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SUBJECT REVIEW

# Skin Wound Classification and Therapeutic Techniques for Skin Repair

## Clasificación de heridas cutáneas y técnicas terapéuticas para la reparación de la piel

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**Abstract**
Skin wounds are a global public health concern, causing around three hundred thousand lives yearly and disabling millions more. More than 95% of these injuries occur in emerging countries where access to health services is limited, and resources are scarce. Variables such as depth, cause, infection, and/or chronicity determine the outcome of skin wounds and whether they hinder the body´s natural healing process. In order to treat deep, chronic and/or complicated skin wounds, various treatments have been developed. Widely used traditional techniques such as asepsis, debridement, and surgery are aimed to prevent further damage and aid scarring but have many disadvantages, including low efficiency results, high healing time rates, and elevated costs. Alternative and novel strategies, such as bioactive dressings and regenerative medicine, are intended to achieve functional and aesthetic tissue recovery while minimizing the rejection risk in other techniques like skin flaps and grafts. The present review outlines the key skin characteristics, a general description of the more common types of wounds and their incidence, and tissue engineered strategies commonly used for skin tissue regeneration.

**Keywords:** Ski; wounds; biomaterial; therapeutic techniques; tissue repair.

**Resumen**
Las heridas de piel son un problema de salud pública mundial, las cuales cobran alrededor de trescientas mil vidas cada año y generan discapacidades a millones más. Más del 95% de estas lesiones ocurren en países en desarrollo, donde el acceso a los servicios de salud es complicado y los recursos son escasos. Variables como la profundidad, la causa, el nivel de infección y/o la cronicidad determinan el resultado de las heridas en la piel y si estas impedirán el proceso de curación natural del cuerpo. Para el tratamiento de heridas cutáneas profundas, crónicas y/o complicadas se han desarrollado diferentes tratamientos. Las técnicas tradicionales ampliamente utilizadas como la asepsia, el desbridamiento y la cirugía, tienen como objetivo prevenir daños mayores y ayudar a la cicatrización, pero tienen muchas desventajas, entre las que se encuentran resultados de baja eficiencia, altas tasas de tiempo de curación y costos elevados. Estrategias alternativas y novedosas como los apósitos bioactivos y la medicina regenerativa pretenden alcanzar una recuperación funcional y estética del tejido, minimizando el riesgo de rechazo presente en otras técnicas como colgajos e injertos de piel. La presente revisión muestra las principales características de la piel, una descripción general de los tipos de heridas más comunes y su incidencia, así como las estrategias de ingeniería tisular que se utilizan para la regeneración del tejido cutáneo.

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**Palabras claves:** Piel; heridas; biomaterial; técnicas terapéuticas; reparación de tejidos.

## Introduction

Skin injuries represent a global health concern, causing more than 300,000 deaths and millions of disabilities yearly [1, 2]. Superficial and partial thickness injuries have the ability to re-epithelialize the damaged zone within a few weeks (two or three depending on the injury depth) without adverse consequences. Deep partial thickness and full-thickness injuries, on the other hand, require grafting treatments to prevent scar tissue formation [3]. Treatment options for deep partial thickness, and full-thickness skin injuries are limited and commonly include autologous skin grafting or alternative permanent skin substitute procedures [4]. These procedures are associated with limitations, including donor site morbidity (in autologous grafts) and lack of immediate availability, resulting in long term hospitalization, increased risk of infections, and costs, among other issues [5, 6].

Independent of the depth of the injury, the immediate clinical goal is to reduce the pain and fluids loss, as well as to prevent bacterial infections, while the wound heals [7, 8]. Skin dressings are materials used to cover wounds, protecting them from the external environment [5]. The development of skin wound dressings has long evolved from passive materials that maintained the wound bed dry and controlled microbial agents to new materials promoting and/or accelerating wound healing [3].

The present review summarizes the overall classification of skin wounds and provides a general description of the most common therapeutic approaches used for deep skin injuries. Furthermore, current directions of research in skin repair applications are discussed.

## Methods

Databases such as PubMed, SciELO, EBSCO, BMJ Journals, Nature and Science Direct, as well as official pages of organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), were used for the to conduct the search process. The search was restricted to literature in English and Spanish,  was not restricted by the year of publication. The search terms included: skin structure, skin functions, skin wounds, skin wound classification, skin wound incidence, skin repair, and regenerative medicine approaches for skin repair. The process allowed for a conceptual framework associated with the classification of skin wounds and included some of the most relevant therapeutic approaches being used for the reparation of skin injuries.

## 1. Structure and functions of the skin

The skin is a metabolically active organ, maintaining homeostasis through regulating body fluids and body temperature and protecting the body from external chemical and physical agents [9]. The skin comprises three tissues (Table 1): epidermis, dermis, and hypodermis (subcutaneous tissue) [3].

**Table 1.** Layers of the skin.

| | Definition/Function | Layer | Position | Composition | Origin | References |
|---|---|---|---|---|---|---|
| **Epidermis** | Outermost layer.<br>Highly regenerative tissue.<br>Responsible of skin renewal approximately every 28 days. | Stratum basale | Innermost | Keratinocytes | Stem cells that differentiate in this layer | (3, 10–12) |
| | | | | Melanocytes | Neural crest cells, differentiated by melanoblasts | (11, 13, 14) |
| | | | | Langerhans cells | Dendritic cells (leukocytes) derived from the bone | (3, 9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Protection and semi-permeability that prevents entry of harmful elements and loss of body fluids. | | | | marrow | |
| | | | | Merkel cells | Unclear, either dermis stem cells or neural crest cells | (9, 15–17) |
| | | Stratum spinosum | Above basale | Keratin filaments | Cytoskeleton | (3, 18) |
| | | | | Desmosomes | Cytoplasm | (3, 19) |
| | | | | Langerhans cells | Embryonic fetal liver monocytes and yolk sac derived macrophages | (20, 21) |
| | | Stratum granulosum | Above spinosum | Flattened epithelial cells with keratohyalin granules | Ectoderm or endoderm | (22, 23) |
| | | Stratum lucid | Above granulosum | Dead and flattened keratinocytes | Stem cells that differentiate in this layer | (3, 11, 12) |
| | | Stratum corneum | Superficial | Corneocytes | From keratinocytes that are completely differentiated and no longer have a nucleus or organelles | (11, 22) |
| **Dermis** | Vascularization and innervation of the skin. Possess glands, hair follicles and nerves. Provides nutrition and sensation. | Stratum reticulare | Innermost | Dense connective tissue. Fibroblasts, macrophages, mast cells, adipocytes, Schwann cells and stem cells. | Mesenchymal | (3, 24–32) |
| | | Stratum papillare | Outermost | Loose connective tissue. Highly vascular. Collagen (type I and III) and elastic fibers (elastin, fibrillin, elaunin, oxytalan). | | |
| **Hypodermis** | Secretion and modulation of hormones and cytokines. Thermal insulation and depth cushioning. | | | Adipocytes, blood vessels, bursa, connective tissue, fibroblasts, hair follicles, lymphatic vessels, macrophages, nerves, sweat glands | Mesoderm. | (3, 33–36) |

## 2. Skin wound clasification

Skin wounds affect the integrity of the skin tissues, exposing internal tissues to the external environment [34, 37, 38]. Wounds are caused by exposure to several factors, such as extreme temperatures, physical pressure, chemical exposure, punctures by sharp objects, abrasion, laceration, and more (Table 2) [38, 39]. The damage, severity, and complications associated with injuries can vary, allowing for many types of wounds to have different characteristics which alter reparative and regenerative capabilities, create challenges in clinical care, and present various levels of risk for patients [40].

## 2.1. Wound types by environment exposure

In open wounds, the skin's external integrity is damaged, leaving the underlying tissue exposed to the environment [40], whereas in closed wounds, damage is present, but the skin is intact [40].

## 2.2. Wound types according to healing time: acute and chronic

Acute wounds undergo an expected healing period of 8 to 12 weeks, closing and repairing the affected area and resulting in fully functional tissue with the correct cellular organization [37, 38, 41]. They progress through the normal healing stages until the functional tissue is renewed [42].

Chronic wounds are defined by the presence of an injury that exceeds the regularly expected reparation period [43], failing to heal or respond to treatments, and taking months or years to completely close [37, 44]. Undiscovered underlying pathologies, and chronic conditions such as diabetes and vascular diseases, are among the common causes of repetitive cycles of tissue damage [44–46].

Variations in normal wound biology characterize chronic wounds, changing their nature and the efficacy of repair mediators and cellular communication [42]. Abnormalities include low growth factor density, inadequate mitosis, and cell motility induction, excessive or insufficient production of an agent, and more [45], reducing the effectiveness of proliferation, cell migration, and response to biochemical cues [47].

The main contributor to chronic wound development is a prolonged inflammation caused by the sustained destruction of ECM elements and the overproduction of proinflammatory cytokines, favoring an unorganized collagen deposition that results in scarring and tissue malformations [47].

## 2.3. Wound types by depth

Depending on the type of damage, wounds can disrupt the epidermis, dermis, and/or hypodermis to different degrees, allowing for wound assessment criteria based on depth [48, 49]. Superficial wounds affect only the epidermis, partial thickness wounds the affect epidermis and dermis, full thickness wounds represent damage on all three tissues (epidermis, dermis, and hypodermis), exposing muscle and bone tissues.

**Table 2.** Wound classification by source of damage.

| Wound type | Source Description | Types | References |
|---|---|---|---|
| Mechanical | External forces applied to the skin damaging its integrity. These types of wounds can be caused by surgical procedures, accidents with sharp objects, falls, sudden movements, constant force application, etc. | **Pressure:** Force is applied to the skin for prolonged periods of time.<br>**Friction:** Resistance to sliding motion between skin and another surface, causing epidermal loss.<br>**Shearing:** Combination of pressure and friction forces between two surfaces or tissue layers.<br>**Incision:** Straight-lined regular wounds caused by sharp objects (knives, glass and surgical devices).<br>**Laceration:** Deep, irregular wounds resulting in skin tears caused by mishandling heavy machinery and sharp objects.<br>**Puncture:** Hole-shaped wounds caused by sharp, pointy agents (nails, gunshots, needles).<br>**Avulsion:** Partial or complete skin and tissue tears caused by heavy accidents. Associated to loss of tissue and functionality.<br>**Bites:** Injuries stemming from applying force to the skin with teeth. They can be irregularly shaped and highly prone to infections depending on the source. Can be caused by animals or other humans. | (44, 50–52) |

| | | | |
|---|---|---|---|
| Burns | Exposure to high temperature elements and abrasive environments that result in skin injury. These types of wounds can be caused by sun overexposure, chemical agents, radiation, electrical currents, hot liquids/objects, etc. | **First degree:** Epidermis is affected. Area is red, dry, and painful. No presence of blisters and long-term damage is rare.<br>**Second degree:** Affection up to the superficial dermis. Area is red and painful with blisters. Inflammation is frequent.<br>**Third degree:** Destruction of epidermis and dermis, frequently damaging the subcutaneous tissue. Area is white or black/charred.<br>**Fourth degree:** Affects all layers of skin and possibly underlying tissue (muscle, organs, bone). Nerves are destroyed. | (53, 54) |
| Pressure injuries | Open sores in the skin or mucous membranes that fail to heal: vascular (arterial, venous), diabetic foot, pressure, mouth and peptic ulcers are among the most frequent. These types of wounds can be caused by recurring injuries, blood supply irregularities, poor wound care/healing, immune reactions and/or preexisting conditions such as diabetes, neuropathy, cardiovascular diseases, etc. | **Stage I:** Integrity of the skin is not impaired. Presence of white coloring around the affected area, insufficient blood flow.<br>**Stage II:** Open superficial damage to the skin affecting the epidermis. Yellow coloring surrounding the wound, presence of initial dead tissue.<br>**Stage III:** Full-thickness wounds affecting the epidermis, dermis, and subcutaneous tissue. No presence of exposed underlying tissue or bone.<br>**Stage IV:** Full thickness wound with underlying tissue, bone and/or tendon exposure. Necrotic tissue surrounding and within the wound. | (44, 55–57) |

# 3. Skin wound incidence

Skin injuries are a documented public health concern (58) and burns, pressure injuries, open wounds, among others, represent a wide and complex range of skin injuries that can be difficult to treat, especially in countries like Colombia, where not all resources are available (59). Many treatment options utilized in developed countries have elevated costs and can be difficult to import (60). By gaining a better understanding of the types of wounds more prevalent in Colombia, along with identifying their incidence, prognosis, and treatment, more informed decisions can be made for managing and solving this public health issue (61).

However, data about this context is scarce and decentralized in developing countries (62, 63); a summary of Colombian epidemiology data for skin injuries is presented below.

## 3.1. Burn injuries

Burn injuries have a high mortality rate, with almost 100% of patients dying when they present a total body surface burn of over 40% (60). At least 1% of the global population will suffer a severe burn during their lifetime, with infections being the number one cause of mortality among burned patients (64, 65).

Colombia's legislation considers extensive burns as catastrophic injuries due to their complexity and associated costs (5261 resolution from 1994, art. 117) (63). The country's mortality rate from burns is 1.28 per 100,000 inhabitants, with males of productive ages being more affected (66), and electricity burns and scalding as the leading causes (67). According to Navarrete and Rodriguez (2016), about half of the people who died from burn injuries in Colombia between 2000 and 2009 did not receive medical treatment, and 38.4% of all deaths happened in medical centers (66). They also stated that both percentages of deaths and mortality rate were higher in rural areas compared to urban ones (66).

## 3.2. Pressure injuries

Pressure injuries are caused by constant pressure on the skin, which causes tissue necrosis by ischemia (68). These injuries are among the more expensive pathologies in the world, third behind cancer and cardiovascular disease (69). The incidence of pressure injuries varies depending on the clinical setting and the reason behind the patient's immobility. For example, up to 85% of patients with a spinal cord injury develop this type of injury, while patients with diabetes who are prone to this type of injury have an incidence of 4 to 10% worldwide for diabetic foot ulcers [69–71]. Meanwhile, the incidence of venous leg ulcers, another common pressure injury, is 1 to 3% worldwide [72]. Age is also an important incidence factor, with about 66% of these sores occurring in people seventy or older [73].

The mortality rate for patients with pressure injuries is high, ranging from of 22% to 69% [69, 74]. Foot complications caused by diabetes, including neuro-ischemic ulcers, are the main reason behind diabetic patients' morbidity and amputations [75]. Unfortunately, these types of wounds do not respond well to traditional treatments (debridement, dressings, and antibiotics) or more advanced ones like skin grafts, with only half of the cases as successful recoveries [76]. Untreated or unsuccessfully treated pressure injuries caused by diabetes, for example, are the main cause of amputations not associated with accidents [71]. As with burn injuries, pressure injuries' epidemiology data is highly decentralized and scarce in developing countries, primarily given the lack of unified medical data systems[62, 77].

The Latin American Diabetes Association (LADA) classifies pressure injuries as hurting public health and patient´s economy [63, 77]. In Colombia, pressure injuries are classified as adverse events that must be considered during health care [78]. These types of sores have increased effects on hospital stays, the workload of the medical team, and the medical supplies needed, explaining why they are among the most expensive disorders in the world [69].

Poverty also influences the incidence and prevalence of these wounds [60]. Factors like poor nutrition and resource constraints are present in developing countries, causing pressure injuries to be a more significant public health issue there than in developed countries.

### 3.3. Incisional wounds

Incisional wounds are of greatest concern during patients´ recovery from surgeries since they are highly susceptible to infections, increasing morbidity and mortality [79]. It has been reported that about a third of patients that undergo a surgical procedure will develop an infection [80]. According to the Centers for Disease Control and Prevention (CDC), 20% of all healthcare related infections are due to surgical site infections, with an increase of 3% on these incidents in 2021 compared to the previous year [80–83]. Countries that are stratified into low-income groups, according to the UN's Human Development Index (HDI), showed a 23.2% incidence of post-surgical infection, compared to a 9.4% and a 14% incidence in high- and middle-income countries respectively [84]. New treatments are needed in low-income countries given their ability to aim in post-surgical wound healing and, therefore, prevent and treat infections.

According to a study completed at the Hospital Mario Correa Rengifo in Cali, Colombia, the most common procedures that were followed by infection were open cholecystectomy, appendectomy, and bowel raffia [85]. Carvajal and Londoño (2012) observed superficial post-surgical infections in 55.3% of patients and deep post-surgical infections in 44.7% of patients in a study carried out in a third level institution in the city of Armenia, Colombia between 2008 and 2009 [86].

## 4. Regenerative medicine-mediated approaches for full- thickness wound healing

It is critical to note the distinction between repair and regeneration. Repair is the process by which the body replaces a damaged part with a connective tissue called a scar. This process intends to recover part of the structure and functionality of the damaged tissue; however, it never fully achieves this [87, 88]. Regeneration, on the other hand, is the process by which damaged tissue is completely replaced by new tissue, fully recovering its structure, appearance, and functionality. In humans, this process is only observed during the fetal state, from the moment of birth the body is only capable of repairing damaged tissue, which causes scars, disabilities, and loss of function, among others (87, 88).

Regenerative medicine is a wide and relatively modern field focusing on the importance of functional tissue regeneration. This type of medicine aims to help the body achieve healing that is similar to the regeneration process that humans lose at birth (88), a more efficient one and with better results regarding functionality and appearance (89). The bioactive factors promoting tissue regeneration (cell mediators, stem cells and biologic molecules) are used alone or combined with delivery platforms (i.e., dressings or scaffolds) (90).

## 4.1. Biomaterials

Natural or synthetically derived biomaterials can provide the tridimensional structure that supports cellular components, restoring organs, tissue, or body functions. A general classification of biomaterials defines them as polymers, ceramics, and metallic materials (91). Due to mechanical and biochemical properties, polymers are amongst the most used biomaterials for skin regenerative medicine approaches. Table 3 summarizes the polymers used in skin wound healing.

**Table 3.** Polymers sources in wound healing techniques.

| Naturally derived (animal, vegetal, bacterial) | Advantages | References |
|---|---|---|
| ECM-derived components<br>Glycosaminoglycans<br>Chitosan<br>Collagen<br>Elastin<br>Alginate<br>Fibrin<br>Hyaluronic acid<br>Silk<br>Laminin<br>Dextran<br>Cellulose | Availability<br>Biodegradability<br>Cell adhesive proteins<br>Signaling pathways<br>Immune response | (92–110) |
| **Synthetic** | **Advantages** | |
| Polyesters<br>Polyvinylpyrrolidone (PVP)<br>Polyvinyl alcohol (PVA)<br>Polyurethane (PU)<br>Polyethylene glycol (PEG)<br>Polydimethylsiloxane (PDMS)<br>Poly 2-hydroxyethyl methacrylate (pHEMA) | Mechanical properties<br>Thermal stability<br>Plasticity<br>Bioinert | |

### 4.1.1. Bandages and dressings

Passive bandages or casts only immobilize and protect the injured area from the exterior. Advanced dressings could be classified based on 1) the nature of the material used (natural or synthetic), 2) permeability (permeable, semipermeable, or occlusive), 3) therapeutic effect (haemostasia, infection, debriding, exudate, or granulation management) or, 4) wound interaction (passive, interactive and bioactive) (94).

Bioactive dressings are of interest in regenerative medicine approaches, characterized by their ability to deliver molecules or components promoting wound healing and minimizing infections, scar formation, chronic inflammation, among other issues (111, 112). Bioactive dressings can act as delivery platforms for bioactive molecules or can be composed of them (113).

Additionally, they're intended to promote debridement and cleaning, prevent or control associated infections, support re-epithelialization, and balance moisture within the wounded area. Moreover, they can ensure proper absorption of exudate, gas exchange, temperature control, and safety removal (98).

### 4.1.2. Scaffolds

Depending on the origin of the components, scaffolds can be classified as natural or synthetic (95, 97). Scaffolds as functional bioactive cell carriers are a promising tool for effective wound regeneration and repair (114). Every tissue has a unique environment, which affirms the importance of electing appropriate biomaterials. Scaffolds should present some characteristics (e.g., porosity, biocompatibility, non-toxicity, adjustable rate of degradability, and appropriate mechanical strength, among others) to bring a proper function (95).

## 4.2. Bioactive factors

### 4.2.1 Pharmacotherapy

Pharmacotherapeutic techniques use bioactive molecules to treat or modulate the events related to wound healing (hemostasis, inflammation, proliferation, and remodeling) while aiding in reducing complications like pain, exudate, exacerbated granulation tissue, and dryness (115). A broad drug spectrum is available for each step of a normal or abnormal healing process, with either topic or systemic presentations (116).

There are several traditional pharmacotherapies with different effects, for instance, antiseptics (e.g., iodine and chlorohexidine), antimicrobials (e.g., sulfadiazine and nitrofurazone), repellants, anti- inflammatory (e.g., corticoids and non-steroidal), hemostats (e.g., tranexamic acid and etamsylate), granulation tissue inhibitors or stimulators, among others (116). The decision to use one or a combination of some depends mainly on the primary cause of the wound, and on its stage of healing (117, 118).

Pharmacotherapies of natural origin for wound healing are widely used, mainly derived from plants, oligo elements, or microorganisms (118, 119). For instance, honey and aloe vera are commonly used because of their availability and effectiveness (115). Honey acts as a hyperosmolar antimicrobial, acting primarily on the debridement and inflammation stages of healing (120). Aloe vera extract has many active compounds, like salicylic acid with antibacterial and anti-inflammatory properties, as well as acemannan, a mucopolysaccharide that enhances fibroblast proliferation, epithelialization, and angiogenesis (118, 120). Uses of oligo elements include silver ions, which are used as antimicrobial dressings, and copper and zinc sulfates, which serve as astringents and cicatrizes in topic preparations (121).

Variables such as dosage, frequency of administration, pharmacokinetics, adverse effects of systemic drugs, and variability among immune systems, are of considerable value; therefore, current investigations are aimed towards developing improved drug delivery systems, some of them based on regenerative medicine and nanotechnology (122, 123).

### 4.2.2 Cell mediators

Platelet-derived products are cell mediators present in a plasma fraction of blood. Platelets comprise two types of cytoplasmic granules (dense and alpha granules) (124). The alpha granules are the main source of bioactive factors like growth factors, cytokines, and mitogens, which are important for intercellular communication, metabolism, angiogenesis, proliferation, and differentiation (125).

Modifications in processing generate a variation of platelet-derived products from the platelet concentrate (PC), referred to as platelet-rich plasma (PRP), platelet-poor plasma (PPP), fibrin glue (FG), and platelet-rich fibrin (PRF) (126). Activation of platelets in the PC, before their use, creates a scaffold-like membrane named platelet gel and an acellular platelet lysate (127). There is limited consensus on variables for clinical applications, such as the total number of platelets, methods of activation, preparation, and presence or absence of white blood cells, among others, that make their use inconsistent and highly variable among research groups [128]. Therefore, standardized methods for platelet-derived products are still required.

In human dermatology, PRP treatment for wound healing is used for the treatment of chronic ulcers (diabetic foot, venous, pressure, leprosy, and other ulcers of multifactorial etiologies) and other acute traumatic wounds [129]. In veterinary medicine, treatments with platelet-derived products are typically used in musculoskeletal conditions, wound defects, and articular lesions, mainly in equine, canine, and feline patients [126]. Typically, all mentioned species, including humans, are treated with PRP or derived products for skin wounds, corneal ulcers, maxillofacial/oral surgeries, tendinopathies, articular injuries, and musculoskeletal problems [128].

### 4.3. Complementary therapies

Complementary therapies are wide ancestral techniques that include Western and Eastern methodologies such as physiotherapy, homeopathy, traditional Chinese medicine, and bioenergetics, among others [130]. Many of these therapies, considered as placebo in Western medicine, have gained allopathic support, due to the activation of chemical (i.e., hormones), neural (i.e., neuropeptides and neurotransmitters), and immune (i.e., cytokines) pathways from tissue manipulation (i.e., acupuncture and electric waves) and from microenvironment changes in the extracellular matrix (i.e., homotoxicology, phytotherapy, and moxibustion) [131–134].

The western physiologic bases of these strategies were recognized largely thanks to extracellular matrix research [131, 135, 136]. The connective tissue is mechanically functional because of an integrated tension of the cells called bio tensegrity, which is possible thanks to different extracellular matrix components, especially, integrins [135, 136]. Furthermore, a cell bio tensegrity also exists intracellularly [137]. The bio tensegrity of the ECM and the cytoskeleton structure drive a dynamic process of signals transduction, where the mechanical energy is converted in chemical or electrical cues (known as mechanotransduction) and have the capacity to alter gene expression [15, 138–141]. ECM mechanical forces elicit the correct interstitial fluids flow, which releases molecules like growth factors, hormones, cytokines, proteins, and immune cells (mastocytes, macrophages, granulocytes and lymphocytes). This creates a constant feedback regulatory state, also called dynamic reciprocity [140].

Tissue manipulation with physical techniques (thermotherapy, and mesotherapy, among others) has enormous effects on perfusion, fluids drainage and cytokines release. For example, there are reports of a mesotherapy treatment type, called connective tissue manipulation (CTM), used for wound healing [142]. Among physiotherapy and mechanotherapy techniques, ultrasound waves, extracorporeal shock wave therapy (ESWT) and laser therapy are found [143]. These techniques are mainly used as complementary treatments in the regeneration of soft tissue injuries (mostly tendons, nerves, and ligaments) and orthopedic trauma rehabilitation. However, their use in integumentary system injuries is in progress [144].

Other therapies that use physical techniques are negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy. In particular, NPWT aims to remove wound exudate, decrease interstitial edema, draw wound edges together, promote blood supply to the wound and, by applying mechanical strain, stimulate cells involved with modulating the inflammatory and proliferative response to injury [145].

## 5. Future trends

Despite the advances in skin injury treatments, important challenges still need to be addressed in injury care, particularly those related to high extension and full-thickness lesions[146]. Composite materials are the most suitable option for obtaining combined properties and providing better outcomes [123, 147, 148] and there is no superior performance of synthetic materials over biological materials or vice versa. The properties of each type of material (naturally derived, biological, or synthetic) need to be maximized to obtain the greatest performance from each one.

Currently, there is research in wound healing applications is scattered, but generally focuses on generating an active environment, where cellular debris and necrotic tissues are drained upon functional reconstruction of the tissue is triggered. Studies with biological materials are being conducted to improve decellularization methods, under quality controls and defined criteria, to minimize the presence of unfavorable immunogenic molecules and to understand the immune host response elicited by the materials under different processing methods [(149)]. On the other hand, investigations with synthetic materials are concentrated in the design of new polymer materials with the required characteristics, especially biocompatibility, mechanical strength, and biodegradability.

Finally, the generation of composites simulating bi-layered structures is gaining attention in the field. With controlled biodegradation rates, bi-layered dressings can facilitate the epithelialization and dermal maturation needed for constructive remodeling. These complex structures are being loaded with various growth factors to improve the functionality of the burn dressings and to promote shorter healing time for wounds [(150)].

# Conclusions

Skin wounds are a complex concern that impact the health, quality of life, physical capacity, appearance, and livelihood of millions of people every year. Proper assessment and care of skin wounds is crucial to guarantee a patient's recovery; however, multiple factors such as preexisting conditions, extension, and infection can alter and greatly delay the skin's repair process. Currently, there are a variety of treatment options being developed to improve wound care, focusing on personalized options for each specific case. Particularly, the most recent personalized therapies are tackling critical challenges, such as availability, biocompatibility, and cost efficiency. Additionally, therapies consider methods of improving functional recovery to reduce disabilities associated with skin wounds and improve the appearance of the repaired tissues.

### Contribution of this manuscript

This article contributes to the current knowledge of the repair of tissues such as the skin, by clearly and concisely outlining the different types of wounds that can occur in the skin (mainly chronic and/or complicated). Additionally, it highlights the epidemiology and emphasizes the Colombian context. Finally, a precise summary is included and outlines various therapeutic techniques, with a focus on regenerative medicine and techniques being currently developed and implemented, in order to achieve more effective, rapid, and efficient skin healing in the presence of wounds.

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### Conflict of interest

No potential conflict of interest relevant to this research paper was reported from any of the authors.

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