Advancements in cell-based therapies for thermal burn wounds: a comprehensive systematic review of clinical trials outcomes

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Abstract

Background Burn trauma is one of the major causes of morbidity and mortality worldwide. The standard management of burn wounds consists of early debridement, dressing changes, surgical management, and split-thickness skin autografts (STSGs). However, there are limitations for the standard management that inclines us to find alternative treatment approaches, such as innovative cell-based therapies. We aimed to systematically review the different aspects of cell-based treatment approaches for burn wounds in clinical trials.

Methods A systematic search through PubMed, Medline, Embase, and Cochrane Library databases was carried out using a combination of keywords, including "Cell transplantation", "Fibroblast", "Keratinocyte", "Melanocyte", or "Stem Cell" with "Burn", "Burn wound", or "Burn injury". Firstly, titles and abstracts of the studies existing in these databases until "February 2024" were screened. Then, the selected studies were read thoroughly, and considering the inclusion and exclusion criteria, final articles were included in this systematic review. Moreover, a manual search was performed through the reference lists of the included studies to minimize the risk of missing reports.

Results Overall, 30 clinical trials with 970 patients were included in our study. Considering the type of cells, six studies used keratinocytes, nine used fibroblasts, eight used combined keratinocytes and fibroblasts, one study used combined keratinocytes and melanocytes, five used combined keratinocytes and fibroblasts and melanocytes, and one study used mesenchymal stem cells (MSCs). Evaluation of the preparation type in these studies showed that cultured method was used in 25 trials, and non-cultured method in 5 trials. Also, the graft type of 17 trials was allogeneic, and of 13 other trials was autologous.

Conclusions Our study showed that employing cell-based therapies for the treatment of burn wounds have significant results in clinical studies and are promising approaches that can be considered as alternative treatments in many cases. However, choosing appropriate cell-based treatment for each burn wound is essential and depends on the situation of each patient.

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Introduction

Burn trauma is one of the major causes of morbidity and mortality worldwide. According to the World Health Organization (WHO), an estimated 180,000 deaths every year are caused by burn injuries. The study of the global burden of disease showed that approximately nine million new cases of burn injury sought medical care in 2019 [1]. Currently, burn wounds' standard of care consists of infection prevention, early debridement, dressing changes, and surgical management (excising the necrotic tissue followed by skin grafting) [2]. Standard treatment for larger burn injuries is meshed split-thickness skin graft (STSG). Prolonged preparation process, less functionality, and donor site-associated morbidities are limitations in severely burned patients [3–5]. Therefore, healing time and prevention of scar formation in patients with severe burn injuries are still major concerns [6], which may not be satisfactory in all patients treated with standard of care. In addition, major burn injuries with ≥15% of the total body surface area (TBSA) [7] are at high risk of infection and consequent co-morbidities, which may also lead to septic shock and death [8]. For this reason, other treatment approaches should also be considered for managing burn wounds.

Innovative cell therapies are rapidly advancing as a regenerative strategy for burn wounds management and may offer great hope in the future [4, 9]. Different types of cells, such as keratinocytes, fibroblasts, mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), umbilical cord stem cells (USCs), and induced pluripotent stem cells (iPSCs), have been assessed for the treatment of burn wounds in preclinical and clinical studies [10, 11]. These cells can be delivered by different routes, including local application (e.g. matrices/scaffold-assisted delivery and spraying methods) [12, 13], local injection (subcutaneously or intradermal) [14], and systemic delivery by intravenous injection [15, 16]. However, an ideal cell type and delivery method for the effective administration of cells for burn wounds has not yet been elucidated. Cell transplantation can be used in autologous, allogeneic, or xenogeneic settings and by cultured or non-cultured methods [17]. Studies have shown that transplantation of autologous [18] and allogeneic [19] keratinocytes and fibroblasts can improve burn wound healing in patients. Nevertheless, the superiority of stem cells over other cell types for the healing of burn wounds has been shown by preclinical and clinical studies [14]. Transplantation of stem cells promotes faster wound healing and effective tissue regeneration through multiple mechanisms: reducing the formation of granulation tissue, enhancing neoangiogenesis, reducing immune cell infiltration, accelerating extracellular matrix (ECM) synthesis, inhibiting inflammatory responses, and reducing infection and fibrosis. In addition, stem cells have the capability to differentiate and proliferate in the transplanted area [20–22]. These cells can also create a favorable niche for wound healing through the secretion of cytokines, chemokines, and growth factors in response to environmental stimuli. Chemokines, cytokines, and growth factors secreted from stem cells cause the migration and proliferation of fibroblasts, endothelial cells and keratinocytes, leading to the acceleration of wound healing [21, 23].

To the best of our knowledge, there is still a lack of a comparative study to outline the advantages and disadvantages of different cell-based treatment approaches. In this systematic review, we outlined the feasibility and effectiveness of cell-based therapy in clinical trials. Some of these clinical trials have used cells alone, while others used a combination of cells with adjuvants, including biomaterials and scaffolds. However, the adjuvants served to optimize the delivery of the cells, while the cells themselves were responsible for the main therapeutic effects. This highlights the importance of the cells in the therapeutic process, with the adjuvants playing a supportive role in enhancing their efficacy. We aimed to review the variations in the used cell types (keratinocytes, melanocytes, fibroblasts, or stem cells), preparation type (cultured or non-cultured), graft type (autologous or allogeneic), and the delivery rout (local application or graft) (Fig. 1), and their influence on the outcomes of the treatment approaches such as wound healing, scar quality, graft take, and complications.

Methods

Literature search strategy

The selection of studies in this review was performed using the PRISMA-2020 scoping review protocol and checklist. A comprehensive search of the electronic databases PubMed, Medline, Embase, and Cochrane Library was conducted for studies published until February 2024 on the clinical use of cell-based therapies for the treatment of burn wounds. Specific search strategies used for each database are presented in the Supplementary file (Table S1); briefly, a combination of the search terms including "Cell transplantation", "Fibroblast", "Keratinocyte", "Melanocyte", or "Stem Cell" with "Burn", "Burn wound", or "Burn injury" was used to search through he databases. Also, a search through google scholar was performed and reference lists of the included studies were screened to minimize the risk of missing relevant studies.
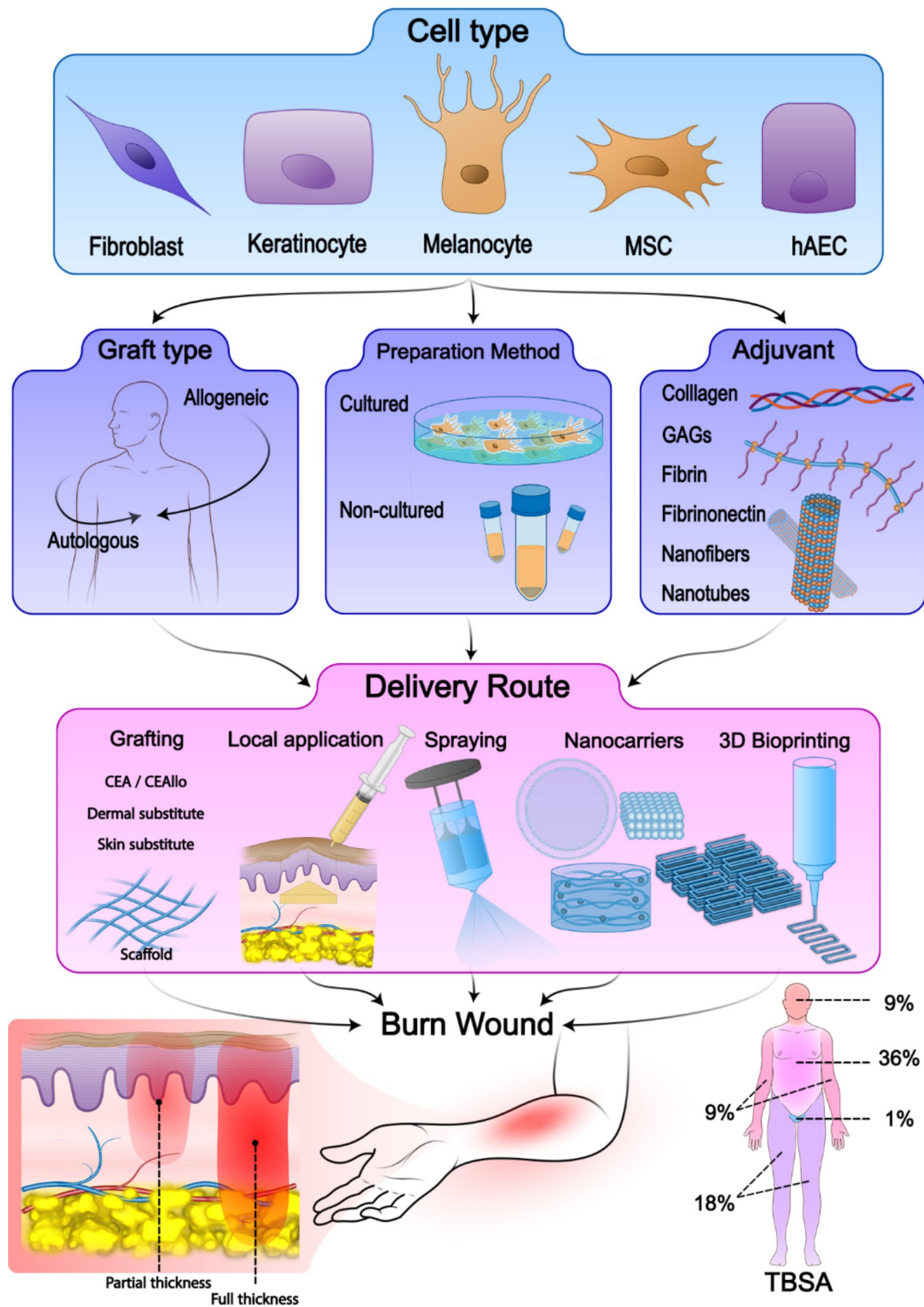
Fig. 1 Different aspects of using cell-based therapies for the treatment of burn wounds

Inclusion and exclusion criteria

The inclusion criteria for this systematic review were all published randomized or non-randomized clinical trials, published until February 2024, and in the English language. The studies must have assessed a cell-based treatment approach for burn wounds in patients of any age.

The exclusion criteria were case-controls, case reports, case-series, observational studies, commentaries, editorials, non-English language studies, and studies not available in full-text, including conference abstracts.

Study screening and reporting

Two authors (YN, YY) independently screened titles and abstracts followed by full-texts using the inclusion criteria and selected studies to be included in the review. The data extracted from these studies include number of participants, mean age, burn degree (superficial-, superficial/deep partial-, or full-thickness), mean TBSA, trial design, cell type (keratinocyte, melanocyte, fibroblast, or stem cell), preparation type (cultured or non-cultured), graft type (autologous or allogeneic), dose (number of cells), biomaterial composition, delivery route (spraying, local application or graft), control type, and combination with other treatments.

Results

Study selection

Overall, 5923 reports were found from databases by the search strategy after removing duplicate reports of these databases (1118 reports), and were screened for titles and abstracts. As a result, 5723 reports were excluded, and 200 reports were searched for the availability of full-texts. A number of 200 full-texts were read thoroughly and carefully for the assessment of their eligibility. Eventually, 22 clinical trials were included from the databases. Also, a search through google scholar was performed, and the reference lists of the included studies from databases were checked for possible remaining studies. Fifteen studies were found from this search, of which, eight studies were included. Overall, a total number of 30 clinical trials were included in this systematic review (Fig. 2).

Main findings

A total of 970 patients were enrolled in all 30 included trials. The minimum mean TBSA was 5%, and the
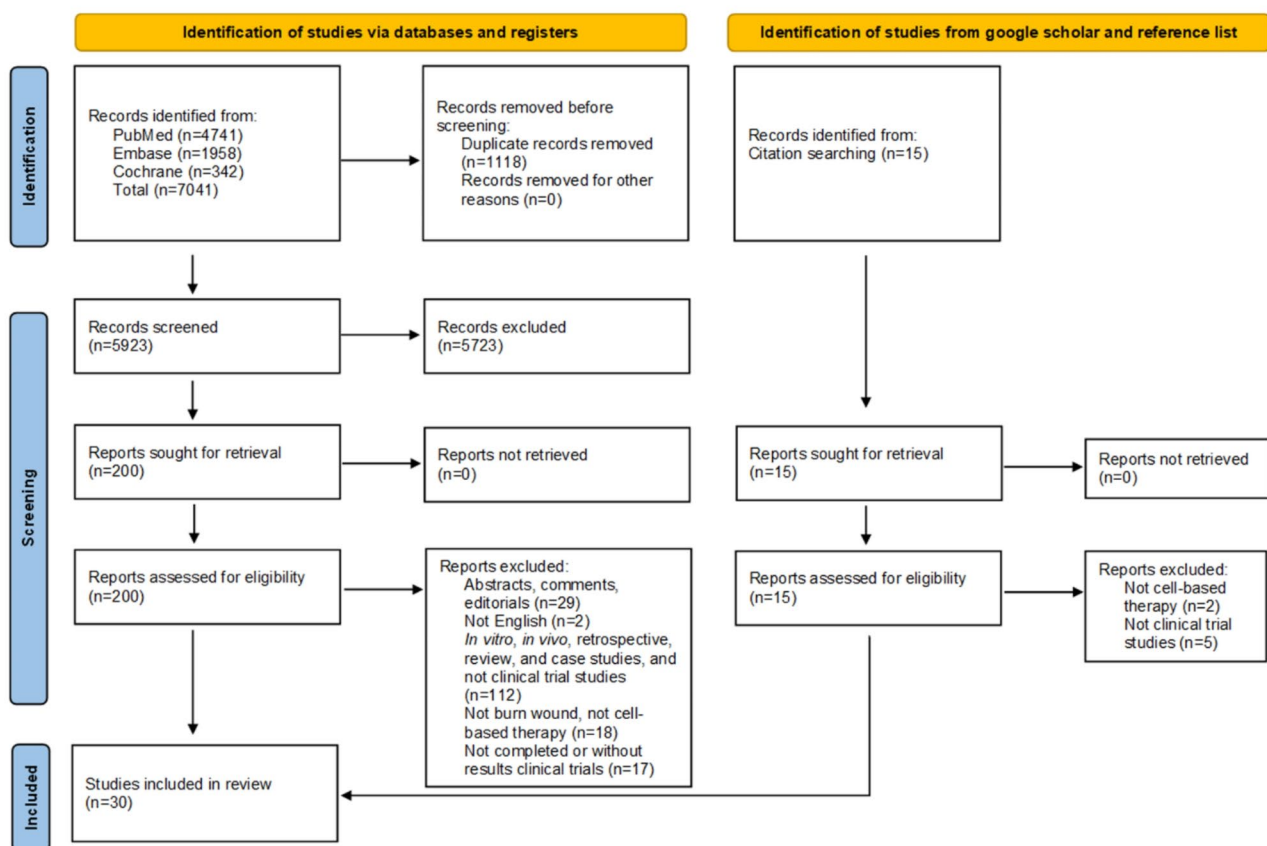
Fig. 2 PRISMA diagram of the included studies

maximum was 76.9% among trials. The degree of burns was partial-thickness in 14 trials [19, 24–36], full-thickness in 11 trials [3, 37–46], and mixed in five trials [18, 47–50]. Six studies used keratinocytes [24, 29, 31, 35, 37, 42], nine used fibroblasts [25–27, 38, 41, 44, 46, 48, 49], eight used combined keratinocytes and fibroblasts [19, 33, 39, 40, 43, 45, 47, 50], one study used combined keratinocytes and melanocytes [3], five used combined keratinocytes and fibroblasts and melanocytes [18, 28, 30, 32, 36], and one study used MSCs [34]. The cultured method was used in 25 trials [3, 19, 24–27, 29, 31, 33–35, 37–50] and the non-cultured method was used in five trials [18, 28, 30, 32, 36]. The graft type of 17 trials was allogeneic [19, 24–27, 29, 31, 33–35, 38, 41, 43, 44, 48–50], and 13 trials were autologous [3, 18, 28, 30, 32, 36, 37, 39, 40, 42, 45–47]. All five non-cultured trials used the autologous method [18, 28, 30, 32, 36], while cultured trials used both allogeneic and autologous [3, 19, 24–27, 29, 31, 33–35, 37–50]. STSG was the most common type of control and combination therapy across all studies. Eighteen studies have also used biomaterials and scaffolds as adjuvants in their cell-based treatment approaches [3, 19, 25–27, 29, 31, 33, 38–40, 43–45, 47–50]. A wide variety of scaffolds and dermal or skin substitutes were used, including Biobrane® synthetic wound dressing, TransCyte®, StrataGraft®, Apligraf®, MatriDerm®, and Alloskin. The most common biomaterial used in these scaffolds and products was collagen type I derived from animal sources.

A summary of the included studies is presented in Table 1, depicting study characteristics, including number of participants, mean age, burn degree (superficial-, superficial/deep partial-, or full-thickness), mean TBSA percentage, trial design, cell type (keratinocyte, melanocyte, fibroblast, or stem cell), preparation type (cultured or non-cultured), graft type (autologous/allogeneic), dose (number of cells), biomaterial composition, delivery route (spraying, local application or graft), control type, and combination with other treatments. There is also a summary of results of the studies, including re-epithelialization, scar quality (the Patient and Observer Scar Assessment Scale; POSAS, and Vancouver Scar Scale; VSS), graft take or loss, and complications which are presented in Table 2.

Discussion
In this section, we offer critical insights into different aspects of cell-based therapies from the included studies, providing the latest updates with more detail in this exciting field of research.

Cell types
Different types of cells have been used in clinical trials to promote healing and tissue regeneration in burn wounds. These trials have mainly compared cell-based therapies with skin grafts and conventional dressings. Cell-based therapy promotes the wound healing process mainly by enhancing re-epithelialization and angiogenesis. Keratinocytes and fibroblasts are the principal cells that are involved in the regeneration of the burnt tissue. Therefore, keratinocytes and fibroblasts are potential therapeutic targets as they are necessary in all three phases of burn wound healing (inflammatory, proliferative, and remodeling phases) [51, 52]. These cells are used in clinical trials in different forms, such as autologous or allogeneic, cultured or non-cultured, and with adjuvant or scaffold-loaded. Here we describe the application of different types of cells and their possible underlying mechanisms of action in skin regeneration.

Keratinocytes are the main cells that participate in epidermal remodeling in the proliferative phase of burn wound healing. Migrating keratinocytes can form a new epidermal layer, regenerate hair follicles and sweat glands, restore barrier functions, promote angiogenesis, and regulation of immune responses via secretion of various proteins, growth factors, and cytokines such as collagen IV, collagen VII, laminin V, migration stimulating factor (MSF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, interleukin (IL)-1 [11, 53]. Epidermal cell transplantation or epidermal substitutes are currently used as biological burn wound dressing in clinical trials. Application of keratinocytes in different forms, such as cultured epithelial autografts (CEA) [29, 35, 37], cultured epidermal allograft (CEAllo) [24, 31], and other bioengineered skin substitute (BSS) [3, 43] in deep partial- and full-thickness burn wounds had promising results. In trials using CEA and CEAllo for deep partial-thickness burns, the wound healing and re-epithelialization time were significantly faster than in the control site [24, 29, 31, 35, 37]. The dried form of CEAllo was recently used in a phase I/II clinical trial. It is more beneficial since it can be stored at room temperature and used as an off-the-shelf product. Dried CEAllo contains bioactive substances involved in the construction of physiological-like niches to promote recipient cell proliferation and migration in the wound bed [35]. Cultured proliferating epidermal cells consisting of allogeneic keratinocytes and melanocytes have been reported to have significantly better epithelialization compared to the standard treatment. Significantly better POSAS score of the observer and of the patient, better melanin and erythema index, improved skin colorimeters, and higher elasticity for the experimental area were also reported in this trial [3].

As the second type of cells, fibroblasts are the main cells responsible for dermal remodeling and connective tissue formation in the proliferative and remodeling phase of burn wound healing. They promote

Table 1 Characteristics of the included clinical trials using cell-based therapies for the treatment of burn wounds

Study	N of participants	Mean age (years)	Burn degree	Mean TBSA (%)	Trial design	Cell type	Preparation type	Graft type	Dose (N of cells)	Biomaterial composition	Delivery route	Control type	Combination
Sakamoto-2022 [35]	5	59.2	Deep partial-thickness	NR	Prospective open label phase I/II clinical trial	Keratinocyte	Cultured	Allogeneic	NR	NR	Local application	NR	NR
Schulman-2022 [34]	10	NR	Deep partial-thickness	NR	Prospective clinical trial	BM-MSC	Cultured	Allogeneic	$2.5\times10^3/cm^2$ and $5\times10^3/cm^2$	NR	Local application	NR	NR
Gibson-2021 [19]	71	NR	Deep partial-thickness	12	Phase III open-label prospective randomized controlled multicenter trial	Keratinocyte and fibroblast	Cultured	Allogeneic	NR	Murine collagen type I	Local application	Autologous meshed STSG	NR
Holmes-2019 [33]	30	41	Deep partial-thickness	13.9	Open-label phase Ib prospective randomized controlled multicenter trial	Keratinocyte and fibroblast	Cultured	Allogeneic	NR	Murine collagen type I	Local application	Autologous meshed STSG	NR
Nilforoush-zadeh-2019 [46]	10	47	Full-thickness	NR	Prospective open-label clinical trial	Fibroblast	Cultured	Autologous	NR	NR	Local application	NR	Low-level laser irradiation
Holmes-2019 [18]	30	NR	Partial- and full-thickness	10	Prospective within patient randomized controlled trial	Keratinocyte, melanocyte, and fibroblast	Non-cultured	Autologous	NR	NR	Spraying	Autologous meshed STSG	Autologous meshed STSG
Holmes-2018 [32]	101	NR	Deep partial-thickness	21	Prospective within patient randomized controlled trial	Keratinocyte, melanocyte, and fibroblast	Non-cultured	Autologous	NR	NR	Spraying	Autologous meshed STSG	NR

Table 1 (continued)

Study	N of participants	Mean age (years)	Burn degree	Mean TBSA (%)	Trial design	Cell type	Preparation type	Graft type	Dose (N of cells)	Biomaterial composition	Delivery route	Control type	Combination
Yoon-2017 [31]	33	42.2	Deep partial-thickness	16.3	Prospective randomized controlled trial	Keratinocyte	Cultured	Allogeneic	$2 \times 10^7/1.5$ mL	Thermosensitive hydrogel	Local application	Silicone net dressing	Silicone net dressing
Boyce-2017 [45]	16	NR	Full-thickness	76.9	Prospective open-label within patient randomized controlled trial	Keratinocyte and fibroblast	Cultured	Autologous	$3.75 – 5 \times 10^5$ fibroblasts/cm^2 and $0.75 – 1 \times 10^6$ keratinocytes/cm^2	Bovine collagen and GAG	Local application	Autologous STSG	NR
Gardien-2016 [3]	40	NR	Full-thickness	24	Prospective randomized controlled trial	Keratinocyte and melanocyte	Cultured	Autologous	$5 \times 10^4/cm^2$	Bovine collagen type I, III, and V coated with bovine elastin	Local application	Autologous meshed STSG	Autologous meshed STSG
Moravvej-2016 [44]	14	14	Full-thickness	16	Prospective double-blind randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	GAG containing silicon sheet	Local application	Autologous meshed STSG	Autologous meshed STSG
Sood-2015 [30]	10	10	Deep partial-thickness	11.4	Prospective randomized controlled trial	Keratinocyte, melanocyte, and fibroblast	Non-cultured	Autologous	NR	NR	Spraying	Autologous meshed STSG (self-control)	Autologous meshed STSG
Yim-2014 [29]	15	NR	Deep partial-thickness	NR	Prospective clinical trial	Keratinocyte	Cultured	Allogeneic	$6.7 \times 10^6/1.5$ mL, $2 \times 10^7/1.5$ mL, $6 \times 10^7/1.5$ mL	Thermosensitive Hydrogel	Local application	Not treated site	NR
Schurr-2012 [43]	15	NR	Full-thickness	NR	Prospective randomized clinical trial	Keratinocyte and fibroblast	Cultured	Allogeneic	NR	Non-bovine collagen type I	NR	Cadaver allograft	NR

Table 1 (continued)

Study	N of participants	Mean age (years)	Burn degree	Mean TBSA (%)	Trial design	Cell type	Preparation type	Graft type	Dose (N of cells)	Biomaterial composition	Delivery route	Control type	Combination
Wood-2012 [36]	13	NR	Partial-thickness	NR	Prospective randomized clinical trial	Keratinocyte, melanocyte, fibroblast	Non-culture	Autologous	NR	NR	Spraying	Local standard treatment (group1)/Biobrane® alone (group 2)	Biobrane®
Yim-2011 [42]	30	42	Full-thickness	40	Prospective clinical trial	Keratinocyte	Cultured (cell suspension)	Autologous	NR	NR	Spraying	NR	Fibrin sealant
Ermolov-2008 [41]	95	NR	Full-thickness	NR	Prospective clinical trial	Fibroblast	Cultured	Allogeneic	NR	NR	Local application	Gauze dressing with levomecol ointment and dressing based on collagen type I with PDGF-BB	NR
Gravante-2007 [28]	82	NR	Deep partial-thickness	NR	Prospective within patient randomized controlled trial	Keratinocyte, melanocyte, fibroblast	Non-cultured	Autologous	NR	NR	Spraying	Autologous STSG	NR
Boyce-2006 [40]	40	NR	Full-thickness	73.4	Prospective open-label randomized within-subject controlled trial	Keratinocyte and fibroblast	Cultured	Autologous	5×10^5 fibroblasts/cm^2 and 1×10^6 keratinocytes/cm^2	Bovine collagen and GAG	Local application	Autologous STSG	NR

Table 1 (continued)

Study	N of participants	Mean age (years)	Burn degree	Mean TBSA (%)	Trial design	Cell type	Preparation type	Graft type	Dose (N of cells)	Biomaterial composition	Delivery route	Control type	Combination
Kumar-2004 [27]	33	3.60	Partial-thickness	5	Prospective non-blinded randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Local application	Biobrane® and silvazine cream	NR
Boyce-2002 [39]	45	NR	Full-thickness	64.6	Prospective non-blinded randomized controlled trial	Keratinocyte and fibroblast	Cultured	Autologous	5×10^5 fibroblasts/cm² and 1×10^6 keratinocytes/cm²	Bovine collagen and GAG	Local application	Autologous STSG	NR
Waymack-2000 [50]	40	36.3	Partial- and full-thickness	23.6	Prospective within patient randomized controlled trial	Keratinocyte and fibroblast	Cultured	Allogeneic	NR	Bovine collagen type I	Local application	Autologous meshed STSG alone and with overlaid allograft	Autologous meshed STSG
Demling-1999 [26]	11 (Major burns)*	41.8	Partial-thickness	30.9	Prospective randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Local application	Bacitracin ointment	NR
Demling-1999 [26]	10 (minor burns)*	30	Partial-thickness	8.5	Prospective randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Local application	Bacitracin ointment	NR
Noordenbos-1999 [25]	14	NR	Partial-thickness	13.3	Prospective randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Local application	Silver sulfadiazine	NR
Purdue-1997 [38]	66	36	Full-thickness	44	Prospective within patient randomized controlled trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Local application	Cadaver allograft	NR

Table 1 (continued)

Study	N of participants	Mean age (years)	Burn degree	Mean TBSA (%)	Trial design	Cell type	Preparation type	Graft type	Dose (N of cells)	Biomaterial composition	Delivery route	Control type	Combination
Hansbrough-1997 [49]	10	33.5	Partial- and full-thickness	39.9	Prospective randomized clinical trial	Fibroblast	Cultured	Allogeneic	NR	Porcine collagen type I coated nylon mesh	Graft	Cadaver allograft	NR
Rivas-Torres-1996 [24]	10	22.3	Deep partial-thickness	28.7	Prospective within patient blinded randomized controlled trial	Keratinocyte	Cultured	Allogeneic	NR	NR	Graft	Autologous STSG	NR
Munster-1996 [37]	64	NR	Full-thickness	70	Prospective controlled trial	Keratinocyte	Cultured	Autologous	NR	NR	Graft	Autologous STSG	NR
Hansbrough-1992 [48]	17	31	Partial- and full-thickness	23.8	Prospective randomized clinical trial	Fibroblast	Cultured	Allogeneic	NR	Polyglactin acid vicryl mesh	Graft	Autologous meshed STSG	Autologous meshed STSG
Hansbrough-1989 [47]	5	NR	Partial- and full-thickness	56	Prospective clinical trial	Keratinocyte and fibroblast	Cultured	Autologous	3.7×10^5 to 6.9×10^5 fibroblasts/ cm^2 and 0.54-1×10^6 keratinocytes/ cm^2	Bovine collagen and GAG	Graft	NR	NR

Abbreviations N=Number, TBSA=Total body surface area, NR=Not reported, BM-MSC=Bone marrow mesenchymal stem cell, NIKS=Near-diploid neonatal human keratinocyte cell line, STSG=Split-thickness skin graft, GAG=Glycosaminoglycan, PDGF-BB=Platelet-derived growth factor-BB

*Patients were defined as having major burns requiring at least seven days hospitalization or minor burns having the potential for outpatient care, based on the criteria of the American Burn Association (ABA)

Table 2 Results of the included clinical trials using cell-based therapies for the treatment of burn wounds

Study	Re-epithelialization	Scar Quality (POSAS, VSS)	Graft Take/loss	Complications	Others
Sakamoto-2022 [35]	- Epithelialization rate at day 7 was 69.9±28.9 and at day 14 was 90.5±13.2	NR	NR	NR	- Resolved local infection (in one patient) - Two cases of skin erosion, and one case of systemic fever - No unresolved adverse events remained
Schulman-2022 [34]	- Wound closure rate of 3.64 cm^2/day in the first dose - Wound closure rate of 10.47 cm^2/day in the second dose (not statistically significant ($P=0.17$))	- Weak significant difference ($P<0.05$) between the two doses	NR	NR	NR
Gibson-2021 [19]	- StrataGraft® treatment resulted in durable wound closure at month 3 without autografting in 92% of patients compared with 95% achieved durable wound closure at the autograft treatment site	- A significant favorable difference in mean POSAS observer total scores between StrataGraft® and autograft donor sites at month 3 ($P<0001$) - POSAS total scores by observer at month 12 demonstrated that cosmetics at the StrataGraft® and autograft treatment sites were clinically similar	NR	- A total of 10 (14.1%) patients experienced at least 1 SAE none of which were related to StrataGraft® treatment	− 96% reduction in mean percent area of StrataGraft® treatment sites that required autografting, compared with autograft treatment sites ($P<0.0001$) - A significant difference in donor site pain intensity through day 14 was observed between StrataGraft® and autograft donor sites ($P<0.0001$)
Holmes-2019 [33]	- The proportion of wounds that achieved closure was not statistically different between StrataGraft® tissue and autograft treatment ($P=0.49$) - Wound-closure rates did not significantly differ across StrataGraft® tissue and autograft treatment sites by month 3 ($P=0.15$) - Re-epithelialization at the StrataGraft® tissue treatment site was not statistically different from the control site within each patient in the groups ($P>0.31$)	- No significant differences in observer total and overall opinion POSAS scores between StrataGraft® tissue and autograft treatment sites at any time point - Significantly higher mean subject-assessment total scores at each time point (i.e., less favorable; $P<0.0001$) for the autograft donor site compared with the StrataGraft® tissue donor site	NR	- Six (20%) subjects had a total of 11 SAEs, all of which were resolved. One subject had a moderately severe SAE of impaired healing	- The percent treatment area autografted by day 28 was 0% for StrataGraft® tissue treatment sites compared with 100% for control autograft treatment sites - Subjects reported lower mean pain scores at the prospectively identified, unharvested, StrataGraft® tissue donor sites compared with the harvested autograft donor sites from day 3 through day 28
Nilforoushzadeh-2019 [46]	- Complete wound healing in all patients in at least three months	NR	NR	NR	NR

Table 2 (continued)

Study	Re-epithelialization	Scar Quality (POSAS, VSS)	Graft Take/loss	Complications	Others
Holmes-2019 [18]	- Non-inferiority of wound closure for the ReCell® group compared to the control group (85% vs. 92% respectively)	- No significant difference for POSAS scores between the two groups	- No significant difference for graft loss between the ReCell® and the control groups (13.3% vs. 16.7% of the areas respectively, $P > 0.05$)	- No significant difference for the number of the portion of the patients with adverse events between the two groups (57% of subjects for both)	- Smaller donor site for the ReCell® group compared to the control group (264 ± 119 cm^2 vs. 368 ± 150 cm^2, 32% decrease, $P < 0.0001$) - No significant difference for postoperative pain subject satisfaction between the groups
Holmes-2018 [32]	- Non-inferiority of ≥ 95% re-epithelialization for the ReCell® group compared to the control group (97.6% vs. 100% of the patients, respectively)	NR	NR	- Less adverse events in the ReCell® group (64.4% vs. 77.2%, $P = 0.004$)	- Smaller donor site for the ReCell® group compared to the control group (4.7 ± 3.2 cm^2 vs. 194.1 ± 158.5 cm^2, 97.5% decrease, $P < 0.0001$) - No significant difference for postoperative pain, scar formation and long-term subject satisfaction between the two groups - Reduced donor site pain in the ReCell® group ($P < 0.005$)
Yoon-2017 [31]	-2.8 ± 2.2 days faster re-epithelialization than control sites at other institutions ($P < 0.001$) and 2.5 ± 3.4 days faster than that of control sites in the same institution ($P < 0.001$)	NR	NR	- No grade 3 adverse events	- Significantly high satisfaction scores on all items provided by patients and doctors (average score of 3 points)
Boyce-2017 [45]	-29.9 ± 3.3% TBSA closed for ESS, and 47.0 ± 2.0% for STSG	NR	-83.5 ± 2.0% engraftment for ESS and 96.5 ± 0.9% for STSG	NR	-The ratio of closed wound to donor areas was 108.7 ± 9.7 for ESS compared with a maximum of 4 ± 0.0 for STSG
Gardien-2016 [3]	- Significant better epithelialization after 5–7 days for the experimental treatment (71%) compared to the standard treatment (67%) ($P = 0.034$)	- Significantly better POSAS of the observer after 3 and 12 months and of the patient after 12 months for the experimental area	- Take rates of the grafts were similar between the groups	- No significant longer stay in hospital (51 vs. 42 days, $P = 0.28$) - No significant differences were found in wound contamination	- Better Melanin index at 3 and 12 months and erythema index at 12 months for the experimental treatment ($P \leq 0.025$) - Improved skin colorimeters between 12% and 23% ($P \leq 0.010$) - Higher elasticity ($P = 0.03$) in the experimental area at 3 months follow-up
Moravvej-2016 [44]	- Significant lower average healing time in the Alloskin side (8.8 ± 1.7 days) compared to the petroleum jelly–impregnated gauze side (13.6 ± 1.7 days)	- Significant lesser mean scar formation after second and fourth months post operation ($P = 0.001$ for both) but not at the end of the 12th month	NR	NR	- Significantly lesser pigmentation score in the second and fourth months ($P < 0.0001$)
Sood-2015 [30]	NR	- No significant difference for the VSS scar score between the groups at week 52	- Comparable graft take in both groups by week 3 postoperation	NR	- Comparable to identical pigmentation between the groups - Comparable pain between the groups - Comparable subjective appearance rate between the groups
Yim-2014 [29]	- Re-epithelialization was 2.8 ± 1.8 days faster than in the control site ($P < 0.0001$)	NR	NR	NR	NR
Schurr-2012 [43]	-100% closure of wounds	- Improvement in the POSAS scores	NR	NR	- Minimal clinical evidence of fibrosis

Table 2 (continued)

Study	Re-epithelialization	Scar Quality (POSAS, VSS)	Graft Take/loss	Complications	Others
Wood-2012 [36]	- Quicker complete wound healing in the Biobrane® only group (median = 16 days) and the Biobrane® and ReCell® group (median = 16 days), and slower in the standard treatment group (median = 36.5 days)	- Mean VSS of 5.6 in the standard treatment group, 4.25 in the Biobrane® only group, and 3.5 in the Biobrane® and ReCell® group	NR	- Graft loss (*n* = 1) - Overgranulation (*n* = 1) in the standard treatment group and wound infection (*n* = 1) in each of the Biobrane® only and Biobrane® and ReCell® groups - Sepsis (*n* = 1) in Biobrane® and ReCell® group	- Reduction in maximum pain scores in Biobrane® only or Biobrane® and ReCell® groups - Median difference pain score of + 1 in the standard treatment group, -2 in the Biobrane® only group, and − 1 in the Biobrane® and ReCell® group
Yim-2011 [42]	NR	The VSS was 5 (4–6.5), 4 (3–6), and 3 (2–4) at weeks 8, 12 and 24 after the Keraheal™ application	The take rate was 96% (90.5–99%) and 100% (98.5–100%) at weeks 2 and 4 after treatment with Keraheal™, respectively	NR	NR
Ermolov-2008 [41]	- Accelerated wound epithelialization (5–7 days) vs. gauze dressing (20–22 days)	NR	NR	- Decreased incidence of suppurative complications	- Epithelialization without hypertrophic cicatrix
Gravante-2007 [28]	- Complete wound healing in 12 days in the ReCell® group and 13 days in the control group (not significant)	NR	NR	NR	- Longer duration of the procedure for the ReCell® group compared to control group (*P* < 0.001) - Smaller donor site for the ReCell® group (*P* < 0.001) - Less postoperative pain in the ReCell® group (*P* = 0.03) - No significant difference for the requirement of a second procedure - No significant difference in pigmentation between the groups
Boyce-2006 [40]	- The percentage of the TBSA closed at POD 28 was 20.5% for CSS and 52.1% for STSG	- No different erythema, pliability, or scar height in VSS scores at first year	- Engraftment at POD 14 was 81.5% for CSS and 94.7% for STSG	NR	- The ratio of closed to donor areas at POD 28 was 66.2 for CSS, and 4 for each harvest of STSG - Deficient pigmentation remained in CSS
Kumar-2004 [27]	- The mean time to re-epithelialization was 7.5 days for TransCyte®, 9.5 days for Biobrane®, and 11.2 days for Silvazine	NR	NR	NR	- Reduced the number of wounds requiring autografting: 5/21 (24%) for Silvazine, 3/17 (17%) for Biobrane®, and 1/20 (5%) for TransCyte®
Boyce-2002 [39]	- The percentage of the TBSA closed at POD 14 was 15.4 ± 2.2% for CSS and 60.0 ± 1.6% for STSG (at POD 28 it was 16.7 ± 2.6% for CSS and 58.7 ± 1.8% for STSG)	NR	- Engraftment at POD 14 was 89.2 ± 2.5% for CSS and 94.9 ± 3.6% for STSG (at POD 28 it was 95.4 ± 1.8% for CSS and 99 ± 0.8% for STSG)	NR	NR

Table 2 (continued)

Study	Re-epithelialization	Scar Quality (POSAS, VSS)	Graft Take/loss	Complications	Others
Way-mack-2000 [50]	- The median number of days to ≥ 75% wound closure were 8 days for the Apligraf® site and 13 days for the control site	- Statistically better VSS scores at the Apligraf® sites compared to the control site at all time points from week 1 to month 24	- The percentage of autograft take of the Apligraf® site was similar to that of the control graft site	- No infections were detected - No humoral or cellular immune response	- Significant better overall cosmetic appearance in the Apligraf® group compared to the control group - Significant better pigmentation in the Apligraf® group compared to the control group by month 24 and 17 (45%) - Normal pigmentation in the Apligraf® sites compared to the control sites ($P = 0.0005$) - Better vascularity at the Apligraf® site (47%) compared to the control site (16%)
Dem-ling-1999 [26] (Major wounds)	- Re-epithelialization time of 8 ± 2 versus 14 ± 4 days in the skin substitute group compared to topical antibiotics ($P < 0.05$)	NR	NR	NR	- Pain scale of 2 ± 1 versus 5 ± 1 days in the skin substitute group compared to topical antibiotics ($P < 0.05$) - Wound care time 0.35 ± 11 versus 1.9 ± 0.5 h in the skin substitute group compared to topical antibiotics ($P < 0.05$)
Dem-ling-1999 [26] (Minor wounds)	- Re-epithelialization time 8 ± 1 versus 12 ± 3 days in the skin substitute group compared to topical antibiotics ($P < 0.05$)	NR	NR	NR	- Pain scale of 2 ± 1 versus 5 ± 1 days in the skin substitute group compared to topical antibiotics ($P < 0.05$) - Wound care time 0.4 ± 0.1 versus 22 ± 0.4 h in the skin substitute group compared to topical antibiotics ($P < 0.05$)
Noorden-bos-1999 [25]	- The mean time until 90% healing of 11.14 days for TransCyte® and 18.14 days for control sites ($P = 0.002$)	- The VSS of 1.39, 0.8, and 0.375 at 3, 6, and 12 after the TransCyte® application ($P < 0.001$ at 3 and 6 months, $P = 0.006$ at 12 months)	NR	- No wound infection in TransCyte® group and 6 mild cellulitis in the control group	NR
Purdue-1997 [38]	- The same percentage of wound closure for both treatments (97% closed at post-graft day 28)	NR	- Mean autograft take of 94.7% for DG-TC and 93.1% for allograft ($P = 0.0001$)	- Minimal Complication in both groups (not significant)	- Twice granulation tissue score for human cadaver allograft compared with DG-TC - Granulation tissue was seen 74.1% at the allograft sites vs. 50.9% at DG-TC sites
Hans-brough-1997 [49]	- No significant differences observed for percent wound closure ($P = 0.11$)	NR	- No significant differences observed for percent take ($P = 0.053$)	NR	NR
Rivas-Tor-res-1996 [24]	- Wound healing in 6.9 ± 0.5 days for the CEAllo group and 11.1 ± 0.7 days for the control group ($P < 0.005$)	- Same frequency of scar formation in both groups (Without quantitative scale)	NR	- Erythema in all of the control group even after one month compared to four erythema cases in the CEAllo group ($P < 0.01$)	- Normopigmentation in 7 sites of the CEAllo group compared to four sites in the control group (No P-value)
Munster-1996 [37]	NR	NR	NR	- The difference of major complications was not significant between the CEA and the control group (50% and 60%, respectively)	- Mortality rate in the CEA group was 48% compared to 14% in the control group ($P < 0.007$) - Total hospital stay in the CEA group was 96.4 ± 15.2 days compared to 54.7 ± 2.9 days in the control group ($P < 0.014$)

Table 2 (continued)

Study	Re-epithelialization	Scar Quality (POSAS, VSS)	Graft Take/loss	Complications	Others
Hansbrough-1992 [48]	- Epithelialization is complete in both the control and experimental sites (the epidermis was slightly thinner in the STSG alone group)	NR	- The values for the percentage of graft take was superior for the STSG alone group (not statistically significant)	NR	NR
Hansbrough-1989 [47]	NR	NR	- Four of 13 grafts failed to take	NR	- Gross examination of a treated area at four weeks after surgery shows a soft, relatively smooth external surface that has good subjective resistance to shear forces - Redevelopment of pigment was seen in one patient - Development of a continuous lamina densa and multiple hemidesmosomes

Abbreviations POSAS=Patient and observer scar assessment scale, VSS=Vancouver scar scale, NR=Not reported, SAE=Serious adverse event, TBSA=Total body surface area, ESS=Engineered skin substitute, STSG= Split-thickness skin graft, POD=Postoperative day, CSS=Cultured skin substitute, CEA=Cultured epidermal autograft, CEAllo=Cultured epidermal allograft

reconstruction of ECM by the deposition of collagen, fibrillin, elastin, and secretion of matrix metalloproteinases (MMPs), the tissue inhibitors of metalloproteinases (TIMPs), fibroblast growth factor (FGF), transforming growth factor (TGF)-β, keratinocyte growth factor (KGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) within the wound site. They can also promote angiogenesis and granulation tissue formation, and they can support the epithelial layer via promoting epidermal cell replication, differentiation, migration, and spreading 56. Autologous and allogeneic fibroblast transplantation trials were designed to accelerate wound healing in the treatment of full-thickness burn wounds. Different sources of fibroblasts were used, including healthy donor skin for allograft [41, 44] and patients' own skin for autograft [46]. Accelerated wound epithelialization and significantly lower average healing time with reduced formation of a hypertrophic cicatrix, mean scar formation and pigmentation score were reported in these studies [41, 44, 46]. FDA-approved allogeneic fibroblast-derived temporary dermal substitute (TransCyte®) (formerly marketed as Dermagraft-TC) is a product that were used in clinical trials for partial-thickness burns. Re-epithelialization time was faster with less hypertrophic scarring and better VSS and pain scale in wounds treated with TransCyte®. The wound care time, and the number of wounds requiring autografting were also less in this approach [25–27, 38, 48, 49].

The combination of keratinocytes and fibroblasts for the management of burn wounds seems to be more efficient than single cell therapy as full-thickness burns do not typically heal completely by themselves and result in scar formation, contracture, changes in skin texture, and loss of sensation. Complete epidermal-dermal replacements are required to minimize these complications and improve quality of life [11, 54]. Complete skin substitutes containing both epidermal and dermal cells have been investigated recently to treat full-thickness burns as a temporary or permanent replacement of both layers. [39, 40, 43, 45, 50]. Complete skin substitutes improve the wound healing process more efficiently than epidermal or dermal substitutes alone. ReCell® spraying device, an FDA-approved cell harvesting device that uses non-cultured autologous skin cell suspension (ASCS) containing viable keratinocytes (about 64%), fibroblasts (about 30%), and melanocytes (about 3.5%) [55], is used in randomized control trials (RCTs) to promote thermal burn wound healing. Using ReCell® in deep partial-thickness burns resulted in complete wound healing and reduction in VSS and maximum pain scores. In addition, less donor site and long-term satisfaction with donor site morbidity compared with the controls was reported in trials using ReCell® [18, 32, 36]. Superiority of ASCS combined with STSG for reduction in donor site area has also been reported in other full-thickness skin defects in a recent RCT [56].

Cultured keratinocytes or fibroblasts alone or in combination with each other were also used in the studies. RCTs using cultured skin substitutes (CSS) containing autologous fibroblasts and keratinocytes, also known as autologous engineered skin substitutes (ESS), reported reduced mortality and requirements for donor skin harvesting for grafting [39, 40, 45, 47]. Apligraf® is an FDA-approved cellular full-thickness skin substitute consisting of living allogeneic neonatal fibroblasts and keratinocytes cultured with bovine type I collagen matrix. Using Apligraf® in an RCT resulted in faster healing time and other clinical improvements, including significant better VSS

score, pigmentation, vascularity, pliability, and overall cosmetic appearance in Apligraf® sites compared to control sites [50]. Near-diploid neonatal human keratinocyte cell line (NIKS)-based BSS, which is another full-thickness skin substitute consisting of keratinocytes combined with fibroblasts, was also used in full-thickness burns, resulted in 100% closure of burn wounds and improvement in the POSAS scores with minimal clinical evidence of fibrosis compared with cadaver allograft [43]. Using StrataGraft®, human skin substitute containing NIKS and human dermal fibroblasts cultured with type I collagen, in deep partial-thickness burns resulted in durable wound closure, significant reduction in required autografting, significant lower mean pain scores [19, 33].

In addition, bone marrow-derived MSCs (BM-MSCs) was the only stem cell used in published clinical trials for burn wounds. The safety and efficacy of local application of BM-MSC were reported in deep partial-thickness burn wounds. BM-MSC therapy for deep partial-thickness burn wounds resulted in 100% wound closure, improvement in the POSAS scores, re-pigmentation, and regenerative changes [34]. Overall, although the use of aforementioned cells has been shown to be promising, the combination of these cells seems to be more beneficial; however, more studies are necessary for choosing the best approach depending on the clinical situation.

Cell preparation methods (cultured/non-cultured)
Both cultured and non-cultured cell-based strategies were used in clinical trials with promising outcomes. However, the advantages and limitations of each strategy should be considered. The cultured-based strategy was the most frequent method that has been used in these clinical trials [3, 19, 24–27, 29, 31, 33, 35, 37–50]. This strategy offers several advantages and also has some disadvantages over non-cultured strategies for burn wound healing. In the cultured-based strategy, the expanded population of cells provides an adequate supply for effective grafting, especially in extensive burns, which have limited donor sites and need more cells for transplantation [57–59]. However, the procedure of culturing is more expensive, complex, and time-consuming and it cannot be used immediately for urgent patients [60]. Improved deposition and remodeling of collagen, formation of the dermo-epidermal junction, keratinocytes survival, decreased myofibroblast formation and decreased wound contraction can be achieved by culturing methods [44]. On the other hand, non-cultured strategies are more simple, cost-effective, and immediately available, but the number of available cells may be limited in some cases. Although the non-cultured strategy was less used in clinical trials [18, 28, 30, 32, 36], it has been shown promising results in improving burn wound repair. Further research is needed to optimize its use and determine long-term

safety and efficacy. Herein, we describe the cell preparation approaches which were used in clinical trials [58, 59].

CEA, CEAllo, cultured fibroblasts, and CSS are cultured-based strategies that were used in clinical trials [3, 19, 24–26, 29, 31, 33, 35, 37–50]. Culturing epidermal keratinocytes were one of the most used cultured-based cell approaches in clinical trials [3, 24, 29, 31, 35, 37]. The epidermal keratinocyte culturing method was first introduced by Rheinwald and Green in 1975 [61] and has developed for a long time in order to accelerate wound healing. CEA and CEAllo are considered alternative care for the homeostatic stage of wound healing. They have been used in sheet or suspension form to accelerate re-epithelialization in burn wounds [29, 42]. There were some culturing-related limitations in clinical trials using CEA and CEAllo. The culture period of CEA and CEAllo is long (approximately 2–4 weeks from biopsy to transplantation) mainly due to the slow proliferation rate of keratinocytes [3, 29, 37]. This long culture time with delayed healing results in an excessive accumulation of ECM and more hypertrophic scarring. Failure to improve scar formation and quality in trials using CEA and CEAllo was associated with this long culture time [24, 29, 31, 35, 37]. Using human undifferentiated keratinocytes (HUKs) instead of using fully differentiated keratinocytes or using biological membranes to promote epidermal cell proliferation was useful to overcome the long culture time in some studies. Significant improvements in skin colorimeters, POSAS, melanin index, and erythema index were reported in a trial using proliferating keratinocytes [3].

In addition to the beneficial role of CSS for full-thickness burns replacement, co-culturing of keratinocytes and fibroblasts in CSS preparation can provide better skin structure. There is a crosstalk between keratinocytes and dermal fibroblasts, which improve the burn wound healing process. Disruption of this crosstalk, as seen in delayed epithelialization, increases the risk of hypertrophic scar formation [62]. Co-cultured keratinocytes and fibroblasts promote proliferation and migration by creating cytokine loops between the two cell types, similar to native skin [63, 64]. Despite these advantages, long culture time of autologous CSS (about four weeks from biopsy to preparation) limits its availability for severe burn patients [39].

The only non-cultured product that was used in clinical trials was ReCell® [18, 28, 32, 36]. This spraying device can be used alone to directly spray epithelial cells isolated from the patients' skin biopsy [28], applied along with STSG [18, 32], or combined with biosynthetic skin dressings [36]. In the comparison of the ReCell® with conventional grafting, biopsy areas, and postoperative pain were significantly smaller [28]. Using ReCell® combined with

STSG reduced the donor site area and increased satisfaction with donor site outcomes [18, 32]. In addition, using ReCell® combined with Biobrane® synthetic wound dressing decreased healing time with fewer dressing changes, less pain, and better scar outcomes [36]. However, the non-inferiority properties of ReCell® have been mainly reported in non-cultured based clinical trials while better re-epithelialization was more significant in the cultured-based trials. This may be due to the less number of keratinocytes in the non-cultured method, which was reported in a preclinical study [65]. ReCell® system needs a smaller harvested area due to its ability to spread cells with a high ratio (1:80) to cover a large area [28]. The main advantages of this non-cultured method are faster procedure time and minimal tissue manipulation, which results in better management in urgent patients and fewer donor site-related complications.

Using non-cultured skin cell suspension or cultured skin cells can be beneficial for re-pigmentation to some degree. But it should be considered that culturing melanocytes alongside with keratinocytes (in CEA) or with fibroblasts and keratinocytes (in CSS) may result in non-uniform pigmentation, as mentioned in some studies. This may be due to a more rapid growth rate of keratinocytes than melanocytes which leads to melanocyte dilution to small proportions known as "passenger melanocytes" [40]. Therefore, using non-cultured skin cell suspension (melanocytes existed in epidermal harvests [55]) or adding selective cultured melanocytes into CEA or CSS may be more appropriate to achieve uniform pigmentation [39, 66].

In conclusion, the choice between cultured and not-cultured methods for burn wound repair depends on several factors, including the severity of the burn wound, the patient's condition and urgency, and available resources.

Type of graft (autologous/allogeneic)

Both autografts and allografts were used in clinical trials, and the most suitable approach differs in every patient. The advantages and limitations of each strategy are mentioned as follows. Autografts are immunologically compatible and do not require immunosuppressive drugs leading to no rejection risk and lower risk of infection, respectively. However, there are some limitations which may interrupt wound healing in some patients. The available donor skin is limited, which may be an obstacle in patients with extensive burns. Surgical procedure is required in autografts leading to increased pain, scarring, infection, and longer recovery time in donor sites. Autografts may not be the first choice in critical patients with extensive burns as the procedure of harvesting is time-consuming, and this may result in complications in patients. On the other hand, allografts are immediately available as "off-the-shelf" products, which are beneficial,

especially for critical patients. These grafts are not limited by the availability of the patient's donor site, so they can cover larger areas with no donor site-associated morbidities. However, there might be an increased risk of rejection as they are immunologically incompatible, and immunosuppressive drugs may be needed to address this risk leading to a higher risk of infection. Some clinical studies have reported better healing outcomes with autografts as they can effectively integrate with the wound bed [67–69].

CEA, autologous fibroblasts, ASCS (ReCell®), and CSS are autografts, and CEAllo, allogeneic fibroblasts, NIKS-based-substitute, TransCyte®, and Apligraf® are allografts which were used in the included clinical trials. Among autografts, ReCell® is the only non-cultured method which doesn't have culture time, but the procedure time is reported to be longer than skin grafts, mainly due to the trypsin digestion time (20 min). This leads to patients' surgical stress and increased economic aspects [28]. Therefore, allografts should be considered in some cases depending on the patient's condition.

It has been noted that using CEA for deep partial-thickness burns may result in contracture of anatomic parts due to delayed re-epithelialization. So, it may not be an optimal option in urgent situations. Using allogeneic keratinocytes as CEAllo for easy and immediate use in burn wounds reduces the procedure time and associated complications. Cultured epidermal allograft releases various growth factors which stimulate the migration and proliferation of autologous keratinocytes and suppress the contraction of fibroblasts leading to accelerated re-epithelialization and wound closure. Therefore, early coverage with CEAllo can reduce the healing time of wounds and prevent the formation of hypertrophic burn scars in deep partial-thickness burns [24].

Despite concerns about immune rejection in allografts, no significant adverse effects, including immunologic reactions were reported in clinical trials. Allogeneic fibroblast is an example that seems to be tolerated by immunologically unmatched donors [41, 44]. Using CEAllo may carry a risk of rejection, but it has been demonstrated that CEAllo accelerates the wound healing process without immune rejection and can be replaced with autologous cells after a needed period [29]. NIKS-based BSS was also acutely non-antigenic and strong immune responses were not present after transplantation [43]. Although some adverse events reported after using StrataGraft®, no patients showed signs of a clinically detrimental immune response to StrataGraft®, such as tissue rejection. No adverse effects or immune rejection were also observed with BM-MSC transplantation [34].

Allograft is used as a temporary cover in some trials to protect the dermis, promote wound healing, and prepare an uncolonized and well-vascularized wound

environment to promote the proliferation and migration of cells. Allograft doesn't seem to remain permanently in the wound bed and may gradually be replaced by the patient's epidermal cells [35]. This may lead to the need for the application of autografts following allografts to complete healing in some cases. Therefore, requiring autografting can be measured in clinical studies using allograft to determine the adequacy of allogeneic transplantation. In some clinical trials that used allograft, faster wound healing resulted in less need for autografting [27].

Combination therapies and biomaterial adjuvants

Among the included studies, 10 studies have used cell-based therapies combined with other treatments [3, 18, 30, 31, 36, 42, 44, 46, 48, 50]. Six of them have used autologous meshed STSG [3, 18, 30, 44, 48, 50], and the others have used Biobrane® synthetic wound dressing [36], silicone net dressing [31], low-level laser irradiation [46], and fibrin sealant [42]. However, the combination effect of these treatments was not assessed for the following reasons: (1) studies did not have a control group [42, 46], (2) studies used the same treatments in the control groups [3, 18, 30, 31, 36, 44, 48, 50], or (3) studies compared the combination of these treatments with a different treatment group [36]. In the latter study [36], the effect of Biobrane® was assessed alone or in combination with ASCS (ReCell®) in comparison to standard care. Both treatment groups healed approximately 50% faster than the control group, and adding ASCS to Biobrane® decreased the healing time by about 15% (statistical analysis was not performed). In one study, ASCS combined with meshed STSG was compared with meshed STSG alone in mixed-depth burn wounds [18]. In order to use ASCS for the treatment of burn wounds, a dermis-containing wound bed is necessary [30]. Similarly, combination of ASCS+STSG was used in a recent RCT for the treatment of other full-thickness skin defects [56]. Consistently, in four other included studies that used ASCS without skin graft, the treatment was used in partial-thickness burn wounds that contained dermis [28, 32, 36]. Therefore, the combination effect of ASCS and STSG was not assessed since ASCS could not be used alone in full-thickness burn wounds.

An important challenge in the process of cell-based therapy approaches is to maintain the viability and functionality of the cells in order to result in favorable outcomes. Major hindering factors include mechanical stress during cell delivery, lack of cell adhesion to wound bed resulting in anoikis (cell death due to ECM detachment), and deficiency of growth factors in wound environment [70].

Formerly, epidermal substitutes were used without a supporting scaffold [71], which had several disadvantages:

(1) these substitutes were weak and easily torn, (2) they had insufficient vascular support, (3) they had lower graft takes leading to post-grafting infections, and (4) their production took a considerable amount of time [60]. Consistently, studies have shown that CEAs were not stable during long-term recovery [66]. Moreover, the lack of dermal support would cause significant scar formation. Afterward, studies used biomaterials as support matrices for grafting, which proposed better outcomes and minimized complications [72]. However, if there is sufficient dermal support in partial-thickness burn wounds, CEAs can be used without a dermal scaffold with acceptable outcomes. Twenty-two of the included studies have used cultured dermal or skin substitutes [3, 19, 24–27, 29, 31, 33, 35, 37–41, 43–45, 47–50]. Except three of these studies [24, 37, 41], all other 19 studies have used biomaterials in the process of dermal or skin substitute production. Moreover, seven studies used topical application of cell suspensions [18, 28, 30, 32, 36, 42, 46] of which two had used biomaterials in the preparation process [36, 42]. Collagen was the mostly used biomaterial in these studies that was used in grafting, local application, and spraying methods.

In skin substitute grafts, collagen plays role as a matrix for the containment of fibroblasts to be grafted alone or with overlaying cultured keratinocytes. Collagen was the only biomaterial in some of the matrices including Apligraf® [50] (bovine type I collagen [73]), Biobrane® [25–27, 38, 49] (a silicon nylon membrane bonded with porcine type I collagen [74]), StrataGraft® (murine type I collagen) [19, 33], and a dermal analog [43] (non-bovine type I collagen [75]). In the other matrices collagen was used in combination with other biomaterials including elastin [3] (MatriDerm®; bovine collagen type I, III, and V coated with bovine elastin [76]) and glycosaminoglycan (GAG) [39, 40, 45, 47] (bovine collagen and chondroitin-6-sulfate [77]). Other used biomaterials in the included studies were thermosensitive hydrogel [29, 31], silicon sheet with GAG (Alloskin) [44], and polyglactin acid vicryl mesh in Dermagraft [48]. Biomaterials were also used in spraying cell suspension studies. Biobrane® [36] and fibrin sealant [42] (containing fibrinogen and thrombin [78]) were biomaterials used in these studies.

GAGs are a group of polysaccharides that are present in the cell membrane and ECM of all tissues in the body [79] and play role in several signaling pathways, including cell migration and proliferation [80]. Despite this role, GAGs alone have been shown to decrease the migration rate of keratinocytes in vitro [81]. Therefore, the majority of products that contain GAGs, especially in skin substitutes, are a combination of GAGs and other materials, including type I collagen [82–84]. Producing scaffolds similar to the skin's structure for wound healing is an important goal. Therefore, the majority of skin

substitutes that consist of a dermal analog, contain type I collagen. Collagen matrix has been used as a model to simulate wound healing process in in vitro studies [85]. Although collagen alone has been used in skin substitutes [43, 50], studies have shown that this method results in a less stable barrier function and delayed keratinization compared to cadaveric skin graft in mice [86]. To overcome this disadvantage, a combination of collagen with other biomaterials can be used [87], including chitosan [88], GAGs [89], and elastin [90].

Using biomaterials as adjuvants of cell therapy for burn wounds seem to be beneficial. However, most of these biomaterials, especially collagens, are xenogeneic materials. Examples for xenogeneic collagens as biomaterials in the included studies are Apligraf® [73], MatriDerm® [76], and Biobrane® [74]. Although animal-derived collagens have been used widely, it has been reported that they are immunogenic [91]. Therefore their clinical use should always be with caution in those who are not previously sensitized to xenogeneic proteins [92].

Degree and extent of burn injury

Another aspect of the included studies that can be discussed is the degree and extent of burn injury. The degree of burn wounds in the included studies were full-thickness/third-degree [3, 18, 37–50] and partial thickness/second-degree [19, 24–36, 47–50]. First-degree burn wounds mainly require conservative treatment [93], and therefore, no study with first-degree burn wounds that had used cell-based therapies was found. From the studies that included full-thickness burn wounds, seven studies have used allogeneic [38, 41, 43, 44, 48–50], and nine studies have applied autologous cells [3, 18, 37, 39, 40, 42, 45–47]. All of the allogeneic cell approaches have used dermal or skin substitutes, while three of the autologous cell studies have used non-cultured approaches (two cell sprays [18, 42] and one local application with sampler [46]). Of the remaining six autologous cell studies with cultured methods, five used dermal or skin substitutes, and one used CEA without a dermal scaffold. From the studies that included partial-thickness burn wounds, 15 used allogeneic cells (12 dermal or skin substitutes [19, 24–27, 29, 31, 33, 35, 48–50], two local applications of hydrogel-cultured cells [29, 31], and one BM-MSC [34]), and five used autologous cells (four ReCell® spraying method [28, 30, 32, 36] and one CSS [47]). It can be understood that most full-thickness burn wounds were treated with cultured grafting methods, especially with the use of dermal or skin substitutes. This can be due to the necessity of wound closure as soon as possible to prevent subsequent complications [94] and also the essential role of ECM in wound healing [95, 96] and in supporting the transplanted cells [70, 97]. This notion is further supported by the two studies that used spraying methods

for CEA and ASCS delivery, which were sprayed in combination with fibrin sealant [42] or over a prior autologous meshed STSG [18]. Although Nilforoushzadeh et al. [46] have not used any scaffolds in combination with the local application of cells for full-thickness burn wounds, they have used autologous fibroblasts which can produce growth factors and ECM components necessary for wound healing [98]. Only one study by Munster et al. [37] used CEA for full-thickness burn wounds, which did not contain any components of dermal ECM. It should be considered that untreated deep partial-thickness burn wounds have compromised healing process and produce high rates of scar tissue. Therefore, early treatment of these wounds are necessary [99]. Moreover, although superficial partial-thickness burn wounds only require standard care or specific wound dressings [100], major superficial partial-thickness burns (TBSA > 15% [7]) need proper cell-based treatment approaches [101].

Depending on the situation, it should be decided which approach is most appropriate. For instance, in full-thickness burn wounds using autologous culturing methods may be more beneficial than other methods. However, these methods require a considerable amount of time to be prepared for grafting [67]. Also, there should be enough healthy donor sites, which is further challenging in extensive burn wounds [68]. Allogeneic dermal or skin substitutes can be used to address this matter since they are ready to use at any time needed, and their production does not require a donor site [69]. However, using allogeneic products have a risk of inducing an immune response [69]. Lack of available donor site is also challenging for extensive partial-thickness burn wounds. Nevertheless, ReCell® autologous cell harvesting device is especially beneficial for these burn wounds if enough donor site is available. It has been shown that using ReCell® reduced the required donor site area by 40 folds compared to STSG for the same wound size [32]. Although, if the extent of the burn wound is so high that enough healthy donor sites cannot not be provided, other cell-based methods should be considered, such as allogeneic dermal or skin substitutes.

Stem cells

Only one study among the included studies used stem cells (local application of allogeneic BM-MSCs) for the treatment of deep partial-thickness burn wounds [34]. The results of this study indicate that BM-MSCs transplantation caused wound healing in all patients with no rejections and improved re-pigmentation. Nevertheless, in the screening process of our study, several studies had used stem cells for the treatment of burn wounds. Although these studies were not included since they were case reports, non-trial clinical studies, or clinical trials with no published results, their assessment

may be helpful for future studies (Table 3). Of these studies, eight were clinical trials of which MSCs were used in six of them (ChiCTR2000040932, EUCTR2018-002870-27-DK, NCT02619851, IRCT201209178177N5, IRCT201202169044N1, EUCTR2012-001596-36-ES) and one study used human amniotic epithelial cells (hAECs, NCT05652816). The source of the MSCs in all

but one trial (allogeneic umbilical cord-derived MSCs, ChiCTR2000040932) was adipose tissue. In one trial, stem cells were derived from burn wounds, but the type of stem cells was not specified (NCT05344521). Allogeneic stem cells were mostly derived from adipose tissue and were used alone (EUCTR2018-002870-27-DK) or loaded on a hydrogel sheet (NCT02619851) or acellular

Table 3 Findings of unincluded studies using stem cells for the treatment of burn wounds

Author/trial ID	Stem cell type	Source	Autologous/allogeneic	Combination/adjuvant	Overall outcome
Yastı-2022 [111]	MSC (SVF)	Adipose	Autologous	NR	- Good cosmetic outcome - Good functional outcome
Kitala-2020 [110]	MSC	Amniotic membrane	Allogeneic	Acellular dermal matrix	- Decreased hospitalization time - Faster wound healing - Decreased pain
Wittig-2020 [103]	MSC	Bone marrow	Allogeneic	Pre-clotted PRP	- Improved re-epithelialization - Improved re-pigmentation - Limited scar formation
Jeschke-2019 [109]	MSC	Umbilical cord-lining/ chorion	Allogeneic	Fibrin sealant	- Improved wound closure - Limited scar formation
Hatzfeld-2019 [115]	MSC	Amniotic membrane	Allogeneic	STSG/MatriDerm®	- Elasticity recovery
Arkoulis-2018 [112]	MSC (SVF)	Adipose	Autologous	Integra®	- Good cosmetic outcomes - Good functional outcomes
Abo-Elkheir-2017 [105]	MSC	Bone marrow/umbilical cord blood	Autologous/allogeneic	NR	- Improved wound healing - Decreased hospitalization time
Portas-2016 [113]	MSC	Cadaveric bone marrow	Allogeneic	NR	NR
Mansilla-2015 [104]	MSC	Cadaveric bone marrow	Allogeneic	Fibrin spray	- Safe to use
Xu-2012 [107]	MSC	Bone marrow	Autologous	STSG	NR
Bhattacharya-2010 [114]	NR	Amniotic membrane and fluid	Allogeneic	NR	NR
Bey-2010 [106]	MSC	Bone marrow	Autologous	STSG	- Complete wound healing and skin reconstruction - Pain relief
Lataillade-2007 [108]	MSC	Bone marrow	Autologous	Surgical treatment	NR
Rasulov-2005 [102]	MSC	Bone marrow	Allogeneic	NR	- Improved wound healing
NCT05652816 [150]	hAEC	Amniotic membrane	Allogeneic	Co-culture with autologous keratinocytes on decellularized amniotic membrane	NR
EUCTR2012-001596-36-ES [151]	MSC	Adipose	NR	NR	NR
IRCT201202169044N1 [152]	MSC	Adipose	Autologous	Silicon sheet scaffold	NR
IRCT201209178177N5 [153]	MSC	Adipose	Allogeneic	Acellular amniotic membrane	NR
NCT02619851 [154]	MSC	Adipose	Allogeneic	Hydrogel sheet	NR
EUCTR2018-002870-27-DK [155]	MSC	Adipose	Allogeneic	NR	NR
ChiCTR2000040932 [156]	MSC	Umbilical cord	Allogeneic	NR	NR
NCT05344521 [157]	Not specified	Burn wound	Autologous	Integra®	NR

Abbreviations MSC=Mesenchymal stem cells, SVF=Stromal vascular fraction, NR=Not reported, PRP=Platelet-rich plasma, STSG= Split-thickness skin graft, hAEC=Human amniotic epithelial cells

amniotic membrane (IRCT201209178177N5). Autologous stem cells (MSCs) were also derived from adipose tissue and were used on a silicon sheet scaffold in one study (IRCT201202169044N1), and in another study, stem cells were derived from patients' own burn wound tissues (no specified type of stem cells) and were loaded on Integra® (NCT05344521). One study did not state whether the MSCs were autologous or allogeneic (EUCTR2012-001596-36-ES). Both deep partial-thickness and full-thickness burn wounds were treated with stem cells in these clinical trials.

A total of 16 non-trial clinical studies and case reports were also found which had used stem cells. The types of these stem cells were mostly MSCs of different sources, including: (1) allogeneic bone marrow (applied alone [102], on pre-clotted platelet-rich plasma [103], and sprayed with fibrin sealant [104]), (2) autologous BM (applied alone [105] and combined with autologous skin graft [106, 107] or surgical treatment [108]), (3) allogeneic umbilical cord blood used alone [105], (4) chorionic tissue alone [109], (5) a combination of allogeneic umbilical cord-lining stem cells used with fibrin sealant [109], (6) allogeneic amniotic membrane with the support of an acellular dermal matrix [110], (7) autologous adipose tissue (in the form of stromal vascular fraction (SVF) used alone [111] or with Integra® [112]), and (8) cadaveric with no specified source tissue [113]. Aside from the mentioned stem cells, amniotic membrane has also been transplanted combined with amniotic fluid stem cells [114] or applied alone [115] for the treatment of burn wounds. Although the treatment effects of amniotic membrane transplantation and amniotic fluid application cannot solely be related to their stem cells content, they should be considered as a way of delivering stem cells to burn wounds. Amniotic membrane contains MSCs alongside with hAECs [116] and amniotic fluid contains a heterogeneous population of cells [117], including MSCs [118].

It can be indicated that MSCs are the most frequently used type of stem cells for the treatment of burn wounds. The studies with available full-text reported that MSCs transplantation improves wound healing [102, 105, 106, 109, 110], re-epithelialization and re-pigmentation [103], decreases pain [110], causes limited hypertrophic scar formation [103, 109], results in good cosmetic and functional outcomes [111, 112], and reduces the time of hospitalization [105, 110].

There are three main sources of stem cells including embryonic stem cells, adult stem cells, and extra-embryonic stem cells. Embryonic stem cell transplantation, in their undifferentiated form, leads to teratoma formation [119, 120], and transplantation of their differentiated form also leads to the induction of immune response [121]. Moreover, providing embryonic stem cells requires the destruction of embryonic structures, and the ethical justification of their use is under debate [122]. Adult stem cells, however, have been widely used since they are found in most body organs (multipotent, oligopotent, and unipotent stem cells) and can be used for autologous purposes [123], but as they are more differentiated, they express more major histocompatibility complex (MHC) molecules and have more immunogenicity; therefore, their allogeneic use is limited. The exceptions are MSCs that despite the low levels of MHC-I and MHC-II antigen expression and being potentially immunogenic [124], induce low levels of immune response due to their immunosuppressive [124] and immunomodulatory effects [125] majorly mediated by MSC-secretome. MSC-secretome mostly contain DNAs, RNAs, micro-RNAs, long non-coding RNAs, surface markers, growth factors, cytokines, and chemokines [126]. This immunomodulatory effect, alongside their migration to the damaged site, induction of skin cell proliferation, and angiogenesis have made them a favorable choice for the treatment of wounds [10]. MSCs can be extracted from various tissues including BM ($0.01-0.001\%$ of the BM sample content), adipose tissue (5000 cells per 1 gr of the tissue, being 500 times more cells than the same amount of BM), and peripheral blood (1.2–13 cells per one million mononuclear cells) [127]. Overall, the trend toward using BM- and adipose tissue-derived MSCs can be explained by the available number of MSCs in these tissues. Although BM-MSCs were mostly used for burn wounds, it has been shown that adipose-derived MSCs have more proliferative capability, immunomodulatory effects, and growth factor secretion than BM-MSCs [128] and are potentially more beneficial for wound treatments.

Although adult MSCs have shown superiority over other stem cells, extra-embryonic tissues (amnion, chorion, and umbilical cord) also contain MSCs and epithelial stem cells. MSCs of these sources have shown significantly lower immunogenicity [129], higher immunosuppressive, proliferative [130], and differentiation capability [131] compared to adult-MSCs. Moreover, they are isolated at $10-30\times10^6$ cells per amniotic membrane [132], their extraction is non-invasive, and there is less argument about the ethical justification of their use. Similar to extra-embryonic MSCs, another population of stem cells are present in amniotic membranes called hAECs. They also have immunomodulatory and immunosuppressive capacities, have low immunogenicity and tumorigenicity potential [133], and are isolated at a considerable amount (about $80-300\times10^6$ cells per placenta) [134]. Although there are approximately ten times more available hAECs than MSCs in an amniotic membrane of a placenta, there are various other parts of a placenta that MSCs can be isolated from [135]. In addition to stem cells isolated from extra-embryonic tissues,

the transplantation of whole amniotic membrane has been shown to improve the wound healing process [136]. Amniotic membrane contains the aforementioned stem cells, and therefore, it has anti-inflammatory, pain relieving, anti-scarring, and re-epithelialization properties with low immunogenicity and rejection, which has been used in both cellularized and decellularized (as a scaffold) forms for the treatment of different conditions [137].

Future aspects

Several aspects can be suggested to direct future studies. The results of the studies that used stem cells for the treatment of burn wounds are promising [102, 103, 105, 106, 109–112]. However, there are still no FDA-approved stem cell-based products for the treatment of these wounds. The interesting characteristics and capabilities of stem cells to evade immune response and induce the wound healing process [124, 125] make them a special target for future studies. Although most of the studies have focused on BM-MSCs and adipose tissue-derived MSCs, other sources of stem cells, especially extra-embryonic sources, can be of interest. Extra-embryonic stem cells can be obtained easily and abundantly while BM and adipose tissue give limited number of stem cells and their extraction is invasive [127]. Of these extra-embryonic sources, hAECs have the potential to differentiate to several types of skin cells, including keratinocytes [138]. Therefore, these cells can be used to improve the outcomes of existing cell-based therapy approaches for burn wound treatment or producing cultured skin substitutes as a replacement for allogeneic skin graft.

Aside from the sources of cells, the methods of delivering cells to the burn wound should also be considered for future studies. The majority of studies have used culturing methods to expand cells on scaffolds or matrices. A limited number of studies have used spraying methods for delivering autologous cells. The spraying delivery method can also be modified for delivering stem cells or a combination of autologous skin cells and stem cells for better wound healing outcomes. Enhanced spraying methods may also be useful such as electro-spray; we previously reviewed different aspects of cell spraying methods, which produce a mist of cells with a more uniform expansion over the wound area [139]. Additionally, cells can also be embedded into dressings for local application. Moreover, 3D bioprinted skin may be inspiring for the treatment of burn wounds. This method can be used to create customized skin grafts with improved functionality and compatibility.

Another aspect for future studies is the combination of cells with other biomaterials. Keratin and chitosan as biomaterials other than collagen can be used as scaffolds for cell delivery [140]. Also, a combined delivery of cells with cell supporting materials for local application of cells can

be considered. Furthermore, studies have used amniotic membrane in different ways for burn wounds; although, using a powder form of this membrane may also be of interest. This amniotic ECM powder can be used in combination with different cells as a supporting component. This combination has been used in our recent pilot study for the treatment of burn wounds (unpublished data). In addition, using nanomaterial in cell therapy for burn wounds may be considered in the future. Nanocarriers can be used to contain cells and protect them from the injured and inflamed environment of the burn wound so that these cells can function better and stay viable. Furthermore, nanofibers and nanotubes can be used for the regeneration of burn wounds by improving the produced ECM, which enhances cell adhesion and growth. Although systemic delivery of stem cells for local injuries like burn wounds seems to be impractical, but nanoparticles or nanocarriers may be useful. Magnetic nanoparticles or nanocarriers may be helpful as they can be used to guide the delivered cells to the injured location. Moreover, nanobiomaterials and nano-enriched bioinks can be employed to help produce a 3D bioprinted skin for the treatment of burn wounds [141]. Considering ecological safety, green biomaterials, which have potential clinical implications [142], can also be used as alternatives to conventionally produced nanomaterials combined with cell-based therapies for burn wounds. As for other adjuvants, plants- and seeds-derived products, such as oil and pulp can be used in combination with cell-based therapies to maintain moisture of the wound area and reduce the harshness of the environment for the delivered cells [143–145]. Another adjuvant that can be combined with cell-based therapy are exosomes. Stem cell-derived exosomes have shown various capabilities in regenerative medicine [146]. Co-delivery of these exosomes with cells may have promising results for the treatment of burn wounds. Also, cells can be delivered with certain growth factors like epidermal growth factor (EGF) or FGFs for further support.

Conclusion

Our study showed that using cell-based therapies for the treatment of burn wounds have promising results in clinical studies. Cell-based therapies are emerging as novel approaches for the treatment of several skin disorders, such as melanoma [147], vitiligo [148], and other skin disorders [149]. Therefore, considering the promising results of our study and the employment of cell-based therapies for various skin disorders, we can suggest these approaches as alternatives to the existing treatments for burn wounds.

However, suggesting an absolute and certain alternative cell-based treatment approach for burn wounds seems to be challenging since different types of burn

wounds require different approaches. Nevertheless, the advantages and limitations of these approaches in different aspects for different types of burn wounds were discussed in this systematic review.

Abbreviations

STSG	Split-thickness Skin Autograft
MSC	Mesenchymal Stem Cell
WHO	World Health Organization
TBSA	Total Body Surface Area
ESC	Embryonic Stem Cell
USC	Umbilical Cord Stem Cell
iPSC	Induced Pluripotent Stem Cell
ECM	Extracellular Matrix
POSAS	Patient and Observer Scar Assessment Scale
VSS	Vancouver Scar Scale
MSF	Migration Stimulating Factor
NGF	Nerve Growth Factor
VEGF	Vascular Endothelial Growth Factor
TNF	Tumor Necrosis Factor
IL	Interleukin
CEA	Cultured Epithelial Autografts
CEAllo	Cultured Epidermal Allograft
BSS	Bioengineered Skin Substitute
MMP	Matrix Metalloproteinase
TIMP	Tissue Inhibitors of Metalloproteinase
FGF	Fibroblast Growth Factor
TGF	Transforming Growth Factor
KGF	Keratinocyte Growth Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
ASCS	Autologous Skin Cell Suspension
RCT	Randomized Control Trial
CSS	Cultured Skin Substitute
ESS	Engineered Skin Substitutes
NIKS	Near-Diploid Neonatal Human Keratinocyte Cell Line
BM	Bone Marrow
HUK	Human Undifferentiated Keratinocyte
GAG	Glycosaminoglycan
hAEC	Human Amniotic Epithelial Cell
SVF	Stromal Vascular Fraction
MHC	Major Histocompatibility Complex

Supplementary Information

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Supplementary Material 1

Author contributions
YY, YN, FN, and HN contributed to the design and conception of the review. YY and YN screened the databases and extracted the clinical trials for the systematic review. YY and YN contributed to the writing of the manuscript. HN and FN supervised and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Declarations

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Competing interests
The authors declare that they have no competing interests.

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