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REVIEW

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A comprehensive evaluation of dermal fibroblast therapy in clinical trials for treating skin disorders and cosmetic applications: a scoping review

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Abstract

Background Fibroblast cells have the ability to improve skin conditions through regenerative medicine and cell-based therapies. The purpose of this scoping review is to assess the contribution of fibroblast cells to skin homeostasis and extracellular matrix deposition in clinical trials involving skin disorders and cosmetic applications.

Methods Using targeted search terms, published publications from January 2000 to August 2023 that addressed fibroblast uses in clinical trials of skin conditions were obtained from bibliographic databases like PubMed, Scopus, and Web of Science (WoS). Precise inclusion and exclusion criteria were used during the screening process. The potential benefits of induction treatment with fibroblasts lead to the choosing of clinical trials for this kind of treatment.

Results Out of the 820 published ppapers initially identified, only 35 studies fulfilled our meticulous eligibility criteria after careful screening. To ensure clarity, we methodically eliminated any duplicate or irrelevant published papers, thereby offering a transparent account of our selection process.

Conclusion This study highlights the advantages of fibroblast therapy in treating skin conditions such as diabetic foot, venous leg ulcers, and cosmetic reasons. Fibroblasts possess remarkable regenerating capabilities, making dermal fibroblast therapy crucial in cell-based and skin regenerative treatments. Nevertheless, additional research is required for more disorders and cosmetic applications.

Keywords Clinical trial, Regenerative Medicine, Fibroblasts, Skin diseases, Wound healing

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Introduction

The human integumentary system, comprising the skin, is a complex organ system that serves as a protective barrier to the body's internal environment [1]. The skin contains three layers: epidermis, dermis, and hypodermis, each with sublayers that perform different skin physiological functions. Among skin layers, the dermis layer is composed primarily of fibroblasts, which maintain the integrity of its connective tissues. There exist three main categories of fibroblasts, and each of these categories includes several subgroups or clusters. Fibroblasts can be broadly classified into distinct groups. Specifically, these three categories consist of ten primary variants, which together make up 92.5% of the fibroblast groups that were analyzed using single-cell RNA sequencing (scRNA-seq) [2]. The classification of fibroblasts into three distinct types, namely papillary fibroblasts, reticular fibroblasts, and dermal-subcutaneous junction fibroblasts, is based on their precise positioning within the dermis. The various attributes of cutaneous fibroblasts are evident in the multitude of cell types (Fig. 1) [3]. Given their common features that confirm them as fibroblasts, they have different potentials (Fig. 1). Ernst Ziegler and Rudolf Virchow first identified fibroblasts as cells generating fresh connective tissue in wounds, and they were later characterized as cells that adhere easily to cultures and proliferate with nourishment [4]. When activated, fibroblasts can change their shape from elongated and pointed to a star-shaped configuration [5]. Most of the body's fibroblasts originate from precursor cells in the paraxial and lateral plate mesoderm, while the dermal fibroblast cells of the craniofacial structures originate from cranial neural crest cells [6]. There are no standard cell markers for fibroblasts, as their markers vary according to subtype and location in the tissues/organs. For instance, cancer-associated fibroblast markers include CD44, CD49b, CD87, CD95, and Ly-6 C [7], while cardiac fibroblast markers include PDGFRα, MEFSK4, DDR2, CD90, and Sca1 [8]. Interestingly, mesenchymal stem cells and dermal fibroblasts exhibit a similar surface marker expression pattern [9]. However, fibroblast separation or confirmation in various studies often relies on typical markers such as platelet-derived growth factor receptor alpha (PDGFRA) [10, 11], but this marker is not exclusively seen in fibroblasts and can also be identified in cells of the central nervous system [11]. By excluding hematopoietic and non-fibroblast cell lineage markers, fibroblasts can be identified through lineage exclusion [6, 12], although this method may encompass non-fibroblast cells if all non-fibroblast cells are not meticulously excluded [11]. However, dermal fibroblasts demonstrate significant Vimentin expression while predominantly negative for Desmin. Additionally, papillary and reticular fibroblasts are positive for CD_{34} [3]. The presence of fibroblasts is crucial

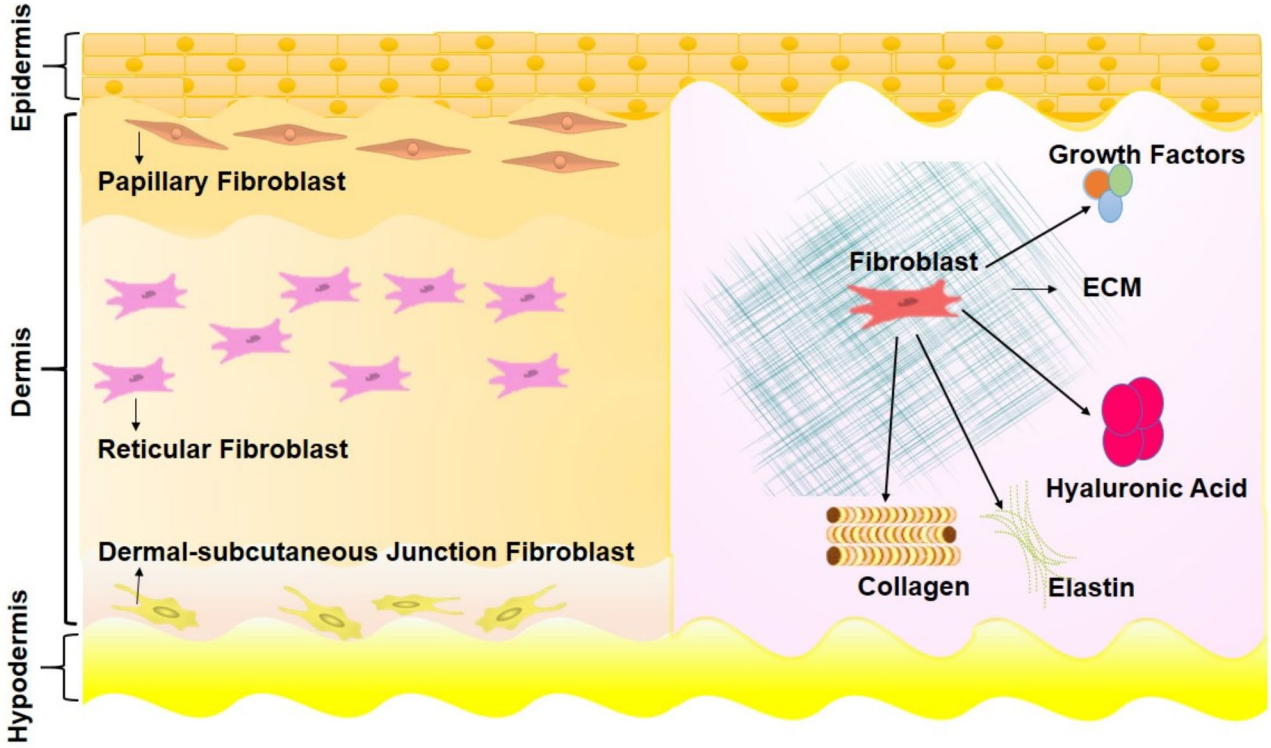

Fig. 1 Fibroblasts support neighboring cells through ECM structure, mechanics, and physiology, as well as by releasing growth factors, cytokines, and metabolites

for many vital organ functions as they construct and preserve connective tissues and the extracellular matrix (ECM). The fibroblast's function is to support neighboring cells through the structure, mechanics, and chemistry of the ECM and by secreting growth factors, cytokines, and metabolites [4, 13]. As mesenchymal cells, fibroblasts develop signaling niches via biophysical and biochemical signals [6]. Indeed, fibroblasts make heterogeneous populations in different parts of the body and display a wide range of phenotypes and functions. Several studies have been conducted on their role in the physiological and pathological activities of the skin [11]. Fibroblasts are unique dynamic cells that can transform into myofibroblasts, function as signaling cells for tissue stem cells, and serve as precursors for specialized mesenchymal cells [6]. The biomechanical input, for example, promotes fibroblast proliferation and induces myofibroblast formation [3]. Despite fibroblasts' crucial role in skin health and tissue repair, their diverse nature and intricate roles challenge consistent identification and understanding. Healthy skin requires the activation of fibroblasts in the dermis to maintain its structure and function. In addition to depositing and organizing the ECM, fibroblasts release growth factors and cytokines and modulate immunity. It is crucial for tissue repair and dermal remodeling that fibroblasts migrate to the injury site. Since fibroblasts are involved in wound healing at an early stage, interact with other efficient cells, synthesize biofactors, and are related to myofibroblasts, they are believed to play a critical role in wound healing (Fig. 2) [3]. Several case reports confirm that fibroblast therapy is a safe and effective option for improving diabetic foot ulcers [14–16]. For instance, a recent case study found that plating normal human fibroblasts on a spongy matrix of hyaluronic acid (HA) and atelocollagen as an allogeneic cultured dermal substitute significantly improved the treatment duration of diabetic foot ulcers [16]. Moreover, research has demonstrated that fibroblasts can be reprogrammed to become induced pluripotent stem cells (iPSCs) or adipocytes [17, 18]. In recent years, several cell-based therapies have been developed based on fibroblasts and their regenerative properties for specific therapeutic purposes, especially for wound healing and cosmetic purposes [19, 20]. Moreover, autologous dermal fibroblast therapy is also used in many other fields, such as gene engineering cell-based therapy, skin tissue engineering,

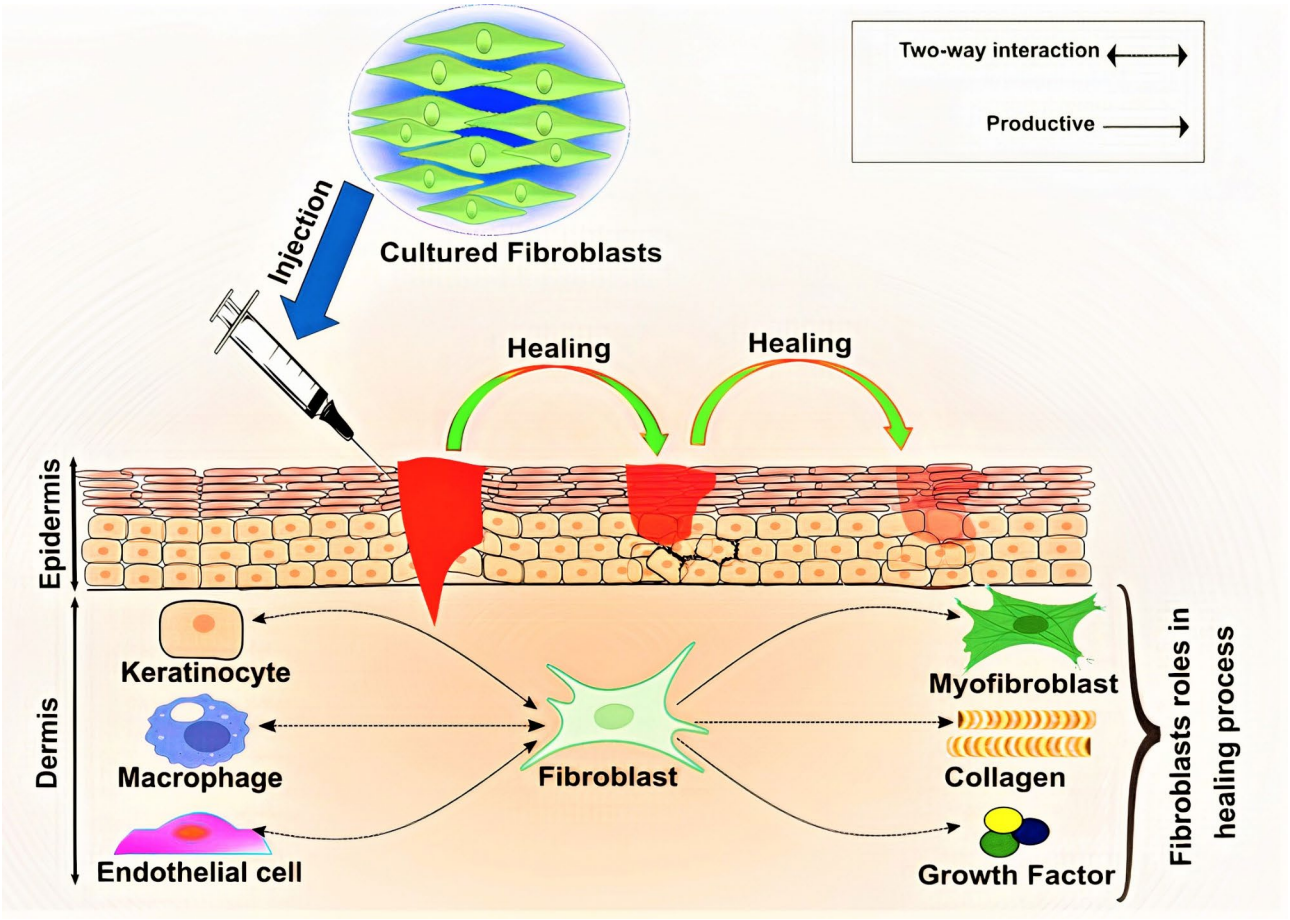

Fig. 2 Fibroblasts support wound healing by creating ECM, collagen, and contracting the wound

and plastic surgery. It should be noted that some fibroblast-based products, including LAVIV® (Azficel-T) and GINTUIT®, have received FDA approval for clinical use [21]. The unique properties of these products allow them to be used safely and effectively for their specific medical purposes. Given the critical fibroblasts' roles in skin health and the emerging clinical approaches that give significant hope for cell-based and regenerative therapies, it seems necessary to review clinical trials involving fibroblast cells. This scoping review focuses on the therapeutic potential of fibroblast therapy for treating different skin disorders. As part of this study, we aim to identify the most effective methods of fibroblast therapy for treating various skin disorders. Therefore, this review provides a valuable resource for further exploring fibroblast cells' therapeutic potential.

Methods

The PRISMA guidelines were followed during the execution of our review paper.

Search strategy and article selection

A comprehensive exploration of pertinent information was conducted across three prominent databases: pubMed, Scopus, and web of Science (wos) platform. The following terms were used for searching each database: ["fibroblasts" or "fibroblasts/transplantation" or "fibroblast therapy"] and ["skin diseases" or "dermatoses" or "dermatosis" or "wounds"] and ["clinical trials"[mesh] or "clinical study"]. The search parameters were limited to english-language publications, including papers, within the timeframe spanning from 2000 to 2023. First, duplicate articles were identified and removed. Two independent reviewers evaluated the abstracts and titles of the identified articles during the screening progression. Exclusion from further consideration was given to studies deemed irrelevant. Following that, the two initial reviewers examined the entire texts of the selected studies to assess if they met the criteria. In case of differing judgments, a third reviewer was brought in to reconcile and ensure the accurate choice of qualified studies.

Inclusion and exclusion criteria

We primarily comprised randomized controlled trials (RCTs) in English. PICOS criteria were considered for eligible clinical studies. These trials were selected that used fibroblast cells as a treatment to tackle various skin diseases. We considered trials published from "the year 2000 to 2023. In contrast, specific criteria were established for exclusion from our study. These criteria encompass studies that did not follow the randomized controlled trial design and research forms, such as review papers, editorials, conference abstracts, and non-English publications. We applied these exclusion criteria to ensure the quality and relevance of the studies in our analysis.

Data extraction

Two independent reviewers extracted data about critical attributes. These attributes encompassed the lead author, publication year, geographic location, trial registration number, disease category, trial phase, efficacy outcomes, safety considerations, and the origin of fibroblast cells.

Quality assessment

The risk-of-bias assessment tool from the Cochrane Handbook (version 5.3.0) was used to evaluate the methodological quality of studies on chronic wounds and cosmetics. Six areas were assessed by the tool, namely random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting risk. Cochrane RevMan version 5.3 was used to generate risk of bias figures (The Nordic Cochrane Centre, Copenhagen, Denmark).

Result

Literature search

Our search efforts generally yielded 820 records, comprising 207 from PubMed, 331 from WOS, and 282 from Scopus. After the elimination of duplicate records, 333 distinct records remained. 258 records were omitted after the initial screening of titles and abstracts. The inclusion criteria led to the exclusion of 40 clinical trial articles that didn't involve fibroblast therapy as a treatment. Finally, we included 35 studies that met the eligibility criteria in this scoping review (Fig. 3).

Study characteristics

We categorized the full-text articles, and the results were grouped into eight segments: 19 studies on chronic wounds, including 2 skin burns, 11 diabetic foot ulcers (DFUs), 6 venous leg ulcers, 5 recessive dystrophic epidermolysis bullosa (RDEB), 9 on cosmetics, and 2 classified under miscellaneous categories.

Quality assessment

The quality assessment findings for chronic wounds and cosmetics studies are graphically represented in Fig. 4 (A and B) and 5 (A and B). In the analysis of nine cosmetic studies, varying levels of bias risk were observed across different domains. For cosmetic studies, random classification generation showed low bias risk in most cases, with some studies having unclear or high risk. Blinding of participants and personnel, blinding of outcome assessment, and selective reporting also exhibited differing levels of bias risk. In chronic wound studies, similar variability in bias risk was noted across domains such as

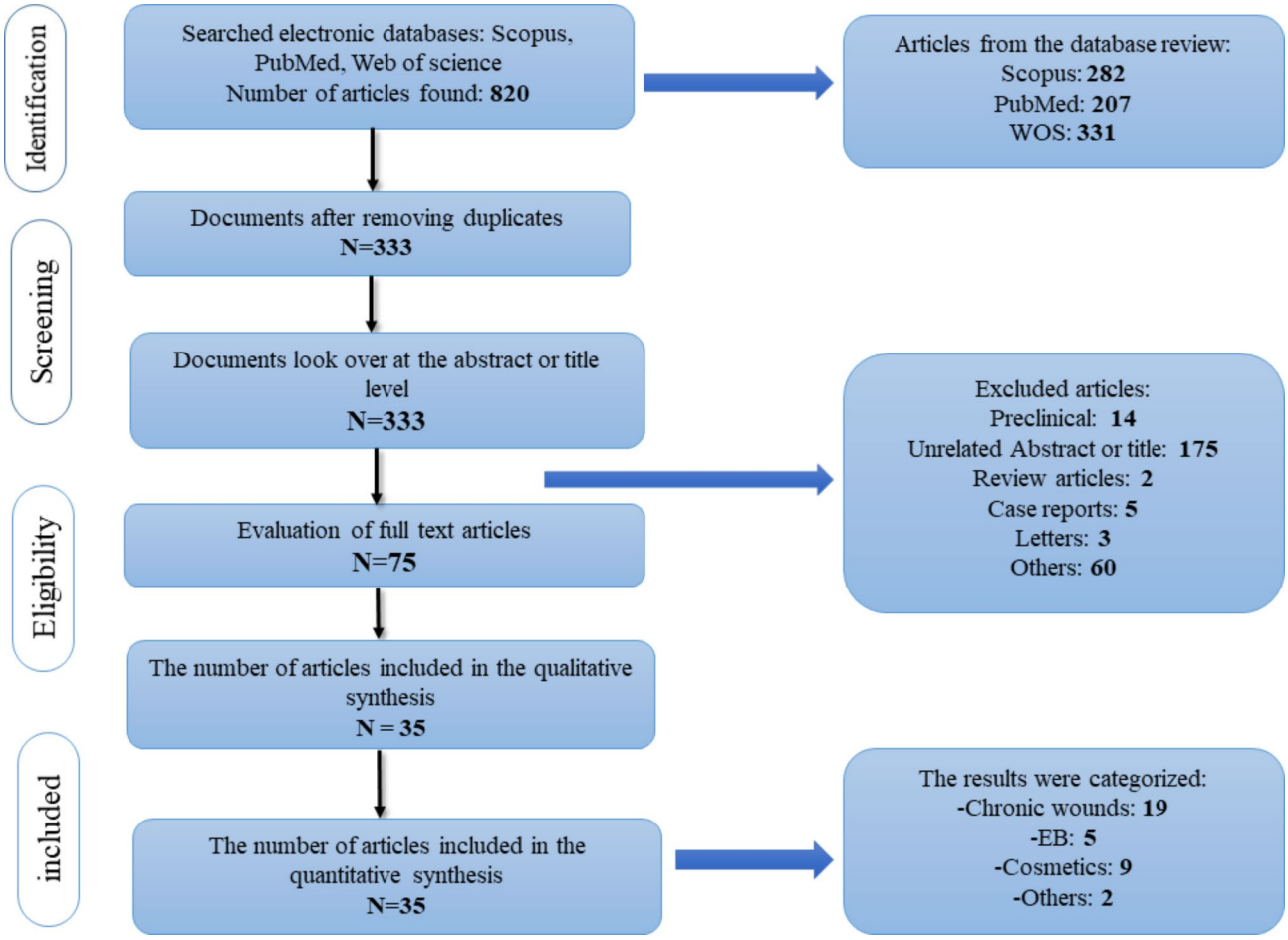

Fig. 3 Flow chart of the literature search, review, and selection of the studies analyzed for systematic review

random sequence generation, blinding, incomplete outcome data, and selective reporting. Random sequence generation generally showed low bias risk in chronic wound studies. Overall, the quality assessment highlights the diverse levels of bias risk present in the included studies on chronic wounds and cosmetics.

Global attention and main points

Fibroblasts have been studied extensively in various countries worldwide, including the United States, United Kingdom, Iran, South Korea and Italy (Fig. 6). The research on fibroblasts has paved the way for innovative therapies, including cell therapy protocols, gene-edited fibroblasts, and iPSCs, demonstrating promising outcomes in treating skin disorders. Furthermore, studies have uncovered fibroblasts' diverse nature and subpopulations, potentially influencing targeted therapy strategies. The research on fibroblasts and their therapeutic potential is ongoing around the world.

Chronic wound

Chronic wounds like diabetic and venous leg ulcers are challenging to heal due to factors like venous insufficiency, diabetes, and impaired mobility [22–24]. Wound depth and length affect chronic wound healing [25]. Fibroblasts, critical in the transplantation of tissue cells, secrete proliferation elements and collagen to aid wound healing. Their capacity to form extracellular matrix structures improves wound repair [26, 27]. Chemotaxis and growth hormones like FGF help fibroblasts migrate to the damage area for wound closure [28, 29]. Fibroblasts also influence keratinocyte movement through epidermal growth factor release, participating in the healing process [30]. Research on fibroblast therapy shows promise in addressing conditions such as burns [31–33], diabetic wounds, scars, and aging skin [34]. Fibroblast treatment clinical trials attempt to improve wound healing.

Diabetic foot ulcer

Foot ulcers affect 15% of diabetics, especially those with acute and unmanageable conditions. Untreated ulcers might induce infections and leg amputation [35]. Men

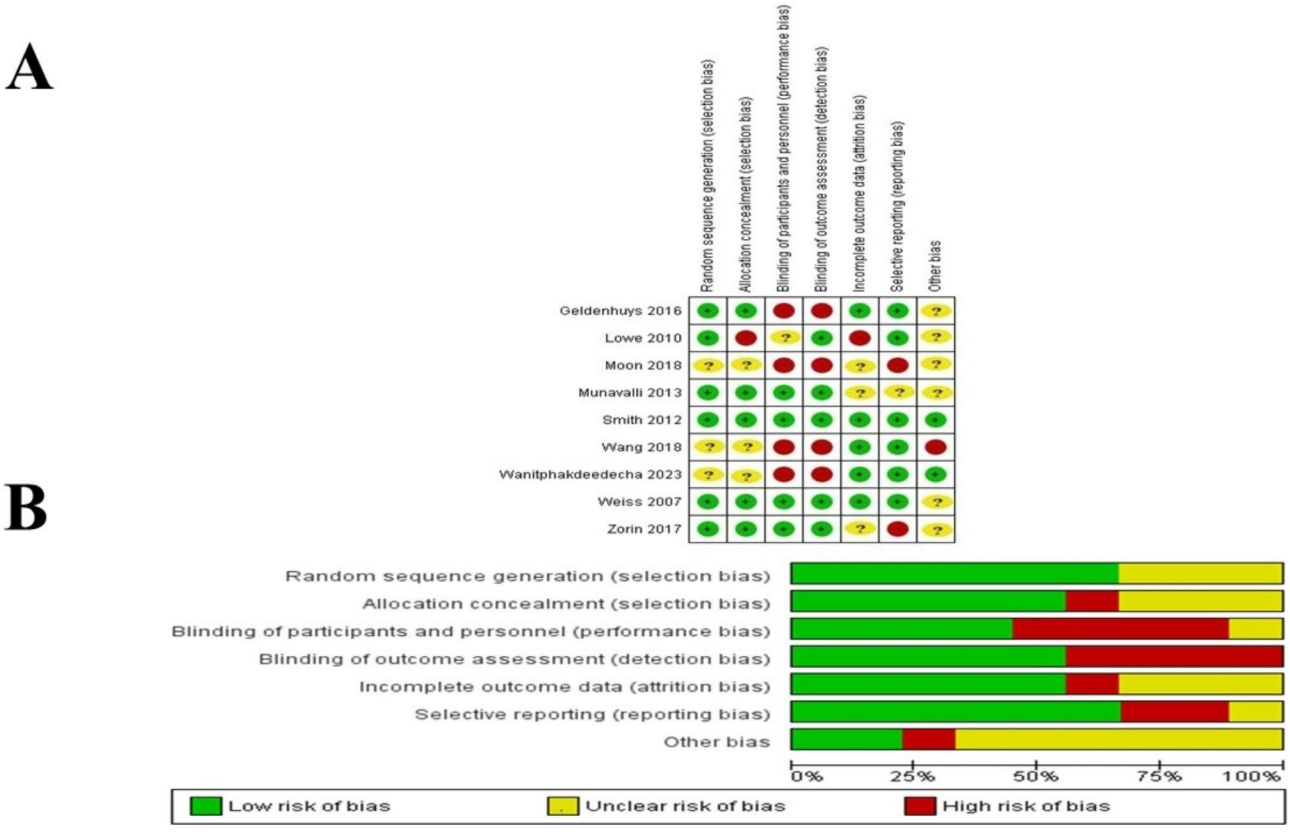

Fig. 4 The outcomes of the quality assessment for cosmetic studies were determined using the risk-of-bias assessment tool delineated in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0). The assessment consisted of two components: (**A**) a summary of the risk of bias, and (**B**) an overall evaluation of the risk of bias

are more vulnerable to this illness than women, and awareness-raising and healthcare use are important [36, 37]. Diabetes, foot ulcers, and other problems can be prevented by better managing diabetes and treating its causes [38]. Diabetic foot ulcers are caused by neuropathy, vascular insufficiency, and secondary infections. Sensory-motor neuropathy can impair foot biomechanics and protect emotions. Vascular insufficiency slows recuperation, causing tissue ischemia. The disease is worsened by secondary infections, often caused by trauma [39]. A system that controls blood glucose may raise sorbitol and fructose synthesis, raising osmotic pressure and lowering nerve transmission, making ulcers more probable [40]. Due to perspiration and autonomic nervous system interruption, diabetes can induce foot dryness and ulcers [41]. The immune system helps repair wounds due to increased cytokine synthesis and active oxygen radicals during secondary illnesses [42]. Due to accelerated products of glycation and enhanced production of cytokines, hyperglycemia causes inflammation and apoptosis [43]. Wound healing and diabetic foot ulcers are greatly affected by MMPs activation and fibroblast death, which lower collagen amounts [44]. Frequent diabetic foot examinations for injury or trauma avoid serious conditions that may result in amputation and speed identification and therapy [45]. Dressing is the main therapy and works with others. Treatment of diabetic foot ulcers employing HSEs is promising. HSE, made of cultivated keratinocytes on a fibroblast-populated collagen lattice, releases growth factors that help diabetic foot ulcers recover [46]. A randomized controlled trial evaluated the effectiveness of Graftskin® (Apligraf®), a living skin equivalent, in treating non-infected, non-ischemic diabetic foot ulcers. This clinical study found that the use of Graftskin® resulted in an 18% increase in complete wound healing compared to the control group [47]. However, HSE is more effective than traditional dressing in preventing the progression of diabetic foot ulcers; its restricted availability hinders its extensive application [35, 47]. A promising new therapeutic approach for DFU involves using stem cells capable of differentiating into various tissues, known as cell-based therapy [48, 49]. This approach can potentially improve healing and lower amputation risk in DFU patients. Fibroblasts play a significant role in DFU, producing the extracellular matrix and promoting wound healing. Disrupted wound healing in DFU can be attributed to impaired angiogenesis, usually due to a decline in angiogenic growth factors, such

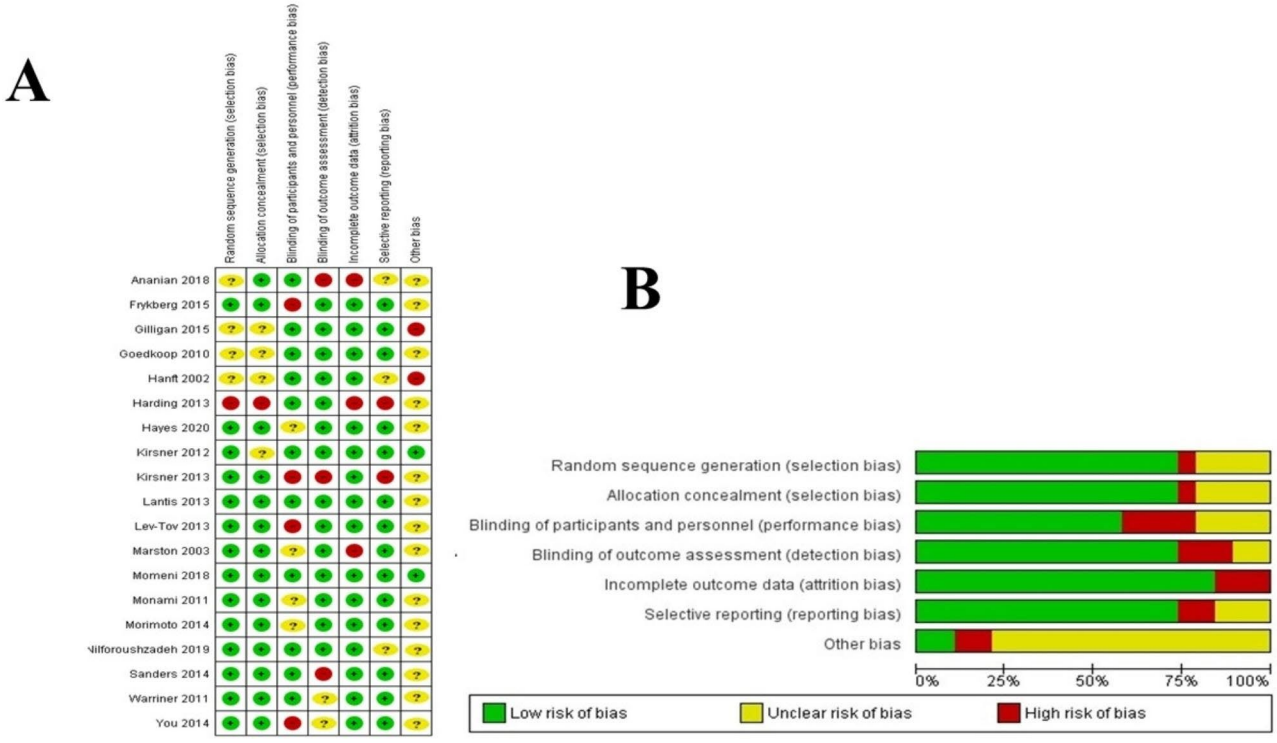

Fig. 5 The outcomes of the quality assessment for chronic wounds studies were determined using the risk-of-bias assessment tool delineated in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.3.0). The assessment comprised two components: (**A**) a summary of the risk of bias, and (**B**) an overall evaluation of the risk of bias

as VEGF and FGF-2. Reduced angiogenic growth factors contribute to fibroblast dysfunction, ultimately causing chronicity and poor healing in DFU [50]. Several clinical trials have demonstrated the efficacy of fibroblasts in treating DFU. (Table 1). As part of the regenerative medicine concept, cells, here fibroblasts, are combined with biomaterials and growth factors [19, 51]. Patients with DFUs were involved in a randomized, controlled study to investigate the effectiveness and safety of the autologous fibroblast-HA complex. The study involved dividing patients into control and treatment groups. An autologous fibroblast-HA complex was administered to the treatment group, while the control group received a non-adhesive foam dressing. The duration of the study was 12 weeks. According to the results, patients in the treatment group saw improvement and had no side effects. Findings from the study demonstrate that using a fibroblast-HA complex derived from the patient's cells can be a suitable treatment option for diabetic foot ulcers, resulting in improved quality of life for patients [52]. Another single-blind study examined the efficacy of human fibroblast-derived dermal substitute (HFDS) and cryopreserved placental membrane (vCMP) for chronic diabetic foot ulcers. During the study, 62 individuals were sampled and randomly divided into two groups consisting of 31 people each, and observed for 9 weeks. According to the results, vCPM is significantly more efficient than HFDS for wounds smaller than 5 cm^2. HFDS heals faster than vCPM. Wounds larger than 5cm^2 saw a slightly higher closure rate with HFDS treatment, although there was no significant difference between the two groups. Moreover, patients who received vCPM experienced fewer side effects, as shown by the study results. Hence, the outcomes of this research indicate that vCPM is a viable treatment alternative, particularly for individuals with a wound surface area of less than 5 cm^2 [53].

Venous leg ulcer

Most leg ulcers, specifically venous leg ulcers, are caused by high blood pressure in the affected area [54, 55]. The severity of this sickness depends on family history, venous problems, weight, and age [56]. This disease reduces quality of life in chronic disease sufferers [57]. From venous blockage to inflammation and persistent edema, the condition increases blood vessel permeability and skin injury [55, 58]. Pressure therapy and wound care are crucial for chronic venous ulcers [59]. Effective therapy requires an appropriate diet, exercise, and wound care. Self-care, combined with blood flow-boosting and blood-clot-preventing medications, can treat This condition takes 6–12 months to treat [60]. venous leg ulcer (VLU) treatment faces challenges like illness recurrence, slow healing, and drug resistance [61]. A growing number of clinical trials have demonstrated the potential of

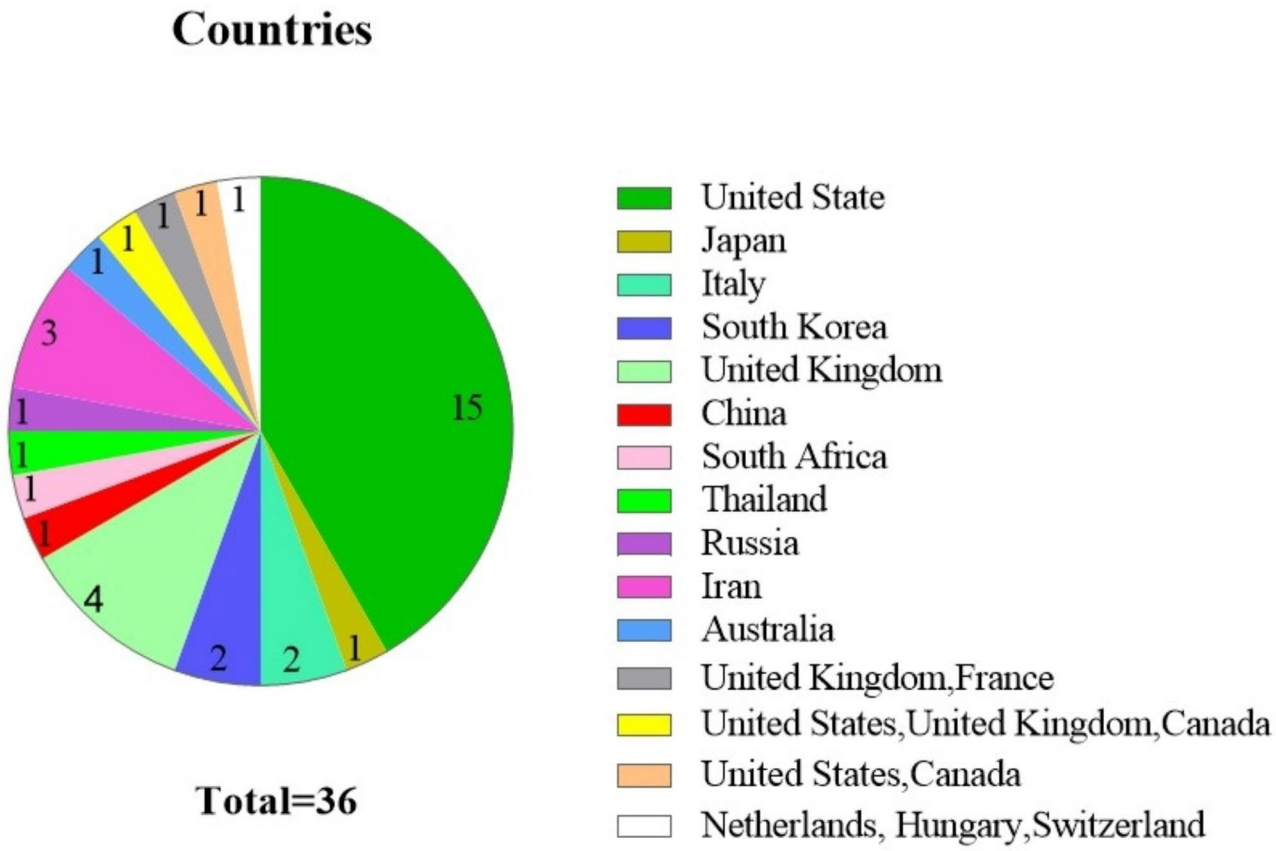

Fig. 6 The histogram depicts the distribution of countries involved in fibroblast therapy clinical trials for skin disorders

fibroblasts to treat this disease, which has attracted a growing amount of interest (Table 2). A clinical trial in 2013 examined the effectiveness and safety of using a HFDS in combination with a four-layer compression dressing to treat venous leg ulcers, comparing it to a four-layer compression dressing alone. The following process was conducted over 12 weeks. Each patient was only examined for one wound, either the largest or selected randomly. The dressing placement varied based on the wound's condition and was monitored throughout the period. In this clinical trial, 366 patients were treated over a few weeks, and patients' progress was assessed weekly. After 12 weeks, HDF was found to have more effect on patients in remission than the control group. Furthermore, the group receiving HDF showed better recovery conditions for cases lasting more than a few months, with consistent results. Even though the target group had a lower rate of adverse side effects, there was no significant difference between the groups with only compression dressing and those with HDF and four-layer compression dressing. In general, HDF may suggest improved safety [62]. The efficacy of HP802-247, a novel cell therapy spray consisting of allogeneic neonatal keratinocytes and fibroblasts, was evaluated in another clinical study for treating chronic venous leg ulcers [63]. Random assignment was used to determine the cell concentrations and dose frequencies of HP802-247 or placebo for patients. The main objective was calculating the average percentage change in wound area after 12 weeks. Active treatment showed a significant mean reduction in wound area compared to placebo, with a dose of 0.5×10^6 cells/ml every 14 days showing the most significant improvement. This cell therapy, at a dosage of 0.5×10^6 cells/ml every 14 days for each patient, was influential in healing venous leg ulcers, as concluded by this study [63].

Burn wounds

Burns can result from flames, hot liquids, chemicals, and hot surfaces. Intricacy and elevated morbidity make burn wounds hard to cure [64]. Recent research shows that burns kill 180,000 people annually. Burns are defined by intensity and skin and tissue damage.

[65]. Epidermis injuries are first-degree. Second-degree burns affect the dermis. But third-degree burns destroy all skin layers and the underlying structures. Fourth-degree burns, which penetrate the epidermis and dermis, can cause necrosis and damage muscle and bone in the subcutaneous area [66]. Burn wounds can cause mental, emotional, and physical problems and death from bacterial infections. Researchers are studying regenerative

Table 1 Clinical trials of fibroblast therapy for diabetic foot ulcers (DFU)

Type of study	Delivery System	Cell type	Outcome	Mechanism of treatment	Ref
Randomized clinical trial	Topical	Human Fibroblast-Derived Dermal Substitute	Cost-effectiveness of ECM therapy compared to HFD, absence of significant difference in clinical effectiveness	ECM materials provide a natural setting for cellular activity, and HFDS provides fibroblasts to help with tissue healing and collagen accumulation, which improves the wound closure process in the final stages.	[54]
Prospective, single-blind, randomized, controlled trial	Topical	Human Fibroblast-Derived Dermal Substitute	Effective wound healing significantly in diabetic foot ulcer patients	HFDD offers a dermal alternative containing fibroblasts, which aid in the production of collagen and the renewal of tissue. This method promotes cellular motility and multiplication at the wound site, resulting in improved wound closure rates and accelerated recovery.	[55]
Prospective, multicenter, randomized, controlled clinical trial	Topical	Human Fibroblast-Derived Dermal Substitute	Effectiveness of human skin allograft compared to HFD.	HFDS functions as a framework that aids in the movement of cells and the regrowth of tissues, while HSA operates as a physiologically functional transplant that improves the formation of epithelial tissue and speeds up the healing of wounds by closely imitating natural skin.	[56]
Open-label, multicenter, controlled	Transplanted	Human Fibroblast-Derived Dermal Substitute	safety and efficacy of HFDS in the treatment of nonhealing DFUs.	HFDS facilitates the healing process in DFUs by offering a framework that aids in the movement, growth, and restoration of cells and tissues. HFDS consists of human fibroblasts that facilitate the deposition of collagen and the replacement of tissues, hence improving the procedure of wound closure.	[57]
Prospective, single-blind, randomized, controlled, phase3	Transplanted	Human fibroblast derived dermal substitute	Dermaghert causes effective improvement compared to routine treatments in people with diabetic foot ulcers	Dermagraft elicits the expulsion of growth factors and angiogenic compounds, enhances fibroblast operation, promotes angiogenesis, helps the migration of keratinocytes, establishes a conducive environment for tissue regeneration, accelerates the pace of epithelialization, and promotes wound closure.	[58]
Prospective, open-labelled, proof-of-concept clinical trial	Transplanted	Autologous fibroblast-seeded cultured dermal substitute	Healing of diabetic ulcers in patients without causing serious complications	AFD secretes growth factors and cytokines that stimulate the formation of new blood vessels and promote the movement of keratinocytes, thus producing a favorable environment for tissue regeneration. By emulating the characteristics of natural skin, it assists in the regeneration of the wound area and expedites the recuperation procedure in comparison to traditional therapies.	[59]
Multicenter, open label, randomized clinical trial	Transplanted	Autologous Skin Fibroblast	Effective healing in most wounds after a few weeks of treatment	Autologous skin fibroblast and keratinocyte transplants improve wound healing by supplying the essential cells needed for tissue regeneration, promoting the growth of new blood vessels, and aiding in the development of a robust protective layer of skin.	[60]
Randomized controlled trial	Topical	human fibroblast-derived dermal substitute	Reducing the incidence of amputation after receiving treatment due to the reduction of infections caused by complications of diabetic foot ulcers	Human fibroblast-derived replacements for skin boost recovery by generating a scaffold rich in fibroblasts, which release growth factors that promote cell migration, expansion, and angiogenesis, thereby minimizing the likelihood of serious issues.	[61]
Multicenter, randomized, single-blind trial	Transplanted	human fibroblast-derived dermal substitute	Patients who received viable cryopreserved placental membrane (vCPM) had a more effective recovery than those who received fibroblasts, and it was also more cost-effective.	The following mechanisms help chronic DFUs recover with vCPM: - providing a biological extracellular matrix for cellular processes. -Boosting fibroblast and blood vessel development. - Production of tissue-restoration growth factors. - Increasing keratinocyte mobility improves wound healing.	[53]
Randomized, single-blind, clinical trial	Topical	bioengineered ECM containing living fibroblasts	There is no significant difference in treatment results between cellular and acellular matrix devices.	Cellular matrix implants consist of living fibroblasts that continuously aid in wound healing by releasing growth factors and facilitating the formation of new blood vessels. On the other hand, acellular matrix devices offer structural reinforcement but do not contain active cellular elements, which could potentially impact the healing procedure.	[62]

Table 1 (continued)

Type of study	Delivery System	Cell type	Outcome	Mechanism of treatment	Ref
Stratified, randomized, controlled, multicenter, phase3	Transplanted	skin fibroblast-hyaluronic acid complex	Observing a higher recovery rate in the treatment group compared to the control group	The autologous fibroblast-hyaluronic acid combination facilitates regeneration by synergistically mixing fibroblasts, which stimulate tissue regeneration, and hyaluronic acid, which moisturizes the wound and improves cell movement, thus providing an ideal milieu for wound closure.	[63]

Table 2 Clinical trials of fibroblast therapy for venous leg ulcers

Type of study	Delivery system	Cell type	Outcome	Mechanism of treatment	Ref
Multicenter, randomized, double-blind, placebo-controlled, explorative, phase II	Spray	Human fibroblasts from discarded tissue from a breast	HP802-247 was effective in terms of efficiency, and the patients recovered within 24 weeks	HP802-247 is derived from human keratinocytes and growth-arrested fibroblasts. Its purpose is to enhance wound healing by creating a cellular matrix. This matrix improves the surrounding milieu for tissue rebuilding and promotes increased activity of fibroblasts and migration of keratinocytes. Promoting the growth of epithelial cells and speeding up the procedure of wound regeneration.	[73]
Multicenter, double-blind, vehicle-controlled, phaseII	spray	Growth-Arrested allogenic fibroblasts	In the treated people, recovery was affected by the time after wound treatment, and in the treatment group, the recovery time was lower than in the control group	This study investigates the effects of multiplication-arrested allogeneic keratinocytes and fibroblasts on angiogenesis and fibroblast reproduction. These cells emit growth factors and cytokines that stimulate the formation of new blood vessels and the growth of fibroblasts. This method improves the healing procedure in venous leg ulcers by enhancing the conditions within the wound and promoting cellular activities that are crucial for tissue restoration.	[74]
multicenter, randomized, vehicle-controlled, phaseII	spray	Human Allogenic fibroblasts	Subjects treated with HP802-247 had significantly improved wound closure compared to standard care. The results were evaluated after a 12-week follow-up	This method improves the movement, growth, and creation of elements in the material surrounding cells, which helps to better close wounds and increase the long-lastingness of healing in chronic venous leg ulcers.	[75]
Open-label, prospective, multicentre, randomised controlled study	Topical	Human fibroblast-derived dermal substitute	A greater number of patients who received the treatment improved over the 12-week period compared to the control group	This technique enhances the mobility, development, and generation of substances in the vicinity of cells, thereby promoting improved wound closure and prolonged recovery in recurrent venous leg ulcers.	[71]
Multicentre, prospective, randomised controlled clinical trial, phaseII	spray	Autologous fibroblast	Skin cell suspension, along with compression therapy, significantly reduces the wound area and effectively heals large wounds	RECELL employs a method of applying autologous skin cells, such as keratinocytes and fibroblasts, using a spray in order to enhance the process of wound repair. This method improves the local wound microenvironment by promoting the movement and growth of cells, aiding in the regeneration of tissues, and enhancing the speed at which venous leg ulcers heal.	[76]
multicentre, double-blind, randomised, placebo-controlled trial, phaseII	Spray	Allogenic neonatal fibroblasts	Reduction in scarring with very low side effects	This technique entails the stimulation of cell multiplication and migration, the release of growth factors that promote the formation of new blood vessels, and the enhancement of the general wound healing conditions in chronic venous leg ulcers.	[72]

medicine and cell therapy to enhance burn treatments by promoting wound healing and skin regeneration, enhancing the quality of life for burn patients, and reducing the need for invasive procedures. In vitro tissue engineering and human skin allografts, especially those from living first-degree relatives, have improved wound healing, decreased microbial wound contamination, and reduced burned individual deaths [67]. Additionally, 3D bioprinting and employing stem cells or fibroblasts to treat and regenerate burn wounds are being studied [51]. Research in regenerative medicine, cell-based therapy, and tissue engineering may improve burn treatment and patient outcomes [19]. Based on our scoping review, fibroblast therapy has been used in clinical trials for healing burn wounds in two published clinical studies and one letter [31–33] (Table 3). The extracellular matrix components such as collagen and elastin, growth factors, and cytokines are produced by fibroblasts and promote cell proliferation, migration, and differentiation [68]. Fibroblasts are being studied as a potential therapy for skin regeneration and burn wound healing [69]. Fibroblasts can be obtained from the patient's skin or a donor source, such

Table 3 Clinical trials of fibroblast therapy for burn wounds

Type of study	Type of Cell	Delivery	Outcome	Mechanism of treatment	Ref.
A randomized, double-blind, phase I clinical trial	Fetal Fibroblast	Transplanted	Improvement in the location of burns in patients after transplantation	Embryonic cell-based skin substitutes boost the healing process and expedite the recovery of donor sites in burn sufferers. They achieve this by offering a physiologically active framework that promotes cell growth, blood vessel formation, and tissue regeneration.	[31]
Open-Label Study phase II-III	Autologous fibroblasts	Injection	Complete recovery of patients after treatment during the period of 12 weeks	Minimal laser therapy enhances cellular activity and boosts circulation, while autologous fibroblast transplantation supplies crucial cells for tissue regeneration, thereby improving the healing procedure for grade 3 burn wounds in diabetes patients.	[32]
phase II	Allogeneic human dermal fibroblasts	Intradermal injection	Improvement in scar condition without adverse effects	Allogeneic fibroblasts induce the synthesis of collagen and elastin. This intervention facilitated the softening and enhancement of the flexibility of the scar tissue, resulting in a decrease in contractions and an enhancement in the visual aspect of the scar.	[86]

as a tissue bank. Allogeneic fibroblasts are a better option than autologous fibroblasts due to a decreased likelihood of donor site morbidity and the ability to obtain many cells for transplantation [70]. Fetal fibroblasts exhibit superior proliferation, extracellular matrix component synthesis, and senescence resistance compared to adult fibroblasts [71]. A study evaluated the safety, feasibility, and potential efficacy of using amniotic membranes seeded with fetal fibroblasts for burn patients to heal their donor sites faster. Ten patients with burns covering 10–55% of their body were enrolled in the study. Each patient's donor site was divided into three equal parts and treated with Vaseline gauze (control group), amniotic membrane (AM group), or amniotic membrane seeded with fetal fibroblasts (AM-F group). According to the results, using amniotic membrane seeded with fetal fibroblasts for treating burn patients' donor sites was safe and significantly sped up the healing process compared to the control group. Fetal fibroblasts have been found to be a promising therapeutic approach for skin disorders, such as burn wounds. Nevertheless, additional research is required to comprehend their effectiveness and safety entirely. More extensive trials are needed with larger populations to draw accurate conclusions [31]. The effectiveness of low-level laser therapy (LLLT) and autologous fibroblast transplantation for healing grade 3 burn wounds in diabetic patients was evaluated in an open-label study. Patients with grade 3 burn wounds and diabetes were enrolled in the study. The treatment protocol involved LLLT and autologous fibroblast transplantation, and the results showed complete healing of wounds within 4–6 weeks without any adverse events. According to the study, using LLLT and autologous fibroblast transplantation together is a secure and efficient cure for grade 3 burn injuries among diabetics. The study indicates that the treatment protocol could be a hopeful therapeutic method for healing burn wounds, especially for diabetic patients who are more prone to complications [32]. Mobility and unsightly appearance are caused by burn contractures, which result from the tightening of the skin and underlying tissues during healing [72].

The United States phase 1/2 clinical trial (NCT01564407) is assessing the safety of ICX-RHY-013 for treating stable, restrictive scars in burn victims [73]. Allogeneic human dermal fibroblasts were utilized to address burn contractures by administering fibroblast injections near the joints. While patients experienced an enhanced range of motion in the contracted joint after 12 weeks, the improvement was not statistically significant in this study. The study suggested that allogeneic human dermal fibroblast injection is safe and well-tolerated, offering a potential nonsurgical treatment for burn scar contractures. Allogeneic fibroblasts, sourced from donors, can be genetically engineered to enhance their potential for wound healing. This approach eliminates the need for harvesting fibroblasts from the patient's skin, making it highly valuable for burn wound treatment [73]. Clinical trials have demonstrated that fibroblast therapy is a more effective treatment for healing burn wounds compared to other approaches, including, low-level laser treatment, pressure garment therapy, hyperbaric oxygen therapy, moist exposed burn ointment (MEBO), and evaluation of adipose-derived mesenchymal stem cells [70, 74, 75]. However, further investigation is needed to determine the protection and effectiveness of fibroblast therapy in various wound-healing contexts.

Cosmetic

Age-related physiological changes include skin texture and function. Wrinkles, folds, and diminished elasticity characterize skin aging. These cosmetic issues can be addressed with various fillers [75]. Some fillers may be more dangerous and ineffective than others. Thus, before using fillers, one must grasp their properties and injection procedures. With the use of fibroblasts, skin cells that produce collagen and elastin, fillers have improved. Fibroblasts have been cultured and injected as fillers to enhance skin quality and reduce aging signs [76, 77]. Owing to the simplicity of the direct fibroblast

injection technique, it has been the subject of extensive research, particularly for its potential to enhance facial aesthetics. Table 4 presents a comprehensive list of published clinical trials on fibroblast therapy for aesthetic purposes, including the number of studies and the time frame of the research.For example, Weiss and colleagues investigated the effectiveness and potential side effects of injecting autologous live fibroblasts to address facial contour defects like acne scars and nasolabial folds. They administered live fibroblasts in three doses, spaced 1 to 2 weeks apart, and assessed the results at 1, 2, 4, 6, 9, and 12 months after the initial injection and compared with placebo. The results show that using live fibroblasts improved skin problems and acne scars more than the placebo. The statistical connotation of this difference was observed at the 6-month mark. Patients who received live fibroblast treatment experienced ongoing positive outcomes, with answer degrees of 75.0% and 81.6% at the 9-month and 12-month check-ins, respectively. Crucially, over 12 months, no severe side effects were reported as a consequence of the treatment [78]. Nevertheless, it is crucial to acknowledge that further research and clinical trials may be necessary to validate and extrapolate these findings to a broader population. Consequently, additional studies focusing on nasolabial folds [76, 79], acne scars [80], and nasojugal grooves

Table 4 Clinical trials of fibroblast therapy for cosmetics

Type of study	Type of cell	Delivery	Outcome	Mechanism of treatment	Ref.
N/A	Autologous PRP mixed with autologous fibroblast	Injection	In the 9-month follow-up, an increase in skin density and thickness, an increase in skin hydration, and an improvement in wrinkles were observed	- The mechanism of operation is based on the combined actions of growth factors and cytokines that are generated from PRP. These substances work together to promote cell development and tissue regeneration. PRP stimulates the formation of new blood vessels (angiogenesis) and the production of collagen. Dermal fibroblasts, on the other hand, offer skeletal reinforcement and release extra growth factors.	[96]
Phase IIa Open-Label Dose-Escalation Pilot Study	Allogeneic fibroblast	Intradermal injection	The increase in patient satisfaction in the 12th week after treatment, along with the low rate of adverse events	Fibroblasts are anticipated to stimulate collagen production and tissue regeneration, hence improving skin suppleness and diminishing the visibility of wrinkles.	[89]
I/II	Autologous fibroblast	Injection	A high rate of recovery in patients after treatment without side effects	Fibroblasts stimulate the synthesis of collagen and facilitate the regeneration of tissues, hence improving the thickness and flexibility of the skin. The objective of this treatment is to enhance the aesthetic look of the nasojugal groove by repairing its structural stability and lowering its depth.	[94]
Randomized multicenter, double-blind, placebo-controlled trial	Autologous fibroblast	Intradermal injection	Fibroblast therapy with a high recovery rate without permanent side effects	Fibroblasts stimulate collagen synthesis and tissue regeneration, resulting in enhanced skin smoothness and a reduced scar appearance.	[93]
Multicenter, Double-Blind, Placebo-Controlled Trial	Autologous fibroblast	Injection	Patients recover after treatment without side effects	Fibroblasts promote the production of collagen and the restoration of tissues, leading to improved skin texture and a diminished appearance of scars. .	[92]
Pilot study	Autologous keratin and fibroblast	Injection	Improvement and rejuvenation of skin wrinkles after treatment, without acute side effects	The process entails placing filler into the dermal layer, which stimulates the production of collagen and tissue regeneration. Keratin offers structural encouragement, whereas fibroblasts promote cell turnover and facilitate healing procedures.	[97]
-	Autologous fibroblast	Injection	Improvement in skin wrinkles after fibroblast treatment	Autologous cultured fibroblast implants function by delivering viable fibroblast cells into the connective tissue, stimulating collagen synthesis and tissue rejuvenation, hence improving skin thickness and suppleness. This method differs from hyaluronic acid (HA) fillers, which generally offer instant volume by virtue of their hydrophilic characteristics.	[95]
III	Autologous fibroblast	Injection	N/A	N/A	[90]
Pilot study	Autologous fibroblast	Injection	An increase in the amount of collagen and skin thickness, as well as an increase in the elasticity of the skin	Autologous fibroblasts, obtained from the individual's own skin, are administered into the specific region to stimulate collagen synthesis and facilitate the process of wound repair. This process enhances regional cellular activity, hence boosting tissue form and performance.	[98]

[81] have been designed to corroborate the applicability of fibroblast injections. Moreover, a separate study comparing autologous cultured fibroblast injections with HA fillers revealed superior improvements in the fibroblast groups without any associated side effects, consistently enhancing aesthetic appearance [82]. These findings have encouraged researchers to explore alternative delivery methods, including combining fibroblasts with other molecules. As a case in point, Geldenhuys and his team combined platelet-rich plasma (PRP) with cultured fibroblasts. They administered a single dose to twenty adults with nasolabial folds and tracked their progress for nine months. The results included an impressive 80% increase in skin thickness adjacent to the nasolabial fold, heightened dermal density, enhanced skin hydration, improved sebum quality, and reduced wrinkle depth. This study underscores the potential of PRP combined with cultured fibroblasts as a viable, long-lasting, and well-received option for non-invasive facial rejuvenation and wrinkle reduction, although direct comparisons with single PRP or fibroblast injections were not made [83]. Expanding upon the investigation of novel combinations, Wang and colleagues conducted a study in which they compared a blend of fibroblast and keratin to HA as a control for the treatment of neck wrinkles in 30 individuals. They administered two doses at two-week intervals and gathered data at multiple time points up to 12 months post-treatment. The findings demonstrated that the fibroblast and keratin mixture maintained a substantial filling effect, ranging from 70 to 90%, even at 12-months. In contrast, HA effects persist for approximately 6 months. These findings indicate that a mixture of fibroblasts and keratin could be a more practical option for reducing neck wrinkles than traditional HA fillers. These results emphasize the importance of continued aesthetic medicine research [84]. A summary of the literature indicates that fibroblasts, alone or in combination with other molecules, significantly affect durable and reliable aesthetic outcomes. Furthermore, fibroblasts have been reported to be safe and well-tolerated without adverse reactions or immunological responses. Additional research is necessary to establish the ideal quantity and dosage of cells for each treatment, compare fibroblasts with approved drugs as control groups, and track patients' long-term outcomes and immunological status.

Dystrophic epidermolysis bullosa

Genetic abnormalities that cause blisters on the skin and mucosa are called epidermolysis bullosa (EB). EB has four primary types: acquired, simple, junctional, and dystrophic, each with many variants [85]. Mutations in the COL7A1 gene produce Recessive Dystrophic Epidermolysis Bullosa (RDEB), an EB variation that can be treated using fibroblast engineering. Lack of type VII collagen and anchoring fibrils in the dermal-epidermal junction (DEJ) causes blisters and soft tissue scarring. RDEB has no cure, so researchers have investigated fibroblasts, which make type VII collagen, as a treatment.

[86]. This section reviews some of the studies mentioned in Table 5. In the realm of cell-based therapies for RDEB, two prominent types are considered: allogeneic fibroblasts, which are cultured from parents or unrelated individuals, and autologous fibroblasts, which are cultured directly from patients themselves. So, in the first clinical study, Wong et al. utilized allogeneic fibroblasts as potential type VII collagen producers. They injected allogeneic fibroblast into the non-wounded skin of 5 subjects with RDEB [87]. 2 to 3 months of follow-up were required. Type VII collagen at the DEJ demonstrated a 1.5- to 2-fold increase, while anchoring fibrils showed a 1.5-fold increase. Autoantibodies to collagen VII were not developed in any of the patients, and skin biopsies showed no significant immune reactions despite their abnormal morphology. Furthermore, they indicate that allogeneic fibroblasts have a significant impact on elevating the recipients' own COL7A1 mRNA levels, resulting in more significant deposition of mutant type-VII collagen at the DEJ and the development of additional rudimentary anchoring fibrils. This mutant protein may possess some functionality and improve adhesion at the DEJ [87]. The injection of allogeneic fibroblasts into chronic wounds in RDEB patients may be a feasible and beneficial therapy for wound healing. However, in cell-based therapy, some clinical trials prefer to employ products that have already been approved. For instance, a suspension of allogeneic human dermal fibroblasts (ICX-RHY-013) has been presented in a sterile solution and contains HypoThermosol-FRS (BioLife Solutions Inc., Bothell, WA, United States). According to the European Medicines Agency, ICX-RHY-013 is classified as an orphan medicinal product designed to treat EB [88]. In a clinical study, ICX-RHY-013 increased initial healing in RDEB wounds. Results showed that a single injection of fibroblasts improved erosion healing within 28 days but not after that [88]. During the other trial, fibroblasts and vehicle injections resulted in a 50% reduction in the area of chronic ulcers after 12 weeks [89]. Other clinical studies have also investigated the benefits of ICX-RHY-013 in improving RDEB wounds, but the results have not been published as an original paper [90, 91]. Possible explanations for these differences are that the two trials used different types of wounds, varied doses and frequencies of injections, varied outcome measures, and different patient populations. The epidermis is affected by erosions, which are superficial wounds, whereas ulcers are deeper wounds that extend into the dermis or subcutaneous tissue. Erosions may heal faster than ulcers but also be more prone to recurrence. In a comparative

Table 5 Clinical trials of fibroblast therapy for dystrophic epidermolysis bullosa

Type of study	Type of cell	Delivery	Outcome	Mechanism of treatment	Ref.
single-center, open-label phase I trial	COL7A1-modified autologous fibroblasts	Intra-dermal injections	Improvement in wound healing and blister reduction during the 12-month follow-up period	The present research employs lentiviral vectors for the delivery of a codon-optimized COL7A1 gene into autologous fibroblasts. This enhances the generation of type VII collagen, which plays a critical role in attaching fibrils to the skin. As a result, it improves skin stability and reduces fragility.	[108]
Phase II Randomized Vehicle-Controlled Trial	Allogeneic and amniotic membrane scaffold	Intra-dermal injections	Reduction in wound size and QWS after treatment during the 2- to 12-week follow-up perio	The utilization of the amniotic membrane scaffold improves the viability, movement, collagen accumulation, and regeneration of fibroblasts in wounds. Allogeneic fibroblasts, when administered, release growth factors and cytokines that promote tissue healing, collagen production, and epithelialization in individuals with dystrophic epidermolysis bullosa.	[106]
prospective, double-blind, randomized, vehicle-controlled phase II trial.	Allogeneic fibroblasts	Intra-dermal injections	Early healing in epidermolysis bullosa wounds without significant difference	Injecting allogeneic fibroblasts into the edges of persistent erosions helps cure the wounds by increasing the proliferation of local fibroblasts, supplying growth factors that encourage the creation of collagen, and boosting the extracellular matrix, which aids in tissue regeneration and healing of the erosions.	[102]
phase II randomized vehicle-controlled trial	Allogeneic fibroblasts	Intra-dermal injections	Faster wound healing and increased collagen expression over a 12-week period	Allogeneic fibroblasts, when injected into the skin, release growth factors and cytokines that help accelerate the healing of local tissues, enhance the production of collagen, and stimulate the creation of new skin cells for individuals with recessive dystrophic epidermolysis bullosa.	[103]
N/A	Allogeneic fibroblasts	Intra-dermal injections	Increasing the expression of collagen and the amount of fibrils	Allogeneic fibroblasts primarily enhance the recipients' own COL7A1 mRNA stages, resulting in increased accumulation of mutant type-VII collagen at the DEJ. This leads to the development of extra-rudimentary anchoring fibrils. The altered protein produced may have some functionality and can enhance adhesion at the DEJ.	[101]

study, Moravvej et al. investigated the efficacy of cultured allogeneic fibroblasts administered via intradermal injection for the treatment of RDEB wounds, juxtaposed against the effects of fibroblasts situated on scaffolds constructed from amniotic membranes (FAMS) [92]. Following periods of 2 and 12 weeks, it was observed that the intradermal injection of fibroblasts demonstrated superior performance in promoting wound healing compared to FAMS. These findings underscore the potential of fibroblast injection as a viable and promising therapeutic strategy for augmenting recovery in RDEB wounds [92]. It is well known that cell and gene engineering approaches are one of the most promising approaches for treating incurable diseases [93]. This vision has led to the design of some clinical trials for treating EB, especially RDEB. Considering this, Lwin et al. designed a self-inactivating lentiviral platform for phase I assessment that carries a codon-optimized COL7A1 cDNA controlled by a human phosphoglycerate kinase promoter [94]. In this open-label trial, four grownups with RDEB were inoculated with modified autologous fibroblasts intradermal three times and followed for a year. Safety, autoimmune responses to recombinant type VII collagen, expression of type VII collagen, and the presence of transgenes were evaluated. Modified fibroblasts showed good tolerance, with no severe adverse reactions or autoimmune responses to recombinant type VII collagen. Regarding efficacy, three out of four subjects showed a significant increase in type VII collagen expression in the injected skin, with two maintaining elevated levels for up to 12 months. Despite the absence of fully mature AFs, transgenes were detected in the subjects' injected skin after a year. In this innovative human study, lentiviral fibroblast gene therapy is proven harmless and possibly effective, as evidenced by the presence of COL7A1 transgene and the renovation of type VII collagen in treated skin one year after gene therapy. As a result of these findings, phase II clinical trials can advance clinical assessment [94]. Our literature review serves as the basis for conducting clinical studies involving more significant numbers of fibroblast cells and participants in individuals with RDEB, paving the way for further research in this area.

Other diseases

In skin repair and regeneration, fibroblasts play an essential role and have also been utilized to regenerate the vulva. The vulva is susceptible to vulvar lichen sclerosis, an inflammatory skin condition characterized by white, patchy, thin skin prone to tearing and bruising [95]. The specific reason for vulvar lichen sclerosus remains unidentified, but it is theorized to be associated with an intense immune system, hereditary aspects, and previous skin injury or annoyance [96]. The early application of topical corticosteroids can potentially prevent vulvar scarring and malformation and also decrease the risk of vulvar cancer [95]. A randomized clinical trial was conducted to determine the effectiveness and safety of human fibroblast lysate cream (HFLC) for treating vulvar

lichen sclerosus. The results demonstrated that HFLC's anti-inflammatory activity could be attributed to the presence of cytokines like IL receptor antagonists (IL-1ra), IL-10, and IL-13, as well as wound-healing growth factors FGFs, VEGF, and EGF. According to the study, HFLC is a viable and effective treatment option for vulvar lichen sclerosus. Instead of potent topical corticosteroids like clobetasol propionate, which cause significant systemic and local side effects, HFLC can be used [97].

As explained later, fibroblasts are responsible for synthesizing and depositing extracellular matrix components, facilitating cell settlement and migration on a three-dimensional (3D) support, thereby contributing to organ-specific architecture development. Additionally, they produce bioactive molecules that participate in various physiological processes, such as angiogenesis and tissue repair. In a clinical trial, autologous three-cellular cultured skin substitutes (CSS) were used to treat ulcers, giant nevi, burns, and tumors. The CSS used in the clinical trial was composed of a structure formed by an epithelial cell surface with melanocytes and a fibroblast basement. This structure was held together by a HA scaffold that could be surgically manipulated and was gradually absorbed and replaced by the host's connective stroma [98].

Future perspectives and challenges

The Cell Therapy Technologies Market is projected to be USD 50.69 billion by 2030, compared to USD 17.02 billion in 2022, with a compound annual growth rate of 14.61% [91]. Some of the most prevalent cell therapies are stem cell therapy, cell vaccines, immuno-cell therapies, fibroblast cell therapies, and chondrocyte cell therapies. In order to improve the concept of fibroblast therapy, several regenerative medicine tools can be used, such as stem cell research, tissue engineering, and genetic engineering [19, 93, 99, 100]. Given that clinical trials have been conducted, significant progress can be achieved in skin cell-based therapies and tissue engineering by using fibroblast cells and their derived products. Nevertheless, the nature of cellular therapies poses some challenges similar to those facing other biological-based therapies. Several factors should be considered, including the threat of immune rejection, ethical concerns, and high treatment costs [48, 101].

A potential breakthrough in this area could involve combining eco-friendly nanoparticles with dermal fibroblast treatment. Green nanoparticles, derived from environmentally benign and renewable sources, provide biocompatibility, antioxidant characteristics, and a minimal environmental footprint, rendering them well-suited for dermatological applications [102]. Their capacity to effectively transport therapeutic substances and improve the functioning of fibroblasts can expedite the process of wound repair and tissue regeneration [103]. Moreover, green nanoparticles exhibit antibacterial characteristics that can reduce the likelihood of infections in skin treatments. These nanoparticles enhance the durability and absorption of active compounds in cosmetic products, hence encouraging healthier skin and offering a sustainable substitute for traditional cosmetic components [104]. Advancements in research may lead to a groundbreaking transformation in skin care. This combination has the potential to provide novel, efficient, and eco-friendly solutions. The incorporation not only tackles certain difficulties linked to cell-based therapies but also corresponds to the increasing need for durable and biocompatible treatment choices in the fields of dermatology and cosmetics. The efficacy of cellular therapies is often limited due to the complexity of cell-based therapies and the limited understanding of cell interactions [19, 101]. One of the main challenges of using fibroblasts as therapeutic biologics is the heterogeneity of fibroblast cells. Fibroblasts, originating from different body parts, can have varying properties [3]. This heterogeneity can make it difficult to standardize the use of fibroblasts in clinical trials. The difficulty of cultivating fibroblast cells for therapeutic purposes was another challenge we encountered during our scoping review. It is important to note that fibroblasts are sensitive to environmental changes and require specific conditions to grow and differentiate into other cell types. Because of this, it is sometimes difficult to produce large quantities of fibroblast cells for clinical purposes due to the limited resources available. There is a need for further research to determine the optimal conditions for using fibroblast cells in clinical trials. These studies must aim to find the most effective source of fibroblast cells, identifying the optimal culture conditions, and developing the most reliable methods for delivering these cells to patients. A standardization of fibroblast use in clinical trials can be achieved by resolving the abovementioned issues. Another approach is to improve the culturing process of fibroblast cells by improving the culture conditions and using advanced techniques such as 3D culture systems and microfluidic device. There is also the possibility of enhancing the procedure of cultivating fibroblast cells by enhancing the circumstances of the culture and making use of technological advances such as bioreactors, microfluidic instruments, and three-dimensional culture methods. It is possible to maximize cell development through the utilization of bioreactors, which enable the production of dermal fibroblasts in greater quantities while maintaining their functionality. Cytogel, for instance, is an intelligent microcarrier that has exhibited over 90% fibroblast adhesion and increased collagen formation. This indicates that it is a promising technique for massive cell culture for medicinal purposes [105].

Also, microfluidic systems exhibit superior energy efficiency compared to alternative technologies and are adept at segregating or concentrating cells based on their particle sizes. Moreover, these systems are cost-effective, adhere to current Good Manufacturing Practices (cGMP), and possess a minimal risk of contamination, rendering them suitable for industrial-scale applications. Gene editing techniques and advanced biomaterials are being investigated to enhance fibroblast cell therapeutic potential. It is crucial to address these challenges to facilitate the development and adoption of fibroblast-based remedies for skin disorders. Although these challenges exist, researchers actively work to overcome them and develop more effective treatments. In conclusion, fibroblasts have the potential to be used in cell-based therapies of skin disorders. Additionally, more studies are required to compare fibroblast therapy with other treatment options for skin diseases. The review emphasizes the potential benefits of fibroblast therapy in improving the quality of life for patients suffering from skin diseases.

Conclusion

This scoping review emphasizes the potential of fibroblast therapy as a promising approach for addressing a variety of skin disorders and implementing it in cosmetic applications. During a thorough and careful evaluation, we found 35 papers that satisfied our rigorous eligibility requirements, highlighting the necessity for additional research in this field. Fibroblast therapy's efficacy was noticeable in diseases such as diabetic foot and venous leg ulcers, where it demonstrated encouraging outcomes in facilitating wound healing and tissue regeneration. Scientific research has shown that when fibroblast therapy is combined with other rejuvenation techniques, such as platelet-rich plasma (PRP), amniotic membrane, biomaterials, and growth factors, it can greatly improve the results of scar treatment. This comprehensive strategy utilizes the distinct characteristics of each element to promote tissue regeneration, diminish scar tissue, and enhance overall wound healing. By combining these different approaches, medical professionals can create more thorough and efficient therapy strategies for scar treatment, finally resulting in better results for patients and a higher overall quality of life. Furthermore, the importance of fibroblasts in promoting the accumulation of extracellular matrix and preserving skin balance highlights their critical role in maintaining skin health and facilitating its regeneration. Although the results of this review are favorable, it is critical to recognize the constraints and deficiencies in the current body of studies. However, further research is required to clarify the most effective procedures for fibroblast therapy, such as determining the best cell sources, delivery systems, and treatment schedules. To summarize, dermal fibroblast therapy has significant potential as a beneficial tool in cell-based therapies and regenerative treatments for skin disorders. Ongoing research and innovation in this domain possess the capacity to completely transform the management of skin disorders and the field of skin tissue engineering, thereby enhancing the quality of life for people across the world. This study highlights the advantages of fibroblast therapy in treating skin conditions such as diabetic foot, venous leg ulcers, and cosmetic purposes. Fibroblasts possess remarkable regenerating capabilities, making dermal fibroblast therapy crucial in cell-based and skin regenerative treatments. Nevertheless, additional research is required for some disorders.

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