

Epidermal Growth Factor in Aesthetics and Regenerative Medicine: Systematic Review

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Abstract

Introduction: Epidermal Growth Factor (rhEGF) is a promising skin antiaging agent that successfully promotes skin wound repair, and it has been investigated in the past decade for these purposes. However, there are no updated systematic reviews, in English or Spanish, that support the efficacy of rhEGF as a regenerative skin treatment or systematic reviews that compile the uses of rhEGF as facial aesthetic therapy and regenerative medicine. **Aim:** To describe the current state of facial aesthetic and regenerative medicine treatments in which rhEGF has been effectively used. **Materials and Methods:** An exhaustive search was carried out in “Medline” (via “PubMed”), “Cochrane,” “Bireme” through the Virtual Health Library (VHL), “Elsevier” via “Science Direct,” “Springer,” “SciELO,” “ResearchGate,” and Google Scholar. Studies related to the use of rhEGF in addressing skin disorders or skin aging are included. **Results:** Overall, 49 articles were found, which described the use of rhEGF for skin regeneration and restructuring. Efficacy in the regeneration of skin wounds was verified through the intradermal and topical application of formulations with rhEGF. Most clinical trials in aesthetics point to an effective inversion of skin aging. However, uncontrolled or randomized trials abound, so that does not represent enough evidence to establish its efficiency. There are transient adverse effects for both cases. **Conclusion:** The rhEGF considers an effective therapeutic alternative for patients with recalcitrant skin wounds and skin aging, as it is a potent and specific mitogenic factor for the skin.

Keywords: Epidermal growth factor, facial aesthetics, regenerative medicine, skin aging, skin ulcers

Key messages:

- ✓ Similarities exist between the aging skin and wound healing, and mostly they involve the same oxidation and repair mechanisms
- ✓ In both cases, it is necessary to biostimulate fibroblasts and keratinocytes, inducing dermal restructuring.
- ✓ The EFG is more effectively applied by intradermal injections and using transdermal patches, thereby reducing the rhytids, folds, and hyperpigmentation and accelerating wound healing.

INTRODUCTION

In recent years, Epidermal Growth Factor (EGF) has been an important innovation.^[1] It is a mitogenic polypeptide that is responsible for the maintenance and protection of the epithelia.^[2] Thanks to genetic recombination, effective and clinically safe recombinant EGF (rhEGF) is available.

On the other hand, there are striking similarities between oxidative events that promote skin aging and the oxidation seen in delayed wound healing. In both cases, the skin's repair mechanisms are overwhelmed, as the production of growth factors slows down, including the production of EGF.^[3]

In both cases, it is necessary to biostimulate fibroblasts and keratinocytes, inducing the replacement of collagen and

elastin and the extracellular matrix.^[3] The success of the use of growth factors as a strategy to reverse photoaging lies in understanding its role in wound healing.^[4] Therefore, the new cosmetic assets with recombinant growth factors as the rhEGF pursue this restructuring.^[5-7]

The rhEGF has been investigated in the past decade as a treatment of facial photoaging.^[8] However, the literature review revealed that there are no systematic reviews, in

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Spanish or English, about the efficacy of rhEFG as facial and regenerative therapy.

Given the lack of this information and the clinical potential of this factor, this systematic review aims at describing the current state of facial aesthetic and regenerative medicine treatments in which rhEGF has been effectively used with an emphasis on cutaneous restructuring.

MATERIALS AND METHODS

Search strategy

The search was started in health databases: Medline (via PubMed), Lilacs (via Bireme), Science Direct, Cochrane Library Virtual Health Library (VHL), SciELO, Medigraphic,

and Google Scholar. To delimit the number of papers to select, the search was filtered by preferred languages (English and Portuguese) and the period 2001–2019 (since the information published in the past five years was not enough).

The logical AND operator was used to combine the following descriptors for the search:

- English (MeSH): facial antiaging therapeutics; skin rejuvenation; EGF recombinant; epidermal growth factor; tissue regeneration; EGF, rhEGF.
- Portuguese: Fator crescimento ou recombinant epidermal carcinoma; rejuvenescimento gives peel; redensificação dermal; com faciais terapias fatores of crescimento; EGF, rhEGF.

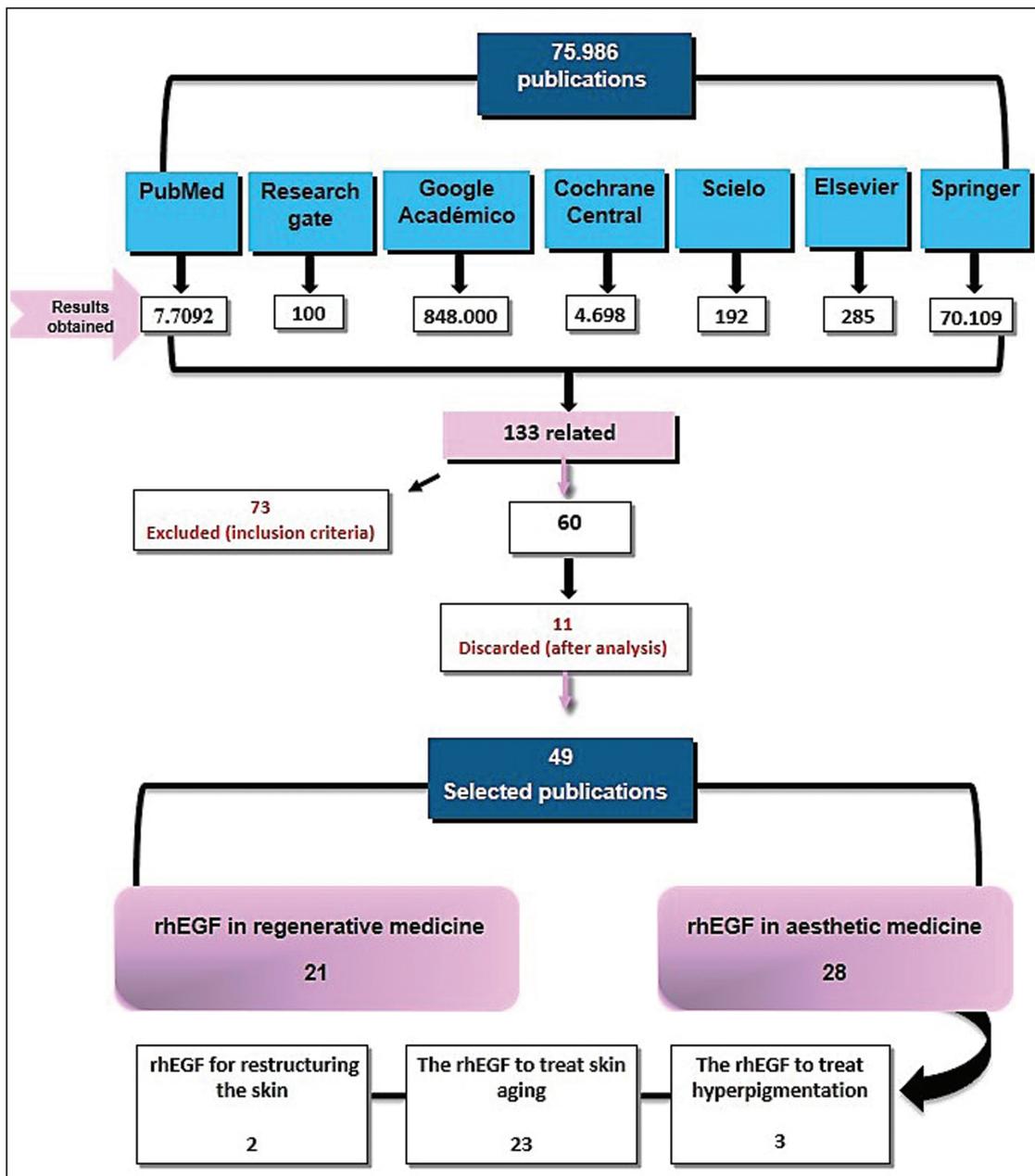


Figure 1: Flowchart of literature search. Source: Prepared by the authors from the study results

Selection of clinical studies

The following inclusion criteria were considered:

- Preclinical and clinical trials related to the use of the rhEGF in skin disorders or skin aging
- Texts that undergo a rigorous evaluation process (peer-reviewed publications and texts from renowned publishers)

Duplicated publications were removed. Literature reviews, case reports, incomplete publications or those did not comply with methodological rigor criteria (e.g. biases selection of participants or biases analysis of information), clinical treatment guidelines, and other irrelevant studies were excluded.

By utilizing skimming and scanning as analysis strategies for information, irrelevant items were discarded by title and abstract. Once the exhaustivity of the search had been confirmed (by depletion of publications of each source consulted), the veracity of the information was confirmed by each author by methodological analysis and the content analysis of each publication.

RESULTS

Seven sources of information were consulted, resulting in 75,986 publications that included the descriptors; of these, only 133 articles were directly related to the subject and they were examined by their title and abstract, and 73 articles were excluded because they did not meet the selection criteria. After reading the full text of the remaining 60 articles, taking into consideration the analysis criteria, 11 articles were removed, leaving a total of 49 articles [Figure 1] with a total sample of 821 patients.

The results indicate that most of the publications on rhEGF applications were led by Korea, followed by the United States and Japan. The years in which it was most published in this regard were 2015 and the period between 2017 and 2019.

Publications were classified according to the information source where they were located [Table 1]. Medline via

Table 1: Corpus according to sources and number of papers selected

Information source	Number of articles	Reference
PubMed	28	[11,12,14,15,18-21,29,33,35,37-39], [10,27,30-32,40-46,48,59]
Research Gate	3	[17,26,36]
Google Scholar	7	[4,16,34,47,50,52,53]
Cochrane Central	1	[9]
Springer	2	[22,51]
SciELO	4	[2,8,23,49]
Elsevier	4	[1,24,25,61]
Total	49	

Source: Prepared by the authors from the study results.

Pubmed was the source that hosted major related scientific evidence.

Likewise, 46 studies corresponded to original research articles, and they are predominantly clinical trials (24 articles) over preclinical trials and case series; also, 13 articles are review articles, 9 are traditional reviews, 2 are systematic reviews, and 2 are meta-analyses [Table 2].

Epidermal growth factor has been used basically in two major areas: regenerative medicine and aesthetic medicine. In aesthetics, there are three emerging categories: its application in hyperpigmentation, skin restructuring, and facial rejuvenation.

The rhEGF in regenerative medicine

Growth factor promotes wound healing,^[9,10] employing the intralesional administration of 75 mg lyophilized powder thrice per week; gel 150 g / g or spray rhEGF topically twice a day until complete healing.^[11]

Of the 21 publications in regenerative medicine, only 14 are clinical or preclinical trials [Table 3]. Korea is the country that has most investigated rhEGF in regeneration and the year in which it was most published was 2013.

The main clinical uses of rhEGF in regenerative medicine include the treatment of alopecia and dermatitis after chemotherapy, burns, diabetic foot ulcers, postsurgical ulcers, oral mucositis, pharyngeal ulcers, and tympanic membrane perforation. This evidence is summarized in [Table 4] next.

In alopecia treatment, the topical EGF-liposomal solution by transfollicular route favored primary hair recovery via the dystrophic anagen pathway.^[12] In this regard, the

Table 2: Corpus according to the type of study and number of articles found

Type of study	Number of articles	Reference
Randomized and controlled clinical trials	15	[18,21,22,26,27,29-32,35-38,40,41]
Quasi-experimental or not controlled clinical trials	9	[16,17,23-25,33,34,39,42]
Preclinical trials	11	[10-12,14,15,19,20,44-47]
Meta-analysis	2	[49,61]
Systematic review	2	[1,9]
Traditional review	9	[2,4,8,48,50-53,59]
Case series	1	[43]
Total	49	

Source: Prepared by the authors from the study results.

Table 3: Research designs under which rhEGF studies were conducted in the area of regenerative medicine

Type of study	Number of articles	Reference
Clinical trials	8	[16-18,21-25]
Preclinical trials	6	[11,12,14,15,19,20]
Total	14	

Source: Prepared by the authors from the study results.

Table 4: Applications of the rhEGF in regenerative medicine

Authors and year of publication	Type of study	Country of origin	Number of participants	Intervention protocol	Follow-up period	Results	Adverse effects
Jeon YJ <i>et al</i> 2019 ^[11]	In vitro preclinical trial	Korea	Dermal cultures	Skin penetration study of CTP-EGF recombinant protein using fluorescent imaging techniques and synthesis of hyaluronic acid study by immunoblotting and ELISA	Between 6 and 48 hours according to the corresponding laboratory test	CTP-EGF has superior ability, compared with EGF alone, to penetrate the skin and induce hyaluronic acid synthesis and collagen formation.	-
Paik SH <i>et al</i> 2013 ^[12]	In vivo preclinical trial	Korea	24 Mice	Four days before chemotherapy, topical pretreatment with EFG was performed on hair follicles.	Days 2 and 4 after chemotherapy	EGF is effective as an anagen inducer protecting against chemotherapy-induced alopecia.	-
Niiyama H And Kuroyanagi Y, 2014 ^[14]	In vitro preclinical trial	Japan	Cell cultures	EGF wound dressing, wound dressing with Vit. C, and dressing with EGF + Vit. C have probed into cytokine production. Fibroblasts were assessed in vitro and cultured.	7 Days for cell culture	The dressing with EGF and Vit. C improved the production of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) compared with the dressing without EGF.	-
Yamamoto A <i>et al</i> 2013 ^[15]	In vitro preclinical trial	Japan	40 Mice	The effectiveness of wound dressings with EGF, Vit. C, and EGF + Vit. C was assessed in diabetic mice.	1 Week (clinical and histologic assessment)	The dressing with EGF promoted best granulation tissue and major angiogenesis being more effectively than the other wound dressings.	No report
Esquirol-Caussa J and Herrero-Vila E, 2019 ^[6]	Quasi-experimental clinical trial	Spain	77 Patients	Ulcers are cured by gel using rhEGF gel once per day.	7 Weeks	The surrounding skin improved in 93.5% of cases. The appearance of the wound improved by 92.2%. The size of the wound was reduced from 66.7% in 43.3% in 4 weeks.	They were not found.
Martinez -Peñalver I and Cuevas -Pérez I, 1998 ^[17]	Quasi-experimental clinical trial	Cuba	12 Patients	Topical application twice a day until healing or improvement that would allow successful reoperation	7 Weeks	8 cases of complete cicatrization and 4 partial closures. Closures are completed in 34 days. The EGF is an option for patients who cannot undergo pharyngoplasty or where it has not been effective.	They were not found.
Kim JW <i>et al.</i> 2017 ^[18]	Clinical trial	Korea	138 Patients	Spray rhEGF (experimental) or placebo was applied in oral mucosa twice a day from the day of chemotherapy until oral mucositis resolved.	28 Days	The spray does not reduce grade 2 of oral mucositis in patients receiving chemotherapy. However, the oral spray reduces pain induced by mucositis.	Transient nausea
Shi HX, <i>et al.</i> 2013 ^[19]	In vitro and in vivo preclinical trial	China	30 Rats	1 ml of EFG every 2 days in skin wounds; the control group received saline at 0.9%	14 Days	EGF regulated the synthesis and degradation of the extracellular matrix. EGF regeneration was promoted in animals and in human cells in vitro.	-
Lee JH <i>et al.</i> 2013 ^[20]	In vivo preclinical trial	Korea	40 Animals	Once the burn was induced 14 days after laser irradiation, the gel was started with EFG once a day.	22 Days	EGF stimulated granulation tissue with accelerated wound closure and minimization of scars, compared with the group without treatment.	It was not observed
Kong Mand Hong SE, 2013 ^[21]	Clinical trial	Korea	40 Patients	EFG cream in the irradiated area thrice a day from the start of radiotherapy until 2 weeks after completion of radiotherapy	Weekly during radiotherapy and 6 weeks after completion	Cream with EGF has a beneficial role in preventing or minimizing radiation dermatitis in patients with breast cancer.	They were not recorded
Hwang IG <i>et al</i> 2016 ^[22]	Clinical trial	Korea	52 Patients	Cream twice a day in skin lesions (ERSEs or skin-related effects of erlotinib)	8 Weeks	It is effective in improving all types of ERSEs, regardless of the dose of erlotinib	They were not reported

Table 4: Continued

Authors and year of publication	Type of study	Country of origin	Number of participants	Intervention protocol	Follow-up period	Results	Adverse effects
Hernández-Cañete CM <i>et al</i> 2017 ^[23]	Quasi-experimental clinical trial	Cuba	17 Patients	Intralesional application thrice a week until complete granulation or healing	8 Weeks or until healing follow-up to 5 years	EGF avoided amputation in 4 diabetic foot ulcers, and 100% evolved to healing.	Muscle spasms
Kahraman M <i>et al</i> 2019 ^[24]	Quasi-experimental clinical trial	Turkey	34 Patients	Intralesional injections thrice per week for 8 weeks or until healing	8 Weeks or until healing follow-up to 5 years	Wound closure in 87.9% of injuries. It is effective in reducing the recurrence of long-term ulcers.	Burning pain
Lou Z. 2019 ^[25]	Quasi-experimental clinical trial	China	24 Patients	Tympanic membrane application once a day	Twice per week for 6 months or until the closure of the tympanic perforation	The closing rate was 100% in 6 days	They were not recorded.

Source: Prepared by the authors from the study results.

mechanism of action consists of EGF, promotes the proliferation and migration of hair follicle outer root sheath cells, and modulates the expression of several follicle-regulatory genes via Wnt/ β -catenin signaling.^[13]

The rhEGF in aesthetic medicine

From fibroblast cell cultures with rhEGF, it was determined that rhEGF promotes the migration and contractility of aged fibroblasts^[10] and increases the production of hyaluronic acid and the synthesis of collagen.^[11] Hence, it possesses potential as a regenerator of skin aging.

Peptides with rhEGF that penetrate the skin when applied topically have been developed^[11]; cosmeceuticals with rhEGF that prevent or improve rhytids and hydrate the skin without significant side effects are being formulated.^[26]

Of the 28 publications in Aesthetic Medicine, 23 are clinical or preclinical trials [Table 5] with a higher level of evidence in aesthetics than in regenerative medicine. The country that has researched this matter the most is Korea, followed by the United States, and the periods of greatest publication were 2015 and 2017.

The rhEGF to treat hyperpigmentation

The EGF is a noninvasive and effective treatment for melasma. Topical serum twice a day for 8 weeks decreased melasma in 73.4% cases of the experimental group without any side effects.^[27]

The EGF acts on the melanocytes by reducing the expression of melanogenesis-associated proteins (e.g. tyrosinase/MITF microphthalmia-associated transcription factor), in consequence inhibiting or regulating melanin synthesis.^[28] It is also effective in preventing postinflammatory hyperpigmentation after fractional carbon dioxide laser treatment; its daily application resulted in significant stimulation of healing with slight pruritus.^[29] Other research confirmed that rhEGF prevents inflammatory hyper pigmentation by laser treatment at 3, 7, and 35 days after its use.^[30]

The rhEGF for restructuring the skin

The EGF contributes to restructuring the skin tissue; it improves facial acne, both inflammatory and noninflammatory, when it is applied as an rhEGF cream for 6 weeks. It also decreases sebum production and increases hydration, whereby the topical rhEGF may be an effective and safe adjuvant treatment option for mild to moderate vulgar acne.^[31]

Table 5: Research designs under which rhEGF studies were conducted in the area of aesthetics

Type of study	Number of articles	Reference
Clinical trials	17	[26,27,29-43,46]
Preclinical trials	5	[10,35,44,45,47]
Total	23	

Source: Prepared by the authors from the study results.

Table 6: Applications of the rhEGF in aesthetic medicine

Authors and year of publication	Type of study	Country of origin	Number of participants	Intervention protocol	Follow-up period	Results	Adverse events
McKnight B <i>et al</i> 2015 ^[37]	Clinical trial	USA	-	Topical daily application of the human epidermal growth factor in the senile purpura	6 Weeks	Topical rhEGF decreases the appearance of senile purpura by thickening the skin, and it prevents late-stage dermatoporosis.	They did not report.
Kwon SB <i>et al</i> 2017 ^[38]	Clinical trial	Korea	40 Patients: 20 in the control group and 20 in the experimental group	Cream with phyto sphingosine-1-phosphate and EGF twice a day for 4 weeks	6 Weeks	Improved elasticity, density, and dermal hydration; reduction of periorcular wrinkles; and phyto sphingosine-1-phosphate showed synergistic effects with EGF.	They were not observed.
Vivó-Sesé I <i>et al</i> 2015 ^[39]	Clinical trial	Spain	18 Patients in A or experimental group and in B or control group	Before peeling, A group received EGF HA product by digital transdermal introduction, and B group received treatment by manual mesotherapy in 2 sessions (day 7 and day 21).	Days 0, 21, and 35	The product effectively attenuates wrinkles. The digital transdermal application produced effects faster, and it was the only one that had effects on the depth of wrinkles.	They were not observed.
Ha JM <i>et al</i> 2017 ^[35]	Clinical trial	Korea	20 Patients on the left and right sides of the face	For 4 weeks, a patch of microspicules with EGF was applied on the experimental side and the control side. The EGF cream was applied on periorcular wrinkles.	Days 0 and 1, 2, 4, and 8 weeks	The patch of EGF produced a statistical increase in dermal density compared with the control group at 4 and 8 weeks.	They were not observed.
Barone F <i>et al</i> 2019 ^[33]	Quasi-experimental clinical trial	USA	41 Patients	Serum with EGF twice per day for 12 weeks. Expert qualifications and evaluations with a corneometer and cutometer were made.	12 Weeks	Improved the firmness and hydration of the skin; improved the appearance of periorcular wrinkles. Ultrasound showed an increase in dermal restructuring.	They did not report.
Techapichethvanich T <i>et al</i> 2018 ^[29]	Clinical trial	Thailand	19 Patients on the right and left side of the face for control and experimental groups	Patients received laser carbon dioxide fractional treatment on both cheeks. They applied EGF ointment daily on one side of the face and Vaseline on the other side.	The hyper pigmentation was evaluated at 2, 3 weeks and at 1, 2 months.	There were no statistically significant differences. However, topical EGF provides significant repair stimulation.	Pruritus
Schouest JM <i>et al</i> 2012 ^[39]	Quasi-experimental clinical trial	USA	21 Patients	Topical application twice a day for 3 months	Every 30 days up to 3 months	Statistical improvement was found in the rhytids, in the reduction of pore size and pigmentary alterations by photodamage.	Mild inflammation controlled
Gawdat HI <i>et al</i> 2017 ^[40]	Clinical trial	Egypt	20 Patients on the experimental side (EGF) and the control side (PRP autologous)	Intradermotherapy every 2 weeks for 3 months, EGF side, and PRP side. The thickness of the epidermis and dermis was evaluated by tomography.	1 Month to 6 months after the previous session.	Both procedures increased skin turgidity and vitality. The thickness of the epidermis and dermis increased in both groups without differences.	Transient burning sensation in both groups
Park GH <i>et al</i> 2015 ^[30]	Clinical trial	Korea	25 Patients	A 532nm laser was applied. In addition, the experimental group applied the cream with growth factor and the control group applied the control cream.	Days 0, 3, 7, and 35	The cream with EGF showed statistically significant differences at the end of the study, being more effective in preventing inflammatory hyper pigmentation after laser treatment.	They did not report.
Draelos ZD 2016 ^[41]	Clinical trial	USA	60 Patients	Daily application of serum hyaluronic acid with serum growth factor	Weeks 2, 4, 8, and 12	Both products improved the skin, with statistically greater differences in serum AH + EGF	They did not report.

Table 6: Continued

Authors and year of publication	Type of study	Country of origin	Number of participants	Intervention protocol	Follow-up period	Results	Adverse events
Lee DH <i>et al</i> 2014 ^[42]	Quasi-experimental clinical trial	Korea	23 Patients	EGF serum and hyaluronic acid were applied to the entire face. Photo damage was assessed with photographs and skin and rhytids with a visometer.	Days 0, 4, and 8 weeks	Periorbital wrinkles improved with statistically significant differences, captured by both the physician and the visometer.	They were not observed.
An JH <i>et al</i> 2019 ^[36]	Clinical trial	Korea	50 Patients divided into experimental and control groups	Patches with acetyl hexapeptide, control patch, and patch with EGF were applied in the nasolabial fold and periorbital area, once a week.	Days 0, 1, 3, 5, 8, and 29	On day 29, there were statistically significant improvements in wrinkles and skin hydration with the microneedle patch / AHP-8.	They were not observed.
Ruri P.2018 ^[43]	Number of cases	Indonesia	8 Patients	rhEGF gel using microneedling, 3 sessions every 10 days	Before and after 4 weeks of treatment	Seven patients showed improvement in texture, fine lines, and wrinkles, especially in the periorbital region, reducing the signs of photoaging	Erythema associated with the microneedling
Seidel R and Moy RL 2015 ^[34]	Quasi-experimental clinical trial	USA	8 Patients	Application twice a day of serum with EGF in the areas of atrophic acne scars for 12 weeks	Before and after, 3 times at 4-week intervals	Overall, 25% of patients improved their hypertrophic scars mid-level Goodman scale. Researchers surveyed a perceived improvement of 49% in 6 patients.	They were not recorded.
Kim J <i>et al</i> 2012 ^[44]	Preclinical trial in vitro and in vivo	Korea	32 Mice	Application of the EGF once a day in the photodamaged and hyperpigmented area for 4 weeks. Previously applied microporation twice a week	28 Days	Hyperpigmentation improved with EGF. EGF decreased wrinkles, and in-depth and histological analysis indicated re-densification.	-
Kim D <i>et al</i> 2015 ^[10]	Preclinical trial in vitro	Korea	Cell cultures of young fibroblasts and aged fibroblasts in collagen 3d matrices	Later cultivation was made: Proliferation assay (72h); migration assay (4h); contractility assay (2h); immunohistochemicals (3 h)		EGF increased migration and contraction of aged fibroblasts. It improved the collagen matrix more efficiently than young fibroblasts.	-
Park B <i>et al</i> 2011 ^[45]	Preclinical trial in vivo	Korea	12 Rabbits	The inguinal fat was grafted with EGF or with saline (control) solution in the auricular pavilion to observe the volume and changes of adipose tissue.	The grafted fat was collected 3 months later.	In EGF, the survival rate was higher than in the control, increased neovascularization, and maintained fat cell morphology.	-
Draelos ZD <i>et al</i> 2017 ^[46]	Quasi-experimental clinical trial	USA	40 Patients	Serum EGF obtained from a culture in dextran to low-tension oxygen tension for 8 weeks was applied daily for 90 days.	At 90 days	Statistically significant improvements were found in skin hydration through corneometry, as well as in the global evaluations of researchers and patients.	Not reported
Yamamoto A <i>et al</i> 2016 ^[47]	Preclinical trial in vitro in hyaluronic acid (HA), collagen (Col), EGF, vitamin C (VC), glucosylceramide (GC), poly (γ-glutamic acid) (PGA), and Argentinina (Arg)	Japan	The proliferation of fibroblasts in culture cells with the product HA, Col, EGF, Vit. C, PGA, and Arg	The amount of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) produced by fibroblasts was evaluated in an in vitro wound model (cultured dermal substitute: CDS) with cultured EGF for 7 days	The media were prepared and stored at 4 ° C or 37 ° C for a different period of 1 day, 2 weeks, and 4 weeks, respectively.	The effectiveness of EGF remained even after 4 weeks. CDS fibroblasts released more VEGF and HGF in culture with EGF. Fibroblast density increased more in the medium with EGF than in the control medium without EGF.	-

Source: Prepared by the authors from the study results.

The EGF also restructures the skin with stretch marks; it is being used as a complementary treatment to the ablative fractional carbon dioxide laser, twice a day until one month after the last session, showing significant improvements in stretch marks. Skin biopsy revealed an increased epidermal thickness and a decrease in elastic fragmentation.^[32]

The rhEGF to treat skin aging

Most clinical trials reported the efficacy of rhEGF to reverse signs of skin aging,^[33,34] such as rhytids, grooves, hyper pigmentation and other senile pigmentations, hydration loss, and a decrease in epidermal and dermal thickness; test topical formulations such as cream, serum, and gel, either as a single therapy applied daily at home or as a complementary treatment after other treatments for facial rejuvenation such as the ablative laser.

Only a few recent publications have studied its incorporation with classic injections of mesotherapy or through the use of patches with microspicules for the transdermal release of the factor.^[35,36] Clinical applications of the EGF factor in facial aesthetics are shown in [Table 6].

DISCUSSION

A skin wound is similar to skin aged by inflammation mediated by reactive oxygen species.^[48] Besides, in wound healing there is angiogenesis and replacement of extracellular matrix, leading to re-epithelialization, but it is in the final phase that the collagen fibers are remodeled and elastin is restructured.^[49] This last phase is characterized by antiaging treatments, and the use of growth factors evokes such dermal restructuring.^[50]

When topical or injectable growth factors are administered, the depleted levels are replenished and the activity of the cells responsible for dermal remodeling is regulated, reversing skin aging.^[48,51,52] The rhEGF replenishes this balance and facilitates wound healing and dermatological conditions, as evidenced in some studies.^[53]

In 1972 Savage *et al.*^[54] completed the sequentiation of EGF for the first time. In 1995 Parries *et al.*^[55] they worked into their isolation and purification. Since this, the mass production of rhEGF has become a formidable task.

From 2002, a heterologous protein such as EGF with an adequate molecular size (6kDa) started being produced in large quantities based on recombinant DNA technology. This placed an increased impetus on the development of more effective and economical methods for industrial purposes.^[56,57] Taking advantage of this technology, in the past two decades, the EGF has been produced and exploited in the cosmetic industry for the purpose of skin treatment.^[58]

For some authors, it is controversial that a growth factor that is applied topically can rejuvenate the skin; however,

due to its large molecular size (> 15,000 Da), its ability to penetrate the stratum corneum and to reach viable keratinocytes in the basal stratum is limited.^[59,60] This limitation was overcome from 2002 onward, because since then the majority of dermatologically and cosmetically commercialized formulations contain an rhEGF of 6kDa (or 6,000 Da) with excellent potential for topical penetration into the stratum corneum.^[61,62]

The rhEGF entry into the skin is through hair follicles and sweat glands. Also, it may be possible to improve their penetration by chemical modification with lipophilic molecules or by facilitating their diffusion by compromised skin, for example, after using microneedling or laser resurfacing,^[63] as observed in all studies cited earlier, in which the EGF exhibits a low molecular size.

The evidence is clear as to the success or effectiveness of rhEGF for facial rejuvenation; however, quasi-experimental, uncontrolled, or randomized clinical trials still abound. The studies assessed its effects while it was applied topically, but the greatest efficiency of the EGF was obtained intradermally, with a greater reduction of rhytids, folds, and a longer response over time. Besides, to guarantee its effectiveness, a possible route of entry for this molecular size is through intradermotherapy.

In regenerative medicine, the EGF has been studied under preclinical trials and clinical trials, mostly quasi-experimental ones that are not uniform in terms of the route of administration, dose, and therapeutic regimen, which indicates the need to shield studies in this area by promoting the control and randomization to give more precise results on the resounding efficacy of the factor in wound regeneration.

CONCLUSIONS

- Products with EGF are an important topical therapeutic modality to treat aging skin efficiently and to treat hyper-pigmentation, rhytids, dryness, and laxity.
- The EGF is effective in the advanced healing of skin wounds, according to the results of multiple investigations in severe cases, although studies are required to establish concentrations and indications of use for each case.
- Injected rhEGF exerts a higher antiaging effect, inducing collagen, elastin, and hyaluronic acid, which are responsible for skin elasticity and turgor. However, more controlled, randomized, and long-term follow-up clinical trials are needed to specify the dose and therapeutic protocol to ensure its efficacy.

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Conflicts of interest

There are no conflicts of interest.

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