Romanian Journal of Laboratory Medicine 2026;34(3):259–268
REVIEW
DOI:10.2478/rrlm-2026-0028

# Recent advances in wound healing, tissue repair, regeneration, and scar management: A literature review

Nino Kuridze[1], Luiza Gabunia[1], Nino Gogokhia[2], Ketevan Ghambashidze[3], Sophio Giorgadze[4], Gvantsa Janigashvili[5], Nino Gvajaia[6]*, Levan Ratiani[7]

1. Department of Clinical Pharmacology, Tbilisi State Medical University, Georgia
2. Department of Laboratory Medicine, Tbilisi State Medical University, Georgia
3. Department of Pathophysiology, Tbilisi State Medical University, Georgia
4. Department of Histology, Tbilisi State Medical University, Georgia
5. Department of Pediatrics, Tbilisi State Medical University, Georgia
6. Department of Medicine, Tbilisi State Medical University, Georgia
7. Department of Anesthesiology and Reanimatology, The First University Clinic of Tbilisi State Medical University, Georgia

## ABSTRACT

Wound healing, tissue repair, and regeneration are biological processes essential for restoring tissue integrity following injury. Disorders in these processes can lead to complications and the formation of scars, impacting both physical and psychological well-being. This review synthesizes recent advancements in the understanding of the molecular and cellular mechanisms governing these processes. We explore the sequential phases of wound healing, the key cellular and molecular players involved, factors influencing healing outcomes, and emerging therapeutic strategies. Special emphasis is placed on novel biomaterials, cell-based therapies, gene therapies, and physical modalities. Modern therapeutic approaches aim to accelerate healing while minimizing complications such as scarring, infection, or chronic inflammation. Available strategies for wound and scar management include topical and intralesional pharmacological treatments, silicone-based products, advanced dressings, physical modalities, and procedural interventions. This review summarizes the mechanisms, clinical applications, limitations, and current evidence supporting these approaches, while selected commercial formulations are discussed only as illustrative examples of different therapeutic mechanisms. Finally, we discuss current challenges and future directions in the field, highlighting the potential for personalized medicine and translational research.

**Keywords:** collagen, fibroblast, interleukin-1 (IL-1), interleukin-6 (IL-6), skin wound healing

Received: 2 March 2026; Accepted: 24 June 2026; Published: 30 June 2026.

## INTRODUCTION

The human body relies on intact tissues for structural support, barrier function, and normal physiology [1-3]. Trauma, surgery, infection, and disease disrupt tissue integrity and initiate coordinated cellular and molecular responses intended to restore continuity and function [4-6]. Wound healing and tissue regeneration therefore, remain central concerns in dermatology, surgery, and chronic disease management [4-6].

Impaired healing may result in chronic wounds, including diabetic foot ulcers, pressure injuries, and venous leg ulcers, which are associated with persistent inflammation, substantial morbidity, reduced quality of life, and considerable healthcare costs [7,8]. Repair may also produce hypertrophic scars or keloids that cause pain, pruritus, functional limitation, and psychosocial distress [9-11]. Healing outcomes vary with wound characteristics, local perfusion and infection, comorbid disease, age, medication exposure, lifestyle factors, and the selected therapeutic strategy [5,8].

Accordingly, this narrative review aims to synthesize current evidence on the biological mechanisms underlying wound healing, tissue repair, regeneration, and scar formation; examine intrinsic and extrinsic factors that influence healing outcomes; and summarize established and emerging therapeutic approaches. The review covers immune regulation, extracellular matrix remodeling, biomaterials, cell-based and gene-based strategies, physical modalities, topical pharmacology, and scar-modulation interventions, while selected commercial formulations are considered only as non-exhaustive examples.

* Corresponding author: Nino Gvajaia, Department of Medicine, Tbilisi State Medical University, Georgia. E-mail: ninogvajaia1@gmail.com

## METHODS

This manuscript was prepared as a narrative review of literature addressing cutaneous wound healing, tissue repair, regeneration, and scar management. Relevant publications were identified through searches of PubMed, Scopus, and Google Scholar, with emphasis on English-language peer-reviewed experimental studies, clinical studies, reviews, and guidance documents relevant to the review scope. Reference lists of selected publications were also screened. The literature was evaluated for topical relevance and synthesized into thematic sections covering the phases and regulation of healing, factors associated with impaired repair, established and emerging therapeutic strategies, and selected product-specific evidence. Dermatix Ultra, Epicyn, Flosteron, and Contractubex were retained as illustrative examples because they represent different formulations, routes of administration, and proposed mechanisms; their inclusion was not intended as a systematic comparison of all scar treatments or as evidence of therapeutic superiority. Because the review used only previously published information and involved no human participants, identifiable patient data, or animal experimentation by the authors, ethics approval was not required.

## MAIN LITERATURE FINDINGS

### Biological framework and phases of wound healing

#### Regeneration and repair

Regeneration restores damaged tissue through proliferation and replacement by functionally similar cells, whereas repair replaces lost tissue with granulation tissue and, ultimately, a fibrous scar. The relative contribution of these processes depends on tissue type, injury depth, cellular proliferative capacity, extracellular matrix integrity, and the local microenvironment [1,2,6]. Labile epithelia generally regenerate efficiently, while most adult neurons and cardiomyocytes have limited intrinsic proliferative capacity [1,2]. Cutaneous healing is conventionally described as four overlapping phases- hemostasis, inflammation, proliferation, and remodeling- rather than as a strictly linear sequence [4-6].

#### Hemostasis

Hemostasis begins immediately after vascular injury. Transient vasoconstriction limits blood loss, exposed matrix proteins promote platelet adhesion and activation, and the coagulation cascade generates fibrin that stabilizes the platelet plug [12]. Activated platelets also release mediators that recruit inflammatory cells and influence later fibroblast, keratinocyte, and endothelial-cell responses [12-14].

#### Inflammation

The inflammatory phase removes microorganisms and damaged material while establishing signals required for repair. Neutrophils usually predominate early, followed by recruitment of circulating monocytes that enter the wound and differentiate into macrophages [15-18]. These cells participate in phagocytosis and release cytokines, chemokines, reactive oxygen species, proteases, and growth factors. An effective response must be sufficient for host defense but limited in duration; failure to resolve inflammation is associated with chronic wounds, excessive matrix degradation, and fibrotic scar formation [4,16-18].

#### Proliferative phase

During proliferation, fibroblasts deposit provisional extracellular matrix, endothelial cells form new microvessels, and keratinocytes migrate and proliferate to restore the epithelial barrier [15,19-21]. Granulation tissue provides vascular support and a temporary matrix for cellular migration. Angiogenesis is regulated by mediators including vascular endothelial growth factor (VEGF), while epidermal growth factor (EGF), fibroblast growth factors (FGFs), transforming growth factor beta (TGF-β), and platelet-derived growth factor (PDGF) coordinate epithelialization, fibroplasia, and matrix production [13,14,19,21].

#### Remodeling and scar formation

Remodeling begins while proliferation is still active and may continue for months. Collagen is reorganized and cross-linked, cellularity and vascularity decline, and matrix metalloproteinases (MMPs) act in balance with tissue inhibitors of metalloproteinases to reshape the extracellular matrix [13,21,22]. The healed tissue does not fully regain the architecture or mechanical properties of uninjured skin [6,21]. Excessive or prolonged fibroblast activation and collagen deposition can produce hypertrophic scars or keloids, with keloids extending beyond the original wound boundaries [9,10,23].

### Immune regulation of wound healing

Immune-cell populations enter and leave the wound at different times, but their activities substantially overlap. Their effects depend on cellular phenotype, local cytokine concentrations, microbial burden, oxygenation, matrix composition, and the stage of repair [15-18].

#### Macrophages

Wound macrophages arise from both tissue-resident populations and recruited blood monocytes. After entering injured tissue, monocytes differentiate in response to local chemokines, cytokines, growth factors, and matrix signals [16-18]. Early macrophage functions include phagocytosis, antimicrobial activity, and production of pro-inflammatory mediators. As healing progresses, macrophage activity generally shifts toward inflamma-

tion resolution, angiogenesis, fibroblast regulation, matrix deposition, and remodeling [16-18]. This response is better viewed as a continuum of context-dependent activation states than as a uniform conversion between fixed M1 and M2 phenotypes [16,17].

### T cells

T lymphocytes can amplify, regulate, or resolve inflammation according to subtype and microenvironment. Regulatory T cells accumulate in wounded skin and, in experimental models, limit excessive inflammation and support re-epithelialization and wound closure [18,24]. Other effector T-cell responses may strengthen antimicrobial defense but can also sustain tissue-damaging inflammation when persistent. Consequently, T-cell effects should not be described as uniformly pro-reparative or pro-inflammatory [18,24].

### Neutrophils

Neutrophils provide rapid antimicrobial defense through phagocytosis, granule enzymes, reactive oxygen species, antimicrobial peptides, and extracellular traps [15,25]. Their apoptosis and clearance by macrophages contribute to inflammatory resolution. However, prolonged neutrophil persistence can expose viable tissue to proteases and oxidants, impair matrix integrity, and delay progression to proliferation [15,18].

### Mast cells

Mast cells release histamine, proteases, cytokines, and growth factors after injury and can influence vascular permeability, leukocyte recruitment, angiogenesis, fibroblast activity, and scar formation [13,26]. Experimental findings suggest that their contribution is stage-dependent and may be beneficial during early defense yet promote inflammation or fibrosis when activation is excessive [26]. The principal immune-cell populations involved in wound healing and their major functions are summarized in Table 1.

### Cytokines and growth factors

Cytokines and growth factors coordinate communication among platelets, leukocytes, fibroblasts, keratinocytes, and endothelial cells. TNF-α, IL-1, and IL-6 support early inflammatory activation; IL-10 contributes to resolution; VEGF promotes angiogenesis; EGF supports keratinocyte migration and proliferation; PDGF recruits and stimulates reparative cells; and TGF-β regulates fibroblast activation, collagen synthesis, and remodeling [13,14,19]. Their effects depend on timing, concentration, receptor expression, and interactions with other mediators. Persistent pro-inflammatory signaling may delay healing, whereas excessive TGF-β activity can favor fibrosis and pathological scarring [13,14,23]. The principal mediators discussed in this review are summarized in Table 2.

## Extracellular matrix remodeling

The extracellular matrix is both a structural scaffold and an active signaling environment. Collagens provide tensile support; fibronectin and laminins regulate adhesion and migration; proteoglycans influence hydration and growth-factor availability; and hyaluronan affects cell migration, inflammation, and matrix organization [22,27,28]. Matrix fragments can also act as biological signals rather than as inert degradation products [27,28].

**Table 1. Principal immune-cell populations in wound healing and their major functions**

| | Typical involvement | Principal contribution to healing | Interpretive or clinical considerations |
|---|---|---|---|
| Neutrophils | Predominate soon after injury and during the early inflammatory phase. | Remove microorganisms and damaged material through phagocytosis and release antimicrobial enzymes, reactive oxygen species, cytokines, and extracellular traps. | Early activity supports host defense; prolonged accumulation or excessive activation can injure viable tissue, degrade extracellular matrix, and sustain inflammation. |
| Circulating monocytes | Recruited from peripheral blood after the initial inflammatory response has begun. | Leave the circulation, enter injured tissue, and differentiate into macrophages under the influence of local chemokines, cytokines, and growth factors. | They are an important source of wound macrophages, but the relative contribution of recruited monocytes and tissue-resident macrophages varies among tissues and wound types. |
| Macrophages | Participate across inflammatory, proliferative, and remodeling phases. | Clear debris; coordinate resolution of inflammation; regulate angiogenesis, fibroblast behavior, matrix deposition, and tissue remodeling through cytokines, growth factors, and proteolytic enzymes. | Macrophage activity is best understood as a continuum of context-dependent states rather than a fixed binary M1/M2 sequence. |
| T-reg cells | Become particularly relevant during inflammatory resolution and tissue repair. | Limit excessive immune activation, support immune homeostasis, and influence repair through mediators that include IL-10 and TGF-beta. | Their effect depends on timing and local conditions; excessive immune suppression may compromise antimicrobial defense. |
| Th17 cells | Most prominent during inflammatory and antimicrobial responses. | Produce IL-17-family cytokines, promote neutrophil recruitment, and contribute to defense against extracellular microorganisms. | Transient activity may be protective, but persistent Th17 signaling can reinforce chronic inflammation and delay repair. |
| Mast cells | Activated early after injury and may remain involved during angiogenesis and remodeling. | Release histamine, proteases, cytokines, and growth factors that affect vascular permeability, leukocyte recruitment, new-vessel formation, and matrix remodeling. | Reported effects are variable and may be beneficial or detrimental depending on wound stage, activation intensity, and scar phenotype. |

Note: The timing and functions shown are overlapping rather than strictly sequential. Abbreviations: IL, interleukin; ROS, reactive oxygen species; TGF-beta, transforming growth factor beta. The information presented in this table was synthesized from references 13–19. Immune-cell involvement overlaps across wound-healing phases and may vary according to wound type and local microenvironment.

Table 2. Major mediators involved in wound healing: Cytokines and growth factors

| Mediator | Major cellular sources | Main functions in wound healing | Potential consequence of persistent imbalance |
|---|---|---|---|
| TNF-alpha | Activated macrophages, neutrophils, keratinocytes, and other immune cells. | Amplifies early inflammatory signaling, supports leukocyte recruitment, and contributes to antimicrobial defense. | Sustained elevation can promote tissue injury, matrix degradation, and delayed progression to repair. |
| IL-1 / IL-1beta | Macrophages, keratinocytes, neutrophils, and damaged tissue cells. | Activates local inflammatory pathways, induces secondary cytokines and chemokines, and supports early host defense. | Prolonged signaling may maintain inflammatory-cell recruitment and contribute to chronic wound activity. |
| IL-6 | Macrophages, fibroblasts, keratinocytes, endothelial cells, and other stromal cells. | Coordinates acute-phase and immune responses and can influence keratinocyte activity and the transition toward repair. | Persistently high levels are associated with dysregulated inflammation and may accompany impaired healing. |
| IL-10 | Regulatory T cells, macrophages, and other leukocyte subsets. | Restrains excessive pro-inflammatory signaling and helps promote resolution of inflammation. | Insufficient activity may permit ongoing inflammation, whereas excessive suppression could weaken antimicrobial responses. |
| TGF-beta | Platelets, macrophages, fibroblasts, keratinocytes, and other tissue cells. | Regulates fibroblast activation, collagen production, extracellular-matrix deposition, immune modulation, and remodeling. | Excessive or prolonged signaling can favor fibrosis, hypertrophic scarring, or keloid formation. |
| VEGF | Macrophages, keratinocytes, fibroblasts, platelets, and endothelial cells. | Promotes endothelial-cell survival, vascular permeability, and formation of new microvessels in granulation tissue. | Insufficient signaling can limit perfusion; excessive or poorly organized signaling may produce abnormal or leaky vasculature. |
| PDGF | Platelets, macrophages, endothelial cells, and other reparative cells. | Attracts and stimulates fibroblasts and smooth-muscle-related cells and supports granulation-tissue development. | Reduced activity may delay cellular recruitment and matrix formation, while excessive signaling may contribute to fibrotic responses. |
| EGF | Platelets, macrophages, keratinocytes, and other epithelial or stromal cells. | Stimulates keratinocyte migration and proliferation and supports restoration of the epithelial barrier. | Inadequate signaling may slow re-epithelialization; excessive signaling may disturb normal epithelial regulation. |
| FGF family | Fibroblasts, macrophages, endothelial cells, keratinocytes, and other tissue cells. | Supports fibroblast proliferation, angiogenesis, matrix production, and repair of epithelial and connective tissues. | Altered signaling may disrupt vascularization, matrix organization, or scar maturation. |

Note: The biological effects of each mediator depend on concentration, timing, cellular source, receptor expression, and the local wound environment. Abbreviations: EGF, epidermal growth factor; FGF, fibroblast growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TGF-beta, transforming growth factor beta; TNF-alpha, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor. The functions summarized in this table were synthesized from references 15, 16, and 19–23.

MMPs and their inhibitors regulate matrix turnover, while integrins and other adhesion receptors enable cells to sense matrix composition and mechanical properties [13,22,27]. The matrix can bind and release VEGF, FGF, TGF-β, and other mediators, thereby shaping the spatial and temporal pattern of repair. Disturbance of matrix synthesis, degradation, or mechanotransduction can contribute to chronic wounds or excessive scarring [13,22,23,27].

## Factors affecting regeneration and repair

### Intrinsic and genetic influences

Healing varies among individuals because of differences in age, genetic background, hormonal state, immune function, nutritional status, and underlying disease [5]. Genetic influences are particularly evident in susceptibility to hypertrophic scars and keloids, although scar development is multifactorial and also depends on wound depth, anatomical site, tension, inflammation, and treatment [10,23]. Claims about individual genetic variants should therefore be interpreted cautiously unless supported by adequately replicated studies.

### Age-related factors

Older age is associated with slower inflammatory-cell recruitment, altered macrophage function, delayed angiogenesis and re-epithelialization, reduced fibroblast activity, and changes in collagen turnover [5,29,30]. Cellular senescence and the senescence-associated secretory phenotype may further modify the wound microenvironment [29]. These changes can delay repair, but age alone does not prevent healing; comorbid disease, perfusion, nutrition, mobility, and medication exposure frequently contribute to clinical outcomes [5,30].

### Pathologies affecting regeneration

Diabetes impairs healing through interacting mechanisms that include vascular dysfunction, neuropathy, altered inflammatory responses, reduced angiogenesis, and greater susceptibility to infection [5,8,31]. Peripheral arterial disease limits oxygen and nutrient delivery, while venous hypertension and edema can sustain inflammation. Obesity is associated with altered perfusion and chronic low-grade inflammation, and immunodeficiency or immunosuppressive treatment can weaken antimicrobial defense [5,8]. Because these disorders often coexist, delayed healing rarely reflects a single isolated mechanism.

### Extrinsic and environmental influences

Local infection, ischemia, repeated trauma, pressure, excessive tension, desiccation, and uncontrolled exudate can disrupt repair [4,5,8]. A balanced moist environment generally supports epithelial migration, whereas excessive moisture can macerate surrounding skin [32,33]. Smoking impairs tissue oxygenation and is associated

with delayed healing [34]. Mechanical offloading and reduction of wound-edge tension are especially important for pressure-related wounds, diabetic foot ulcers, and scars developing in high-tension sites [8,10,35].

Microorganisms in chronic wounds may form biofilms that are tolerant of host defenses and antimicrobial treatment. Biofilms have been demonstrated more frequently in chronic than in acute wounds and can sustain inflammation and complicate infection control [8,36]. Their presence cannot be inferred solely from routine culture, and management commonly requires repeated assessment, cleansing or debridement, treatment of clinically evident infection, and correction of underlying perfusion or pressure problems [8,35-37].

### Medication and lifestyle factors

Systemic and topical medications may alter healing according to dose, duration, timing, and patient susceptibility. Corticosteroids can suppress inflammation, fibroblast activity, collagen synthesis, and angiogenesis, while other immunosuppressive or cytotoxic treatments may impair cellular proliferation and host defense [5,38,39]. Adequate protein and micronutrient intake is necessary for repair, particularly in malnourished patients [40]. Psychological stress and smoking are associated with delayed healing, whereas correction of nutritional deficiencies and smoking cessation are clinically relevant supportive measures [35,40-42].

## Therapeutic strategies

### Wound-bed optimization and infection control

Management begins with identification and correction of factors that prevent healing, including ischemia, pressure, edema, infection, necrotic tissue, and inadequate moisture balance [8,35]. Cleansing and appropriate debridement reduce devitalized material and may disrupt biofilm, while dressings should control exudate, protect surrounding skin, and maintain an environment compatible with epithelialization [32,33,36,37]. Antimicrobial products should be selected according to clinical indication rather than used routinely, because evidence and tolerability vary among iodine, polyhexamethylene biguanide, hypochlorous acid, honey, and topical antibiotic preparations [43-47].

### Immunomodulatory and matrix-targeted approaches

Experimental immunomodulatory strategies seek to limit persistent inflammation without compromising antimicrobial defense. Approaches under investigation include modulation of macrophage activation, enhancement of regulatory immune pathways, inhibition of selected pro-inflammatory mediators, and delivery of growth factors or extracellular-matrix components [13,16-18,22,27]. Because the same mediator may have beneficial or harmful effects at different stages, timing and local delivery are central challenges. Evidence from preclinical models should not be interpreted as established clinical efficacy.

### Cell-based therapies

Mesenchymal stromal cells, epidermal progenitor cells, and induced pluripotent stem-cell-derived products are being studied for their capacity to support re-epithelialization, angiogenesis, immune regulation, and matrix repair [20,48-50]. Much of the observed benefit appears to arise from paracrine signaling rather than stable replacement of damaged cells. Clinical translation remains limited by cell-source variability, manufacturing standards, delivery and retention, immune compatibility, long-term safety, and cost [48,50].

### Advanced dressings and biomaterials

Modern dressings include hydrogels, hydrocolloids, alginates, foams, films, hydrofibers, and antimicrobial or bioactive materials. Their selection should reflect wound depth, exudate, infection risk, surrounding skin, and patient comfort rather than an assumption that one category is universally superior [33,51]. Hydrogels provide a hydrated matrix and can serve as drug- or cell-delivery systems, while scaffolds made from natural or synthetic polymers can support cell adhesion and tissue organization [51,52].

Extracellular-matrix-derived materials and bioengineered skin substitutes seek to reproduce structural and biochemical features of native tissue [52,53]. Smart dressings integrate sensors or responsive delivery systems to monitor variables such as temperature, pH, moisture, or biochemical markers and to release therapy when predefined conditions are detected [54]. Three-dimensional bioprinting may eventually enable more individualized skin constructs, but reproducibility, vascularization, manufacturing, regulation, and cost remain substantial barriers [55].

### Gene- and RNA-based therapies

Small interfering RNA, microRNA, messenger RNA, viral and non-viral gene delivery, and genome-editing platforms are being investigated to modify inflammatory, angiogenic, fibrotic, and regenerative pathways [56-58]. These approaches may permit localized and time-limited expression or suppression of therapeutic targets, but delivery efficiency, off-target effects, immune responses, durability, and long-term safety remain unresolved. Current evidence is predominantly preclinical, and claims of scarless healing are premature [56-58].

### Physical modalities, debridement, and digital technologies

Physical approaches include negative-pressure wound therapy, low-level light or laser therapy, therapeutic ultrasound, and electrical stimulation. Their effectiveness varies by wound type, protocol, comparator, and outcome measure [59-62]. Negative-pressure therapy can

support exudate control and granulation in appropriately selected wounds, while debridement may be autolytic, enzymatic, sharp, or mechanical according to tissue characteristics and clinical expertise [37,59].

Artificial intelligence and machine-learning methods are being explored for wound segmentation, measurement, classification, and prediction of healing trajectories [63]. These tools may improve documentation and consistency, but performance depends on representative training data, image quality, external validation, and integration into clinical workflows. They should support rather than replace clinical assessment [63].

### Topical pharmacological approaches

Topical delivery can achieve high local exposure while reducing systemic drug levels, although penetration depends on the formulation, wound barrier, molecular properties, and delivery system [64-66]. Available agents include topical antibiotics for selected localized infections, antiseptics, debriding agents, anti-inflammatory preparations, growth-factor products, hyaluronan-based formulations, and drug-containing dressings [33,43-47,65]. Evidence is indication-specific; products that reduce microbial burden do not necessarily accelerate closure, and cytotoxicity or contact reactions may offset potential benefit [33,43-47].

Becaplermin is an example of a recombinant growth-factor product used for selected diabetic foot ulcers in conjunction with comprehensive wound care [14]. By contrast, topical vitamin E has not shown consistent benefit for scar appearance and may cause irritation [68]. Newer carriers, including liposomes, nanoparticles, polymeric fibers, and hydrogels, are being evaluated to improve stability, penetration, and controlled release [51,65,66].

### Scar-modulation strategies

Prevention and treatment of hypertrophic scars and keloids should be individualized according to scar type, maturity, anatomical site, symptoms, skin characteristics, previous response, and patient preference [10,23,68,69]. Conservative measures include silicone gels or sheets, pressure or tension-reduction strategies, moisturization, and scar massage. Established pathological scars may require intralesional corticosteroids, 5-fluorouracil, cryotherapy, laser or light-based procedures, surgical revision, or multimodal therapy [68-70]. Excision alone carries a substantial risk of keloid recurrence, so adjunctive treatment is often considered [10,23,69].

No single intervention is consistently effective for every patient. Silicone products have the most established evidence among non-invasive topical scar therapies, while evidence for onion-extract and other combination gels is less consistent [70,71]. Comparative interpretation is limited by heterogeneous scar types, outcome scales, follow-up periods, and treatment protocols. Treatment recommendations should therefore distinguish evidence from randomized trials, observational studies, mechanistic reports, and expert consensus.

### Selected product-specific examples

Dermatix Ultra, Epicyn, Flosteron, and Contractubex are included as non-exhaustive examples of distinct therapeutic categories. Dermatix Ultra is a silicone-based topical gel containing a vitamin C ester [72]; the broader evidence base supports silicone gel or sheeting for prevention and treatment of hypertrophic scars and keloids, although evidence specific to individual branded formulations is more limited [70,72].

Epicyn is a stabilized hypochlorous acid formulation intended to provide antimicrobial and anti-inflammatory local effects; hypochlorous acid studies report activity against microorganisms and acceptable tolerability, but product-specific scar evidence remains limited [46,73-76].

Flosteron is an injectable betamethasone preparation rather than a topical scar gel. Its rationale is related to the anti-inflammatory and antiproliferative effects of corticosteroids. When corticosteroids are administered intralesionally for pathological scars, recognized local adverse effects include dermal atrophy, telangiectasia, and pigment alteration [68,69].

Contractubex combines onion extract, heparin, and allantoin; studies have reported variable effects on scar symptoms and appearance [71]. The comparative reports cited for these four products originate from overlapping author groups and should not be considered independent replications; differences in design, outcome assessment, and sample characteristics further limit firm conclusions [77-79]. Their composition, proposed mechanisms, indications, and evidence are summarized in Table 3.

## LIMITATIONS

This review has several limitations. As a narrative review, it did not employ a preregistered systematic-review protocol, a fully standardized article-selection process, or a formal assessment of study quality and risk of bias. Although relevant literature was identified through searches of major biomedical databases and reference lists, the selection and interpretation of publications may have been influenced by author judgment, creating a possibility of selection bias. The emphasis on English-language publications may also have resulted in language bias and the exclusion of relevant evidence published in other languages. In addition, the included studies were heterogeneous in terms of study design, patient populations, wound and scar types, treatment protocols, outcome measures, and follow-up duration. A quantitative meta-analysis was therefore not performed, and direct

**Table 3. Comparison of four commercial products for skin wound healing and scar treatment**

| Feature | Dermatix Ultra | Epicyn | Flosteron | Contractubex |
|---|---|---|---|---|
| Primary base | Silicone gel | Stabilized hypochlorous acid formulation | Injectable corticosteroid (betamethasone) | Topical gel (onion extract, heparin, allantoin) |
| Key additional Ingredient | Vitamin C ester | Hypochlorous acid (HOCl) | None | None |
| Mechanism | Occlusion, hydration, antioxidant, anti-pigmentary | Occlusion, hydration, antimicrobial, anti-inflammatory | Anti-inflammatory, anti-proliferative | Anti-inflammatory, anti-proliferative, keratolytic, moisturizing |
| Route | Topical | Topical | Intralesional injection | Topical |
| Primary use | Prevention and management of linear hypertrophic scars, keloids | Prevention and management of hypertrophic scars, keloids; wounds with high bioburden | Established hypertrophic and keloid scars | Management of various scar types |
| Recent evidence | Generally supportive; effective for scar improvement and symptom reduction | Shows promise, potentially superior to silicone alone in some aspects | Effective for reducing established hypertrophic/keloid scars; often used in combination | Mixed evidence; some studies show modest benefits, others less so |

Note: The products included in this table are illustrative examples and do not represent a comprehensive list of available scar treatments. They were not selected through a systematic comparative process, and the summarized evidence should not be interpreted as establishing the superiority of one formulation over another.

comparisons among therapeutic approaches should be interpreted cautiously. The evidence supporting individual topical and intralesional products was variable in quantity and methodological quality, and the product-specific comparative reports cited in this review were produced by overlapping author groups rather than independent research teams [77-79]. Consequently, the conclusions of this review should be regarded as a qualitative synthesis of the available literature rather than as definitive comparative evidence of treatment superiority.

## CONCLUSIONS

Chronic wounds remain a major clinical challenge because impaired perfusion, infection, persistent inflammation, mechanical stress, and comorbid disease often interact. Advances in immune biology, extracellular-matrix research, biomaterials, cell-based approaches, gene and RNA technologies, and physical modalities have expanded the range of potential interventions. However, many emerging strategies remain supported primarily by preclinical or heterogeneous clinical evidence. Future research should prioritize standardized outcomes, adequately powered comparative studies, long-term safety assessment, and translation of mechanistic findings into clinically meaningful treatment pathways.

Scar prevention and treatment require an individualized and multimodal approach that may include silicone-based therapies, intralesional treatments, physical modalities, laser-based procedures, surgery, and selected combination regimens. Evidence for individual interventions and commercial formulations remains variable, and direct comparisons are limited by differences in scar type, study design, outcome measurement, and follow-up. Treatment choices should therefore reflect scar characteristics, patient preferences, safety, and the strength and independence of the available evidence.

Combination therapies, targeted delivery systems, and personalized approaches are important areas for further investigation, but their clinical value should be established through rigorous and independently replicated studies before broad adoption.

## ABBREVIATIONS

EGF – Epidermal growth factor

FGF – Fibroblast growth factor

IL – Interleukin

MMPs – Matrix metalloproteinases

PDGF – Platelet-derived growth factor

RNA – Ribonucleic acid

TGF-β – Transforming growth factor beta

TNF-α – Tumor necrosis factor alpha

VEGF – Vascular endothelial growth factor

## ACKNOWLEDGEMENT

None.

## AUTHORS' CONTRIBUTION

NK – literature search, investigation, preparation of the original draft, and manuscript revision.

LG – conceptualization, supervision, and critical revision of the manuscript.

NGo – literature search, evidence interpretation, preparation of the original draft, and critical revision of the manuscript.

KG – methodology, evidence synthesis, validation, and critical revision of the manuscript.

SG – supervision and critical revision of the manuscript.

GJ – literature organization, preparation of the comparative material, and critical revision of the manuscript.

NGv – conceptualization, literature search, review design, preparation of the original draft, and critical revision of the manuscript.

LR – evidence synthesis, preparation of the comparative table, evidence presentation, and manuscript revision.

All authors have read and approved the final version of the manuscript.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest related to this manuscript. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No external funding or commercial sponsorship was received for the preparation of this manuscript.

The authors have no affiliation with the manufacturers of the products discussed, including Dermatix Ultra, Epicyn, Flosteron, and Contractubex. None of the authors has been involved in the production, branding, marketing, sale, or promotion of these products, and none has received any financial or non-financial support, incentive, or compensation from the manufacturers or related entities.

Publisher's Note: The Editorial Office stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2026 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

## REFERENCES

1. Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 6th ed. New York: Garland Science; 2015.
2. Lodish H, Berk A, Zipursky SL, et al. Molecular Cell Biology. 8th ed. New York: W.H. Freeman; 2016.
3. Martini FH, Nath JL, Bartholomew EF. Fundamentals of Anatomy & Physiology. 11th ed. Pearson Education; 2018.
4. Landén NX, Li D, Ståhle M. Transition from acute to chronic wound healing. Cell Mol Life Sci. 2016;73(20):3861-3885. DOI:10.1007/s00018-015-2119-4
5. Guo S, DiPietro LA. Factors affecting wound healing. J Dent Res. 2010;89(3):219-229. DOI:10.1177/0022034509359125
6. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;453(7193):314-321. DOI:10.1038/nature07039
7. Olsson M, Järbrink K, Divakar U, Bajpai S, Upton Z, Schmidtchen A. The humanistic and economic burden of chronic wounds: a systematic review. Wound Repair Regen. 2019;27(1):114-125. DOI:10.1111/wrr.12683
8. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care (New Rochelle). 2015;4(9):560-582. DOI:10.1089/wound.2015.0635
9. Bayat A, McGrouther DA, Ferguson MWJ. Skin scarring. BMJ. 2003;326(7380):88-92. DOI:10.1136/bmj.326.7380.88
10. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med. 2011;17(1-2):113-125. DOI:10.2119/molmed.2009.00153
11. van der Wal MB, Tuinebreijer WE, Bloemen MC, Verhaegen PD, Middelkoop E, van Zuijlen PP. Rasch analysis of the Patient and Observer Scar Assessment Scale (POSAS) in burn scars. Qual Life Res. 2012;21(1):13-23. DOI:10.1007/s11136-011-9924-5
12. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359(9):938-949. DOI:10.1056/NEJMra0801082
13. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003;83(3):835-870. DOI:10.1152/physrev.2003.83.3.835
14. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen. 2008;16(5):585-601. DOI:10.1111/j.1524-475X.2008.00410.x
15. Borregaard N. Neutrophils, from marrow to microbes. Immunity. 2010;33(5):657-670. DOI:10.1016/j.immuni.2010.11.011
16. Koh TJ, DiPietro LA. Inflammation and wound healing: the role of the macrophage. Expert Rev Mol Med. 2011;13:e23. DOI:10.1017/S1462399411001943
17. Mantovani A, Sica A, Sozzani S, et al. The chemokine system in diverse forms of macrophage activation. Trends Immunol. 2004;25(12):677-686. DOI:10.1016/j.it.2004.09.015
18. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol. 2007;127(3):514-525. DOI:10.1038/sj.jid.5700701
19. Tonnesen MG, Feng XH, Clark RAF. Angiogenesis in wound healing. J Investig Dermatol Symp Proc. 1996;1(1):40-46. DOI:10.1046/j.1087-0024.2000.00014.x
20. Fuchs E. The tortoise and the hair: slow-cycling cells in the stem cell race. Cell. 2009;137(5):811-819. DOI:10.1016/j.cell.2009.05.002
21. Grose R, Werner S. Regulation of wound reepithelialization by growth factors and cytokines. Wound Repair Regen. 2004;12(3):241-256. DOI:10.1111/j.1067-1927.2004.012306.x
22. Watt FM, Huck WTS. Role of the extracellular matrix in regulating stem cell fate. Nat Rev Mol Cell Biol. 2013;14(8):467-473. DOI:10.1038/nrm3620
23. Ogawa R. Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. Wound Repair Regen. 2017;25(5):647-657. DOI:10.1111/wrr.12574
24. Nosbaum A, Prevel N, Truong HA, Mehta P, Ettinger M, Scharschmidt TC, et al. Cutting edge: regulatory T cells facilitate cutaneous wound healing. J Immunol. 2016;196(5):2010-2014. DOI:10.4049/jimmunol.1502139
25. Ganz T. Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol. 2003;3(9):710-720. DOI:10.1038/nri1180
26. Wulff BC, Parent AE, Meleski MA, DiPietro LA, Schrementi ME, Wilgus TA. Mast cells contribute to scar formation during fetal wound healing. J Invest Dermatol. 2012;132(2):458-465. DOI:10.1038/jid.2011.324
27. Hynes RO. The extracellular matrix: not just pretty fibrils. Science. 2009;326(5957):1216-1219. DOI:10.1126/science.1176009
28. Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. Annu Rev Cell Dev Biol. 2007;23:435-461. DOI:10.1146/annurev.cellbio.23.090506.123337

29. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol. 2007;8(9):729-740. DOI:10.1038/nrm2233
30. Swift ME, Burns AL, Gray KL, DiPietro LA. Age-related alterations in the inflammatory response to dermal injury. J Invest Dermatol. 2001;117(5):1027-1035. DOI:10.1046/j.0022-202x.2001.01539.x
31. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest. 2007;117(5):1219-1222. DOI:10.1172/JCI32169
32. Winter GD. Formation of the scab and the rate of epithelialization of superficial wounds in the skin of the young domestic pig. Nature. 1962;193(4812):293-294. DOI:10.1038/193293a0
33. Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. Wound healing dressings and drug delivery systems: a review. J Pharm Sci. 2008;97(8):2892-2923. DOI:10.1002/jps.21210
34. McDaniel JC, Browning KK. Smoking, chronic wound healing, and implications for evidence-based practice. J Wound Ostomy Continence Nurs. 2014;41(5):415-423. DOI:10.1097/WON.0000000000000057
35. Krasner DL, editor. Chronic Wound Care: The Essentials: A Clinical Source Book for Healthcare Professionals. 1st ed. Malvern, PA: HMP Communications; 2014.
36. James GA, Swogger E, Wolcott R, Pulcini E, Secor P, Sestrich J, et al. Biofilms in chronic wounds. Wound Repair Regen. 2008;16(1):37-44. DOI:10.1111/j.1524-475X.2007.00321.x
37. Atkin L. Understanding methods of wound debridement. Br J Nurs. 2014;23(Suppl 12):S10-S15. DOI:10.12968/bjon.2014.23.sup12.S10
38. Mehta AB, Nadkarni NJ, Patil SP, Godse KV, Gautam M, Agarwal S. Topical corticosteroids in dermatology. Indian J Dermatol Venereol Leprol. 2016;82(4):371-378. DOI:10.4103/0378-6323.178903
39. Fisher DA. Adverse effects of topical corticosteroid use. West J Med. 1995;162(2):123-126.
40. Demling RH. Nutrition, anabolism, and the wound healing process: an overview. Eplasty. 2009;9:e9.
41. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am. 2011;31(1):81-93. DOI:10.1016/j.iac.2010.09.010
42. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346(8984):1194-1196. DOI:10.1016/S0140-6736(95)92899-5
43. Dallo M, Patel K, Hebert AA. Topical antibiotic treatment in dermatology. Antibiotics (Basel). 2023;12(2):188. DOI:10.3390/antibiotics12020188
44. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon JK, Wa CTC, Villa MA. Povidone iodine in wound healing: a review of current concepts and practices. Int J Surg. 2017;44:260-268. DOI:10.1016/j.ijsu.2017.06.073
45. Rippon MG, Rogers AA, Ousey K. Polyhexamethylene biguanide and its antimicrobial role in wound healing: a narrative review. J Wound Care. 2023;32(1):5-20. DOI:10.12968/jowc.2023.32.1.5
46. Fazli MM, Kirketerp-Møller K, Sonne DP, Balchen T, Gundersen G, Jørgensen E, et al. A first-in-human randomized clinical study investigating the safety and tolerability of stabilized hypochlorous acid in patients with chronic leg ulcers. Adv Wound Care (New Rochelle). 2024;13(11):529-541. DOI:10.1089/wound.2024.0040
47. Tashkandi H. Honey in wound healing: an updated review. Open Life Sci. 2021;16(1):1091-1100. DOI:10.1515/biol-2021-0084
48. Caplan AI. Mesenchymal stem cells: time to correct misconceptions. Stem Cells Transl Med. 2017;6(6):1445-1451. DOI:10.1002/sctm.17-0051
49. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663-676. DOI:10.1016/j.cell.2006.07.024
50. Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell. 2015;17(1):11-22. DOI:10.1016/j.stem.2015.06.007
51. Ahmed EM. Hydrogel: preparation, characterization, and applications: a review. J Adv Res. 2015;6(2):105-121. DOI:10.1016/j.jare.2013.07.006
52. O'Brien FJ. Biomaterials & scaffolds for tissue engineering. Mater Today. 2011;14(3):88-95. DOI:10.1016/S1369-7021(11)70058-X
53. Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. Semin Immunol. 2008;20(2):109-116. DOI:10.1016/j.smim.2007.11.003
54. Pang Q, Yang F, Jiang Z, Wu K, Hou R, Zhu Y. Smart wound dressing for advanced wound management: real-time monitoring and on-demand treatment. Mater Des. 2023;229:111917. DOI:10.1016/j.matdes.2023.111917
55. Di Stefano AB, Urrata V, Schilders K, Franza M, Di Leo S, Moschella F, et al. Three-dimensional bioprinting techniques in skin regeneration: current insights and future perspectives. Life (Basel). 2025;15(5):787. DOI:10.3390/life15050787
56. Nguyen Thi YV, Ngo AD, Chu DT, Lin SC, Wu CC. RNA therapeutics for regenerative medicine. Prog Mol Biol Transl Sci. 2024;204:163-176. DOI:10.1016/bs.pmbts.2023.12.002
57. Chen T, Heller E, Beronja S, Oshimori N, Stokes N, Fuchs E. An RNA interference screen uncovers a new molecule in stem cell self-renewal and long-term regeneration. Nature. 2012;485(7396):104-108. DOI:10.1038/nature10940
58. Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. Cell. 2014;157(6):1262-1278. DOI:10.1016/j.cell.2014.05.010
59. Armstrong DG, Lavery LA; Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005;366(9498):1704-1710. DOI:10.1016/S0140-6736(05)67695-7
60. Avci P, Gupta A, Sadasivam M, Vecchio D, Pam Z, Pam N, et al. Low-level laser (light) therapy in skin. Semin Cutan Med Surg. 2013;32(1):41-52. DOI:10.12788/j.sder.0023
61. Saber AA, Saber A. Therapeutic ultrasound: physiological role, clinical applications and precautions. J Surg. 2017;5(3-1):61-69. DOI:10.11648/j.js.s.2017050301.22
62. Rajendran SB, Challen K, Wright KL, Hardy JG. Electrical stimulation to enhance wound healing. J Funct Biomater. 2021;12(2):40. DOI:10.3390/jfb12020040
63. De A, Sarda A, Gupta S, Das S. Use of artificial intelligence in dermatology. Indian J Dermatol. 2020;65(5):352-357. DOI:10.4103/ijd.IJD_418_20
64. Lane ME. Skin penetration enhancers. Int J Pharm. 2013;447(1-2):12-21. DOI:10.1016/j.ijpharm.2013.02.040
65. Zhao L, Chen J, Bai B, Song G, Zhang J, Yu H, et al. Topical drug delivery strategies for enhancing drug effectiveness by skin barriers, drug delivery systems and individualized dosing. Front Pharmacol. 2024;14:1333986. DOI:10.3389/fphar.2023.1333986
66. Vogt A, Wischke C, Neffe AT, Ma N, Alexiev U, Lendlein A. Nanocarriers for drug delivery into and through the skin-do existing technologies match clinical challenges? J Control Release. 2016;242:3-15. DOI:10.1016/j.jconrel.2016.07.027

67. Baumann LS, Spencer J. The effects of topical vitamin E on the cosmetic appearance of scars. Dermatol Surg. 1999;25(4):311-315. DOI:10.1046/j.1524-4725.1999.08237.x

68. Mustoe TA, Cooter RD, Gold MH, Hobbs FDR, Ramelet AA, Shakespeare PG, et al. International clinical recommendations on scar management. Plast Reconstr Surg. 2002;110(2):560-571. DOI:10.1097/00006534-200208000-00031

69. Gold MH, Berman B, Clementoni MT, Gauglitz GG, Nahai F, Murcia C. Updated international clinical recommendations on scar management: part 1 - evaluating the evidence. Dermatol Surg. 2014;40(8):817-824. DOI:10.1111/dsu.0000000000000049

70. Wang F, Li X, Wang X, Jiang X. Efficacy of topical silicone gel in scar management: a systematic review and meta-analysis of randomised controlled trials. Int Wound J. 2020;17(3):765-773. DOI:10.1111/iwj.13337

71. Hosnuter M, Payasli C, Isikdemir A, Tekerekoglu B. The effects of onion extract on hypertrophic and keloid scars. J Wound Care. 2007;16(6):251-254. DOI:10.12968/jowc.2007.16.6.27070

72. Yang X, Lohsiriwat V, Chang FCS, et al. Real-world management of abnormal scarring using topical silicone gel: expert consensus and case series from the Asian SCARS Expert Group. Drugs Context. 2023;12:2023-4-3. DOI:10.7573/dic.2023-4-3

73. Del Rosso JQ, Bhatia N. Status report on topical hypochlorous acid: clinical relevance of specific formulations, potential modes of action, and study outcomes. J Clin Aesthet Dermatol. 2018;11(11):36-39.

74. Gold MH, Andriessen A, Bhatia AC, Bitter P Jr, Chilukuri S, Cohen JL, et al. Topical stabilized hypochlorous acid: the future gold standard for wound care and scar management in dermatologic and plastic surgery procedures. J Cosmet Dermatol. 2020;19(2):270-277. DOI:10.1111/jocd.13280

75. Sakarya S, Günay N, Karakulak M, Ertugrul B. Hypochlorous acid: an ideal wound care agent with powerful microbicidal, antibiofilm, and wound healing potency. Wounds. 2014;26(12):342-350.

76. Burian EA, Sabah L, Kirketerp-Møller K, Gundersen G, Ågren MS. Effect of stabilized hypochlorous acid on re-epithelialization and bacterial bioburden in acute wounds: a randomized controlled trial in healthy volunteers. Acta Derm Venereol. 2022;102:adv00727. DOI:10.2340/actadv.v102.1624

77. Kuridze N, Gabunia L, Ghambashidze K, Lobzhanidze K, Mtvarelishvili G, Avagimyan A, Kaladze T. Optimizing skin wound healing outcomes: a comparative analysis of cytokine response and tissue remodeling after treatment with polysiloxane-siloxane, silicone, betamethasone, and heparin-based preparations. World Med J Biomed Sci. 2024;1(12):112-125.

78. Kuridze N, Gabunia L, Ghambashidze K, Rtveladze T, Iosebidze T, Gvishani M, Shoshiashvili V. Comparative analysis of different methods of treatment on pro-inflammatory cytokines and the skin wound healing outcomes. Acta Sci Med Sci. 2025;9(1):57-64. DOI:10.31080/ASMS.2024.09.1991

79. Kuridze N, Gabunia L, Ghambashidze K, Giorgadze S, Pkhaladze M. The skin wounds and effects of Epicyn, Flosteron and Contractubex on IL-1 and IL-6 cytokines in the dynamic of healing process. World Med J Biomed Sci. 2024;1(4):90-98.