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Literatur Review: Prospects of Stem Cell Secretomes for the Treatment of Hair Loss/Alopecia

Literature Review: Prospek Sekretom Sel Punca untuk Pengobatan Rambut Rontok/*Alopecia*

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Abstract
The goal of this literature review is to find out the role of MSC in stimulating hair growth, particularly in people who suffer from hair loss/alopecia. Literature reviews were conducted using an electronic database such as Researchgate, PubMed, GoogleScholar, and ScienceDirect. MSC secretome for hair growth, secretome for hair growth, ADSC-Exosome for hair growth, ADSC-CM for alopecia, secretome conditioned medium for baldness, and formulation of hair tonic preparations to stimulate hair growth were the keywords used. From these keywords, 13 relevant research articles were found, 11 of which used patients with alopecia as research subjects in randomized clinical trials to examine hair growth. MSC therapy for alopecia has been shown to stimulate hair growth, density, and thickness.
Keywords:
Secretome, ADSC-CM, Alopecia, Hair Growth

Abstrak
Tujuan dari tinjauan literatur ini adalah untuk mengetahui peran MSC dalam merangsang pertumbuhan rambut terutama pada orang yang mengalami rambut rontok/alopecia. Studi literatur dilakukan pada basis data publikasi ilmiah Researchgate, PubMed, GoogleScholar, dan ScienceDirect. Adapun kata kunci yang digunakan adalah MSC secretome for hair growth, secretome for hair growth, ADSC-Exosome for hair growth, ADSC-CM for alopecia, secretome conditioned medium for baldness, formulation of hair tonic for hair growth, dan formulasi sediaan hair tonic perangsang pertumbuhan rambut. Dari kata kunci tersebut, didapatkan 13 artikel penelitian yang sesuai dimana 11 diantaranya menggunakan pasien dengan alopecia sebagai subjek penelitian dalam uji klinis acak untuk melakukan analisis terhadap pertumbuhn rambut. Terapi MSC pada rambut rontok/alopecia terbukti dapat meningkatkan pertumbuhan rambut, meningkatkan kepadatan dan ketebalan rambut.
Kata Kunci
Sekretom, ADSC-CM, Alopecia, Pertumbuhan Rambut

INTRODUCTION

Alopecia, or baldness, is hair loss from any part of the head or body [1]. Some people experience psychological distress due to hair loss [2]. Currently, only two FDA-approved drugs are topical minoxidil and oral finasteride for alopecia. However, their effects could be more satisfactory and transient, as well as causing various side effects [3], [4]. Another

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option for hair loss therapy is hair transplant surgery, which is very costly [5].

Several growth factors derived from stem cells and mesenchymal stem cell secretions have been shown to promote hair growth. VEGF (vascular endothelial growth factor) has been shown to affect hair growth and follicle size [1]. Stem cells can be found in a variety of tissues throughout the body. MSC, bone marrow, and human embryo stem cells are the three types of stem cells used in therapy. Adult stem cells that are widely used in research and clinical therapy include adipose tissue mesenchymal stem cells (ATMSCs), which can differentiate into adipogenic, osteogenic, and chondrogenic cells [2]–[4]. ATMSCs can be obtained from various adipose tissues throughout the body. Because tissue is removed via subcutaneous lipoaspiration. Furthermore, when compared to embryonic stem cells derived from human embryos, ATMSCs pose no ethical concerns [4].

ATMSCs are obtained through a culture process in growth media containing substrates that support cell growth, such as essential nutrients (amino acids, carbohydrates, vitamins, minerals), growth factors, and hormones. Gases (O2, CO2) and environmental conditions (pH, osmotic pressure, temperature) can all have an impact on cell growth in the media [5].

The secretome comprises extracts or secretions from stem cells and MSCs (mesenchymal stem cell) that grow in culture media and resemble the MSC. The main benefit of the secretome is that it can be stored in the freezer and easily made into a preparation, making it easier to apply stem cells. Secretome MSC can accelerate tissue re-epithelialization and re-modeling and reduce cell apoptosis and inflammatory responses [6].

As a result, the information in this review article will focus on the effect of preparations containing MSC secretome on hair growth in people who suffer from hair loss/alopecia.

METHOD

The method used to create review articles are electronic databases from various international and national journal publications, such as Researchgate, PubMed, Google Scholar, and ScienceDirect, are used for research journal searches.

The keywords for this review were MSC. Secretome for hair growth, secretome for hair growth, ADSC-Exosome for hair growth, ADSC-CM (adipose-derived stem cell conditioned medium) for alopecia, secretome conditioned medium for baldness, formulation of hair tonic preparations to stimulate hair growth, then the search was carried out manually based on the relevant literature. Journals and articles published in the last ten years that contained information about testing the effects of hair growth from preparations containing adipose tissue mesenchymal stem cell secretomes in people with hair loss/alopecia were included. The review included thirteen journals that met the suitable criteria.

RESULT AND DISCUSSIONS

This literature review discovered 13 articles that met the inclusion criteria. Table 1 summarizes the research on the use of ADSC-CM or secretomes for alopecia or hair loss.

Table 1. Studies on various subjects, source of conditioned medium, and outcome.

Disease	Subject	Source secretome	Results	Reference
Transplanted hair	Human	ADSC Autologous	The continuous growth of the transplanted hair	[7]
Alopecia	Human	ADSC-CM	Hair numbers were significantly increased	[8]

Female Pattern Hair Loss	Human	ADSC-CM	Hair density and hair thickness increased	[9]
Alopecia	Human	ADSC secretom	ADSC secrete facilitates hair regrowth by improving the scalp with minimal rebound effect	[10]
Alopecia	Human	ADSVCs (Adipose-derived stromal vascular cells)	Increased hair growth, Hair diameter	[11]
Androgenetic Alopecia	Human	hUCB-MSC)	The hair density significantly increased	[12]
Hair Growth	Mice	ADSC-CM combined with ECM/SVF-gel)	Improved strategy for promoting hair growth	[13]
Androgenetic Alopecia	Human	ADSC-CE	Changes in hair count and thickness from the baseline	[14]
Alopecia Androgenic	Human	Human Umbilical Cord	Increased hair density, thickness, and growth rate	[15]
Alopecia	Human	ADSC-CM	Hair density and anagen hair rate increased significantly	[16]
Alopecia Areata	Human	ASC-CM	Increased hair regrowth	[17]
Hair Follicle	Nude Mice	ADSC Exosomes	ADSC-Exos could promote in vivo hair follicle regeneration	[18]
Immune-Mediated Alopecia	Invitro and In vivo (Mice)	ADSC Exosomes	Positively affected the promotion of hair regrowth	[19]

Source: [20][21][22] [23]

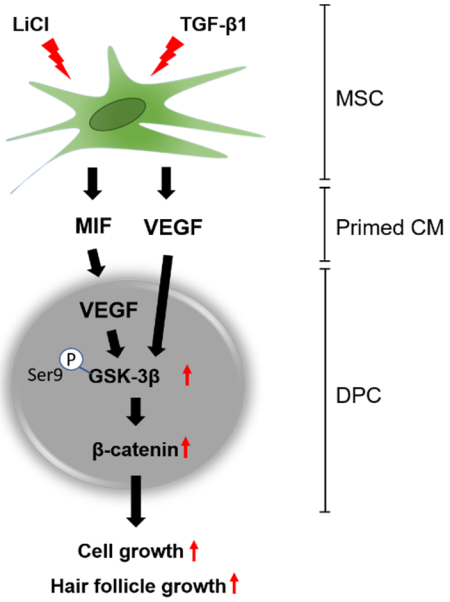

Figure 1. The role of stem cells in stimulating hair growth [15]

Growth factors (GFs) such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), platelet-derived growth factor, and insulin-like growth factor (IGF-1) are abundant in adipose-derived stem cell-conditioned medium. Through angiogenesis,

VEGF regulates follicle cyclic and hair. The HGF is involved in hair follicle cyclic growth. The anagen phase of hair follicle is induced and maintained by the platelet-derived growth factor. IGF-1 regulates hair growth and shaft differentiation. Each GFs appears to activate anagen phase and increase hair growth in patients with hair loss when treated with ADSC-CM. Because GFs affect cells in a dose-dependent manner, the dose dependence of the effects of ADSC-CM on alopecia should be investigated further in the future [24]. Several previous research findings support this.

Zanzottera et al. [11] used the Rigenera system and an autologous adipose tissue mesenchymal stem cell solution to perform hair transplantation. During the transplant, hair growth is evaluated once a month. The addition of mesenchymal stem cell solution resulted in significant hair growth two months after transplantation.

Fukuoka et al., [8] conducted a study on 22 patients with alopecia, 11 men and 11 women ranging in age from 20 to 73 years. ADSC-CM secretome is administered via intradermal injection into the patient's scalp for 3-5 weeks. The study's findings revealed increase hair loss in 10 male and 12 female alopecia patients compared to placebo, as measured by thrichograms.

Shin et al., [9] conducted a clinical trial of ADSC-CM in patients with Female Pattern Hair Loss. (FPHL). The study lasted 12 weeks and involved 27 patients. The data was then analyzed using photolithographic images. After 12 weeks of therapy, the application of ADSC-CM demonstrated efficacy in treating FPHL. The density of hairs per cm2 increased from 105.4 to 122.7 ($P<0.001$). The thickness of the hair increased from 57.5 μm to 64.0 μm ($P<0.001$). None of the patients experienced severe adverse effects.

Fukuoka et al., [10] continued a clinical trial of 21 alopecia patients 2017 with several new test parameters. A clinical trial was conducted for six months on 21 androgenetic alopecia (16 people) and female pattern hair loss (5 people). There was a significant increase in hairs three months after administration compared to before administration (141.3 ± 31.4 and 109.8 ± 43.5, respectively; $P<0.01$). Furthermore, there is an increase in the number of hairs visible to the patient during the anagen phase.

Furthermore, Anderi et al., [11] accomplished a clinical trial on 20 patients suffering from hair loss (alopecia), with nine women and 11 men participating. After receiving an autologous ADSVC injection of 4-4.7 x 10^6 cells, hair growth was monitored for six months. The test revealed a significant increase in hair growth and an increase in hair density from 85.1 ± 8.7 to 121.1 ± 12.5 hair/cm^2, $P < 0.0001$). Hair diameter also increased as well (60.5 ± 1.8 vs. $80.8\pm 2.4\mu$, $P < 0.0001$).

Then, Han et al., [12] investigated hair tonic preparations containing conditioned medium derived from hUCB-MSC. This study aims to assess the safety of using a hair tonic on 30 patients with Androgenetic Alopecia. They were investigated in this double-blind, placebo-controlled clinical study. Phototrichograms were used to evaluate after 4, 8, and 16 weeks of treatment to determine treatment efficacy. The hair density, thickness, and rate of hair growth in the hair tonic group increased significantly.

Xiao et al., [13] studied the effects of CM derived from ECM/SVF-gel (ECM/SVF-CM) and stem cells (SVF-CM) on hair growth in mice. ECM/SVF-CM stimulated hair growth more than SVF-CM by promoting dermal papilla and bulge cell proliferation, neovascularization, and anagen induction. Thus, ECM/SVF-CM may provide a more effective and improved strategy for promoting hair growth. These findings lay the theoretical groundwork for the clinical application of ECM/SVF-CM for hair loss treatment.

Simultaneously, Tak et al., [14] conducted a clinical trial on 38 patients, 29 of whom were males, who had androgenetic alopecia and were treated with ADSC-CE topical solution for

16 weeks. According to the results of the tests, the patient had an increase in the number of hairs at week 8, which was analyzed using a Phototrichogram. The hair diameter of the patients who received ADSC-CE topical solution increased by 14.2% at week 16 compared to 6.3% for the control group. This demonstrates that ADSC-SE has the potential to stimulate hair growth and thus increase hair density and thickness safely.

Oh et al., [19] performed a clinical trial on patients with androgenetic alopecia who were topically given a 5% secretome. This study lasted 16 weeks and included three hair measurements in patients at weeks 4, 8, and 16. The findings show that a 5% secretome derived from human umbilical cord mesenchymal stem cells can increase the amount of hair, hair density, hair length, and hair thickness in these patients. The hair growth rate increased from 0.262 to 0.312 mm/day without adverse effects on the patient.

The following study was published by Narita et al., [16], who conducted a clinical trial to see the effect of ADSC-CM on hair follicles and interfollicular scalp in 40 patients ranging in age from 23 to 74 years by administering ADSC-CM intradermal injections every month for six months. Trichograms, gical examinations, and ultrasonographic evaluations are performed in three stages. The findings revealed that hair density and anagen hair length both increased significantly.

Lee et al., [21] studied the clinical efficacy and safety of ASC-CM in combination with CO2. From March 2017 to August 2020, 14 patients with Alopecia Areata were treated with ASC-CM in combination with a 10,600 nm CO_2 fractional laser or micro-needling. The treatment was determined by the percentages of hair growth in the problematic areas. Of the 14 patients enrolled, 9 (64.3%) had > 50% hair regrowth, and 6 (42.9%) had complete recovery. The average time to achieve > 50% hair regrowth in the responder group.

Wu et al., [18] also used test animals in their research. ADSC was isolated from 6-week-old C57BL/6 mice for the study. The ADSC-Exosomes were then separated from the ADSCs. Exosome markers were identified using Western blotting. NanoSight dynamic light scattering was used to examine the particle size and distribution of the exosomes. Twelve naked mice were randomly assigned to one of two groups (n = 6 each): the ADSC-Exosome and the control group. The findings suggested that ADSC-Exosome could stimulate in vivo hair follicle regeneration.

Li et al., [19] conducted in vitro and in vivo studies on mice, finding that ADSC-Exosome significantly increased DPC proliferation and migration while decreasing apoptosis. Furthermore, compared to the control group, ADSC-Exosome-treated mice had more hair follicles (HFs) and a thicker dermis. RNA-seq analysis revealed that the miR-22 and TNF-signaling pathways were significantly downregulated in DPCs following ADSC-Exosome treatment. Furthermore, the Wnt/-catenin signaling pathway was activated in the skin of ADSC-Exosome-treated mice, according to qRT-PCR and western blotting results.

An adipose-derived stem cell-conditioned medium (ADSC-CM) rejuvenates the skin and promotes hair growth. Changes to the interfollicular scalp in the therapeutic application of ADSC-CM for alopecia are unknown, though some evidence suggests hair growth-promoting effects.

All of the studies found that ADSC-CM or treatments improved outcomes. However, there was considerable variation in the methods used to prepare ADSCs. There currently needs to be a universal protocol for fat grafting.

CONCLUSION

Alopecia treatment with ADSC-CM is highly successful and could open up new possibilities for hair regrowth therapy. More information about ADSC-CM treatment is needed in the

future, such as long-term effects and histological changes.

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