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The role of Latin America medicinal plants in wound healing

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Wound healing represents a global public health problem when it is not treated correctly, which can cause complications for the patient, such as functional loss of an organ, amputation, and even death. At a biological level, wound healing involves a complex mechanism in which the immune system and cellular biochemical cascades intervene in a coordinated manner, whose development occurs in stages such as inflammation, proliferation, and remodeling. Therefore, therapies have been developed to accelerate wound healing and have proven effective. However, factors such as diabetes mellitus limit the healing process because it causes alterations in microvascular dysfunction, as well as in the inflammatory response and greater oxidative stress. This is reflected in an abnormal healing process; therefore, the search for healing compounds has become an area of interest. In this regard, medicinal plants have been used for centuries to treat wounds in different cultures in the world. Hence, this review documents the main plant species used in Latin America due to its great biodiversity and numerous species that are potentially important for the development of new active healing compounds. In this review, 62 plant families with wound healing studies were found, highlighting Fabaceae, Asteraceae and Euphorbiaceae family. Additionally, 32 natural compounds with diverse structural nature were found, whose effects have been evaluated in *in vivo* and *in vitro* models, which are essential for studying the pathogenesis of the tissue repair mechanism, detecting new biomarkers, and evaluate new treatments. Currently, several models are used to study the wound healing process, including *in silico*, *in vitro,* and *in vivo* models. On the other hand, there is no appropriate model to determine the wound healing effect, and, in many cases, they are combined to provide sufficient scientific evidence. Therefore, this review demonstrates that Latin America is a potential region for research into sources of healing molecules. Nevertheless, other species are still being studied whose scientific findings allow generating viable alternatives for the solution of health problems associated with wound healing.

KEYWORDS

wound healing, medicinal plants, biological assays, natural products, biodiversity

Introduction

Wound healing is a natural repair mechanism that aims to restore the affected tissue quickly (Yang et al., 2021). Although literature reports research associated with biological, immune, and biochemical events, they all converge in that healing is a process that occurs in specific stages where perfectly coordinated cells participate. In addition, it has been demonstrated that factors can compromise healing to the extent of making it impossible to recover the function of the affected organ (Järbrink et al., 2017). On the other hand, demonstrating the efficacy of wound-healing therapies is a complex challenge because the available models that demonstrate wound-healing activity allow exploring wound healing in stages, and it is necessary to use several models to determine the level of the wound-healing effect (Singh et al., 2017). Modern medicine applies therapies that promote healing, all of which have a specific basis. On the other hand, there are drugs whose active ingredients are synthetic or natural molecules, and others are still under research and development because there is no special treatment that can resolve all wounds as a general way (Zindle et al., 2021).

Natural molecules are extracted from biological sources, and plants are the most used source. Since the dawn of humanity, man has used plants to treat his health problems, while the WHO reports that 80% of the population uses them to treat their ailments (World Health Organization, 2024). That is why the present review focuses on healing medicinal plants, particularly those from Latin America, since it covers around 15% of the Earth's surface and contains a wide biodiversity (Quijas et al., 2019; Raven et al., 2020; Alarcon Ruiz et al., 2023). Therefore, the analysis of the reports for these species provides relevant information regarding the use of medicinal plants as a source of secondary metabolites, as well as their validation of popular use by vulnerable populations whose health culture is mainly based on herbal medicine.

In the present review, Latin American scar-healing plants were selected regardless of the year because no similar review exists. The search keywords were: "healing effect of secondary plant metabolites," "healing medicinal plant," "healing plant extract," "healing plants," "wound healing," "wound healing," "wound healing process," "wound healing mechanism," "factors influencing wound healing," "skin and wound healing," "wound healing therapies," "wound healing secondary metabolites," "stages of wound healing," "wound healing complications," "wound treatment alternatives," "wound healing models," "wound healing effect," "wound healing activity," "wound healing biochemistry," "wound healing effect assays." The search yielded 477 scientific publications, of which those that were not written in English or did not have precise information were discriminated. Scientific articles on wound-healing plants that were not from Latin America were discriminated; the topics of wound-healing therapies, models of biological wound-healing trials and wound-healing treatments were considered to be 10 years old. Databases were created in order to present relevant information on plants, biological models, and therapies in tabular and graphical formats. The databases were created using Elsevier, SciFinder, PubMed, and Google Scholar, selecting the most representative sources, and a total of 223 references were considered.

Importance of wound healing in human health

Wound care is reported to be a multi-billion-dollar problem worldwide and only in USA it affects 5.7 million people (~2% of the population) at an annual cost of $20 billion, i.e., nearly 15% of Medicare beneficiaries (8.2 million patients), and a conservative estimate of its annual cost is $28 billion (Järbrink et al., 2017; Nussbaum et al., 2018). In other countries such as the UK, chronic wound treatment and care accounts for 3% of total healthcare expenditure in developed countries (Järbrink et al., 2017). Chronic wounds are expected to remain a major clinical, social, and economic challenge, particularly in low- and middle-income country economies, although there are preclinical studies on scaffolds and dressings with promising results, translational evidence supporting their application (Jodheea-Jutton et al., 2022).

Skin accounts for 16% of the body weight, covering an average surface area of 1.85 m^2, representing the human body's largest organ. It also plays a pivotal role in maintaining homeostasis and as a protective barrier against the external environment to prevent infections and fluid losses (Díaz-García et al., 2021; Ellis et al., 2018). A skin wound results from the breakdown of the epidermal layer integrity with anatomical integrity disruption and functional loss (Jakovija and Chtanova, 2023; Cioce et al., 2024). Since the skin serves as the protective barrier against physical and chemical threats, exposure to radiation or thermal stress, and pathogen entry, a wound radically compromises its functionality (Petkovic et al., 2021), therefore, the ability of an organism to repair or regenerate tissues is a definite advantage for surviving (Díaz-García et al., 2021; Cioce et al., 2024). A wound that has failed to heal in 4 weeks is defined as a chronic wound (Järbrink et al., 2017) however, delayed wound healing in specific populations might be prevented or improved with appropriate therapies to lessen morbidity, loss of limb, and mortality (Falanga et al., 2022; Cioce et al., 2024). Chronic wounds are more susceptible to infections, and poor healing is a challenging problem for both patients and caregivers, affecting them physically, mentally, and socially, causing repercussions on their quality of life (Järbrink et al., 2017).

Skin and healing

The skin is the largest organ in the body; anatomically, it has multiple cells that fulfill the role of protection, temperature regulation, water regulation, and aesthetic functions (Cañedo-Dorantes and Cañedo-Ayala, 2019). Therefore, it is the organ most exposed to all external agents, whereby, it has developed defense mechanisms such as healing to avoid compromising its functioning, using the different layers of the skin with their respective cells (Cañedo-Dorantes and Cañedo-Ayala, 2019; Larouche et al., 2018). Likewise, the rest of the body organs have a healing mechanism that is activated when they experience a trauma or stimulus, in general, healing is a set of physiological, dynamic, synchronized, and interdependent mechanisms that try to rebuild the skin, the mucosa or other tissue that has been damaged. It is made up of different phases, depending on the severity of the trauma; the healing time can last days, months, and even years.

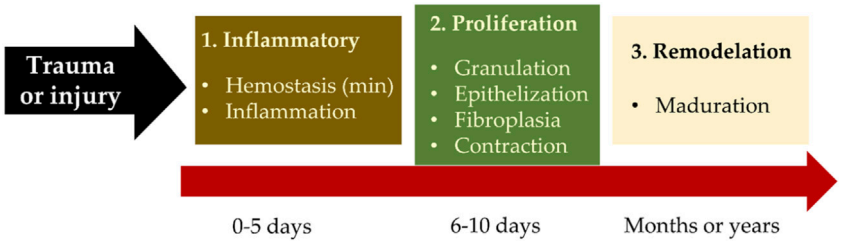


FIGURE 1
Overall wound healing process.

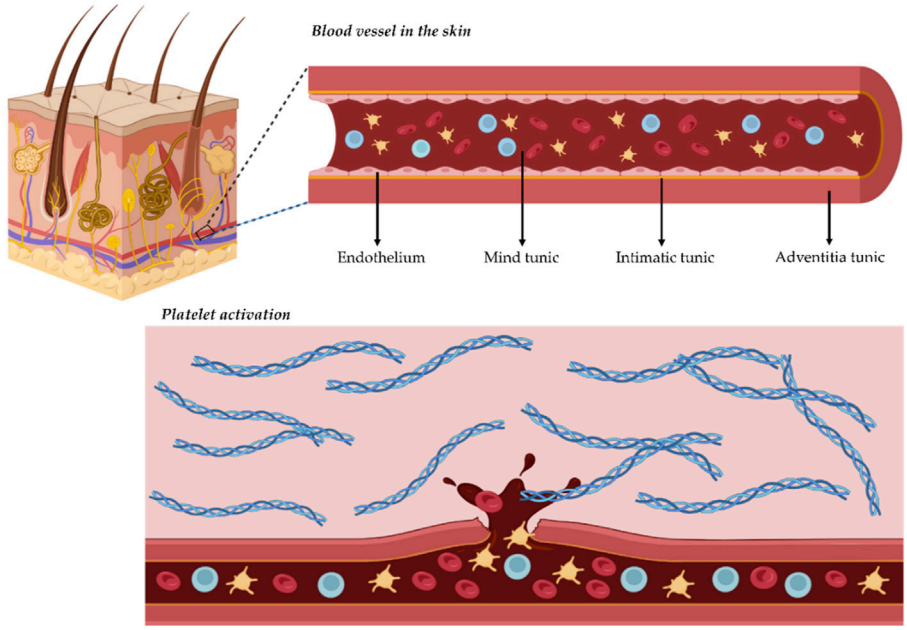


FIGURE 2
Activation of wound healing.

Figure 1 shows the phases and subphases of healing (Kucharzewski et al., 2019; Díaz-García et al., 2021; Cioce et al., 2024).

The skin has three layers (epidermis, dermis, and hypodermis), in each of which some cells work synchronously to perform the functions of the skin. However, it can have lesions that must be repaired through the healing mechanism to recover its functions (Rodrigues et al., 2019).

This complex mechanism involves numerous biochemical, immunological, and physiological reactions. Healing encompasses the phases of hemostasis, inflammation, proliferation, and remodeling. Each phase simultaneously repairs the injury (Rodrigues et al., 2019; Kucharzewski et al., 2019).

With the rupture of any of the structural levels of the blood vessel such as the external superficial tunica or adventitia, the tunica media made up of muscle fibers or the tunica intima or endothelium, primary hemostasis is activated (Figure 2), defined as the physiological phenomenon that stops bleeding, acts as a defense mechanism, and helps to protect the integrity of the vascular system. The blood that leaves the ruptured endothelium releases von Willebrand factor (vWF), and upon contact with the collagen of the vascular wall, it promotes the activation of platelets, transforming the blood into a solid clot through tissue factor (TF), which seals the injured area and stops the bleeding (Rodrigues et al., 2019; Sorg and Sorg, 2023).

The platelet plug at this stage is weak and matures through secondary hemostasis, involving the coagulation cascade, which is responsible for creating a mature and stable fibrin plug. The coagulation cascade is activated by the extrinsic (first to appear) and intrinsic (amplification of the coagulation process) pathways. The first pathway releases thrombin through tissue factor (TF), which is activated when the blood vessel ruptures, while the intrinsic pathway is triggered by platelet activation; together they generate a provisional matrix that guides fibroblast migration and ultimately repairs the wound (Rodrigues et al., 2019; Sorg and Sorg, 2023; Díaz-García et al., 2021). The process involves coagulation factors that form fibrin and anticoagulant proteins that regulate and control coagulation by preventing factors activated at a specific point from dispersing and producing generalized coagulation (Petkovic et al.,

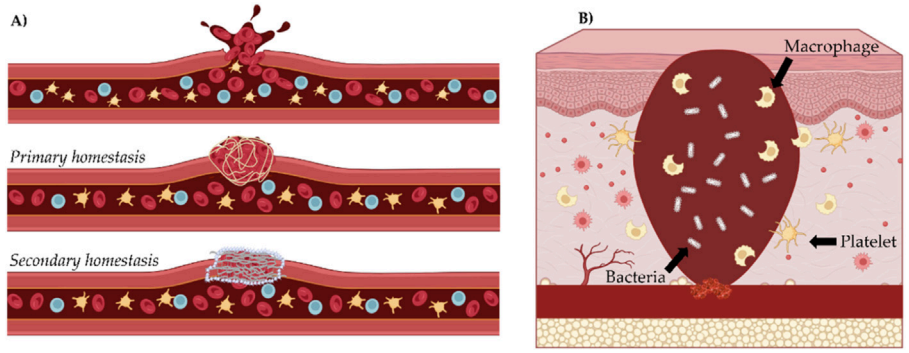


FIGURE 3
Inflammatory phase of wound healing. **(A)** homeostasis, **(B)** inflammatory.

2021; Kucharzewski et al., 2019). Finally, the fibrinolysis phase is triggered. This process eliminates unnecessary fibrin, thus achieving vessel repair and reestablishing vascular flow. This phase is promoted by tissue plasminogen activators and urinary plasminogen activators, whose task is to diffuse from endothelial cells and convert plasminogen absorbed in the fibrin clot into plasmin (Petkovic et al., 2021; Kucharzewski et al., 2019). Plasmin degrades the fibrin polymer into small fragments degraded by the monocyte-macrophage clearance system (Figure 3A).

Following hemostasis, vasodilation subsides and favors circulating cells that reach the wound site. Histamine, complement derivatives, prostaglandins, bacterial peptides, and fibrin degradation products promote this stage by attracting monocytes and neutrophils. Monocytes transform into macrophages, reaching a maximum population between 24 and 48 h, and enter the wound to destroy bacteria and remove harmful agents.

Inflammation is the defensive phase; its objective is to destroy bacteria and eliminate debris, allowing the wound bed to grow new tissue in a clean area. Neutrophils migrate to the injury site, releasing elastase and collagenase enzymes to destroy the damaged tissue and phagocytize the bacteria in the wound. Subsequently, they are trapped in the clot and eliminated by apoptosis (Figure 3B) (Rodrigues et al., 2019; Ellis et al., 2018).

Additionally, macrophages perform several tasks simultaneously; some participate in the debridement of damaged tissue, and at the same time, others undergo a genetic change in their mRNA and secrete cytokines (growth factors and interleukins) that drive the wound healing phases, stimulate cells such as fibroblasts and epidermal cells for wound closure (Ellis et al., 2018; Kimura and Tsuji, 2021). Platelets, macrophages, lymphocytes, and endothelial cells release these growth factors and interleukins into the wound. Macrophages secrete most of the substances that promote healing. The inflammatory phase lasts 4–6 days and manifests as edema, redness, heat, and pain (Rodrigues et al., 2019; Larouche et al., 2018; Leonida et al., 2016).

Growth factors and interleukins secreted by macrophages are released into the wound area, stimulating fibroblast migration to form the extracellular matrix and epithelialization from the wound edges. Fibroblasts form collagen fibers, hyaluronic acid, and proteoglycans; in addition, they are receptors of fibronectin, which allows them to migrate through the clot and synthesize collagen; when the granulation tissue progresses, macrophages reabsorb the clot into the wound bed allowing the passage of collagen fibers type I, II, and III into the connective tissue (Rippon et al., 2022; Kimura and Tsuji, 2021).

Fibroblastic migration is accompanied by neovascularization of the area, and fibroblasts secrete angiogenic factors promoting capillary formation and providing oxygen and nutrients for collagen synthesis. Gradually, the granulation tissue turns reddish in response to the angiogenesis, which proceeds smoothly (Figure 4A). During the resorption of the clot, the provisional extracellular matrix is formed, the main composition of which is fibroblasts, collagen I, II, III, and the fundamental substance formed by hyaluronic acid and proteoglycans (Kimura and Tsuji, 2021; Petkovic et al., 2021).

Subsequently, a more stable secondary matrix is formed, promoted by TGF-b and hyaluronic acid. The fibroblasts change their structure (their Golgi apparatus and endoplasmic reticulum increase in size to produce a greater amount of proteins). A new type of collagen I, III, V, and elastin are synthesized, providing elasticity to the matrix. On the other hand, some fibroblasts acquire smooth muscle properties. These changes promote wound epithelialization (Larouche et al., 2018; Petkovic et al., 2021).

In the epithelialization phase, the stages of migration of epithelial cells from the borders, multiplication, and differentiation of the formed dermis develop. Simultaneously, the synthesis of the dermo-epidermal junction occurs because of the interaction between the dermis and epidermis. Growth factors coordinate this interaction. Keratinocytes proliferate from the edges of the wound towards the center. They are stimulated by growth factors released by epithelial cells (epidermal growth factor, transforming growth factor alpha, fibroblast growth factor, and keratocyte growth factor) (Rippon et al., 2022; Leonida et al., 2016).

Once the granulation tissue matures, the keratinocytes proceed to transit the fibronectin of the extracellular matrix; this fact favors the formation of the basement membrane and binding proteins, which in turn allows for normal epidermal proliferation (Rippon et al., 2022; Leonida et al., 2016).

Next, the collagen fibers undergo remodeling, while the capillaries exhibit necrosis and are reabsorbed by macrophages,

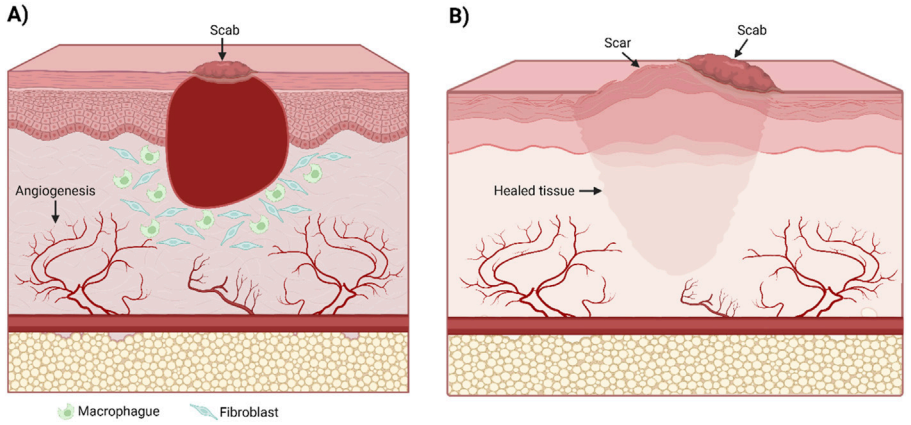


FIGURE 4
Angiogenesis **(A)** and epithelization **(B)** phases.

and their space is replaced by collagen fibers (Figure 4B). This stage consequently generates a change in the texture of the scarred skin. The wound proceeds to contract and may last from months to years, depending on the wound area and depth (Larouche et al., 2018; Petkovic et al., 2021).

It should be noted that the stages of healing are still being studied, as well as the factors that promote ideal conditions. However, it is important to note that when healing does not flow, and some stages are delayed, tissues can be compromised. The inability of patients to close wounds for prolonged periods drastically affects their quality of life, causing pain, loss of mobility, social isolation, and risk of depression, especially in patients where chronic wounds are associated with a higher risk of amputation, without considering that they can also be associated with life-threatening infection (Rippon et al., 2022; Larouche et al., 2018). For this reason, therapies, medications, and alternatives have been developed to induce healing. Some of them are described below.

Factors impacting the wound healing process

Various factors can contribute to impaired wound healing. Broadly, these factors can be divided into local and systemic categories. Local factors directly affect the wound's specific characteristics, considering systemic factors pertaining to the individual's overall health or underlying conditions that influence their healing capacity (Guo and DiPietro, 2010).

Local factors include foreign bodies, venous insufficiency, oxygenation (tissue hypoxia), and infections (Guo and DiPietro, 2010). Among these factors, infections are particularly significant as they occur when a skin injury allows microorganisms, normally confined to the surface, to penetrate the underlying tissues. The classification (Khalil et al., 2017) cation of the wound (whether as contaminated, colonized, locally infected/critically colonized, or suffering from spreading invasive infection) depends on the presence and replication status of these microorganisms (Edwards and Harding, 2004). Bacteria and endotoxins can prolong the inflammatory phase by sustaining elevated levels of proinflammatory cytokines. If unresolved, this persistent inflammation can lead to chronic wounds that fail to heal (Menke et al., 2007). Oxygenation also plays a critical role in wound healing. Oxygen supports cellular metabolism, prevents wound infections, promotes angiogenesis, and aids keratinocyte differentiation, migration, and epithelialization (Rodriguez et al., 2008). It further enhances fibroblast proliferation, collagen synthesis, and wound contraction (Bishop, 2008; Cialdai et al., 2022). While temporary hypoxia following an injury can stimulate healing, prolonged or chronic hypoxia impairs the process (Hong et al., 2014).

On the other hand, systematic factors include chemotherapy, nutrition, stress, age, and disease. For example, studies report that chemotherapy drugs and anticoagulants prevent the inflammation phase of the healing process and, therefore, increase the risk of wound infection, increasing healing time. Also, other medications, such as low-dose topical corticosteroids and antibiotics, accelerate wound healing (Khalil et al., 2017; Wagner et al., 2008). However, the authors report that other factors, such as being over 65 years of age, pressure/friction/shear, non-adherence to treatment, infection, obesity, stress, anxiety, and depression, are also important in poor wound healing and increased wound complications significantly affecting healing times, regardless of pharmacological treatment (Ubbink et al., 2015).

On the other hand, reactive oxygen species (ROS) play a crucial role in both the physiological and pathological aspects of wound healing. They are involved in various processes of skin tissue regeneration, including the regulation of inflammation, cell proliferation, angiogenesis, granulation tissue formation, and extracellular matrix development (Dong and Wang, 2023; Xu et al., 2020). Overproduction and accumulation of ROS obstruct the change of wound tissue from the inflammatory stage to the proliferative stage. Consequently, the wound area becomes chronically inflamed, resulting in delayed wound healing (Deng et al., 2019).

As already mentioned, psychological conditions can directly influence wound healing processes. Psychological stress can indirectly modulate the repair process by promoting the adoption

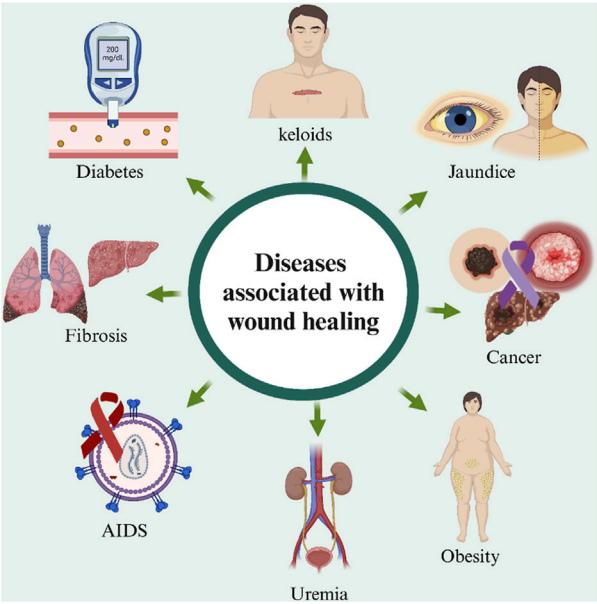


FIGURE 5
Some diseases associated with wound healing.

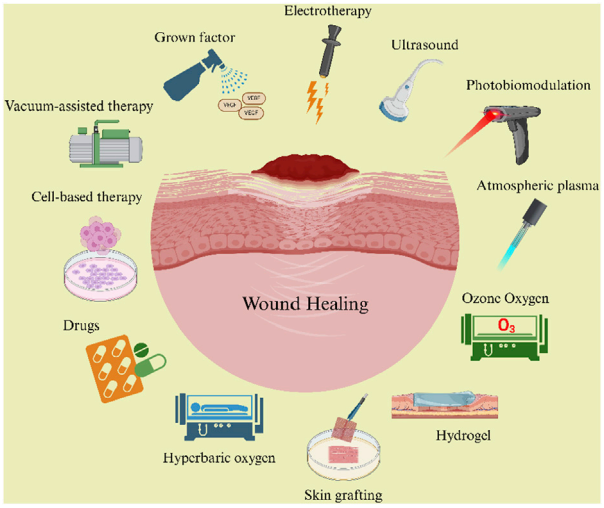


FIGURE 6
Wound healing therapies.

of unhealthy behaviors. Furthermore, increased production of glucocorticoids and catecholamines while under stress, or decreased expression of proinflammatory cytokines at the wound site, can directly influence several components of the healing process, such as the initial inflammatory phase (Ebrecht et al., 2004; Gouin and Kiecolt-Glaser, 2011).

This highlights that successful wound healing is a multifactorial process influenced by external factors and each patient's individual internal conditions.

Diseases associated with wound healing

Chronic wounds are characterized by their inability to heal within an expected timeframe. Over the last several decades, they have emerged as an increasingly important clinical problem due to their higher incidence and greater recognition of associated morbidity and socio-economic burden 3 (Falanga et al., 2022). Chronic wounds are often related to conditions (Figure 5) such as obesity, diabetes, and old age and fall into three categories: pressure ulcers, arterial or venous ulcers, and diabetic ulcers (Nuutila et al., 2014).

Pressure injuries are localized skin and soft tissue injuries that develop due to prolonged pressure exerted over specific areas of the body, typically bony prominences; common locations for these ulcers include over the sacrum, ischial tuberosity, greater trochanter, heel, and lateral malleolus(Gaspar et al., 2019; Mervis and Phillips, 2019). Most people affected by pressure ulcers are those who have mental or physical health conditions that favor immobility, especially those who are confined to bed or chair for prolonged periods (Leblebici et al., 2007). External and internal factors co-occur to form these ulcers; externally, prolonged pressure, friction, shear force, and moisture can lead to tissue deformation and ischemia. Internal factors such as malnutrition, anemia, and endothelial dysfunction can speed up the process of tissue damage (Anders et al., 2010; Bansal et al., 2005).

Venous ulcers are late manifestations of chronic venous insufficiency and venous hypertension. That can cause disability and severe complications (Bonkemeyer Millan et al., 2019). As the global population ages, the disease has shown a worldwide growing incidence (Robles-Tenorio et al., 2024). Most risk factors for developing venous ulcers are non-modifiable, and patients often present more than one. These involve a family history of chronic venous insufficiency, advanced age, female sex, previous thrombosis or pulmonary embolism, multiparity, lipodermatosclerosis, and musculoskeletal and joint disease (Santler and Goerge, 2017). Modifiable risk factors such as obesity and sedentarism are also associated with venous disease (Santler and Goerge, 2017).

Diabetes mellitus is a metabolic endocrine disorder due to an overall deficiency of insulin (Type 1) or defective insulin function (Type 2), which causes hyperglycemia (Meulendijks et al., 2020). A complication of diabetes mellitus is diabetic ulcers, which leads to increased overall morbidity in patients. Patients with diabetes mellitus type 1 or 2 have a total lifetime risk of a diabetic foot ulcer complication as high as 25% (Packer et al., 2023). Diabetic foot ulcers are classified as neuropathic, ischemic, or a combination of both, that is, neuroischemi (Boulton et al., 2008). However, around 90% of diabetic foot ulcerations are diabetic peripheral neuropathy.

Chronic wounds harm health-related quality of life due to the physical injury, the treatment required, the chronicity of the condition, and the likelihood of recurrence. The likelihood of wound healing is highly associated with wound-based and patient-based factors or attributes, such as age and associated diseases, such as diabetes (Guo and DiPietro, 2010).

Common therapies that improve wound healing

As described, wound healing is the process of tissue repair involving the tissue response to injury (Steed, 1997). Any failure in the normal wound healing process results in abnormal scar formation and a chronic state more susceptible to infection (Díaz-García et al., 2021; Kolimi et al., 2022). Currently, the therapeutic strategies used for wound healing depend on the type of wound and the intrinsic regenerative capacity (Edmonds et al., 2000; Kolimi et al., 2022). Treatments for wounds, including surgical and non-surgical, are shown in Figure 6.

Growth factors

Growth factors (GFs) are polypeptides that bind to specific receptors on the cell surface, initiating signaling pathways that activate key molecules. These activated molecules may further stimulate cytoplasmic proteins or promote the transcription of new proteins (Singer and Clark, 1999). GFs regulate cell growth, differentiation, and metabolism through these mechanisms across the three phases of wound healing (Steed, 1997). In addition to driving the proliferation, differentiation, and migration of repair cells like keratinocytes, fibroblasts, and vascular endothelial cells, GFs also influence repair cell apoptosis, extracellular matrix composition, DNA, RNA, and protein synthesis, glycolysis, and tissue remodeling (Han et al., 2020).The topical application of growth factors shows promise in treating various skin wounds by accelerating healing or preparing healthy beds for surgical intervention (He et al., 2024). Key growth factors in wound healing and skin regeneration include PDGF, VEGF, EGF, TGF-α, IGF, bFGF, KGF, and TGF-β1–3 (Park et al., 2017). Growth factors are essential in skin regeneration, highlighting their importance in regenerative medicine and wound treatment (Mitchell et al., 2016).

Electrotherapy

The wound healing process is also influenced by our skin's endogenous electric potential, also dubbed the endogenous *skin battery* (Farber et al., 2014). These endogenous electric fields play a critical role in wound healing, resulting in endogenous currents acting as cues for cellular migration, which concomitantly help heal wounds (Sun, 2017; Zhao, 2009). The therapeutic use of electrical stimulation in medical practice has been established, particularly in pain and wound management (Rajendran et al., 2021). Electrotherapy may have multiple modes of action in wound healing; one possible mechanism is introducing an exogenous electrical signal in the complex cellular and biochemical events within the wound itself. Another method consists of increasing blood circulation through the wound site by stimulating the operation of the peripheral arterial and vascular systems through an electrical signal applied to the muscle motor nerve (Sun, 2017; Zhao, 2009). Commonly used waveforms for electrical stimulation therapy are direct current, alternating current, pulsed current, and degenerate wave (Kloth, 2014).

Vacuum-assisted closure and negative-pressure therapy

Vacuum-assisted closure is a non-invasive, negative pressure healing technique to treat chronic, non-healing wounds. This technique uses controlled subatmospheric pressure to remove excess wound fluid from the extravascular space, i2mproving local oxygenation and peripheral blood flow (Enoch et al., 2006; Genecov et al., 1998). This promotes angiogenesis and the formation of granulation tissue, which are particularly useful in deep cavitating wounds to expedite the filling of the wound space (Enoch et al., 2006; Kairinos et al., 2009). This method requires thorough debridement, adequate hemostasis, and application of sterile foam dressing. A fenestrated tube is embedded in the foam, and the wound is sealed to make it airtight. The fenestrate tube is connected to a vacuum pump with a fluid collection container. The machine delivers continuous or intermittent suction, ranging from 50 to 125 mmHg (Timmers et al., 2005). Using vacuum-assisted closure and negative-pressure therapy, it is possible to stabilize the wound, reduce edema and bacterial load, improve tissue perfusion, and stimulate granulation tissue (Agarwal et al., 2019).

Hyperbaric oxygen therapy

Hyperbaric oxygen has been recommended as an adjunctive therapy to treat a variety of non-healing wounds (as many non-healing tissues are hypoxic) (Enoch et al., 2006). It promotes neutrophil-mediated bacterial killing ability in hypoxic tissue. Also, it prevents the release of proteases and free radicals in specific injuries, thereby decreasing vasoconstriction, edema, and cellular damage (De Smet et al., 2017). The treatment is administered by increasing atmospheric pressure in a chamber while the patient is exposed to 100% oxygen. Since wounds need oxygen to heal correctly, exposing one to 100% oxygen can speed healing (Jones and Cooper, 2023).

Ozone oxygen therapy

Ozone therapy has accelerated healing by minimizing inflammation and reducing edema (Naik et al., 2016). Suggested mechanisms of therapeutic enhancement are that it acts as a potent oxidizing agent (Sagai and Bocci, 2011) and enhances tissue repair by removing defective cells, bacteria, and viruses by acting as a powerful disinfectant (Greer et al., 2012). It has also been shown to promote angiogenesis and stimulate fibroblast activity, further accelerating wound healing (Pchepiorka et al., 2020). This therapy has proven particularly effective in treating diabetic foot ulcers, ischemic wounds, and peripheral vascular disease, representing some of its most common applications (Adhikari and Khanal, 2013) (Smith et al., 2017). On the other hand, the route of administration can be by exposure to gaseous ozone within a hyperbaric chamber, application of ozonized oils, or ozonized water (Azarpazhooh and Limeback, 2008; Fitzpatrick et al., 2018).

Cold atmospheric plasma therapy

Plasma, the fourth state of matter, is an ionized gas comprising both stable components (gases) and reactive elements such as ions, energetic particles, and radicals (Adhikari and Khanal, 2013). The use of plasma for wound healing and tissue regeneration has been advanced by developing the "Plazon" system. This system employs a rapidly quenching hot air plasma jet, resulting in a relatively high nitrogen oxide (NO) concentration with significant therapeutic effects (Shekhter et al., 1998). A plasma device operates in two distinct modes: the "hot mode," in which the plasma jet is used for rapid coagulation, sterilization of wound surfaces, removal and desiccation of dead tissue and pathological growths, as well as tissue dissection, and the "cold mode," which provides a flow of nitrogen oxide-enriched plasma gas at a temperature of 20°C–40°C to stimulate regenerative processes and enhance wound healing (Fridman et al., 2008). The physical mechanism of plasma-based treatment involves the generation of free radicals and reactive species for the desired wound healing-promoting effects. In contrast, the biological mechanism exploits various cellular processes responsible for DNA and cell membrane damage of bacteria (Kolimi et al., 2022).

Photobiomodulation

Photobiomodulation (PBM) involves the use of nonionizing forms of light from sources including lasers, light-emitting diodes (LEDs), and broadband light in the visible and near-infrared (NIR) spectra to cause physiological changes and therapeutic benefits (Houreld, 2019). Both *in vitro* and *in vivo*, it effectively promotes wound healing and cell proliferation. PBM has been used successfully in the healing of diabetic wounds because it reduces oxidative stress and inflammation, accelerates essential cell proliferation and extracellular matrix deposition, and enhances tissue repair (Mgwenya et al., 2024). On the other hand, It has been suggested that laser irradiation in the red light region increases activity in the plasma membrane of cells (Kujawa et al., 2014). The optimal wavelength for treatment is generally considered to be 810 nm. However, wavelengths ranging up to 950 nm are needed to reach cutaneous tissue sites and below the tissue (Wang et al., 2017). It is currently considered that stem cell bioactivity, such as cell migration, proliferation, survival, and overall cellular niche, can be enhanced or positively modulated by PBM (Zamani et al., 2020). Despite this, PBM is not used in mainstream medicine, and this is largely due to a lack of comprehension of the therapy and the molecular mechanisms underlying it (Mgwenya et al., 2024).

Skin grafting

Skin grafting is the transfer of cutaneous tissue from one portion of the body to another, often used to cover large wounds. It provides a barrier function that limits wound desiccation, fluid loss, and bacterial contamination and protects underlying viable tissue. In addition, it improves the granulation tissue and becomes incorporated into the recipient tissue bed (Braza and Fahrenkopf, 2023; Hermans, 2011). Autografts are derived from a patient's healthy skin. Challenges in autograft use include the introduction of a new wound, contracture and scar formation, infection and bleeding risk, and decreased or increased sensation (Shi and Ronfard, 2013). However, autografts provide the advantages of availability and decreased immunogenicity (Chandler et al., 2020).

Skin allografts, or homografts, are tissues harvested from a donor site of the same species with different genetic components (Hermans, 2011). The main lines of attack on the allograft problem are the host's immune response and the possibility of disease transmission (Megahed et al., 2021).

Skin xenografts may be a temporary, initial treatment that prepares the wound bed for autologous transplantation. When using xenografts, factors such as immunogenicity and disease transmission must be considered (Ma et al., 2008). The most common xenografts used to treat chronic wounds include porcine, bovine, and, more recently, fish (Stubenitsky et al., 2009; Yamamoto et al., 2018).

Hydrogels dressings

Hydrogels are intricate three-dimensional structures composed of hydrophilic polymer chains and exhibit a quick swelling response upon contact with water, forming a partially solid material (Ahmed, 2015). They have been proposed as potential remedies because they provide a moist environment that facilitates wound healing (Gounden and Singh, 2024). Hydrogels can be classified according to polymeric composition as homopolymeric hydrogels are referred to polymer networks derived from a single species of monomer, copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic and multipolymer interpenetrating made of two independent cross-linked synthetic and natural polymer components, contained in a network form (Hacker and Mikos, 2011; Maolin et al., 2000). Hydrogels possess biodegradability and biocompatibility, allowing them to serve as a temporary template throughout the re-epithelialization and remodeling of chronic wounds (Maaz Arif et al., 2021).

Cell-based therapy

Cell therapy can be applied for both acute and chronic wounds. In acute treatment wounds, cell therapy can increase the wound healing rate, reduce scar contracture, and minimize donor-site morbidity. On the other hand, in treating chronic wounds, including diabetic ulcers, attempts are made to convert the wound bed into an environment where maximum wound healing can be achieved by transplanting cells with an excellent wound healing capacity to the wound bed (Park et al., 2010; You and Han, 2014). Cell therapy can use autologous or allogeneic cells. Autologous cells accelerate wound healing by reducing the time needed for the host cells to invade the wound tissue and by early synthesis of new skin (Seo et al., 2007). Allogeneic cells promote migration and proliferation of host cells from the wound beds and edges because these cells release growth factors, extracellular matrices, and basement membrane components (You and Han, 2014).

TABLE 1 Some drugs that promote wound healing.

Drug	Effect	References
Alantoina	It acts by exerting an epithelializing action and increasing the moisturizing capacity. It has keratolytic properties, which favor penetration, has anti-inflammatory effects and attenuates the itching that frequently occurs during healing	Martín-Aragón and Marcos (2008)
Ascorbic acid (Vitamin C) Vitamin A Vitamin E	Are crucial to the manufacture of collagen. A lack of these vitamins causes fibroblasts to create unstable collagen, which offers a flimsy foundation for repair	Chattopadhyay and Raines (2014), Vivcharenko et al. (2021)
Hyaluronic acid	Its application focuses on modifying wound physiology, providing a moist environment, and improving granulation and epithelialization	Antoszewska et al. (2024)
Topical zinc	Stimulates leg ulcer healing by enhancing re-epithelialization and decreasing inflammation and bacterial growth	Ogawa et al. (2018)
Retinoic acid	Enhance production of extracellular matrix components such as collagen type I and fibronectin, increase proliferation of keratinocytes and fibroblasts, and decrease levels of degrading matrix metalloproteinases	Polcz and Barbul (2019)
Centella asiatica extract	It acts by incorporating and binding alanine and proline to collagen, stimulating granulation tissue, and facilitating correct epithelialization by stimulating the biosynthesis of glycosaminoglycans	Divins (2010)
Peru Balsam	Promotes epithelialization and, in addition to having an antiseptic effect	Divins (2010)

Ultrasound

Ultrasound waves have emerged as a promising alternative or adjunctive strategy for chronic wounds (Alkahtani et al., 2017). These waves are delivered to the body and soft tissues and undergo diffusion. The molecules progressively lose their energy through vibrating as the waves pass through the tissue. The range of ultrasonic frequencies that are utilized for therapeutic ultrasound spans ranges from 20 kHz to about 3 MHz (Mason, 2011). *In vitro* studies have shown that the therapeutic outcomes of ultrasonic waves on tunneling, or debilitation wounds are mainly through killing multi-drug resistant bacteria (Serena et al., 2009). Several *in vitro* studies have shown that these waves improve cell proliferation, collagen production, bone formation, and angiogenesis (Speed, 2001).

Drugs

Antimicrobial

Infections are a worrying complication of skin wounds, which can lead to delayed healing and, in severe cases, sepsis and death. Infected wounds present clinically with erythema, heat, edema, and local pain or tenderness (Yousefian et al., 2023). Usual practice suggests the use of topical or dressing antiseptics, which can be classified into different classes according to their mechanism of action, including emulsifiers, oxidants, acids, heavy metals, alcohols, aldehydes, anilides, bisphenols, and phenols (Cambiaso-Daniel et al., 2018). In clinical practice, the most used are Silver-Based or Iodine-Based Wound Dressings and various classes of antibiotics, including aminoglycosides, beta-lactams, glycopeptides, quinolones, sulfonamides, and tetracyclines, incorporated or not into wound dressings, some examples are listed in Table 1 (Jones and Cooper, 2023; Simões et al., 2018).

Anti-inflammatories

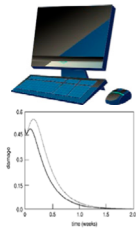
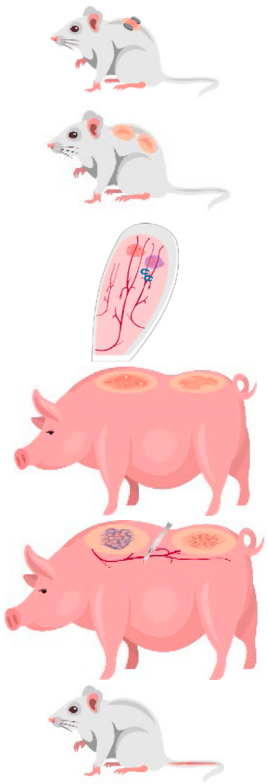
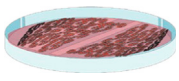
Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have a depressant effect on wound healing while simultaneously decreasing the granulocytic inflammatory reaction (Su et al., 2010). However, these are prescribed post-soft-tissue injury or post-surgery to assist with pain control management and to diminish inflammation. Short-term use of NSAIDs, such as ibuprofen, after surgery is beneficial for its analgesic effect, but patients with chronic wounds or diabetes could be more dramatically affected by NSAID's effect on fibroblast inhibition (Legendre et al., 2008). So, it is important that in these conditions, NSAIDs should be used with caution.

All the procedures described above are applied in different cases, depending on the type of wound, the patient's state of health, allergies, diet, and age. Pharmacological methods have been scientifically developed to determine and measure the efficacy of treatments at different stages of wound healing. These trials are vital since numerous therapies are still under development that could promote the healing process in various stages and contribute to patient treatment alternatives. It should be noted that the population is diverse, and the health system is not the same worldwide. Hence, the availability of treatments for wound healing is an important measure to avoid complications that compromise the survival of individuals due to the complications that can arise from wounds that do not heal progressively.

Biological assays in the study of the healing effect

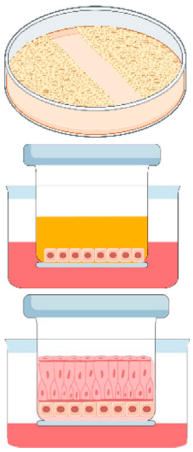
The characteristics of the wound, its etiological nature, and other factors in the clinical history, together with regular follow-up, help the healthcare team to know at what stage of the healing process the wound is in and to decide the best therapeutic approach. The investigation of any physiological process depends on the use of

TABLE 2 General models of wound healing.

Type	Model	Methodology	Advantages	Limitations
In silico 	System of ODEs (x-variables)	Computational model of acute wound healing designed to allow a system-level analysis with healing wound variables equations (Menke et al., 2010)	These models have focused especially on analyzing strongly interrelated local factors (internal inflammation, fibroblast function, etc.) as well as wound depth and shape, wound contraction, epithelialization, etc. (Menke et al., 2010)	They remain theoretical until biologically confirmed by *in vitro* and or *in vivo* models. Biologically and can involve the physical characteristics of the skin (Sami et al., 2019)
	• Molecular Docking (protein targets: TNF-*α*, *TGF-β* receptor type-1, etc.)	Docking approach like against TNF-α, TGFBR1,IL-1β, Metalloelastase and Metalloproteinase etc. (Balachandran et al., 2023; Shady et al., 2022)	Molecular docking is useful for measuring compound affinities to the screened receptors related to the healing process (Balachandran et al., 2023; Shady et al., 2022) No animals are required for testing	
In vivo 	Excisional Wound (Rodents/ Rabbits/ Pigs)	In rodents and pigs, full-thickness injuries are done on the dorsal side, in rabbits full-thickness are done on the ventral side of the ears (Sami et al., 2019)	Rodent models represent cost-effectiveness, ease of handling and husbandry, simplistic surgical approach, multiple wounds per animal, pathologies with specific characteristics such as diabetes, splinting minimizes contraction, methodological variations (excision size) (Grada et al., 2018; Sami et al., 2019; Zindle et al., 2021) Rabbit models are conducive to partial and full-thickness wounds, exhibit epithelization and granulation, multiple sampling locations, are relatively inexpensive, well-suited to testing potential therapeutics because rabbit and human skin respond similarly to aging, delayed healing, and various topical drugs, several wounds in the same ear, larger-caliber vessels make ischemic ligation easier and can be adapted for study of hypertrophic (Grada et al., 2018; Zindle et al., 2021) Porcine models have phenotypic similarities to human skin, appropriate for therapeutic interventions, the hypertrophic scarring model, large size allows for larger and more numerous wounds and, in general very relevant for preclinical studies (Grada et al., 2018; Zindle et al., 2021)	It is considered the least effective type of wound model (contraction of the panniculus carnosus), while the human wound heals by re-epithelialization, genomic, immune, and inflammatory responses in mice differ significantly from those in humans after injury, the use of splints to prevent contraction introduces foreign material into the wound area (Grada et al., 2018; Sami et al., 2019) Limited genetic traceability, breeding requirements - Not cost-effective wound contraction in full-thickness wounds, complicated surgical approach in rabbit models Porcine models have husbandry requirements, complicated surgical approach, are expensive to maintain and in the administration, long gestational times, poor genetic tractability, and few transgenic lines available (Grada et al., 2018; Zindle et al., 2021)
	Incisional Wound (Rodents)	Longitudinal incisional wound parallel to the midline on the dorsal side (through the epidermis, dermis, and subcutaneous tissue)	It is the second most common wound model. It is mostly used for studying wound scarring	
In vitro 	Monolayer cell cultures	Keratinocytes cultured on a layer of fibroblasts within a collagen gel are commonly disrupted using a sterile wounding instrument (scratch assay)	Monolayer cultures are easy, inexpensive, and relatively quick to show results. The scratch assay is a technically non-demanding and cheap, thus popular, assay, which	Fibroblasts or keratinocytes alone cannot provide adequate insight into the complexity of the problem, autocrine factors are easily removed during cell culturing with the media

(Continued on following page)

TABLE 2 (*Continued*) General models of wound healing.

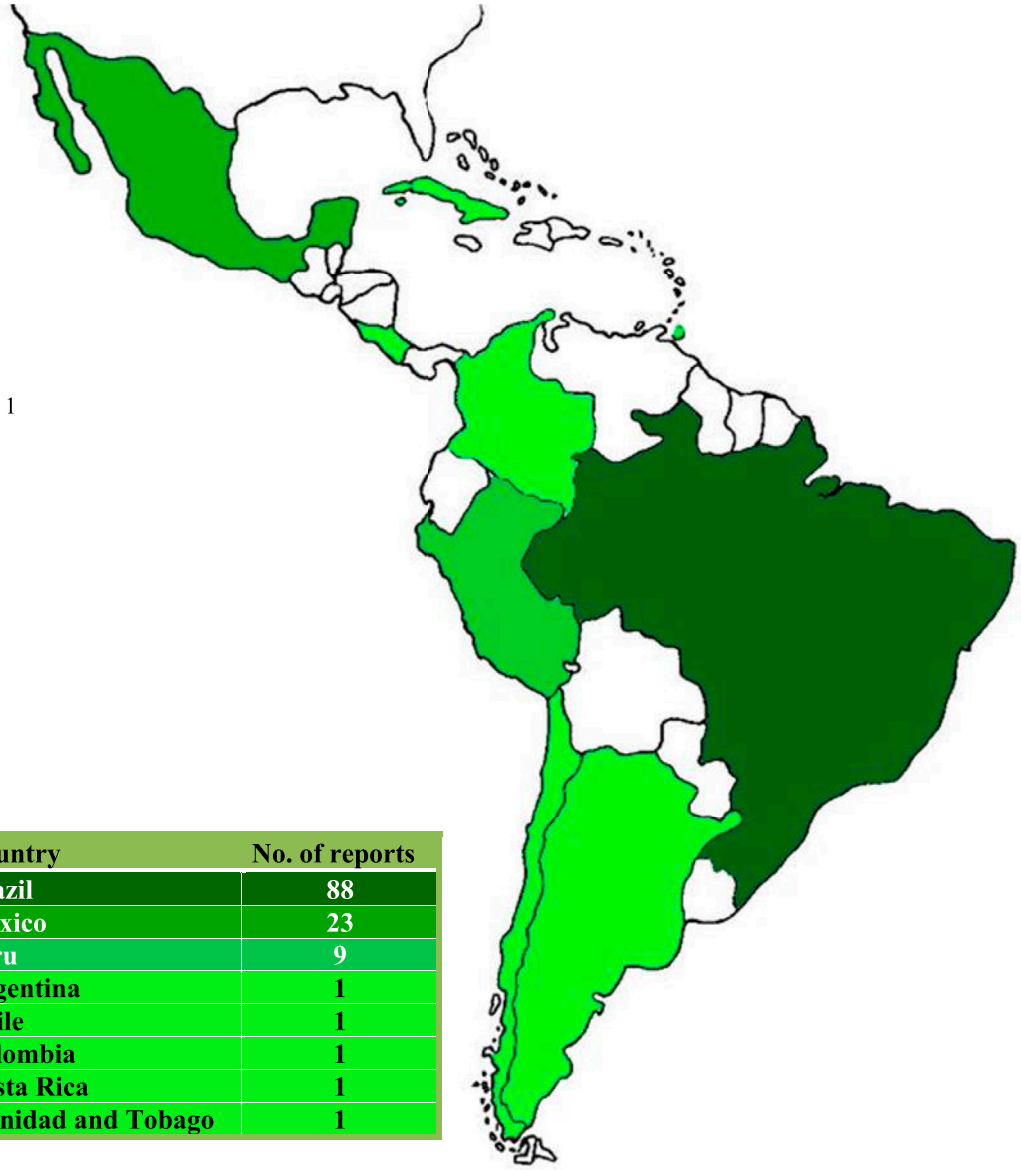
Type	Model	Methodology	Advantages	Limitations
			allows studying the migration of cells on 2D surfaces (Hofmann et al., 2023; Sami et al., 2019)	removal, the scratches, if performed manually, are often unevenly thick, cells may stick to the border of the scratch, re-attach, and start migrating into the wound, leading to biased results. Additionally, scratching may mechanically destroy the plastic surface and/or the coating (alters migration behavior)
	• Co-cultured cell cultures	The trans-well systems using monolayers of keratinocytes and fibroblasts allowed us to study the keratinocytes-fibroblasts interaction. Employs a chamber that is separated into two compartments using a filter membrane with a pore size that dictates active migration	Co-cultures give more insight regarding cell-cell interaction, and this provides more information than normal monolayer cultures. Multiple cells are activated to work harmoniously together during injury and healing processes *In vitro* models of chronic wounds would feature key aspects of chronic human wounds of different etiologies (e.g., venous leg ulcer, diabetic foot ulcer, pressure ulcer, and arterial insufficiency)	Co-cultures are still insufficient to accurately represent what happens *in vivo*
	• Skin explants or 3D cultures (*ex vivo*)	Skin explant is an organotypic cell culture in which the subcutaneous layers and fat contaminants are removed, and the remaining tissue is cultivated	Used to study wound repair and inflammation, have the advantage of providing a 3D structure that shows inter-cellular interaction such as one between keratinocytes and fibroblasts. Skin models will be more complex (three layers), composed of pathological-tissue-derived cells comprising immune cells as well as a vasculature, micro-biota (healthy versus pathogenic). Other examples of *ex vivo* studies conducted to analyze scars and stretch marks, including keloid and hypertrophic scars that evaluate novel anti-fibrotic therapies. They also examine the effect of photodynamic therapy (stretch marks and other scars) (Hofmann et al., 2023; Sami et al., 2019)	Skin explants lack innervation which is integral for the understating of skin repair and scar formation and desquamation of cells cannot be observed. Not immunocompetent and lack vasculature in almost all types of matrix (collagen, elastin, fibrine, etc.) (Hofmann et al., 2023; Sami et al., 2019)

models; there is no single appropriate model due to the lack of an ideal comprehensive model that approximates humans; a combination of models is a better alternative to studying the complex cellular and molecular interactions that take place during the wound healing process in an appropriate biological environment (Masson-Meyers et al., 2020; Menke et al., 2010; Parnell and Volk, 2019; Sami et al., 2019).

Type of models

Over the last few decades, efforts to understand the healing process have been redoubled, and experimental models of wound healing have been developed to try to fully explain tissue regeneration and test new treatment strategies (Masson-Meyers et al., 2020; Wilhelm et al., 2017). These models are currently divided into *in vitro*, *in vivo,* and *in silico* (Table 2).

In vitro and *in vivo* models have provided valuable information for many medical discoveries and advances. *In vitro* models, such as cell culture, scratch model, and skin explant culture, are essential in several of these studies; *in vivo* models involve wounding a laboratory animal and observing wound closure over time (Ansell et al., 2012; Grada et al., 2018; Masson-Meyers et al., 2020). However, they are not always adequate and in many cases are unable to support finding the actual etiology of lesions; for example, the intricate biological pathway that takes place during



Country	No. of reports
Brazil	88
Mexico	23
Peru	9
Argentina	1
Chile	1
Colombia	1
Costa Rica	1
Trinidad and Tobago	1

FIGURE 7
Latin American countries with studies of plants with wound-healing activity.

wound healing is not always reflected in animal models, so it is necessary to consider human models, because these models are not always good predictors, but provide helpful insight into acute wound disease pathology. On the other hand, several mathematical equations have been used to evaluate the phases of healing in the *in silico* models, but one of the disadvantages is that they lack the biophysical characteristics of human skin and remain theoretical until biologically confirmed by *in vitro* or *in vivo* models (Sami et al., 2019). The usual course of healing is known, but for a thorough understanding of the kinetics of cell types and subtypes and the signaling pathways or intermediates involved, to cite a few examples, it is necessary to address the problem both in the laboratory and the clinic (Nuutila et al., 2014; Zindle et al., 2021; 2021). Even in the clinical area, it is difficult to understand chronic wound processes because human models are not always good predictors, and it is difficult to have adequate volunteers with chronic wounds, so human models of chronic wounds provide a better opportunity to understand the wound healing process. Several factors can influence wound healing (aging, infections, medications, nutritional status, obesity, diabetes, venous insufficiency, and peripheral arterial disease) (Grada et al., 2018; Wilhelm et al., 2017). The lack of optimal preclinical models capable of adequately recapitulating human wounds remains a significant challenge and is worth further study.

Certainly, the therapies described in this review are widely used and recommended, as are biological assays to determine their efficacy. However, since the beginning of mankind, man has used medicinal plants to solve his health

TABLE 3 *In vitro* wound healing promoting activity of medicinal plants in Latin America.

Plant Family	Plant Name	Plant Part	Solvent/ Compound/ Vehicle/ Administration	Model of Study	Healing Activity %	References
Amaranthaceae	Iresine diffusa f. herbstii (sayn. Iresine herbstii)	Aerial parts, flowers, and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	34.44% ethanolic extract and 28.26% hexanic extract at 10 μg/mL	Schmidt et al. (2009)
Anacardiaceae	Schinus molle	Aerial parts, flowers, and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	76.22% ethanolic extract and 50.76% hexanic extract at 10 μg/mL	Schmidt et al. (2009)
Annonaceae	Annona crassiflora	Seeds	Methanol-acetone-water (7:7:6 v/v/v)	Scratch assay, HaCaT cells	54% at 1.8 μg/mL, and 73% at 3.6 μg/mL	Prado et al. (2020)
Apocynaceae	Hancornia speciosa	Leaves	96% ethanol	Scratch assay, primary human gingival	42.8% at 25 μg/mL	Geller et al., (2015)
		Leaves	Bornesitol, quinic acid, rutin, DMSO 0.5%	Scratch assay primary human gingival fibroblasts	80.8% at 50 μM (B) 69.1% at 50 μM (QA) 39.6% at 50 μM (R)	Geller et al., (2015)
Aquifoliaceae	Ilex paraguariensis	Aerial parts	Water	MTT assay, Swiss mouse fibroblasts	Effect at 200 μg/mL	Romana-Souza et al. (2015)
Arecaceae	Attalea speciosa (syn. Orbignya speciosa)	Essential oil, fruit	DMSO (maximal final concentration of 0.5%)	Scratch assay, L929 fibroblasts	Concentration-dependent manner 3.12-12.5 μg/mL (AUC)	Santos et al. (2020)
Asteraceae	Achyrocline saturejoides	Aerial parts	Ethanol	MTT assay, HaCaT cells, stimulated keratinocyte	Proliferation at 1 μg/mL	Alerico et al. (2015)
	Bidens pilosa	Aerial parts	Ethanol and decoction	MTT assay, HaCaT cells	No effect	Alerico et al. (2015)
	Chaptalia nutans	Aerial parts	Ethanol and decoction	MTT assay, HaCaT cells	No effect	Alerico et al. (2015)
	Chromolaena laevigata (syn. Eupatorium laevigatum)	Aerial parts, flowers and leaves	Ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	30.14% at 10 μg/mL	Schmidt et al. (2009)
	Galinsoga parviflora	Aerial parts, flowers and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	64.3% hexanic extract and 59.83% ethanolic extract at 10 μg/mL	Schmidt et al. (2009)
	Matricaria chamomilla (syn. Matricaria recutita)	Aerial parts	Water and ethanol	MTT assay, HaCaT cells	Concentration dependent	Alerico et al. (2015)
	Pluchea sagittalis	Aerial parts, flowers and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	43.93% ethanolic extract and 40.66% hexanic extract at 10 μg/mL	Schmidt et al. (2009)
	Xanthium strumarium	Aerial parts and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	9.94% ethanolic extract and 41.17% hexanic extract at 10 μg/mL	Schmidt et al. (2009)
Basellaceae	Ullucus tuberosus	Tuber	Acetone and pulp	Scratch assay, HDFa cells	29% tuber pulp and 53% acetone extract at 200 μg/mL)	Heil et al. (2017)
Bignoniaceae	Fridericia chica (syn. Arrabidaea chica)	Leaves	Methanol/0.3% citric acid solution	MTT assay, confluent primary human fibroblast	Growth stimulation (0.25-250 μg/mL). EC50= 30 μg/mL	Jorge et al. (2008)
Burseraceae	Bursera morelensis	Stems	Essential oil, DMEM	Scratch assay, human fibroblasts	↑ Cell migration at 0.01 mg/mL	Salas-Oropeza et al. (2020)
Borraginaceae	Cordia americana	Leaves	Ethanolic extract, rosmarinic acid	Scratch assay, Swiss 3T3 albino mouse fibroblasts cells	11.8% at 10 μg/mL	Geller et al. (2010)

(Continued on following page)

TABLE 3 (*Continued*) *In vitro* wound healing promoting activity of medicinal plants in Latin America.

Plant Family	Plant Name	Plant Part	Solvent/ Compound/ Vehicle/ Administration	Model of Study	Healing Activity %	References
		Leaves	Ethanol, 0.084 μg/mL of rosmarinic acid	Scratch assay, Swiss 3T3 mouse fibroblasts	9.8% at 1 μg/mL	Geller et al. (2010)
Cactaceae	Pereskia aculeata	Leaves	95% ethanol, DMEM (v/v)	Scratch assay, L929 mouse fibroblasts cells	No effect	Carvalho et al. (2014)
Crassulaceae	Sedum dendroideum	Aerial parts and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	32.71% ethanolic extract and 27.86% hexane extract at 10 μg/mL	Schmidt et al. (2009)
Euphorbiaceae	Croton lechleri	Tree	Taspine hydrochloride, PBS	Scratch assay human foreskin fibroblast	27 ± 1.83 no. cells/cm at 2 ng/mL	Vaisberg et al. (1989)
Farbaceae	Bauhinia ungulata	Stem wood	n-hexane and ethanol Liquid-liquid fractioning, ethyl acetate fraction	Scratch assay, A549 human epithelial cells	↑Cell migration process and ↓lesion aerial to approximately 32.6% and 22% at 10 and 100 μg/mL	De Oliveira Rodrigues et al. (2020)
	Cenostigma pluviosum (syn. Poincianella pluviosa)	Bark	Ethanol-water (1:1 v/v)	MTT and BrdU incorporation assays, HaCaT cells and human primary dermal fibroblasts (pNHDF)	Stimulation of mitochondrial activity and ↑keratinocyte proliferation	Bueno et al. (2014)
	Dipteryx alata	Nuts	95% ethanol, DMEM/ F12 medium	Scratch assay, A549 adenocarcinoma cell line	After 72 h 83% and 67% at 0.5 and 1 mg/mL	Coco et al. (2022)
	Parapiptadenia rigida	Bark	Ethanol, epicatechin3-O-gallate, 4′-O-methylepicatechin-3-O-gallate, DMSO	Scratch assay, Swiss 3T3 albino mouse fibroblasts	Ethanolic extract ~40% at 10 μg/mL ~58% increased cell numbers at 1 μM ~60% increased cell numbers at 1 μM	Schmidt et al. (2010)
Hypericaceae	Hypericum carinatum	Aerial parts	n-hexane and cold acetone, phloroglucinol-enriched fractions	Scratch assay, HaCaT cells	138.7% cell proliferation at 15 μg/mL	Bridi et al. (2017)
	Vismia baccifera (syn. Caopia baccifera)	Leaves	n-hexane, methanol and ethyl acetate	MTT, Scratch assay,human fibroblasts	No effect	Hernández-Pasteur et al. (2019)
Loranthaceae	Struthanthus marginatus (syn. Struthanthus vulgaris)	Leaves defatted with hexane	Ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	56.2% al 100 μg/mL	Vittorazzi et al. (2016)
Lythraceae	Lafoensia pacari	Leaves	Hydroethanolic solution (1: 10 w/v), DMEM medium	Scratch assay, L920 cells	↑Proliferation/ migration of 23.1% and 35.5% at 0.1 and 0.03 μg/mL	Pereira et al. (2018)
Malvaceae	Waltheria communis (syn. Waltheria douradinha)	Aerial parts, flowers, and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	79.70%hexanic extrac and 54.73% ethanolic etract at 10 μg/mL	Schmidt et al. (2009)
Meliaceae	Melia azedarach	Aerial parts	Water and ethanol	MTT assay, HaCaT cells	Concentration dependent	Alerico et al. (2015)
Moraceae	Sorocea guilleminiana	Leaves	Water, topical, 0.1% DMSO in DMEM	Scratch assay, N3T3 fibroblasts	~90% proliferation/ migration rate at 4 μg/mL	Figueiredo et al. (2020)
Myrtaceae	Eugenia dysenterica	Leaves	Essential oil, hydro distillation	Scratch assay, L920 cells	100% at 542.2 μg/mL	Mazutti Da Silva et al. (2018)
		Fruit peels	50% ethanol solution (v/v)	Scratch assay, L920 cells	No effect	Pitz et al. (2016)

(Continued on following page)

TABLE 3 (*Continued*) *In vitro* wound healing promoting activity of medicinal plants in Latin America.

Plant Family	Plant Name	Plant Part	Solvent/ Compound/ Vehicle/ Administration	Model of Study	Healing Activity %	References
	Plinia cauliflora (syn. Plinia peruviana)					
Nyctaginaceae	Mirabilis jalapa	Aerial parts	Ethanol and decoction	MTT assay, HaCaT cells	Stimulated keratinocyte proliferation at 25 μg/mL, both extracts	Alerico et al. (2015)
Petiveriaceae	Petiveria alliacea	Aerial parts, flowers and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 albino mouse fibroblasts	Ethanolic 10.26% at 10 μg/mL	Schmidt et al. (2009)
Piperaceae	Peperomia galioides	Whole plant	Ethanol, (+)-epi-α-bisabolol	Swiss 3T3 albino mouse fibroblasts	No effect	Villegas et al. (2001)
	Piper regnellii	Aerial parts, flowers and leaves	Ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	Ethanolic 22.11% at 10 μg/mL	Schmidt et al. (2009)
Plantaginaceae	Plantago australis	Leaves	Hydroethanolic solution (30% water and 70% ethanol), verbascoside,	Scratch assay, HaCaT cells	Extract: 81.06% at 25 μg/mL Compound: 58.7% and 57.77% at 5 and 10 μg/mL	De Moura Sperotto et al. (2018)
Scrophulariaceae	Buddleja cordata	Leaves	CH2Cl2-methanol (1:1), DMSO-DMEM-F12	Scratch assay, fibroblasts FBH	33.1% at 25 μg/mL	Hernández-Pasteur et al. (2019)
Solanaceae	Brugmansia suaveolens	Aerial parts, flowers, and leaves	n-hexane and ethanol	Scratch assay, Swiss 3T3 mouse fibroblasts	26.66% hexanoic extract and 9.83 ethanolic extract at 10 μg/mL	Schmidt et al. (2009)
	Solanum diploconos	Fresh ripe fruit	95% ethanol	Scratch assay, Murine L929 cells	↑ Fibroblast migration at 1, 10 or 100 μg/ml	Benvenutti et al. (2021)
Rosaceae	Fragaria x ananassa	Fruit	Methanol-Water 80:20, polyphenolic-enriched extract, anthocyanin-enriched fraction	Migration and proliferation assay, HDFa fibroblasts	50% fibroblast migration at 1 μg/mL (anthocyanin-enriched fraction) and 30% at 1 μg/mL (polyphenolic-enriched extract)	Van De Velde et al. (2019)
	Rubus fruticosus	Fruit	Methanol-Water 80:20, polyphenolic-enriched extract, anthocyanin-enriched fraction	Migration and proliferation assay, HDFa fibroblasts	50% fibroblast migration at 1 μg/mL (anthocyanin-enriched fraction)	Van De Velde et al. (2019)
Rubiaceae	Remijia ferruginea	Aerial parts, leaves and branch	Water/alcohol (v/v) 1:1, catechins, rutin and quercetin	MTT assay, Swiss 3T3 mouse fibroblasts	Concentration dependent	Sarandy et al. (2022)

problems, and the treatment of wounds with medicinal plants is no exception.

Medicinal plants used in traditional medicine as healing agents

Numerous reports validate the widespread use of different plant species in traditional medicine with a healing effect. Our review focuses on plant species that grow in the area known as Latin America, which stands out for having about 50% of the planet's biodiversity, which allows it to sustain natural ecosystems that provide welfare to society. Unsurprisingly, Latin American countries have species used in traditional medicine as healers (Armenteras et al., 2021).

Brazil reports 88 wound-healing plant species, making it the country with the most excellent knowledge of its plants with wound-healing effects. On the other hand, Mexico reports 23 species, while Peru has 9, and the rest of the countries report fewer species. It is worth mentioning that Argentina, Chile, Colombia, and Costa Rica have at least one study on healing plants (Figure 7). Only a few of the plants studied were introduced into the region, which indicates that the research focuses on native plants. These data suggest that the study of

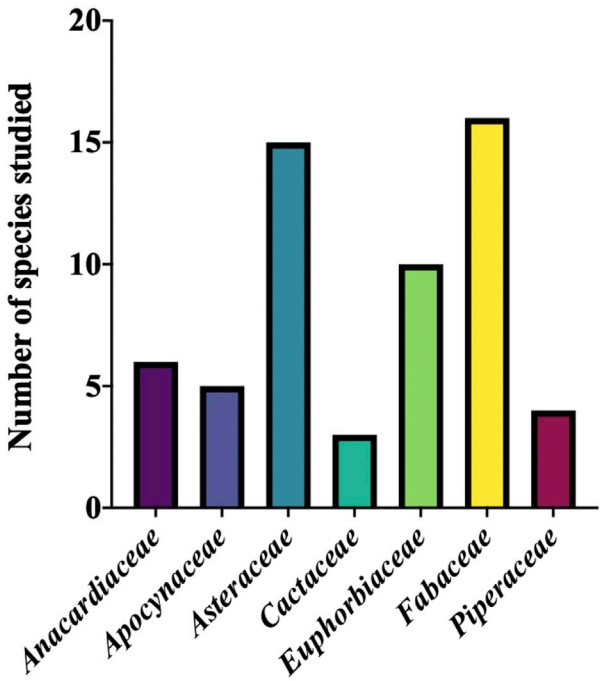


FIGURE 8
Families with more studies of wound-healing activity in Latin America.

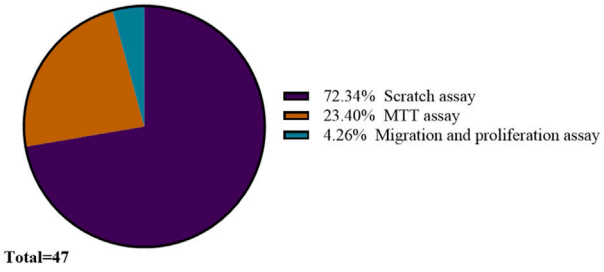


FIGURE 9
In vitro models were used to assess the wound-healing effect in Latin America.

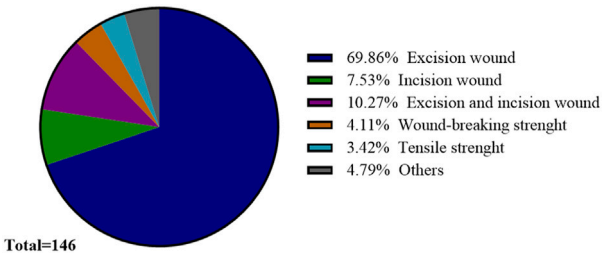


FIGURE 10
In vivo models were used to assess the wound-healing effect in Latin America.

medicinal plants with wound-healing uses is fundamental because plants are the primary source of natural products.

The bar chart looks at the seven botanic families most studied in Latin America for their wound-healing effect. However, 62 botanic families are reported in research articles. Despite this, only five families have three or more published articles (Table 3; Supplementary Table S1).

There is a noticeable increase in the number of studied species of Fabaceae. This family has 17 species with scientifically proven research, followed by Asteraceae and Euphorbiaceae, which have 15 and 10, respectively. The other families only have one or two reports (Figure 8).

The chart shows that the three main models used to evaluate the wound-healing capacity *in vitro* are: Scratch assay is the most common model, with 72.34% of research, followed by MTT assay, with 23.40%. The sum of these two models is approximately 95% of research made (Supplementary Table S2).

On the other hand, Fibroblasts from Swiss mice and HaCaT cells were used in the Scratch assay and MTT assay, and healing effects were shown in both models (Figure 9).

On the other hand, the most popular *in vivo* assay is the excisional wound model, used in more than 50% of the investigations performed in Latin America. The incisional wound is also frequently used, sometimes in comparison with the excisional wound. These models were mostly tested in Wistar rats or Swiss mice; other biological models were also used (Figure 10).

On the other hand, bioactive compounds from different plant species have been reported; the main ones are shown in Figure 11. These compounds are of different chemical nature, suggesting that there are still compounds with healing potential (Supplementary Table S3).

Among the species worth highlighting from the families shown in Figures 8, 9, is the effect of the alcoholic extract of Achillea asiatica flowers belonging to the Asteraceae family, with an impact on cutaneous wound healing (*in vitro* and *in vivo*), demonstrating that the treatment significantly increased epithelialization and accelerated wound healing in a rat model (Dorjsembe et al., 2017). A relevant species of the Fabaceae family is Glycyrrhiza glabra, with a healing effect on full-thickness dermal wounds in a rat model, gastric wound healing, oral mucosal, ulcers, and colitis, and even the extract of this plant was effective in wound healing in guinea pig (Hanafi et al., 2018). Very recently, in a study with *Jatropha mollissima* (Pohl) Baill. (Euphorbiaceae) which is widely used in traditional medicine to treat skin disorders; a topical gel containing the hydroethanolic extract of its leaves showed potential for wound healing, providing an accelerated wound healing effect (process in 3 and 5 days) in rats (Passos et al., 2024).

Future perspective

Although some studies claim that multiple drugs are necessary to ensure combined pro-regenerative functions, drugs do not follow the wound healing cascade in real time, so it is essential to develop new treatments that can act on pathogenic molecules and cells with multiple targets and intervene in the cascade.

It is, therefore, essential to develop new treatments that can act on pathogenic molecules and cells with multiple targets and

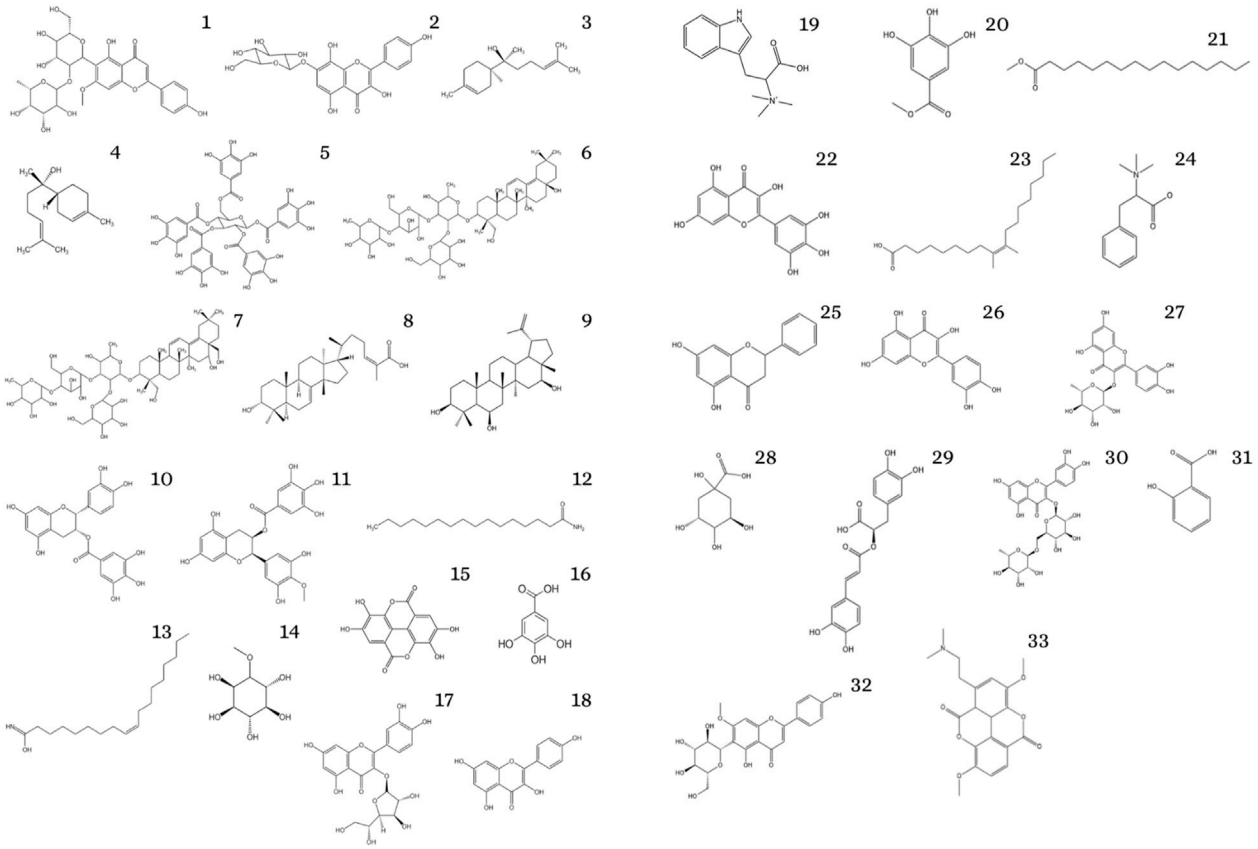


FIGURE 11
Reported wound healing compounds. 1: 2″-O-rhamnosylswertisin, 2: 7-O-(β-d-glucopyranosyl)-galactin, 3: (+)-anymol, 4: (+)-epi-α-bisabolol, 5: 1,2,3,4,6-pentagalloylhexose, 6: 3-O-α-L- rhamnopyranosyl- (1→4)-β-D- glucopyranosyl- (1→3)-[β-D- glucopyranosyl-(1→2)]-β-D- fucopyranosyl-16,23,28-dri, 7: 3-*O*-α-L- rhamnopyranosyl- (1→4)-β-D- glucopyranosyl- (1→3)-[β-D- glucopyranosyl-(1→2)]-β-D- fucopyranosyl- 16,23,28-trihydroxyoleane- 11,13(18)-diene, 8: 3α-hydroxy masticadienoic acid, 9: 3β, 6β,16β-trihydroxylup- 20(29)-ene, 10: epicatechin3-*O*-gallate, 11: 4′-*O*- methylepicatechin-3- *O*-gallate, 12: 9-palmitamide, 13: octadecenamide, 14: Bornesitol, 15: ellagic acid, 16: gallic acid, 17: isoquercitrin, 18: kaempferol, 19: lenticin, 20: methyl gallate, 21: methyl hexadecanoate, 22: myricetin, 23: oleic acid, 24: phenylalanine-betaine, 25: pinocembrin, 26: quercetin, 27: quercitrin, 28: quinic acid, 29: rosmarinic acid, 30: rutin, 31: salicylic acid, 32: swertisin, 33: taspine hydrochloride.

intervene in the wound-healing cascade (Cai et al., 2023). Therefore, it is essential to continue searching and testing treatments that either come directly from medicinal plants and are used as herbal medicines or are based on the structural relationship of some bioactive molecules found in plant species, which allow us to have more alternatives that are essential, given the increase in chronic degenerative diseases that lead to the development of wounds such as diabetic foot ulcer.

Conclusion

Wound healing is a global health problem that requires attention because its phases must flow synchronously. When wound healing is prolonged, and its phases do not heal promptly, complications may arise that compromise the recovery of the damaged tissue. Wound healing depends on the patient's state of health, age, and diet, among other factors. For this reason, it is suggested that treatments that promote healing be incorporated and validated using appropriate trials to guarantee their safe use. On the other hand, medicinal plants are a privileged source of healing compounds. Unfortunately, most of them have not been scientifically validated. Particularly, Latin American countries are geographically favored because they have environmental conditions that allow high biodiversity; taking advantage of natural resources to solve health problems is a valuable contribution that gives back significantly to society. Finally, the species reported now with healing effects come from different families. Therefore, continuing ethnomedical studies of species popularly used as healers is essential.

Author contributions

MS-R: Writing–original draft, Investigation. AR-B: Writing–original draft, Formal Analysis, Investigation. ST-C: Writing–original draft, Formal Analysis, Investigation. AR-G: Writing–review and editing, Validation. MC-P: Writing–original draft, Validation. AG-A: Conceptualization, Writing–review and editing. AB-A: Formal Analysis, Supervision, Writing–original draft. DO-R: Investigation, Writing–review and editing. FC-S: Writing–review and editing, Conceptualization.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fceng.2024.1514962/full#supplementary-material

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