Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Adipose-Derived Stem Cell Products and Combination Therapies for the Treatment of Pathological Scars: A Review of Current Preclinical and Clinical Studies

Nayla Majeda Alfarafisa[1,2,*], Yoan Chou[3,*], Resti Santika[2,4], Betha Egih Riestiano[2,5], Hardisiswo Soedjana[5], Mas Rizky AA Syamsunarno[1,2]

[1]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jatinangor, West Java, Indonesia; [2]Metabolic in Medicine Working Group Study, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia; [3]Graduate School of Master Program in Anti Aging and Aesthetic Medicine, Faculty of Medicine, Universitas Padjadjaran, Jatinangor, West Java, Indonesia; [4]Faculty of Medicine, Universitas Padjadjaran, Jatinangor, West Java, Indonesia; [5]Division of Plastic Reconstructive and Aesthetic Surgery, Department of Surgery, Faculty of Medicine Universitas Padjadjaran - Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

*These authors contributed equally to this work

Correspondence: Nayla Majeda Alfarafisa, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jalan Raya Bandung – Sumedang Km 21, Jatinangor, West Java, 45363, Indonesia, Tel +62-22-7795594, Email nayla.alfarafisa@unpad.ac.id

Introduction: Pathological scars, including hypertrophic, keloid, and atrophic scars, remain challenging to treat, with current therapies offering limited success. Adipose-derived stem cell (ADSC) products, classified into cell-based therapies (stromal vascular fraction [SVF], ADSCs) and cell-free therapies (adipose tissue extract [ATE], secretomes, exosomes, extracellular vesicles), have emerged as potential treatments.

Purpose: This review examines the therapeutic potential of ADSC products for pathological scars in preclinical and clinical trials, aiming to bridge the gap between experimental research and clinical application. The effectiveness of ADSC products as monotherapies and in combination with other treatments has also been explored.

Methods: A comprehensive literature search followed the PICO framework, utilizing electronic databases such as PubMed and Scopus. Original research articles, including both preclinical and clinical trials, were included.

Results: This review included 43 studies that demonstrated the potential of ADSC products to improve pathological scars. ADSC products improve scar texture by regulating ECM, promoting adipogenesis and angiogenesis, and reducing inflammation in hypertrophic and keloid scars. In addition, ADSC products also prevented collagen degradation in atrophic scars. Although their effectiveness varied, ADSC products also showed potential when combined with treatments such as fractional CO_2 laser, PRP, botulinum toxin, and photo-modulation.

Conclusion: ADSC products show promise in treating pathological scars, with varying effectiveness in monotherapy or combination therapy.

Keywords: adipose-derived stem cells, atrophic scars, fibroblast, hypertrophic scars, keloid scars

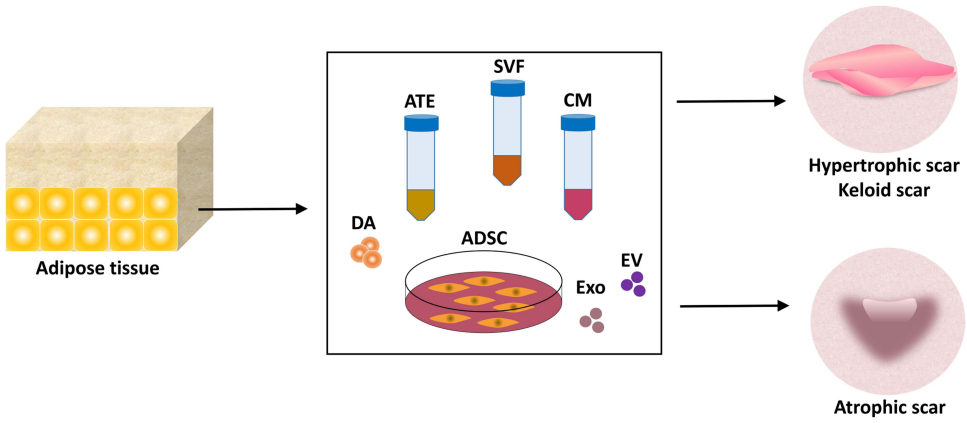
Introduction

Pathological Scar

Scar formation restores tissue integrity after injury and is influenced by factors such as age, gender, wound location, and tension.[1–3] It is a complex process that is strictly controlled by biological mechanisms that require the cooperation of numerous cell types, growth factors, cytokines, and extracellular matrix (ECM).[1] Scars can be classified as normal or pathological. Normal scars undergo a structured healing process, while pathological scars—such as hypertrophic, keloid,

Received: 8 December 2024
Accepted: 20 March 2025
Published: 27 May 2025

Graphical Abstract



and atrophic scars—result from dysregulated wound healing. A normal scar consists of loose, fibrous connective tissue that progressively strengthens and becomes more rigid throughout the healing process. This process involves four key stages: hematoma formation, inflammation, proliferation, and remodeling.[4] On the other hand, abnormal scars can be classified into hypertrophic scars (HS), keloid scars (KS), and atrophic scars (AS).[3,5,6] Pathological scars result from imbalances in ECM remodeling, inflammatory response, and fibroblast regulation, leading to excessive or insufficient collagen deposition.[3,7]

Fibroproliferative scars include hypertrophic and keloid scars.[6] Hypertrophic scars form within wound margins, expanding for 4–8 weeks before stabilizing. Excessive ECM deposition by fibroblasts prolongs inflammation and fibrosis, leading to red, stiff, elevated, itchy, and painful scars.[4,8–10] In contrast, keloid scars may develop months to years after injury, expanding beyond wound margins due to excessive ECM deposition. Collagen production in keloids is up to 20 times higher than in normal skin with fibronectin (FN) biosynthesis and is four times greater than normal scars.[11] Unlike hypertrophic scars, keloids are influenced by genetic factors and have high recurrence rates, often causing skin contraction and functional impairment.[6,8] Clinically, keloids present as raised, hard-textured lumps or bands on the skin's surface.[12] In fibro-proliferative scars, another contributing mechanism is the involvement of myofibroblasts, which express alpha-smooth muscle actin (α-SMA). These cells play a critical role in excessive collagen accumulation, resulting in an ECM imbalance.[4,7]

Occasionally, a scar may become depressed or thinned as it matures into an atrophic scar. This occurs when collagen synthesis diminishes and inflammation falls below normal.[6] Another source reports that prolonged inflammation significantly reduces both elastic and collagen fibers, and the decrease in epidermal proliferation is closely linked to the development of atrophic scars.[13] Atrophic scars are among the most challenging and persistent conditions to treat.[6] These factors make atrophic scars a particularly difficult target for effective therapeutic intervention.

Pathological scars can lead to irritation, restricted mobility, functional and aesthetic alterations, and significant psychological distress.[3,6] Consequently, the search for the most effective therapy for these scars continues. Researchers have established various experimental models to advance therapeutic development, including in-vitro, ex-vivo, and in-vivo systems using both animal and human skin.[14,15] The most commonly utilized in-vitro models are human fibroblast cell (HFC) and keloid fibroblast cell (KFC) cultures, which are derived from human tissue biopsies.[15,16] Additional in vitro methods involve inducing myofibroblast differentiation with TGF-β1 and developing tissue-engineered human hypertrophic scar models.[7,10,17] Ex-vivo techniques utilize explant models to investigate scar formation in tissue samples.[18] In-vivo research often employs rodent and rabbit ear models, where full-thickness wounds are created down to the cartilage, and samples are examined four weeks after wounding to assess scar development.[19,20] Additionally, human hypertrophic or keloid skin grafts are frequently used in animal models, typically involving nude mice.[14,21]

For atrophic scars, there is currently no ideal preclinical model. However, extensive clinical research has been conducted on therapies for atrophic skin. Human skin biopsies from atrophic scars can be used to elucidate the underlying molecular mechanisms.[13] Although numerous therapeutic techniques for pathological scars exist, it is widely recognized that current treatments still need to be improved.[10] Conventional therapies, such as corticosteroids, have high recurrence rates and side effects.[22,23] Current treatments improve atrophic scars but do not completely eliminate them, highlighting the need for alternative approaches like mesenchymal stem cell (MSC) therapy.[6]

Adipose-Derived Stem Cell Products

MSC has emerged as a popular therapeutic option for scars.[24] MSC can be harvested from various tissues, including bone marrow, adipose tissue, and umbilical cord.[25,26] Compared to bone marrow-derived MSC, adipose-derived stem cells (ADSC) are more accessible to harvest and yield a richer supply of stem cells.[22]

Various therapies containing ADSC and their derivatives (hereafter referred to as ADSC products) are commonly used in regenerative medicine, particularly for treating pathological scars.[22,27] Previous studies have shown that they are beneficial and safe in monotherapy or combined with other treatment methods.[24] Generally, these therapies can be categorized into cell-based and cell-free therapies.[28] Cell-based therapy includes stromal vascular fraction (SVF) and ADSCs, while cell-free therapy encompasses adipose tissue extract (ATE), secretomes, exosomes (ADSC-Exo), and extracellular vesicles (ADSC-EV) (Figure 1).[27,29] These products can be extracted from human adipose tissue through liposuction, followed by a series of procedures to produce either cell-based or cell-free therapies.[22]

Stromal vascular fractions can be harvested from human adipose tissue obtained via liposuction from various regions such as the abdomen, thighs, and buttocks.[30] SVF contains a heterogeneous cell population, including MSC, pericytes, other progenitor cells, and nucleated cells. These cells exhibit multi-lineage differentiation potential and are considered a rich source of adult stem cells.[22] SVF can be characterized by the expression of MSC surface markers (CD44, CD90,

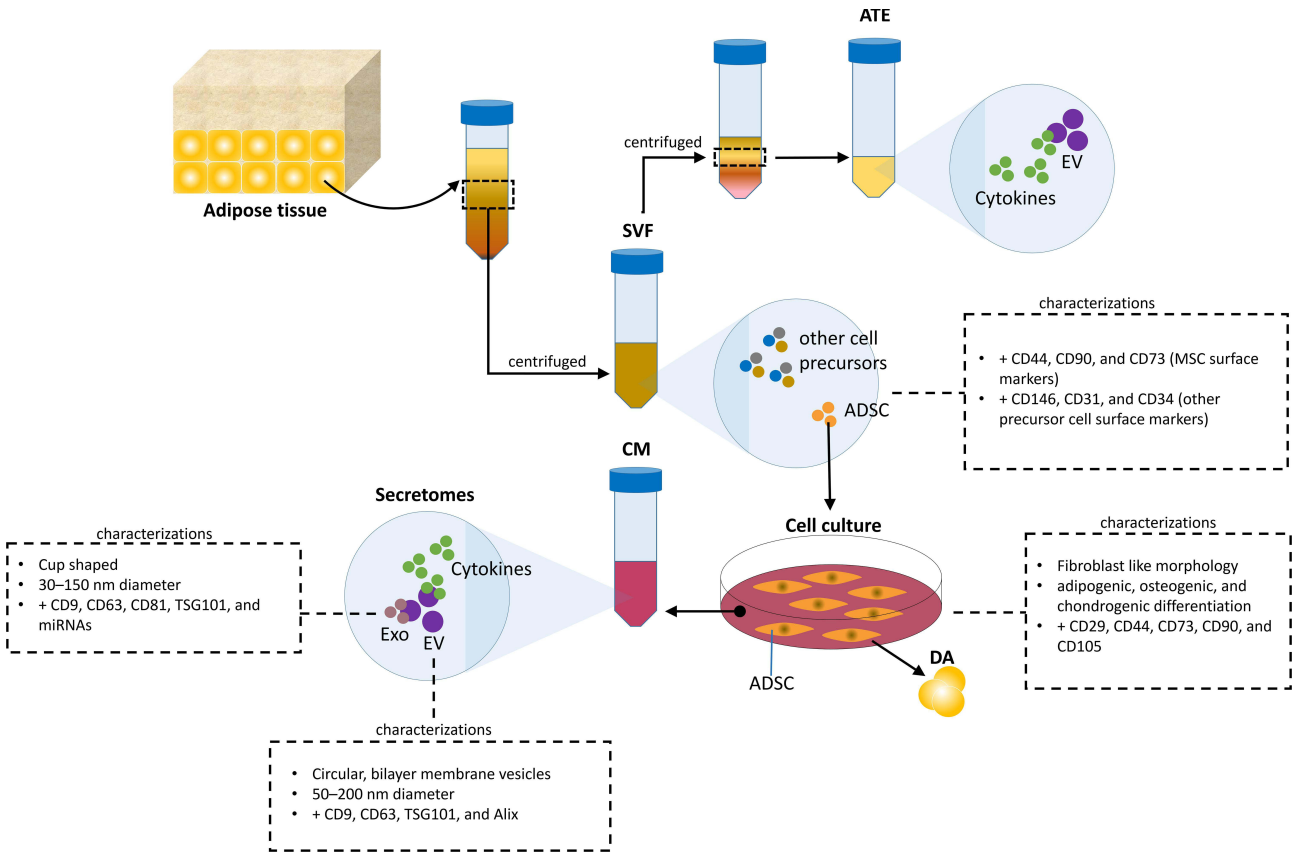


Figure 1 ADSC products.

https://doi.org/10.2147/CCID.S511067

CD73) and precursor cell markers (CD146, CD31, CD34).[31] There are several types of SVF commonly used in therapy, including SVF-gel and SVF-cells.[32] To generate SVF-gel, lipoaspirates are mechanically processed to remove lipids and fluids, leaving only SVF cells and fractionated extracellular matrix (ECM). The process involves emulsification and centrifugation of the lipoaspirate, yielding three layers: oil (top), SVF-gel (middle), and blood (bottom), with the middle layer isolated to obtain SVF.[20,23] This product is enriched in adipose-derived stem cells (ASCs), vascular endothelial cells (ECs), and native adipose ECM.[32] SVF cells are further isolated through collagenase digestion, and the cell pellet is filtered using a 100 μm mesh to obtain the final product.[32]

Adipose derived stem cells can be isolated through lipoaspirate samples and SVF culture.[30] ADSCs exhibit a fibroblast-like morphology and have the capability for trilineage differentiation into adipogenic, osteogenic, and chondrogenic lineages.[11,32] They express mesenchymal cell surface markers including CD29, CD44, CD73, CD90, and CD105.[18,33]

Adipose tissue extracts can be obtained through physical methods by isolating the middle-fat layer after centrifugation, followed by mechanical emulsification. Subsequent repeated centrifugation separates the fat into four layers. The liquid from the third layer, ATE, is then collected. ATE has a high concentration of cytokines and extracellular vesicles.[19,27]

Secretomes are products that are secreted by ADSCs within the conditioned medium (ADSC-CM) that regulate various biological processes.[26] Secretomes contain numerous molecules responsible for cell signaling, including cytokines, growth factors, chemokines, EV, and other active substances.[2] According to a study by Zhang et al, ADSC-derived secretomes secreted 12,221 peptides and 2349 proteins. Some molecules were involved in tissue repair, such as heat shock protein 90 kDa α (HSP90 α) for wound closure, tubulin alpha chain (TAC) for apoptosis of hypertrophic scar fibroblasts, and elongation factor 1-α 1 (EF-1α) for scarless healing.[34] Research has demonstrated that mature adipocytes may transform to a more primitive phenotype and recover proliferative capacity using in vitro dedifferentiation procedures, known as dedifferentiated adipocytes (DAs).[35] Secretomes derived from differentiated adipocytes (DA-CM) have also been reported as potential therapeutic agents.[7] Differentiated adipocytes can be characterized by Oil Red O staining.[7] According to a study by Hoerst et al, differentiated adipocytes secreted 288 proteins. Some were involved in wound healing and regeneration.[7]

Extracellular vesicles (EVs) are particles found within secretomes and are isolated from conditioned media through ultracentrifugation.[36] EVs are characterized by their circular shape, bilayer membrane structure, and a size range of 50–200 nm.[36,37] EVs express markers such as CD9, CD63, TSG101, and Alix while showing minimal expression of VEGFA, PDGFB, and TGFβ1.[36,37] Small extracellular vesicles exocytosed into the extracellular space are called exosomes.[26] Exosomes are molecules that participate in cell-to-cell communication, presenting genetic material such as mRNAs, miRNAs, proteins, and lipids.[38] Exosomes are characterized by their cup-shaped structure, with a size of 30–150 nm in diameter.[27,39,40] They also express markers like CD9, CD63, CD81, and TSG101.[38–40] Additionally, miRNAs, which serve as critical mediators in intercellular communication, have been detected in exosomes, including miR-21, miR-23a, miR-125b, miR-29a, miR-145, miR-125b-5p, miR-10a-5p, miR-23a-3p, miR-21-5p, and miR-92a-3p.[40,41]

ADSC products offer advantages over conventional treatments for pathological scars.[23] Therefore, we explore the potential use of ADSC products in the treatment of pathological scars, summarizing current research trends, mechanisms, and clinical applications. We aim to bridge the gap between preclinical and clinical studies and evaluate ADSC products as monotherapies or combination therapies to identify optimal therapeutic strategies for managing pathological scars.

Methods

A comprehensive literature search was conducted, guided by the PICO framework: population (cellular, animal, and clinical models of hypertrophic, keloid, and atrophic scars); intervention (ADSC products and derivatives, either as single or combination therapies); comparison (control groups/standard treatment (corticosteroid/other treatments); and outcome (effects related to scar modifications). The literature sources utilized were electronic databases, namely PubMed and Scopus. The search keywords are provided in supplementary file 1. The selected articles were original research articles (preclinical and clinical trials) published in English or Indonesian until July 19, 2024. We excluded the following types of articles: (1) Reviews, study protocols, conference papers, letters, and case reports; (2) Stem cell therapies derived from

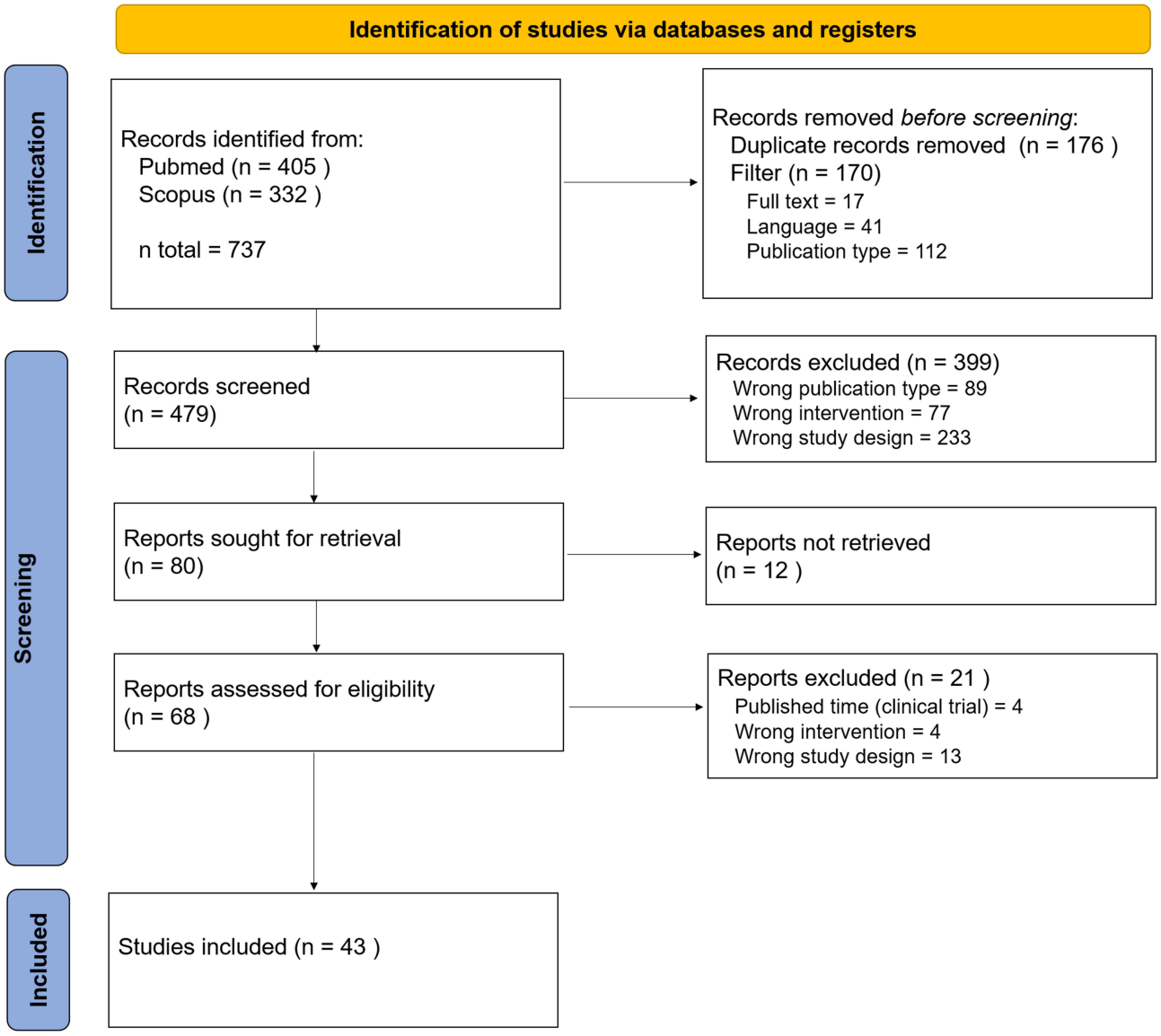


Figure 2 Prisma flow diagram.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. Published online March 29, 2021:n71.[42]

non-adipose tissue sources; (3) Studies focused on typical wound healing phases, acute wounds, infected wounds, diabetic wounds, or acute burn injuries. Specifically, we excluded articles published before January 20, 2023, for clinical trials on hypertrophic and keloid scars. The search results were screened by two independent reviewers (NMA and YC) using the Rayyan application. The selection process of the articles is detailed in the PRISMA flow diagram (Figure 2).

Results

A total of 737 studies were identified from the electronic databases. Among these, 176 duplicates were removed, and 170 studies were excluded after the initial screening. A total of 479 articles were screened using Rayyan, resulting in 43 studies that met the inclusion criteria (Figure 2). Our systematic search identified current research trends focusing on adipose-derived products, including ADSC, adipose subcutaneous tissue (ADT), ATE, SVF, DA-CM, ADSC-CM, and exosomes or extracellular vesicles derived from ADSC (ADSC-exo/EVs). With advancements in technology, various

methods were being investigated to enhance the effectiveness of these therapies, such as modifying stem cells with TGFβ3, IL10, miRNAs, and electrospun membranes.

In the included preclinical studies, six studies used ADSC products derived from animals, and 28 studies used ADSC products derived from humans as interventions on keloid or hypertrophic cell or tissue models (Table 1 and Table 2). No studies using atrophic scar models were identified in the preclinical trials. We also included six clinical trials consisting of 43 subjects with hypertrophic scars, eight subjects with keloid scars, and 73 subjects with atrophic scars (Table 3).

To identify the best therapy for pathological scars, we explored the potential of ADSC products and derivatives in combination with other treatments. We found seven articles investigating combination therapies involving fractional CO_2 laser, platelet-rich plasma (PRP), botulinum toxin (BTA), or photo-modulation therapy. Among these, four preclinical studies used keloid and hypertrophic scar models with fractional CO_2 laser, BTA, or photo-modulation therapy combinations. At the clinical level, four studies involving 32 patients with atrophic scars used a combination of fractional CO_2 laser and PRP. However, no combination therapies for keloid or hypertrophic scars were identified in the clinical studies (Table 4).

Discussion

Different types of ADSC are likely to influence their effectiveness. For instance, research by Domergue et al compared the effects of SVF versus ADSC, finding that ADSC yielded superior results overall.[56] Zhang et al compared ADSC with ADSC-CM, further confirming the efficacy of ADSC and finding that ADSC continued to provide superior outcomes.[57] Other research comparing SVF-gel and SVF-cells demonstrated that SVF-gel yielded superior results overall.[32] Additionally, higher therapy concentrations in ADSC-CM and ADSC-exo may lead to better results, as indicated by several previous studies.[34,49,53] However, comparative studies on the effectiveness of ADSC products based on type or concentration are still limited and require further exploration.

ADSC Products for Hypertrophic and Keloid Scar

The therapeutic potential of ADSC products in treating hypertrophic and keloid scars arises from their ability to modulate molecular pathways. ADSC products exhibited distinct effects on normal and hypertrophic/ keloid fibroblasts. ADSC products reduced migration, proliferation, and collagen expression in hypertrophic/ keloid fibroblasts, whereas these parameters were increased in normal fibroblasts.[47] This review outlined the mechanisms of ADSC products in keloid and hypertrophic scars, focusing on ECM remodeling, cell density regulation, adipogenesis, angiogenesis, antioxidant regulation, mechanical properties, and anti-inflammatory effects. Furthermore, ADSC products improve scar structure and function, promoting tissue regeneration. At the clinical level, these effects translated to improvements in itch symptoms and scar texture, including size, color, texture, and thickness of the scar. No serious adverse effects were reported[22,31] (Figure 3).

ECM Remodeling

ECM significantly influenced the development and persistence of hypertrophic and keloid scars. The balance of ECM components was maintained by normal fibroblasts, which regulated collagen synthesis and degradation. However, this balance was disrupted in hypertrophic and keloid scars, leading to fibrosis and excessive collagen deposition.[11,43,52]

ADSC products were shown to modulate fibroblast differentiation into myofibroblasts, thereby reducing fibrosis.[7,44] The studies we reviewed, we identified several molecules targeted by ADSC products, including the inhibition of pro-fibrotic signaling pathways such as P38/MAPK, TGFβ1/SMAD3, SMAD7, pAKT/ERK1/2, and NOTCH1/JAG1.[7,16,18,33,46,49,53] This modulation led to downregulating fibrotic markers like α-SMA, αSM22, CTGF, CXCL1, CCL2, and LIF.[16,43,47,48] Additionally, ADSC enhanced anti-fibrotic pathways, including BMP4/SMAD1,5,9 and PPARγ, which counterbalanced the pro-fibrotic signals.[7]

ADSC products also influenced ECM remodeling by reducing collagen deposition and enhancing collagen degradation. They reduced collagen synthesis by downregulating COL genes (particularly COL1, COL3, COL11, COL12) or interfering with procollagen genes (especially procollagens I and III) responsible for COL formation.[7,16,48] Furthermore, ADSC products modulated enzymes that degrade COLs by upregulating metalloproteinases (MMPs) such as MMP-1,

Table 1 In-vitro/ex-vivo Results

No	Ref.	ADSC Type	ADSC Source	Cell Line	Outcomes	Mechanism
1	Ruan et al, 2024[37]	ADSC-EV	Human	KFC	**Proliferation assay**: • Decreased in cell proliferation **Migration assay**: • Decreased in cell migration **RT-qPCR** • Increased in SOCS1 expression **Western blot** • Decreased in JAK2/STAT3 expression • Increased in SOCS1 expression that result to autophagy & JAK2/STAT3 modulation • Decreased in COL-I & III expression **Immunofluorescence**: • Autophagy inhibition	• ECM component reorganization • Cell proliferation • Cell migration • Autophagy
2	Nukui et al, 2024[43]	ADSC	Human	KFC cultured with TGF-β1	**Immunofluorescence**: • Decreased in α-SM22, COL-1, TGF-β1, MMP-2, SMAD-2, SMAD-3, PDGFRα, and TGFβR1 expression **RT-qPCR and Western blot**: • Decreased in α-SM22, COL-1, TGF-β1, MMP-2, SMAD-2, SMAD-3, PDGFRα, and TGFβR1 expression **Collagen gel contraction assay**: • Decreased in cell contraction	• ECM component reorganization by antagonize TGF-β's fibrotic actions.
3	Xu C et al, 2024[41]	ADSC-exo- miR-125b-5p	Human	HFC	**Migration assays**: • Decreased in cell migration **Immunofluorescence**: • Decreased in Ki67 expression • Decreased in α-SMA expression • Decreased in SMAD2 expression **Western blot**: • Decreased in COL-1, COL-3, and α-SMA expression • Decreased in SMAD2 and p-SMAD2 expression **RT-qPCR** • Decreased in SMAD2 expression **Other results**: • High levels of miR-125b-5p were expressed by ADSC-exo, and miR-125b-5p reduced the activity of Smad2–3 UTR-wt.	• Cell migration • Cell proliferation • Anti-fibrotic activity by miR-125b-5p/SMAD2 pathway

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https://doi.org/10.2147/CCID.S511067

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Table 1 (Continued).

No	Ref.	ADSC Type	ADSC Source	Cell Line	Outcomes	Mechanism
4	Wang W et al, 2023[44]	ADSC or ADSC-enriched-TGFβ3 or ADSC-enriched-IL10 or ADSC-enriched-TGFβ3 & IL10	Human	KFC Ex vivo keloid explant	**Proliferation assay**: • Decreased in KFC proliferation. ADSCs$^{TGF\text{-}\beta3}$ and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ yielded superior results • Decreased in KFC viability. ADSCs$^{TGF\text{-}\beta3}$ and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ yielded superior results **Migration assay** • Increased in KFC migration. ADSCs$^{TGF\text{-}\beta3}$ and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ yielded superior results **Flow cytometry** • Increased in KFC apoptosis. ADSCs^{IL10} and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ yielded superior results • Higher rate of KFC in the G0/G1 phase. ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ yielded superior results **RT-qPCR** • ADSCs$^{TGF\text{-}\beta3}$ increased MMP-1 and MMP-12 expression. • ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ increased MMP12, MMP1, and MMP8 expression. • ADSCs$^{TGF\text{-}\beta3}$ decreased COL3A1 expression. • No significant differences in COL1A1 expression **Western blot**: • ADSCs$^{TGF\text{-}\beta3}$ and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ increased MMP-1, MMP-8, and MMP-12 expression • ADSCs^{IL10} increased MMP-1 expression **Immunofluorescence**: • ADSC, ADSCs^{IL10} and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ decreased α-SMA expression **Ex vivo results**: • ADSCs$^{TGF\text{-}\beta3}$ and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$ decreased cellularity, microvasculature, and ECM components. • ADSCs$^{TGF\text{-}\beta3}$-CM and ADSCs$^{TGF\text{-}\beta3\ +\ IL10}$-CM decreased COL-1 & COL-3 expression	• Morphogenetic factor: TGFβ3 • Immunosuppressive factor: IL10 • Cell proliferation • Cell migration • Cell viability/apoptosis • ECM component reorganization: MMPs, COLs • Vascularity
5	Wu et al, 2023[45]	ADSC-exo-miRNA7846-3p	Human	KFC	**EdU labelling assay** • Decreased in cell viability **Proliferation assay** • Decreased in cell proliferation **TUNEL** • Decreased apoptosis resistance **Tube formation assay** • Angiogenesis inhibition **RT-qPCR and Western blot**: • Decreased in NRP2 expression • Hedgehog pathway suppression: SHH, SMO, and GLI1.	• Cell viability/ apoptosis • Cell proliferation • Angiogenesis • Hedgehog pathway
6	Chen J et al, 2023[39]	ADSC-exo	Human	HFC	**RT-qPCR or Western blot**: • Decreased in COL-1, COL-3, and α-SMA expression • Decreased miR-181a expression • Decreased in the TGF-β1 effect related to myofibroblast differentiation • Increased in SIRT1 expression	• MicroRNA-181a/SIRT1 pathway regulation • Myofibroblast transdifferentiation • ECM component reorganization: COL-1, COL-3, α-SMA

7	Raktoe el al, 2023[17]	Adipose subcutaneous tissue (ADT)	Human	3D HFC-like skin organotypic cultures	**Immunohistochemistry or immunofluorescence**: • Decreased in Ki67, LOR, α-SMA expression • Decreased in epidermal thickness	• Dermal-epidermal reorganization • Cell proliferation
8	Xie F et al, 2022[46]	ADSC-IL10 (ADSC with modified IL10)	Rabbit	HFC	**Proliferation assay**: • Decreased in cell proliferation. **Migration assay** • Decreased in cell migration **Western blot** • Decreased in COL-1, COL-3, FN, and α-SMA expression	• Cell proliferation • Cell migration • ECM component reorganization: collagen I, collagen III, FN, and α-SMA
9	Zhou J et al, 2022[47]	ADSC	Human	KFC vs normal fibroblast	**Migration assay**: • KFC migration decreased, but the normal fibroblast migration increased. **Proliferation assay**: • KFC survival rate decreased, but the normal fibroblast survival rate increased. **RT-qPCR and Western blot**: • Decreased in COL-1 and P-4-HB expression in KFC **Western blot**: • Decreased in COL-3, CTGF, and P-4-HB expression in KFC, but the expression was increased in normal fibroblast.	• Cell migration • Cell proliferation • ECM component reorganization
10	Li et al, 2022[12]	ADSC	Human	HFC	**Proliferation assay**: • Decreased in cell proliferation. **Migration assay**: • Decreased in cell migration **Immunofluorescence**: • Decreased in proliferation protein-Ki67 expression • Decreased in Nrf2 expression **Flow cytometry**: • Increased in G1 phase • Increased in apoptosis rate • Decreased in ROS accumulation **RT-qPCR**: • Decreased in antioxidant-Nrf2 and antioxidant enzymes-NQO1 expression **Western blot**: • Decreased in Nrf2, HO-1, and Nrf2-nucleus expression • Changes in apoptotic proteins: increased in BAX and cleaved Caspase 3 expression, and decreased in BCL-2 expression **Enzyme immunoassay analyzer**: • Decreased in T-SOD activity	• Cell migration • Cell proliferation: Ki67 • Cell cycle and apoptosis • Antioxidant activity: Nrf2/NQO1/SOD

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Table 1 (Continued).

No	Ref.	ADSC Type	ADSC Source	Cell Line	Outcomes	Mechanism
11	Imai et al, 2022[48]	ADSC-CM	Human	KFC and keloid fibroblast (KF) disc	**FPCL contraction assay**: • Decreased in cell contraction **RT-qPCR**: • Decreased in α-SMA, COL1A1, COL3A1, TGF-β1, and IL-6 expression **GSEA analysis** • Decreased in CXCL1, CCL2, CXCL8, CTGF, LIF, IL-6, α-SMA, TGFβ-1, COL1A1, COL11A1, and COL12A1 expression • Decreased in inflammation-related genes • Decreased in migration and proliferation-related genes • Increased in ECM regulators: MMP-3 and MMP-1 • Decreased in fibrosis-related genes: CTGF **Histology examination in KF disc**: • Decreased in cell number • Decreased in collagen density	• Cell proliferation • ECM component reorganization • Anti-inflammatory activity
12	Li Y et al, 2021[38]	ADSC-exo- miR-192-5p	Human	HFC	**Migration assays**: • Decreased in cell migration **Immunofluorescence**: • Decreased in Ki67 expression • Decreased in α-SMA expression **Flow cytometry**: • Decreased in cell proliferation • Increased in G0/G1 phase • Decreased in S phase **RT-qPCR or Western blot**: • Decreased in COL-1, COL-3, and α-SMA expression • Compared to ADSC, ADSC-exo exhibited higher levels of miR-192-5p. • Reduced expression of IL-17RA, which resulted in decreased expression of collagen, α-SMA, p-SMAD2, and p-SMAD3, and increased expression of SIP-1	• Cell migration • Cell proliferation • Anti-fibrotic activity by miR-192-5p/IL-17RA/Smad pathway
13	Yang et al, 2021[21]	ADSC-CM	Human	KFC	**Proliferation assay**: • Decreased in cell proliferation **Flow cytometry**: • Increased in apoptosis **RT-qPCR and Western blot**: • Increased in caspase-3 expression • Decreased in BCL-2 expression • Increased in COX-2 expression, no significant changes in COX-1 expression **ELISA** • Increased in AA and PGE-2 expression **Immunohistochemistry** • Reduced rate of cell proliferation	• Apoptosis: caspase-3/BCL-2 • COX-2/caspase-3/BCL-2 pathway

14	Wu ZY et al, 2021[49]	ADSC-exo (0, 1, 10, and 100 μg/mL)	Human	KFC	**Proliferation assays**: • Decreased in cell proliferation. **Flow cytometry**: • Increased apoptosis rate. **Hydroxyproline assay**: • Decreased collagen synthesis. **Western blot and RT-PCR**: • Decreased in α-SMA, TGF-β1, and SMAD-3 expression The highest concentrations yielded superior results overall.	• Cell proliferation • Cell migration • Apoptosis • ECM component reorganization: α-SMA, TGF-β1/Smad3 pathway
15	Zhang C et al, 2021 [34]	ADSC-CM (CM, CM5, CM10)	Rabbit	KFC	**Proliferation assay**: • CM & CM5 promoted cell proliferation. • CM10 reduced proliferation. **Flow cytometry**: • CM & CM5 reduced apoptosis. • CM10 increased apoptosis. **Immunofluorescence**: • CM5 & CM10 reduced α-SMA expression	• Cell proliferation • Apoptosis • Fibrosis activity: α-SMA
16	Yuan et al, 2021[40]	ADSC-exo-miR29a	Human	HFC	**Proliferation assay**: • Decreased in cell proliferation **Migration assay**: • Decreased in cell migration **RT-qPCR and Western blot**: • Decreased in TGF-β2, p-SMAD3, COL-1, COL-3 and α-SMA expression	• TGF-β2/Smad3 pathway targeted by miR29a • ECM remodeling by TGF-β2/Smad3 pathway
17	Li J et al, 2021[11]	ADSC-exo	Human	KFC	**RT-qPCR**: • Decreased in TGF-β2, FN, COL-1, COL-3, and α-SMA expression • Decreased in MMP-1 • Increased in TIMP-1 expression **Western blot**: • Decreased in TGF-β2, FN, COL-1, COL-3, and α-SMA expression **Immunofluorescence** • Decreased in COL-1 and FN expression **Ex vivo results**: • Reduced COL production • Decreased in angiogenesis marker: CD34 & CD31-positive-microvessels • Decreased in Smad3, Notch-1, and TGF-β2 expression • Increased in TGF-β3 expression, • No significant changes in TGF-β1 expression	• ECM component reorganization by TGF-β2/Smad3 and Notch-1 pathway • Angiogenesis
18	Chen et al, 2020[50]	ADSC-CM loaded in electrospun membrane	Human	HFC	**Proliferation assay**: • Decreased in cell proliferation. **Migration assay**: • Decreased in cell migration **RT-qPCR and Western blot**: • Decreased in COL-1, COL-3, and α-SMA expression	• Cell migration • Cell proliferation • ECM component reorganization

(*Continued*)

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Table 1 (Continued).

No	Ref.	ADSC Type	ADSC Source	Cell Line	Outcomes	Mechanism
19	Han B et al, 2019[16]	ADSC-CM	Human	KFC HFC	**Proliferation assay**: • Decreased in cell proliferation. **Migration assay**: • Decreased in cell migration **Hydroxyproline assay**: • Decreased in collagen expression **Western blot**: • Decreased in TGF-β1, Notch-1, JAG-1, SMAD3 expression **RT-qPCR**: • Decreased in procollagen I & III, CTGF, FN, and α-SMA expression	• Notch1/JAG-1 and TGF-β1/SMAD3 pathway • ECM component reorganization • Cell proliferation • Cell migration
20	Hoerst et al, 2019[7]	Differentiated adipocyte-CM (DA-CM) or TGF-β1-induced ADSC-CM	Human	HFC Myofibroblast	**ELISA**: • Increase in BMP-4 expression. The adipocyte-CM group yielded superior results **Western blot**: • Decreased α-SMA, COL-1, and COL-3 expression for adipocyte-CM group. The effects of the ADSC-CM group were less significant. • Decreased in p-ERK 1/2 expression. The adipocyte-CM group yielded superior results • Adipocyte-CM activates PPARγ. • PPARγ & BMP-4 inhibition increased α-SMA expression • Decreased in p38 expression (non-canonical TGF-β effectors). The adipocyte-CM group yielded superior results. • Myofibroblasts incubated with adipocyte-CM showed an increase in p-SMAD 1/5/9, a BMP signal.	Myofibroblast reprogramming by: • BMP-4/SMADs/PPARγ activation • TGF-β1/ERKs inhibition • TGF-β1/p38 inhibition
21	Chu et al, 2018[51]	ADSC	Rabbit	HFC	**ELISA**: • Decreased in COL-1, TGF-β1 expression **RT-qPCR and Western blot**: • Decreased in α-SMA expression • Increased in DCN expression **Immunofluorescence**: • Decreased in α-SMA expression • Increased in DCN expression	ECM component reorganization
22	Deng et al, 2018[52]	ADSC	Human	HFC	**Proliferation assay**: • Decreased in cell proliferation **Flow cytometry**: • Decreased in G2/M phase • Increased in G0/G1 phase **RT-qPCR** • Decreased in COL-1, COL-3, FN, and α-SMA expression • Increased in MMP-1/TIMP-1 expression • Decreased in TGF-β1, IL-6, IL-8, and CTGF expression **FPCL contraction assay** • Decreased in cell contractility **Migration assay**: • Decreased in cell migration **ELISA** • Decreased in TGF-β1 expression **Western blot** Decreased in pSMAD-2, pSMAD-3, pSTAT-3, and pERK-1/2 expression	• Cell cycle • ECM component reorganization • Cell proliferation • Cell migration • Cell contractility • Anti-inflammatory activity

23	Wang X et al, 2018[18]	ADSC-CM	Human	KFC Ex-vivo keloid tissue	**RT-qPCR**: • Decreased in PAI-1, COL-1, and TIMP-1 expression **Western blot**: • Decreased in intracellular signaling of pAKT, ERK1/2, and JNK **Flow cytometry**: • Decreased in G2/M phase • Increased in G0/G1 phase **Cell invasion assay**: • Decreased in migrated cell number **Histological & Immunohistochemical assays**: • Decreased in angiogenesis as seen as depleted number of CD31+ and CD34+ vessels expression	• Cell proliferation • Cell migration • Cell cycle • ECM component reorganization: COL-1, TIMP-1 • Angiogenesis: CD31+ and CD34+ • Intracellular signaling: pAKT, ERK1/2, and JNK
24	Chai et al, 2018[53]	ADSC-CM 10%, 20%, 40%, or 80%	Human	HFC	**Migration assay**: • Decreased in cell migration **RT-qPCR**: • Decreased in COL-1, COL-3, FN, and α-SMA expressions. ADSC-CM 80% treatment yielded superior results. No significant changes for ADSC-CM 10% treatment **Western blot**: • Decreased in COL-1, COL-3, FN, and α-SMA expressions. ADSC-CM 80% treatment yielded superior results • Decreased in p38 expression. ADSC-CM 80% treatment yielded superior results. No significant changes for ADSC-CM 10% treatment • Collagen deposition by Anisomycin treatment, a p38/MAPK pathway activator. **Immunofluorescence**: • ADSC-CM 80% treatment decreased α-SMA expression	• Cell migration • ECM component reorganization • P38/MAPK pathway
25	Liu et al, 2017 [54]	ADSC-CM	Human	KFC	**Proliferation assay**: • Decreased in cell proliferation **Migration assay**: • Decreased in cell migration **Flow cytometry**: • ADSC-CM did not exhibit cell apoptosis **RT-qPCR**: • Decreased in TGF- β1, TGF- β2, and TGF- β3 expression • Increased in DCN & MMP-1 expression • Decreased in IL-6 & IL-8 expression • Decreased in α-SMA, COL-I & III expression **FPCL contraction assay** • Decreased in cell contractility	• ECM component reorganization • Cell proliferation • Cell migration • Anti-inflammatory activity • Cell contractility

(*Continued*)

https://doi.org/10.2147/CCID.S511067

https://doi.org/10.2147/CCID.S511067

Table 1 (Continued).

No	Ref.	ADSC Type	ADSC Source	Cell Line	Outcomes	Mechanism
26	Li Y et al, 2016[33]	ADSC-CM	Human	HFC	**RT-qPCR**: • Decreased in COL-1, COL-3, and α-SMA expression **Western blot and ELISA** • Decreased in p-p38 expression, particularly at 20%, 40%, and 80% concentrations • Decreased in COL-1, COL-3, and α-SMA expression • Collagen deposition by Anisomycin treatment, a p38/MAPK pathway activator **Immunofluorescence** • Decreased in α-SMA expression **Ex vivo results**: • Reduced thickness with uniformly arranged collagen • Decreased in COL-1, COL-3, and α-SMA expression	• ECM component reorganization • P38/MAPK pathway
27	Kim SW et al, 2015[55]	ADSC	Human	KFC	**Morphology**: • KFC without ADSC co-culture exhibited a larger and flatter appearance. KFC co-cultured with ADSC exhibited more regularity and narrow intracellular spaces **Proliferation assay**: • Increased in cell growth **Live dead cell staining**: • Decreased in apoptosis **Western blot**: • Decreased in COL-1 expression • Increased in α-SMA expression	• Morphology arrangement • ECM component reorganization
28	Broek et al, 2012[10]	ADSC	Human	Tissue-engineered human hypertrophic scar	**Skin organotypic visual observation**: • The tissue exhibited greater contractility. • Decreased in tissue surface area **Histological & Immunohistochemical assays**: • Increased in epidermis thickness, epidermal cell layers, and α-SMA staining **ELISA** • Increased in COL-1 expression • Decreased in CXCL8 expression **Migration assay** • Decreased in keratinocyte migration	• Morphology arrangement • Anti-inflammatory

Notes: a: see Table 2 for in vivo results; b: see Table 4 for combination therapy results.

Abbreviations: AA, arachidonic acid; ADSC, adipose derived stem cell; AKT, protein kinase B; α-SM22, alpha smooth muscle 22; α-SMA, alpha smooth muscle actin; BCL, B-cell lymphoma; BMP, bone morphogenetic protein; CCL, C-C motif chemokine ligand; CM, conditioned medium; COL, collagen; COX, cyclooxygenase; CTGF, connective tissue growth factor; CXCL, C-X-C motif chemokine ligand; DCN, decorin; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; Exo, exosomes; EV, extracellular vesicles; FN, fibronectin; FPCL, fibroblast populated collagen lattice; GSEA, gene set enrichment analysis; HFC, hypertrophic fibroblast cells; HO, heme oxygenase; IL, interleukin; JAK, Janus kinase; JAG, Jagged; JNK, c-Jun N-terminal kinase; Ki67, marker of proliferation Ki-67; KFC, keloid fibroblast cells; LIF, leukemia inhibitory factor; LOR, loricrin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf, nuclear factor erythroid 2–related factor; NRP, neuropilin; PDGF, platelet-derived growth factor receptor; PGE, prostaglandin E; PPAR, peroxisome proliferator-activated receptor; P-4-HB, prolyl 4-hydroxylase beta; SHH, sonic hedgehog; SIRT, sirtuin; SMO, smoothened; SOD, superoxide dismutase; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases.

Table 2 In vivo Results

No	Ref.	ADSC Type	Dosage	ADSC Source	Methods of ADSC Application	Animal Model	Lesion Profile	Outcomes for ADSC Group	Related Pathway
1	Qian Y et al, 2023[20]	SVF-gel	1 mL	Rabbit	Injection	Rabbit ear	Linear HS	**Visual observation**: • Appearance improvement at weeks 4 and 8 • Improvement in quantitative assessment (using Manchester Scar Scale – MSS) **Histological examination**: • Improvement in pathological features of scar • Reduction of collagen fiber density **Immunohistochemistry/ Western blot**: • Decreased in the expression of proliferation-related-Ki-67 cell & α-SMA • Decreased in inflammatory cells: CD45, IL-1β • Decreased in TGF-β1/Smad3 activity	• Anti-fibrosis activity: Ki-67, α-SMA • Anti-inflammatory activity: CD45, IL-1β • TGF-β1/Smad3 pathway
2	Cai Y et al, 2023[19]	ATE	0.1 mL/cm2	Human	Injection	Rabbit ear	HS	**Visual observation**: • Improvement in color, thickness, and texture of the scar • Improvement in quantitative assessment (Vancouver Scar Scale-VSS) **Histological examination**: • Decreased in epidermis and dermis thickness • Decreased in inflammatory cell infiltration • Decreased in scar hyperplasia index • Decreased collagen deposition **Immunohistochemistry**: • Decreased in the expression of α-SMA **Immunofluorescence**: • Increased in perilipin expression **qPCR**: • Increased in C/EBPα and PPARγ mRNA expression	• Anti-inflammatory activity • ECM component reorganization: • Adipogenesis: perilipin, C/EBPα and PPARγ
3	Chen J et al, 2023[39]	ADSC-exo	5 μg/g body weight; 4 times	Human	Injection	Dorsal skin mice	HS	**Histological examination**: • Decreased collagen deposition **RT-qPCR** • Decreased in COL 1, COL 3, and α-SMA expression • Decreased in miR-181a expression	• ECM component reorganization
4	Li et al, 2022[12]	ADSC	2×10^6 /0.2 mL	Human	Injection	Nude mouse with human HS graft	HS	**Visual observation**: • Decreased in scar weight **Histological examination**: • Regularly arranged collagen fibers **TUNEL**: • Increased in apoptotic cells. **Western blot**: • Changes in apoptotic proteins: increased in BAX and cleaved Caspase 3 expression, and decreased in BCL-2 expression • Decreased in Nrf2 and HO-1 expression **Immunofluorescence**: • Decreased in proliferation protein-Ki67 expression • Decreased in Nrf2 expression	• ECM component reorganization • Cell proliferation • Antioxidant activity: Nrf2/HO-1 • Apoptosis

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https://doi.org/10.2147/CCID.S511067

https://doi.org/10.2147/CCID.S511067

Table 2 (Continued).

No	Ref.	ADSC Type	Dosage	ADSC Source	Methods of ADSC Application	Animal Model	Lesion Profile	Outcomes for ADSC Group	Related Pathway
5	Xie F et al, 2022[46]	ADSC-IL10	0,5 x 10^6 cells/100 μL	Rabbit	Injection	Rabbit ear	HS	**Immunohistochemistry**: • Decreased in collagen I/III expression **Immunoblotting**: • Decreased in COL I/III expression **RT-qPCR**: • Decreased in MIP, MIP-1β, IL-1β, and IL-6 expression **Western blot**: • Decreased in TGF-β1, p-Smad 2/Smad 2, Smad 7, p-IκBα/IκBα, and p-p65/p65 expression **Immunofluorescence**: • Decreased in immune cell marker: CD45 and CD3	• Anti-inflammatory activity • ECM component reorganization • TGF-β/Smads pathway: cell proliferation and migration • NF-κB pathway: inflammation
6	Zhang C et al, 2021 [34]	ADSC-CM gel	CM, CM5, CM10	Rabbit	Injection	Rabbit ear	HS	**Histological examination**: • Decreased in scar elevation index. CM5 yielded the best outcome • Decreased in collagen deposition (CM5 & CM10)	• ECM component reorganization
7	Yang et al, 2021[21]	ADSC-CM	0.1 mL	Human	Injection	Nude mouse with human KS graft	KS	**ELISA** • Increased in AA, COX-2, PGE-2 expression	• Anti-inflammatory activity
8	Zhu YZ et al, 2020[36]	ADSC-EV	0.1 mL	Human	Injection	Rabbit ear	HS	**Histological examination**: • Decreased in scar elevation index. • Improvement in collagen structure **Immunofluorescence**: • Decreased in α-SMA expression **Western blot** • Decreased in α-SMA & COL-I expression	• ECM component reorganization:
9	Wang J et al, 2019[32]	SVF-gel or SVF-cells	SVF-gel: 1 mL; SVF cells: 10^5 cells/mL	Rabbit	Injection	Rabbit ear	HS	**Visual observation**: • Improvement in size, color, texture, and thickness of the scar **Histological examination**: • Improvement in epidermis and dermis thickness. • Decreased collagen deposition **Immunohistochemistry**: • Decreased in myofibroblast - α-SMA expression **Immunofluorescence**: • Increased in perilipin expression • Decreased in macrophages (CD 206+) infiltrations **RT-qPCR** • Decreased in MCP-1 & IL-6 expression • Decreased in COI-1 expression The SVF-gel yielded superior results overall.	• Anti-inflammatory activity • ECM component reorganization • Adipogenesis: perilipin

10	Liu et al, 2017[54]	ADSC-CM	200 μL/week	Human	Injection	Mouse with human keloid graft	KS	**Visual observation**: • Decreased in scar weight **Histochemistry & immunohistochemistry**: • Decreased in immunomarker: CD68 & CD31 • Loosely packed collagen with few fibrils was observed	• Anti-inflammatory • Vascularization
11	Domergue et al, 2016[56]	SVF or ADSC	SVF: 10^6 ADSC/100 μL; ADSC: 10^6 cells/100 μL	Human	Injection	Nude mice with human skin graft	HS	**Visual observation**: • Improvement in scar appearance **Histological examination**: • Decreased skin thickness • Improvement in collagen structure • Reduction of fibrosis based on Scar Score **Dye binding assay**: • Decreased in collagen quantification **RT-qPCR** • Decreased in TGF-β1 & VEGF expression for SVF treatment • Decreased in VEGF expression for ADSC treatment • Increased in TGF-β3, MMP-2, MMP-2/TIMP-2, HGF expression for ADSC treatment • No significant changes for COl-1, COl-2, α-SMA, MMP-1, MMP-13, MMP-9, IL-6, TNFα, IFN α expression **Immunofluorescence**: • Decreased in α-SMA expression ADSC yielded superior results overall	• Anti-fibrosis activity: TGFβ3 and HGF • Collagen remodeling: MMP-2 and MMP-2/TIMP-2 • Collagen remodeling
12	Zhang et al, 2015[57]	ADSC or ADSC-CM	4×10^6 cells/0.2 mL	Rabbit	Injection	Rabbit ear	HS	**Visual observation**: • Improvement in scar appearance **Ultrasonography**: • Decreased in scar elevation index **Histological examination**: • Decreased in scar elevation index • Decreased in collagen deposition **RT-qPCR**: • Decreased in α-SMA, COL-1 expression ADSC yielded superior results overall	• ECM component reorganization

Notes: a: see Table 1 for in vitro results; b = see Table 4 for combination therapy results.

Abbreviations: AA, arachidonic acid; ADSC, adipose-derived stem cell; ATE, adipose tissue extract; BAX, Bcl-2-associated X protein; BCL, B-cell lymphoma; C/EBPα, CCAAT/enhancer-binding protein alpha; CD, cluster of differentiation; CM, conditioned medium; COL, collagen; COX, cyclooxygenase; ECM, extracellular matrix; EV, extracellular vesicles; Exo, exosome; HO, heme oxygenase; HS, hypertrophic scar; IκBα, inhibitor of kappa B alpha; IL, interleukin; Ki-67, marker of proliferation Ki-67; KS, keloid scar; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; MSS, Manchester Scar Scale; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF, nuclear respiratory factor; PGE, prostaglandin E; PPARγ, peroxisome proliferator-activated receptor gamma; SVF, stromal vascular fraction; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VSS, Vancouver Scar Scale; α-SMA, alpha smooth muscle actin.

https://doi.org/10.2147/CCID.S511067

Table 3 Clinical Results

No	Ref.	Study Design	ADSC Type	Dosage, Frequency,	Follow Up	Methods of ADSC Application	Subject (N; Age in Years)	Lesion profile	Outcomes for ADSC Group
1	Mbiine et al, 2023[22]	RCT – pilot, Phase 1	SVF	Single dose, 1 mL/cm^3	3 months	Intralesional injection	8; 18–65 years old	KS	**Visual observation**: • Improvement in quantitative assessment (POSAS score) • Improvement in itch symptoms & scar texture **Adverse event**: none **Other results**: SVF showed better outcomes in comparison to triamcinolone acetate intralesional injection
2	Vingan el al, 2023[58]	Nonrandomized prospective – pilot study	SVF		6 months	Intradermal lipoaspirate grafting	10; 18–60	AS	**Visual observation**: • Improvement in quantitative assessment (GAIS score) • Improvement in scar depression and texture **Biophysical Evaluations**: • Improvement in collagen density **Histological examination**: • Increased in epidermis thickness **Protein/ gene analysis**: • Decreased in MMP-2 expression **Adverse event**: Brief edema and erythema
3	L'Orphelin et al, 2021[59]	Retrospective	Microfat		18 month	Injection	43	AS/ sclerotic	**Patient satisfaction**: • Good satisfaction after the treatment
4	Eitta et al, 2019[30]	Prospective study	SVF	Single dose, 1 mL	3 months	Intradermal injection	10; 20–45	AS - post acne	**Visual observation**: • Improvement in scar severity based on Goodman's & Baron qualitative global acne grading system • Decreased in scar area percentage **Biophysical Evaluations**: • Improvement in skin hydration **Patient satisfaction**: • Good satisfaction after the treatment **Other results**: ADSC showed as effective as three sessions of fractional carbon dioxide laser treatment
5	Gentile et al, 2017[31]	Prospective study	SVF		12 months	Nanofat grafting	43; 21–73	Post-burn/ post-traumatic scar	**Histological examination**: • Skin regeneration, collagen remodeling • Increased in epidermal-dermal thickness **Adverse event**: none

https://doi.org/10.2147/CCID.S511067

6	Elkahky et al, 2016[60]	RCT	SVF		3 months	Intradermal injection	10; 20–45	AS - post acne	**Visual & Biophysical Evaluations**: • Improvement in total surface area of scar **Histological examination**: • Improvement in dermal-epidermal junction. • There was an indication of collagen remodeling. **Patient satisfaction**: • Good satisfaction after the treatment **Adverse event**: • Minimal pain and edema **Other results**: PRP was discovered to be superior to SVF therapy

Abbreviations: GAIS, Global Aesthetic Improvement Scale; HS, hypertrophic scar; KS, keloid scar; MMP, matrix metalloproteinase; POSAS, The Patient and Observer Scar Assessment Scale; PRP, platelet-rich plasma; RCT, randomized controlled trial; SVF, stromal vascular fraction.

https://doi.org/10.2147/CCID.S511067

Table 4 Combination Therapy

No	Ref.	Study Design	Therapy	Subject of Interventions and Wound Model	Follow up	Outcomes in Combination Therapy
1	Roohaninasab et al, 2023[61]	Randomized clinical trial – Double blind	SVF injection + Fractional laser CO2	AS – post burn on 10 patients	3 months; 1x/ month	Improvement in VSS criteria, skin density, complete density, epidermal thickness, melanin index and patient satisfaction in the combination group
2	Cai Y et al, 2023[19]	In vivo	ATE injection + Fractional laser CO2	HS on rabbit ear	90 days	• Combination therapy was superior to ATE and laser treatments. • ATE outperformed laser monotherapy. • No significant difference in perilipin expression between ATE and combination therapy.
3	Qian Y et al, 2023[20]	In vivo	SVF-gel injection + BTA	HS – linear on rabbit ear	8 weeks	• BTA showed the best outcomes, followed by combination therapy and SVF. • The difference between combination therapy and SVF was not significant.
4	Xiao S et al, 2023[23]	In vivo, Clinical trial	0.1 mL/cm^2 SVF-gel injection + Fractional laser CO2	HS on rabbit ear & 6 humans (21–49 years old)	12 weeks (in vivo); 6 months (clinical trial)	**In Vivo Combination Therapy**: • SVF + laser showed the best results. • For adipogenesis, SVF gel alone outperformed laser monotherapy. **Clinical Trial Combination Therapy**: Visual Observation: • Improvement in quantitative assessment (VSS score). • Improvement in itch symptoms and scar texture. **Other Results**: • SVF showed better outcomes compared to triamcinolone acetate intralesional injection + laser. • Clinical improvement was superior with SVF gel + laser compared to triamcinolone + laser.
5	Nilforoushzadeh et al, 2022[62]	Clinical trial	SVF injection + PRP + autologous fat graft	AS on 9 patients	6 months	**Biometrics assessment**: Improvement in skin pores, melanin content, spots, skin brightness, skin elasticity, TEWL (transepidermal water loss), and skin layers in both the epidermis and dermis **Patient satisfaction**: Good satisfaction after the treatment
6	Han B et al, 2019[16]	In vitro	ADSC-CM + 4 J/cm2 photomodulation therapy	KFC HFC	48 hours	• The combination therapy demonstrated safety, as the cells did not exhibit signs of apoptosis or cytotoxicity. • Overall, the combination therapy produced superior results.

https://doi.org/10.2147/CCID.S511067

7	Zhou B et al, 2016[63]	Clinical trial	ADSC-CM topical after 3 sessions fractional CO2 laser	AS on 13 patients	1 months	**Visual observation**: • Improvement in scar severity based on Goodman & Baron's qualitative global acne grading system • Improvement in quantitative assessment (ECCA score) **Biophysical Evaluations**: • Lower melanin index in combination therapy compared to single therapy • Improvement in skin elasticity, roughness, TEWL, and hydration **Histological examination**: • Increased collagen dermal density **Patient satisfaction**: Good satisfaction after the combination therapy **Adverse events**: minimal erythema Overall, the combination therapy produced superior results.

Abbreviations: ADSC, adipose-derived stem cell; AS, atrophic scar; ATE, adipose tissue extract; BTA, botulinum toxin A; CM, conditioned medium; HFC, hypertrophic fibroblast cells; HS, hypertrophic scar; KFC, keloid fibroblast cells; KS, keloid scar; PRP, platelet-rich plasma; SVF, stromal vascular fraction; TEWL, transepidermal water loss; VSS, Vancouver Scar Scale.

https://doi.org/10.2147/CCID.S511067

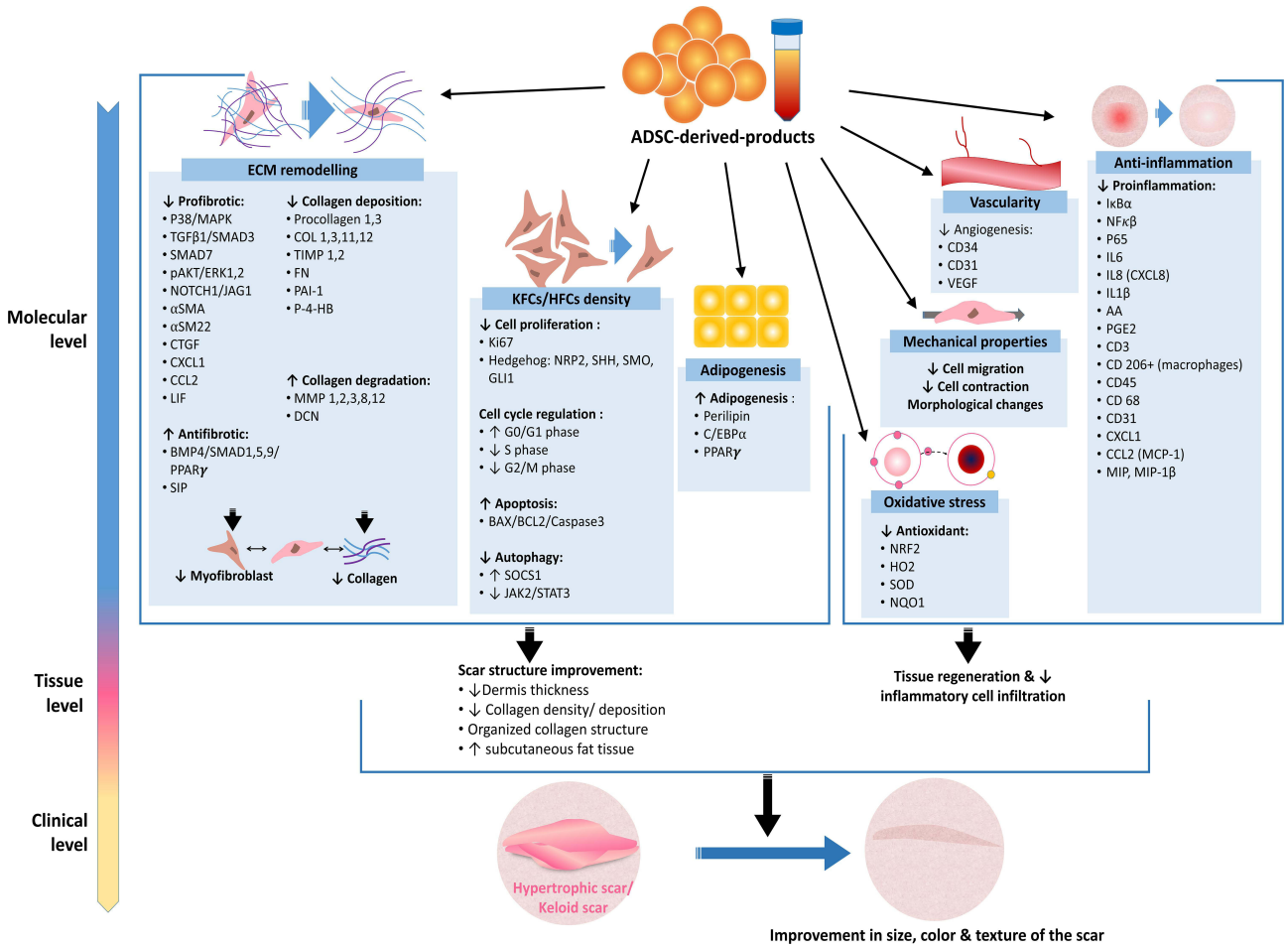

Figure 3 Molecular to clinical changes of hypertrophic or keloid scar with ADSC products intervention.
Notes: ↑ indicates an upregulation of molecular expression or an increase in clinical parameters, while ↓ indicates a downregulation of molecular expression or a decrease in clinical parameters.

MMP-2, MMP-3, MMP-8, and MMP-12, while downregulating TIMPs, the inhibitors of MMPs.[44,48,56] Moreover, P-4-HB expression was downregulated by ADSC products, a protein that stabilizes the collagen triple helix structure.[47] ADSC products decrease collagen accumulation by reducing the activity of fibronectin (FN) and PAI-1 while increasing Decorin (DCN), a small leucine-rich proteoglycan that promotes collagen degradation and inhibits excessive collagen formation.[51,52,54] The presence of DCN in fibroblasts further reduced α-SMA activity, contributing to its anti-fibrotic effect.[51,54]

Consequently, the molecular-level ECM remodeling induced by ADSC products led to improved scar phenotypes at the tissue level. Previous studies demonstrated that ADSC products decreased collagen density and deposition while improving collagen structure, resulting in more organized collagen fibers within the tissue.[12,20,34] This process contributed to a reduction in dermal thickness.[19,32]

Cell Density Regulation

KFC and HFC play a central role in forming fibro-proliferative scars characterized by excessive proliferation and apoptosis resistance.[12,21,37,44] This abnormal cellular behavior is driven by pathways such as the Hedgehog signaling pathway involving NRP2, which regulates SHH, SMO, and GLI1, and is marked by the overexpression of Ki67, a proliferation marker.[12,45]

ADSC products mitigated this abnormal proliferation by leading to cell cycle arrest in the G0/G1 phase and reducing progression through the S and G2/M phases, thereby decreasing cell growth.[38,52] Additionally, ADSC products enhanced apoptosis by triggering the BAX/BCL2/Caspase3 pathway.[12] Through inhibition of the JAK2/STAT3 pathway

by SOCS1, ADSC products also suppressed autophagy, collagen deposition, cell migration, and cell proliferation.[37] By regulating these pathways, ADSCs effectively reduce the density of KFCs and HFCs, therefore reducing collagen density at the tissue level and contributing to decreased dermis thickness.[34,56]

Adipogenesis

Restoring the subcutaneous adipose layer is essential to alleviate fibro-proliferative scars. The presence of adipocytes within the scar contributes to these improvements due to their crucial roles in regulating metabolism and immunity and promoting wound repair.[19,32] ADSCs stimulated adipogenesis, as evidenced by the upregulation of subcutaneous regeneration marker perilipin, along with adipoblast differentiation markers such as C/EBPα and PPARγ.[19,32] Following the restoration of the subcutaneous adipose layer and alterations to dermal ECM components, the overall scar texture was enhanced.

Angiogenesis

Fibro-proliferative scars were frequently characterized by abnormal angiogenesis, contributing to their persistence and severity. ADSC products inhibited endothelial cell angiogenesis to suppress scar development.[45] ADSCs were shown to downregulate key angiogenic markers, including vascular endothelial growth factor (VEGF), which played a central role in promoting angiogenesis and markers such as CD34 and CD31.[11,18,56] This reduction in angiogenesis helped decrease excessive blood vessel formation within the scar tissue, contributing to the normalization of the scar tissue and supporting overall tissue regeneration.

Antioxidant Regulation

Elevated reactive oxygen species (ROS) levels were detected in HFCs and KFCs.[12] ADSC facilitated regeneration by inhibiting antioxidant defense mechanisms within the scar tissue through the downregulation of NRF2, a crucial protein in antioxidant signaling[12] This suppression resulted in reduced activity of antioxidant enzymes, including superoxide dismutase (SOD), NAD(P)H: quinone oxidoreductase 1 (NQO1), and heme oxygenase 1 (HO-1). Consequently, the accumulation of ROS increased, leading to enhanced cell apoptosis within the fibro-proliferative scar.[12]

Mechanical Properties Modulation

The mechanical properties of scar tissue, including cell migration and contraction, are crucial to the formation and persistence of hypertrophic and keloid scars. ADSC products have been shown to reduce the migration rate of KFCs and HFCs.[37] In contrast, they enhanced cell migration in normal fibroblasts, which is essential for wound healing.[47] These differential effects on cell migration were likely influenced by the PI3K/AKT, MAPK, and SOCS1/JAK2/STAT3 pathways.[12,37]

Previous studies also indicated that myofibroblasts exhibited high contractile activity, contributing to scar contracture.[43] Wound contraction occurs after skin damage, marked by skin tightness.[48] ADSCs inhibited this contractile activity, which was associated with reduced scar contracture at the tissue level.[43,48,52] These phenomena were likely due to the changes in cell morphology observed with ADSC therapy, where cells exhibited a more regular shape and narrower intracellular spaces, in contrast to the wider morphology seen in cells without ADSC treatment.[55]

Anti-Inflammatory Effects

Inflammation influenced scar formation, particularly in the development of hypertrophic scars associated with excessive wound repair. This process resulted from a combination of local inflammation and abnormal cytokine secretion.[46,48] IL-10, a multifunctional cytokine known for regulating cell growth and differentiation, played a pivotal role in inflammatory and immune responses and was recognized as an inflammation and immunosuppressive factor.[44,46] In studies where ADSC was modified with IL-10, it was demonstrated that ADSC significantly reduced the expression of macrophage inflammatory protein (MIP), MIP-1β, IL-1β, and IL-6, all of which are critical mediators of inflammation.[46,48]

Additionally, ADSC-treated cells exhibited a decrease in other immune markers, including CD45 and C31, a marker for white blood cells, CD3 for T lymphocytes, CXCL1 for neutrophils, MCP-1 (CCL2) for monocytes, and CD68 and CD206 for macrophages, indicating reduced immune cell infiltration at the site of inflammation.[32,44,54]

ADSC also suppressed the NFκB inflammatory pathway by regulating the levels of p-IκBα/IκBα and p-p65/p65, critical indicators of NFκB activity, which led to decreased levels of pro-inflammatory cytokines, such as IL-1β and IL-6.[46] Furthermore, ADSC was shown to modulate arachidonic acid (AA) and prostaglandin E2 (PGE2), both of which are essential mediators in the inflammatory process.[21] This modulation contributed to the overall anti-inflammatory effects of ADSC in the hypertrophic and keloid scar, thus promoting tissue regeneration.

ADSC Products for Atrophic Scar

Our systematic search has identified several clinical-level studies on atrophic scars. We identified that current studies research atrophic scars at the clinical level using SVF and microfat therapies. The results of SVF treatments involving 30 patients include improvements in scar severity index, scar area percentage, scar depression, and texture. Increases in epidermis thickness and collagen density were also noted.[58] Biophysical and histological examinations further revealed improved epidermal thickness, enhanced collagen density, a better dermal-epidermal junction, and indications of collagen remodeling.[58,60] Skin hydration also improved and patients reported good satisfaction with the treatment.[30,60] In studies involving microfat with 43 patients, the treatment was associated with good satisfaction outcomes.[59] Overall, ADSC products at the clinical level did not show adverse effects or exhibited only expected minimal side effects such as minor pain, brief edema, and erythema.

The exact mechanisms by which ADSC affected atrophic scars are not fully understood. However, existing studies emphasized the significant role of TGF-β1 signaling and inflammation in the development of atrophic scars.[13] Atrophic scars occur due to severe collagen and elastic fiber degradation in the dermis, followed by incomplete healing. This mechanism was related to a marked decrease in epidermal proliferation and elevated inflammation, fueled by T-helper cells and innate immunity.[13] The marked elevation of TGF-β1 further implicated it in these pathological processes. By regulating ECM, TGF-β1 signaling, and inflammation differently from normal fibroblasts, ADSC products have been demonstrated to alleviate scarring in hypertrophic and keloid scar models.[13] ADSC products also prevent collagen degradation by reducing MMP expression, which results in increased collagen density.[58] This suggested that ADSC may, presumably in the opposite effect, similarly regulate these variables in atrophic scars. Further research was crucial to explore and confirm these mechanisms (Figure 4).

Combination and Comparison to Other Treatments

Research has increasingly focused on combination therapies involving ADSC products and other therapeutic modalities to improve clinical efficacy. Combinations with fractional CO_2 laser or botulinum toxin A have been explored for hypertrophic scars. Cai et al reported that combining ATE injections with fractional CO_2 laser significantly outperformed the individual therapies in a rabbit ear model. However, ATE alone was more effective than laser therapy, and the combination therapy did not show a significant difference in adipogenesis expression compared to ATE alone, indicating that ATE monotherapy could be sufficiently effective in treating hypertrophic scars.[19] In contrast, a study by Xiao et al demonstrated that SVF-gel combined with fractional CO_2 laser yielded superior results in animal and human studies, improving scar texture, quantitative assessment, and reducing itch symptoms. This combination therapy was also found to be more effective than the standard treatment of triamcinolone acetate injection with laser therapy. However, in terms of adipogenesis, SVF gel monotherapy outperformed laser monotherapy.[23] Additionally, Qian et al found that combining SVF-gel injection with Botulinum Toxin A produced better outcomes than SVF monotherapy, even though the difference between combination therapy and SVF monotherapy was insignificant. Nevertheless, it was discovered that botulinum toxin A monotherapy produced the best results.[20] These findings suggest that Botulinum Toxin A as a therapy for hypertrophic scars warrants further clinical exploration to understand its potential fully. Moreover, another combination therapy using photo-modulation therapy and ADSC-CM has shown promising results. This combination was safe and yielded superior outcomes in keloid and hypertrophic scar models compared to monotherapy.[16] However, this study was conducted in vitro, indicating that further exploration and validation in clinical settings are necessary to confirm its effectiveness. Based on these findings, combination therapies for hypertrophic scars can lead to varying outcomes, highlighting the need for further exploration, particularly at the clinical level.

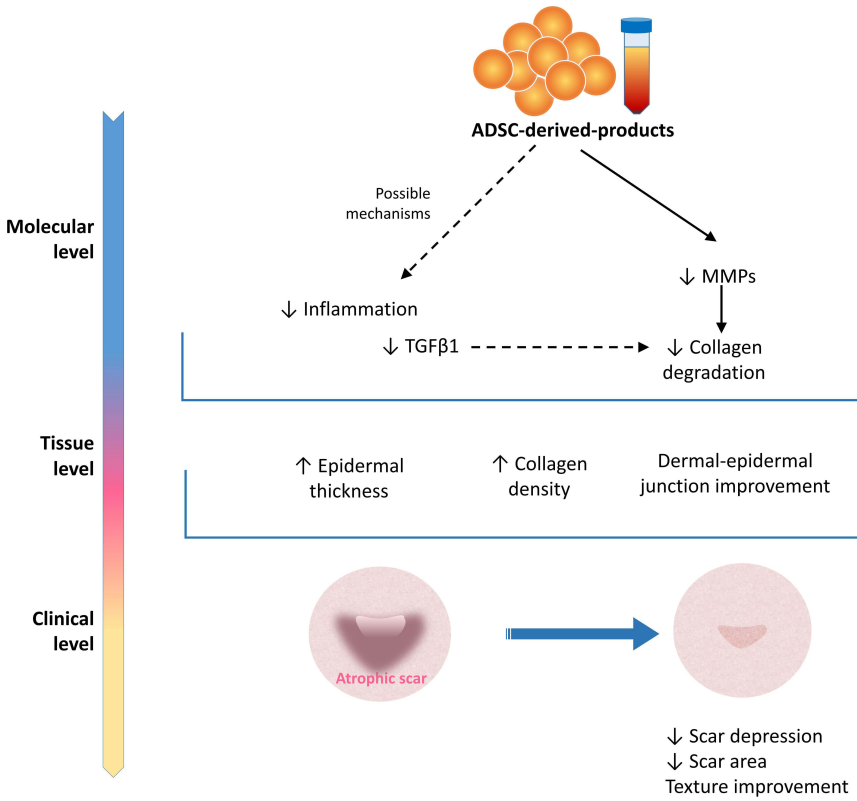

Figure 4 Molecular to clinical changes of atrophic scar with ADSC products intervention.
Notes: ↑ indicates an upregulation of molecular expression or an increase in clinical parameters, while ↓ indicates a downregulation of molecular expression or a decrease in clinical parameters.

Combination therapies involving ADSC products have been investigated at the clinical level for atrophic scars, particularly with fractional CO_2 laser and PRP combined with autologous fat grafting. Roohaninasab et al observed that combining SVF injections with fractional CO_2 laser in post-burn atrophic scars significantly improved skin density, epidermal thickness, and overall patient satisfaction.[61] These findings were further supported by Zhou et al highlighting that ADSC-CM after fractional CO_2 laser treatment in patients with atrophic scars improved scar severity and skin elasticity and increased collagen density, all with minimal adverse effects.[63] Additionally, Nilforoushzadeh et al extended these findings by demonstrating that the combination of SVF injection with PRP and autologous fat grafting enhanced skin quality, including improvements in elasticity and melanin content, along with high levels of patient satisfaction.[62] Overall, these results suggest that combination therapies for atrophic scars show promising outcomes. Nevertheless, other results by Eitta et al showed that ADSC monotherapy was as effective as three sessions of fractional CO_2 laser treatment based on improvements in scar severity, decreases in scar area percentage, enhanced skin hydration, and overall treatment satisfaction.[30] In addition, the findings by Elkakhy et al revealed that PRP monotherapy was superior to SVF monotherapy[60] (Table 4).

Modified ADSC

Technological advancements also enable the enhancement of ADSC therapies through various modifications. Current research includes preclinical models investigating ADSC products enriched with TGFβ3, IL10, and miRNAs or loaded into electrospun membranes for treating hypertrophic or keloid scars. The combination of ADSC-enriched-TGFβ3 & IL10 demonstrated superior outcomes by further reducing cell proliferation, enhancing cell migration, reducing cell viability and increasing apoptosis, reducing cellularity and vascularity, and anti-fibrotic effects by increasing the expression of MMP-1, MMP-8, and MMP-12, while decreasing both COL3A1 and COL1A1 expressions.[44]

Meanwhile, ADSC-enriched-TGFβ3 significantly reduced cell proliferation and viability, enhanced cell migration, diminished cellularity and vascularity, and anti-fibrotic effects by increasing the expression of MMP-1 and MMP-12 expression while decreasing COL3A1 expression.[44] Conversely, ADSC-enriched-IL10 also reduced cell proliferation and viability; and diminished cellularity and vascularity; but was more effective in inducing apoptosis and an anti-fibrotic effect by elevating MMP-1 while reducing α-SMA expression.[44] Further studies have demonstrated that ADSC-enriched-IL10 can reduce proliferation and migration, exhibit anti-inflammatory effects via NF-κB pathway suppression, and display anti-fibrotic properties through the TGF-β/Smads pathway.[46]

ADSC-exo enriched with specific miRNAs show promising results. For example, ADSC-exo-miR-125b-5p exhibits anti-fibrotic activity via the miR-125b-5p/SMAD2 pathway, reducing cell migration and proliferation.[41] ADSC-exo-miRNA7846-3p decreases cell viability, proliferation, and apoptosis resistance, suppresses angiogenesis, and inhibits the Hedgehog pathway.[45] ADSC-exo-miR-192-5p and ADSC-exo-miR29a also reduce migration, proliferation, and viability and show anti-fibrotic effects.[38,40] Moreover, ADSC-conditioned media (ADSC-CM) loaded in electrospun membranes has decreased cell proliferation, migration, and fibrosis.[50]

Research on these approaches in hypertrophic and keloid scar models remains limited, particularly at the clinical level, and to our knowledge, trials have yet to be conducted on atrophic scars. Further exploration of these strategies is necessary to understand their potential and efficacy fully.

Challenges and Limitations

This review discusses the effects of ADSC products on pathological scars in general without specifying the impact based on the type of therapy. It is recognized that the type and concentration of ADSC products may influence their effectiveness; however, the lack of detailed information on these factors highlights the need for further studies. We have yet to identify any preclinical research on atrophic scars, possibly due to the challenges in creating representative preclinical models. Additionally, further exploration of combination therapies or modifications of ADSC products at the clinical level is needed, as treating pathological scars remains challenging and requires significant advancements.

Conclusion

ADSC products can improve hypertrophic and keloid scar texture and severity by remodeling the ECM, regulating cell density, promoting adipogenesis and angiogenesis, modulating mechanical properties, regulating antioxidants, and exerting anti-inflammatory effects. ADSC products have also shown potential in improving atrophic scar texture and severity, as demonstrated by increased scar depth; however, the underlying mechanisms require further exploration. While modifications or combinations of ADSC products may enhance their effectiveness, further exploration at the clinical level is necessary.

Acknowledgments

We express our gratitude to the Faculty of Medicine, Universitas Padjadjaran, for their invaluable support in completing this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The author(s) report no conflicts of interest in this work.

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