Research Article

The clinical effectiveness and safety of using epidermal growth factor, fibroblast growth factor and granulocyte-macrophage colony stimulating factor as therapeutics in acute skin wound healing: a systematic review and meta-analysis

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Abstract

Background: Promoting wound healing is crucial to restore the vital barrier function of injured skin. Growth factor products including epidermal growth factor (EGF), fibroblast growth factor (FGF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been used for decades although no systematic evaluation exists regarding their effectiveness and safety issues in treating acute skin wounds. This has resulted in a lack of guidelines and standards for proper application regimes. Therefore, this systematic review and meta-analysis was performed to critically evaluate the effectiveness and safety of these growth factors on skin acute wounds and provide guidelines for application regimes.

Methods: We searched PubMed/Medline (1980–2020), Cochrane Library (1980–2020), Cochrane CENTRAL (from establishment to 2020), ClinicalTrials.gov (from establishment to 2020), Chinese Journal Full-text Database (CNKI, 1994–2020), China Biology Medicine disc (CBM, 1978–2019), Chinese Scientific Journal Database (VIP, 1989–2020) and Wanfang Database (WFDATA, 1980–2019). Randomized controlled trials (RCTs), quasi-RCTs and controlled clinical trials treating patients with acute skin wounds from various causes and with those available growth factors were included.

Results: A total of 7573 papers were identified through database searching; 229 papers including 281 studies were kept after final screening. Administering growth factors significantly shortened the healing time of acute skin wounds, including superficial burn injuries [mean difference (MD) = −3.02; 95% confidence interval (CI): −3.31 to −2.74; p < 0.00001], deep burn injuries (MD = −5.63; 95% CI: −7.10 to −4.17; p < 0.00001), traumata and surgical wounds (MD = −4.50; 95%
Compared with non-growth factor treatment, administering growth factors significantly shortened the healing time while decreasing scar scores. The incidence of adverse reactions was lower in the growth factor treatment group than in the non-growth factor group.

**Conclusions:** The studied growth factors not only are effective and safe for managing acute skin wounds, but also accelerate their healing with no severe adverse reactions.

**Key words:** Growth factors, Skin wounds, Meta-analysis, Wound healing

**Highlights**

- This study is the first to comprehensively evaluate the effectiveness and safety of using growth factors as therapeutics in acute skin wounds healing.
- Compared with non-growth factor treatment, administering growth factors significantly shortened the healing time while increasing the healing rate of acute skin wounds with lower scar scores and fewer adverse reactions.

**Background**

Skin maintains internal homeostasis and provides a barrier between our body and the outside environment [1]. Acute skin wounds break the barrier and expose the body to the risk of pathogen infections and fluid losses. Therefore, restoring skin integrity as soon as possible after wounding is the body’s most effective way to restore the environment’s balance, fight infections and prevent fluid and electrolyte disturbances from occurring. The speed of wound healing is of essential importance and can impact on the patient’s prognosis [2].

Several factors can influence the speed of wound healing, such as the growth factors secreted by activated local cells. Numerous studies have recognized and elaborated upon growth factors’ crucial roles in advancing angiogenesis, re-epithelialization, granulation tissue formation and inflammatory response regulation [3]. Until now, the growth factors reported to promote wound healing mainly include vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), transforming growth factor-β1 (TGF-β1), epidermal growth factors (EGFs), granulocyte-macrophage colony stimulating factor (GM-CSF), hepatocyte growth factor (HGF), etc. [3–6].

In 1971, Frati and Scarpa reported the treatment of mouse burns with EGF [7]. The first human recombinant FGF-2 was reported in 1988 [8]. In 1989, Brown et al. reported in the *New England Journal of Medicine* that epidermal growth factor significantly accelerated the rate of healing of partial thickness skin wounds in a randomized clinical trial [9]. The development of growth factor products targeted at promoting wound healing has been thriving ever since and the clinical application of growth factors has become popular. In 1998, Fu et al. reported the result of a randomized placebo-controlled trial investigating the effect of recombinant bovine basic fibroblast growth factor (rbFGF) on burns healing. The study showed that rbFGF effectively decreased the time and improved the quality of healing. These favorable results started a wider trend of using growth factors in wound management [10]. In 2007, Ma et al. reported the use of recombinant human acidic FGF (rh-aFGF) for treating deep partial-thickness burns and skin graft donor site through a randomized, multicenter, double-blind and placebo-controlled trial. The study demonstrated that rh-aFGF can promote the healing of both burn wounds and skin graft donor sites [11], which further strengthened the evidence of applying growth factor products to promote acute wound healing, including both burns and surgical wounds.

Currently, EGF, bFGF, aFGF and GM-CSF are approved growth factor products for use on acute skin wounds. During the past decades, the therapeutic use of these growth factors in acute wounds management has gradually become a customary practice in China, however, controversies have raged about the benefits and safety of the clinical implementation of distinct kinds of growth factor products. It is known that acute wounds naturally hold plenty of growth factors, which can stimulate cell proliferation and matrix production at the wound bed. Whether the growth factor receptors are saturated prior to the application of more growth factors to acute wounds is unknown. Secondly, deep acute wounds usually heal with hypertrophic scars. It is still unclear whether deep acute wounds heal with more (or less) severe scars under the use of growth factors. Moreover, in light of the economic costs and possible side-effects (such as carcinogenesis) of high local/systemic growth factor levels, it is unclear whether the practice of using exogenous growth factors for the therapy of acute wounds is a real necessity. In addition, whether growth factor treatments provide true benefits remains uncertain given their instability and short in vivo half-life [4,12,13].

Notably, a systematic evaluation of the effectiveness and safety of the available growth factor products used for acute skin wound therapy is missing. There is still the need to investigate whether the routine administration strategies used in clinical treatments suffice to guarantee the growth factor products’ benefits. To address these issues, we performed the present systematic review and meta-analysis to assess the clinical effectiveness and safety of all currently clinically available growth factor products in treating acute skin wounds as compared to non-growth factor treatments. The results of
this study will supply the evidence to strengthen the future therapeutic use of growth factors in clinical settings.

**Methods**

This systematic review was conducted according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [14]. It was based on the planned Participants, Intervention, Control, Outcome and Study design (PICOS) elements.

**Search strategy**

The searched databases included: PubMed/Medline (1980–2020); Cochrane Library (1980–2020); Cochrane CENTRAL (from establishment to 2020); ClinicalTrials.gov (from establishment to 2020); Chinese Journal Full-text Database (CNKI, 1994–2020); China Biology Medicine disc (CBM, 1978–2019); Chinese Scientific Journal Database (VIP, 1989–2020); and Wanfang Database (WFDATA, 1980–2019). With the combination of subject words and free words, the search terms included two categories: (1) ‘epidermal growth factor’, ‘basic fibroblast growth factor’, ‘acid fibroblast growth factor’, and ‘granulocyte-macrophage colony stimulating factor’; and (2) ‘trauma’, ‘wound’, ‘burn’, and ‘surgery’. The logical relationship was created with ‘OR’ and ‘AND’; and the search formula was thereafter developed according to the characteristics of the different databases. For example, the search strategy for PubMed was: (epidermal growth factor OR EGF) OR (basic fibroblast growth factor OR bFGF) OR (acid fibroblast growth factor OR aFGF) OR (granulocyte-macrophage colony stimulating factor OR GM-CSF) AND ((superficial OR surgical OR burn) AND wounds)). A pre-retrieval process improved the searches strategy. In addition, we conducted a manual search of unpublished studies and conference materials, tracking also the references of the included literature. For the analysis we included studies reported in both Chinese and English.

**Inclusion and exclusion criteria**

The inclusion and exclusion criteria are listed in Table 1.

**Study selection** Two researchers independently read the titles and abstracts to exclude the literature that did not meet the inclusion criteria. As a further safeguard, the full texts of the literature that might have met the inclusion criteria were read and evaluated. At the same time, the following information was extracted: author, publication date, research type, characteristics of research objects, sample number, loss of or withdrawal from interview, intervention measures and measurement indicators, and more. For multiple studies published in the same literature, the required data were acquired according to their research contents. In the case of repetitive reports, the study included only the latest or the most comprehensive ones.

**Quality evaluation** The quality of the included research method was evaluated via Jadad’s scale, which is an internationally recognized clinical trial scoring standard, as it includes data about random method, allocation concealment, blind use, loss of follow-up, withdrawal and outcome. The score range was 1–5 points, including 1–2 points for lower quality and 3–5 points for higher quality.

**Meta-analysis** The RevMan5.4 software recommended by Cochrane Collaboration served for meta-analysis. Subgroups considered types of wounds and outcome variables. The relative risk (RR) consisted of the joint effect size for the counting data, while the weighted mean difference (WMD) was used for the measurement data. All effects were conveyed with their 95% confidence interval (CI). Results heterogeneity...
was assessed by the chi square test. When the homogeneity of each study was statistically significant \((p > 0.1, I^2 < 50\%)\), the fixed effect model was used; otherwise, the random effect model was used. Subgroup results from single studies were noted down.

Results
Study selection and characteristics
In total, our preliminary screening selected 7573 papers. After screening titles, abstracts and full-texts (Figure 1) we kept 229 papers including 281 studies, which consisted of 207 randomized controlled trials (RCTs) and 74 clinical controlled trials (CCTs) with a total of 30562 patients. The basic characteristics of the included studies and the results of the methodological quality evaluations are shown in Table 2 [10,11,15–241]. All the growth factors in these studies were applied topically. In all studies, the patients’ basic characteristics were comparable \((p > 0.05)\) between intervention groups and control groups.

Healing time comparison of second-degree burn wounds
A total of 76 studies [10,15–25,27–55,57–86,144,230,234, 236,237] enrolling 8915 cases compared the healing time of superficial second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the presence of statistical heterogeneity \((p < 0.00001; I^2 = 88\%)\). Therefore, the random effect model was used for meta-analysis (Figure 2). The results showed that the

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*Some articles containing multiple studies

**Figure 1.** PRISMA flow diagram for inclusion or exclusion of studies used for this systematic review. PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses
Table 2. Characteristics of included studies

| Author                  | Year | Study Design | Country | Wound Type                  | Sample size (Treatment) | Sample size (Control) | Jadad's Score |
|-------------------------|------|--------------|---------|-----------------------------|-------------------------|-----------------------|---------------|
| Pan et al. [15]         | 2009 | CCT          | China   | Superficial Second-degree Burns | rhEGF+R1 + 1%SD-Ag Cream(n = 64) | 1%SD-Ag Cream(n = 64) | 3             |
| Wu et al. [16]          | 2013 | CCT          | China   | Superficial Second-degree Burns | rhEGF + Zn-SD Gel(n = 19) | Zn-SD Gel(n = 19) | 1             |
| Guo et al. [17]         | 2017 | RCT          | China   | Superficial Second-degree Burns | Er Huang Ointment + rhGM-CSF Gel(n = 49) | Ag-SD Cream(n = 49) | 2             |
| Ma et al. [18]          | 2014 | CCT          | China   | Superficial Second-degree Burns | VSD + rb-bFGF(n = 9) | VSD(n = 9) | 1             |
| Huang et al. [19]       | 2004 | RCT          | China   | Superficial Second-degree Burns | 1% SD-Ag Cream + rhEGF(n = 30) | 1% SD-Ag Cream(n = 26) | 2             |
| Li et al. [20]          | 2002 | RCT          | China   | Superficial Second-degree Burns | rhEGF(n = 566) | 0.9% NS(n = 167) | 2             |
| Chen et al. [21]        | 2001 | RCT          | China   | Superficial Second-degree Burns | bFGF(n = 30) | SD-Ag Cream(n = 30) | 2             |
| Guo et al. [22]         | 2004 | CCT          | China   | Superficial Second-degree Burns | bFGF(n = 1.5) | Blank(n = 1.5) | 1             |
| Huo et al. [23]         | 1996 | CCT          | China   | Superficial Second-degree Burns | bFGF Spray(n = 29) | Blank(n = 29) | 1             |
| Li et al. [24]          | 2004 | CCT          | China   | Superficial Second-degree Burns | bFGF(n = 191) | Blank(n = 191) | 1             |
| Hu et al. [25]          | 2012 | RCT          | China   | Superficial Second-degree Burns | GM-CSF + AD-Ag Cream(n = 42) | SD-Ag Cream(n = 42) | 2             |
| Gong [26]               | 2007 | RCT          | China   | Superficial Second-degree Burns | rhEGF Spray(n = 30) | Standard care(n = 30) | 2             |
| Luo et al. [27]         | 2014 | CCT          | China   | Superficial Second-degree Burns | 1% Povidone iodine + rb-bFGF(n = 5) | 1% Povidone iodine(n = 5) | 2             |
| Liao et al. [28]        | 1996 | CCT          | China   | Superficial Second-degree Burns | EGF + 1% SD-Ag(n = 48) | 1% SD-Ag(n = 48) | 2             |
| Guo et al. [29]         | 2009 | RCT          | China   | Superficial Second-degree Burns | rhEGF Hydrogel + Vaseline | Vaseline gauze(n = 32) | 2             |
| Liu et al. [30]         | 2001 | RCT          | China   | Superficial Second-degree Burns | rh-bFGF + 1% SD-Ag(n = 23) | 1% SD-Ag(n = 23) | 1             |
| Liu et al. [31]         | 2012 | CCT          | China   | Superficial Second-degree Burns | rh-bFGF + 1% SD-Ag(n = 12) | 1% SD-Ag(n = 13) | 1             |
| Guo et al. [32]         | 2019 | CCT          | China   | Superficial Second-degree Burns | rh-EGF Spray + Burn Cream(n = 90) | Povidone iodine(n = 60) | 1             |
| Li [33]                 | 2003 | RCT          | China   | Superficial Second-degree Burns | rhEGF+1% SD-Ag(n = 32) | 1% SD-Ag(n = 32) | 2             |
| Liu et al. [34]         | 2005 | CCT          | China   | Superficial Second-degree Burns | bFGF(n = 149) | Blank(n = 149) | 1             |
| Lin et al. [35]         | 2014 | RCT          | China   | Superficial Second-degree Burns | rb-bFGF Gel(n = 37) | Blank(n = 36) | 3             |
| Guo et al. [36]         | 2002 | CCT          | China   | Superficial Second-degree Burns | rb-bFGF Lyophilized powder(n = 566) | Standard Care(n = 167) | 1             |
| Fan et al. [37]         | 2018 | RCT          | China   | Superficial Second-degree Burns | rh-bFGF Gel + Vaseline gauze(n = 45) | Vaseline gauze(n = 45) | 2             |
| Meng et al. [38]        | 2018 | RCT          | China   | Superficial Second-degree Burns | rh-bFGF(n = 63) | Standard care(n = 63) | 3             |
| Guo et al. [39]         | 2010 | RCT          | China   | Superficial Second-degree Burns | SD-Ag Cream + rhEGF(n = 20) | SD-Ag cream(n = 19) | 2             |
| Fang et al. [40]        | 2014 | RCT          | China   | Superficial Second-degree Burns | rhEGF(n = 35) | Blank(n = 37) | 2             |
| Liang et al. [41]       | 2007 | CCT          | China   | Superficial Second-degree Burns | rhEGF(n = 60) | Normal saline(n = 60) | 3             |
| Liang et al. [42]       | 2006 | CCT          | China   | Superficial Second-degree Burns | rhEGF(n = 60) | Normal saline(n = 60) | 3             |
| Huo et al. [43]         | 2001 | CCT          | China   | Superficial Second-degree Burns | rhEGF+Topical antibiotics(n = 26) | Topical antibiotics(n = 26) | 1             |

(Continued)
| Author          | Year | Study Design | Country | Wound Type                        | Sample size (Treatment)                  | Sample size (Control)                  | Jadad’s Score |
|-----------------|------|-------------|---------|-----------------------------------|-----------------------------------------|----------------------------------------|---------------|
| Fu et al. [44]  | 2003 | CCT         | China   | Superficial Second-degree Burns   | rh-EGF(n = 51)                          | Blank(n = 51)                          | 1             |
| Liao et al. [45]| 2003 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF+SD-Ag(n = 39)                    | 1%SD-Ag cream(n = 39)                  | 2             |
| Li et al. [46]  | 2004 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF+Wuhuang oil(n = 20)             | Wuhuang oil(n = 2.5)                  | 2             |
| Liu et al. [47] | 2005 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF Lyophilized powder +1%SD-Ag(n = 23) |                              | 2             |
| Chao et al. [48]| 2003 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF + Vaseline gauze(n = 30)        | Vaseline gauze(n = 30)                 | 2             |
| Guo [49]        | 2006 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF+1%SD-A(n = 24)                 | 1%SD-Ag(n = 2.5)                       | 2             |
| Liu [50]        | 2014 | RCT         | China   | Superficial Second-degree Burns   | rh-aFGF(n = 50)                        | Normal saline(n = 50)                  | 1             |
| Chen [51]       | 2014 | CCT         | China   | Superficial Second-degree Burns   | rh-aFGF(n = 15)                        | Normal saline(n = 15)                  | 1             |
| Sun et al. [52] | 2011 | RCT         | China   | Superficial Second-degree Burns   | bFGF+Bashi Cream(n = 48)               | Vaseline gauze(n = 45)                 | 2             |
| Qu et al. [53]  | 2018 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF+Chitosan(n = 40)               | Chitosan(n = 40)                       | 3             |
| Sun et al. [54] | 2018 | RCT         | China   | Superficial Second-degree Burns   | bFGF + Topical antibiotics(n = 46)     | Topical antibiotics(n = 46)            | 1             |
| Tan et al. [55] | 2005 | RCT         | China   | Superficial Second-degree Burns   | Topical antibiotics+bFGF(n = 16)       | Topical antibiotics(n = 18)            | 1             |
| Chen et al. [56]| 2003 | CCT         | China   | Superficial Second-degree Burns   | rh-EGF(n = 30)                         | 0.5%Complex iodine(n = 41)             | 1             |
| Shi [58]        | 2019 | RCT         | China   | Superficial Second-degree Burns   | Nano-Ag + rh-EGF(n = 25)               | Nano-Ag(n = 26)                       | 3             |
| Sun et al. [59] | 2015 | RCT         | China   | Superficial Second-degree Burns   | aFGF(n = 21)                           | SD-Ag(n = 2.5)                        | 3             |
| Tan et al. [60] | 2001 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF+5%SD-Ag(n = 51)                 | 5%SD-Ag(n = 51)                       | 2             |
| Wang et al. [61]| 2004 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF(n = 30)                         | Normal saline(n = 30)                  | 2             |
| Yang et al. [62]| 2000 | CCT         | China   | Superficial Second-degree Burns   | bFGF(n = 80)                           | Blank(n = 80)                         | 1             |
| Wang et al. [63]| 2000 | CCT         | China   | Superficial Second-degree Burns   | bFGF(n = 14)                           | Blank(n = 14)                         | 1             |
| Ye et al. [64]  | 2008 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF+SD-Ag(n = 30)                   | SD-Ag(n = 30)                         | 2             |
| Wang et al. [65]| 2010 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF + Nano-Ag(n = 40)               | 0.5%PVP-1(n = 38)                      | 2             |
| Xiong et al. [66]| 2010| CCT         | China   | Superficial Second-degree Burns   | rh-EGF + Ammon(n = 15)                 | Ammon(n = 15)                         | 1             |
| Wang et al. [67]| 2009 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF + Vaseline gauze(n = 31)       | Vaseline gauze(n = 31)                 | 1             |
| Xiong [68]      | 2019 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF +SD-Ag(n = 60)                 | SD-Ag(n = 60)                         | 2             |
| Wang et al. [69]| 2002 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF Spray +SD-Ag(n = 206)           | SD-Ag(n = 206)                        | 3             |
| Xu et al. [70]  | 2016 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF Hydrogel(n = 49)               | Standard care(n = 51)                 | 2             |
| Xiong [71]      | 2018 | RCT         | China   | Superficial Second-degree Burns   | rh-EGF Hydrogel(n = 46)                | Zhenshi Burn cream(n = 46)             | 2             |
| Yang et al. [72]| 2002 | RCT         | China   | Superficial Second-degree Burns   | rh-bFGF+SD-Ag(n = 11)                  | SD-Ag(n = 11)                         | 2             |

(Continued)
| Author               | Year | Study Design | Country | Wound Type                        | Sample size (Treatment) | Sample size (Control) | Jadad's Score |
|----------------------|------|--------------|---------|-----------------------------------|-------------------------|-----------------------|---------------|
| Wang et al. [73]     | 2003 | CCT          | China   | Superficial Second-degree Burns   | rh-bFGF (n = 12)        | Normal saline (n = 12)| 1             |
| Zhou et al. [74]     | 1999 | RCT          | China   | Superficial Second-degree Burns   | bFGF+Vaseline gauze (n = 20) | Vaseline gauze (n = 20) | 2             |
| Zhou et al. [75]     | 2005 | RCT          | China   | Superficial Second-degree Burns   | bFGF (n = 72)           | Vaseline gauze (n = 80) | 2             |
| Zhan [76]            | 2015 | RCT          | China   | Superficial Second-degree Burns   | Nano-Ag + rh-EGF (n = 20) | Nano-Ag (n = 18)      | 2             |
| Zhang et al. [77]    | 2014 | RCT          | China   | Superficial Second-degree Burns   | rh-bFGF Hydrogel (n = 37) | Topical antibiotics (n = 37) | 2             |
| Zhang et al. [78]    | 2001 | CCT          | China   | Superficial Second-degree Burns   | rh-bFGF (n = 31)        | Blank (n = 31)         | 1             |
| Zhou et al. [79]     | 2015 | RCT          | China   | Superficial Second-degree Burns   | rhEGF+Nano-Ag (n = 44)  | Nano-Ag (n = 44)      | 3             |
| Zou et al. [80]      | 2017 | RCT          | China   | Superficial Second-degree Burns   | rhEGF+Nano-Ag (n = 29)  | Chlorhexidine (n = 27) | 3             |
| Zhou et al. [81]     | 2001 | RCT          | China   | Superficial Second-degree Burns   | rhEGF+SD-Ag Cream (n = 95) | SD-Ag Cream (n = 67) | 3             |
| Zhang [82]           | 2012 | RCT          | China   | Superficial Second-degree Burns   | rhEGF+SD-Ag Cream (n = 30) | SD-Ag Cream (n = 30) | 2             |
| Zhen et al. [83]     | 2003 | RCT          | China   | Superficial Second-degree Burns   | rh-aFGF+Hydrogen peroxide solution (n = 50) | Hydrogen peroxide solution (n = 50) | 1             |
| Zhou et al. [84]     | 2014 | CCT          | China   | Superficial Second-degree Burns   | bFGF+Hydrocolloid dressing (n = 45) | Vaseline gauze (n = 43) | 3             |
| Wu et al. [85]       | 2015 | RCT          | China   | Superficial Second-degree Burns   | bFGF+1%SD-Ag Cream (n = 53) | 1%SD-Ag Cream (n = 61) | 1             |
| Lu [86]              | 2002 | CCT          | China   | Superficial Second-degree Burns   | rhEGF+Insulin+1%SD-Ag (n = 56) | 1%SD-Ag (n = 56) | 3             |
| Pan et al. [15]      | 2009 | CCT          | China   | Deep Second-degree Burns          | rhEGF+Insulin+1%SD-Ag (n = 22) | PVP1-Vaseline gauze + SD-Ag (n = 21) | 3             |
| Hu [87]              | 2013 | RCT          | China   | Deep Second-degree Burns          | bFGF Hydrogel+Far infrared therapy (n = 22) | Local oxygen therapy + rhFGF (n = 53) | 3             |
| Huang et al. [88]    | 2012 | RCT          | China   | Deep Second-degree Burns          | Local oxygen therapy + bFGF (n = 53) | Vaseline gauze (n = 29) | 3             |
| Liu et al. [89]      | 2011 | RCT          | China   | Deep Second-degree Burns          | rhGM-CSF Hydrogel (n = 29) | Vaseline gauze (n = 29) | 3             |
| Hong et al. [16]     | 2013 | CCT          | China   | Deep Second-degree Burns          | bFGF+SD-Zn (n = 15)   | SD-Zn (n = 15) | 1             |
| He et al. [90]       | 2018 | RCT          | China   | Deep Second-degree Burns          | Compound polymyxin     | Compound polymyxin | 3             |
| Cheng et al. [91]    | 2011 | RCT          | China   | Deep Second-degree Burns          | rhGM-CSF Hydrogel + Fulin honey (n = 56) | Placebo +SD-Ag Cream (n = 56) | 4             |
| Huang et al. [19]    | 2004 | RCT          | China   | Deep Second-degree Burns          | 1%SD-Ag + rhEGF (n = 21) | 1%SD-Ag (n = 20) | 2             |
| Li et al. [20]       | 2002 | RCT          | China   | Deep Second-degree Burns          | rhFGF (n = 354) | Normal saline (n = 142) | 2             |
| Chen et al. [21]     | 2001 | RCT          | China   | Deep Second-degree Burns          | bFGF (n = 30) | SD-Ag Cream (n = 30) | 2             |
| Gao et al. [22]      | 2004 | CCT          | China   | Deep Second-degree Burns          | bFGF (n = 9) | Blank (n = 9) | 1             |
| Huo et al. [23]      | 2018 | RCT          | China   | Deep Second-degree Burns          | bFGF+1%SD-Ag Cream (n = 89) | 1%SD-Ag SD-Ag Cream (n = 89) | 1             |
| Author       | Year | Study Design | Country | Wound Type                  | Sample size (Treatment) | Sample size (Control) | Jadad’s Score |
|--------------|------|--------------|---------|-----------------------------|-------------------------|-----------------------|---------------|
| Li et al. [24] | 2004 | CCT          | China   | Deep Second-degree Burns    | bFGF(n = 54)            | Blank (n = 54)        | 1             |
| Chen et al. [92] | 2013 | RCT          | China   | Deep Second-degree Burns    | Collagen + rh-EGF Hydrogel (n = 44) | SD-Ag (n = 44) | 2             |
| Chen et al. [93] | 2012 | RCT          | China   | Deep Second-degree Burns    | MEBO + bFGF (n = 66)    | MEBO (n = 69)         | 2             |
| Liao et al. [94] | 2018 | RCT          | China   | Deep Second-degree Burns    | Nano-Ag + rh-bFGF (n = 48) | Nano-Ag (n = 48) | 3             |
| Li et al. [95] | 2015 | RCT          | China   | Deep Second-degree Burns    | Nano-Ag + rhEGF Hydrogel (n = 48) | Nano-Ag (n = 48) | 1             |
| Liao et al. [28] | 1996 | CCT          | China   | Deep Second-degree Burns    | EGF (n = 32)            | Normal saline (n = 20) | 2             |
| Han [96]      | 2018 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 35)        | Antibacterial         | 3             |
| Lin et al. [97] | 2017 | RCT          | China   | Deep Second-degree Burns    | rhGM-CSF Hydrogel (n = 50) | 1%SD-Ag + Vaseline ga(ze(n = 50) | 3             |
| Zeng [98]     | 2012 | RCT          | China   | Deep Second-degree Burns    | rhGM-CSF Hydrogel (n = 50) | PVP-I (n = 50) | 3             |
| Li [99]       | 2014 | RCT          | China   | Deep Second-degree Burns    | Insulin + rh-EGF (n = 29) | Insulin (n = 29) | 2             |
| Meng et al. [100] | 2005 | RCT          | China   | Deep Second-degree Burns    | rh-EGF + SD-Ag (n = 56) | SD-Ag (n = 42) | 2             |
| Liu et al. [30] | 2001 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF + 1% SD-Ag (n = 39) | 1% SD-Ag (n = 39) | 1             |
| Liu et al. [31] | 2012 | CCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 32)        | 1% SD-Ag (n = 35) | 1             |
| Gao et al. [32] | 2019 | CCT          | China   | Deep Second-degree Burns    | rh-EGF (n = 153)        | PVD-I (n = 147) | 1             |
| Liu et al. [34] | 2005 | CCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 399)       | Blank (n = 399) | 1             |
| Lin et al. [35] | 2014 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 23)        | PVD-I (n = 24) | 3             |
| Guo et al. [36] | 2002 | CCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 354)       | Standard care (n = 142) | 1             |
| Meng et al. [38] | 2018 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 28)        | PVD-I (n = 30) | 3             |
| Guo et al. [39] | 2010 | RCT          | China   | Deep Second-degree Burns    | SD-Ag + rhEGF (n = 20) | SD-Ag (n = 21) | 2             |
| Fang et al. [40] | 2014 | RCT          | China   | Deep Second-degree Burns    | rhEGF (n = 32)          | Blank (n = 30) | 2             |
| Liang et al. [41] | 2007 | CCT          | China   | Deep Second-degree Burns    | rh-EGF (n = 60)         | Normal saline (n = 60) | 3             |
| Liang et al. [42] | 2006 | CCT          | China   | Deep Second-degree Burns    | rhEGF (n = 60)          | Normal saline (n = 60) | 3             |
| Huo et al. [43] | 2001 | CCT          | China   | Deep Second-degree Burns    | rhEGF (n = 16)          | Normal saline (n = 16) | 1             |
| Han et al. [101] | 2017 | RCT          | China   | Deep Second-degree Burns    | rhEGF + SD-Zn Gel (n = 34) | SD-Zn Gel (n = 34) | 3             |
| Chen et al. [102] | 2017 | CCT          | China   | Deep Second-degree Burns    | rhEGF + Mupirocin ointment (n = 300) | MEBO (n = 300) | 1             |
| Li [103]      | 2016 | RCT          | China   | Deep Second-degree Burns    | rhEGF Hydrogel (n = 32) | SD-Ag (n = 32) | 2             |
| Hua [104]     | 2019 | RCT          | China   | Deep Second-degree Burns    | rhEGF (n = 50)          | MEBO (n = 50) | 3             |
| Fu et al. [44] | 2003 | CCT          | China   | Deep Second-degree Burns    | rhEGF (n = 28)          | Blank (n = 28) | 1             |
| Liao et al. [45] | 2003 | RCT          | China   | Deep Second-degree Burns    | rhEGF (n = 21)          | 1% SD-Ag | 2             |
| Li et al. [46] | 2004 | RCT          | China   | Deep Second-degree Burns    | rhEGF + Wuhuang oil (n = 20) | Wuhuang oil (n = 25) | 2             |
| Liu et al. [47] | 2005 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 39)        | Normal saline (n = 39) | 2             |
| Jin et al. [105] | 2014 | CCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 36)        | SD-Ag (n = 37) | 1             |
| Chao et al. [48] | 2003 | RCT          | China   | Deep Second-degree Burns    | rh-bFGF (n = 50)        | Vaseline gauze (n = 50) | 2             |
| Author            | Year | Study Design | Country | Wound Type                     | Sample size (Treatment) | Sample size (Control) | Jadad's Score |
|-------------------|------|--------------|---------|--------------------------------|-------------------------|-----------------------|---------------|
| Guo et al.        | 2006 | RCT          | China   | Deep Second-degree Burns       | rh-bFGF (n = 16)        | Normal saline (n = 15)| 2             |
| Liu et al.        | 2014 | RCT          | China   | Deep Second-degree Burns       | rh-bFGF (n = 4)         | Standard care (n = 3) | 2             |
| Cai et al.        | 2017 | RCT          | China   | Deep Second-degree Burns       | rhGM-CSF Hydrogel (n = 35) | Blank hydrogel (n = 35) | 2             |
| Lin               | 2013 | RCT          | China   | Deep Second-degree Burns       | rhGM-CSF Hydrogel (n = 30) | Standard care (n = 40) | 2             |
| Chen et al.       | 2014 | RCT          | China   | Deep Second-degree Burns       | rh-aFGF (n = 50)        | PVD-I (n = 50)        | 1             |
| Cai et al.        | 2016 | RCT          | China   | Deep Second-degree Burns       | rh-aFGF + Vaseline gauze (n = 30) | Vaseline gauze (n = 30) | 3             |
| Sun et al.        | 2011 | RCT          | China   | Deep Second-degree Burns       | rh-aFGF (n = 15)        | Blank (n = 15)        | 1             |
| Qu et al.         | 2010 | RCT          | China   | Deep Second-degree Burns       | rh-bFGF + Bashi cream (n = 38) | Vaseline gauze (n = 37) | 2             |
| Sui et al.        | 2010 | RCT          | China   | Deep Second-degree Burns       | rh-bFGF + Vaseline gauze (n = 132) | Vaseline gauze (n = 132) | 2             |
| Tong et al.       | 2004 | CCT          | China   | Deep Second-degree Burns       | rhEGF (n = 32)          | 0.5% Complex iodine (n = 32) | 1             |
| Shi et al.        | 2019 | RCT          | China   | Deep Second-degree Burns       | Nano-Ag + rh-EGF (n = 15) | Nano-Ag (n = 14)      | 3             |
| Tong et al.       | 2017 | RCT          | China   | Deep Second-degree Burns       | rhEGF + 3D-Zn(n = 53)   | SD-Zn(n = 53)        | 2             |
| Song et al.       | 2018 | RCT          | China   | Deep Second-degree Burns       | rh-FGF Hydrogel (n = 37) | SD-Zn (n = 37)        | 3             |
| Sun et al.        | 2011 | RCT          | China   | Deep Second-degree Burns       | rh-aFGF (n = 24)        | Normal saline (n = 22) | 1             |
| Sun et al.        | 2011 | RCT          | China   | Deep Second-degree Burns       | rhEGF (n = 20)          | Normal saline (n = 22) | 1             |
| Qu et al.         | 2017 | RCT          | China   | Deep Second-degree Burns       | rhGM-CSF Hydrogel + Vaseline gauze (n = 48) | Vaseline gauze (n = 48) | 3             |
| Wang              | 2014 | RCT          | China   | Deep Second-degree Burns       | rhGM-CSF (n = 15)       | Placebo hydrogel (n = 15) | 4             |
| Xu                | 2019 | CCT          | China   | Deep Second-degree Burns       | rh-bFGF (n = 15)        | SD-Ag(n = 15)        | 1             |
| Wang et al.       | 2018 | CCT          | China   | Deep Second-degree Burns       | rhGM-CSF Hydrogel (n = 36) | Blank (n = 36)       | 1             |
| Xu                | 2017 | RCT          | China   | Deep Second-degree Burns       | rhPEG (n = 50)          | Normal saline (n = 50) | 3             |
| Yan et al.        | 2012 | RCT          | China   | Deep Second-degree Burns       | Silver ion dressing + rh-EGF hydrogel (n = 32) | Baiken (n = 32)      | 4             |
| Wang et al.       | 2004 | RCT          | China   | Deep Second-degree Burns       | rhEGF (n = 30)          | Normal saline (n = 30) | 2             |
| Yang et al.       | 2000 | CCT          | China   | Deep Second-degree Burns       | rh-bFGF (n = 37)        | Blank (n = 37)       | 1             |
| Xiong et al.      | 2010 | CCT          | China   | Deep Second-degree Burns       | rh-EGF + Amnion (n = 15) | Amnion(n = 15)       | 1             |
| Yang et al.       | 2018 | RCT          | China   | Deep Second-degree Burns       | Mupirocin ointment + GM-CSF hydrogel (n = 64) | Mupirocin (n = 64)  | 3             |
| Wang              | 2009 | CCT          | China   | Deep Second-degree Burns       | rh-bFGF + Vaseline gauze (n = 31) | Vaseline gauze (n = 31) | 1             |
| Yang              | 2014 | RCT          | China   | Deep Second-degree Burns       | rhGM-CSF Hydrogel (n = 38) | Vaseline gauze (n = 38) | 3             |
| Xiong et al.      | 2019 | RCT          | China   | Deep Second-degree Burns       | rh-bFGF (n = 39)        | SD-Ag(n = 41)        | 2             |

(Continued)
| Author            | Year | Study Design | Country | Wound Type         | Sample size (Treatment)                          | Sample size (Control)     | Jadad’s Score |
|-------------------|------|--------------|---------|--------------------|-------------------------------------------------|---------------------------|---------------|
| Wang et al. [69]  | 2002 | RCT          | China   | Deep Second-degree Burns | rh-EGF Derivative (n = 138)                       | SD-Ag (n = 138)           | 3             |
| Wen et al. [121]  | 2016 | RCT          | China   | Deep Second-degree Burns | GM-CSF Hydrogel + Mupirocin ointment (n = 25)     | Mupirocin ointment (n = 25) | 3             |
| Yang et al. [122] | 2018 | RCT          | China   | Deep Second-degree Burns | rh-aFGF (n = 49)                                 | Standard care (n = 45)    | 2             |
| Xie et al. [123]  | 2018 | RCT          | China   | Deep Second-degree Burns | rh-aFGF (n = 43)                                 | Standard care (n = 43)    | 2             |
| Wang [124]        | 2015 | RCT          | China   | Deep Second-degree Burns | rh-bFGF (n = 78)                                 | Nano-Ag (n = 78)          | 3             |
| Wang [125]        | 2015 | RCT          | China   | Deep Second-degree Burns | rh-bFGF Hydrogel (n = 60)                         | Vaseline gauze (n = 60)   | 2             |
| You et al. [126]  | 2010 | RCT          | China   | Deep Second-degree Burns | rhEGF Hydrogel (n = 16)                           | Placebo (n = 16)          | 4             |
| Yang [127]        | 2013 | RCT          | China   | Deep Second-degree Burns | rhEGF (n = 30)                                   | SD-Ag (n = 30)            | 4             |
| Yang et al. [72]  | 2002 | RCT          | China   | Deep Second-degree Burns | rh-bFGF (n = 8)                                  | SD-Ag (n = 8)             | 2             |
| Wang et al. [73]  | 2003 | CCT          | China   | Deep Second-degree Burns | rh-bFGF (n = 20)                                 | Normal saline (n = 20)    | 1             |
| Zhang et al. [128]| 2014 | RCT          | China   | Deep Second-degree Burns | rh-bFGF + Nano-Ag (n = 40)                        | Normal saline (n = 30)    | 3             |
| Zhou et al. [74]  | 1999 | RCT          | China   | Deep Second-degree Burns | bFGF (n = 20)                                    | Vaseline gauze (n = 20)   | 2             |
| Zhou et al. [75]  | 2005 | RCT          | China   | Deep Second-degree Burns | bFGF (n = 80)                                    | Vaseline gauze (n = 62)   | 2             |
| Zhou et al. [129]| 2015 | RCT          | China   | Deep Second-degree Burns | rhEGF + SD-Ag (n = 30)                            | Normal saline (n = 30)    | 3             |
| Zhang et al. [130]| 2010 | RCT          | China   | Deep Second-degree Burns | rhEGF + SD-Ag (n = 30)                            | SD-Ag (n = 30)            | 2             |
| Zhang et al. [131]| 2011 | RCT          | China   | Deep Second-degree Burns | rhEGF + SD-Ag (n = 30)                            | SD-Ag (n = 30)            | 2             |
| Zhan et al. [76]  | 2015 | RCT          | China   | Deep Second-degree Burns | Nano-Ag + rh-EGF (n = 19)                         | Nano-Ag (n = 18)          | 2             |
| Zhou et al. [132]| 2016 | RCT          | China   | Deep Second-degree Burns | Nano-Ag + rh-bFGF (n = 15)                        | Nano-Ag (n = 15)          | 2             |
| Zhao et al. [133] | 2001 | RCT          | China   | Deep Second-degree Burns | rh-bFGF (n = 52)                                 | Vaseline gauze (n = 52)   | 2             |
| Zhang [134]       | 2019 | RCT          | China   | Deep Second-degree Burns | GM-CSF Hydrogel (n = 80)                          | Vaseline gauze (n = 80)   | 2             |
| Zhang et al. [78] | 2001 | CCT          | China   | Deep Second-degree Burns | rh-bFGF (n = 80)                                 | Blank (n = 80)            | 1             |
| Zou et al. [80]   | 2017 | RCT          | China   | Deep Second-degree Burns | rh-EGF + Nano-Ag (n = 27)                         | Chlorhexidine (n = 28)    | 3             |
| Zhou et al. [81]  | 2001 | RCT          | China   | Deep Second-degree Burns | rhEGF (n = 109)                                  | Placebo (n = 76)          | 3             |
| Zhang et al. [82] | 2012 | RCT          | China   | Deep Second-degree Burns | rhEGF + SD-Ag Cream (n = 38)                     | SD-Ag Cream (n = 38)      | 3             |
| Zhang et al. [135]| 2010 | RCT          | China   | Deep Second-degree Burns | rh-EGF (n = 21)                                  | Ag-Zn Cream (n = 16)      | 2             |
| Zhang et al. [136]| 2016 | RCT          | China   | Deep Second-degree Burns | rhGM-CSF (n = 20)                                | Rifampicin (n = 20)       | 3             |
| Zhou et al. [84]  | 2014 | CCT          | China   | Deep Second-degree Burns | rh-aFGF (n = 45)                                 | Blank (n = 45)            | 1             |
| Deng [137]        | 2017 | CCT          | China   | Deep Second-degree Burns | rhGM-CSF + SD-Ag (n = 33)                         | SD-Ag (n = 33)            | 1             |
| Chen et al. [138] | 2009 | RCT          | China   | Deep Second-degree Burns | Fulin honey + rh-EGF Hydrogel (n = 60)           | Povidone iodine (n = 60)  | 3             |

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| Author      | Year | Study Design | Country   | Wound Type                   | Sample size (Treatment) | Sample size (Control) | Jadad's Score |
|-------------|------|--------------|-----------|------------------------------|-------------------------|-----------------------|---------------|
| Liu et al.  | 2016 | RCT          | China     | Deep Second-degree Burns    | rhGM-CSF(n = 177)       | PVD-I(n = 181)         | 2             |
| Yan et al.  | 2016 | RCT          | China     | Deep Second-degree Burns    | rh-EGF Hydrogel + Nano-Ag(n = 40) | Nano-Ag(n = 40)       | 3             |
| Jiao et al. | 2014 | CCT          | China     | Deep Second-degree Burns    | rhGM-CSF + SD-Ag(n = 15) | SD-Ag(n = 15)         | 1             |
| Xia et al.  | 2013 | CCT          | China     | Deep Second-degree Burns    | rhGM-CSF(n = 30)        | Standard care(n = 28) | 1             |
| Ma et al.   | 2008 | RCT          | China     | Deep Second-degree Burns    | rh-aFGF(n = 32)         | Placebo(n = 32)        | 3             |
| Shi et al.  | 2018 | RCT          | China     | Deep Second-degree Burns    | Dragon blood powder + rb-bFGF Hydrogel(n = 100) | Jingwanhong ointment + Kangfuxin liquid(n = 100) | 2             |
| Liu et al.  | 2016 | RCT          | China     | Deep Second-degree Burns    | rhGM-CSF+ Nano-Ag(n = 30) | Nano-Ag(n = 30)       | 3             |
| Yan et al.  | 2016 | RCT          | China     | Deep Second-degree Burns    | Gentamicin + Red light therapy + Heparin + bFGF Hydrogel(n = 60) | Gentamicin(n = 58)     | 2             |
| Ge et al.   | 2001 | CCT          | China     | Trauma and Surgical Wound  | bFGF(n = 53)            | Furacilin + Vaseline gauze(n = 66) | 1             |
| Niu et al.  | 2016 | CCT          | China     | Trauma and Surgical Wound  | rh-aFGF(n = 90)         | Vaseline gauze(n = 90) | 1             |
| Dong        | 2016 | RCT          | China     | Trauma and Surgical Wound  | bFGF + Mupifloxacin(n = 42) | Vaseline gauze(n = 42) | 2             |
| Chen et al. | 2017 | RCT          | China     | Trauma and Surgical Wound  | rh-EGF(n = 143)         | Infrared radiation(n = 143) | 3             |
| Hao et al.  | 2015 | RCT          | China     | Trauma and Surgical Wound  | Compound schizonepeta fumigation lotion + rh-bFGF(n = 165) | Kangfuxin liquid(n = 144) | 2             |
| Liu et al.  | 2004 | CCT          | China     | Trauma and Surgical Wound  | bFGF(n = 58)            | Vaseline gauze(n = 48) | 1             |
| Li et al.   | 2013 | RCT          | China     | Trauma and Surgical Wound  | rh-EGF(n = 30)          | 40% Magnesium sulfate glycerin(n = 30) | 3             |
| Guo et al.  | 2003 | RCT          | China     | Trauma and Surgical Wound  | bFGF(n = 68)            | Furacilin + Vaseline gauze(n = 41) | 2             |
| Huang et al.| 2010 | RCT          | China     | Trauma and Surgical Wound  | bFGF(n = 30)            | Standard care(n = 30) | 2             |
| Chen et al. | 2010 | RCT          | China     | Trauma and Surgical Wound  | bFGF(n = 20)            | Gentamicin(n = 20)    | 3             |
| Li et al.   | 2015 | RCT          | China     | Trauma and Surgical Wound  | rh-EGF + ACRSC(n = 27)  | ACRSC(n = 27)          | 2             |
| Ge et al.   | 2002 | RCT          | China     | Trauma and Surgical Wound  | bFGF(n = 87)            | Furacilin + Vaseline gauze(n = 53) | 2             |
| Li et al.   | 2002 | CCT          | China     | Trauma and Surgical Wound  | bFGF(n = 89)            | Standard care(n = 84) | 1             |
| Li et al.   | 2016 | RCT          | China     | Trauma and Surgical Wound  | rh-EGF(n = 120)         | TCM lotion(n = 120)    | 2             |
| Fu et al.   | 2015 | RCT          | China     | Trauma and Surgical Wound  | rh-EGF(n = 36)          | Vaseline gauze(n = 36) | 3             |
| Qi et al.   | 2009 | CCT          | China     | Trauma and Surgical Wound  | rh-EGF(n = 183)         | 0.1% Rivanol(n = 204)  | 1             |
| Author       | Year | Study Design | Country   | Wound Type                          | Sample size (Treatment)       | Sample size (Control)            | Jadad's Score |
|--------------|------|--------------|-----------|-------------------------------------|-------------------------------|----------------------------------|---------------|
| Li et al.    | 2012 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 84)                | Standard care(n = 83)           | 3             |
| Li et al.    | 2016 | RCT          | China     | Trauma and Surgical Wound          | Cosmetic suture + rh-EGF(n = 55) | Ordinary suture(n = 55)         | 2             |
| Fan et al.   | 2011 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 50)                | TCM gauze(n = 50)                | 3             |
| Deng         | 2008 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 35)                | TCM gauze(n = 35)                | 3             |
| Liu et al.   | 2019 | RCT          | China     | Trauma and Surgical Wound          | GM-CSF Hydrogel(n = 55)       | Artificial dermis(n = 55)        | 3             |
| Li et al.    | 2015 | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 25)               | Sanqi Shengji ointment(n = 25)   | 3             |
| Li et al.    | 2019 | CCT          | China     | Trauma and Surgical Wound          | rh-aFGF(n = 30)               | Vaseline gauze(n = 30)           | 1             |
| Huang et al. | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 29)               | Fu Zhi Qing(n = 30)             | 3             |
| He           | 2015  | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 40)               | Vaseline gauze(n = 40)           | 2             |
| Long et al.  | 2014 | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF + Arnebia oil gauze(n = 50) | Arnebia oil gauze(n = 50) | 2             |
| Guo et al.   | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 40)                | Standard care(n = 40)           | 2             |
| Li et al.    | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF Hydrogel(n = 30)       | Standard care(n = 30)           | 2             |
| Li et al.    | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF Solution(n = 30)       | Standard care(n = 30)           | 2             |
| Li et al.    | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 24)                | Standard care(n = 24)           | 2             |
| Liu et al.   | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 45)                | Vaseline gauze(n = 45)           | 3             |
| Liao et al.  | 2008 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 60)                | Vaseline gauze(n = 60)           | 2             |
| Lu et al.    | 2017 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF Hydrogel(n = 68)       | Normal saline(n = 68)           | 2             |
| Huang et al. | 2004 | CCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 30)                | PVD-I gauze(n = 30)             | 1             |
| Lin et al.   | 2019 | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 50)               | Blank(n = 50)                   | 2             |
| Liu et al.   | 2018 | RCT          | China     | Trauma and Surgical Wound          | rh-aFGF(n = 30)               | Normal saline(n = 30)           | 3             |
| Jiang        | 2008 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF(n = 22)                | Vaseline gauze(n = 18)           | 2             |
| Sun et al.   | 2011 | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF F(n = 22)             | Vaseline gauze(n = 16)           | 2             |
| Sun et al.   | 2014 | RCT          | China     | Trauma and Surgical Wound          | rh-aFGF(n = 22)               | Shengji Yuhong ointment(n = 46)  | 1             |
| Sun et al.   | 2009 | CCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 50)               | Shengji Yuhong ointment(n = 46)  | 1             |
| Shi et al.   | 2016 | RCT          | China     | Trauma and Surgical Wound          | Erythromycin ointment + rh-EGF Hydrogel(n = 65) | Erythromycin ointment(n = 65) | 3             |
| Shi et al.   | 2012 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF Hydrogel(n = 53)       | Vaseline gauze(n = 53)           | 2             |
| Teng et al.  | 2015 | RCT          | China     | Trauma and Surgical Wound          | rh-EGF Hydrogel(n = 22)       | Standard care(n = 22)           | 2             |
| You          | 2019  | RCT          | China     | Trauma and Surgical Wound          | rh-bFGF(n = 30)               | Chlorophyll derivative(n = 30)   | 3             |

(Continued)
| Author          | Year | Study Design | Country | Wound Type                  | Sample size (Treatment)                  | Sample size (Control) | Jadad's Score |
|-----------------|------|--------------|---------|-----------------------------|-----------------------------------------|-----------------------|---------------|
| Wang [191]      | 2018 | RCT          | China   | Trauma and Surgical Wound   | rb-bFGF + HydroSorb (n = 16)             | HydroSorb (n = 16)    | 2             |
| Wang et al. [192] | 2014 | RCT          | China   | Trauma and Surgical Wound   | rb-aFGF (n = 52)                        | Gelatin sponge (n = 52) | 5             |
| Wang et al. [193] | 2008 | RCT          | China   | Trauma and Surgical Wound   | bFGF (n = 46)                           | Gentamicin (n = 50)   | 2             |
| Wen et al. [194] | 2005 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF (n = 86)                         | 1% PVD-I (n = 73)     | 2             |
| Wang [195]      | 2016 | RCT          | China   | Trauma and Surgical Wound   | rb-EGF + 2% Iodine (n = 50)             | Anisodamine + Gentamicin + Insulin + Normal saline (n = 50) | 2             |
| Wang [196]      | 2019 | RCT          | China   | Trauma and Surgical Wound   | Cosmetic suture + rh-EGF (n = 30)       | Cosmetic suture (n = 30) | 2             |
| Yao et al. [197] | 2014 | RCT          | China   | Trauma and Surgical Wound   | rh-aFGF (n = 81)                        | Normal saline (n = 86) | 2             |
| Wu et al. [198] | 2016 | RCT          | China   | Trauma and Surgical Wound   | rh-bFGF (n = 37)                        | PVD-I (n = 39)        | 3             |
| Wang et al. [199] | 2018 | RCT          | China   | Trauma and Surgical Wound   | rb-bFGF Hydrogel (n = 30)               | Jiyuhong ointment (n = 30) | 2             |
| Wu et al. [200] | 2004 | RCT          | China   | Trauma and Surgical Wound   | rbFGF (n = 36)                          | Blank (n = 36)        | 2             |
| Xu et al. [201] | 2000 | RCT          | China   | Trauma and Surgical Wound   | rbFGF (n = 69)                          | Normal saline (n = 20) | 2             |
| Wei [202]       | 2017 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF + bFGF (n = 80)                  | rh-EGF (n = 80)       | 3             |
| Xie et al. [203] | 2013 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF Hydrogel (n = 53)                | Vaseline gauze (n = 55) | 3             |
| Wu et al. [204] | 2004 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF (n = 31)                         | Mayinglong ointment (n = 35) | 2             |
| Wang et al. [205] | 2014 | CCT          | China   | Trauma and Surgical Wound   | EGF (n = 30)                            | Normal saline (n = 30) | 1             |
| Wu et al. [206] | 2013 | CCT          | China   | Trauma and Surgical Wound   | aFGF (n = 58)                           | Titanovine (n = 58)   | 3             |
| Zhi et al. [207] | 2007 | RCT          | China   | Trauma and Surgical Wound   | EGF (n = 54)                            | Vaseline gauze (n = 53) | 2             |
| Zha et al. [208] | 2006 | CCT          | China   | Trauma and Surgical Wound   | rh-EGF (n = 24)                         | Blank (n = 26)        | 1             |
| Zhang et al. [209] | 2015 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF (n = 148)                        | PVD-I (n = 148)       | 1             |
| Zhong et al. [210] | 2015 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF (n = 78)                         | Normal saline (n = 72) | 2             |
| Zhai et al. [211] | 2010 | RCT          | China   | Trauma and Surgical Wound   | rh-bFGF (n = 23)                        | Vaseline gauze (n = 22) | 2             |
| Zhang et al. [212] | 2007 | RCT          | China   | Trauma and Surgical Wound   | bFGF (n = 50)                           | Blank (n = 10)        | 2             |
| Zhang et al. [213] | 2001 | CCT          | China   | Trauma and Surgical Wound   | bFGF (n = 120)                          | Mupirocin ointment (n = 80) | 1             |
| Zhou et al. [214] | 2011 | RCT          | China   | Trauma and Surgical Wound   | rb-bFGF (n = 64)                        | Longhu ointment (n = 64) | 2             |
| Mei et al. [215] | 2019 | RCT          | China   | Trauma and Surgical Wound   | rh-EGF + Cosmetic suture (n = 47)       | Standard Care (n = 46) | 2             |
| Zhang et al. [216] | 2012 | RCT          | China   | Trauma and Surgical Wound   | bFGF + Compound Shuangshui liquid (n = 80) | Standard Care (n = 80) | 3             |

(Continued)
| Author          | Year | Study Design | Country | Wound Type                      | Sample size (Treatment) | Sample size (Control)          | Jadad's Score |
|-----------------|------|--------------|---------|---------------------------------|-------------------------|--------------------------------|---------------|
| Zhu et al. [217] | 2012 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF(n = 24)          | Vaseline gauze(n = 24)          | 2             |
| Zhu et al. [218] | 2015 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF Hydrogel(n = 56) | Metronidazole                 | 2             |
| Zhao et al. [219] | 2019 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF(n = 54)          | Ethacridine Lactate(n = 56)    | 3             |
| Zhu [220]       | 2007 | CCT          | China   | Trauma and Surgical Wound       | bFGF(n = 30)            | Metronidazole(n = 54)          | 1             |
| Zhang [221]     | 2019 | RCT          | China   | Trauma and Surgical Wound       | rh-aFGF(n = 60)         | Gelatin sponge(n = 60)         | 3             |
| Zhang [222]     | 2004 | RCT          | China   | Trauma and Surgical Wound       | rh-bFGF(n = 65)         | Shengji Yuhong ointment(n = 51)| 2             |
| Zhu [220]       | 2007 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF(n = 61)          | Standard care(n = 63)          | 2             |
| Huang [224]     | 2017 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF Hydrogel(n = 40) | Metronidazole(n = 40)          | 3             |
| Xu [225]        | 2017 | RCT          | China   | Trauma and Surgical Wound       | EGF(n = 24)             | PVD-I(n = 24)                  | 3             |
| Zhang et al. [226] | 2017 | RCT          | China   | Trauma and Surgical Wound       | bFGF(n = 30)            | Kangfuxin(n = 30)              | 2             |
| Luo [227]       | 2018 | RCT          | China   | Trauma and Surgical Wound       | rh-bFGF(n = 30)         | PVD-I(n = 30)                  | 2             |
| Wang [228]      | 2016 | RCT          | China   | Trauma and Surgical Wound       | GM-CSF Hydrogel(n = 30)| Metronidazole(n = 30)          | 2             |
| Sun et al. [229] | 2010 | RCT          | China   | Trauma and Surgical Wound       | rh-EGF Spray(n = 38)    | Gentamicin(n = 20)             | 3             |
| Fu et al. [230] | 2000 | CCT          | China   | Second Degree Burns             | rh-FGF(n = 330)         | Placebo(n = 324)               | 2             |
| Ishito et al. [231] | 2007 | CCT          | Japan   | Trauma and Surgical Wound       | rh-EGF(n = 58)          | Standard care                  | 2             |
| Yang et al. [232] | 2017 | RCT          | China   | Deep Second-degree Burns        | rhGM-CSF(n = 95)        | Placebo(n = 95)                | 3             |
| Lin et al. [233] | 2015 | RCT          | China   | Deep Second-degree Burns        | rhGM-CSF(n = 21)        | Mupirocin ointment(n = 21)     | 2             |
| Akita et al. [234] | 2008 | RCT          | Japan   | Superficial Second-degree Burns | bFGF(n = 51)           | Vaseline gauze(n = 5)           | 2             |
| Nie et al. [235] | 2010 | RCT          | China   | Deep Second-degree Burns        | bFGF+Oxygen therapy(n = 44)| Oxygen therapy(n = 41)        | 2             |
| Hayashida et al. [236] | 2012 | RCT          | Japan   | Superficial Second-degree Burns | bFGF(n = 10)           | Placebo(n = 10)                | 2             |
| Fu et al. [10]  | 1998 | RCT          | China   | Second Degree Burns             | bFGF(n = 300)          | Placebo(n = 300)               | 2             |
| Ma et al. [11]  | 2007 | RCT          | China   | Deep Second-degree Burns        | aFGF(n = 39)           | Placebo(n = 39)                | 3             |
| Wang et al. [237] | 2002 | RCT          | China   | Second Degree Burns             | EGF(n = 105)           | Placebo(n = 105)               | 2             |
| Wang et al. [238] | 2003 | RCT          | China   | Second Degree Burns             | EGF(n = 37)            | Placebo(n = 37)                | 2             |
| Wang et al. [239] | 2008 | RCT          | China   | Deep Second-degree Burns        | GM-CSF(n = 214)        | Placebo(n = 107)               | 2             |
| Yan Hong et al. [240] | 2012 | RCT          | China   | Deep Second-degree Burns        | rhGM-CSF(n = 32)       | Placebo(n = 33)                | 3             |
| Zhang et al. [241] | 2009 | RCT          | China   | Deep Second-degree Burns        | GM-CSF(n = 60)         | Placebo(n = 30)                | 2             |

ACRSC avene cicalafe restorative skin cream, CCT controlled clinical trial, EGF epidermal growth factor, FFG fibroblast growth factor, GM-CSF granulocyte-macrophage colony stimulating factor, MEBO moist exposed burn ointment, PVP-I polyvinyl pyrrolidone, PVD-I povidone ioxide, rhbFGF recombinant bovine basic fibroblast growth factor; rhaFGF recombinant human acidic fibroblast growth factor, RCT randomized controlled trial, TCM traditional chinese medicine.
wound healing time was 3.02 days shorter in the growth factor group than in the control group (MD = −3.02; 95% CI: −3.31 ～ −2.74; p < 0.00001).

A total of 113 studies [10,11,15,16,19 ～ 24,28,30 ～ 32,34 ～ 36,38 ～ 53,57,58,61,62,66 ～ 69,72 ～ 76,78 ～ 80,82,84,87 ～ 97,100 ～ 110,112,115 ～ 120,122,123,125 ～ 134,136 ～ 143,145,146,230,232,233,235,237,238,240,241] enrolling 12,465 cases were conducted to compare the healing time of deep second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the occurrence of statistical heterogeneity (p < 0.00001; I² = 100%). Therefore, the random effect model was used for meta-analysis (Figure 3). The results showed that the wound healing time was 5.63 days shorter in the growth factor group than in the control group (MD = −5.63; 95% CI: −7.10 ～ −4.17; p < 0.00001).
| Study or Substudy | Experimental Mean | Control Mean | Mean Difference (MD) | CI confidence interval | P Value | Wk | Z Score | Sample Size |
|------------------|------------------|-------------|----------------------|-----------------------|---------|----|---------|-------------|
| Beijing 2018     | 14.0 ± 1.6       | 20.1 ± 1.3  | -6.1 ± 2.4           | -7.7 to -4.5           | 0.001   | 10 | 9.4     | 49           |
| Shanghai 2010    | 19.8 ± 0.5       | 33.0 ± 0.5  | -13.2 ± 0.5          | -13.8 to -12.6         | 0.001   | 10 | 9.4     | 49           |
| Ningbo 2010      | 12.2 ± 2.2       | 21.1 ± 2.3  | -8.9 ± 2.2           | -10.7 to -8.2          | 0.001   | 10 | 9.4     | 49           |
| Changsha 2010    | 12.0 ± 2.0       | 31.4 ± 2.0  | -19.3 ± 2.0          | -21.5 to -17.1         | 0.001   | 10 | 9.4     | 49           |
| Shenyang 2010     | 11.0 ± 3.1       | 33.0 ± 3.1  | -21.9 ± 3.1          | -24.9 to -19.0         | 0.001   | 10 | 9.4     | 49           |
| Guangzhou 2014   | 15.4 ± 4.4       | 20.1 ± 4.4  | -4.7 ± 4.4           | -8.4 to -1.0           | 0.02    | 10 | 9.4     | 49           |
| Hefei 2010        | 15.9 ± 4.6       | 26.8 ± 4.6  | -9.9 ± 4.6           | -13.6 to -6.1          | 0.001   | 10 | 9.4     | 49           |
| Wuhan 2001       | 15.9 ± 2.3       | 27.0 ± 2.3  | -11.1 ± 2.3          | -12.9 to -9.2          | 0.001   | 10 | 9.4     | 49           |
| Changchun 2010    | 16.1 ± 1.5       | 30.5 ± 1.5  | -14.3 ± 1.5          | -15.9 to -12.8         | 0.001   | 10 | 9.4     | 49           |
| Shenyang 2015     | 16.8 ± 2.6       | 30.5 ± 2.6  | -13.7 ± 2.6          | -15.5 to -11.9         | 0.001   | 10 | 9.4     | 49           |
| Shenyang 2016     | 16.8 ± 2.6       | 28.5 ± 2.6  | -11.7 ± 2.6          | -13.5 to -9.9          | 0.001   | 10 | 9.4     | 49           |
| Taiyuan 2016      | 18.3 ± 2.4       | 32.6 ± 2.4  | -14.2 ± 2.4          | -16.3 to -12.1         | 0.001   | 10 | 9.4     | 49           |
| Hefei 2016        | 16.0 ± 2.6       | 28.5 ± 2.6  | -12.4 ± 2.6          | -14.5 to -10.4         | 0.001   | 10 | 9.4     | 49           |
| Shenyang 2016     | 16.9 ± 2.6       | 28.5 ± 2.6  | -11.6 ± 2.6          | -13.7 to -9.6          | 0.001   | 10 | 9.4     | 49           |

Figure 3. Comparative meta-analysis of the healing time of deep second-degree burn wounds. CI confidence interval, MD mean difference.
Healing rate comparison of second-degree burn wounds

Healing rate was defined as the proportion of healed wound area compared with the total wound area. Seventeen studies [15,17,20,36,41,42,44,51,52,54,61,68,69,71,72,77,81] enrolling 3184 cases were conducted to compare the healing rate of superficial second-degree burn wounds between growth factor and other non-growth factor treatments. The results showed the presence of statistical heterogeneity (p < 0.00001; I² = 99%). Therefore, the random effect model was used for meta-analysis (Figure S1, see online supplementary material). The results showed that the infection rate was lower in the growth factor group than in the non-growth factor treatment group (RR = 0.52; 95% CI: 0.39–0.69; p < 0.00001). Seventeen studies [107,110,119,124,132,136,138,145,156,164,177,181,190,192,194,196,203,205,206] including 413 patients compared growth factor with other non-growth factor treatments concerning the deep second-degree burn scar score. The follow-up time was between 6 and 12 months. The results showed the presence of statistical heterogeneity (p = 0.004; I² = 74%). Therefore, the random effect model was used for meta-analysis (Figure 4). The results showed that the Vancouver scar scale score of the growth factor treatment group was improved as compared with that of the non-growth factor group (5.23 ∼ 5.67 vs 6.51 ∼ 8.4, i.e. 2.45 lower than that of the non-growth factor treatment group) (MD = −2.45; 95% CI: −3.29 ∼ −1.6; p = 0.004).

Adverse reactions of deep second-degree burn wounds

Three studies [95,96,124], including 522 patients with deep second-degree burn wounds, compared the incidence of adverse reactions after the treatment with growth factor vs. other non-growth factor treatments. The results showed that no statistical heterogeneity occurred (p = 0.29; I² = 20%), so the fixed effect model was used for meta-analysis (Figure S5, see online supplementary material). The results showed that the incidence of adverse reactions was lower in the growth factor treatment group than in the non-growth factor group (RR = 0.35; 95% CI: 0.19–0.67; p = 0.001).

Healing time comparison between traumata and surgical wounds

A total of 67 studies [48,147–156,158–164,166–173,175–177,179,181,184–188,190,192–194,196–203,205,206,208–214,216,218–226] including 7106 cases with traumata or surgical wounds served to compare the wound healing time between growth factor and other non-growth factor treatments. The results showed that statistical heterogeneity occurred (p = 0.00001; I² = 99%). Hence, the random effect model was used for meta-analysis (Figure 5). The results showed no statistical heterogeneity (p = 0.54; I² = 0%). Hence, the fixed effect model was used for meta-analysis (Figure S4, see online supplementary material). The results showed that the infection rate was lower in the growth factor group than in the non-growth factor treatment group (RR = 0.52; 95% CI: 0.42 ∼ 0.64; p < 0.00001).

Figure 4. Comparative meta-analysis of the scar score of deep second-degree burn wounds. CI confidence interval, MD mean difference

| Study or Subgroup | Experimental Mean | Experimental SD | Total | Control Mean | Control SD | Total | Weight | Mean Difference | (IV, Random, 95% CI) |
|-------------------|-------------------|----------------|-------|--------------|------------|-------|--------|----------------|---------------------|
| Baogen Xie 2018   | 5.57              | 2.15           | 43    | 8.36         | 9.6        | 43    | 8.5%   | -2.79          | (−5.73, 0.15)       |
| Jingning Cai 2016 | 5.67              | 2.22           | 30    | 8.4          | 2.12       | 35    | 20.4%  | -2.73          | (−3.79, −1.67)      |
| Ruyoue Hua 2019   | 5.34              | 1.64           | 50    | 8.35         | 2.04       | 50    | 24.6%  | -3.01          | (−3.74, −2.28)      |
| Yue Han 2017      | 5.23              | 1.25           | 34    | 8.51         | 1.42       | 34    | 25.7%  | -1.28          | (−1.92, −0.64)      |
| Zuxian Yang 2018b | 5.6              | 2.2            | 49    | 8.4          | 2.1        | 45    | 22.8%  | -2.60          | (−3.67, −1.93)      |

Total (95% CI) = 206
Heterogeneity: Tau² = 0.62; Chi² = 15.57; df = 4 (p = 0.004); I² = 74%
Test for overall effect: Z = 5.87 (p < 0.00001)
showed that the healing time was 4.50 days shorter in the growth factor group than in the control group (MD = −4.50; 95% CI: −5.55 to −3.44; p < 0.00001).

Healing rate comparison of traumata and surgical wounds
Thirteen studies [148, 155, 163–167, 169, 170, 184, 185, 191, 193, 203, 228] enrolling 1017 patients with trauma or surgical wounds allowed to compare the rate of wound healing between growth factor and other non-growth factor treatments. The results showed that statistical heterogeneity was present (p < 0.00001; I² = 99%), so the random effect model was used for meta-analysis (Figure S6, see online supplementary material). The results showed that the wound healing rate in the growth factor group was 7.63% higher than in the control group (MD = 7.63; 95% CI: 4.44 to 10.82; p < 0.00001).
Adverse reaction of traumata and surgical wounds
Six studies [157,171,197,215,219,221] including 622 patients with traumata and surgical wounds compared the incidence of adverse reactions after growth factor treatment or other non-growth factor treatment methods. The results were statistically heterogeneous ($p < 0.00001; I^2 = 84\%$). Hence, the random effect model was used for meta-analysis (Figure S7, see online supplementary material). The results showed that the incidence of adverse reactions was lower in the growth factor group than in the control group (RR = 0.55; 95% CI: 0.46 ~ 0.65; $p < 0.00001$).

Discussion
Growth factors are important biologically active molecules which can markedly impact on the wound environment, leading to rapid increases in cell migration, proliferation and differentiation, while regulating the cellular responses inherent to the wound healing process [14]. Recombinant growth factors have been used as adjunctive treatments for acute wounds to accelerate healing, however, the effectiveness and safety of administering these growth factor products under such conditions had not been systematically analyzed. In 2016, Zhang et al. [242] performed a meta-analysis concerning growth factor therapy in cases of partial thickness burns. Thirteen studies with a total of 1924 participants were included and the results showed that the topical application of growth factors including FGF, EGF and GM-CSF significantly reduced wound healing time as compared with standard wound care alone. Although these preliminary results seemed to be encouraging, the authors pointed out that high-quality and adequately powered trials were still needed to further confirm their conclusions. Another meta-analysis performed by Abdelhakim et al. included 9 clinical studies and has shown that local bFGF treatment accelerated wound healing and prevented pathological scarring. In a similar fashion, the author pointed out that further research was needed to indicate more clinical advantages [243].

In this systematic review, we performed a comprehensive search of relevant clinical studies published in either Chinese or English. We included many studies published in Chinese which had not been considered for evaluation before. Our data show that as compared to non-growth factor treatments, the therapeutic use of growth factor products including FGF, EGF and GM-CSF for acute wounds significantly changed the healing outcome in terms of lessening healing time, heightening healing rate and reducing incidence of infections and adverse reactions. Therefore, our study results positively support the therapeutic use of the current clinically available growth factor products for acute wounds, especially in the case of wounds that tend to have longer healing time.

However, one must point out that out of the 229 studies considered, only 3 were conducted outside China (i.e. in Japan) and reported in English, while the remaining 226 articles, including 7 reported in English and 219 in Chinese, were all carried out within China and reported by Chinese researchers. During the screening period, one randomized clinical trial conducted in the USA showed that epidermal growth factor accelerated skin-graft-donor sites wound healing significantly [9]. However, the types of outcome measurements in this study could not be combined with those from other included studies to conduct meta-analysis. Thus although it was eventually excluded, the results of this study did support our general conclusions. We have to admit that the lack of clinical data from other countries and areas has reduced the evidence’s power level. This is especially true considering that most of the included studies are rated as low-quality ones (Jadad score: 1–2 for 202 papers, 4–5 for 6 papers only). The lack of sufficient clinical data from other countries and areas outside Asia is likely caused by the lack of available growth factor products for treating acute wounds in these places. Becaplermin in Regranex® is the only U.S. Food and Drug Administration (FDA) approved recombinant PDGF product and is only indicated for the treatment of neuropathic ulcers in diabetics. This product carried a boxed warning from the FDA and due to safety issues has been withdrawn in Europe [244]. We were only able to find one study using PDGF gel to treat acute full-thickness punch biopsy wounds on 7 healthy subjects [245]. The results of the study showed PDGF gel was effective in promoting wound healing, which was in accord with the general results of this meta-analysis. Since PDGF has not been officially approved for use on acute wounds, we did not include PDGF in this meta-analysis. However, we believe that when PDGF becomes more widely used for treating acute wounds in the future, it will be meaningful to conduct a more comprehensive evaluation regarding the efficacy and safety issues of all the important growth factor products that are still lacking evidence for clinical use today.

Although this meta-analysis has brought to light encouraging results, the collection of the latter from limited countries and areas (mainly in China) increases the bias of the study. From this standpoint, the evidence supporting the routine therapeutic use of growth factor products for acute wounds is still weak. More high-quality clinical studies and clinical studies from outside of China are needed to further confirm the efficacy, necessity and safety of their clinical application. Despite the possible bias of the conclusions drawn from clinical studies, the current data do show some potential merits of using growth factors to promote acute wound healing. It is interesting to note that several of the included studies focused on the healing of surgical wounds entailing high risks of contamination and infection, such as in the case of perianal surgery [154,214,218,219,223,224,226]. Growth factors were beneficial as they decreased the healing time of such wounds, and therefore decreased the chances of infection and of the development into chronic wounds. Thus, the therapeutic use of growth factors in cases with surgical wounds susceptible to contamination and infection could be a beneficial practice. Again, the need remains for more evidence reported by higher-quality studies.
Moreover, we noted that therapeutically using growth factors for acute wounds not only increased the speed of healing, but also improved the quality of healing in the case of deep wounds. It is well worth pointing out that with growth factors treatments, deep second-degree burn wounds healed with lower scar scores [101,104,108,122,123], which is an important indicator for routine clinical use. It is well known that an increased wound healing time is an important risk factor for hypertrophic scarring in second-degree burns [246]. The current data showed that, instead of causing ‘an overgrowth’, growth factor treatments safely reduced wound healing time by 5.63 days while concurrently decreasing the degree of hypertrophic scarring. Similarly, in their study Abdelhakim et al. [243] also pointed out that bFGF might prevent pathological scarring through several cellular mechanisms, such as interfering with myofibroblasts formation and inducing apoptosis. However, longer follow-up times and large-scale clinical trials are still needed to confirm this scar-reducing effect and the causal relationship with reduced wound healing times.

Notably, most of the studies included in this systematic review used only a single growth factor either by itself or combined with other non-growth factor treatments and proved their effectiveness. However, it is yet to be proven that combining different growth factors achieves better clinical results, or whether the contrary is true. Since applying supraphysiological doses of growth factor(s) correlates with an increased risk of cancer, the importance of controlling the spatial–temporal release of growth factors at the wound site and of overcoming this challenge is probably crucial for any successful growth factor-based therapy [244]. Also, as different growth factors partake in the various stages of the wound healing process, using a single growth factor may not suffice for best wound healing. A sophisticated growth factor delivery system enabling a controlled spatial–temporal delivery [13], mimicking the synergistic wound healing activity of the combined release profiles of growth factors in real physiological situations, could be a promising direction for future research. Currently, the use of platelet rich plasma (PRP) to promote refractory wound healing has already supplied a hint for applying growth factor compounds in a more effective fashion. However, PRP has not been routinely used on acute wounds due to economic considerations. More in-depth study of the PRP’s spatial–temporal working mechanism might provide stronger evidence to develop recombinant growth factor combination products for promoting acute wound healing in the future.

Conclusions

With the systematic review and evaluation of the currently available evidence, we conclude that the therapeutic use of growth factors including EGF, FGF and GM-CSF is effective and safe in the treatment of acute skin wounds, especially in the case of wounds entailing higher risks of infection. However, the need still remains for more higher-quality studies to further strengthen our conclusion.

Supplementary data

Supplementary data is available at Burns & Trauma Journal online.

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Abbreviations

CI: Confidence interval; EGF: Epidermal growth factor; FGF, Fibroblast growth factor; GM-CSF: Granulocyte-macrophage colony stimulating factor; MD, Mean difference; PDGF: Platelet-derived growth factor; PRP: Platelet rich plasma; rbFGF: Recombinant bovine basic fibroblast growth factor; rh-aFGF: Recombinant human acidic fibroblast growth factor; RR: Relative risk.

Authors’ contributions

YW and JL conducted the study, screened the included papers and wrote the manuscript. YH, XL, LZ, MY, JD and XW collected and extracted data from the included studies. XL performed primary data analysis. XF and JW designed the study and provided guidance for the manuscript preparation.

Conflicts of interests

None declared.

Data availability

Data are available from PubMed/Medline, Cochrane Library, Cochrane CENTRAL, ClinicalTrials.gov, Chinese Journal Full-text Database (CNKI), Chinese Scientific Journal Database (VIP), and Wanfang Database (WFDATA).

References

1. Cañedo-Dorantes L, Cañedo-Ayala M. Skin acute wound healing: a comprehensive review. Int J Inflam. 2019;2019:3706315.
2. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. Physiol Rev. 2019;99:665–706.
3. Nour S, Imani R, Chaudhry GR, Sharifi AM. Skin wound healing assisted by angiogenic targeted tissue engineering: a comprehensive review of bioengineered approaches. J Biomed Mater Res Part A. 2021;109:453–78.
4. Li S, Liu Y, Huang Z, Kou Y, Hu A. Efficacy and safety of nanosilver dressings combined with recombinant human epidermal growth factor for deep second-degree burns: a meta-analysis. Burns. 2021;47:643–53.
5. Lin XY, Wang H, Tan Y. Role of hepatocyte growth factor in wound repair. Acta Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2018;40:822–6.
6. Brem H, Howell R, Criciutelli T, Senderowicz A, Siegert N, Gorenstein S, et al. Practical application of granulocyte-macrophage Colony-stimulating factor (GM-CSF) in patients with wounds. Surg Technol Int. 2018;32:61–6.
7. Frati C, Scarpa C. Treatment of experimental mouse burns with E.G.F. (epidermal growth factor) applied locally as a lotion. G Ital Dermatol Minerva Dermatol. 1971;46:73–6.
8. Benington L, Rajan G, Locher C, Lim LY. Fibroblast growth factor 2—a review of stabilisation approaches for clinical applications. Pharmaceutics. 2020;12:508.

9. Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger LJ, 3rd, et al. Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med. 1989;321:76–9.

10. Fu X, Shen Z, Chen Y, Xie J, Guo Z, Zhang M, et al. Randomised placebo-controlled trial of use of topical recombinant bovine basic fibroblast growth factor for second-degree burns. Lancet. 1999;352:1661–4.

11. Ma B, Cheng DS, Xia ZF, Beng DF, Lu W, Cao ZF, et al. Randomized, multicenter, double-blind, and placebo-controlled trial using topical recombinant human acidic fibroblast growth factor for deep partial-thickness burns and skin graft donor site. Wound Repair Regen. 2007;15:795–9.

12. Yamakawa S, Hayashida K. Advances in surgical applications of growth factors for wound healing. Burns & trauma. 2019;7:10.

13. Park JW, Hwang SR, Yoon IS. Advanced growth factor delivery Systems in Wound Management and Skin Regeneration. Molecules. 2017;22:1259.

14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

15. Pan YJ, Zong YX, Bai SP, Zhang SZ, Yang H. Repair of 58 cases of diabetic burns. Jiangxi Medical Journal. 2009;44:1089–90.

16. Hong W, Li SF, Gan ZL. BFGF combined compound sulfadiazine zinc Pmint gel with Vaseline gauze therapy for II burn wound in children. China Medicine And Pharmacy. 2013;3:112–38.

17. Guo Y, Wang SC. Clinica study of Er Huang ointment combined with recombinant human granulocyte macrophage stimulating factor gel in the treatment of superficial II degree burns. Zhong Yi Yao Dao Bao. 2017;23:90–2.

18. Ma JB. Effect of vacuum sealing drainage combined with recombinant bovine basic fibroblast growth factor on electric burn wound of extremities. Chin J Crit Care Med (Electronic Edition). 2014;7:126–8.

19. Huang YY, Qin QH, Bian JM. Effect of sulfadiazine silver cream combined with recombinant human epidermal growth factor on burn wounds in children. Guang Xi Yi Ke Da Xue Xue Bao. 2004;21:895–6.

20. Li XK, Hong A, Xu H, Yao CC, F XB, Lin J. The clinical study of recombinant bovine basic fibroblast growth factor on wounds healing. Journal of Jinan University (Medicine Edition). 2002;23:22–7.

21. Chen ZJ, Wang Y, Wang ZH. Application of basic fibroblast growth factor bFGF in small area burn wound healing. Tianjin Yao Xue. 2001;13:46–8.

22. Gao JM, Chen CH, Kou JB, Zhang LS, Li GC, Fan YN, et al. Effect of basic fibroblast growth factor on wound healing. Shanxi Med J. 2004;33:967–8.

23. Huo ZL, Ge SD, Chen WL, Zhao XL, Mu XX, Liu SK. Application of basic fibroblast growth factor in burn wound. Acad J Second Mil Med Uni. 1996;81:94–6.

24. Li ZY, Huang LB, Yang XB, Wang CG. Application of basic fibroblast growth factor in burn wound. Acad J Second Mil Med Uni. 2004;25:3.

25. Hu XM, Ma J, Zhang YF, Wang WB. Effect of Jinfuning combined with silver sulfadiazine cream in the treatment of children with second degree scald burns. Medical Journal of GEH. 2012;14:220–1.

26. Gong YJ. Effect of Genetime on small area superficial second degree burn. Modern Nursing. 2007;13:732.

27. Luo HX. Study on The Application of Chitosan in Children’s Superficial Second-Degree Burn Wounds. Chongqing Medical University, 2014.

28. Liao ZJ, Huang BG, Xiang J, Xu WS. Clinical evaluation of epidermal growth factor in human burn wounds. Acta University Medicinalis Secondae. 1996;16:266–8.

29. Guo Y, Yu JJ, Lv GZ. The clinical observation of applying recombinant human epidermal growth factor to treat superficial second-degree burn. Chin J Injury Repair and Wound Healing. 2009;4:683–7.

30. Liu XH, Tang MR, Zhang SD, He J. The clinical study of recombinant human basic fibroblast growth factor stimulating the wound surface healing. J Chin Med Univ. 2001;30:8–9.

31. Liu H, Tao HJ. A study of the treatment of 67 cases of face and neck burns in children. Journal of Clinical and Experimental Medicine. 2012;11:31–2.

32. Gao DL, Gao DD, Xue HB, Yang XM, Bai C. Application of in situ regeneration combined with rh-EGF in the treatment of facial burn patients. Xin Li Yue Kan. 2019;17:21–2.

33. LiHX. Effect of recombinant epidermal growth factor on wound healing of second degree burn. International Medicine and Health Guidance News. 2003;9:33–4.

34. Liu Y, Fu YX. Healing effect of bFGF on burn wound degree II of children. J Pediatr Pharm. 2005;11:20–1.

35. Lin J, Dai ZQ. Clinical observation of recombinant bovine basic fibroblast growth factor gel for treatment mild burns. Chinese Journal of Medicinal Guide. 2014;16:1016–7.

36. Guo LJ, Li XK, Xu H, Yao CC. Curative effect of recombinant bovine basic fibroblast growth factor on burn wound degree II. Chin J Biologicals. 2002;15:310–1.

37. Fan GC, Rong XZ, Zhang T, Li SZ. Clinical observation of recombinant bovine basic fibroblast growth factor in the treatment of burn wounds. Guang Zhou Yi Yao. 2018;49:25–39.

38. Meng SY, Zhao P, Ma YN, Xu WH. Effect of recombinant bovine basic fibroblast growth factor on burn wound. J Med Theor & Prac. 2018;31:539–40.

39. Guo X, Tan MY, Guo L, Xiong AB, Li YG, He XC. Clinical study on repair of burns wounds of degree II with recombinant human epidermal growth factor in elderly patients. Chinese Journal of Reparative and Reconstructive Surgery. 2010;24:462–4.

40. Fang WF, Li HL. Clinical observation of recombinant human epidermal growth factor in promoting wound healing of second degree burn. Journal of China Prescription Drug. 2014;12:23–6.

41. Liang ZQ, Li HM, Meng CY. Repair of second degree facial burns in children using recombinant human epidermal growth factor. Journal of Clinical Reconstructive Tissue Engineering Research. 2007;11:1974–5.

42. Liang ZQ, Li HM, Meng CY, Sun XF. A comparison of repaired effect of recombinant human epidermal growth factor for the facial degree II burn wounds. Chinese Journal of New Drugs. 2006;15:812–4.
43. Huo LZ, Liu XL, Huang J, Li XJ, Zhong SH, Liang DR. Effect of recombinant human epidermal growth factor in treatment of burn wound and donor site. *Academic Journal of Guangdong College of Pharmacy*. 2001;17:60–1.

44. Fu JF, Chen B, Zhang J, Liang M, Cao WD, Wei DN, et al. Clinical observation of recombinant human epidermal growth factor in the treatment of burn wounds. *J Trauma Surg*. 2003;5:385.

45. Liao Y, Guo L, Ding EY, He XC, Xie XQ, Xia DL. A comparative study on burn wound healing treated by different methods of recombinant human epidermal growth factor. *Chinese J Reparative and Reconstructive Surgery*. 2003;17:301–2.

46. Li DQ, Li JB, Liang MH. The negative result of recombinant human epidermal growth factor effecting on wounds. *Yi Xue Wen Xuan*. 2004;23:133–4.

47. Liu XH, Jiang N, Tan C, Tang MR. The clinical study of recombinant human basic fibroblast growth factor in stimulating the wound surface healing. *Acta Academiae Medicinae Jiangxi*. 2005;45:92–4.

48. Chao SW, Li Y, Wang XZ. Application of recombinant human basic fibroblast factor in burn wound. *China Journal of Modern Medicine*. 2003;13:52–3.

49. Guo XH. Clinical observation on recombinant human basic fibroblastic growth factor treating II burn. *Mod Diagn Treat*. 2006;17:215–6.

50. Liu BF. Recombinant human basic fibroblast growth factor in treating burns and other skin injuries. *Mod Diagn Treat*. 2014;25:535–7.

51. Chen GQ. Clinical study of recombinant human acidic fibroblast growth factor in burn treatment. *Lin Chuang Yan Jiu*. 2014;11:47–8.

52. Sun RP, Zhao JK, Sun J. Clinical observation of rh-aFGF in the treatment of second degree burn. *Hebei Medical Journal*. 2011;33:2293–4.

53. Qiu DL, Lin YH, Li CG. Clinical research of bFGF combined with Bashigao in treating II burned wound. *Hebei Medicine*. 2010;16:331–3.

54. Sun RP, Zhao JK, Sun J, Li DJ, Huai Q, Xu LJ. Clinical observation of modified chitin combined with recombinant human basic fibroblast growth factor in treating Superfical partial-thickness burn wound. *Chin J Injury Repair and Wound Healing*. 2018;13:269–72.

55. Tan JT, Zhang B, Wei P, Yu LY. Effect of basic fibroblast growth factor on burn wound healing. *China Journal of Modern Medicine*. 2000;10:10–1.

56. Song XN, Jing HP, Zou YH. Effect of basic fibroblast growth factor on 50 cases of burn wounds. *Zong Zhuang Bei Bu Yi Xue Xue Bao*. 2003;5:32–3.

57. Tong YLT, Zhu JH, Miao HC, Pan K, Yang FW, Kong ZB, et al. A clinical observation of Kangfushuang to treat the partial and full thickness burn wounds. *Chinese Journal of Rehabilitation Medicine*. 2004;19:3.

58. Shi FC. Clinical analysis of Nano silver dressing combined with recombinant human epidermal growth factor in the treatment of second degree burn. *J Huaihai Med*. 2019;37:177–9.

59. Sun RP, Zhao JK, Sun J, Xu LJ, Zheng WL, Li DJ. Effect of external application of lyophilized recombinant human acidic fibroblast growth shadow in the treatment of superficial second degree burn. *Zhong Guo Xiang Can Yi Yao Za Zhi*. 2015;22:11–2.

60. Tan JT, Zhang B, Yu LY, Li W. Effect of recombinant human epidermal growth factor on wound healing of second degree burn. *Shi Yong Yi Xue Za Zhi*. 2001;17:872–3.

61. Wang PH, Qi SZ, Peng YZ. Comparison of the wound healing Acceleraton of recombinant human epidermal growth factor and recombinant human fibroblast growth factor in the treatment of burn wounds. *Clín J Med Offic*. 2004;32:33–7.

62. Yang ZW, Yang X, Zhou M. Basic fibroblast growth factor promotes burn wound healing. *Modern Rehabilitation*. 2000;4:73.

63. Wang XH, Gu CZ, Chen ZY, Li HJ, Li JX. Clinical observation of basic fibroblast growth factor on promoting burn wound healing. *Xin Jiang Yi Xue*. 2000;30:27.

64. Ye WG, Xue RH, Ye PG, Zhou B. Observation on the effect of combined application of Genetime and silver sulfadiazine in dressing change of second degree burn wound. *J Med Theor & Prac*. 2008;21:1189–90.

65. Wang JX, Hu QX, Liu Q. Clinical observation of Genetime combined with Nano silver dressing in the treatment of second degree burn wound. *Inner Mongolia Med J*. 2010;42:830–1.

66. Xiong HL, Zhong XJ, Fu XH. Clinical study of Genetime combined with amniotic membrane covering in the treatment of burn wounds. *Hu Shi Jin Xiu Za Zhi*. 2010;25:349–50.

67. Wang JH, Xu GS, Wang Y, Zhu ZJ. Clinical observation of the effects of Trolamine cream on burn wounds. *Acta Acadmiae Medicinae Qindao Universitatis*. 2009;45:5.

68. Xiong WL. Comparative analysis of external application of recombinant bovine basic fibroblast growth factor and silver sulfadiazine in the treatment of burn wounds. *Guide of China Medicine*. 2019;17:154–5.

69. Wang SL, Chai JK, Shen ZY, Zhou YP, Liao ZJ, Zhou L, et al. Phase IV Multicenter clinical study of recombinant human epidermal growth factor derivative. *Chinese Critical Care Medicine*. 2002;14:5.

70. Xu FR, He MW, Yang F. The clinical effect of recombinant bovine basic fibroblast grow promote wound healing after burn. *Chin J of Clinical Rational Drug Use*. 2016;9:35–8.

71. Xiong WL. Efficacy of recombinant human epidermal growth factor gel in children with superficial second degree burn wounds. *Guide of China Medicine*. 2018;16:138.

72. Yang YM, Zhang ZX, Sun YW. Effect of recombinant human basic fibroblast growth factor on the repair of burn wound. *Xi Bei Yao Xue Za Zhi*. 2002;17:26.

73. Wang HJ, Qi SZ, Yang JM, Li XD. Clinical observation of rh-bFGF in treatment of II burns in man. *China Pharmacy*. 2003;14:480–1.

74. Zhou XM, Wang XM. Observation of bFGF on burned wound. *Hebei Medicine*. 1999;5:29–30.

75. Zhou PY, Yang XM. Effect of bFGF on treatment of 152 cases of second degree burn wound. *Zhong Guo She Que Yi Shi*. 2005;7:41.

76. Zhan WB. Efficacy of recombinant human epidermal growth factor combined with Nano-siver dressings on second-degree burns. *Chinese Journal of General Practice*. 2015;13:926–8.

77. Zhang BL, Zhang N, Zhang T. Curative effect analysis of recombinant bovine basic fibroblast growth factor gel on burn wound. *Chinese Community Doctors*. 2014;30:58–9.

78. Zhang C, Hong SW, Gu C, Huang ZX, Du SL. Clinical observation of recombinant bovine basic fibroblast growth factor in the treatment of second degree burn wounds. *Chin J Burns*. 2001;17:246.
79. Zhao PD, Liu YL. Effect of recombinant human epidermal growth factor on second degree burn wound healing. *International Medicine and Health Guidance News*. 2015;21:2819–21.

80. Zou YT, Lian ZP, Lin S, Zhang BQ, Dai SG. Effect of recombinant human epidermal growth factor combined with Nano silver dressing on second degree burn. *Practical Clinical Medicine*. 2017;18:53–4.

81. Zhou L, Wang SL, Ma JL, Chai JK, Li LG. A Multicenter study of recombinant human epidermal growth factor for topical treatment of burn wounds. *Chin J New Drugs Clin Rem*. 2001;20:337–40.

82. Zhang B. Recombinant human epidermal growth factor in treatment of second degree burn wounds. *Med J West China*. 2012;24:561–2.

83. Zheng ZZ, Liu JF, Xie WG, Wu RZ, Zhou HP, Wan SY. Application of recombinant human epidermal growth factor in the treatment of children with second degree burn. *J Huazhong Univ Sci Tech*. 2003;32:667–8.

84. Zhou SY, Li H, Wang JH, Liu XY, Qi CC, Zhang MZ. Application of recombinant human acidic fibroblast growth factor in burn treatment. *Shanxi Med J*. 2014;43:185–6.

85. Wu XY, Qin XQ. Observation on the effect of bFGF combined with Comfeel hydrocolloid gauze in the treatment of mild to moderate burns in infants. *Int J Nurs*. 2015;34:2430–2.

86. Lu DP. Application of basic fibroblast growth factor in Pediatric burn wound wound. *Acta Medicinae Sinica*. 2002;15:43–4.

87. Hu BY. Clinical research of BFGF and far infrared ray to promote Adustum. *Chinese Journal of General Practice*. 2013;11:1565–6.

88. Huang YB, Chen WB, Hu J, Su YS. Clinical study of bFGF combined with local oxygen therapy in promoting deep second degree burn wound healing. *Asia-Pacific Traditional Medicine*. 2012;8:147–8.

89. Liu JS, Fang Y, Yao M, Yu WR, Li XG. Effect of recombinant human granulocyte-macrophage Colony-stimulating factor on wound debridement and healing of deep II thickness burn. *Chinese Journal of Reparative and Reconstructive Surgery*. 2011;25:1059–62.

90. He XL, Zhang B, Li W, Li Z, Chen B. Clinical effect of epidermal growth factor combined with Polymyxin B for wound scar in elderly patients with deep-second-degree burns. *Pract Geriatr*. 2018;32:828–30.

91. Cheng ZH, Peng XP, Peng WF, Zhou PY. Clinical observation of Fulin honey combined with topical recombinant human granulocyte macrophage stimulating factor gel in the treatment of deep second degree burns. *Chin J Injury Repair and Wound Healing (Electronic Edition)*. 2011;6:239–63.

92. Chen BQ, Peng WY, Yu JC, Qiu JC, Liu BF, Zhao WF. Research on the therapeutic effect of epidermal growth factor gel and collagen dressing in the treatment of facial deep II degree burn. *Lin Chuang Yi Xue Gong Cheng*. 2013;20:1127–8.

93. Chen JP, Wen SH, Li Z. Combined Administration of Moist Exposed Burn Ointment (MEBO) and basic fibroblast growth factor (bFGF) in children deep II degree burn wounds. *Lin Chuang Yi Xue Gong Cheng*. 2012;19:1134–5.

94. Liao MR, Wang HL, Guo ZX. Effect of Nano-silver dressing combined with recombinant bovine basic fibroblast growth factor on the expression of inflammatory factors, EGF and VEGF in deep second degree burn wounds. *China Modern Doctor*. 2018;56:89–96.

95. Li Y, Jiao JQ, Huang Z, Hu WG. Safety and effectiveness of Nano silver dressing combined with recombinant human epidermal growth factor gel on patients with deep II degree burn wounds. *Chinese Journal of Medicinal Guide*. 2015;17:941–2.

96. Han BX. Effect of recombinant human basic fibroblast growth factor on deep second degree burn. *Chin J of Clinical Rational Drug Use*. 2018;11:60–1.

97. Lin XS, Wang L, Liu SJ, Cai YN. Clinical observation of recombinant human granulocyte/macrophage Colony stimulating factor hydrogel for topical application in treating burn wounds. *Modern Practical Medicine*. 2017;29:516–8.

98. Zeng JD. Clinical Study on Treating Deep Second Degree Burn Wounds with Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor Hydrogel. *Luzhou Medical College*, 2012.

99. Li L. Effect of insulin combined with recombinant human acidic fibroblast growth factor on deep second degree burn wound healing. *Shan Dong Yi Yao*. 2014;54:75–6.

100. Meng JS, Li CM, Xu LF, Wang J, Zhang K, He ZY. Effect of growth factor on deep second degree burn wound. *Ren Min Jun Yi*. 2003;48:570–1.

101. Han Y, Ren J, Wu JH, Wang Y. Effect of recombinant human epidermal growth factor combined with sulfadiazine zinc gel on deep second degree burn wounds. *Journal of Guangxi Medical University*. 2017;34:1354–7.

102. Chen YF, Shi HZ. Effect observation of rh EGF combined with mupirocin in the treatment of deep second burn wound. *Lin Chuang Yi Xue*. 2017;93–4.

103. Li Y. Clinical analysis of recombinant human epidermal growth factor gel combined with Nano silver antibacterial gel in treatment of deep second degree burn wounds. *Henan Journal of Surgery*. 2016;22:59–60.

104. Hua RY. Application of rhEGF in the process of facial deep second degree burn wound repair. *Chinese Journal of Aesthetic Medicine*. 2019;28:36–8.

105. Jin GY, Fan YF, Chen C, Zhang C, Wu TB. Effect of recombinant human basic fibroblast growth factor on deep second degree burn wound healing. *Modern Practical Medicine*. 2014;26:480–508.

106. Cai JN, Sun YJ, Xie XF, Li B, Zou XF. The effect analysis of wound dissolution on second deep degree burn by rhGM-CSF. *Zhong Guo Lin Chuang Yi Sheng Za Zhi*. 2017;45:39–42.

107. Lin HB. Effect of recombinant human granulocyte macrophage Colony stimulating factor gel on burn wounds. *Contemporary Medicine*. 2013;19:46–8.

108. Cai JN, Li B, Xie XF, Zou XF, Wu SJ, Li BL. Effect of recombinant human acidic fibroblast growth factor on deep second degree burn. *Zhong Guo Lin Chuang Yi Sheng Za Zhi*. 2016;44:69–71.

109. Sui ZF, Gu TM, Yang RY, Zhao ZL, Gu Y. Clinical observation of Gauft in treating deep burn wounds. *Chinese Journal of Aesthetic Medicine*. 2010;19:753–4.

110. Tong ZJ, Li Y. Clinical observation on therapeutic effects of combined recombinant human epidermal growth factor (Rh-EGF) gel and sulfadiazine zinc silver ointment in the treatment of deep II degree burn wounds. *Asia-Pacific Traditional Medicine*. 2017;13:3.

111. Song ML, Yang CB, Li CL, Luo GC, He XD, Xiao Y, et al. Clinical effect of recombinant bovine basic fibroblast growth factor gel in Assisting wound Repair for deep second degree burn wound. *China Prac Med*. 2018;13:139–40.
112. Sun RP, Zhao LK, Sun J, Ma JY, Li DJ, Zheng WL, et al. Effect of recombinant human aFGF on deep second degree burn. Chinese Journal of Reparative and Reconstructive Surgery. 2011;25:639–40.

113. Qu KP. Effects of Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor Hydrogel on Healing of Deep Partial-Thickness Burn Wounds and Its Mechanism Analysis. Qingdao University, 2017.

114. Wang H. Study of Recombinant Human Granulocyte Macrophage Colony-stimulating Factor on the Healing of Deep Partial Thickness Facial Burns in Pediatric Patients. Jilin University, 2014.

115. Xu XF. Effect of rh-bFGF on deep second degree burn wound healing. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine. 2019;29:195–6.

116. Wang ZX, Yu Q, Xiao JZ. Comparative analysis between rhGM-CSF gel and acellular xenografts dermis on wound healing effects in patients with deep second degree burn. Med & Pharm J Chin PLA. 2018;30:54–71.

117. Xu LH. Effect of VSD technique combined with epidermal growth factor solution on wound healing and inflammatory response in patients with deep burn. Chinese Journal of Aesthetic Medicine. 2017;26:4.

118. Yan Y, Huang GY, Wang HW, Chen G, Ding WX, Zhou PY. Observation of clinical efficacy of Ai Kang Fu aFGF dressings combined with recombinant human epidermal growth factor gel to treat deep II burn residual wounds. China Medical Herald. 2012;9:35–7.

119. Yang ZX, Li T, Xu JC. Therapeutic effect of mupirocin ointment combined with recombinant human gametocyte-macrophage Colony stimulating factor gel in external use on deep second degree burn wounds. Hebei Medical Journal. 2018;40:1845–8.

120. Yang SK. Relationship between wound treatment and healing of deep second degree burn. Chinese and Foreign Medical Research. 2014;12:132–3.

121. Wen CQ, Zhao XZ, Zhang GA. Clinical curative effect observation of recombinant human granulocyte-macrophage Colony-stimulating factor gel on wound healing in patients with deep partial thickness burns. Chin J Injury Repair and Wound Healing. 2016;11:215–8.

122. Yang ZX, Li T, Xu JC. Effect of rh-aFGF on deep second degree burn after Escharectomy. Ji Lin Yi Xue. 2018;39:697–9.

123. Xie BG, Huang YX, Chen J, Xu ZX. Evaluation of the efficacy of rh-aFGF in the treatment of second degree deep burns after tangential excision. China Medical Cosmetology. 2018;8:54–7.

124. Wang L. Recombinant bovine basic fibroblast growth factor gel combined with Nano silver dressing for promoting wound healing in 78 cases. Clin Med. 2015;24:2.

125. Wang ZD. Observation on effect of recombinant bovine basic fibroblast growth factor (rh-bFGF) gel for treating Pediatric mild to moderate deep II degree burn wounds. China & Foreign Medical Treatment. 2015;15:5.

126. You XE, Deng JY, Zhu XF. Clinical observation of recombinant human epidermal growth factor gel in treating deep second degree wounds. Hai Xia Yao Xue. 2010;22:170–1.

127. Yang BM. Clinical observation of recombinant human epithelial growth factor in the acceleration of deep II degree burn wound healing. China Modern Medicine. 2013;20:99–100.

128. Zhang L, Guo JJ, Zhu CL, Gu ZQ. Clinical study of rb-bFGF combined with Nano silver dressing in the treatment of non-functional deep second degree burn wounds in children. Qingdao Med J. 2014;46:433–4.

129. Zhou J, Li YX, Chi YF. Observation on effect of vacuum-assisted closure treatment combined with flushing with epidermal growth factor solution in treating deep II degree burn wound. Infect Inflamm Rep. 2015;16:49–51.

130. Zhang B, Wei SQ, Xu H, He HM, Yang WB, Wei YF, et al. Clinical observation of sulfadiazine silver cold cream mask containing recombinant human epidermal growth factor in treating 22 cases of deep II degree burn of the face. Guangxi Medical Journal. 2010;32:561–3.

131. Zhang B, Xu H. Clinical observation on the healing of facial deep II degree burn wounds with recombinant human epidermal growth factor mask. Chin J Injury Repair and Wound Healing (Electronic Edition). 2011;6:3.

132. Zhou JL, Guo JL, Jin XM, Zhang TJ. The clinical research of combined application of Nano silver antimicrobial dressing with Rh-bFGF in children with deep II degree burn wound. Acta Acad Med Weifang. 2016;38:394–6.

133. Zhao M, Zheng Y. Application of recombinant basic fibroblast growth factor in deep burn injury. Modern Rehabilitation. 2001;5:94.

134. Zhang J. Therapeutic effect of recombinant human granulocyte macrophage Colony-stimulating factor gel on deep II degree burn wounds. J Cin Yi Xue Xue Tan. 2019;23.

135. Zhang J, Zhang XZ, Li H. Clinical observation of recombinant human epidermal growth factor in promoting deep second degree burn wound healing. Chinese Primary Health Care. 2010;24:127–8.

136. Zhang LS, Tian P. Comparison of recombinant human granulocyte-macrophage Colony stimulating factor gel and acellular skin of treating deep second degree burn wound in clinical effect. Journal of Clinical and Experimental Medicine. 2016;15:662–4.

137. Deng ZY. Clinical observation on the treatment of deep second degree burn with rhGM-CSF and silver sulfadiazine. J Clin Res. 2017;34:932–4.

138. Chen HD, Bian HN, Zheng SY, Gao H, Xiong B, Liu ZA, et al. Combined use of Fulin honey and recombinant human epidermal growth factor gel for treatment of deep II degree burn of the face. Chin J Traumatol. 2009;25:2.

139. Liu J, Xiao ZJ, Zhang Q. Phase IV clinical trial for external use of recombinant human granulocyte-macrophage Colony-stimulating factor gel in treating deep partial-thickness burn wounds. Chin J Burns. 2016;32:542–8.

140. Yan J, Wang HZ, Wang P. Efficacy of recombinant human epidermal growth factor gel in the treatment of deep second degree burn wounds. Chinese Journal of Trauma and Disability Medicine. 2016;24:173–4.

141. Jiao XG, Li H, Jiang ZJ, Yang L, Zhou JM, Li F, et al. Effect of recombinant human granulocyte-macrophage Colony stimulating factor combined with silver sulfadiazine on deep second degree burn wound caused by nitrate fire. Chin J Burns. 2014;30:367–9.

142. Xia WD, Wan L, Yang RJ, Ling XW, Lin C. Comparison of clinical effects of recombinant human granulocyte Colony stimulating factor gel and xenograft on deep second degree burn wounds. Chin J Burns. 2015;31:216–7.

143. Ma B, Zhu SH, Cheng DS, Xiao SC, Wang GY, Ben DF, et al. Clinical observation of recombinant human acidic fibroblast growth factor in the treatment of deep second degree burn wounds. Chin J Burns. 2008;24:223.
fistula after hypospadias repair operation. *Henan Journal of Surgery*. 2017;23:10–2.

179. Huang Y, Zhou JY, Li Y, Qi YH. Clinical observation of recombinant human epidermal growth factor in the treatment of mustard gas second degree skin injury. *Med J Chin PLA*. 2004;29:178.

180. Lin L, Liu W, Wang CM, Li HC, Xu RZ. Treatment effect of recombinant human basic fibroblast growth factor-assisted cosmetic suture technique on emergency open traumatic wounds. *Lin Chuang Yi Xue Gong Cheng*. 2019;26:821–2.

181. Liu JN, Wang W, Jia B. A randomized clinical study of recombinant human acidic fibroblast growth factor in the treatment of open wounds. *Journal of Hebei Medical University*. 2018;39:714–6.

182. Jiang WM. Clinical observation on 35 cases of vitiligo treated with autologous epidermal transplantation combined with traditional Chinese and western medicine. *Southern China Journal of Dermato venerology*. 2006;13:106–7.

183. Sun CQ, Yang LH, Yu GZ, Yuan SK. Efficacy of bevacizumab combined with mupirocin in the treatment of Condy-loma Acuminatum after CO2 laser surgery. *China Prac Med*. 2017;12:127–8.

184. Sun RP, Zhao LK, Sun J, Ma JY, Li DJ, Li M, et al. Clinical observation of rh-aFGF application after early Escharectomy on deep second degree burn wound. *Hebei Medical Journal*. 2011;33:2144–5.

185. Sun RP, Zhao LK, Sun J. Clinical observation of tangential excision of eschar and application rh-aFGF on limbs deep second degree burn wound. *Chinese Journal of Aesthetic Medicine*. 2014;2:5.

186. Sun YL, Zhao WH, Zhang L. Rh-bFGF on healing of wound after operation for anal fistula. *Chinese Journal of Practical Nervous Disease*. 2009;12:74–5.

187. Shi CF, Zhao ZL. Effect observation of recombinant human epidermal growth factor gel for wound repair after Freckle & Mole Laser Surgery. *China Medical Herald*. 2016;13:134–6.

188. Shi ZY, Wang YQ. The effect on using of recombinant human epidermal growth factor hydrogel after anal fissure operation. *Lin Chuang Tao Lun*. 2012;50:126–7.

189. Teng ZH, Wang YX, Xue WY, Zhu X, Li W, Qi JC, et al. Observation on the effect of recombinant human epidermal growth factor gel in urethral fistula after hypospadias operation. *Hebei Medical Journal*. 2015;37:1372–4.

190. You S. Clinical Effect of Chlorophyll Derivatives on Postoperative Wound Healing of Low-order Simple Anal Fistula. North China University of Science and Technology, 2019.

191. Wang SX. Application of rh-bFGF combined with wet dressing in hand mechanical injury. *Journal of Yanan University*. 2018;16:100–2.

192. Wang EW, Wu CX, Wang YG. Effect of the application of recombinant human acidic fibroblast growth factor on wound healing and scar after procedure for prolapse and Hemor-hoids. *China Medical Herald*. 2014;11:56–9.

193. Wang ZR, Liu T, Xu X, Li J, Lu K, Li ZY. Clinical effect of basic fibroblast growth factor on the healing of the skin wound. *Chin Hosp Pharm J*. 2008;28:638–40.

194. Wen SJ, He LF, Huang T. Observation on the effect of Genetime solution in the treatment of infectious wound. *Journal of Qilu Nursing*. 2005;11:1548.

195. Wang GL. Clinical observation of two dressing changes in the treatment of diabetic skin Suppurative infection. *Diabetes New World*. 2016;69–70.

196. Xu MC. Clinical study of cosmetic surgery debridement suture combined with recombinant human epidermal growth factor in the treatment of maxillofacial trauma. *China Prac Med*. 2019;14:2.

197. Yao MY, Huang X, Guo QH. Prospective randomized con-trolled clinical trial of rhFGF on cure of Cesarean incision on patients with highly infective risk factors. *China Modern Doctor*. 2014;52:26–31.

198. Wu YJ, Nie M, Li DC, Jiang LH, Tian YY, Ying Y, et al. Effect of human Recombinant fibroblast growth factor on wound healing in urology minimally invasive surgery. *Infect Inflamm Rep*. 2016;17:32–3.

199. Wang JD, Yang WZ, Deng TT, Hua XK, Peng LF, Zhang ZY. Effect of recombinant bovine basic fibroblast growth factor on the healing of mixed Hemorrhoids. *Journal of External Therapy of TCM*. 2018;27:4–5.

200. Wu ZX, Shou XM. Effect of recombinant bovine basic fibroblast growth factor on surgical wound. *Modern Journal of Integrated Traditional Chinese and Western Medicine*. 2004;13:2277–8.

201. Xu H, Sun DS, Hu YY. Application of recombinant bovine basic fibroblast growth factor in wound healing. *Chinese Journal of Trauma*. 2000;16:344.

202. Wei D. Effect of recombinant human epidermal growth factor combined with Beifuxin on the incision healing of facial plastic surgery. *Journal of Chengdu Medical College*. 2017;12:4.

203. Xie YM, Chen MH, Ji Y, He YB. Clinical observation of recombinant human epidermal growth factor gel external use combined with Chinese medicine sit bath treatment for promoting wound surface healing after anal fistula surgery. *Journal of New Chinese Medicine*. 2013;45:58–60.

204. Wu XZ, Xia JY, Chen SH. Study on the effect of recombination human epidermal growth factor on wound healing of anal fissure. *Da Chang Gang Men Bing Wai Ke Za Zhi*. 2004;10:100–2.

205. Wang XH, Zhao XM, Zhao ZJ. The application of rhEGF in the Repairment of wound. *Chinese Journal of Aesthetic Medicine*. 2014;23:175–6.

206. Wu XJ, Sun YF, Liu Y. A multiple Center, randomized, controlled trial of recombinant human acidic fibroblast growth factor in promoting wound healing after anal fissure surgery. *Chin J Clinicians (Electronic Edition)*. 2013;7;11321–4.

207. Zhi XY, Chen XS, Zeng XX. Observation on the effect of recombinant epidermal growth factor on grade II trauma. *China Trop Med*. 2007;7:70–1.

208. Zhu SR, Wang XL, Tang GX, Yao XJ, Ji YX. Effect of rhEGF on wound healing after combined radical operation of oral cancer. *Lin Chuang Kou Quan Yi Xue Za Zhi*. 2006;2:107–8.

209. Zhang C, Chai SQ, Ma BB. Clinical observation of rhEGF in the treatment of severe bruising and contusion wounds. *Journal of Dali University*. 2015;14:47–9.

210. Zhong XD, Lin HH, Chu ZH. Clinical observation of recombinant human epidermal growth factor in wound healing after Hemorrhoids surgery. *Lingnan Modern Clinics in Surgery*. 2015;13:166–8.

211. Zhai YD, Cai N, Wei X. Treatment of 45 cases of anal fistula with recombinant bovine basic fibroblast growth factor. *Journal of Qiaman Medical College for Nationalities*. 2010;23:176–7.

212. Zhang MF, Xu CP. Effect of basic fibroblast growth factor on promoting wound healing in acute sports injury. *Fujian Sports Science and Technology*. 2007;26:34–5.
213. Zhang SH, Han CY. Effect of basic fibroblast growth factor on wound healing after CO2 laser surgery. *Chin J Dermatol.* 2001;34:1.

214. Zhou J, Wu JX, Liu LX, Li JH, Wang YF, Kong LY. Effect of Longzhua ointment combined with Jinxuan Zhike fumigation powder on wound healing after perianal abscess operation. *Herald of Medicine.* 2011;30:1600–1.

215. Mei JC, Chen Z, Deng FM, Xiao R, Chen B. Cosmetic plastic debridement and suture combined with recombinant human epidermal growth factor in the treatment of maxillofacial trauma. *Modern Medicine and Health Research.* 2019;3:67–70.

216. Zhang RH, Tian ZB. Randomized controlled trial on application of recombinant basic fibroblast growth factor and compound four yellow liquid wound dressing for pollution wound treatment. *China Modern Medicine.* 2012;19:60–1.

217. Zhu B, Dai L. Clinical study of recombinant human epidermal growth factor promoting wound healing after complex anal fistula operation. *Chin J Mod Drug Appl.* 2012;6:21–2.

218. Zhou KL, Zou XJ. Effects of recombinant human epidermal growth factor on wound healing of perianal abscess after operation. *J Clin Surg.* 2015;23:286–7.

219. Zhao K, Xu X. Clinical observation of recombinant human epidermal growth factor combined with thread drawing therapy in the treatment of high perianal abscess. *Technique Communication.* 2019;22:213–5.

220. Zhu WZ. Effect and cost comparison of recombinant human basic fibroblast growth factor on wound healing. *Zhong Guo Xiang Cun Yi Yao Za Zhi.* 2007;14:28–9.

221. Zhang HK. Effect of recombinant human acidic fibroblast growth factor on wound healing and scar of mixed Hemorrhoids after Hemorrhoidectomy. *Chin Med J Metall Indus.* 2019;36:604–5.

222. Zhang ZM. Beifuji for promoting healing of wound after operation for Hemorrhoids. *Chin J Coloproctol.* 2004;24:8–9.

223. Yun J, Yang GG, Liu ZY. Impact of basic fibroblast growth factor on wound surface healing of perianal infection. *Chinese J Coloproctol.* 2007;27:2.

224. Huang W. Effects of recombinant human epidermal growth factor on wound healing of perianal abscess after operation. *Chin J Prim Med Pharm.* 2017;24:2026–9.

225. Xu Q. Observation on the effect of epithelial growth factor in the superficial trauma wound care. *Chinese Journal of Trauma and Disability Medicine.* 2017;25:30–1.

226. Zhang B, Han YM. Clinical analysis of efficacy of Shengji Baiyu Gao on wound-surface healing after perianal abscess operation. *Chin J Coloproctol.* 2017;37:2.

227. Luo Y. Clinical Effect of Recombinant Human Basic Fibroblast Growth Factor for External Use on Wound Healing after Lumbar Surgery. Southwest Medical University, 2018.

228. Wang DX. Effect of external using recombinant human granulocyte-macrophage Colony Stimulating factor gel on wound-surface healing after anal fistula surgery. *Chin J Coloproctol.* 2016;36:23–5.

229. Sun LH, Song Y, Hua N. Clinical observation of recombinant human epidermal growth factor in the repair of auricle skin defect. *Chin J Postgrad Med.* 2010;33:66–7.

230. Fu XB, Shen ZY, Chen YL, Xie JH, Guo ZR, Zhang ML, et al. Recombinant bovine basic fibroblast growth factor accelerates wound healing in patients with burns, donor sites and chronic dermal ulcers. *Chin Med J (Engl).* 2000;113:367–84.

231. Ono I, Akasaka Y, Kikuchi R, Sakemoto A, Kamiya T, Yamashita T, et al. Basic fibroblast growth factor reduces scar formation in acute incisional wounds. *Wound Repair Regen.* 2007;15:617–23.

232. Yan DX, Liu S, Zhao XC, Bn HJ, Yao XW, Xing JP, et al. Recombinant human granulocyte macrophage colony stimulating factor in deep second-degree burn wound healing. *Medicine.* 2017;96.

233. Lin Y, Chen MH, Ding FF, Wang RX, Liang ZQ, Meng CY, et al. Study of the use of recombinant human granulocyte-macrophage colony-stimulating factor hydrogel externally to treat residual wounds of extensive deep partial-thickness burn. *Burns.* 2015;41:1086–91.

234. Akita S, Akino K, Imaizumi T, Hirano A. Basic fibroblast growth factor accelerates and improves second-degree burn wound healing. *Wound Repair Regen.* 2008;16:635–41.

235. Nie KY, Li PC, Zeng XQ, Sun GF, Jin WH, Wei ZR, et al. Clinical observation of basic fibroblast growth factor combined with topical oxygen therapy in enhancing burn wound healing. *Chinese J Reparative and Reconstructive Surgery.* 2010;24:643–6.

236. Hayashida K, Akita S. Quality of pediatric second-degree burn wound scars following the application of basic fibroblast growth factor: results of a randomized, controlled pilot study. *Ostomy Wound Manage.* 2012;58:32–6.

237. Wang SL, Ma JL, Chai JK, Zhou L, Liao ZJ, Huang YS, et al. Acceleration of burn wound healing with topical application of recombinant human epidermal growth factor ointments. *Chinese J Reparative and Reconstructive Surgery.* 2002;16:173–6.

238. Wang GY, Xia ZF, Zhu SH, Tang HT, Huan JN, Chen YL, et al. Clinical observation of the Long-term effects of rh-EGF on deep partial-thickness burn wounds. *Chin J Burns.* 2003;19:167–8.

239. Wang ZY, Zhang Q, Liao ZJ, Han CM, Lv GZ, Luo CQ, et al. Effect of recombinant human granulocyte-macrophage Colony stimulating factor on wound healing in patients with deep partial thickness burn. *Chin J Burns.* 2008;24:107–10.

240. Yan H, Chen J, Peng X. Recombinant human granulocyte-macrophage colony-stimulating factor hydrogel promotes healing of deep partial thickness burn wounds. *Burns.* 2012;38:877–81.

241. Zhang LP, Chen J, Han CM. A multicenter clinical trial of recombinant human GM-CSF hydrogel for the treatment of deep second-degree burns. *Wound Repair Regen.* 2009;17:685–9.

242. Zhang Y, Wang T, He JG, Dong JS. Growth factor therapy in patients with partial-thickness burns: a systematic review and meta-analysis. *Int Wound J.* 2016;13:334–66.

243. Abdellahim M, Lin X, Ogawa R. The Japanese experience with basic fibroblast growth factor in cutaneous wound management and scar prevention: a systematic review of clinical and biological aspects. *Dermatol Ther (Heidelb).* 2020;10:569–87.

244. Briquez PS, Hubbell JA, Martino MM. Extracellular matrix-inspired growth factor delivery Systems for Skin Wound Healing. *Adv Wound Care (New Rochelle).* 2015;4:479–89.

245. Cohen MA, Eagleton WH. Recombinant human platelet-derived growth factor gel speeds healing of acute full-thickness punch biopsy wounds. *J Am Acad Dermatol.* 2001;45:857–62.

246. Chipp E, Charles L, Thomas C, Whiting K, Moiemen N, Wilson Y. A prospective study of time to healing and hypertrophic scarring in paediatric burns: every day counts. *Burns Trauma.* 2017;5:3.