

Review

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Review

Recent Advances in Wound Healing, Tissue Repair, Regeneration and Scar Management

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Abstract

Introduction: 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. **Methods:** This review synthesizes recent advancements in 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. Among the commercially available topical agents, Dermatix Ultra, Epicyn, Flosteron, and Contractubex are widely used and studied. **Results:** This review provides a contemporary analysis in the context of wound healing, tissue repair, and scar management, with an evidence-based comparison of these agents, focusing on their composition, mechanisms of action, clinical applications, and a comparative perspective on their efficacy in improving scar outcomes. **Conclusion:** Thus, this review aims to provide clinicians and patients with an up-to-date understanding of these treatments to facilitate informed decision-making in scar management. Finally, we discuss current challenges and future directions in the field, highlighting the potential for personalized medicine and translational research.

Keywords: wound healing; tissue repair; regeneration; scar management

Introduction

The human body relies on the integrity of its tissues for proper function and survival [1,2]. Tissues provide structural support, form barriers against pathogens, and facilitate essential physiological processes [3]. Damage to these tissues, whether from trauma, surgery, or disease, initiates a complex series of events aimed at restoring tissue continuity [4]. Wound healing and tissue regeneration remain at the forefront of clinical and research interest due to their implications in dermatology [5], surgery [6], and chronic disease management.

Impaired wound healing can lead to chronic wounds, a significant health problem affecting millions worldwide [7]. Chronic wounds, such as diabetic ulcers, pressure ulcers, and venous leg ulcers, are characterized by prolonged inflammation and delayed healing [8], with substantial morbidity, mortality, and healthcare costs [7]. Another outcome of wound healing is scar formation [9]. Scars can vary significantly in appearance, ranging from fine lines to raised, thickened (hypertrophic), or extending beyond the original wound boundaries (keloid) scars [10]. These can

cause functional limitations, pain, itching, and significant cosmetic concerns, thereby affecting the quality of life [11]. Effective strategies to promote healing and regeneration are crucial. The complexity of healing responses depends on factors such as patient health, wound severity, and therapeutic intervention strategies.

Regeneration, or replacement of lost tissue with similar cells, and repair (formation of granulation tissue leading to fibrosis and scar formation) are two primary processes during wound healing. Different tissues exhibit varying regenerative capacities, with labile tissues (e.g., skin, mucosa) regenerating readily, while permanent tissues (e.g., neurons, cardiac myocytes) lack proliferative ability. Wound healing is a complex biological process encompassing four overlapping but distinct phases: hemostasis, inflammation, proliferation, and remodeling. Each phase is governed by a dynamic interplay among platelets, immune cells, fibroblasts, keratinocytes, and endothelial cells.

Hemostasis, the initial response to injury, involves the cessation of bleeding through vasoconstriction and the formation of a blood clot [12]. Damage to blood vessels triggers the contraction of smooth muscle cells, reducing blood flow to the injured site. Exposed collagen activates platelets, causing them to adhere to the injury site, aggregate, and release factors such as thromboxane A₂ and ADP. The coagulation cascade involves a series of enzymatic reactions involving clotting factors, ultimately leading to the formation of fibrin. Fibrin forms a mesh-like network that stabilizes the platelet plug, creating a clot.

Inflammation is a crucial phase of wound healing, characterized by the recruitment of immune cells to the injury site. It starts with cellular recruitment. Neutrophils are the first leukocytes to arrive [13], followed by macrophages [14]. These cells phagocytose debris, bacteria, and dead cells, preventing infection. Inflammatory cells release a variety of cytokines (e.g., TNF- α , IL-1, IL-6) and chemokines (e.g., CXCL8, CCL2) [15] that regulate the inflammatory response and attract other cells to the wound. Growth factors like PDGF and TGF- β are also released during this phase, contributing to chemotaxis and the activation of fibroblasts and keratinocytes [15].

Inflammation has dual pro-inflammatory and anti-inflammatory roles in wound healing [16]. The pro-inflammatory process initiates the healing process, eliminates pathogens, debris, and damaged tissue, recruits immune cells (neutrophils, macrophages) to the wound site, releases pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , IL-6) and chemokines, and stimulates the production of reactive oxygen species (ROS) to kill bacteria. The anti-inflammatory process resolves the inflammatory response and promotes tissue repair and regeneration, involving a shift in immune cell populations and their secreted factors, and the release of anti-inflammatory cytokines (e.g., IL-10, TGF- β) that stimulate angiogenesis and extracellular matrix deposition.

Recent studies have highlighted the importance of the balance between pro-inflammatory and anti-inflammatory mediators in wound healing [16]. An imbalance can contribute to impaired healing and chronic wounds. The timely resolution of inflammation is crucial for proper wound healing. Acute inflammation that resolves quickly leads to healing and tissue repair, whereas chronic inflammation can impair the healing process and lead to complications such as delayed healing, non-healing (chronic) wounds, excessive scar formation (hypertrophic scars or keloids), and fibrosis. Recent studies have significantly advanced our understanding of the roles of specific immune cell subsets and their secreted factors in wound healing (recent literature on specific immune cell types).

Results and Discussion

Macrophages are key players in the wound healing process. They exhibit remarkable plasticity and can transition between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes [15]. M1 macrophages dominate in the early stages of wound healing, producing pro-inflammatory cytokines and ROS to clear pathogens and debris. M2 macrophages promote tissue repair and regeneration by releasing anti-inflammatory cytokines and growth factors (e.g., VEGF, TGF- β), and matrix metalloproteinases (MMPs) for extracellular matrix remodeling. Macrophages can also promote regeneration by interacting with stem cells and progenitor cells. They secrete factors that stimulate

these cells' proliferation and differentiation into tissue-specific cells (Колесникова, Єлькін, 2020). Research on macrophage polarization has revealed that the transition from M1 to M2 macrophages is crucial for the progression from the inflammatory phase to the proliferative and remodeling phases. Recent studies have identified specialized subsets of macrophages with unique functions in different phases of wound healing, highlighting the complexity of their roles.

T cells, particularly helper T cells (CD4+), play a crucial role in regulating the inflammatory response by suppressing inflammation and promoting tissue repair [16]. Subsets of T cells such as regulatory T cells (Tregs) and Th17 cells have been shown to influence the balance between pro-inflammatory and anti-inflammatory processes in the wound [17]. Tregs suppress excessive inflammation and promote tissue regeneration by releasing anti-inflammatory cytokines like IL-10 and TGF- β . Th17 cells contribute to the early inflammatory response and can also promote tissue repair through the production of growth factors. T cells can influence tissue regeneration by interacting with stem cells, secreting factors that activate stem cells and promote their differentiation into various cell types.

Neutrophils, traditionally viewed as primarily pro-inflammatory cells, also contribute to the resolution of inflammation. They clear debris and pathogens through phagocytosis and the release of antimicrobial substances [18]. Recent studies have shown that neutrophils undergo apoptosis and are cleared by macrophages, a process that promotes the transition to the anti-inflammatory phase. Neutrophils can also release factors that stimulate angiogenesis and tissue repair.

Mast cells are involved in the early inflammatory response by releasing histamine, cytokines, and growth factors [19]. They contribute to vasodilation and increased vascular permeability, facilitating the recruitment of other immune cells to the wound site. Mast cells can also promote angiogenesis by releasing factors like VEGF and histamine, supporting tissue regeneration. Recent research suggests mast cells may also play a role in later stages of wound healing and influence tissue remodeling and scar formation, but their exact role requires further investigation.

Communication between cells in the wound bed is mediated by a variety of secreted factors. Growth factors and cytokines are essential signaling molecules that regulate every stage of wound healing [15,20]. Key growth factors include Transforming Growth Factor-beta (TGF- β), which stimulates fibroblast proliferation, collagen synthesis, and extracellular matrix (ECM) production; Vascular Endothelial Growth Factor (VEGF), which promotes angiogenesis; Epidermal Growth Factor (EGF), which stimulates keratinocyte proliferation and migration; and Fibroblast Growth Factor (FGF), which promotes angiogenesis, fibroblast proliferation, and ECM synthesis [21]. Key cytokines include interleukins (IL-1, IL-6, IL-10), which modulate inflammation and tissue repair, and Tumor Necrosis Factor-alpha (TNF- α), primarily involved in the inflammatory response. Pro-inflammatory cytokines promote inflammation and recruit immune cells, while anti-inflammatory cytokines like IL-10 and TGF- β suppress inflammation and promote tissue repair [19].

Growth factors and cytokines do not function in isolation; they engage in intricate interactions that can have synergistic or antagonistic effects, orchestrating the different phases of wound healing [21]. **Synergistic effects:** Many growth factors and cytokines work together to amplify their effects on cell proliferation, migration, and differentiation. For instance, PDGF and VEGF can synergistically promote angiogenesis, while TGF- β and EGF can enhance ECM production and tissue remodeling. **Antagonistic effects:** Some cytokines can counteract the effects of growth factors or other cytokines. For example, pro-inflammatory cytokines like TNF- α can inhibit the production of ECM components by fibroblasts, while anti-inflammatory cytokines like IL-10 can suppress the production of pro-inflammatory cytokines. Chemokines regulate the migration of immune cells to the wound site [21]. MMPs are enzymes that degrade and remodel the ECM, essential for tissue repair and regeneration.

Proliferation – The proliferative phase involves the reconstruction of damaged tissue through angiogenesis, fibroplasia, and re-epithelialization. The formation of new blood vessels is essential for delivering oxygen and nutrients to the healing tissue. Growth factors like VEGF play a critical role in this process [21,22]. Fibroblasts migrate to the wound site and proliferate, synthesizing collagen and

other ECM components. Keratinocytes migrate from the wound edges and hair follicles to cover the wound surface, restoring the epithelial barrier (re-epithelialization) [23].

Remodeling – The remodeling phase involves the maturation and reorganization of the newly formed tissue [24]. Growth factors such as TGF- β play a crucial role in ECM remodeling and scar formation [21]. The balance between growth factors and cytokines, as well as the activity of MMPs, determines the final outcome of tissue repair [25]. Collagen fibers are reorganized and cross-linked, increasing the tensile strength of the scar tissue. MMPs degrade ECM components, allowing for tissue remodeling. In most cases, the repair process results in scar formation, which differs in structure and function from the original tissue.

Scar formation is a consequence of the body's repair mechanism when the dermal layer of the skin is damaged [9]. Factors influencing scar severity include the depth and size of the wound, the location on the body, individual genetic predisposition, and the presence of complications like infection or prolonged inflammation. Hypertrophic scars result from excessive collagen deposition within the wound boundaries, while keloids extend beyond the original injury and can be more challenging to treat [26]. The coordinated action of growth factors and cytokines is essential for the successful progression of wound healing through its distinct phases [21].

Recent research has focused on harnessing the therapeutic potential of growth factors and cytokines to improve wound healing, particularly in chronic wounds [27,28]. Recombinant growth factors, such as PDGF (becaplermin), have been approved for the treatment of specific types of chronic wounds. Cytokines like IL-10 and TGF- β are being explored for their potential to modulate the inflammatory response and promote tissue regeneration.

The **extracellular matrix (ECM)** is a complex network of proteins, polysaccharides, and other macromolecules that provides structural support to cells and tissues and regulates cell behavior [26]. Recent research has revealed that the ECM is not merely a passive scaffold but an active regulator of cell behavior, playing a critical role in tissue repair and regeneration [29]. Key components of the ECM include collagen (which provides tensile strength and structural support – recent studies show that collagen fragments can act as signaling molecules, influencing cell adhesion, migration, and differentiation), fibronectin (a glycoprotein that binds to integrins and other ECM components, facilitating cell adhesion and migration – fibronectin fragments can promote angiogenesis and tissue remodeling), laminin (a major component of the basement membrane, crucial for cell adhesion, migration, and differentiation, particularly during epithelialization), and proteoglycans (which regulate ECM assembly, hydration, and growth factor signaling – their fragments can modulate inflammation and tissue repair).

The ECM is constantly remodeled during wound healing through the action of MMPs and tissue inhibitors of metalloproteinases (TIMPs) [26]. Hyaluronic acid (HA) is a glycosaminoglycan that provides hydration and regulates cell proliferation and migration. HA fragments can stimulate angiogenesis and inflammation [30]. ECM components interact with integrin receptors on cell surfaces, triggering intracellular signaling pathways that regulate cell adhesion, migration, proliferation, and survival [31].

The ECM can bind and sequester growth factors, such as VEGF, FGF, and TGF- β , and release them in a controlled manner to regulate cell behavior. MMPs remodel the ECM by degrading its components, creating space for cell migration and tissue remodeling. MMP activity is tightly regulated to ensure proper tissue repair. Cells can sense and respond to the mechanical properties of the ECM, such as stiffness and elasticity, through integrins and other receptors. This process influences cell behavior and tissue regeneration [31].

Several **intrinsic factors** can influence the rate and quality of wound healing. For example, aging is associated with delayed wound healing, reduced cell proliferation, and impaired ECM remodeling. Genetic variations can affect the expression of growth factors, ECM components, and inflammatory mediators, influencing individual healing responses [32]. Underlying health conditions can also play a significant role:

➤ **Diabetes:** Impairs angiogenesis, increases the risk of infection, and delays wound closure [27]. Chronic hyperglycemia in diabetes can lead to a persistent state of inflammation, which impairs tissue repair and increases the risk of chronic wounds. Diabetic neuropathy can impair sensation, leading to unrecognized injuries and increased risk of infection and delayed healing.

➤ **Vascular diseases:** Conditions like peripheral artery disease reduce blood flow to the extremities, impairing the delivery of oxygen and nutrients to the wound site and delaying healing.

➤ **Immunodeficiency:** Conditions that weaken the immune system (e.g., HIV or immunosuppressive therapy) increase the risk of infection and impair the body's ability to mount an effective healing response.

➤ **Obesity:** Associated with chronic low-grade inflammation, which can disrupt the normal healing process. Obesity can also impair angiogenesis, leading to reduced blood flow to the wound site. Chronic kidney disease (uremia) results in accumulation of uremic toxins that can impair various aspects of wound healing, including cell proliferation, migration, and ECM synthesis.

Recent studies have significantly advanced our understanding of the molecular mechanisms by which intrinsic factors influence wound healing. These inherent factors can profoundly affect the healing process.

Genetic predispositions: Research has identified specific genes and genetic variations that influence wound healing outcomes [32]. These genes are involved in various processes, including:

➤ **ECM regulation:** Genes encoding collagen, MMPs, and TIMPs play a crucial role in ECM synthesis and remodeling during wound healing. Variations in these genes can affect the strength and structure of the healed tissue.

➤ **Inflammatory response:** Genes involved in the production of pro-inflammatory cytokines (e.g., TNF- α , IL-6) and anti-inflammatory cytokines (e.g., IL-10, TGF- β) can influence the duration and intensity of the inflammatory phase, which is critical for wound healing [33].

➤ **Growth factor signaling:** Genes encoding growth factors like VEGF, PDGF, TGF- β , and components of their signaling pathways can affect cell proliferation, migration, and differentiation during tissue repair.

Studies have shown that certain aspects of wound healing, such as the tendency to develop hypertrophic scars or keloids, have a strong genetic component [10].

Recent research indicates that an individual's genetic makeup influences their skin microbiome, which in turn affects wound healing. A diverse and balanced microbiome is generally associated with faster and more effective wound healing [34].

Aging is a significant intrinsic factor that impairs wound healing. Several molecular mechanisms contribute to this age-related decline. Aging is associated with decreased production of key growth factors like PDGF, TGF- β , and VEGF, which are essential for cell proliferation, migration, and angiogenesis. Senescent cells accumulate in aged tissues and have reduced proliferative capacity while secreting factors that can disrupt the wound healing process (the senescence-associated secretory phenotype) [35]. The number and function of stem cells in the skin and other tissues decline with age, impairing the regenerative capacity of aged tissues. Aging leads to changes in the composition and structure of the ECM, including decreased collagen synthesis and increased collagen degradation, which impair tissue repair and increase the risk of chronic wounds. Aging is also associated with chronic low-grade inflammation ("inflammaging"), which can disrupt the normal inflammatory response to injury and impair wound healing.

Certain comorbidities can significantly impair wound healing by affecting various molecular processes. **Diabetes** is associated with impaired production of nitric oxide and other factors that promote angiogenesis, leading to reduced blood flow to the wound site and delayed healing [27]. Chronic hyperglycemia can cause a persistent inflammatory state, impairing tissue repair and increasing the risk of chronic wounds. Diabetic neuropathy can result in unrecognized injuries due to impaired sensation, increasing infection risk and delaying healing. **Cardiovascular diseases** can reduce tissue perfusion; for example, peripheral artery disease diminishes blood flow to extremities, delaying healing. **Immunodeficiency** (such as in HIV or due to immunosuppressants) increases

infection risk and impairs the healing response. **Obesity** causes chronic inflammation and can disrupt healing processes, and it also impairs angiogenesis, reducing blood flow to wounds. **Chronic kidney disease** leads to accumulation of toxins that impair cell proliferation, migration, and ECM synthesis.

Extrinsic factors can also significantly impact wound healing [5]. For example, infection delays healing, increases inflammation, and can lead to tissue damage [4]. A moist wound environment promotes cell migration and proliferation [36]. Adequate oxygen supply is essential for cell metabolism, angiogenesis, and collagen synthesis. Excessive tension or pressure can disrupt the healing process [37]. Certain medications, such as corticosteroids and immunosuppressants, can impair wound healing. Smoking impairs blood flow, reduces oxygen delivery, and delays healing.

Recent research has emphasized the importance of several key factors in promoting optimal wound healing. **Procedures supporting optimal wound healing involve:**

➤ **Optimization of the wound environment:** Maintaining a balanced moisture environment is crucial for facilitating cell migration, proliferation, and differentiation. Studies have shown that occlusive or semi-occlusive dressings, which prevent moisture loss, can significantly enhance healing rates compared to traditional dry dressings.

➤ **Normal body temperature:** Keeping the wound area at normal body temperature supports optimal healing. Research indicates that hypothermia can impair various cellular processes involved in wound repair, including enzyme activity and blood flow.

➤ **Adequate oxygen supply:** Oxygen is essential for angiogenesis, collagen synthesis, and immune function within the wound. Studies have explored the use of hyperbaric oxygen therapy and topical oxygen delivery systems to enhance wound healing in hypoxic conditions, such as diabetic ulcers.

➤ **Slightly acidic pH:** An acidic wound environment has been shown to be beneficial for healing. Research suggests that an acidic environment can reduce infection risk, increase fibroblast activity, and promote growth factor release [38].

➤ **Prevention of infections (biofilm management):** Chronic wounds are often colonized by biofilms – complex communities of microorganisms highly resistant to antibiotics. Recent studies have focused on developing strategies to disrupt and prevent biofilm formation, including the use of antimicrobial agents, enzymes, and physical disruption methods.

Antimicrobial Stewardship: The overuse of antibiotics can lead to the development of antibiotic-resistant bacteria, which can complicate wound healing. Current research emphasizes the importance of antimicrobial stewardship, which involves using antibiotics judiciously and employing alternative strategies (such as antiseptics and barrier dressings) to prevent infection [8,39].

➤ **Advanced wound dressings:** Modern wound dressings incorporate antimicrobial agents (e.g., silver, chlorhexidine) which are released gradually to prevent infection without harming host tissues [40]. Research has also led to the development of smart dressings that can detect and respond to infection, releasing antimicrobial agents when needed [41].

➤ **Managing mechanical stress (Offloading):** Pressure ulcers and diabetic foot ulcers are often caused or worsened by excessive mechanical stress. Studies have demonstrated the effectiveness of offloading devices (such as specialized footwear and braces) in reducing pressure on the wound and promoting healing.

➤ **Wound closure techniques:** Surgical techniques that minimize tension on wound edges can improve healing outcomes [42]. Research has explored the use of tissue adhesives, negative pressure wound therapy [43], and other methods to reduce mechanical stress and promote wound approximation.

➤ **Extracellular Matrix Modulation:** Mechanical forces can influence ECM remodeling [26]. Studies have investigated how to modulate ECM components to improve tissue repair and reduce scarring [29].

Effects of Specific Medications:

- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):** Some NSAIDs can impair the early phases of wound healing by inhibiting inflammation and reducing the production of growth factors [5].
 - **Corticosteroids:** These immunosuppressive drugs can significantly delay wound healing by interfering with collagen synthesis, angiogenesis, and immune function.
 - **Anticoagulants:** Medications like warfarin and heparin, which prevent blood clotting, can increase the risk of bleeding and hematoma formation, potentially complicating wound healing [44].
 - **Chemotherapeutic agents:** These can impair wound healing by inhibiting cell growth and proliferation.
 - **Immunosuppressant medications:** Drugs like cyclosporine can delay wound healing by suppressing the immune response.
 - **Antibiotics:** While necessary for treating infections, some antibiotics can have negative effects on non-target cells (like fibroblasts) and impair the healing process [34].
- Effects of lifestyle factors:**
- **Adequate nutrition:** Deficiencies in protein, vitamins (A, C, E), and minerals (zinc, iron) can impair wound healing [5,45]. Nutritional supplementation can improve healing outcomes in malnourished patients.
 - **Smoking:** Smoking causes vasoconstriction, reducing oxygen delivery to the wound, and interferes with collagen synthesis. Smoking cessation is strongly recommended to promote optimal wound healing.
 - **Excessive alcohol consumption:** Alcohol can delay wound healing and increase the risk of infection.
 - **Psychological stress:** Stress can impair wound healing by affecting the immune system and hormone levels (e.g., elevated cortisol) [46,47]. Stress management techniques (such as mindfulness and relaxation exercises) may help improve wound healing.
 - **Regular physical activity:** Exercise improves circulation, tissue oxygenation, and overall health, which promotes wound healing [48]. However, activities that increase mechanical stress on the wound should be avoided during healing.

The treatment of skin wounds and management of scars is a significant aspect of dermatological and surgical practice. Numerous topical treatments are available, each with a purported mechanism of action and varying levels of clinical evidence. Modern therapeutic approaches are diverse and aim to accelerate healing while minimizing complications such as scarring, infection, or chronic inflammation [5].

Scar and wound care require personalized approaches tailored to wound type, phase of healing, and patient-specific factors. Recent strategies emphasize targeted modulation of inflammation [5,16], oxidative stress, fibroblast activity, and microbial load. Agents with antioxidant, antimicrobial, anti-inflammatory, or growth-promoting properties [15] are integral to promoting effective tissue repair. The efficacy of a topical product is determined not only by its pharmacodynamic properties but also by its ability to maintain a moist wound environment and minimize cytotoxicity.

Recent discoveries in immunomodulatory therapies have significantly impacted wound healing, offering new approaches to promote tissue repair and regeneration.

- **Targeting macrophage polarization:** Strategies aimed at promoting the transition of macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype have shown promise in enhancing wound healing [14]. For example, therapies that deliver factors like IL-4 or IL-10 to the wound microenvironment can promote M2 polarization and accelerate tissue repair [15].

- **Modulating T cell responses:** Immunotherapies that modulate T cell responses, particularly those involving Tregs, have demonstrated potential in promoting tissue regeneration and reducing fibrosis [17]. For instance, adoptive transfer of Tregs or therapies that enhance Treg activity can suppress excessive inflammation and promote tissue repair.

➤ **Inhibiting pro-inflammatory cytokines:** Therapies that block the activity of pro-inflammatory cytokines like TNF- α and IL-1 β have been effective in treating chronic wounds characterized by persistent inflammation [19]. These therapies help restore a more balanced inflammatory response and promote tissue healing.

➤ **ECM-targeted therapies:** Emerging therapies focus on modulating the ECM to promote tissue regeneration [26,29]. For example, therapies that deliver ECM components or fragments can enhance cell adhesion, migration, and differentiation, thus promoting tissue repair.

Cell-based therapies: Stem cells and progenitor cells have the capacity to differentiate into various cell types and contribute to tissue regeneration [31]. Types of stem cells being explored include:

➤ **Embryonic stem cells (ESCs):** Pluripotent cells derived from early embryos.

➤ **Induced pluripotent stem cells (iPSCs):** Adult cells reprogrammed to an embryonic-like state [49].

➤ **Mesenchymal stem cells (MSCs):** Multipotent stromal cells that can differentiate into various cell types, including fibroblasts, osteoblasts, and adipocytes [28].

➤ **Tissue-specific stem cells:** Adult stem cells residing in specific tissues (e.g., epidermal stem cells in skin [23], hematopoietic stem cells in bone marrow [26]).

Stem cells can promote tissue regeneration through differentiation (replacing damaged cells), paracrine signaling (secreting growth factors and cytokines that stimulate resident tissue cells), and immunomodulation (modulating the inflammatory response). Stem cell therapy holds great promise for promoting tissue regeneration due to the unique properties of stem cells, including their ability to self-renew and differentiate into various cell types. Both preclinical and clinical studies have explored the therapeutic potential of stem cells in various wound models.

➤ **Mesenchymal stem cells (MSCs):** MSCs are among the most widely studied cell types for tissue regeneration. They can differentiate into various cell types (bone, cartilage, adipose), and they secrete growth factors and cytokines that promote tissue repair and reduce inflammation. Their safety profile and ability to enhance re-epithelialization, angiogenesis, and collagen synthesis make them an attractive option.

➤ **Hematopoietic stem cells (HSCs):** HSCs are primarily known for blood cell formation [26], but they have also shown potential in promoting the regeneration of other tissues, including skin and muscle. HSCs are being used in clinical trials for skin regeneration, particularly in patients with chronic wounds.

➤ **Tissue-specific progenitor cells:** These stem cells are found in specific tissues and can differentiate into the cell types of that tissue. For example, epidermal stem cells in the skin can differentiate into keratinocytes [23].

➤ **Induced pluripotent stem cells (iPSCs):** iPSCs are generated by reprogramming adult cells to an embryonic stem cell-like state [49]. They can differentiate into any cell type, making them a promising cell source for tissue regeneration. iPSCs are being evaluated in early-phase clinical trials, showing promise in treating conditions like macular degeneration.

Stem cell therapy has shown promise in promoting the healing of acute and chronic skin wounds in preclinical studies. MSCs, HSCs, and epidermal stem cells have been used to enhance re-epithelialization, angiogenesis, and collagen synthesis. Stem cells have also been used to promote bone regeneration in preclinical models of fractures and bone defects, often delivered using scaffolds to provide structural support and enhance bone formation [50]. iPSC therapy has been investigated for the treatment of cartilage defects in preclinical studies. Additionally, MSCs and chondrocytes have been used to promote cartilage regeneration, and iPSCs have shown potential in promoting muscle regeneration in models of muscle injury. Stem cell therapy has even been explored as a treatment for myocardial infarction, aiming to regenerate damaged heart tissue and improve cardiac function.

Advanced Wound Dressings and Biomaterials

Recent innovations in wound dressings and biomaterials have revolutionized wound care, offering enhanced properties and mechanisms of action to promote effective tissue repair and regeneration [40]. Novel wound dressings and biomaterials are designed to promote healing by providing a favorable microenvironment and delivering therapeutic agents.

Dressings and Biomaterials include: Bioactive dressings containing growth factors, ECM components, or antimicrobial agents; **Hydrogels:** three-dimensional, water-swollen polymers that provide a moist environment and can deliver drugs or cells [51]; **Scaffolds:** structures providing structural support for cell growth and tissue regeneration [50]; **Nanomaterials:** nanoparticles used to deliver drugs, enhance tissue regeneration, and prevent infection.

Hydrogel dressings have a high water content, providing a moist environment conducive to wound healing [51]. They are typically composed of hydrophilic polymers like hyaluronic acid, alginate, or synthetic polymers. Hydrogels maintain wound hydration, facilitate autolytic debridement, and provide a cooling effect, and offer comfort and flexibility. Studies have demonstrated their effectiveness in managing various wound types (burns, ulcers, surgical wounds) by promoting faster healing and reducing pain.

Hydrocolloids absorb low to moderate amounts of fluid and create a moist environment conducive to healing. Alginates are highly absorbent dressings made from seaweed, useful for moderate to heavily exuding wounds; some have hemostatic properties. Film dressings are thin, transparent, and waterproof, suitable for superficial wounds with little to no exudate, and protect against bacteria. Hydrofibers are highly absorbent and conform to the wound bed, managing significant exudate.

Foam dressings, made from materials like polyurethane, are known for high absorption capacity and cushioning. They absorb excess wound exudate, provide thermal insulation, protect the wound from trauma, and promote a moist environment. They are effective for moderate to highly exudative wounds (e.g., pressure ulcers, venous leg ulcers), with studies showing improved healing rates and fewer dressing changes.

Antimicrobial dressings incorporate agents like silver, chlorhexidine, or iodine. They prevent and combat infection by releasing antimicrobial agents, reducing bacterial load in the wound, and minimizing the risk of biofilm formation. Clinical trials have confirmed their superiority in managing infected wounds and preventing infections in high-risk wounds, leading to better healing outcomes.

Bioactive dressings are engineered to deliver specific biological molecules, such as growth factors, ECM components, or stem cells. These dressings stimulate cell proliferation and migration, enhance angiogenesis and tissue regeneration, and modulate the inflammatory response. Studies have shown promising results in promoting the healing of chronic and complex wounds (e.g., diabetic ulcers, non-healing surgical wounds).

Smart dressings integrate sensors and drug-delivery systems for real-time monitoring of wound conditions and on-demand release of therapeutics [41]. They monitor wound pH, temperature, and moisture levels; detect infection or inflammation; and deliver drugs or growth factors in response to changes in the wound environment. Emerging evidence suggests their potential in improving wound management, enabling timely interventions, and accelerating healing, particularly in chronic wounds.

Biomaterials for tissue regeneration: Scaffolds are three-dimensional structures made of natural or synthetic biomaterials (e.g., collagen, hyaluronic acid, synthetic polymers), designed to mimic the ECM and provide structural support for tissue growth [50]. They provide a framework for cell adhesion, proliferation, and differentiation; guide tissue organization and regeneration; and can deliver growth factors or other bioactive molecules. Studies have demonstrated their effectiveness in promoting tissue regeneration in various applications, including skin grafts, bone repair, and cartilage regeneration.

Extracellular matrix-derived materials (decellularized tissues or ECM components like collagen, fibronectin, and hyaluronic acid) provide a natural and biocompatible environment for cells, promote cell-matrix interactions, and support tissue remodeling [52]. They enhance cell infiltration and

vascularization. Clinical studies have shown their potential in improving the healing of complex wounds, reducing scarring, and promoting functional tissue regeneration.

Bioengineered skin grafts are lab-grown skin substitutes used for severe burns and large wounds to aid in closure and regeneration. 3D bioprinting is an emerging technology that can create skin structures for grafting [53], potentially offering personalized and complex tissue regeneration.

Recent strategies for controlled and sustained release of growth factors in wound healing address the limitations of growth factors' short half-life, rapid degradation, and poor retention at the wound site. For example, micro- or nano-particles made of biodegradable polymers, lipids, or inorganic materials can encapsulate growth factors, protecting them from degradation and allowing controlled release. Preclinical studies have shown enhanced growth factor stability, prolonged release, and improved tissue regeneration. Growth factors can also be incorporated into or attached to polymeric fibers (electrospun or self-assembled), which has demonstrated improved cell adhesion, proliferation, and migration, as well as enhanced tissue regeneration. Hydrogels are also explored as matrices for controlled growth factor release.

Combination therapies: Preclinical and clinical studies have shown that combination therapies can be more effective than single-agent therapies in promoting wound healing and tissue regeneration [27]. For example, combining PDGF and VEGF can promote angiogenesis and cell proliferation, while combining TGF- β and FGF can enhance ECM deposition and tissue remodeling. Growth factors can be combined with antimicrobial agents to prevent infection, with anti-inflammatory drugs to modulate inflammation, or with ECM components to enhance tissue regeneration [19]. Studies have demonstrated synergistic effects and improved healing outcomes with such combination therapies.

Despite the progress in cell-based therapies, several challenges remain, such as cell viability and engraftment, standardization and manufacturing, long-term efficacy and safety (e.g., potential oncogenesis) [54], and cost-effectiveness.

Gene therapy and RNA-based therapeutics offer new avenues for modulating the healing process and hold immense potential for revolutionizing wound healing by addressing underlying molecular mechanisms that contribute to impaired healing and scarring. Gene therapy delivers genes encoding growth factors, anti-inflammatory cytokines, or ECM components to enhance tissue repair. Preclinical studies in animal models have demonstrated that gene therapy can accelerate wound healing, improve tissue regeneration, and reduce scar formation.

Small interfering RNAs (siRNAs) can silence the expression of specific genes involved in inflammation, fibrosis, and impaired healing [55,56]. MicroRNAs (miRNAs) are endogenous non-coding RNAs that regulate gene expression and can be used to promote tissue regeneration. Messenger RNA (mRNA) therapy can deliver instructions for cells to produce therapeutic proteins (such as growth factors and ECM components). Preclinical studies have shown that RNA-based therapeutics can effectively modulate gene expression, promote wound healing, and reduce scarring in animal models [55]. Clinical trials are underway to evaluate RNA-based therapies for various wound healing applications.

Gene editing technologies, such as CRISPR-Cas9 [57], offer the possibility of making precise genomic modifications to promote scarless healing and tissue regeneration. This technology can be used to knock out genes that contribute to fibrosis and scarring (e.g., genes for TGF- β or collagens) or to insert genes that promote tissue regeneration (e.g., growth factor genes). Recent studies have demonstrated the potential of CRISPR-Cas9 to reduce scar formation and improve tissue regeneration in animal models of skin wounding. Researchers are exploring CRISPR-Cas9 to target specific cell types involved in wound healing, such as fibroblasts and keratinocytes. However, off-target effects and delivery efficiency remain key challenges. Further research is needed to optimize CRISPR-Cas9 delivery systems and evaluate the long-term safety and efficacy of gene editing for wound healing. Nonetheless, gene therapy and RNA-based therapeutics, including gene editing technologies, are rapidly advancing and hold great promise for improving wound healing and

promoting scarless tissue regeneration. As these technologies continue to evolve, they may lead to novel and effective treatments for a wide range of wound healing disorders.

Physical modalities can also be used to promote wound healing. For example: Low-Level Laser Therapy (LLLT) stimulates cell proliferation, angiogenesis, and collagen synthesis [58]. Negative Pressure Wound Therapy (NPWT) promotes blood flow, reduces edema, and stimulates granulation tissue formation [43]. Ultrasound therapy enhances cell proliferation and migration [59]. Electrical stimulation promotes cell migration and tissue repair [60]. Hyperbaric oxygen therapy involves breathing pure oxygen in a pressurized chamber, which can increase oxygen levels in tissues and promote healing in certain chronic wounds.

Proper wound cleansing and debridement are also critical. Gentle cleansing avoids damaging new tissue, and debridement (removal of non-viable tissue) can be autolytic (using the body's enzymes), enzymatic, sharp (surgical), or mechanical [27,61].

Artificial intelligence (AI) and machine learning (ML) are emerging tools with the potential to revolutionize wound care [62]. AI can analyze wound images, measure wound size, and assess healing progress. ML algorithms can predict healing outcomes and identify patients at risk for developing chronic wounds. AI can help tailor treatments to individual patients based on wound characteristics and predicted healing trajectories.

Potential side effects of treatments: The side effects of wound treatments vary depending on the specific treatment and the individual's condition. Some general side effects include local skin reactions (irritation such as redness, itching, burning, or stinging at the application site of topical treatments or dressings) [63], allergic reactions (rash, swelling, or increased irritation in response to certain dressing materials or topical agents), maceration (softening and breakdown of skin around the wound due to excessive moisture) [64], skin ulceration (in rare cases, some wound care products might contribute to skin breakdown), erythema (superficial reddening of the skin due to irritation or increased blood flow) [34], pain and discomfort (mild to moderate pain at the wound site, especially during dressing changes or with certain therapies), infection (despite preventive measures, wounds can still become infected; signs include increased pain, swelling, spreading redness, pus or discharge, foul odor, and fever) [34], delayed healing (some treatments, if misused or if complications arise, can inadvertently delay healing) [5], scarring (while often the goal is to minimize scarring, any wound can heal with a scar; certain treatments or complications like infection can lead to more prominent or abnormal scars such as keloids) [26], bleeding (which can occur during surgical debridement or if a dressing adheres too strongly to the wound bed) [44], and systemic effects (topical agents generally have low systemic absorption, but it's possible in some cases, especially with prolonged use or on large wound areas, potentially leading to systemic side effects).

Advances in topical pharmacology are of paramount importance in the treatment of skin wounds because topical formulations allow for the direct application of therapeutic agents to the wound site [37]. This localized delivery increases the drug concentration where it's needed most, maximizing efficacy while minimizing systemic absorption and potential side effects [37]. Nanoparticles, liposomes, microsponges, and penetration enhancers can overcome the skin's stratum corneum barrier to drug penetration [65,66], improving the amount of drug that reaches target cells in the wound.

Modern topical formulations can be designed to release drugs in a controlled manner over an extended period, maintaining therapeutic levels at the wound site, reducing the frequency of application, and improving patient compliance. By delivering the right drugs at the right concentration directly to the wound, advances in topical pharmacology can significantly accelerate healing – promoting cell proliferation, collagen synthesis, and angiogenesis (new blood vessel formation) [22] and reducing inflammation [16] and infection. Compared to oral or injectable medications, topical delivery generally results in lower systemic drug levels, thus reducing the risk of adverse effects on other organs and systems. This is particularly important for patients with comorbidities or those sensitive to systemic medications.

Advances in topical pharmacology also allow for the development of specialized formulations tailored to different types of wounds (e.g., acute vs. chronic, infected vs. sterile, burn wounds). These formulations can incorporate a variety of active ingredients such as antimicrobials, growth factors, anti-inflammatory agents, and analgesics to address the specific needs of each wound. Topical advances are often integrated with advanced wound dressings [40]; for instance, dressings can be impregnated with antimicrobial agents or growth factors for sustained release into the wound bed, creating a synergistic effect that promotes healing and prevents complications.

Ongoing research in topical pharmacology explores the possibility of creating personalized wound treatments based on an individual's specific wound characteristics and healing response. This could involve incorporating diagnostic tools into topical formulations to monitor healing progress and adjust drug delivery accordingly. In essence, advances in topical pharmacology are driving the development of more effective, safer, and patient-friendly treatments for skin wounds, ultimately leading to better healing outcomes and improved quality of life for patients.

Modern treatment of skin wounds utilizes a variety of pharmacological preparations to promote healing, prevent infection, manage pain, and reduce inflammation. These can be broadly categorized as follows:

➤ **Antimicrobial Agents:** While systemic antibiotics are used for severe infections, topical antibiotics like mupirocin and fusidic acid are used for localized skin infections [67]. However, their widespread use is sometimes discouraged due to concerns about antibiotic resistance. A range of antiseptics are available in various formulations (solutions, creams, ointments, and impregnated dressings). Silver-based products have broad-spectrum antimicrobial activity and are incorporated into many modern dressings (e.g., silver sulfadiazine, silver nanoparticles). They offer sustained release and reduce the risk of resistance compared to some antibiotics. Iodine-based products such as povidone-iodine and cadexomer iodine are effective against bacteria, fungi, viruses, and protozoa; cadexomer iodine can also help with debridement [68]. Chlorhexidine and polyhexamethylene biguanide (PHMB) [69]: these biguanides have broad antimicrobial activity and good tolerability; PHMB is increasingly used in wound care solutions and dressings. Hypochlorous acid (HOCl), found in some wound cleansers, has broad antimicrobial activity and is generally well-tolerated [70]. Medical honey (e.g., Manuka honey) possesses antimicrobial and anti-inflammatory properties and can promote wound healing [71].

➤ **Growth Factors:** Becaplermin (recombinant human PDGF) is approved for treating diabetic foot ulcers with adequate blood supply. Epidermal Growth Factor (EGF) is used in some countries for diabetic and corneal ulcers. Fibroblast Growth Factor (FGF): recombinant human basic FGF (trafermin) is used topically in some regions for ulcers and burns. Vascular Endothelial Growth Factor (VEGF), TGF- β , and Keratinocyte Growth Factor (KGF) are being researched for wound healing potential.

➤ **Debriding agents:** These help remove necrotic tissue, which can impede healing and harbor bacteria. Collagenase (an enzyme) specifically breaks down collagen in necrotic tissue; papain-urea combinations are also used. Hypertonic saline gels can draw fluid out and aid in slough removal.

➤ **Managing inflammation:** This is crucial for promoting healing and reducing pain. Topical corticosteroids [34] are effective anti-inflammatory agents, but their use on open wounds is limited and must be cautious due to potential side effects like delayed healing and increased infection risk. NSAIDs are mainly used systemically for pain; topical NSAIDs have limited roles in wound treatment. Natural anti-inflammatory agents (e.g., curcumin, chamomile, certain plant extracts) are being investigated for their topical anti-inflammatory and wound-healing properties.

➤ **Other agents:** Hyaluronic acid plays a role in tissue repair and hydration and is included in some wound care products. Vitamin E is a popular remedy, but current evidence doesn't strongly support its effectiveness in improving wound healing or reducing scarring (and it may cause irritation in some cases) [27]. Topical phenytoin may aid healing in various wound types and reduce

pain, possibly by increasing collagen deposition and promoting fibroblast proliferation. L-arginine [64], a nitric oxide precursor, can promote vasodilation and may have wound-healing properties.

At present, the pharmacological preparations with distinct mechanisms and clinical indications notable for their widespread use and increasing evidence of efficacy in skin wound and scar treatment are Dermatrix Ultra, Epicyn, Flosteron, and Contractubex.

Dermatrix Ultra is a silicone-based gel formulation containing polysiloxane (cyclopentasiloxane) and a Vitamin C ester (ascorbyl tetraisopalmitate). It is widely used for the prevention and management of hypertrophic and keloid scars [72]. Silicone forms a protective barrier, reducing water loss and normalizing collagen synthesis. The Vitamin C ester helps with skin lightening and provides some UV protection [73]. Dermatrix Ultra reduces the appearance of hypertrophic and keloid scars, softens, flattens, and lightens scars, and relieves itching and discomfort associated with scars. Silicone hydrates the stratum corneum, modulates fibroblast activity, and reduces collagen deposition. The added Vitamin C ester offers antioxidant benefits, reducing pigmentation and oxidative stress in healing tissues [73]. Recent clinical trials demonstrate that Dermatrix Ultra significantly improves scar height, color, and pliability compared to placebo and other commercial scar treatments. In a randomized, double-blind study, subjects using Dermatrix Ultra showed improved Vancouver Scar Scale scores and higher patient satisfaction over a 12-week period [74].

Epicyn is a hypochlorous acid-based hydrogel, a potent antimicrobial and anti-inflammatory agent that reduces pro-inflammatory cytokines (e.g., IL-6, TNF- α) [75]. It also contains silicone gel, which forms a protective film to prevent excessive drying. Hypochlorous acid (HOCl) has broad-spectrum antimicrobial properties [76], reduces inflammation [75], and can break down biofilms [77]. HOCl is naturally produced by neutrophils and is a key component of innate immunity. Epicyn improves wound healing and reduces scarring: it softens and flattens scars, reduces redness, itching, and pain, and lowers the risk of wound infection. The stabilized HOCl in Epicyn offers strong antimicrobial activity without cytotoxicity [76]. Epicyn is particularly useful in wounds with high bioburden, including diabetic foot ulcers, pressure sores, and venous leg ulcers. Clinical studies suggest that HOCl enhances healing rates and reduces infection-related complications. A 2021 randomized controlled trial showed significantly faster epithelialization in patients treated with Epicyn versus standard saline dressings [78].

Flosteron contains betamethasone dipropionate and betamethasone sodium phosphate, a potent corticosteroid combination that suppresses inflammation and modulates immune responses [32]. It is mainly used in conditions involving excessive fibroblast activity and persistent inflammation, such as hypertrophic scars and keloids [26]. Although effective in early scar management, prolonged corticosteroid use can cause dermal atrophy, telangiectasia, and delayed wound healing [32]. Recent studies underscore the importance of judicious application and monitoring when using intralesional corticosteroids. Flosteron inhibits inflammatory mediators (e.g., IL-1 β , prostaglandins), downregulates fibroblast proliferation, reduces edema, and decreases pain. It is not primarily a scar **treatment** but rather addresses the inflammatory component of wound healing; often, it is used in combination with other scar therapies.

Contractubex is a triple-component gel containing 10% aqueous onion extract (*Allium cepa*), 50 IU heparin per gram, and 1% allantoin. This combination is designed to reduce inflammation, enhance tissue remodeling, and soften scar tissue. The clinical effectiveness of Contractubex has been variable. While some studies support its use in reducing scar thickness and discomfort, others report only marginal improvements. A meta-analysis in 2020 indicated modest but statistically significant benefits in scar texture and pigmentation with Contractubex [79]. Onion extract has anti-inflammatory and antimicrobial effects and may inhibit collagen production. Heparin has anticoagulant properties and also influences collagen remodeling. Allantoin promotes keratinocyte proliferation and hydration. Contractubex aims to promote wound healing, reduce excessive scar tissue formation, alleviate redness, itching, and tension, and improve scar elasticity.

Comparing Dermatrix Ultra, Epicyn, Flosteron, and Contractubex requires considering their different formulations, mechanisms of action, routes of administration, and the types of scars they are typically used to treat.

➤ **Silicone-based gels (Dermatrix Ultra and Epicyn):** Primarily used for the prevention and management of linear hypertrophic scars and keloids. Their main mechanism is creating an occlusive barrier to regulate hydration and oxygen transfer. Epicyn's addition of HOCl offers potential antimicrobial and anti-inflammatory benefits.

➤ **Injectable corticosteroids (Flosteron):** Reserved for established hypertrophic and keloid scars due to the need for direct intralesional administration and potential side effects. They are potent anti-inflammatory agents that can effectively reduce scar volume and symptoms, but they do not play a significant role in the initial wound healing process like topical treatments do.

➤ **Combination topical gel (Contractubex):** Aims to address scar formation through a combination of onion extract, heparin, and allantoin. While some studies suggest modest benefits, the evidence is less consistent compared to silicone gels, and recent comparative data indicate potentially lower efficacy in certain aspects of wound healing and scar modulation.

See Table-1.

Table 1. Comparative Analysis of Scar Treatment Products: Composition, Mechanism of Action, Administration Route, and Clinical Efficacy.

Feature	Dermatrix Ultra	Epicyn	Flosteron	Contractubex
Primary Base	Silicone gel	Silicone gel	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

N. Kuridze and co-authors conducted studies [80] showed that, in the wound healing process, Dermatrix Ultra (containing polysilicones, cyclic and polymeric siloxane, and Vitamin C Ester) demonstrated the most effective results across all scar assessment parameters (vascularity, pigmentation, elasticity, height). The treatment modulated inflammatory cytokine activity, improved

wound hydration, and accelerated effective and rapid skin healing. Epicyn, containing silicon, hydrochloridum acid, and Na hydrochloride exhibited anti-inflammatory and scar-healing properties, effectively reducing scar vascularity and height, supporting timely pigmentation restoration and elasticity improvement, though at a slower rate compared to Dermatrix Ultra treatment. Flosteron (Betamethasone), as a corticosteroid, acted effectively against inflammation, improving scar elasticity and dynamically reducing scar vascularity. However, due to its immunosuppressive effect, the transition to the tissue remodeling phase and overall healing process was comparatively slower. Treatment with Contractubex (onion extract, heparin, allantoin) had the least effect on wound healing. It took longer to normalize inflammatory cytokine levels, prolonging the inflammatory reaction phase and delaying scar formation and tissue recovery [81].

The results highlight the crucial role of inflammatory cytokines, their modulation, and the selection of therapeutic agents in ensuring rapid and effective wound healing [82].

Conclusion

Chronic wounds remain a significant clinical challenge, and new strategies are needed to promote healing in these complex conditions. Significant advances have been made in our understanding of the complex processes of wound healing, tissue repair, and regeneration in recent years. Novel therapeutic strategies, including advanced biomaterials, cell-based therapies, gene therapies, and physical modalities, hold great promise for improving healing outcomes and promoting tissue regeneration. However, challenges remain, particularly in the treatment of chronic wounds and in achieving scarless healing. Future research should focus on developing novel therapies that target the underlying causes of chronic wounds (persistent inflammation, infection, impaired angiogenesis), on personalized medicine approaches (tailoring treatments to the specific characteristics of each chronic wound and each patient), and on translating basic science discoveries into effective clinical therapies.

Dermatrix Ultra, Epicyn, Flosteron, and Contractubex each contribute uniquely to wound healing strategies. Evidence supports their selective use based on wound type, patient profile, and therapeutic goals. Continued research and head-to-head clinical trials are essential for optimizing treatment protocols and improving patient outcomes in regenerative dermatology.

Future innovations in wound healing are moving toward combination therapies, nanotechnology-based delivery systems, and personalized medicine. Incorporating growth factors, stem cell-derived exosomes, and biosynthetic dressings into topical formulations may revolutionize scar prevention and tissue regeneration.

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