

# Topical Agents for Scar Management: Are They Effective?

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## ABSTRACT

Scar formation is the body's natural healing response to reestablish dermal integrity following an injury. Excessive scarring, however, can cause significant cosmetic, functional, and psychological problems. A wide variety of topical creams, lotions, and oils are available for scar treatment or wound healing. Sieving through the options and selecting the best option for their patients can be challenging for clinicians, especially given that clinical evidence for many of the active agents in commonly used topical treatments is lacking. The goal of this review is to provide an overview of topical treatments utilized for scar management, including their mechanism of action and evidence of efficacy. As knowledge of the wound healing process is critical to understanding the effects of topical treatments, the pathophysiology of wound healing is also reviewed.

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## INTRODUCTION

Scarring or scar formation is the body's natural healing response to reestablish dermal integrity following an injury. Scars, however, are structurally different and can be functionally deficient and cosmetically less appealing than normal human skin. Pathologically, a spectrum of scars is recognized from thin almost invisible scars to stretched, depressed, and/or contracted scars to hypertrophic and keloid scars, depending on whether or not the wound healing process was regulated correctly. Scars may also be associated with a spectrum of symptoms ranging from inflammation, erythema, dryness, and pruritus to no symptoms. Excessive scarring can cause significant cosmetic, functional, and psychological problems.<sup>1</sup>

Over the past 2 decades, research efforts have been channeled into understanding the pathophysiology of the wound healing process as well as in developing treatments for the management and prevention of scars. Consequently, a variety of treatments are currently available. While variety provides the clinician as well as the patient with choices, it also creates confusion as to how to select the most appropriate treatment for a particular type of scar.

### Pathophysiology of Wound Healing

Wound healing is a complex, organized, coordinated process, which in the short-term aims to prevent infection and reestablish skin integrity and in the long-term aims to remodel and strengthen the newly formed tissue. Accordingly, wound healing may be regarded as consisting of three main stages— inflammatory, proliferative, and remodeling or maturation—that are not mutually exclusive (reviewed in Clark; Slemp et al; Eming et al; Hantash et al; Berman et al).<sup>2-6</sup>

#### *Inflammatory Phase*

The inflammatory phase is initiated immediately following skin injury and lasts for 48 to 72 hours. It is a highly regulated

process involving the nervous system, several cell types (keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets), and a network of signaling molecules (cytokines, chemokines, and growth factors) that reach the wound through vasodilation and increased blood flow to the site of injury. Clinically the inflammatory phase manifests with erythema, heat, swelling, and pain.

The release of the proinflammatory cytokine interleukin-1 (IL-1) alerts surrounding cells of tissue injury and begins the reparative process. Hemorrhage from tissue damage releases blood components into the wound that activate the clotting cascade. Temporary blanching (vasoconstriction) of the wound occurs that lasts for approximately 10-15 minutes. Vasoconstriction is mediated by prostaglandins, serotonin, thromboxanes, circulating epinephrine, and norepinephrine and serves to reduce hemorrhage immediately following injury. Platelets attach and aggregate to the exposed subendothelium leading to clot formation (primary plug formation). The clot stops the bleeding, stabilizes the wound, and provides a matrix for the influx of inflammatory cells, platelets, and plasma proteins. Platelet aggregation also activates the platelets. Activated platelets degranulate, releasing growth factors (epidermal growth factor [EGF]), platelet-derived growth factor [PDGF], and transforming growth factor-beta [TGF-β]), vasoactive agents, and proteases.

Thrombin activation by the coagulation cascade results in the migration of inflammatory cells to the site of tissue injury. Mast cells produce histamine and leukotrienes, which stimulate vasodilation. Capillary vasodilation results in extravasation of serum proteins into the wound site. Polymorphonuclear (PMN) cells (neutrophils, eosinophils, and basophils) are the first inflammatory cells to arrive at the wound site. PDGF, IL-1, IL-8, and growth related oncogene play a role in attracting the PMN

cells. PMN cells are the “cleaners” of the wound. By removing cellular debris, foreign particles, and bacteria from the wound, they protect the wound from being infected. Peak PMN cell population occurs between 24-48 hours, which coincides with peak edema level within the site of injury. PMN cells also stimulate other growth factors and cytokines, including IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, and tumor-necrosis factor-alpha (TNF- $\alpha$ ).

Circulating monocytes arrive at the injury site after PMN cells and are activated and transformed into macrophages by TGF- $\beta$ . Peak levels of macrophages are seen at 48-72 hours after injury and these cells remain from days to weeks. Macrophages secrete an array of cytokines (notably IL-1 and IL-6) and growth factors (fibroblast growth factor [FGF], EGF, TGF- $\beta$ , and PDGF) and play a complex role in wound healing, propagating the inflammatory response, preventing infection, tissue debridement, fibroblast and smooth muscle proliferation, and angiogenesis.

#### *Proliferative Phase*

The proliferative phase may begin as early as 4 days after injury and lasts up to 7 weeks. During this phase, the wound is repaired and blood circulation and the structure and function of the skin are restored.

#### *Granulation Tissue Formation*

Approximately 4 days after tissue injury, macrophages initiate granulation tissue formation that replaces the blood clot formed immediately after injury. Granulation tissue is composed of macrophages, fibroblasts, blood vessels, collagen, proteoglycans, and hyaluronic acid. Fibroblasts are key elements in wound healing; they produce the collagen-based extracellular matrix (ECM) and reapproximate wound edges through their contractile properties.

#### *Migration of Fibroblasts*

Various matrix components, including fibrin, vitronectin, fibronectin, and hyaluronic acid, are released in an organized fashion to signal the migration of fibroblasts. Fibroblasts are recruited to the site of injury by FGF, TGF- $\beta$ , and PDGF released by macrophages. Specific matrix metalloproteinases (MMPs), MMP-1,-2,-3 (stimulated by TGF- $\beta$ ), and MMP-19 (stimulated by TNF- $\alpha$ ), cleave the way for fibroblasts to act at the injury site. MMPs are a group of enzymes which play a critical role in development, angiogenesis, fibroblast migration, and wound healing.

#### *Production of ECM*

Fibroblasts produce collagen and initiate formation of the permanent ECM. A number of growth factors are involved in activating fibroblasts to produce collagen, including PDGF, TGF- $\beta$ , FGF-2, and connective tissue growth factor. The cofactors, oxygen, vitamin C,  $\alpha$ -ketoglutarate, and ferrous iron, partake in collagen production (ie, in the hydroxylation of the

lysine and proline residues of procollagen). In normal skin or mature scars, 80-90% of dermal collagen are type I, the remaining being type III. In early wound healing, 30% of the collagen is type III.

In addition to collagen, the ECM is composed of glycosaminoglycan (GAG) and proteoglycans. GAGs play a prominent role in the dermis as a lubricant or as a shock absorber. There are 4 types of GAGs, hyaluronic acid, keratan sulfate, chondroitin sulfate, and heparin sulfate. Hyaluronic acid is predominant during the first 2 weeks of wound healing. Elastin, present in normal skin, is not a constituent of scar ECM. The absence of elastin makes scar tissue less compliant and firmer than normal skin.

Fibroblasts also produce nerve growth factor (NGF) which stimulates nerve ingrowth in the affected tissue area. NGF also helps in cutaneous wound healing by enhancing proliferation of molecular expression on human dermal microvascular and endothelial cells.

#### *Angiogenesis*

Damaged blood vessels are replaced by branches or out sprouts of intact capillaries around the wound site. Angiogenesis is triggered by local changes in tissue (increased lactate, decreased pH, and low oxygen) and stimulated by FGF-2, vascular endothelial growth factor-alpha (VEGF- $\alpha$ ), and TGF- $\beta$ . Endothelial cells begin to migrate after day 2. They need an ECM and an area free of other endothelial cells. These cells must express integrins and MMPs to successfully navigate. MMP-1 (also known as collagenase) for example, allows for the cells to migrate (or plow through) a type I collagen matrix. Most of these integrins are not found in normal cells and they are not found once the granulation tissue has matured. New vessels are initially leaky but normalize once mature.

#### *Reepithelialization*

Reepithelialization occurs within hours of injury and is usually completed within 24-48 hours in shallow or sutured wounds. Epithelial cell (keratinocyte) migration and proliferation is stimulated by the growth factors, EGF, TGF- $\alpha$ , and FGF, and the presence of low calcium, high magnesium, and hypoxia. Keratinocytes are derived from cells in close proximity to the wound and nearby hair bulges (stem cells). Contact guidance allows for keratinocytes to migrate across the granulation tissue from edge to edge until they establish a continuous connection. When reepithelialization is complete, keratinocytes undergo stratification and differentiation to restore the skin barrier.

#### *Maturation Phase*

The maturation phase usually begins from 14 to 21 days after tissue injury. During this phase, the ECM deposited in the granulation tissue is remodeled and rearranged, resulting in

contraction; reduction in redness, thickness, and induration; and increased strength of the scar. The maturation phase is initiated during granulation tissue formation in the proliferative phase and can span over a period of weeks to months or even years following injury.

The haphazard arrangement of collagen in granulation tissue is rearranged to a more organized manner and involves a balance between collagen production and breakdown. The process is mediated by MMP and tissue inhibitors of metalloproteinases. The synthesis of Type I collagen is increased while that of Type III is decreased. Type I collagen is arranged in bundles which differs from the basket-weave orientation seen in normal skin. Consequently, scar tissue lacks the strength of native human skin.

Net production of collagen increases until 21 days postinjury. After this period, the rate of collagen synthesis declines. Interferon- $\gamma$  and TNF- $\alpha$  stimulate fibroblasts to decrease collagen synthesis. Although maximum collagen synthesis is at 21 days, scar strength is 20% of the normal dermis at this point. After 6 weeks, scar strength is 80%-90% of its long-term strength.

Wound contraction begins 4-5 days after injury and continues for 2 weeks. Fibroblasts are converted into myofibroblasts by TGF- $\beta$  and PDGF. The activated myofibroblasts migrate to the periphery of the ECM and contract, which closes the wound and reduces the area of the scar. Immature blood vessels in the ECM regress due to reduced metabolic demand, forming an avascular scar.

### Topical Treatments for Scar Management

Generally, scar management is undertaken during the maturation phase wherein the scar begins to contract, vascularity decreases, collagen formation decreases, and ultimately the trend toward an organized array of a collagen matrix occurs. The goal of scar management is to ensure that these events occur appropriately and as expected for the particular scar. Numerous topical scar treatments are available in the form of creams, lotions, and oils. Some of the ingredients of topical agents that have a scientific basis are reviewed here.

#### *Silicone Gel*

Silicone gel is widely used in scar management since its first reported use in 1983.<sup>78</sup> Improvements in scar characteristics, such as elasticity, color, hardness, extensibility, height, smoothness, elevation, blood flow, volume, pruritus, redness, thickness, pliability, and pigmentation have been reported with its use in randomized controlled trials. Silicone gel works by a mechanism of hydration and occlusion, which reduces water loss from the scar, restores homeostasis to the scar, and reduces capillary hyperemia. The reduction in capillary activity reduces collagen deposition via modulation of keratinocytes which act on skin fibroblasts.

#### *Hyaluronic Acid*

Hyaluronic acid is a natural hydrator present in the ECM. It occurs in abundance in fetal scarless wounds,<sup>9</sup> where it facilitates the wound matrix to be more permissive for fibroblast migration and proliferation, creating an environment that promotes regenerative healing. Conversely, decreased hyaluronic acid deposition in the ECM leads to excessive scarring. External administration of high molecular weight hyaluronic acid can replenish the ECM and prevent scar formation. Hyaluronic acid is used widely as an ingredient in topical creams and lotions to hydrate and rejuvenate the skin as well as in grafts and dressings used in wound care.

#### *Vitamin C*

Vitamin C (ascorbic acid) is an antioxidant and a cofactor of collagenase. As an antioxidant, it neutralizes reactive oxygen species and free radicals produced from cellular metabolism and from exogenous sources such as ultraviolet radiation.<sup>10</sup> It, thus, protects against ultraviolet damage and suppresses ultraviolet-induced cutaneous pigmentation. As a cofactor, it stimulates collagen synthesis; thus, promoting wound healing, improving skin elasticity, and reducing redness. Vitamin C is used extensively in sunscreens and skin care products. It is also used in combination with hyaluronic acid or silicone gel for scar treatment.<sup>11,12</sup>

#### *Vitamin E*

Similar to vitamin C, vitamin E (tocotrienol) is an antioxidant that is extensively used in skin care products.<sup>13</sup> Its efficacy in scar treatment, however, is questionable, given the lack of evidence. A double-blind study found no difference in overall surgical scar appearance following 16 weeks of treatment with vitamin C compared with placebo.<sup>14</sup>

#### *Emu Oil*

Emu oil is believed to have anti-inflammatory and antioxidant properties and is used in traditional Aboriginal medicine for treating wounds.<sup>15</sup> Long chained triglyceride esters (oleic acid and linoleic acid) and saturated fatty acids (palmitic acid and stearic acid) are its main oil components while carotenoids, flavons, polyphenols, and tocoferols are its main non-oil components. The scientific basis for its wound healing effects is, however, controversial. In animal studies, emu oil appears to delay wound healing,<sup>15,16</sup> although it increased the number of hair follicles in wound margins.<sup>15</sup>

#### *Onion Extract*

Onion extract (*extractum cepae*) has antioxidant, anti-inflammatory, and antiinfective properties and is used in the treatment of burns and hypertrophic and keloid scars and in healing wounds. By upregulating MMP-1 expression, it induces the breakdown of newly formed collagen, thus reducing scar formation. Onion extract also plays a role in ECM modelling

as it inhibits fibroblast proliferation.<sup>17</sup> Several onion extract containing products are available (including Mederma®, Contractubex,® Cybele® Scagel, Erase® Gel, and Kaloidon gel) with data supporting their use as scar treatment.<sup>13</sup>

#### *Centella asiatica*

*Centella asiatica* is a medicinal herb used in Asian traditional medicine for wound healing and reduce scar formation.<sup>18</sup> Asiaticoside, asiatic acid, and madecassic acid are its most important active components. When applied to wounds, *Centella asiatica* extract increases cellular hyperplasia, collagen production, epithelization, and angiogenesis, leading to more rapid cross-linking of collagen, reepithelialization, wound maturation, and wound contraction. In keloid-derived fibroblast cultures, the addition of asiaticoside reduces fibroblast proliferation, inhibits type I and type III collagen protein and mRNA expression, reduces the expression of TGF-βRI and TGF-βRII, and increases the expression of Smad7 protein; all of which contribute to down-regulating excessive scarring.

#### *Curcumin*

Curcumin, the most active component of *Curcuma longa* (turmeric), is used extensively in Ayurvedic medicine.<sup>19</sup> It is an antioxidant, a free radical scavenger, and an antimicrobial and antiinflammatory agent that plays an important role in the wound healing process. Curcumin regulates the inflammatory response during wound healing by inhibiting the production of IL-1 and TNF-α, which activate monocytes and macrophages. Curcumin also accelerates the proliferation phase by exerting an apoptotic effect early in wound healing. In addition, it facilitates wound reepithelization, thereby reducing the time to complete reepithelization.

#### *Hippophae rhamnoides*

*Hippophae rhamnoides* (sea buckthorn) is another medicinal plant with antioxidative, immunomodulatory, cytoprotective, and tissue regenerative properties that is extensively used in traditional medicine. It is rich in bioactive compounds, including flavonoids; carotenoids; steroids; vitamins C, E, and K; tannins; and glycerides of palmitic, stearic and oleic acids.<sup>20</sup> Leaf extract and seed oil from this plant has proven efficacy in dermal wound healing. In animal studies, topical application of *Hippophae rhamnoides* leaf extract and seed oil were found to augment the wound healing process by upregulating MMP-2 and MMP-9, collagen type-III, and VEGF in granulation tissue. They also reduced reactive oxygen species in granulation tissue and increased wound contraction.<sup>21,22</sup>

#### *Bulbine frutescens*

In South African traditional medicine, *Bulbine frutescens* leaf gel extract is commonly used for the treatment of skin wounds and burns. The wound healing properties of the leaf gel have been evaluated in animal studies. When applied to excisional

and incisional wounds, *Bulbine frutescens* leaf gel extract accelerated wound contraction and increased the tensile strength of the wounds. Treated wounds had higher collagen, DNA, and protein content.<sup>23</sup> On histological studies, the increased tensile strength was attributed to increased fibroplasia, differentiation of fibroblasts into myofibroblasts, and increased collagen deposition and maturation.<sup>24</sup>

#### *Oleuropein*

Oleuropein, rich in polyphenolics, is the principle component of olive leaf extract.<sup>25</sup> With antioxidative and antiinflammatory properties, it has been used as a natural remedy in Iran for the treatment of skin diseases and wounds. Olive leaf extract and oil are also used extensively in skin care products. In animal studies, intradermal injections of olive leaf extract were found to accelerate skin wound healing via increased collagen fiber deposition, faster reepithelialization, and increased blood supply to the wound; thus, supporting a role for its use in wound healing.<sup>26,27</sup>

## Topical Agents in Development

### *TGF-β*

It is well known that fetal tissue heals without scarring and this may be partly attributed to differential expression of TGF-β isoforms.<sup>28</sup> Fetal tissue has higher levels of the TGF-β 3 isoform and lower levels of isoforms 2 and 3 while adult scar tissue has lower levels of isoform 3 and higher levels of isoforms 1 and 2. These observations suggest that isoform 3 prevents while isoforms 1 and 2 promote scar formation. In in vitro studies, exogenously administered TGF-β 3 peptide or antibodies to TGF-β 1 and 2 reduced neovascularization; reduced fibronectin, collagen III, and collagen I deposition; and improved the ECM matrix architecture to resemble native human skin.<sup>29</sup> In early phase clinical trials, single intradermal injections of recombinant human TGF-β 3 (avotermin) had shown promise in improving scarring,<sup>30</sup> but failed to make study endpoints in Phase III trials. Perhaps a more continuous application of the growth factor may provide better long term clinical results in scar appearance.

### *EGF*

EGF is another growth factor that is implicated in scarless healing. Upregulation of EGF is seen in early stages of fetal healing while in scar-forming tissue, there is downregulation of EGF.<sup>31</sup> In an animal model, the application of a topical recombinant human EGF (rhEGF) decreased TGF-β 1 expression, thereby reducing collagen deposition and cutaneous scarring.<sup>32</sup> Further, in a pilot clinical study, significant improvements in scar severity were reported following 12 weeks of twice-daily application of rhEGF serum on Grade II-IV atrophic acne scars.<sup>33</sup>

EGF is also implicated in chronic wounds. Its upregulation significantly accelerates reepithelialization and increases the tensile strength of wounds; conversely, downregulation of EGF prevents reepithelialization, resulting in chronic wounds. In clinical

trials of chronic wounds (skin graft donor-healing sites, venous ulcers, and diabetic foot ulcers), the application of topical rhEGF shortened healing time by increasing reepithelialization.<sup>34-36</sup>

### IL-10

IL-10 is a potent anti-inflammatory cytokine that plays an important role in fetal scarless healing (reviewed in King et al.).<sup>37</sup> It suppresses the pro-inflammatory cytokines IL-6 and IL-8, which promote fibrosis and scarring. In addition, it plays a role in the regulation of the ECM, optimization of fibroblast function and differentiation, and upregulation of endothelial progenitor cells. In animal studies, overexpression of IL-10 in post-natal wound mimics fetal healing. A recombinant human IL-10 is in clinical development, with early studies demonstrating treated incisions healing with better macroscopic scar appearance and less red scars.<sup>38</sup>

### CONCLUSION

Although a variety of topical scar treatments are available, clinical evidence is limited to silicone gel and hyaluronic acid. The plant-based ingredients, however, have a scientific basis that supports their use for wound healing or scar treatment. Emerging agents that target key growth factors or cytokines in the wound healing process further hold the promise of changing the therapeutic landscape of scar management.

### DISCLOSURES

The author has no conflicts of interest to declare.

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