

# Mesenchymal Stem Cell Secretome for Dermatology Application: A Review

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**Abstract:** Secretome, also known as conditioned medium, is a secreted molecule from mesenchymal stem cells (MSCs) that has a variety of biological activities that can be used in various therapies, especially on the skin applications. A lack of conventional therapies makes secretome as a promising alternative therapy. The presence of growth factors, cytokines, and extracellular vesicles including microvesicles and exosomes in secretome has been widely reported, which serves in improving the proliferation and migration of cells to help in skin regeneration. Therefore, we were able to optimize the use of this secretome in a well-needed special review related to its work in addressing various skin problems. So, in this article, we discussed the benefits and biological activity of secretome on the skin application. This review was compiled based on the approval of several sites, such as Scopus, PubMed, Science Direct, and Google Scholar with the terms “MSC secretome for skin,” “secretome for skin,” “secretome dermatology,” “secretome conditioned medium for skin,” “secretome conditioned medium for skin wound,” “secretome conditioned medium for aging,” “secretome conditioned medium for hair growth,” and “secretome conditioned medium for psoriasis.” A total of 215 articles were collected for selection, of which 90 articles were used. Based on the results, it was concluded that secretome has a variety of useful activities to regenerate and repair tissue damage that have not been used on the skin, such as for wound healing, photoprotection, promotion of hair growth, psoriasis treatment, and other application as antimicrobial.

**Keywords:** MSC secretome, conditioned medium, biological activity, skin application

## Introduction

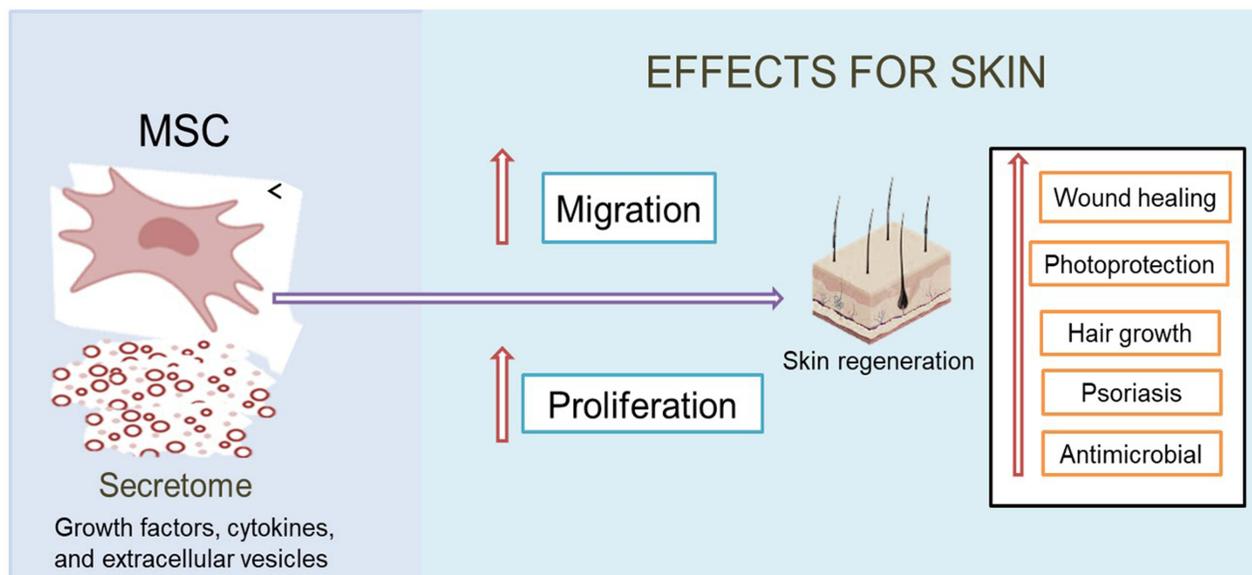
The skin is the largest organ of the body and serves as the first defense against various disorders and external stimuli causing susceptibility to infection and inflammation.<sup>1</sup> Various skin problems are often found, ranging from acute to chronic skin disorders that can impair the structure and function of the skin to triggering various reactions on the skin. In chronic skin conditions, such as infection, inflammation, ultraviolet (UV) exposure and others, general therapy is not able to restore the function and structure of injured skin tissue under normal circumstances. Thus, triggering the development of more effective therapies.<sup>2</sup>

The development of stem cell-based therapies continues to today, especially in skin disease therapy. Stem cells, in particular mesenchymal stem cells (MSCs), can secrete trophic factors responsible for regenerating tissue and repairing tissue damage.<sup>3–5</sup> However, this therapy using MSCs shows low cell survival and engraftment rates after the transplant process, cell retention, and, in case of mutations from stem cells, can lead to cancer.<sup>1,2,6,7</sup> The main mechanism of action of MSCs is

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## Graphical Abstract



associated with the paracrine effect of important factors secreted by secretome. Because of awareness related to the work of MSCs based on the secretion of its secretome, it can be used as an alternative to overcome problems related to the use of living cells.<sup>8</sup>

Secretome is a bioactive molecule secreted by MSCs in conditioned media. It contains a large number of growth factors, cytokines, and various macromolecules and extracellular vesicles including microvesicles and exosomes that can stimulate various biological reactions, especially in modulation of various new tissue formations.<sup>8-12</sup> These factors play an important role in communication between cells and are involved in a variety of physiological processes, including signal transduction to provide a biological response.<sup>13</sup> Therapy using secretome can answer challenges related to the problem of living cell use. The secretome's ability to regenerate and repair damaged tissues makes it one of the alternatives related to the handling of various skin problems that have been widely reported in various studies. So, in this article, we will review the use of secretome for skin application is described in Table 1.

## Methodology

This article is based on the results of the expansion of several sites, such as Scopus, PubMed, Science Direct, and

Google Scholar with the keywords "MSC secretome for skin," "secretome for skin," "secretome dermatology," "secretome conditioned medium for skin," "secretome conditioned medium for skin wound," "secretome conditioned medium for aging," "secretome conditioned medium for hair growth," and "secretome conditioned medium for psoriasis." A flowchart of the article collection described in Figure 1.

## Secretome Isolation and Secretome Culture

Isolation is the first step in obtaining a secretome. Secretome of MSCs can be isolated from various adult tissues, including the spinal cord,<sup>38</sup> adipose tissue,<sup>39</sup> skin tissue,<sup>16</sup> peripheral blood,<sup>21</sup> and neonatal tissue, such as Wharton jelly,<sup>40</sup> umbilical cord,<sup>17</sup> amniotic membrane,<sup>41</sup> and placenta.<sup>42</sup> The isolation process is done to obtain the network that is being used. After the isolation process, cell culture is carried out. Based on Park et al, cell cultures were carried out by incubating isolated cells for 5 hours at a temperature of 37°C in the growth medium using Dulbecco's Modified Eagle Medium (DMEM), which contains 10% fetal bovine serum (FBS), to provide cell nutrition needs and 250 U/mL collagenase type 1. It was then filtered with 40 µm strainer cells and then planted in a growth medium

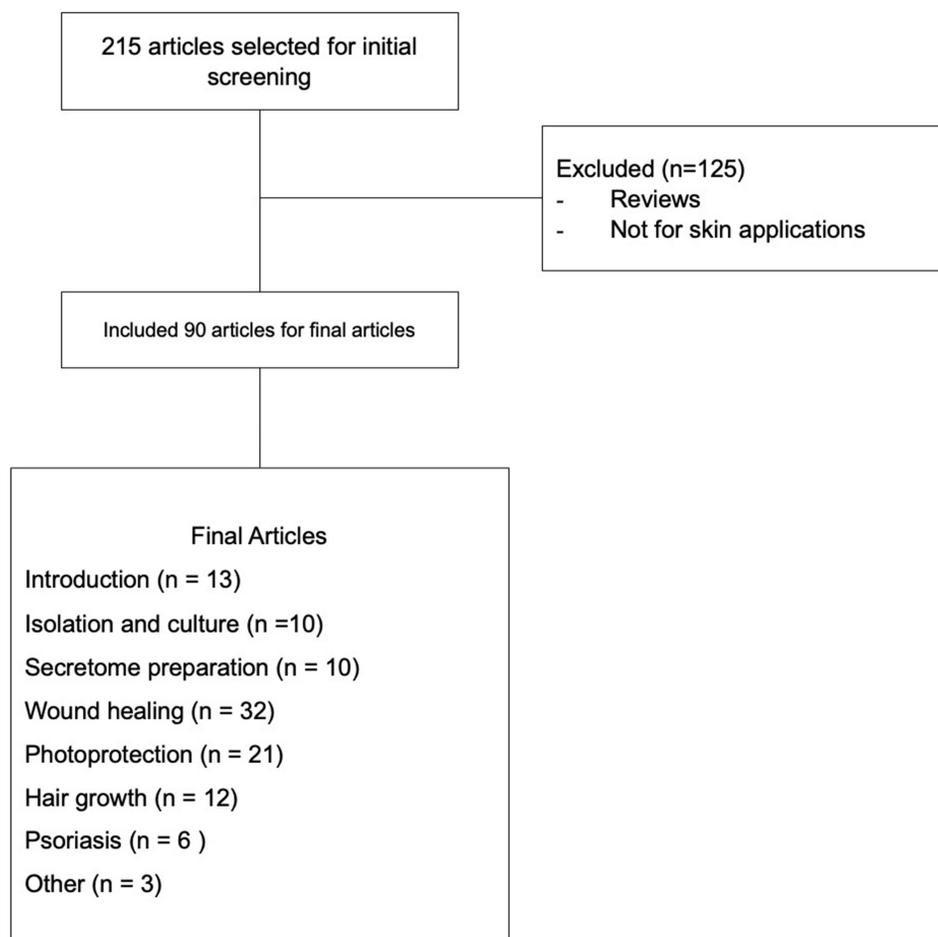
**Table I** Secretome Test Objects for Skin Application

No.	Biology Activity	Test Object	Testing	Ref
1.	Cutaneous wound	Human foreskin fibroblasts (HFFs)	In vitro	[14]
		Human immortalised keratinocytes (HaCaTs)	In vitro	[4,5]
		Human dermal microvascular endothelial cells (HDMECs)	In vitro	[14]
		Human dermal fibroblasts (HDFs)	In vitro	[8,15]
		Human endothelial cell	In vitro	[8]
		Human umbilical vein endothelial cells (HUVECs)	In vitro	[16]
		L929 Fibroblast	In vitro	[5]
		Wistar rats	In vivo	[17,18]
		C57BL/6J mice	In vivo	[19]
		Lepr <sup>db/db</sup> mice	In vivo	[20]
		Porcine models/ pigs	In vivo	[21]
		Rabbit ear	In vivo	[22]
		Female SCID Mice 8–9 weeks	In vivo	[4]
		Male volunteers	Clinic Phase I	[23]
2.	Photoprotection	Human dermal fibroblasts (HDFs)	In vitro	[24,25]
		Normal human dermal fibroblast (NHDF)	In vitro	[26]
		Human dermal fibroblast (HFF-1)	In vitro	[27]
		Human immortalized keratinocytes (HaCaTs)	In vitro	[28]
		NIH-3T3 cell	In vitro	[29]
		Nude mice	In vivo	[24,28]
		Human Skin	Clinical test	[30]
3.	Hair Growth	Human follicle dermal papilla cells (HFDPs)	In vitro	[31–33]
		Human epithelial keratinocytes (HEKs)	In vitro	[31]
		Outer root sheath cells (ORC)	In vitro	[34]
		C3H/NeH mice	In vivo	[31,34]
		C57BL/6 mice	In vivo	[33,35]
		Nude mice	In vivo	[32]
4.	Psoriasis	Wistar rats	In vivo	[36]
5.	Other (antimicrobial)	Rats	In vivo	[37]

(ie, basal growth of medium EBM-2 endothelial cells and equipped with EGM-2 supplements at 37°C and 5% CO<sub>2</sub>).<sup>2,38,43</sup>

### Preparation of Secretome

Secretome preparation was performed when the cell reached 80–90% confluence, and it was then washed



**Figure 1** Flowchart of the article collection.

with PBS two times and incubated in DMEM (without FBS and antibiotics). Conditioned medium, or secretome, was collected after being incubated for 48 hours and centrifuged at 1500 rpm for 3 minutes two times, then filtered with a syringe filter 0.45  $\mu\text{m}$  to remove debris and dead cells. The obtained conditioned medium was stored at  $-80^{\circ}\text{C}$  before use in testing.<sup>2,44</sup>

In some circumstances, due to the concentration of bioactive factors is low in the culture medium to produce a therapeutic effect, there are several methods were used to increase the secretion of these factors, namely culture in hypoxic conditions<sup>44,45</sup> and planting in a two- (2D) or three-dimensional (3D) matrix.<sup>17</sup> Culturing MSCs in hypoxic in vitro conditions can increase the proliferation and migration effects of keratinocytes and dermal fibroblasts, which are related to the upregulation of angiogenesis factors, such as VEGF and bFGF, and increased collagen production compared to normoxia.<sup>45-47</sup> Sun et al stated that protein levels in hypoxic cultures were 15 times greater than those in normal cultures.<sup>48</sup>

In 3D cultures, there was an increase in re-epithelialization related to success in wound closure as compared to normal cultures.<sup>49</sup>

To identify the various proteins contained in the secretome, analysis techniques were required. Analysis techniques were performed to identify various proteins contained in the secretome. Conventional ELISA methods and the multiplex method were generally used.<sup>27</sup> These methods can identify a number of proteins contained in the secretome, such as growth factors and cytokines.<sup>50,51</sup> Research by Amirthalingam et al revealed that there are 28 protein analytes in the secretome of BM. The presence of growth factors, such as VEGF and TGF- $\beta$ , in the secretome plays an important role in skin health.<sup>27</sup>

## The Role of Secretome on the Skin Application

Secretome is known to have a variety of benefits in the treatment of various diseases. The main factor that plays

a role is the secreted protein, which can help repair and regenerate damaged tissue. Secretome of MSCs plays an important role as a therapeutic agent in dealing with various skin problems. A list of potential effect of secretome in skin application can be seen in Table 2.

## Wound Healing

Wound healing is a natural process of the body that repairs and regenerates damaged tissues and consists of three main phases—*inflammation, proliferation, and remodeling* that occur in overlap. Wound healing is still a challenge in clinical management therapy problems, especially in chronic conditions.<sup>2</sup> The use of secretome as an alternative therapy in dealing with skin injuries has been widely reported, including accelerating wound closure.<sup>42</sup> Various studies to assess the benefits of secretome to wound healing have been done, both *in vitro* and *in vivo*. *In vitro* testing is generally done by looking at the migration and proliferation capabilities of cells. Use based on cell models has been tested using components of different types of skin cells, such as human immortalized keratinocytes (HaCaTs),<sup>14</sup> human dermal fibroblasts (HDFs),<sup>15</sup> human foreskin fibroblasts (HFFs),<sup>66</sup> human dermal microvascular endothelial cells (HDMECs),<sup>14</sup> and human umbilical vein endothelial cells (HUVECs).<sup>16</sup> Cell migration capability can be determined using the assay migration method and/or starch assay.<sup>2</sup> This test was conducted by comparing the speed of wound closure between control and treatment groups. To confirm the effects of cell migration, it can also be done by identifying the expression levels of MMP2 and MMP9, both of which are involved in the migration processes of cells.<sup>2</sup> The proliferation ability of cells can be curated using the assay proliferation method, WST-1 assay and MTT assay.<sup>2,14,15</sup> This test aims to see if there is an increase in viability of the cells after secretome administration. Another supporting method can also be done by looking at the ability of angiogenesis using the angiogenesis assay.<sup>16</sup>

Secretome from a variety of different sources (such as bone marrow, adipose tissue, neonatal tissue, skin tissue and peripheral blood) have been shown to improve the migration ability of various dermal cells, such as fibroblasts, endothelial cells and keratinocytes, and the epidermis was able to stimulate the proliferation of these cells *in vitro*.<sup>19,67</sup> Research by Miranda et al also stated that secretome from umbilical cord tissue-derived (UCX<sup>®</sup>) was able to increase HDF and HaCaT cell migration based on

scratch test results.<sup>4</sup> Sera et al also noted that there was an increase in expression of ki67 markers involved in cell proliferation by treatment using secretome with MTT assay method.<sup>2</sup> The use of secretome was also able to modulate tube formation based on *in vitro* angiogenesis tests along with the migration and proliferation HUVECs.<sup>16,68–70</sup> The speed of healing of wounds could be attributed to the trophic effects of MSCs, which affect dermal fibroblasts and keratinocytes.<sup>5</sup> Interestingly, Topouzi et al used secretome from the dermal papilla fibroblast follicles for wound healing therapy and showed that the wound healing increased by 1.8 times faster than control.<sup>57</sup>

*In vivo* experimental animal models can be used in the form of mice,<sup>53</sup> rats,<sup>55</sup> and pigs.<sup>21</sup> This method has been tested on animal models with various conditions, such as chronic wounds,<sup>58</sup> burns,<sup>38</sup> diabetic foot ulcers,<sup>71</sup> skin ulcers,<sup>53</sup> and radiation wounds,<sup>72</sup> which require special handlers. The results showed that wound treatment with secretome was able to accelerate wound healing by increasing the effect of cell migration and proliferation and triggering angiogenesis, re-epithelialization, neovascularization and deposition of collagen that play a role in the wound healing process.<sup>53,73–75</sup> According to Bari et al, secretome components in ADSC such as decorin (Dcn) and tenascin (Tnc) play an important role in epidermal growth factor receptor (EGFR) regulation.<sup>53</sup>

Various studies have been conducted to support data related to the benefits of secretome *in vivo*. Hackers et al studied the effects of secretome from peripheral blood mononuclear cells (SecPBMCs) and PBMC apoptosis (Apo-SecPBMC) on models of pigs with burns, showing an increase in the number of CD31+, which is especially greater in treatment with Apo-SecPBMCs, as well as a decrease in the number of mast cells in the wound area.<sup>21</sup> Using the same secretome source, Mildner et al found that there was a significant increase in the number of CD31+ cells that play a role in the angiogenesis process in the SecPBMCs group.<sup>19</sup> Similarly, Wagner et al revealed that the use of secretome from PBMCs is a promising therapy in improving wound healing that has been tested on *Lepr<sup>db/db</sup>* mice.<sup>20</sup> Secretome of adipose stromal stem cell (ASCs) in hypoxia showed a greater reduction in wound area compared to that in normoxia.<sup>47</sup>

The use of SecPBMCs has been further thoroughly related to toxicity testing using animal models of mice (assessing systemic toxicity) and mini pigs (local toxicity studies). The results showed that the minimum dose and

**Table 2** Potential Effect of Secretome in Skin Applications

No.	Application	Source and Kind of Secretome	Signaling and Bioactive Molecules Involved	Effects	Ref
1.	Cutaneous wound	ADSC-CM	EGF, bFGF, HGF	Increased proliferation and cell migration, angiogenesis and vascularization	[2]
			VEGF, IL-6, EGF, uPAR, MCP-3, G-CSF, and Tie-2,	Promoted angiogenesis (CD31), epithelialization, and decreased wound area	[52]
			Tnc, Dcn and EGFR.	Accelerated re-epithelialization and deposition of collagen	[53]
		MAPC-CM	HGF, VEGF	Increased keratinocytes, fibroblasts, and endothelial cells as well as cell proliferation	[14]
		WJSC-CM	EGF	Enhanced proliferation and cell migration as well angiogenesis	[54]
		BMSC-CM	VEGF and angiotensin-II	Stimulated cell proliferation, and decreased level of granulation tissue and fibrous	[39,54]
			EGF, bFGF,	Increased proliferation and cell migration as well as fibroblast in diabetic wounds	[15]
		PBMCs-CM	CD31+, $\alpha$ -SMA+	Increased the thickness of epidermis, angiogenesis, and reduced the level of mast cells	[17,19-21]
		UCSC-CM/UCX®	HGF, IL-6, FGF-2, TGF- $\beta$ 1, G-CSF, VEGF-A	Improved angiogenesis, elastin formation capillary maturation and vascularity level,	[17,55]
		DPSC-CM	Angiogenin, EGF, bFGF, IL-6, IL 8, PDGF-AA, VEGF, HGF, GM-CSF	Increased migration and proliferation and angiogenesis cell	[56]
DPFi-CM	sAXL and CCL19	Enhanced re-epithelialization and wound closure	[57]		
Fetal dermal cells-CM	VEGF, IL-8, HGF, CXCL-12, CCL-2, CXCL1	Improved angiogenesis, re-epithelialization and neovascularization	[16]		
2.	Photoprotection	BMSC-CM	VEGF, TGF $\beta$	Stimulated procollagen synthesis, suppressed the production of MMP1 and CPD formation	[24]
		ADSC-CM	TGF $\beta$ -1 PDGF-AA	Increased procollagen synthesis, inhibited MMP1 and MMP9 production, sub G1 phase and cellular apoptosis as well as enhanced skin hydration effect and, improved mRNA expression	[25,28,58-60]
		UCSC-Exo	$\downarrow$ NRF2 signaling	Suppressed ROS accumulation and DNA damage	[61]
		EPC-CM	IL-6, Angiotensin-II, TIMP-1 and TIMP-2	Stimulated proliferation and collagen production and inhibited ROS formation	[26]

3.	Hair Growth/ Alopecia	ADSC-CM	Increase level of IGFBP-1, IGFBP-2, M-CSF, M-CSF R, PDGF R- $\beta$ , and VEGF	Enhanced proliferation of HFDPCs and HEKs cell	[31]
		KCs-CM	VEGF, BMP2, TGF- $\beta$ 1, IL-6, IGFBP-2 and 5, PDGF-AA	Improved proliferation of dermal papilla (DP) cell	[32,34]
		AF-MSC-CM	IGF, PDGF, bFGF, and Wnt7a	Accelerated telogen to anagen transition in hair follicles (HF) and increased HF density	[33]
		BMSC-EV	AKT phosphorylation, Bcl2, VEGF and IGF-1	Accelerated the conversion of telogen to anagen	[62]
		DPC-CM	SDF1, MMP3 and biglycan, LTBPI	Induced regeneration of hair follicle	[63]
4.	Psoriasis	Skin mice	IL1B, IL10, F4/80, CD11C	Inhibited dendritic cells (DC) and IL-17	[64]
		ADSC-CM	LL-37	Inhibited the growth of <i>S. aureus</i>	[65]
5.	Antimicrobial activity	ADSC-CM	LL-37	Inhibited the growth of <i>S. aureus</i>	[65]

the maximum dose considered for the treatment of diabetic foot ulcers (DFUs) were 0.42 U/kg and 3.3 U/kg, respectively.<sup>76</sup>

The results showed that the administration of secretome was able to accelerate the wound healing process compared to control. Secretome with a dose of 30  $\mu$ g/mL of bone marrow (BMSC-CM) resulted in a maximum wound closure of 90% on the fifth day after treatment.<sup>2</sup> While the secretome of the multipotent adult progenitor cell (MAPC-CM) used a dose of 100  $\mu$ L of 20 $\times$  the concentration of conditioned medium to test wound healing in trial animals receiving intradermal injections.<sup>14</sup> In clinical testing, phase 1 included secretome from PBMCs (Apo-SecPBMCs) for chronic wound treatment. This study was conducted to assess the safety of dosages used for topical applications, supernatant of 12.5 $\times$ 10<sup>6</sup> low dose PBMCs and equivalents of 25 $\times$ 10<sup>6</sup> PBMCs resuspended in NuGel Hydrogel high doses. Their results showed the use of Apo-SecPBMCs with low and high doses is safe and well-tolerated by the skin and has an effect on the reduction of the wound area.<sup>23</sup>

## Photoprotection

Ultraviolet (UV) radiation can cause some skin problems, especially photoaging. Photoaging is skin aging caused by excessive UV exposure, which causes morphological and physiological changes of the skin such as the appearance of wrinkles and reduced skin elasticity.<sup>27</sup> Research into the secretome as a therapy to prevent the influence of photoaging has been reported. Several in vitro models of skin cells, HDFs and HaCaTs, both of which are cells that function against defenses due to UVB radiation, were used.<sup>28</sup> UV radiation can cause inhibition of the cell proliferation rate and reductions of collagen I, collagen III and elastin due to downregulation of expression of mRNA.<sup>58</sup> UV radiation can also cause increased levels of MMP1 and MMP9, resulting in inhibited synthesis of procollagens and triggering activation of various signaling pathways, namely mitogen activated protein kinase (MAPK), protein activator 1 (AP-1) and nuclear factor kappa B (NF- $\kappa$ B), which contributes to cell damage due to ROS formation and can trigger the apoptosis of skin cells, so as to inhibit skin regeneration and be able to inflict DNA damage in keratinocytes.<sup>24,25,28,29,77</sup>

Various studies have been conducted to investigate the effects of secretome as an agent in the fight against photoaging. In vitro testing was done by various methods. Methods that were used looked at cell proliferation

activity, cellular aging and cellular apoptosis, intracellular ROS levels, and pyrimidine cyclobutane dimer assay (CPD).<sup>26,27,29,58,78</sup> Wang et al reported that there was an increase in cell proliferation from adipose-derived stem cells (ADSC-CM) use, as well as a decrease in the number of cells undergoing apoptosis and a decrease in cellular aging in HDFs.<sup>58</sup> Kim et al also found ADSC-CM can decrease the number of cell deaths from apoptosis (characterized by a decrease in the sub-G1 phase) and increase collagen I synthesis, as well as inhibit the production of MMP1 in HDFs.<sup>60</sup> Using the same method of sub-G1 assay, Dewi et al also reported a reduction in the percentage of apoptosis after treatment with the human umbilical cord blood mesenchymal stem cell (hUCB-MSC-CM) conformation 5%, 10% and 20% from 94.2% to 46.8%, 31.8% and 31.5%, respectively.<sup>29</sup> The use of secretome was able to reduce intracellular ROS levels using the DCFDA fluorescent assay,<sup>26</sup> as well as able to increase cell migration and reduce the level of formation of CPD in vitro.<sup>27</sup>

The secretome of ADSCs had the effect of providing photoprotection. This is related to the content of biological factors that play a role in particular platelet-derived growth factor AA (PDGF-AA), which can promote deposition and remodeling of the extracellular matrix.<sup>25</sup> This effect is also associated with the content of TGF- $\beta$ 1 in the secretome, which can stimulate mRNA expression and increase collagen production.<sup>59</sup> This mechanism is also related to the upregulated expression of wnt3a and catenin in the Wnt/ $\beta$ -catenin signaling pathway, which is associated with increased expression of TGF- $\beta$ 2 (which is important for the synthesis of procollagen type I).<sup>79</sup>

Other tests performed on the test animals, which were generally nude mice, pertained to UVB exposure. The results revealed a reduction in wrinkles and skin distress by improving skin hydration after macroscopic use of secretome and increased collagen synthesis based on Masson trichrome analysis.<sup>24,27,28</sup>

In some studies, it has been reported that secretome can be used as an active ingredient in cosmetics, reminding us of its benefits in regenerating the skin. Generally, research utilizes secretome as a skin care therapy to prevent various aging factors, including photoaging. Amirthalingam et al formulated secretome as an antiaging cosmetic product in the form of semi-solid serum preparations, with the following doses used 0.25%, 0.5% and 1%.<sup>27</sup> Similar research by Kim et al utilized secretome as raw material in the manufacture of cosmetics applied

using an air brush, with secretome concentration as high as 5%. The results showed a reduction in test parameters, such as wrinkles, and increased skin moisture.<sup>80</sup> Similarly, Kim et al also used secretome as a raw material cosmetic material in the form of cream preparations. The secretome concentration used was 1%, which was cultured in 3D culture. The use of secretome can increase collagen synthesis greater than control and reduced aging by improving skin elasticity.<sup>30</sup>

## Hair Growth

Alopecia is a term used to state the condition of baldness or hair loss due to abnormalities in the scalp that can be caused by various factors.<sup>33</sup> This condition causes the active phase of hair growth (anagen stage) to be inhibited, while the rest phase (telogen stage) becomes faster in the hair growth cycle.<sup>35,81</sup> So, a lot of research focuses on understanding the cycle of hair growth. The effect of secretome therapy on hair growth has been reported in various studies. In vitro testing is generally conducted to determine the proliferation ability of hair cells. Used human papilla cells of human follicles (HFDPCs), outer root sheath cells (ORCs) and human epithelial keratinocytes (HEKs),<sup>31,34,82</sup> which are types of cells located in hair follicles that can stimulate hair growth and regeneration through reciprocal communication processes with epithelial cells.<sup>31-33</sup>

Zhang et al investigated the paracrine factors that may be involved in hair follicle regeneration using secretome from dermal papilla cells (DPCs). The results showed that the use of the secretome of DPCs in passage 3 secreted a large amount of CXCL12, MMP3 and biglycan, which played a role in the activation of the Wnt/ $\beta$ -catenin signaling line, as well as LTBP1.<sup>63</sup> Activation of this pathway is known to trigger the proliferation of hair follicle cells.<sup>83,84</sup> The use of secretome is able to trigger the proliferation of HFDPCs and ORCs, to accelerate the telogen phase to anagen and ex vivo can induce proliferation of the hair matrix. In the application using animal models in the form of mice C3H/HeN, secretome was able to induce hair follicle growth.<sup>34</sup> Pu et al also reported that secretome was able to trigger proliferation and increase hair follicle growth in mice ischemia/reperfusion- (I/R-) models.<sup>85</sup>

## Psoriasis

Psoriasis is a chronic inflammatory condition of the skin that causes increased levels of expression of interleukin

(IL-17). In psoriasis, Langerhans cells represent a disorder in the migration of epidermis cells that serve as an immune response associated with T cell responses, particularly Th17-mediated.<sup>86</sup> This condition also causes abnormalities in cytokine production that can cause epidermis hyperplasia as well as abnormal keratinocyte apoptosis (KCs).<sup>87</sup> Psoriasis is characterized by the appearance of patches or rashes with thick white scales on the skin and nails.<sup>88</sup>

Studies on secretome in the treatment of psoriasis have been conducted. Psoriasis modeling can be used using imiquimod with Wistar rats models. Imiquimod causes inflammation characterized by the presence of coarse lamella and excoriation. The use of secretome is able to reduce the effects of inflammation caused by the use of imiquimod (IMQ) better than control.<sup>36</sup> Zhang et al stated that exosomes (secretome) is able to decrease psoriasis score in IMQ rats model through inhibiting of maturation and activation of dendritic cells (DC) and IL-17 in HaCaTs.<sup>89</sup> Seetharaman et al reported that the secretome of adipose tissue, which is administered topically, showed a significant decrease in the amount of erythematous plaque and silver scales on the scalp of the sufferer after administration of the secretome for 2 weeks and disappeared after one month of administration.<sup>88</sup>

## Other Application

Secretome is reported to have antimicrobial activity. Antimicrobial is a compound that can inhibit or suppress the growth of microbes. Various drugs that are resistant to microbes continue to increase. The use of secretome can be one of the alternatives to prevent drug resistance. In some studies, secretome is known to release antimicrobial peptides such as cathelicidin LL-37, calprotectin, hepcidin, RNase3, lipocalin-2 and human  $\beta$ -defensins.<sup>37</sup> Yagi et al reported secretome of adipose tissue is able to suppress the growth of *S. aureus* through increased activity of cathelicidin.<sup>65</sup> Harman et al investigated the antibacterial effects of secretome on bacteria found in skin wounds, tested using *S. aureus* and *E. coli*. The results showed that the use of secretome can inhibit the growth of gram-positive bacteria *S. aureus* and gram negative *E. coli* from the production of secreted factors that can affect bacterial membranes.<sup>90</sup>

## Conclusion

Secretome, a bioactive factor secreted by MSCs, has a variety of benefits on the skin as a therapeutic agent for various regenerative diseases. Research on the use of secretome for skin applications and formulation

development are still very limited. Several studies reported that the process to obtain secretome from MSCs was through isolation from various adult tissues and cultured in a medium of growth. The culture process can affect the level of expression of the resulting factors. Applications of the secretome for skin include wound healing, photoprotection, promotion of hair growth, psoriasis treatment, and other application as antimicrobial. Considering the various constituents of secretome, it has a lot of potential in various diseases needing the development of and more in-depth studies in order to be maximally used.

## Abbreviations

$\alpha$ SMA, smooth muscle cell-specific alpha actin; ADSC, adipose-derived stem cell; AF-MSC, amniotic fluid-derived mesenchymal stem cell; Bcl-2; B-cell lymphoma 2; bFGF, basic fibroblast growth factor; BMSC, bone marrow stem cell; CD, cluster of differentiation; CM, Conditioned medium; Dcn, decorin; DPFi, dermal papilla fibroblasts; DPSC, dental pulp stem cell; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EPC, endothelial progenitor cells; EV, extracellular vesicle; Exo, Exosome; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IL, Interleukin; KCs, interfollicular keratinocytes; LTBP1, latent TGFbeta binding protein 1; MAPC, multipotent adult progenitor cell; M-CSF, Macrophage-colony stimulating factor; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; PBS, phosphate buffered saline; PBMC, peripheral blood mononuclear cells; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SDF1, stromal cell-derived factor 1; TGF- $\beta$ , transforming growth factor- $\beta$ ; TIMP-1, tissue inhibitor metalloproteinase 1; Tnc, tenascin; UV, ultraviolet; UCSC, umbilical cord stem cells; VEGF, vascular endothelial growth factor; WJSC, wharton's jelly stem cells.

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## Disclosure

The authors report no conflicts of interest in this work.

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