are identified in the bone marrow.[6] MSCs can be taken from several types in the body, such as adipose tissues, trabecular bone, skin, skeletal muscle, pericytes, umbilical cord blood, periosteum, peripheral blood, synovial membrane, dermis, dental pulp, periodontal ligament, and even tumours. Even though stem cells can be taken from many sources, the amount to be taken from each source is limited. However, adipose tissue is a potential source of stem cells since it exists in most body parts and can be taken in a large amount with lower donor morbidity. Subcutaneous tissue can be taken from the abdomen, thighs, and arms.[6]

ADSCs have better proliferation capacity than Bone Marrow Mesenchymal Stem Cells (BMSCs). ADSCs can maintain the normal diploid karyotype for 100 generations of culture and produce 40 times more than BMSCs. ADSCs have better epithelial regeneration and better collagen formation than BMSCs.[7] A study also showed that the proliferation of ADSCs from T lymphocytes as a product of reduced cell surface of histocompatibility antigens inhibits Mixed Lymphocytes Reaction (MLR); thus, if it is compared to the other sources of stem cells, ADSCs have immunocompatibility and are strongly suitable for autotransplantation.[7]

ADSCs and Wound Healing

Wound healing is dynamic and complex, where it consists of releasing cytokines, growth factors, and chemokines. There are several phases of wound healing: homeostasis, inflammation, proliferation, remodelling, or maturity.[7] The homeostasis phase happens immediately after the wound, followed by vasoconstriction, thrombosis, cytokine release, and activation from endogenous and exogenous coagulation pathways. The inflammation phase occurs in the first three days after the injury happens.

When the inflammatory cells migrate to wounds and mast cells produces vasoactive factors for dilating blood vessels. In this phase, neutrophils play a role in eliminating necrotic tissues and bacteria, and macrophage facilitates the release of inflammatory cytokines, including transforming growth factor, Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and Epithelial Growth Factor (EGF).[7] The proliferation phase occurs 3-21 days after the injury when the angiogenesis, granulation tissue formation, collagen formation, and epithelial tissue formation happen. In the last phase, namely maturity or remodelling, collagen cross-linking and contraction of wounds occur; in this phase, fibroblast and collagen fibres have an important role. Good maturity of wounds will cause good wound tissue formation. ADSCs increase the neovascularization of ischemic tissue. Therefore, it can be said that adipocytes can be the source of cells for angiogenesis in patients with ischemic disease. Another study showed that ADSCs could be differentiated into endothelial cells and increase blood perfusion and angiogenesis process in ischemic in the lower extremity.[7] ADSCs are not only differentiated into vascular endothelial cells and epithelial cells to improve the structure of blood vessels and epithelial tissue formation of sounds, but they also improve the angiogenic factor, such as hepatocytes growth factor (HGF) and vascular endothelial growth factor (VEGF) to enhance the process of wound angiogenesis. Hypertrophic scars occur due to an imbalance of collagen tissue formation.[7]

Hypertrophic scars are characterized by the total proliferation and production from fibroblast and extracellular matrix formation. ADSCs increase the proliferation and differentiation of fibroblast on wound area, but they also inhibit the excessive proliferation and migration from fibroblast and decrease the expression of the effect of cytokines.[7]

Types of Stem Cells

The types of stem cells produced by the body are classified based on the maturity level of their constituent tissues. Based on the maturity level of tissues, stem cells are divided into two types, namely embryonic stem cells and adult stem cells. Stem cells can be classified into 4 types based on their origin: embryonic stem cells, fetal stem cells, infant stem cells, and adult stem cells.[3]

Hypoxic and Normoxic Cultures of ADSCs

Hypoxic culture from ADSCs with a low oxygen level can increase the proliferation and stemness of stem cells, increasing the potency of stem cells to differentiate into multipotent and better long-term expansion.[3,8] For the last few years, the hypoxic culture has been widely used in in-vitro studies. In reality, the hypoxic culture showed that it could stimulate the proliferation of ADSC without changing the phenotypes of ADSC. Hypoxic culture is considered to prevent senescence as a genomic stability inducer and increase the viability, motility, and tropism. This can happen due to the stimulation of Hypoxia-Inducible Factor 1- á (HIF-1á), Reactive Oxygen Species (ROS) formation, and the decrease in the phosphorylation of Platelet-Derived Growth Factor Receptor â (PDGFRâ), extracellular signal-regulated kinases ½ (ERK1/2), and Akt pathway. The previous study also shows a significant increase in VEGF expression in the ADSCs cultured in a hypoxic condition compared to the ADSCs cultured in a normoxic condition.[9]

Conventional culture with normoxia in bone marrow mesenchymal stem cells was widely reported to cause senescence cells, apoptosis, and gene mutation. This results in a decrease in stem cell viability before being transplanted.[3] After being transplanted, stem cells will experience lysis of around 93 – 99% on the third to the seventh day of post-transplantation, and it even reaches 99% on the first day of transplantation. The normal oxygen level in the medium in-vitro MSC is at a concentration level of 20%, usually known as normoxia. The culture condition with Low O_2 tension (hypoxia) supports the microenvironment during the in-vitro culture to keep it viable when transplanted. The hypoxic condition causes stem cells to have Long-Term Maintenance (LTM). LTM can happen when stem cells are at the G0 phase, but they still proliferate and do not differentiate.[3] A previous study on the hypoxic condition for supporting the in-vitro microenvironment (niche) in some sources of stem cells was conducted, for instance, on hematopoietic stem cells (HSC) with an O_2 concentration of around 0–5%, on adipose-derived stem cells of 5%, on neural stem cells (NSC) of approximately 1-5 %, and Human Cord Blood of 3% for 7 days.[3] During the culture of stem cells, the hypoxic condition becomes the factor of an in-vitro niche that can control the proliferation of stem cells to stay viable and undifferentiated without experiencing apoptosis, senescence cell formation, and gene mutation.[3] It was agreed in consensus with Acta-Bioenergetics for Biochemicals and Biophysics in 2008, and hypoxia was at an oxygen level of 3%-5% or 30-50 µM. MSC grown at an oxygen level of around 0.4% to 2.3% causes an increase in apoptosis cells. The best oxygen expression for increasing the production of the paracrine effect of VEGF and angiogenesis is 5%.[3]

Paracrine effect of ADSCs

ADSCs can secrete many kinds of cytokines, growth factors, and chemokines to regulate angiogenesis and immune response in a paracrine mechanism; thus, they can stimulate tissue damage. Many studies showed that ADSCs secrete many bioactive factors through the paracrine mechanism to activate endogenous cells.[7-10] Consequently, they stimulate angiogenesis, epithelial regeneration, and remodelling of wounds. The wound healing process is a combination of many cytokines' effects, such as Transforming Growth Factor (TGF-β), Hepatocytes Growth Factor (HGF), Matrix Metalloproteinases (MMP), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interleukins, EGF, FGF, and Tumor Necrosis Factor-α (TNF-α).[7] In a repairing process from blood vessels, the role of ADSCs is important to produce angiogenesis activity factors for activating wound healing. ADSCs produce many cytokines that can activate the angiogenesis process: GM-CSF, PDGF, SDF-1, VEGF, b-FGF, HGF, TGF- α, MMP, IL-6, and IL-8. VEGF is the most important factor in the

angiogenesis process. VEGF can stimulate the mobilization process, recruitment, and migration from endothelial progenitor cells to accelerate the angiogenesis process.[7] A study conducted by Heo SC et al., showed that TNF-α activated by ADSCs would produce pro-inflammatory cytokines, namely IL-6 and IL-8, to initiate the angiogenesis process on the wound and epithelial regeneration that eventually accelerate the wound healing process.[10]

Mechanisms of Tissue Regeneration by Stem Cells

Stem cells that are systemically or directly injected into the targeted tissues will initiate the regeneration mechanism of damaged tissues. The improvement of damaged tissues is done through 2 mechanisms: stem cell differentiation and growth factor production of stem cells.[1,3]

In order to reach optimum effectiveness, the type of stem cell being used is adjusted to the desired differentiation path, for example, patients with blood disorders generally use hematopoietic stem cells because the ability of stem cells to differentiate into several types of progenitor cells that can differentiate into erythrocytes, leukocytes, and thrombocytes (platelets).[3] However, stem cells can be stem cells outside their differentiation path. This phenomenon is known as transdifferentiation. The normal example is that hematopoietic stem cells can only differentiate into myeloid progenitor cells and lymphoid progenitor cells (myeloid and lymphoid cells). Still, in several in-vitro studies, hematopoietic stem cells can differentiate into the striated muscle cells, cardiomyocytes, neurons, renal epithelial cells, epidermal stem cells of the skin, lung epithelial cells, and intestinal epithelial cells.[3]

Stem from outside the body can stimulate the stem cells from inside an individual's body to simultaneously perform regeneration tasks for damaged tissues. One point that is supposed to be the factor causing this is the number of elements produced by stem cells transplanted to the body that can stimulate the production of stem cells from many organs in the patients' bodies. These factors are cytokines and growth factors.[3]

ADSCs Mechanism in Increasing IL-10 in Wound Healing Process

Pluripotent stem cells can differentiate into some cells. A study conducted by Burkitts Lymphoma with a hypoxic condition shows that ADSCs increase the secretion of IL-10. ADSCs have a strong paracrine effect.[11] IL-10 is a cytokine immunoregulator affecting the inflammation process. ADSCs are strongly promising in structuring soft tissue, clinical treatment for inflammation and pathological condition of autoimmune. ADSCs are a population having the ability to self-renew the multipotent adult stem cells in stromal vascular cells within adipose tissue that has an important role in the development, post-natal growth, maintaining the homeostasis of tissues, and tissue improvement and regeneration.[11] ADSCs, if stimulated, can differentiate into some types of cells, namely adipocytes, osteocytes, neurons, vascular endothelial cells, cardiomyocytes, pancreatic cells, and hepatocytes. To date, the mechanisms of ADSCs providing therapeutical effects are only revealed partially. There are 3 mechanisms believed to improve wound healing, namely 1) Multi-differentiation Potency, 2) self-renewal ability, 3) Immunomodulatory capacity. From several studies like in the cardiology sector, ADSCs can increase anti-inflammation and pro-angiogenic, namely increasing the IL-10 level through immunomodulatory effect through paracrine mechanism.[12]

Effect of ADSCs on TNF-α in Wound Healing Process

A study conducted by Cai C et al., obtained that providing Adipose-Mesenchymal Stem Cells (AMSCs) could increase remodelling by decreasing the gene expression of proinflammation, inflammation, and fibrosis if it was compared to those without AMSCs therapy.[13] This study also obtained a decrease in IL-1β and TNF-α expression that was treated with AMSCs. In this study, IL-1β and TNF-α are involved in stenosis after conducting Percutaneous Transluminal Angioplasty (PTA). AMSCs have an anti-inflammatory effect and can decrease stenosis formation after performing PTA. ADSCs were pluripotent and easy to find since they are available in most body parts.[13]

A study conducted by Li JZ et al. showed that ADSCs and BMSCs resulted in a decrease in inflammation factor secretion (TNF-α and IL-6) and an increase in the IL-10 level.[14] Several studies showed that Mesenchymal Stem Cells (MSCs) regulate the immunogenicity of macrophages.[14] Thus, the phagocytosis and immunogenicity of macrophages will be regulated through cytokine release by ADSCs. In those studies, ADSCs regulated immunogenicity and ox-LDL-stimulated M1 of macrophages through the secretion of cis-9, trans-11. ADSCs increase the secretion of anti-inflammatory cytokines, such as IL-10, and decrease the secretion level of pro-inflammatory cytokines, such as TNF, IL-6, and IL-8. Even though many previous studies investigated ADSCs with their ability to inhibit TNF-α, few studies explain how ADSCs can interfere with TNF-α.[14] TNF-α is known as pro-inflammatory cytokines by stimulating the release of microbicidal reactive oxygen species and protease. A study investigating the skin treated with Adipose-tissue Mesenchymal Stem Cells (AT-MSCs) showed a significant decrease in TNF-α on the 3rd, 5th, and 7th day after treatment. Pro-inflammatory macrophages (M1) are the source of TNF-α formation. The study showed a surprising result that AT-MSCs injection, even though showing a decrease in TNF-α, increase the number of macrophages. 2 types of macrophages are M1 and M2, where M1 distracts the wound healing process, and M2 behaves as anti-inflammation, initiating the formation of matrix and remodelling phase to improve tissues. Providing 70% AT-MSC from macrophages shows the CD163 expression indicating the particular characteristics of M2 that does not express TNF-α.[15]

Effect of ADSCs on FGF 2 expression in Wound Healing Process

The existence of FGF 2 can increase ADSCs proliferation through several signalling pathways. Src activation is important in activating the FGF 2 pathways for mediating the ADSCs proliferation.[16] Another study stated that Fibroblast Growth Factor 2 (FGF2) was secreted by ADSCs.[17]

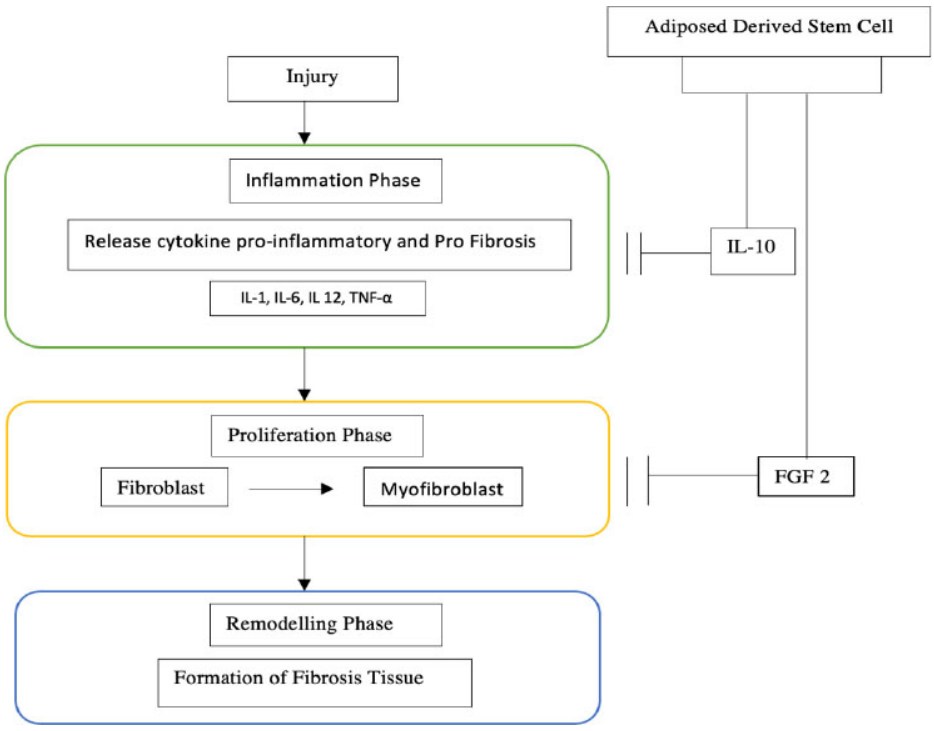

Figure 1. ADSCs can prevent the formation of fibrosis tissue by increasing Il-10 and FGF 2. IL-10 will suppress cytokine pro-inflammatory and FGF 2 will decrease the myofibroblast formation, leading to inhibited fibrosis tissue formation.

Effect of ADSCs on Myofibroblast in Wound Healing Process

MSC have the potential ability in decreasing fibrosis. MSC are multipotent cells that can be collected from some cells and have been proven to reduce fibrosis in the lungs, livers, kidneys, and hearts, as well as Peyronie's disease.[18] Adipose-derived stem cells in humans will show a positive result in CD13, CD29, CD44, CD73, CD90, CD105, and CD166, a negative result in CD14, CD31, and CD45.[18]

ADSCs can decrease the expression of α-Smooth Muscle Actin (α-SMA) and prevent fibrosis formation through the paracrine mechanism.[19] Moreover, ADSCs decrease the expression of ACTA2 in fibroblasts.[19] A study conducted on tunica albuginea myofibroblasts treated with ADSCs showed that ADSCs could prevent the formation of tunica albuginea myofibroblasts, decrease collagen production and suppress the myofibroblast concentration through Smads and RhoA/ROCK signalling.[18] ADSCs also reduce collagen deposition and increase the apoptosis of tunica albuginea myofibroblasts through MMPs and caspases. ADSCs from mice's fats will express CD29, CD44, CD73, and CD90, and the negative expression of CD45 and CD34. ADSCs will degrade collagen by increasing the expression of matrix metalloproteinase-9. ADSCs have an ability to synthesize the MMP-2, -3, -9, and -13 functioning for degrading collagen. ADSCs can increase MMPs in myofibroblast. ADSCs increase the expression of MMP2 and MMP9 and decrease the TIMP-1 expression. TGF-β can induce kidney fibrosis and atherosclerosis. Providing ADSCs can inhibit TGF-β through the TGF-β/Smad signalling pathway.[14,20] Figure 1 represents ADSCs' schematic situation in preventing the formation of fibrosis tissue by increasing Il-10 and FGF 2.

CONCLUSION

ADSCs are the cell-based therapeutic source that is strongly visible to be currently used. ADSCs can prevent the formation of fibrosis tissue in wound healing by increasing anti-inflammatory cytokines, namely IL-10 and FGF 2, as well as suppress proinflammatory cytokines, namely TNF- α, and myofibroblast. Using hypoxic culture with an oxygen level of 5% from ADSCs can increase the viability and proliferation of stem cells when being transplanted to the tissues.

CONFLICT OF INTERESTS

There was no conflict of interest. There were no financial supports or relationships between authors and any organization or professional.

ETHICAL STATEMENT

This material is the authors' original work, which has not been previously published elsewhere based on COPE guidelines. All sources used are correctly disclosed (correct citation).

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AUTHOR CONTRIBUTIONS

All authors contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the analysis-synthesis of literature study through publication.

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