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REVIEW ARTICLE

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The use of epidermal growth factor in dermatological practice

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Abstract

Epidermal growth factor (EGF) is a growth factor that plays a pivotal role in wound healing and maintaining tissue homeostasis by regulating cell survival, proliferation, migration, and differentiation. Exogenous administration of bioidentical human recombinant epidermal growth factor (rhEGF) has been known to promote skin wound healing, although rhEGF is increasingly being used in drug delivery systems and nanotechnology. However, despite considerable attention being focused on the potential clinical applications of rhEGF in several dermatological conditions beyond wound healing, the number of studies still remains relatively low. Herein, we conducted a literature search of PubMed/Medline and Google Scholar databases to retrieve published literature related to rhEGF and summarised the effects of rhEGF in the treatment of various wound types, radiotherapy or chemotherapy-related skin reactions, atopic dermatitis, skin aging, and post-inflammatory hyperpigmentation.

KEYWORDS

cosmetics, dermatology, epidermal growth factor, wound

Key Messages

- epidermal growth factor is an important endogenous mitogenic factor which regulates cell growth, proliferation, differentiation and survival
- recent development of drug delivery systems and nanotechnologies enabled the use of human recombinant epidermal growth factor (rhEGF) in various clinical indications
- this review aimed to help better understand the benefits of rhEGF in the treatment of dermatological conditions including wounds, acneiform disorders, dermatitis, hair loss, and potential aesthetic applications

1 | INTRODUCTION

Epidermal growth factor (EGF) is a well-known mitogenic polypeptide that was first isolated from the submaxillary gland of mice by Stanley Cohen in the early 1960 seconds.[1] EGF exerts mitogenic effects by binding to its membrane receptor (epidermal growth factor receptor [EGFR]), which can then regulate cell growth, proliferation, differentiation, and survival, among other biological effects.[1] EGFRs are expressed in a variety of human tissues including most epithelial tissues, fibroblasts, and endothelial cells, meaning that EGF plays a key role in wound healing and maintaining tissue integrity.[2]

Advances in recombinant DNA technology have enabled the production of human recombinant EGF (rhEGF) in large quantities. Consequently, in-depth studies of rhEGF and the healing of surgical wounds, burn wounds, and diabetic foot ulcers have been carried out.[3] However, because of its short half-life, large molecular weight, and lack of efficient formulation,[4-6] delivering rhEGF transdermally poses a significant clinical challenge. With the recent development of drug delivery systems and nanotechnologies stabilised the rhEGF, therefore the use of rhEGF in the dermatologic field has also been resurgent.[7-11] In addition, research has shown that EGF does not appear to be involved in the malignant transformation of wound bed cells and does not initiate tumorigenesis, thereby increasing its clinical usefulness.[12,13] Hence, this narrative review aims to highlight the benefits of using rhEGF in the treatment of dermatological pathologies including wounds (eg, traumatic, surgical), acneiform disorders, dermatitis, and hair loss, and also discusses potential aesthetic applications.

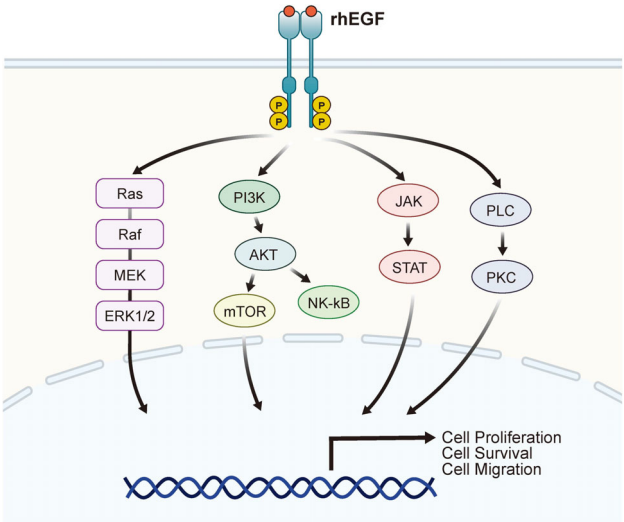

FIGURE 1 Schematic view of intracellular signalling pathways involved in rhEGF function

2 | WOUND HEALING AND SCAR PREVENTION

Wound healing is a highly complex process of inflammation, cellular proliferation, differentiation, and remodelling, and involves multiple cytokines and growth factors including EGF.[14] As such, modulating this process is challenging, so numerous studies have attempted to investigate the role of rhEGF in treating acute or chronic wounds. rhEGF is known to facilitate wound healing by promoting re-epithelialisation, and angiogenesis, and can stimulate myofibroblast activation and proliferation via the PI3K/AKT and ERK/MAPK signalling pathways (Figure 1).[15,16] In a rat model, EGF was also shown to protect fibroblasts from oxidative stress by scavenging already formed toxic oxidation products during the acute wound healing phase.[17]

Several clinical trials evaluating the effects of topical applications of rhEGF on diabetic foot ulcers, including a phase 3 trial conducted in Korea, showed that rhEGF significantly improved wound healing by reducing the wound healing time.[18-20] rhEGF was also shown to be beneficial in treating pressure sores, second-degree burns, and chronic, non-healing traumatic wounds in a small number of case series and small clinical trials, including our own clinical experiences (Figure 2).[21-23] However, topical rhEGF ointment was difficult to apply to open wounds because of the wound exudate and because rhEGF is degraded by biofilm proteases.[24] Drug delivery systems such as polymeric nanoparticles and biomedical scaffolds have been developed and have improved the bioavailability of rhEGF.[25]

Additional studies have linked rhEGF with the treatment of surgical wounds. Suh et al. reported that rhEGF ointment successfully treated the excisional wound of keratoacanthoma without a primary closure, which took less time than normal healing.[26] Additionally, Shin et al. demonstrated that rhEGF significantly improved scar pliability and thickness in thyroidectomy scars after four weeks, compared with the control group.[27]

Kao et al. conducted a study with 60 Taiwanese women[28] regarding microencapsulated rhEGF on the cutaneous scar after a caesarean section. Their results showed that scar vascularity, pigmentation, elasticity, and the Vancouver Scar Scale (VSS) total score after nine months were all significantly lower in the rhEGF group than in the silicone gel group (control group). Ryu et al. reported that rhEGF ointment decreased the length and area of excision scars and also showed similar short-term cosmetic results—as reflected in the melanin index and the erythema index—to mupirocin ointment.[29] Their results indicate that rhEGF may reduce antibiotic resistance by reducing the use of topical antibiotics after clean wound surgeries.[29] Although well-designed controlled trial data are still relatively scarce, the use of rhEGF in

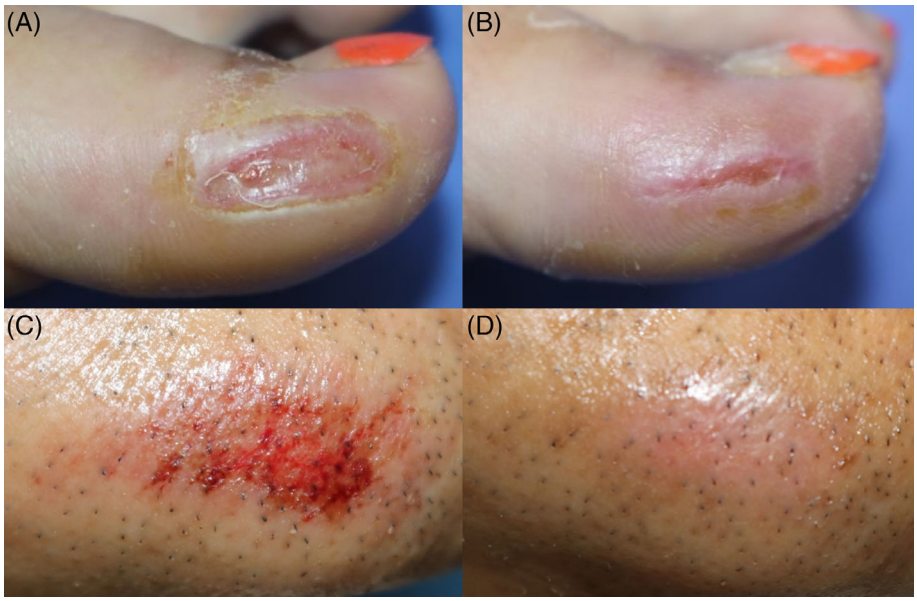

FIGURE 2 (A) Clinical photographs of a chronic and recalcitrant traumatic wound in a 35-year-old female before, and (B) after two weeks of treatment with rhEGF ointment. (C) Clinical photographs of a traumatic abrasion wound in a 62-year-old male before, and (D) after three days of treatment with rhEGF ointment

scar prevention is expected to become more prevalent in future.

3 | CHEMOTHERAPY AND RADIATION-RELATED SKIN REACTIONS

Radiation therapy can cause skin injuries such as erythema, itching, blisters, desquamation, and non-healing ulcers, which often interrupts the radiotherapy treatment schedule for cancer patients. Therefore, the effectiveness of rhEGF in the treatment of radiation dermatitis has also been studied.

Hong et al. first reported a case of a chest ulcer caused by radiation successfully treated with rhEGF ointment, which was refractory to conservative wound dressings and debridement.[30] They also showed that rhEGF accelerated the proliferation of radiation-induced fibroblasts and keratinocytes in vitro,[31] and demonstrated that the systemic injection of rhEGF ameliorated radiation-induced mucosal damage in a mouse model.[31] The topical application of rhEGF was shown to accelerate wound healing and prevent the recurrence of radiodermatitis in a mouse model.[32] In a separate study, Kong et al. evaluated the topical application of rhEGF-containing cream in 20 breast cancer patients and found that the severity of radiation dermatitis decreased significantly compared with supportive skin care.[33]

A large multicentre observational study of 1172 patients who received more than 50 Gy of radiotherapy showed that rhEGF-containing cream assisted in the prevention or alleviation of radiation dermatitis without any severe adverse events.[34]

Several EGFR inhibitors were developed as chemotherapeutic agents once the role that EGF played in tumorigenesis was confirmed.[35] EGFR inhibition can interrupt normal keratinocyte growth and migration, resulting in epidermal thinning, xerosis, and acneiform eruption, which may adversely impact the patient's quality of life.[35] In human epidermal keratinocytes, rhEGF was shown to activate EGFR signalling and attenuate the expression of pro-inflammatory cytokines such as IL-1, IL-8, and TNF-α, which were induced by EGFR inhibitors.[36] Kim et al. also demonstrated that rhEGF treatment normalises the proliferation and differentiation of keratinocytes in 3D-cultured human skin tissue, as well as in the skin lesions of patients with EGFR inhibitor-related skin toxicities.[36] Furthermore, a pilot phase 3 trial of rhEGF for treating EGFR inhibitor-induced skin toxicities showed that rhEGF ointment significantly improved skin lesions and patients' quality of life when compared with a placebo.[37]

There have been concerns, recently, that rhEGF may be involved in tumorigenesis; however, a recent literature review shows that there is no evidence that topical rhEGF preparation stimulates cancer cell proliferation.[13]

4 | ACNE

Acne is one of the most common inflammatory skin conditions and affects approximately 80%–90% of adolescents. Occasionally, it can lead to scarring, which can be unsightly. Both EGF and the EGFR pathway are known to affect commensal and pathogenic bacteria associated with acne pathogenesis, such as *Cutibacterium acnes* (*C. acnes*) and *Staphylococcus epidermidis*.[38,39] Recently,

studies have showed the therapeutic efficacy of rhEGF on acne inflammation and acne scarring.

An in vitro study by Kim et al. showed that rhEGF inhibits the mRNA expression of pro-inflammatory cytokines including IL-1α, IL-8, and TNF-α induced by *C. acnes* in cultured human keratinocytes.[40] The *C. acnes*-induced expression of toll-like receptor 2 (TLR2) and nuclear factor kappa B (NF-κB) activity were also reduced by rhEGF. Interestingly, they also found that the inhibition of EGFR by gefitinib attenuated the inhibitory effect of rhEGF on the expression of pro-inflammatory cytokines as well as TLR2 and NF-κB activity.

Kim et al. also performed a split-face study evaluating the efficacy of rhEGF-containing cream in 20 Korean patients with mild-to-moderate acne.[41] After six weeks of application, the rhEGF-treated side showed a significant reduction in inflammatory and non-inflammatory acne lesions, sebum output, and overall acne severity compared with the vehicle-treated side. Additionally, rhEGF-containing cream was well-tolerated and no significant adverse events were reported.

During a 12-week trial, Ronald et al. demonstrated the beneficial effects of topical rhEGF in acne scarring by showing how the mean investigator global assessment (IGA) score and the Goodman grade—a qualitative scar grading system for acne scarring—improved with rhEGF treatment.[42-44] More recently, a split-face study of 36 patients with mild-to-moderate acne demonstrated that topical application of rhEGF significantly reduced the acne lesions and scar counts, with decreased IGA and ECCA scar grades.[45]

Additionally, rhEGF increased the expression of TGF-β1, elastin, and collagen type 1 and 3, and decreased keratin 16, NF-κB p65, IL-1α, and IL-8 expression, which implies that rhEGF has anti-inflammatory properties.[45] Collectively, these studies suggest that rhEGF may be a possible therapeutic adjuvant for both acne and acne scarring.

5 | ATOPIC DERMATITIS

In contrast to the aforementioned studies regarding the efficacy of rhEGF in wound healing or radiation dermatitis, studies on the efficacy of rhEGF in atopic dermatitis (AD) have mostly been conducted in vitro. In a study by Zhang et al., EGF treatment in an AD-like mice model significantly attenuated transepidermal water loss (TEWL), epidermal thickness, AD inflammation, and total and allergen-specific immunoglobulin E (IgE) levels induced by cutaneous allergen rechallenge.[46] More specifically, EGF suppressed allergen-induced expression of IL-17A, CXCL1, CXCL2, neutrophil accumulation, and IL-6 production in atopic skin. Based on these findings, the authors suggested that EGF played a protective role in AD by modulating Th17 responses in the skin.[46] Similarly, Kim et al. reported that topical application of EGF improved skin lesion severity, skin thickness, epidermal hyperplasia, scratching behaviours, serum total IgE level, and TEWL in a 2,4-dinitrochlorobenzene (DNCB)-induced AD mice model.[47] They also reported that EGF increased the expression of skin barrier-related proteins including filaggrin, involucrin, loricrin, occluding, and zonula occludens-1. In addition, EGF attenuated the expression of protease-activated receptor-2 (PAR-2) and thymic stromal lymphopoietin (TSLP), which plays a key role in pruritus and Th2 immune response in AD. Choi et al. also demonstrated that topical EGF application suppressed *S. aureus*-induced inflammation in human epidermal keratinocytes and DNCB-induced AD mice models.[48] These findings suggest that by regulating skin barrier function and immune response, rhEGF may be an adjuvant therapeutic option in AD cases.

Nevertheless, the mechanisms underlying the protective effects of rhEGF are not fully understood and clinical data are insufficient. Further research is necessary to verify the therapeutic efficacy and mechanism of rhEGF in AD.

6 | HAIR LOSS

The exact role of EGF on the development and growth of hair follicles has yet to be fully elucidated and there is still controversy about whether rhEGF can reduce hair loss. An older paper by Philpott et al. showed that EGF stimulated hair elongation and DNA synthesis in the outer root sheath (ORS) and was also able to induce an artificial catagen-like effect in isolated human hair follicles.[49] Zhang et al. reported similar results using a mink model, showing that EGF promotes the proliferation, and migration of ORS cells and induces the catagen phase.[50] They also suggested that EGF activates the Wnt/β-catenin signalling pathway, the most important signalling pathway that regulates hair regeneration.[50,51] A more recent study by Bai et al. found that EGF induces the proliferation of hair follicle-derived mesenchymal stem cells through the ERK and AKT signalling pathways.[52] By contrast, however, Mak et al. showed that the continuous expression of EGF in transgenic mice arrested follicular growth and development during the final stage of hair follicle morphogenesis.[53] Moreover, EGF has been shown to inhibit hair shaft elongation and change the morphology to catagen growth patterns by suppressing mitotic regulators including RCC2 and Statmin1.[54,55] El-Refai et al. also reported that EGF negatively impacts hair follicle growth and may be linked to the pathogenesis of alopecia areata.[56]

TABLE 1 Overview of applications of EGF in dermatological fields

Indication	Mechanism of action	Preclinical/clinical model	Clinical function
Wound/scar	• Accelerates epidermal proliferation rate[15] • Modulates wound contraction via myofibroblast proliferation and collagen deposition[15,16] • Increases fibroblast proliferation[16] • Acts as antioxidants by scavenging toxic oxidation products[17]	Acute full thickness wound/Rat[15]	• Increased the rate of epidermal proliferation and accelerated the level of wound contraction
		Diabetic foot ulcers/Human[19,20]	• Promoted the epithelialisation of the wound bed, and reduced the wound area[19] • Reduced the healing time[20]
		Pressure ulcers/Human[21]	• Alleviated ulcer wound, pain, and inflammation
		Ulcers, surgical or traumatic wounds, burns, and scars/Human[22]	• Perilesional skin improved in 93.5% of the cases • Lesion margin and wound bed appearance improved in 92.2% • 44.64% of ulcers healed more than 40% in four weeks
		Second-degree burns/Human[23]	• Reduces the healing time
		Excisional wound of keratoacanthoma without a primary closure/Human[26]	• Wound fully epithelialised without scarring after two weeks
		Surgical scars after thyroidectomy/Human[27]	• Improved total VSS, pliability, and thickness
		Surgical scars after Caesarean section/Human[28]	• Total VSS score, vascularity, pigmentation, and elasticity significantly improved by silicone gel with microencapsulated rhEGF compared with silicone gel only group and no scar treatment group after six and/or nine months
		Surgical wounds after cutaneous resection/Human[29]	• Length and area of wounds improved compared with antibiotic ointment treatment
Radiation dermatitis	• Ameliorates radiation-induced cell death of fibroblasts and keratinocytes[31] • Increases cell proliferation[31]	Radiation-induced oral mucosal dermatitis/Mouse[31]	• Ameliorated radiation-induced mucosal damage by increasing the epithelial cell layer thickness and the proliferation of basal layer cells
		Radiation dermatitis/Mouse[32]	• Lowered the recurrence rate of radiation dermatitis
		Breast cancer with postoperative radiation treatment/Human[33]	• Lowered the incidence of grade 3 radiation dermatitis
		Malignancies with radiation treatment/Human[34]	• May be effective in preventing or alleviating radiation dermatitis with no severe adverse events
EGFRI-related skin toxicity	• Normalises the proliferation and differentiation of keratinocytes and reduces inflammatory cytokines affected by EGFRIs[36]	EGFRI-related adverse skin events/Human[37]	• Effective in treating EGFRI-related skin adverse events and improving patient's quality of life
Acne and acne scars	• Attenuates *C. acnes*- induced inflammatory responses through	Mild-to-moderate acne vulgaris/Human[41]	• Both inflammatory and non-inflammatory acne lesions reduced

TABLE 1 (Continued)

Indication	Mechanism of action	Preclinical/clinical model	Clinical function
	the modulation of TLR2 signalling[39] • Decreases inflammation and stimulates the production of matrix proteins[43,44]	Atrophic acne scarring/Human[42,43] Acne and acne scarring/Human[44]	• Sebum output decreased and skin hydration level increased • IGA and Goodman grades improved • Acne lesion and scar counts decreased and IGA, SGA, and ECCA grades improved
Atopic dermatitis	• Modulates Th17 responses[45] • Regulates Th1/Th2-mediated cytokines, mast cell hyperplasia, and protease-activated receptor-2 and thymic stromal lymphopoietin[46] • Increases level of skin barrier-related proteins (filaggrin, involucrin, loricrin, occludin, and zonula occludens-1)[46]	AD/Mouse[46-48]	• Alleviated AD exacerbation through reducing erythema, transepidermal water loss, ear/epidermal thickness, cutaneous inflammation, and total and allergen-specific IgE[45-47]
Hair loss	Positive effects • Promotes the proliferation and migration of outer root sheath cells and upregulating the expression of follicle-regulatory genes via Wnt/β-catenin signal pathway[49] • Induces proliferation of hair follicle-derived mesenchymal stem cells through the ERK and AKT signal pathways[50] • resulting in retardation of follicle progression to dystrophic catagen	Chemotherapy-induced alopecia/ Mouse[57]	• Delayed progression of chemotherapy-induced alopecia and promotes primary hair recovery[56]
	Negative effects • Triggers catagen entry associated with premature cessation of proliferation in the hair follicles[53] • Blocks hair follicle induction and promotes interfollicular epidermal differentiation[54]	Alopecia Areata/Human[56]	• Elevated serum EGF level is significantly higher in alopecia areata than control group and associated with recurrence, severity, and involvement area
Cosmetic application	• Improves migration, cluster formation, and contractility of aging fibroblast[57] • Boosts hyaluronic acid synthesis[58] • Promotes type I/III collagen synthesis and decreasing matrix metalloproteinase-1,3 and 9[59] • Regulates laser-induced melanogenesis.[63]	Photodamaged aging skin/ Human[61] Periocular wrinkles/Human[62] Aging face/Human[63] Senile lentigines/Human[65] Solar lentigines/Human[66]	• Fine lines, rhytids, skin texture, pore size, and dyschromatic conditions improved • Micro-spicule containing EGF improved periorbital wrinkle, but not EGF alone • Microneedle patch containing rhEGF improved wrinkle and skin hydration • Melanin index and incidence of PIH after Q-switched 532-nm Nd:YAG laser treatment decreased[64,65]

(Continues)

TABLE 1 (Continued)

Indication	Mechanism of action	Preclinical/clinical model	Clinical function
		Post-laser resurfacing wound/ Human[67]	• Slightly lowered the risk of PIH, duration of post-laser erythema and wound healing, but no statistical significance

Abbreviations: AD, atopic dermatitis; ECCA, échelle d'évaluation clinique des cicatrices d'acné; *C. acnes*, *Cutibacterium acnes*; EGFRI, epidermal growth factor receptor inhibitor; IGA, Investigator global assessment; Nd:YAG, neodymium-doped yttrium aluminium garnet; PIH, post-inflammatory hyperpigmentation; rhEGF, recombinant human epidermal growth factor; *S. aureus*, *Staphylococcus aureus*; SGA, scar global assessment; VSS, vancouver scar scale.

Additionally, a recent paper by Paek et al. showed that topical application of rhEGF promoted primary hair recovery through the dystrophic anagen pathway in a mouse model of cyclophosphamide-induced alopecia.[57] As the evidence for this is currently weak, further research will be necessary to understand the exact roles of the EGF in hair follicle morphogenesis and cycling, as well as their therapeutic potential for reducing hair loss.

7 | COSMETIC APPLICATIONS

rhEGF has also been studied in aesthetic applications. In vitro studies have shown that rhEGF promotes the migration and contractility of aged fibroblasts and increases both hyaluronic acid and collagen synthesis.[58,59] Based on this experimental background, several preclinical and clinical studies on the effect of rhEGF on photoaged skin have been published. For example, Shin et al. demonstrated that EGF-containing hyaluronic acid filler induces type 1 and 3 collagen production and down-regulates the expression of MMP-9.[60] Schouest et al. showed that a three-month topical application of EGF-containing serum significantly improved brown pigmentation, skin texture, pore size, and wrinkles in 29 females with photoaged skin.[61] Ha et al. reported that a four-week application of micro-spicule containing EGF cream was effective for the clinical improvement of periocular wrinkles in 20 Korean women.[62] Additionally, a newly developed hyaluronic acid-based microneedle patch containing rhEGF significantly improved the appearance of wrinkles compared with a microneedle patch alone.[63] However, these studies are underpowered because of their small sample size and lack of a control group. Therefore, the clinical efficacy of rhEGF in improving the appearance of photoaged skin remains unclear.

Recent studies have demonstrated that rhEGF is beneficial for treating laser-induced post-inflammatory hyperpigmentation (PIH). Yun et al. reported that rhEGF alleviates melanogenesis in a PIH model by using laser-treated keratinocyte-conditioned culture media.[64] In their study, human melanocytes responded to EGF via ERK signalling, without any alterations in cell proliferation.[64] They also suggested that EGF may regulate the action of pro-inflammatory cytokines generated by laser-irradiated keratinocytes including PGE2, which can stimulate melanogenesis.[52] Based on these results, a few clinical studies have attempted to investigate the therapeutic effects of rhEGF on laser-induced PIH. Park et al. conducted a randomised controlled trial, with a control group, to evaluate the effect of rhEGF-containing cream after the 532-nm Q-switched neodymium-doped yttrium aluminium garnet (Nd:YAG) laser irradiation of 25 Korean patients with senile lentigines.[65] The incidence of PIH and melanin index was significantly lower in the EGF-containing cream group than in the control group. Kim et al. recently conducted a similar study evaluating the effect of EGF-containing ointment for treating solar lentigines as an adjuvant to Q-switched 532 Nd:YAG laser.[66] Techapichetvanich et al. also performed a split-face study comparing the efficacy of rhEGF ointment after fractional ablative CO_2 resurfacing with petrolatum ointment in 19 Thai patients.[67] Although not statistically significant, topical rhEGF ointment did slightly lower the risk of PIH compared with the control group (52.6% vs. 57.9%). However, when analysing the efficacy of the laser-induced wound healing process, there was no significant difference in the duration of scab shedding, the duration of post-laser erythema, or transepidermal water loss compared with the control.

Taken together, these studies indicate the therapeutic potential of rhEGF in the prevention of laser-induced PIH, although further robust clinical studies are needed to further explore the potential benefits of rhEGF.

8 | CONCLUSION

The extant literature demonstrates the therapeutic potential of rhEGF in dermatological conditions including various wounds, acne, radiation-induced dermatitis, skin aging, and laser-induced hyperpigmentation (Table 1). We expect this review article to provide a deeper insight into rhEGF for dermatologists and hope that further

research will be conducted to elucidate the precise mechanisms underlying EGF signalling in various skin conditions.

AUTHOR CONTRIBUTIONS

Sun Hye Shin: Original draft, investigation. Young Gue Koh: Validation, investigation. Woo Geon Lee: Validation, investigation. Joon Seok: Conceptualisation, methodology, review, and editing of the manuscript. Kui Young Park: Conceptualisation, methodology, review, and editing of the manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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